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Cerebral Haemodynamics in Mild Cognitive Impairment: A Systematic Review

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Running Title (44 characters)

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Abstract and Key Words

Introduction

The incidence of dementia is projected to rise over the coming decades, but with no sensitive diagnostic tests available. Vascular pathology precedes the deposition of amyloid, and is an attractive early target.

Objective

The aim of this review was to investigate the use of cerebral haemodynamics and oxygenation as a novel biomarker for mild cognitive impairment (MCI), focussing on Transcranial Doppler ultrasonography (TCD) and near-infrared spectroscopy (NIRS).

Methods

2698 articles were identified from Medline, Embase, PsychINFO and Web of Science databases. 306 articles were screened and quality assessed independently by 2 reviewers; 26 met the inclusion criteria. Meta-analyses were performed for each marker with 2 or more studies and limited heterogeneity.

Results

Eleven studies were TCD, 8 NIRS, 5 magnetic resonance imaging, and 2 positron/single photon emission tomography. Meta-analyses showed reduced tissue oxygenation index, cerebral blood flow and velocity, with higher pulsatility index, phase and cerebrovascular resistance in MCI compared to controls. The majority of studies found reduced CO_2 reactivity in MCI, with mixed findings in neuroactivation studies.

Conclusions

Despite small sample sizes and heterogeneity, meta-analyses demonstrate clear abnormalities in cerebral haemodynamic and oxygenation parameters, even at an early stage of cognitive decline. Further work is required to investigate the use of cerebral haemodynamic and oxygenation parameters as a sensitive biomarker for dementia.

Key words

Transcranial Doppler ultrasonography

Near-infrared spectroscopy

Functional neuroimaging

Neurovascular coupling

Cognitive dysfunction

1. Introduction and Aims

The world prevalence of Alzheimer's disease (AD) is expected rise to 74.7 million by 2030 [1-3], with significant associated morbidity, mortality and economic impact [1, 2, 4]. A key priority is the identification of a sensitive marker for early cognitive decline to facilitate potential disease modifying interventions. Mild cognitive impairment (MCI) is an attractive target as an early state of cognitive impairment but importantly characterised by retained functional independence [5]. However, not all patients with MCI progress to dementia, at a conversion rate of 6-12% per year, and the reasons for this remain unclear [5].

Until recently, vascular pathology as a mechanism in dementia was thought to be confined to vascular dementia (VaD), but it is becoming increasingly understood that impaired vascular structure and function are important in the development of Alzheimer's disease [6-9]. The two hit hypothesis combines both the vascular and amyloid cascade hypotheses, acknowledging that vascular dysfunction (first hit), is likely to result in amyloid beta deposition (second hit), and ultimately neurodegeneration and cognitive decline [10, 11]. Wierenga et al advocate a cyclical model of deterioration, where progressive hypoperfusion leads to tau and amyloid deposition, in turn leading to further hypoperfusion [6-8]. Certainly, a number of studies have demonstrated that impaired cerebral blood flow or perfusion deficits are present prior to the development of dementia [6, 7, 12]. Therefore, a sensitive marker of early changes in cerebral vasculature function could potentially be used as a screening tool for early cognitive decline [6-9]. Furthermore, augmentation of impaired cerebral perfusion could be targeted with interventions that modulate or improve cerebral haemodynamics in patients with MCI [8].Transcranial Doppler ultrasonography (TCD) is a non-invasive, inexpensive, and portable imaging modality used to determine cerebral blood flow velocity (CBFv) and small vessel resistance through intra- and extra-cranial arteries [8, 13]. TCD is advantageous in that it is well tolerated by patients, does not use ionising radiation, and has good

inter-observer reliability [8, 13]. However, it is disadvantaged by lack of structural imaging and low spatial resolution [13].

There are numerous outcome makers measurable by TCD, and this review examines the most commonly reported of these. Firstly, cerebral blood flow velocity is measured as an approximation of CBF [14]. Cerebrovascular resistance describes the resistance of the small vessels and is given by the equation [14, 15]:

$$CVR = \frac{Mean\ arterial\ pressure}{CBF}$$

Where CBFv is used as surrogate for CBF, the cerebrovascular resistance index can be described by [14, 15]:

$$CVRi = \frac{Mean\ arterial\ pressure}{CBFv}$$

Transfer function analysis measures the efficiency of the autoregulatory process through; gain, phase and coherence [13, 16]. Gain is the ability of the system to dampen the changes in BP (input) on CBF (output), and therefore higher gain represents a more efficient system [13, 16]. Phase examines the changes in BP and CBFv waveforms within the same time period, where changes in CBF should recover more quickly than those in blood pressure, and thus greater positive phase represents a greater ability of the system to respond rapidly to changes in blood pressure [13, 16]. Coherence assesses the reliability of the BP-CBFv relationship. Lower values reflect poor signal to noise ratio, a non-linear relationship or multiple influences on CBF [13, 16]. Although others have suggested it could reflect impaired cerebral autoregulation, this would only apply to high values of coherence (i.e. >0.7) in the frequency region <0.10 [13, 16]. The autoregulatory index (ARI) describes a scale on which autoregulation, that is the brain's ability to maintain a relatively constant cerebral blood flow (CBF) in response to significant changes in cerebral perfusion pressure, can be assessed; 0 represents no autoregulation, and 9 represents best autoregulation [14]. Vasomotor reactivity describes the ability

of the cerebrovascular circulation to respond to peripheral changes in CO_2, blood pressure or metabolites by adjusting CBFv through vasoconstriction or dilation, and can be assessed by; breath holding, CO_2 inhalation, or pharmacologically with intravenous acetazolamide [17]. The breath holding index can be described by the following equation [18]:

$$BHI = \frac{\%\Delta CBFv}{Duration\ of\ breath\ hold\ (s)}$$

Pulsatility index describes the pulsatility of the CBFv waveform, and has traditionally been used to report cerebrovascular resistance [19]. However, a recent study demonstrated that pulsatility index is actually a complex interplay between multiple haemodynamic parameters (i.e. heart rate, cerebral perfusion pressure, arterial blood pressure, arterial compliance, and cerebrovascular resistance)[19]. Neuroactivation is the term used to describe the stimulation of increased neuronal activity, commonly induced by cognitive or sensorimotor testing [20, 21]. This is a common method used to investigate neurovascular coupling where increasing neuronal activity is tightly coupled to increasing cerebral blood flow to meet rising metabolic demands [21, 22].

TCD studies have largely focussed on the role of haemodynamics in Alzheimer's disease and vascular dementia [8, 23, 24]. Results have been heterogeneous, but have consistently demonstrated reduced CBFv and higher pulsatility index (PI), which can discriminate between dementia sub types [8, 23, 24]. Furthermore, increased PI, micro-emboli and lower vasoreactivity were the most consistent discriminators of dementia from normal ageing [24].

Near infrared spectroscopy (NIRS) is another non-invasive technique measuring changes in the relative concentrations of oxygenated (HbO_2) and deoxygenated (HbR) haemoglobin by infrared light absorbance [25]. The combined total concentration (HbT) can measure blood flow and activation in response to cognitive stimuli (neurovascular coupling (NVC)) [25]. Studies have demonstrated reduced HbO_2 response to the verbal fluency task in the parietal cortex, with loss of lateralisation in AD [25]. The tissue oxygenation index (TOI), a measurement of cerebral oxygenation, can be measured using

NIRS, and has been shown to correlate well with CBFv as measured by TCD, with good sensitivity and specificity for cerebral ischaemia [26].

Functional magnetic resonance imaging (fMRI) studies of perfusion and activation in MCI, have yielded conflicting findings with increased [27-30], decreased [31-33] and mixed areas of activation [34-36], likely due to methodological differences and heterogeneity of MCI populations [6, 7]. Nonetheless, predictors of progression to dementia have been identified as: increased perfusion in the parahippocampal gyrus [30], impaired posterior-medial cortex deactivation [27], and hypoperfusion in the right precuneus, cingulate gyrus, and posterior cingulate cortex [7, 37, 38]. A meta-analysis of task activation found hypoactivation in the visual networks, hyperactivation in the somatomotor networks, and mixed activation in the fronto-parietal and default networks [12]. Activation patterns were more subtle in MCI than Alzheimer's disease [12], with greater areas of compensatory hyperperfusion [6, 7, 39].

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging use radiolabelled tracers to measure changes in metabolic activity which are accompanied by changes in CBF [40, 41]. MCI studies consistently show reduced metabolism in the medial temporal lobes, precuneus, posterior cingulate cortex and the parietal lobe [41, 42]. These are predictive of patients who progress to Alzheimer's disease, with good sensitivity (84-88%) and specificity (84.9-89%) [41, 42] [42, 43].

The aim of this systematic review was to evaluate the utility of functional imaging methods to examine cerebral haemodynamics and oxygenation in MCI. Studies examining task activation and resting CBFv using fMRI or SPECT have been reviewed comprehensively in a number of recent systematic reviews [12, 44, 45]; therefore the focus of this review was studies of TCD and NIRS in MCI. In addition, we included fMRI, PET, and SPECT studies of vasoreactivity or small vessel resistance, which have not been examined by recent reviews. In addition, we aimed to meta-analyse common outcomes reported between studies.

2. Methods

Medline (1946-March 2017), Web of science (1970-March 2017), EMBASE (1974-March 2017) and PsychINFO (1975-March 2017) were searched using the strategy detailed in Appendix 1, for human studies published in English.

The initial search yielded 2698 references. Following removal of duplicates, and title/abstract screening, 306 references remained for full text review, Figure 1. These were evaluated by two reviewers independently (LB, VJH). Study quality was evaluated using a pre-defined set of criteria used previously by this group (Appendix 2) [46]. All studies included in this review had a quality score of ≥10. Summary charts and tables for risk of bias are presented as supplementary material (Supplementary Figures 1 and 2). Data were extracted to Microsoft Excel, and studies were sub-classified according to imaging modality and study type. Studies were reported descriptively if meta-analysis was not possible. Summary tables are provided for all of the included studies (Table 1, Supplementary Tables 2 and 3).

Inclusion criteria:

1) Participants with MCI and not dementia
2) TCD, MR, PET, SPECT, NIRS imaging modality
3) Marker included a measure of cerebral haemodynamics or oxygenation

Exclusion criteria:

1) Dementia
2) No measure of cerebral haemodynamics or oxygenation

Meta-analysis was performed where there were data from two or more studies, with minimal to moderate heterogeneity, (CBF, CBFv, cerebrovascular resistance index (CVRi), tissue oxygenation index (TOI), PI, and phase). Meta-analysis was performed using RevMan 5 software © for Windows

using a random effects model. All outcomes were continuous variables using the inverse variance method. Studies were excluded from meta-analysis if there were fewer than 2 studies examining the same vessel, no standard deviations provided, no control data, or control and MCI groups presented as mixed data. Where studies presented data for both the right and left MCA [47], both data were included in meta-analyses, as were data for proximal and distal MCA measures [48].

Heterogeneity between studies was reported as I^2 index, where:

$$I^2 = [Q\text{-}df/Q]x100\%$$

(Q= X^2 statistic, df= degrees of freedom).

I^2 index represents the percentage variation due to heterogeneity [49]. I^2= 25% was considered low, I^2 = 50% moderate and I^2=75% high heterogeneity, and was significant if $p<0.01$ [49]. Finally, funnel plots were produced to detect publication bias. Meta-regression analysis was not possible to explore heterogeneity as a sub-group analysis as all meta-analyses contained fewer than 10 studies [49].

3. Results

3.1 Summary of characteristics of the studies

Twenty-six studies were suitable for inclusion, of which eight were TCD [18, 47, 48, 50-55], three combining TCD and NIRS [47, 56, 57], eight NIRS only [58-64], five fMRI [15, 65-67] and two using PET or SPECT [20, 40] (Table 1). Median quality score was 13/15. All studies lacked sample size calculations, and few demonstrated testing for validity and reliability (Supplementary Figures 1 and 2).

Twenty-two of the twenty-six studies were cross sectional [15, 18, 20, 40, 47, 48, 53-69], and the remaining four studies were longitudinal [50-52, 60] (2 mixed design) [52, 60]. Follow-up time in the longitudinal studies ranged from five weeks to two years [50-52, 60]. Sample sizes were small for most studies, (total sample size range: 15-127).

The diagnostic classification system used for MCI varied between studies, five had no formal criteria [18, 20, 47, 53, 68], the majority used the Petersen criteria (n=14) [40, 48, 51, 52, 54, 56-62, 67], and fewer used the Mayo [50, 55], Winbald [65], Jak [15, 64, 69], and Reisberg [66] criteria. Several studies had extensive exclusion of other neurodegenerative, psychiatric conditions [15, 48, 50-52, 57-60, 62, 63, 66, 67], psychotropic medications, [59, 62, 67]. Some studies restricted their population to solely amnestic MCI [47, 51, 56-59, 65, 67]. Fifteen of the 24 studies collected data on vascular risk factors in addition to age, sex and education years [15, 18, 48, 51, 53-58, 60, 63, 66, 67]; four reported antihypertensive use [15, 56, 57, 60].

The mean age of participants varied between 57-80 years, and few had an equal gender split between participants. All studies reported MMSE except four [15, 64, 68, 69]. All participants had an MMSE>24, or equivalent, except one study (mean MMSE 23.7) [54]. One study stratified participants by ApoE4 genotype [55]. The vessel insonated varied; seven measured solely the MCA [47, 51-54, 57], two insonated the vertebral artery (VA) and internal carotid artery (ICA) [50, 56], and four examined multiple vessels [18, 48, 55, 68].

3.2 Markers and Meta-analysis

3.2.1 Cerebral blood flow (CBF)

Six studies measured baseline or change in CBF [40, 50, 56, 66-68]. Three studies [56, 66, 67] did not find any difference in baseline CBF between controls and MCI. Liu et al found total CBF was significantly lower in the MCI group, when normalised for total brain volume [56]. Akkawi et al found that a threshold CBF of 558 ml/min, had a sensitivity of 68.4%, and specificity of 72.2% for detection of MCI [50]. Rivera-Rivera et al examined multiple intra-cranial vessels using arterial spin labelling and 4D-MRI but only demonstrated significantly lower CBF in the proximal posterior cerebral artery compared to age-matched controls [68].

In a meta-analysis of two studies, CBF corrected for brain volume was significantly lower in MCI (SMD: -0.51 (-0.94, -0.07), p=0.02) (Figure 2).

3.2.2 Cerebral blood flow velocity (CBFv)

Eight studies reported CBFv, but only one showed a significant difference between MCI and controls [55]. Six studies [18, 47, 48, 52, 54, 57] were suitable for meta-analysis (n MCI= 219, n controls = 327); CBFv was significantly lower in MCI than controls (MD: -3.92 (-5.29, -2.55), p<0.01) (Figure 3).

Sun et al demonstrated significantly lower CBFv across all MCI patients compared with controls (P<0.005-0.001) [55]. ApoE4 positive carriers had significantly reduced CBFv compared to non-carriers [55] .

Roher et al could not discriminate between MCI and control groups with sufficient sensitivity based on CBF [48], likely due to small sample size and heterogeneity [48]. Results were significant when the MCI group were restricted to amnestic sub type only [48].

In a study by Gommer et al, five patients with MCI developed AD during the study and had a significantly lower mean CBFv (35 (5) vs. 51 (11) cm/s), than those with stable MCI [52].

3.2.3 Pulsatility index (PI)

Five studies reported pulsatility index, only two studies demonstrated a significantly higher PI in MCI [47, 68]. Rivera-Rivera et al found increased PI was only significant in the inferior internal carotid artery and proximal posterior cerebral artery in MCI [68]. The remaining three studies did not show any significant differences [48, 51, 54]. In a meta-analysis of three studies, PI was significantly higher in MCI (n=159), (MD: 0.15 [0.10, 0.20] p<0.01) (

	MCI			Control				Mean Difference	Mean Diffe
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random,
Roher 2011 dLMCA	1.18	0.24	9	1.11	0.24	50	7.2%	0.07 [-0.10, 0.24]	
Roher 2011 dRMCA	1.16	0.28	11	1.06	0.21	50	6.8%	0.10 [-0.08, 0.28]	
Roher 2011 pLMCA	1.19	0.28	11	1.11	0.22	50	6.7%	0.08 [-0.10, 0.26]	
Roher 2011 pRMCA	1.14	0.22	11	1.04	0.2	50	10.4%	0.10 [-0.04, 0.24]	
Shim 2015	1.38	0.53	75	1.18	0.44	52	7.3%	0.20 [0.03, 0.37]	
Viola L MCA 2013	1.06	0.21	21	0.88	0.03	10	24.8%	0.18 [0.09, 0.27]	
Viola R MCA 2013	1.07	0.16	21	0.9	0.05	10	36.9%	0.17 [0.09, 0.25]	
Total (95% CI)			**159**			**272**	**100.0%**	**0.15 [0.10, 0.20]**	

Heterogeneity: Tau² = 0.00; Chi² = 3.26, df = 6 (P = 0.78); I² = 0%
Test for overall effect: Z = 6.42 (P < 0.00001)

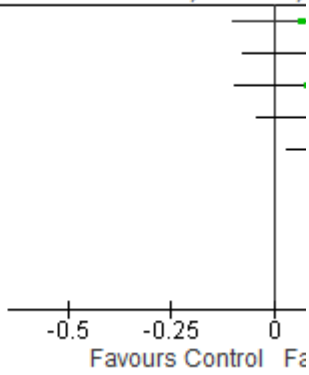

Figure ***4***).

Viticchi et al did not find any significant differences in PI between stable (n=96) and progressive (n=21) MCI patients over 1 year [51].

3.2.4 Breath Holding Index (BHI)

Two studies measured breath holding index, one cross sectional [18] and the other longitudinal [51]. Zavoreo et al demonstrated significantly reduced BHI in MCI (n=20) compared to control (n=60) (0.69 vs. 1.35 respectively, p<0.05) [18].

Viticchi et al demonstrated both BHI and carotid wall thickness (IMT) were predictive of those who progressed to dementia (BHI odds ratio: 5.80 (1.83-18.37) $p<0.05$, IMT OR: 3.08 (1.02-9.33 $p<0.05$) [51]. Breath holding index was a more sensitive marker of progression than carotid wall thickness [51].

3.2.5 Cerebrovascular resistance/index (CVR/CVRi) and resistance index (RI)

Six studies examined cerebrovascular resistance, but there was significant heterogeneity between outcome measures [15, 52, 54, 56, 57, 68]. Four of the six studies did not find any significant difference in CVR/CVRi between groups [15, 52, 54, 57]. Two studies measured CVRi (mean arterial pressure/ mean blood flow velocity), and are described in a meta-analysis below [52, 57]. Liu et al measured CVR (mean arterial pressure/ cerebral blood flow), which was increased by 13% in MCI relative to controls [56]. Although Gommer et al did not demonstrate any difference in baseline CVRi, it was predictive in a small group of MCI patients (n=5) who progressed to dementia [52]. In a 4D-MRI study, resistance index was found to be significantly increased only in the inferior ICA, but there were no differences in vessel cross-sectional area in MCI [68].

In a meta-analysis of two studies [52, 57], CVRi was significantly higher in MCI (n=46) patients compared to controls (n=35), (0.17 [0.06, 0.29], $p=0.03$) (Figure 5).

3.2.6 Autoregulatory index (ARI)

One study reported the autoregulatory index, with no difference between MCI and control groups [52].

3.2.7 Vasomotor reactivity (VMR)

Eight studies examined cerebrovascular reactivity, but varied in imaging type; MR [52, 65-67], PET/SPECT [20, 40], TCD [53, 54], NIRS [59], and method of inducing changes in haemodynamics, which precluded meta-analysis (**Error! Reference source not found.**). Five studies used CO_2 inhalation, two studies used intravenous acetazolamide [20, 40], and one utilised breath holding to induce

hypercapnia [54]. Five studies demonstrated reduced reactivity in MCI compared to controls [54, 59, 65-67], and one reported no difference [53].

Babiloni et al combined NIRS and electroencephalogram (EEG) to investigate vasomotor reactivity (in response to CO_2) and coherence [59]. Subjects with amnestic MCI showed lower EEG coherence both before and after CO_2 inhalation and demonstrated poorer reactivity of coherence during CO_2 inhalation [59], suggesting an early loss of neurovascular coupling in amnestic MCI [59].

Ponto et al used PET to measure vasoactivation using intravenous acetazolamide (ACZ) and neurovascular coupling by neuroactivation with cognitive tasks in MCI (n=15) [40]. Participants were sub-classified into better or worse cognitive function but CBF, vasomotor reactivity and ACZ challenge did not differ between the two groups [40]. Change in CBF was a better predictor of cognition than vasomotor reactivity [40]; in contrast to Glodzik et al who found reactivity rather than CBF was a better discriminator from normal ageing [66].

3.2.8 Transfer function Analysis (TFA)

Two studies used transfer function analysis to report phase, gain and coherence [52, 57]. Both studies found intact dynamic autoregulation in MCI compared to healthy controls [52, 57]. Tarumi et al reported higher gain between tissue oxygenation index (TOI), and CBFv was related to poorer memory performance in MCI [57]. Meta-analysis of gain between two studies, [52, 57] was non-significant, but phase was significantly higher in MCI (MD: 0.1 (0.07, 0.14), $p<0.01$) (Figure 6).

3.2.9 Tissue oxygenation index (TOI)

Three studies examined tissue oxygenation index using NIRS [47, 56, 57]; which was significantly lower in MCI patients compared to controls (-7.51 [-13.80, -1.23] p=0.02), but with significant heterogeneity at meta-analysis (I^2=85%, P<0.01) (Figure 7).

Tarumi et al measured functional coupling between CBFv (TCD) and tissue oxygenation index (NIRS)[57]. TOI was lower at rest in MCI , and correlated with memory, and executive function [57] suggesting a pathological de-coupling between oxygenation and CBFv in MCI [57]. Sit-to-stand manoeuvres made differences in tissue oxygenation between MCI and controls more apparent (p=0.047 Vs p=0.03) [57].

Viola et al also found tissue oxygenation was significantly reduced in MCI, most obviously in the temporo-parietal cortex [47]. Using receiver-operator characteristic (ROC) curves, TOI at a cut off of 59%, had a sensitivity of 81% and specificity of 95% in distinguishing MCI from controls, and was more sensitive than PI (cut off of 0.96, Sensitivity: 69%, Specificity: 98%) [47].

In contrast, Liu et al did not find differences in TOI, or oxygen extraction fraction (OEF) [56]. However, cerebral metabolic rate of oxygen ($CMRO_2$) was significantly reduced by 11% in MCI [56]. Furthermore, there was a significant correlation between CBF and $CMRO_2$ in controls but not MCI, suggesting early loss of neurovascular coupling [56] .

3.2.10 Activation and neurovascular coupling (NVC)

Nine studies measured activation to cognitive tasks; seven NIRS [58, 60-64], one PET [40], and one SPECT [20]. Five studies demonstrated reduced activation during retrieval task [58], verbal fluency task [61], working memory task [62, 69], and verbal fluency task during walking [63]. Uemura et al demonstrated reduced activation bilaterally in the dorso-lateral prefrontal cortex during a retrieval task, with no differences in memory encoding [58]. Yeung et al demonstrated significant loss of lateralisation during the category fluency task in MCI, which was more significant in the non-amnestic sub-group [64]. In a later study by Yeung et al, MCI patients had similar performance on working memory tasks, and comparable frontal activation pattern to matched-controls at low task load [69]. On increasing the working memory task from low to high load, the increase in frontal activation in healthy controls was not apparent in the MCI group [69].

Vermeij et al found no differences in activation in patients with MCI pre and post a 5-week computer based memory training program [60]. The MCI group did have improved behavioural performance at lower load working memory task, indicating a potential clinical benefit from cognitive training [60].

Arai et al found oxygenation was significantly lower in the right parietal region during the verbal fluency task compared to controls (p=0.0012) [25, 61]. Using the right parietal area, sensitivity for distinguishing MCI from controls was only 40%, but specificity was high at 94% [61].

Doi et al compared cortical oxygenation during a normal walking and walking whilst performing the verbal fluency task in MCI [63], where the latter resulted in increased prefrontal activation. Executive function was significantly correlated with walking during the verbal fluency task, but not with normal walking [63].

In a neuroactivation PET study, more challenging cognitive tasks (memory vs. counting task) demonstrated a more significant relationship between change in CBF and the ability to learn from experiences [40]. Performance on the Trails B test was predicted by change in CBF during a more challenging task, which was lost in the non-learning group [40]. Change in CBF was found to be a better predictor of cognition than vasomotor reactivity [40].

Knapp et al demonstrated 30% of MCI patients had perfusional defects in the parieto-temporal regions with SPECT [20]. Vasoactivation with acetazolamide, decreased the number of defects [20], whereas neuroactivation with cognitive tasks increased the number of defects, and may be more useful clinically [20].

3.2.11 Other vessel measures

A number of studies measured CBFv and other parameters in the anterior cerebral artery (ACA), posterior cerebral artery (PCA), vertebral and basilar arteries (VA, BA), and the internal carotid arteries (ICA). The number of studies examining these vessels was fewer, and therefore meta-analyses

included small numbers of studies and could only be performed for ACA, ICA and VA measurements of CBFv.

Only one study examined the PCA [48], and there were no significant differences in CBFv or pulsatility index between MCI and controls [48]. Two studies measured CBFv in the basilar artery [48, 55], but meta-analysis was precluded as one study did not provide data for MCI and control groups [55]. Both studies report no statistically significant differences in CBFv in the BA between groups [48, 55]. In a meta-analysis of two studies for CBFv in the ACA [18, 48], CBFv was significantly lower in MCI compared to controls (MD: -5.00 [-8.64, -1.36], $p<0.05$) (Figure 8). Furthermore, although Sun et al did not provide the data for these measures, they also report significantly lower flow velocities ($p<0.05$) in the ACA in MCI, but not between ApoE4 carriers and non-carriers [55]. Two studies were included in meta-analyses of ICA and VA measures [48, 56], but neither showed any significant differences in flow velocities between MCI and controls in these vessels (Figures 9 and 10).

4. Discussion

4.1 Summary of results

On meta-analysis, CBF, CBFv and tissue oxygenation were all significantly lower in MCI, with increased pulsatility index, CVRi and phase. Reactivity to CO_2 and the breath holding index were found to be lower in most studies of MCI, and neuroactivation in response to cognitive tasks was generally reduced [58, 61, 62], with only one study demonstrating an increase in activation [63]. Few studies have examined validity, but thresholds have been determined for CBF, tissue oxygenation index, and A-index (amplitude of change in the HbO_2 waveform) to either predict progression or discriminate between MCI and normal ageing [47, 50, 61].

Studies of activation in MCI show mixed findings, with both increased [63] and reduced prefrontal activation [58]. These inconsistencies are likely to be explained by methodological differences, particularly activation techniques, imaging modality, pre-training and population heterogeneity (i.e. phenotype, education level, co-morbidities) [69].

Comparable to results from studies of AD and VaD [23, 24], measures using reactivity to CO_2, small vessel resistance, or neurovascular coupling may be more consistent and reliable markers of MCI, than CBF or CBFv, but further studies are required for confirmation.

4.2 Implications of findings

Despite the heterogeneity of studies examining MCI, on pooled analysis of individual studies, clear abnormalities in vascular physiology become apparent. In particular, reduced levels of cerebral blood flow and tissue oxygenation indicate that hypoperfusion may be an important pathological mechanism influencing the deposition or acceleration of tau and amyloid plaques [6, 11]. The complete picture remains elusive on the exact interplay of vascular pathology and that of tau and amyloid deposition, but it is likely to be a complex relationship [11], where both mechanisms exacerbate one another and thus resulting in progressive, cyclical neurodegeneration [7]. Reduced

cerebral blood flow not only reduces the delivery of essential nutrients and oxygen to neurones, but it also impairs the important clearance of neurotoxic metabolites and proteins that subsequently accumulate [11, 68]. Indeed, other disorders of amyloid, such as cerebral amyloid angiopathy, demonstrate microvascular abnormalities that result in increased amyloid formation [11]. Hypoperfusion can occur with, or independently, to blood-brain barrier degeneration, but neurotoxicity is less marked with the latter [11]. Blood brain barrier dysfunction leads to the accumulation of circulating proteins and the generation of reactive oxygen species resulting in microvascular dysfunction [9, 11]. Once established, hypoperfusion disrupts key cellular processes within highly metabolically active neurones, causing; altered pH, loss of action potentials, and electrolyte disturbance [11]. As a result, deposition of neurotoxic proteins, such as amyloid is exacerbated [11]. Animal models using artificial induction of hypoperfusion have demonstrated enhanced oligomerisation and deposition of amyloid [9, 11]. The sequence in which these pathological mechanisms occur remains unclear, and further studies have demonstrated that amyloid can also exacerbate hypoperfusion through vasoconstriction [9, 11]. According to the two hit hypothesis, tau hyperphosphorylation can result independently from both amyloid accumulation and hypoperfusion, but it is most likely to occur as a mixed disease process [11]. In addition, cognitively intact, at–risk individuals, can have impaired cerebral perfusion and functional neurovascular de-coupling, prior to amyloid deposition or clinically detectable cognitive deficits [11]. This early de-coupling is supported by the neuroactivation studies in this review demonstrating a reduced ability of the brain to increase blood flow, despite introducing increasing cognitive demand [58, 59, 61, 62]. Furthermore, the reduced ability of cerebral vessels in MCI to rapidly respond to intravascular changes, such as rising CO_2 [59], suggests the mechanisms to protect neurones under these conditions have become compromised. In line with recent studies of Alzheimer's disease [15, 24, 68], small vessel resistance was increased on meta-analysis, and is thought to occur as a combination of amyloid mediated vasoconstriction, arterial stiffening and reduced compliance, capillary microstructural changes, small vessel disease and atherosclerosis [11, 15, 68]. The interpretation of the apparent rise in pulsatility

index is more complex, with numerous haemodynamic parameters contributing to the observed change [19]. A recent study suggests that the pulsatility index can reflect the cerebral perfusion pressure [19], and the higher indices demonstrated in this review, may be indicative of a compensatory increase in CPP to counteract the falling CBFv as a result of structural microvascular changes [70]. Lower breath holding indices are in line with studies demonstrating reduced CO_2 reactivity, but this measure needs to be interpreted with caution given the limitations to this method [17, 71]. The higher phase demonstrated in the meta-analysis reported here, is suggestive of better autoregulation in MCI, but is not consistent with the overall pattern of results suggestive of poorer cerebral haemodynamics in this review. This may be as a result of the small number of studies and sample sizes included in this analysis. Higher phase values can also be due to a lack of attention to phase "wrap around", with negative values of phase more likely to occur in healthy subjects, being added to averages, thus reducing the values reported in controls [72]. However, the two studies conclude that dynamic autoregulation remains intact in MCI [52, 57]. Therefore increased phase could be due to compensatory mechanisms in early disease, in keeping with studies demonstrating hyperactivation [63]. The meta-analyses from this review support the notion that hypoperfusion occurs early in cognitive impairment, although compensatory hyperperfusion has also been demonstrated in MCI [63]. In reality this is likely to represent a spectrum of disease, where individuals with MCI present at various stages of compensation through to decompensation (i.e. hyper to hypoperfused states). Given that not all patients with MCI progress to dementia, longitudinal studies examining the predictive power of individual haemodynamic or autoregulatory markers would provide additional information on the specific vascular pathological mechanisms that are implicated in this conversion from mild decline to fulminant dementia. Furthermore, this could provide the opportunity for the development of therapeutics targeting specific stages of vascular dysfunction. Vermeij et al demonstrated that greater pre-frontal activation at higher working memory load predicted greater training gains from a cognitive training programme [60]. Therefore, haemodynamic biomarkers offer the potential to predict the utility of interventions in specific patient groups.

4.3 Limitations

The majority of the meta-analyses had low heterogeneity; however, the tissue oxygenation index analysis is limited by a relatively high and statistically significant heterogeneity.

The imaging techniques reviewed here all have their limitations. It is important to note that CBFv measures using TCD rely on the assumption that the vessel diameter remains relatively constant, despite significant fluctuations in blood pressure or CO_2 [14, 73, 74]. A number of recent studies have shown that BHI measured by TCD can vary significantly during large fluctuations in blood pressure or CO_2, can be inadequately performed, and is subject to a number of confounding factors, therefore limiting the usability of this marker over other protocols for the assessment of CO_2 reactivity with TCD [17, 71, 73, 74]. Pulsatility index reflects a complex construct of multiple haemodynamic parameters and this can limit the clinical application [19].

Small sample sizes, heterogeneous MCI populations and the cross-sectional design of the majority of individual studies are further limitations. Furthermore, some study populations were restricted to solely amnestic MCI [47, 51, 56-59, 65, 67]. Chao et al demonstrated important differences in perfusion between sub types of MCI, and therefore differences in MCI populations could introduce significant heterogeneity [75]. The classification systems for MCI vary between studies; as the concept of MCI has evolved, this is reflected by the variability in inclusion and exclusion criteria. The Petersen criteria [5] were the most widely used, but others included the Mayo criteria [5] and DSMV classification of neurocognitive disorders [76, 77]. Some studies included participants with subjective memory complaints, but no objective deficit on testing, and so variants of normal ageing are likely to be included in analyses [20]. Severity of cognitive impairment also varied; one study even recruited patients with an average MMSE score below the threshold for AD [54]. Changes in cerebral haemodynamics are likely to be more detectable in these patients, which may confound thresholds used to distinguish AD, MCI and normal ageing.

Concerns have been raised about the use of MMSE as a diagnostic tool for MCI and for determining inclusion into clinical studies [78]. In a recent study, MMSE had only 18% sensitivity for detecting MCI, compared to Montreal cognitive assessment (MoCA), which had 90% sensitivity [78].

Information on comorbidities was often limited and, given the increased prevalence of cardiovascular risk factors amongst those with MCI and impaired autoregulation [9, 66, 79, 80], is an important confounder. A recent pilot randomised controlled trial demonstrated reduced CO_2 reactivity and CBFv in hypertensive patients with executive dysfunction randomised to lisinopril or hydrochlorothiazide [81], but few studies reported the number of participants taking antihypertensive or vasoactive medications. Furthermore, asymptomatic carotid stenosis, which can occur in up to 10% of older people and significantly affect CBF, was not routinely assessed [66].

There were limited analyses on drop-out rates, and frequently these will be patients with more severe cognitive deficits [66]. The setting for recruitment is also important; the majority of participants were recruited from memory clinics. These participants are likely to present with a more advanced form of MCI, and be subject to more detailed and specialist evaluation than those presenting in the community, limiting the generalisability of the findings [5].

Only one of three studies reporting validity of imaging methods used receiver-operator characteristic curves to determine sensitivity and specificity [47]. ROC curves are the most robust method of determining diagnostic validity, and is therefore an important limitation to studies using single measures [82].

4.4 Further Work

Longitudinal studies with larger sample sizes are required to confirm the findings of this review, with a more comprehensive analysis of co-morbidities and concurrent medications. Consensus is required on the classification of MCI, and a move to more accurate neuropsychological testing should provide

greater homogeneity in populations being studied. Analysis of drop-outs from studies will help identify bias and patients that are currently under-represented [66].

Few studies have examined changes in CBFv in MCI during cognitive tasks with TCD. This may be a clinically useful method to examine neurovascular coupling. The feasibility of this has been demonstrated in a number of SPECT, PET and NIRS studies in this review [20, 40], but the accessibility and ease of use of TCD makes this an attractive option.

5. Conclusions

Studies of cerebral haemodynamics and oxygenation in MCI are small and heterogeneous. Despite this, pathological changes are demonstrated when compared to normal ageing and can predict those who progress to dementia. Meta-analyses suggest that small studies have been underpowered to detect these differences, and comprehensive larger studies are now required to confirm these findings. Studies thus far are likely to have underestimated the scope and significance of haemodynamic and oxygenation changes in MCI, and there is significant potential for the use of cerebral haemodynamics or oxygenation as an early and sensitive marker of cognitive decline.

6. Conflicts of Interest

The authors have no conflicts of interest to report.

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8. Figures

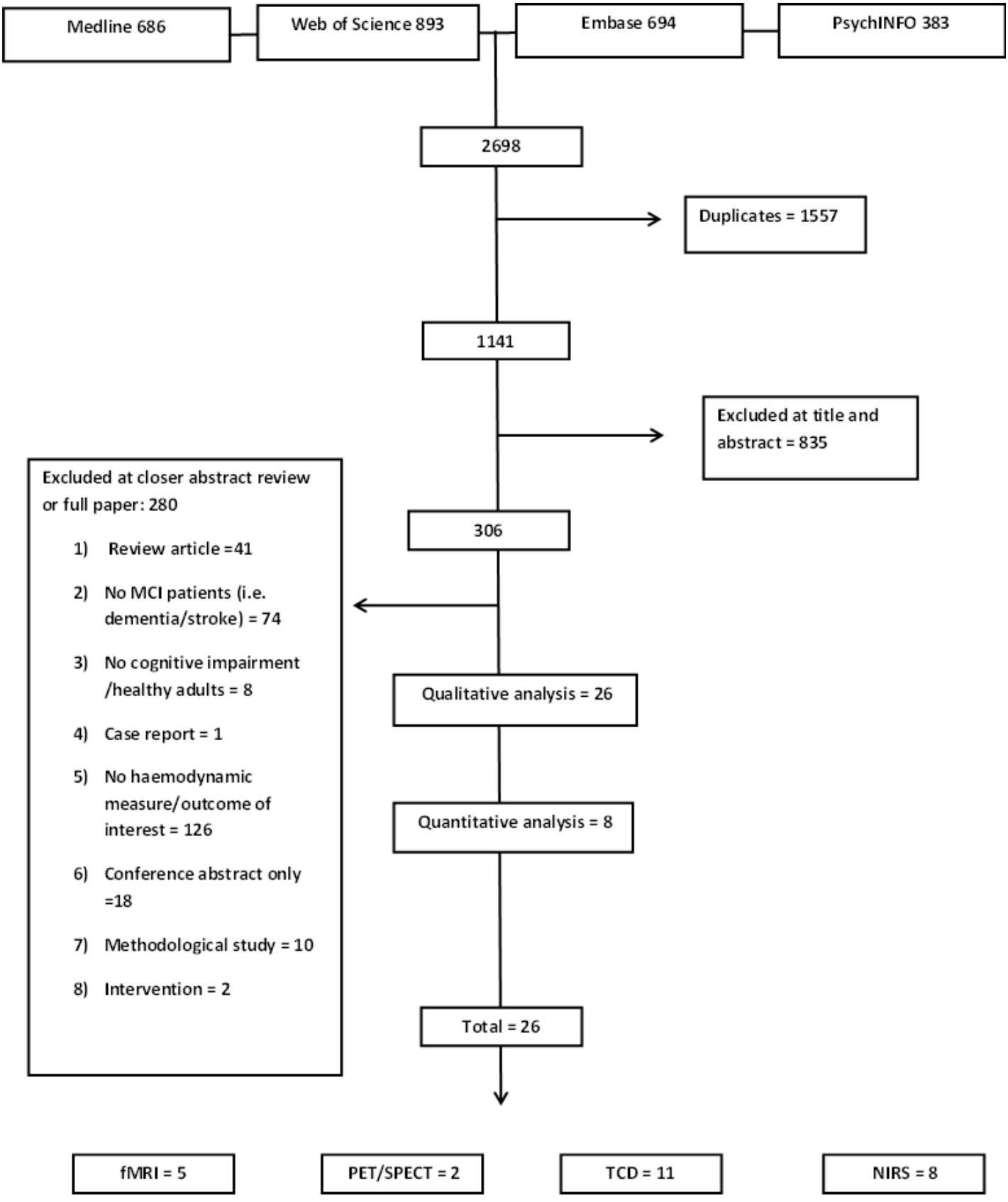
Medline 686
Web of Science 893
Embase 694
PsychINFO 383
2698
Duplicates = 1557
1141
Excluded at title and abstract = 835
306
Excluded at closer abstract review or full paper: 280
1) Review article =41
2) No MCI patients (i.e. dementia/stroke) = 74
3) No cognitive impairment /healthy adults = 8
4) Case report = 1
5) No haemodynamic measure/outcome of interest = 126
6) Conference abstract only =18
7) Methodological study = 10
8) Intervention = 2
Qualitative analysis = 26
Quantitative analysis = 8
Total = 26
fMRI = 5
PET/SPECT = 2
TCD = 11
NIRS = 8

Figure 1. Flow chart for inclusion and exclusion of studies throughout review. NVC = neurovascular coupling, fMRI= functional magnetic resonance imaging, PET = positron emission tomography, SPECT = single photon emission tomography, TCD = transcranial Doppler ultrasonography, NIRS = near infrared spectroscopy.

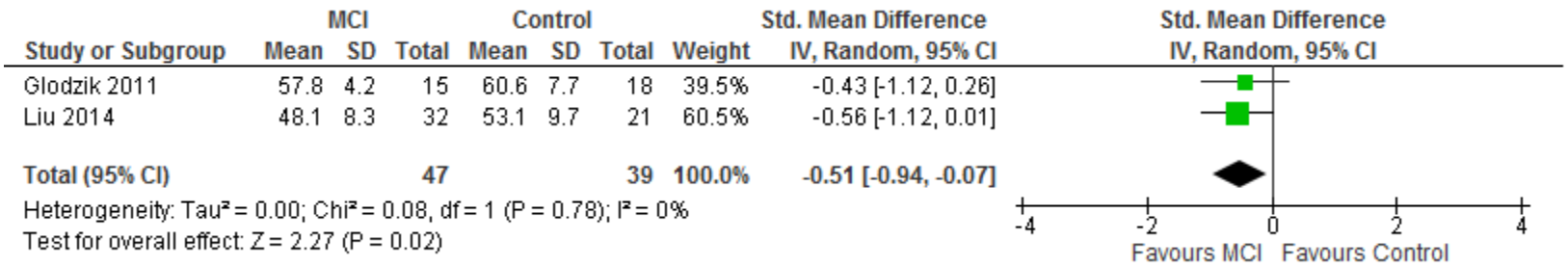

Figure 2. Forest plot for a meta- analysis of normalised CBF.

Data is pooled from 2 studies [56, 66]. Results are reported as standardised mean differences (95% confidence interval) as individual results are reported on different scales (ml/min/100 grams, and ml/min/100ml). Statistical significance set at $p<0.05$. Results show significantly reduced CBF in patients with MCI ($p=0.02$). Heterogeneity was low ($I^2=0$), and non-significant ($p=0.78$). There were no differences in heterogeneity or effect size between random or fixed effects models.

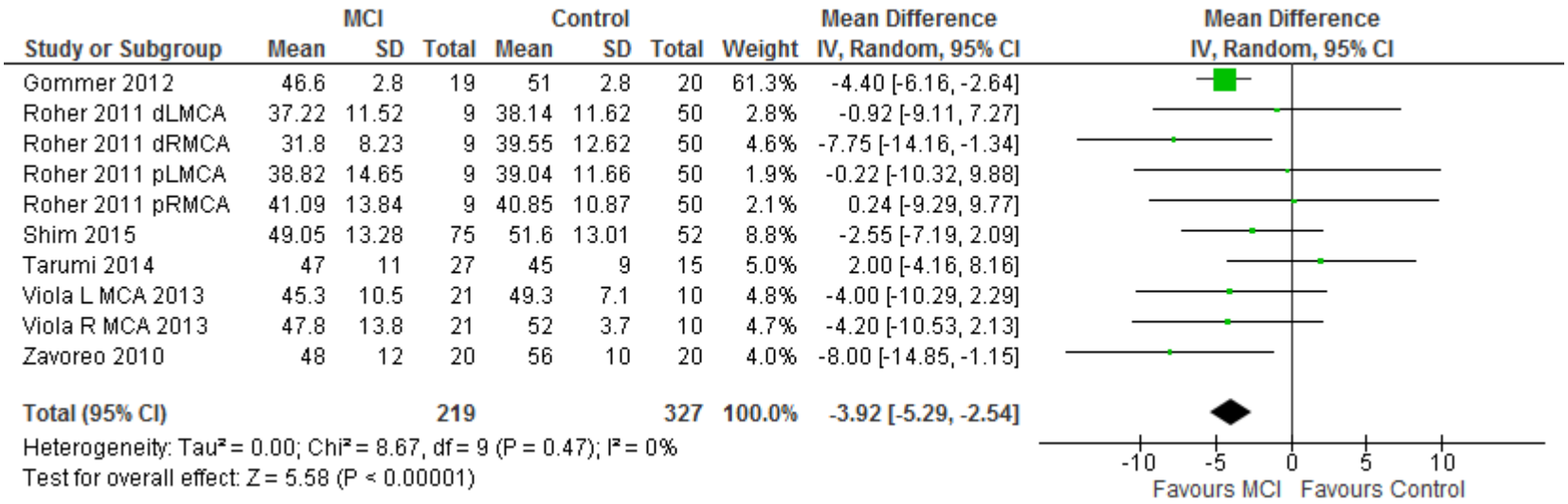

Figure 3. Forest plot for a meta-analysis of CBFv.

Data is pooled from 6 studies [18, 47, 48, 52, 54, 57]. Roher et al included multiple measurements [48] and Viola et al measured both MCA [47], all results for MCA are included. Results are mean difference (95% confidence interval). Statistical significance set at $p<0.05$. CBFv is significantly lower in MCI ($p<0.01$). Heterogeneity was low ($I^2=0\%$), and non-significant ($p=0.47$). There were no differences in heterogeneity or effect size between random or fixed effects models.

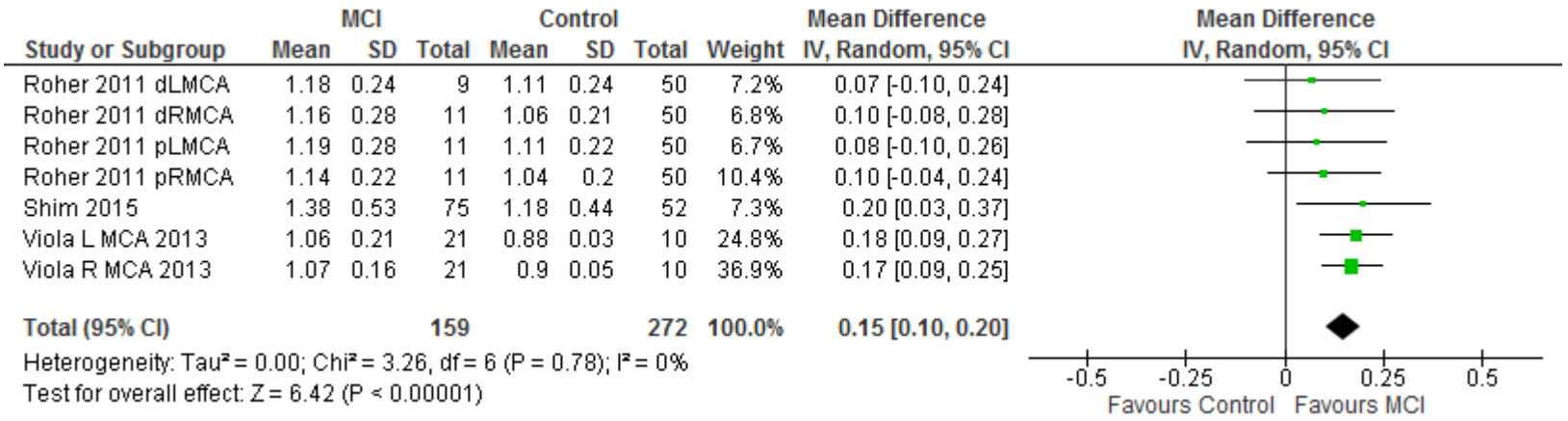

Figure 4. Forest plot for a meta-analysis of PI.

Data is pooled from 3 studies [47, 48, 54]. Roher et al took multiple measurements, all MCA measurements are included [48], and Viola et al measured both the right and left MCA [47], both measures are included. Results are mean difference (95% confidence interval). Statistical significance set at $p<0.05$. Results show significantly higher pulsatility index in MCI compared to controls ($p<0.01$). Heterogeneity was low and non-significant ($I^2=0\%$, $P=0.78$). There were no differences in effect size or heterogeneity between random and fixed effects models.

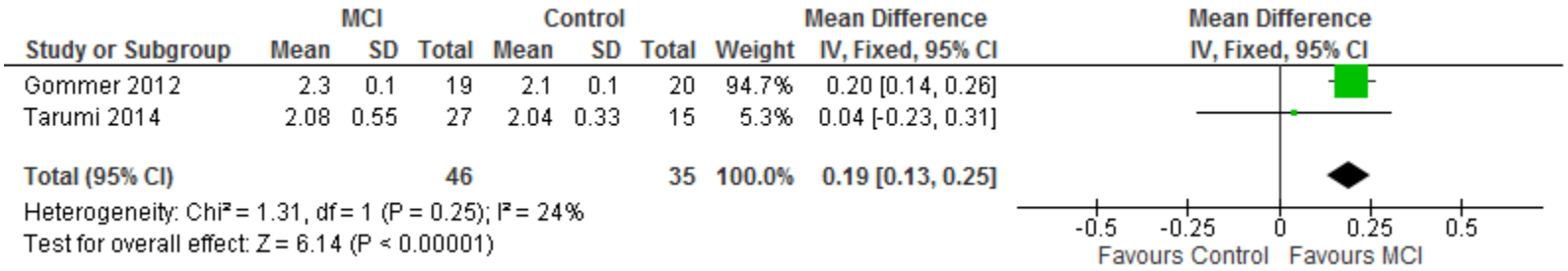

Figure 5. Forest plot for a meta-analysis of CVRi.

Data is pooled from 2 studies [52, 57]. Results are mean difference (95% confidence interval). Statistical significance set at $p<0.05$. Results show CVRi is significantly higher in MCI versus controls ($p=0.003$). Heterogeneity is low, and non-significant ($I^2=24\%$, $p=0.25$). In a fixed effects model, heterogeneity remained the same, effect size: 0.19 (0.13, 0.25), $p<0.001$.

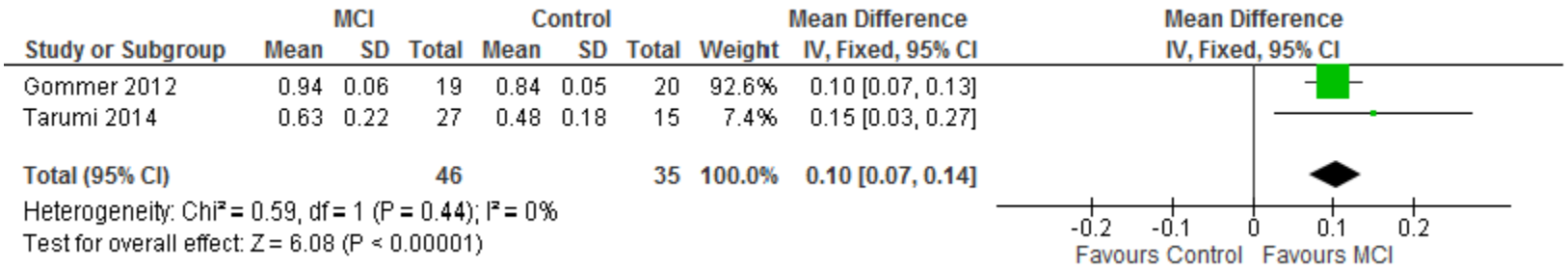

Figure 6. Forest plot for meta-analysis for phase.

Data is pooled from 2 studies [52, 57]. Results are mean difference (95% confidence interval). Statistical significance set at p<0.05. Results show significantly increased phase in MCI compared to controls (p<0.01). Heterogeneity was low (I^2=0%, p=0.44). There were no differences in effect size or heterogeneity between random and fixed effects models.

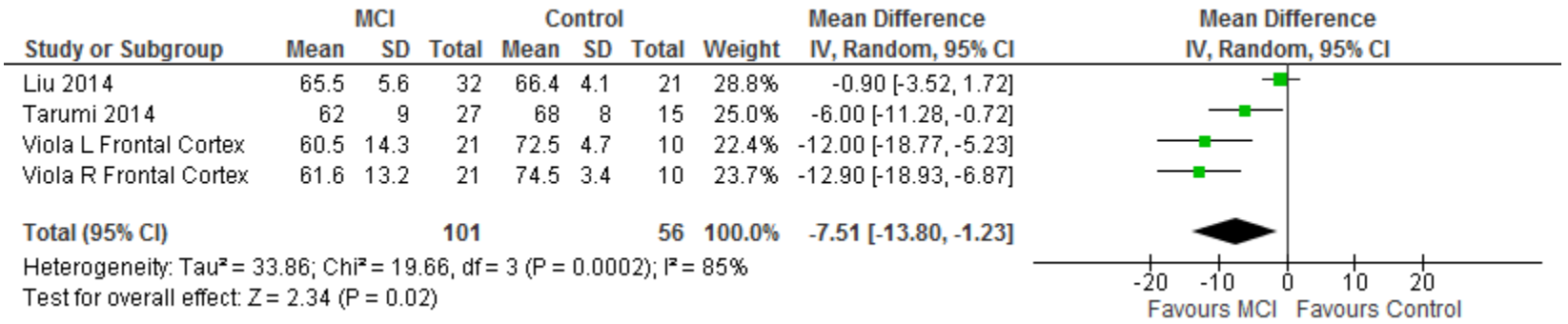

Figure 7. Forest plot for meta-analysis of TOI.

Data is pooled from 3 studies [47, 56, 57]. Viola et al measured both right and left frontal cortex, and both measures were included. Results are mean difference (95% confidence interval). Statistical significance set at p<0.05. Results show a significantly lower TOI in MCI compared to controls (p=0.02). Heterogeneity was high, and statistically significant (I^2=85%, p<0.01). In a fixed effects model, heterogeneity remained the same, and the effect size was smaller: -4.16 (-6.24, -2.08), p<0.001.

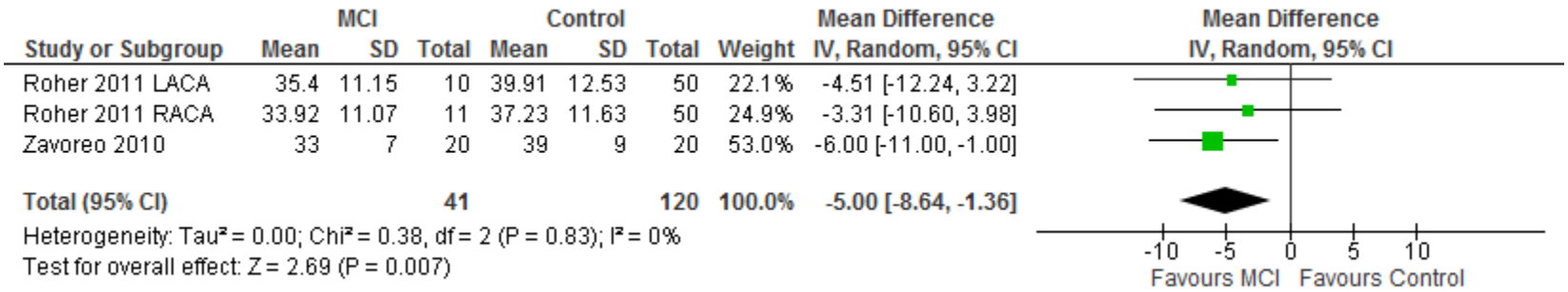

Figure 8. Forest plot for meta-analysis of CBFv (anterior cerebral artery).

Data is pooled from 2 studies [18, 48]. Roher et al [48]measured both right and left ACA CBFv, and both measures were included. Results are mean difference (95% confidence interval). Statistical significance was set at p<0.05. Results show significantly reduced CBFv in MCI compared to controls (p=0.007). Heterogeneity was low and non-significant (p=0.83). The effect size was no different between random or fixed effects models.

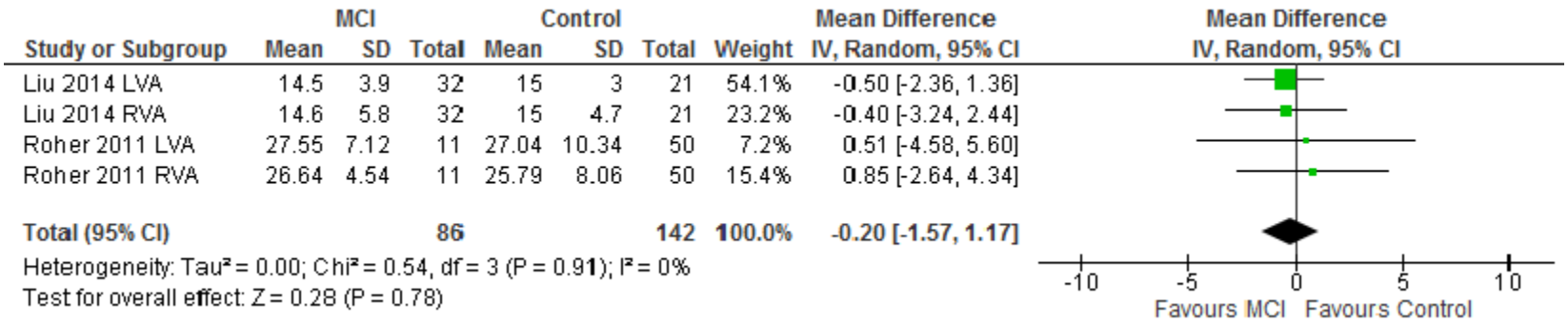

Figure 9. Forest plot for meta-analysis of CBFv (vertebral artery).

Data is pooled from 2 studies [48, 56]. Both studies measured the right and left vertebral arteries, and both measures are included in the analysis. Results are mean difference (95% confidence interval). Statistical significance was set at p<0.05. Results show no significant differences between MCI and controls (p=0.78). Heterogeneity was low and non-significant (p=0.91). The effect size was no different between random or fixed effects models.

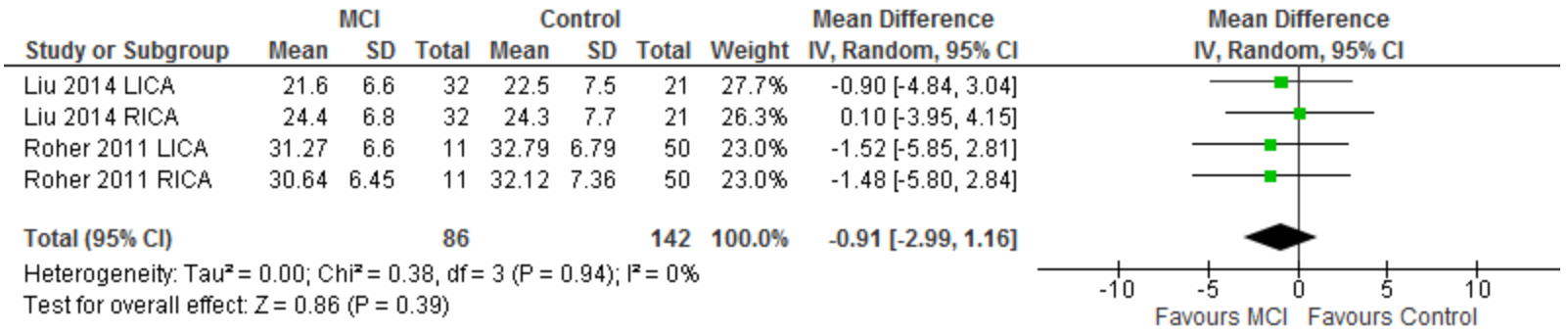

Figure 10. Forest plot for meta-analysis of CBFv (internal carotid artery).

Data is pooled from 2 studies [48, 56]. Both studies measured the right and left internal carotid arteries, and both measures are included in the analysis. Results are mean difference (95% confidence interval). Statistical significance was set at $p<0.05$. Results show no significant differences between MCI and controls ($p=0.39$). Heterogeneity was low and non-significant ($p=0.94$). The effect size was no different between random or fixed effects models.

9. Tables

Author	Quality /15	Study design	MCI criteria	No. MCI	No. Controls	Male: Female		Age (years, SD)		MMSE (SD)		Outcomes Markers
TCD						MCI	Controls	MCI	Controls	MCI	Controls	
Akkawi 2005 [50]	11	Longitudinal (2 yr F/U)	Mayo clinic	37 P: 19, S: 18	0	P: 8:11 S: 6:12	N/A	P: 72.4 (3.2) S: 70.3 (4.3)	N/A	P: 27.8 (3.1) S: 28 (1.4)	N/A	Mean baseline CBF Validity
Viticchi 2012 [51]	13	Longitudinal (1 yr F/U)	Petersen	117 P: 21, S: 96	0	P: 7:14 S: 53:43	N/A	P: 77.2 (4.2) S: 75 (4)	N/A	P: 27 (1.56) S: 27.14 (1.76)	N/A	Carotid PI Carotid IMT BHI (CO_2)
Gommer 2012 [52]	14	Cross sectional and longitudinal	Petersen	19	20	11:8	10:10	70 (2)	70 (1)	27.6 (0.3)	29 (0.3)	CBFv CVRi Gain Coherence Phase ARI
Anzola 2011 [53]	13	Cross sectional	No formal criteria	15	28	7:8	17:11	72 (9)	67 (9.5)	MCI: 27.1 (1.3)	28.6 (1.1	CBFv VMR (CO_2 reactivity)
Roher 2011 [48]	12	Cross sectional	Petersen	11	50	NR	NR	80 (4.7)	79 (6.4)	26 (1.9)	29 (1.1)	CBFv PI Validity
Shim 2015 [54]	13	Cross sectional	Petersen	75	52	21:54	17:35	69.4 (8.2)	66.2 (6.5)	23.7 (3)	28.2 (1.5)	CBFv PI RI VMR (% reactivity)
Sun 2007 [55]	14	Cross sectional	Mayo clinic	30	30	17:13	22:8	69.13 (7.24)	68.77 (7.08)	26.67 (1.24)	28.5 (1.17)	CBFv MSV EDV
Zavoreo	10	Cross sectional	No formal criteria	20	20	10:10	10:10	NR	NR	28 (1)	28 (1)	CBFv BHI

2010 [18]												
TCD + NIRS												
Tarumi 2014 [57]	13	Cross sectional	Petersen	27	15	11:16	9:6	65 (96)	67(8)	29 (1)	29 (1)	CBFv CVRi Gain Coherence Phase Sit-stand manoeuvre TOI %
Liu 2014 [56]	12	Cross sectional	Petersen	32	21	13:19	8:13	67 (7)	67 (7)	28.9 (1.4)	29.1 (0.8)	CBF CBFv CVR TOI % OEF % $CMRO_2$
Viola 2013 [47]	12	Cross sectional	No formal criteria	21	10	10:11	4:6	70.2 (7.3)	69.5 (6.8)	NR	NR	CBFv PI Validity TOI %
NIRS												
Uemura 2015 [58]	12	Cross sectional	Petersen	64	66	34:30	33:33	71.8 (4.3)	71.7 (3.9)	26.7 (2.9)	27.7 (1.6)	Oxy-Hb (F values)
Babiloni 2014 [59]	14	Cross sectional	Petersen	10	10	6:4	5:5	70.7 (2.43)	70.8 (2.5)	25.4 (1.02)	29.1 (0.7)	Oxy-Hb (F values) CO_2 reactivity EEG coherence
Vermeij 2016 [60]	13	Cross sectional and Longitudinal	Petersen	14	21	10:4	13:8	66.1 (3.9)	69.5 (5.4)	27.1 (2.4)	29.2 (1)	Oxy-Hb
Arai 2006 [61]	12	Cross sectional	Petersen	15	32	7:8	16:16	63 (6.4)	57.3 (6.4)	26.3 (1.6)	29.1 (0.8)	A index Validity

Doi 2013 [63]	13	Cross sectional	Petersen	16	0	10:6	N/A	75.4 (7.2)	N/A	26.4 (2)	N/A	Oxy-Hb (F values)
Yeung 2016 [64]	13	Cross sectional	Jak et al	26	26	6:20	7:19	69.07 (6.2)	68.87 (6.08)	NR	NR	T values
Niu 2012 [62]	12	Cross sectional	Petersen	8	16	NR	NR	64.8 (7.2)	63.1 (5.3)	26.3 (2.3)	28.4 (1.1)	T values
Yeung 2016 [69]	14	Cross sectional	Jak et al	26	26	7:19	7:19	69.15	68.87	NR	NR	Oxy-Hb
MRI												
Cantin 2011 [67]	11	Cross sectional	Petersen	7	11	5:2	5:6	64.1 (9)	65.4 (9.3)	27.4 (1.8)	29.5 (0.5)	VMR (reactivity to CO_2) CBF
Nation 2013 [15]	13	Cross sectional	Jak et al	23	46	13:10	16:30	74.3 (8.5)	73.8 (7.7)	NR	NR	CVRi
Richiardi 2015 [65]	13	Cross sectional	Winbald et al	15	28	6:9	10:18	71 (10)	73 (7)	28 (2)	29 (1)	VMR (reactivity to CO_2) VMR velocity (to CO_2)
Glodzik 2011 [66]	14	Cross sectional	Reisberg et al	15	18	6:9	8:10	73.4 (8.2)	69.8 (6.9)	27.5 (2.4)	29.2 (1)	CBF VMR (reactivity to CO_2)
Rivera-Rivera 2016 [68]	14	Cross sectional	No formal criteria	43	59	7:34	43:16	73	74	NR	NR	CBF PI RI
SPECT/ PET												
Ponto 2006 [40]	11	Cross sectional	Petersen	15	0	5:10	N/A	71.8 (6.2)	N/A	MCI: 29.3 (1.0)	N/A	CBF % VMR (reactivity to CO_2)

Knapp 1996 [20]	10	Cross sectional	No formal criteria	50	14	45:55	N/A	65 (10.4)	67.2 (3.4)	27.3 (2.1)	28.6 (1.2)	% activation

Table 1. Demographics of participants and studies included in the systematic review. N/A = not applicable, P = progressive MCI, S= stable MCI, NR = not reported, SD = standard deviation, CBF = cerebral blood flow, CBFv = cerebral blood flow velocity, MSV = mean systolic velocity, EDV = end diastolic velocity, CVR = cerebrovascular resistance, CVRi = cerebrovascular resistance index, VMR = vasomotor reactivity, PI= pulsatility index, BHI = breath holding index, ARI = autoregulatory index, RI = resistance index, TOI = tissue oxygenation index, OEF = oxygen extraction fraction, $CMRO_2$ = cerebral metabolic rate oxygen.