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Global brain hypoperfusion and oxygenation in amnestic mild cognitive impairment

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Abstract

Background: To determine if global brain hypoperfusion and oxygen hypometabolism occur in patients with amnestic mild cognitive impairment (aMCI).

Methods: Thirty-two aMCI and 21 normal subjects participated. Total cerebral blood flow (TCBF), cerebral metabolic rate of oxygen ($CMRO_2$), and brain tissue volume were measured using color-coded duplex ultrasonography (CDUS), near-infrared spectroscopy (NIRS), and MRI. TCBF was normalized by total brain tissue volume (TBV) for group comparisons (nTCBF). Cerebrovascular resistance (CVR) was calculated as mean arterial pressure divided by TCBF.

Results: Reductions in nTCBF by 9%, $CMRO_2$ by 11%, and an increase in CVR by 13% were observed in aMCI relative to normal subjects. No group differences in TBV were observed. nTCBF was correlated with $CMRO_2$ in normal controls, but not in aMCI.

Conclusions: Global brain hypoperfusion, oxygen hypometabolism, and neurovascular decoupling observed in aMCI suggest that changes in cerebral hemodynamics occur early at a prodromal stage of Alzheimer's disease, which can be assessed using low-cost and bedside-available CDUS and NIRS technology.

Keywords: Mild cognitive impairment; Cerebral blood flow; Cerebral metabolic rate of oxygen; Ultrasonography; Near-infrared spectroscopy; MRI

1. Introduction

Alzheimer's disease (AD) may begin years and even decades before its clinical appearance [1]. For early detection or treatment of AD, the term mild cognitive impairment (MCI), or the amnestic type of MCI (aMCI) in particular, has been coined to describe a prodromal stage of AD [2]. The etiology of sporadic AD is not clear and is likely to be multifactorial involving genetic and environmental factors [3].

Brain perfusion is fundamentally important for normal neuronal function. Brain hypoperfusion, even insufficient to produce ischemic cell death, can affect brain protein synthesis and lead to neuronal dysfunction [4]. Accumulating evidence suggests brain hypoperfusion/cerebrovascular dysfunction may play an important role in AD onset and progression [4]. In this regard, regional brain hypoperfusion and hypometabolism have been observed in aMCI patients mainly in the temporal-parietal lobe and posterior cingulate

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cortex [5]. However, an increase rather than a decrease in regional brain perfusion also has been observed in aMCI and has been interpreted to reflect a compensatory effect [6]. These observations reflect the complexity of changes in regional brain perfusion and metabolism at a prodromal stage of AD.

So far, few studies have measured global brain perfusion in patients with aMCI and AD [7–9]. To our knowledge, only one study reported that a reduction in global brain perfusion in aMCI patients was related to the risk of AD conversion [9]. Large population-based studies have demonstrated that global brain hypoperfusion as indicated by a low cerebral blood flow (CBF) velocity in the middle cerebral artery (MCA) was related to the high risks for developing AD in older adults [10]. The color-coded duplex ultrasonography (CDUS) and spatially resolved near-infrared spectroscopy (NIRS) are well established methods for measurement of CBF and brain tissue oxygenation in human subjects [11,12]. These methods are noninvasive, inexpensive, and available at bedside; therefore, they have a great potential to be used in large population studies. Using these methods, this study tested the hypothesis that reductions in global brain perfusion and cerebral metabolic rate for oxygen utilization ($CMRO_2$) occur in aMCI patients relative to normal control subjects. Obtaining this information may help us to better understand the role of cerebrovascular dysfunction in AD onset and progression [4].

2. Methods

2.1. Participants

Thirty-two aMCI subjects and 21 normal cognitive controls were recruited from local newspaper advertisements, senior centers, and the University of Texas Southwestern Medical Center Alzheimer's Disease Center. The diagnosis of aMCI was based on Petersen criteria [1] as modified by the Alzheimer's Disease Neuroimaging Initiative (ADNI) project (http://adni-info.org). Further clinical evaluation was performed according to the Alzheimer's Disease Cooperative Study (ADCS) recommendations (http://www.adcs.org) using standard diagnostic criteria. The results of cognitive assessment using the Mini-Mental State Examination (MMSE) [13], Clinical Dementia Rating (CDR) scale [14], and Wechsler Memory Scale Logical Memory (LM) for immediate and delayed recalls are shown in Table 1. Inclusion criteria for normal subjects and patients with aMCI were both sexes and age 55∼80 years. Exclusion criteria were major psychiatric disorders, major or unstable medical conditions, uncontrolled hypertension, diabetes mellitus, or chronic inflammatory diseases. Subjects with a heart pacemaker or any metal plates or pins in their body that prevented them from MRI were also excluded. Group demographics and clinical features are presented in Table 1. All subjects and/or their study partners signed the informed consent approved by the institutional review boards of the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital of Dallas.

Table 1
Demographics and clinical characteristics of study participants

Variables	NC (n = 21)	aMCI (n = 32)	P
Age, years	67 (7)	67 (7)	.802
Education, years	16 (3)	16 (3)	.874
Female sex, n (%)	13 (62%)	19 (59%)	>.999
Race, n (%)			
Caucasian	19 (90%)	29 (91%)	>.999
African American	2 (10%)	3 (9%)	>.999
Height, cm	169 (7)	167 (10)	.432
Weight, kg	75 (16)	79 (17)	.461
Body mass index, kg/m^2	26.1 (4.2)	28.0 (4.3)	.122
Hematocrit, %	41.7 (3.8)	41.4 (3.3)	.767
$ETCO_2$, mmHg	40.1 (2.9)	40.0 (3.9)	.953
Blood pressure, mmHg			
Systolic blood pressure	120 (12)	123 (11)	.220
Diastolic blood pressure	72 (9)	74 (7)	.250
MAP	88 (9)	91 (8)	.194
Pulse pressure	48 (7)	49 (10)	.591
HR, bpm	64 (8)	61 (9)	.192
Cardiac output (echo), L/min	3.62 (0.88)	3.39 (1.00)	.388
Medical history			
Treated hypertension	9 (43%)	14 (44%)	>.999
Hypercholesterolemia	7 (33%)	11 (34%)	>.999
Hypothyroidism	3 (14%)	4 (13%)	>.999
Medication use			
Calcium-channel blocker	3 (14%)	5 (16%)	>.999
β-blocker	3 (14%)	4 (13%)	>.999
ARBs	2 (10%)	3 (9%)	>.999
ACE inhibitors	4 (19%)	6 (19%)	>.999
Diuretics	3 (14%)	4 (13%)	>.999
Statin	4 (19%)	6 (19%)	>.999
Psychometric test scores			
MMSE	29.1 (0.8)	28.9 (1.4)	.669
CDR	0	0.5	–
LM immediate recall	14.9 (1.8)	10.8 (2.3)	<.001
LM delayed recall	14.5 (2.6)	8.2 (2.2)	<.001

Abbreviations: NC, cognitively normal controls; aMCI, amnestic mild cognitive impairment; $ETCO_2$, end-tidal CO_2; MAP, mean arterial pressure; HR, heart rate; bpm, beats per minute; ARBs, angiotensin receptor blockers; ACE, angiotensin converting enzyme; MMSE, Mini-Mental State Examination score; CDR, clinical dementia rating; LM, Wechsler Memory Scale Logical Memory subtest.

NOTE. Values are the mean (standard deviation) or number (percentage).

2.2. MRI measurement of brain tissue volume

Magnetization-prepared rapid acquisition gradient echo (MPRAGE) images were acquired on a 3T system (Philips Achieva MR system) to measure cortical and subcortical brain tissue volumes. Sagittal images were obtained with a field of view (FOV) of 256 × 256 mm, a matrix size of 256 × 256, and a slice thickness of 1 mm without gap. Image sequence parameters were repetition time (TR) = 8.1 ms, echo time (TE) = 3.7 ms, inversion time (TI) = 1100 ms, shot interval 2100 ms, and flip angle (FA) = 12° with a sensitivity encoding (SENSE) factor of 2. A total of 140 images were collected to cover the whole brain. MPRAGE images were processed using FreeSurfer software (http://nmr.mgh.

harvard.edu/martinos). Details of the procedures for measuring brain tissue volume were published previously [15]. Total brain tissue volume (TBV) was obtained as a sum of measured cortical and subcortical gray matter (GM) and white matter (WM) volumes, including the brainstem and cerebellum. Intracranial volume (ICV) was measured using the atlas-based spatial normalization procedures to delineate cerebral spinal fluid (CSF)/skull borders [15]. Individual TBV, GM, and WM volumes were divided by ICV to obtain the normalized values (nTBV, nGM, and nWM).

2.3. Measurement of brain perfusion, tissue oxygenation, and systemic hemodynamics

A 3- to 12-MHz linear array transducer on the CDUS system (CX-50, Phillips Healthcare) was used for CBF measurements. The CBF measurements for the internal carotid artery (ICA) were performed at least 1 cm above the carotid bulb (Fig. 1A), and for the vertebral artery (VA) they were performed between the C_4 and C_6 intertransverse segments (Fig. 1B). A straight vessel segment with a parallel wall view was identified where the luminal diameter (D) remained the same for a length of at least 0.5 cm to enhance the uniformity of Doppler sample volume. The sample volume was positioned at this site to cover the entire vessel lumen (Fig. 1, C and D) to measure the angle-corrected mean velocity (i.e., spatially averaged blood flow velocity across the whole vessel lumen assuming a laminar flow) [16]. For calculation of volumetric blood flow, at least five complete cardiac cycles of consecutive blood flow velocity waveforms were recorded to obtain the time-averaged mean velocity (TAMV) (Fig. 1, C and D). For vessel diameter measurement, the distance between the parallel internal layers at the sample volume site was measured (Fig. 1, A and B). Specifically, pulsatile changes of the vessel diameter were recorded continuously for approximately 5 seconds on high-resolution B-mode video with a 21-Hz frame rate in a longitudinal view for ICA and VA. Changes of vessel diameter at the sampling segment (with a length of $\sim$0.5 cm) were measured using an edge-detection and wall-tracking technology to obtain the time-averaged vessel diameter from three consecutive cardiac cycles (Brachial and Carotid Analyzer, Medical Imaging Applications). The velocity and diameter measurements were repeated 3 times for each vessel with their mean values used for CBF calculation. This procedure was taken to reduce the intrinsic CBF variability associated with respiratory and other low-frequency oscillations [17]. Blood flow of each vessel was calculated as the product of the TAMV and the cross-sectional area (A) of the vessels as $CBF = TAMV \times A \times 60 = TAMV \times [(D/2)^2 \times \Pi] \times 60$. Total CBF (TCBF) was obtained as a sum of CBFs of bilateral ICAs and VAs and was normalized by TBV (nTCBF) for group comparisons.

Spatially resolved NIRS (NIRO-200NX, Hamamatsu Photonics) was used to measure brain tissue oxygenation (i.e., the ratio of intravascular oxygenated to total hemoglobin concentration) expressed as a tissue oxygenation index (TOI) [12]. This technology is based on the photon diffusion theory to assess the slope of light attenuation versus the distances traveled by the light to calculate absolute brain tissue oxygen saturation and has been validated and used extensively to assess brain tissue oxygenation under various clinical conditions [18]. It has been shown that TOI can provide a quantitative estimation of cerebral venous oxygenation under certain model assumptions [19]. Thus, cerebral oxygen extraction fraction (OEF) can be estimated as $OEF = (SaO_2 - TOI)/SaO_2$, in which SaO_2 is the arterial blood oxygen saturation; and $CMRO_2$ can be calculated as $CMRO_2 = nTCBF \times (SaO_2 - TOI) \times (Ca/\rho)$ on the basis of Fick's law [20], in which Ca is the maximal amount of oxygen that a unit volume of blood can carry (8.337 μmol/mL) [21] and ρ is a constant of brain tissue density 1.06 g/mL [22]. Six aMCI subjects (three females) and three controls (two females) had no TOI measurements for technical problems.

Brachial arterial pressure was measured using a sphygmomanometer (Tango+, Suntech), and SaO_2 was measured at finger using a pulse oximeter (Biox 3700, Ohmeda). Cerebrovascular resistance (CVR) was calculated as mean arterial pressure (MAP) divided by TCBF ($CVR = MAP/TCBF$). Electrocardiograph (Hewlett-Packard) was measured to determine heart rate (HR). End-tidal CO_2 ($ETCO_2$) was monitored with a capnograph (Capnogard, Novamatrix). Cardiac output was measured with echocardiography from the apical four-chamber view using a modified Simpson's rule method [23].

All data collections were performed in the supine position after at least 20 minutes of rest in an environmentally controlled laboratory with an ambient temperature of 23°C to allow stabilization of systemic and cerebral hemodynamics. Subjects were asked to refrain from high-intensity exercise, alcohol, or caffeinated beverage at least 24 hours before the test. The time used for vascular imaging and blood flow measurement using CDUS was approximately 20 minutes for each individual subject. HR, TOI, and $ETCO_2$ were recorded continuously using data acquisition software (Acknowledge, BIOPAC Systems) and averaged for data analysis. Thus, the total time used for the test including supine rest was approximately 40 minutes. During data collection, subjects were instructed not to speak and were not cognitively engaged (e.g., reading, watching TV etc.). The experimental protocol was the same for aMCI and normal subjects to minimize potential influences of differences in cognitive activity on the CBF and TOI measurements [24].

Clinical cognitive assessments, measurements of cerebral hemodynamics, and MRI were performed during three visits. The time intervals among these visits were more than 1 week but less than 3 months.

2.4. Measurement reproducibility

Fifteen individuals were randomly selected from the 21 normal subjects to assess the CBF and TOI measurement reproducibility. Two measurements were obtained within

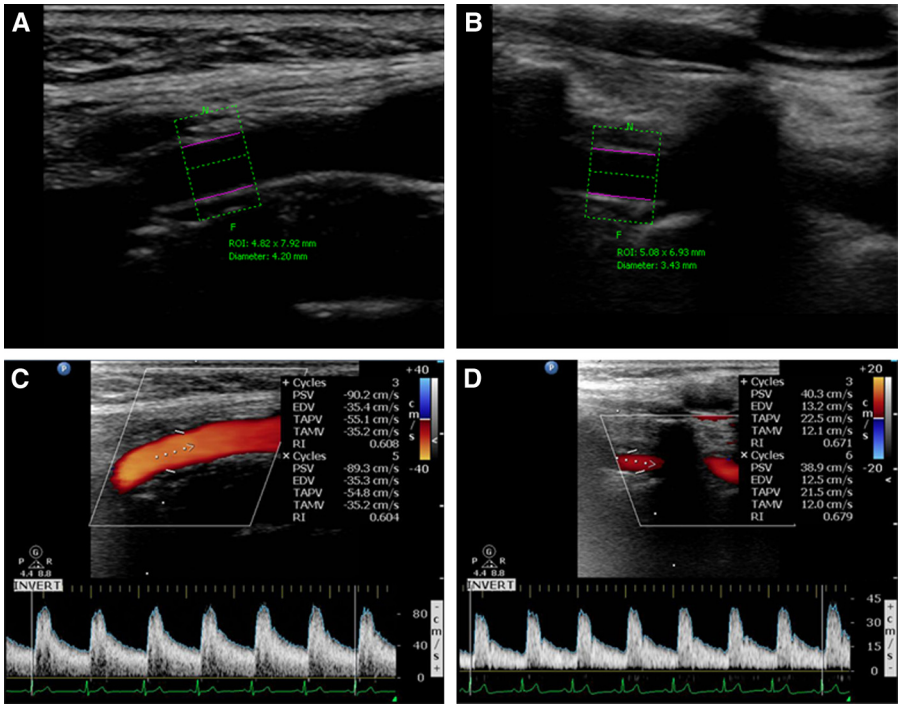

Fig. 1. Measurements of cerebral blood flow in internal carotid artery (ICA) and vertebral artery (VA). (A) Diameter of ICA on high-resolution B-mode video was measured using an automated wall-tacking and edge-detection software (see text). (B) Diameter of VA was measured in the same way. (C) Measurement of time-averaged mean velocity (TAMV) at ICA. (D) Measurement of TAMV at VA.

a time period of 3 months. The coefficients of variation between the measurements for TCBF and TOI were 4.7% and 5.5%, respectively. Bland-Altman plots confirmed that test-retest differences were distributed within a mean difference ± 2 standard deviations (SD) without systemic bias for TCBF (–3 ± 48 mL/min) and TOI (0.2 ± 7.2%).

2.5. Statistical analysis

Data were presented as mean ± SD. Group comparisons were performed using independent sample *t* tests for continuous variables or χ^2 tests for categorical variables. The relationship between brain perfusion and $CMRO_2$ was examined using Pearson product-moment correlation analysis to assess neurovascular coupling. $P < .05$ was considered statistically significant.

3. Results

The aMCI and normal subjects were similar with respect to age, sex, education, body size, hematocrit, $ETCO_2$, blood pressure, and cardiac output (Table 1). No differences in either absolute (TBV, GM, and WM) or normalized brain volumes (nTBV, nGM, and nWM) were observed between the two groups (Table 2).

No group difference in diameter, blood flow velocity, or CBF was found in bilateral ICAs and VAs, although a trend of lower TCBF (~7%) was observed in aMCI subjects relative to normal controls (547 ± 97 vs. 588 ± 101 mL/min, $P = .142$) (Table 2). Notably, nTCBF was reduced significantly by 9% (48.1 ± 8.3 vs. 53.1 ± 8.7 mL/min/100 mL, $P < .05$, Fig. 2A) in aMCI relative to the normal controls associated with an significant increase in CVR by 13% (0.171 ± 0.033 vs. 0.152 ± 0.025 mmHg·min/mL, $P < .05$, Fig. 2B).

TOI and OEF also showed no group differences. However, $CMRO_2$ was reduced significantly by 11% in aMCI relative to normal controls (113.6 ± 15.7 vs. 127.1 ± 17.1 μmol/100 g/min, $P < .05$, Fig. 2C).

Finally, a significant correlation between nTCBF and $CMRO_2$ ($r = 0.556$, $P < .05$, Fig. 3A) was observed in normal controls but not in aMCI (Fig. 3B).

4. Discussion

In this study, we found that global brain perfusion and $CMRO_2$ were reduced and CVR was increased significantly in aMCI patients as compared with normal controls. Furthermore, a linear correlation between nTCBF and $CMRO_2$ was found in normal subjects but not in aMCI, suggesting the presence of neurovascular decoupling in these patients. Taken together, these findings suggest that cerebral hemodynamics or CBF regulation is compromised at a prodromal stage of AD, which can be assessed using low-cost and bedside-available CDUS and NIRS technology.

4.1. Methodological considerations

Numerous imaging modalities have been used to measure brain perfusion and the metabolic rate of oxygen or

Table 2
Measurements of brain volume, perfusion, and tissue oxygenation

Variables	NC (n = 21)	aMCI (n = 32)	P
Brain volume			
ICV, mL	1516 (212)	1550 (212)	.561
TBV, mL	1110 (98)	1140(107)	.299
GM, mL	608 (47)	611 (56)	.852
WM, mL	502 (56)	529 (57)	.088
nTBV, %ICV	73.9 (6.9)	74.1 (5.3)	.938
nGM, %ICV	40.6 (4.6)	39.7 (3.1)	.393
nWM, %ICV	33.3 (2.7)	34.3 (2.7)	.177
Regional brain perfusion			
Diameter, mm			
RICA	4.55 (0.74)	4.35 (0.61)	.290
LICA	4.49 (0.52)	4.48 (0.66)	.950
RVA	3.12 (0.62)	3.04 (0.45)	.581
LVA	3.21 (0.47)	3.20 (0.48)	.925
TAMV, cm/s			
RICA	24.3 (7.7)	24.4 (6.8)	.938
LICA	22.5 (7.5)	21.6 (6.6)	.663
RVA	15.0 (4.7)	14.6 (5.8)	.773
LVA	15.0 (3.0)	14.5 (3.9)	.600
CBF, mL/min			
RICA	233 (80)	211 (46)	.211
LICA	207 (58)	201 (64)	.756
RVA	73 (36)	64 (30)	.349
LVA	76 (31)	70 (27)	.492
Global brain perfusion			
TCBF, mL/min	588 (101)	547 (97)	.142
nTCBF, mL/min/100 mL	53.1 (8.7)	48.1 (8.3)	.038
CVR, mmHg·min/mL	0.152 (0.025)	0.171 (0.033)	.029
Brain tissue oxygenation indices			
SaO_2, %	97.0 (1.6)	97.2 (1.3)	.570
TOI, %	66.4 (4.1)	65.5 (5.6)	.562
OEF, %	31.4 (4.3)	32.5 (5.9)	.524
$CMRO_2$, μmol/100 g/min	127.1 (17.1)	113.6 (15.7)	.010

Abbreviations: NC, cognitively normal controls; aMCI, amnestic mild cognitive impairment; ICV, intracranial volume; TBV, total brain-tissue volume; WM, white matter; GM, gray matter; nTBV, normalized TBV; nWM, normalized WM; nGM, normalized GM; RICA, right internal carotid artery; LICA, left internal carotid artery; RVA, right vertebral artery; LVA, left vertebral artery; TAMV, time-averaged mean velocity; CBF, cerebral blood flow; TCBF, total CBF; nTCBF, normalized TCBF; CVR, cerebrovascular resistance; SaO_2, arterial blood oxygen saturation; TOI, tissue oxygenation index; OEF, oxygen extraction fraction = $(SaO_2 - TOI)/SaO_2$; $CMRO_2$, cerebral metabolic rate of oxygen = $nTCBF \times (SaO_2 - TOI) \times (8.337/1.06)$.

NOTE. Values are the mean (standard deviation).

glucose, including positron emission tomography (PET), single-photon emission computed tomography (SPECT), and perfusion MRI [25]. These methods in general are expensive, are not available at the bedside, and are used mainly at academic research centers. In addition, these modalities either require injection of radioactive tracers (PET and SPECT) or are not feasible in patients who may have claustrophobia or metal implants in their body (MRI). This study demonstrated the feasibility of using noninvasive, low-cost, bedside-available CDUS and NIRS methods to measure brain perfusion and $CMRO_2$ in aMCI patients. Further studies using these technologies to assess changes in cerebral hemodynamics in aMCI or AD in longitudinal or interventional studies are likely to establish its value in the clinical study of AD.

Two technical issues related to the use of CDUS for measuring CBF deserve attention. First, in this study, blood velocity in a given vessel was measured using the TAMV across the whole vessel lumen over at least five complete cardiac cycles. Thus, the obtained TAMV represents the spatial (across the whole vessel lumen) and temporal (five or more cardiac cycles) averaged blood velocity [16]. Under steady-state conditions, TAMV is the most accurate index used for CBF calculation when compared with other methods [26]. Second, for CBF calculation that is based on the product of TAMV and the vessel luminal area, the importance of vessel diameter measurement cannot be overemphasized. In the study presented here, high-resolution ($\approx$0.01 mm) longitudinal views of the ICA and VA were acquired and the vessel diameter was measured using an automated edge-detection and wall-tracking software (Fig. 1, A and B) [27]. These procedures enhanced the accuracy and reliability of vessel diameter measurements by avoiding the potential manual measurement errors and/or the rater's subjective bias. Furthermore, the vessel diameter waveforms over the consecutive cardiac cycles were averaged to minimize the influences of diameter pulsatility on the blood flow calculation. With these improvements in the methodology, TCBF measured using CDUS was remarkably consistent with the reported values using the standard Kety-Schmidt method [28].

Spatially resolved NIRS was used to measure brain tissue oxygenation expressed as TOI [12]. It should be realized that TOI reflects a mixture of intravascular oxygenation status from the veins, arteries, and capillaries with a proportion of approximately 75:20:5 in adults [29]. Under steady-state conditions, changes in TOI reflect primarily changes in cerebral venous oxygen saturation [30,31]. In the study presented here, no group differences in arterial oxygen saturation were observed. Thus, $CMRO_2$ can be estimated based on Fick's law [20] by using TOI as a surrogate for cerebral venous oxygen saturation.

It is likely that $CMRO_2$ assessed in this study reflects primarily cortex oxygen utilization because TOI measured from the forehead is likely to be lower than the internal jugular vein oxygen saturation, which also incorporates blood from the deep brain structures that generally extract less oxygen [32]. In addition, assessment of $CMRO_2$ assumed that the proportional contributions of blood oxygenation from the veins, arteries, and capillaries to the TOI did not differ between patients with aMCI and the normal controls. Verification of this assumption needs to be determined in future studies.

4.2. *Brain hypoperfusion, increases in CVR, and reduction of $CMRO_2$ in aMCI*

Regional brain hypoperfusion and a reduction in the metabolic rate of glucose have been observed in aMCI patients in the temporal-parietal lobe and posterior cingulate cortex similar to that observed in patients with AD [33,34]. These

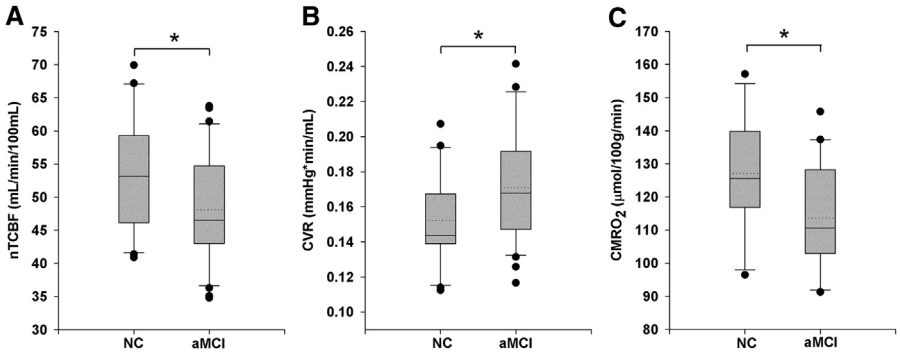

Fig. 2. Box plots of (A) normalized total cerebral blood flow (nTCBF), (B) cerebrovascular resistance (CVR), and (C) cerebral metabolic rate of oxygen ($CMRO_2$) in cognitively normal controls (NC) and amnestic mild cognitive impairment (aMCI) group. The horizontal dotted and solid lines within the box represent the mean and median, respectively. $*P < .05$.

observations have been interpreted to reflect a reduced neuronal activity in these regions at a prodromal stage of AD [35]. However, changes in regional brain perfusion or metabolism in aMCI patients are inconsistent and likely to be a dynamic process associated with AD progression [6]. In addition, changes in brain perfusion or metabolism could be complicated by the presence of heterogeneous regional neural and/or vascular compensatory mechanisms [36]. For example, increases rather than decreases in brain perfusion [37] or neuronal activity [38] have been observed in the prefrontal lobe or hippocampus in aMCI patients despite the presence of regional brain atrophy [39]. Thus, spatially heterogeneous changes in regional brain perfusion or metabolism in aMCI may lead to non-net changes in total brain perfusion.

Using the CDUS method, a few studies have documented global brain hypoperfusion in AD patients [7,8]; and only one study of aMCI has reported a reduced TCBF in those patients who converted to AD after 2 years of follow-up when compared with nonconverters [9]. These findings are consistent with the large population-based studies that showed that low CBF velocity measured using transcranial Doppler (TCD) was related to a high risk of developing AD in older adults [10]. The study presented here demonstrated for the first time that global volumetric CBF measured using CDUS was reduced in aMCI patients when compared with normal controls with similar demographic characteristics and cardiovascular risk factors and that reduction in CBF in aMCI was associated with a significant increase in CVR.

It is interesting to note that increases in CVR also have been observed in aMCI patients in a recent study based on TCD measurement of CBF velocity in the MCA. In addition, the obtained CVR index for aMCI was between those of the normal controls and patients with AD [40]. The study presented here extends these findings by having a larger sample size and used global measurement of volumetric CBF. Of note, because blood pressure was similar between the groups, increases in CVR suggest the presence of cerebral vasoconstriction in aMCI. It is possible that impairment of cerebral endothelial function and/or brain amyloid-β deposition on the vessel wall may lead to cerebral vasoconstriction in aMCI [41–43].

Furthermore, associated with changes in cerebral hemodynamics, a recent study found that cardiac baroreflex gain

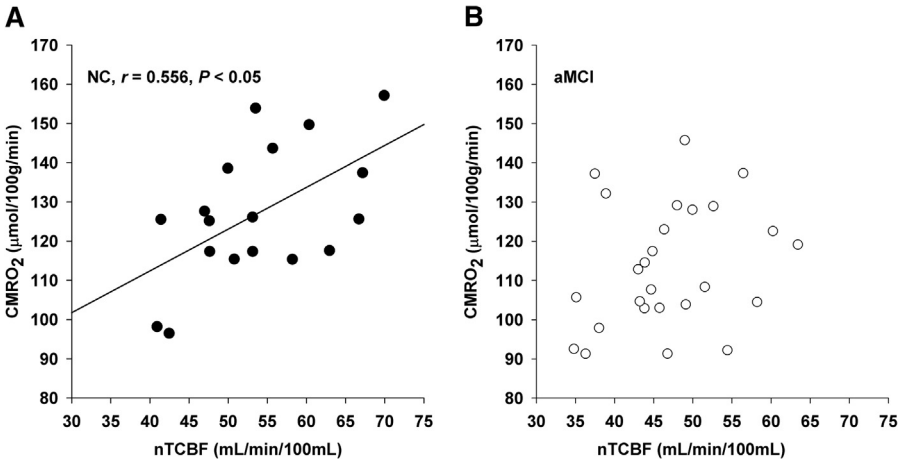

Fig. 3. Linear correlation analyses between cerebral metabolic rate of oxygen ($CMRO_2$) and normalized TCBF (nTCBF) in cognitively normal controls (NC) (A, solid dots) and amnestic mild cognitive impairment (aMCI) group (B, open circles). $CMRO_2$ showed a significant correlation to TCBF in NC but not the aMCI group. r = Pearson's correlation coefficient.

was also reduced in aMCI patients who had values between those of the normal controls and AD patients [44]. The underlying mechanism(s) between changes in cerebral hemodynamics and baroreflex function in aMCI are not clear. However, these findings do suggest that progressive changes in peripheral and central hemodynamics are associated with AD progression [44].

Finally, in this study, we found that $CMRO_2$ was reduced in aMCI patients. Because SaO_2 and TOI did not differ between the groups, reduction in $CMRO_2$ in aMCI could be simply due to a reduction in CBF, reflecting decreases in brain neuronal activity. On the other hand, a primary reduction in CBF due to vascular dysfunction can lead to a reduction in $CMRO_2$ [4]. The cause-effect relationship cannot be determined in this study.

4.3. Neurovascular decoupling in aMCI

Neurovascular coupling generally refers to increases in regional brain blood flow in response to brain activation [4]. Under resting conditions, global brain perfusion is also related to the brain volume and/or brain oxidative metabolic rate [45]. This view of neurovascular coupling is consistent with the findings that in the normal subjects, brain perfusion (nTCBF) was correlated with $CMRO_2$ (Fig. 3A). The new findings of the study presented here are that the neurovascular coupling relationship observed in normal subjects appears to be diminished in patients with aMCI (Fig. 3B). The underlying mechanisms for these observations cannot be determined in this study. It is possible that the presence of compensatory mechanisms or dysregulation of brain perfusion or metabolism may have led to the observed neurovascular decoupling in aMCI.

4.4. Strengths and limitations

Strengths of this study include that all normal subjects were strictly screened and matched to aMCI patients, which allowed us to study the main influence of aMCI by balancing other confounding factors that may affect brain perfusion and metabolism (Table 1). Another strength of this study is the use of low-cost and bedside-available CDUS and NIRS methods to measure brain perfusion and $CMRO_2$. Both of these methods are readily available in clinical settings and can be applied in large population studies. In addition, the automated method used for vessel diameter measurement is likely to enhance the accuracy and reliability of CBF measurements. However, it should be noted that brain perfusion and $CMRO_2$ values overlapped considerably among individuals with and without aMCI, although statistically significant differences between group-averaged mean values were observed (Figs. 2 and 3). Thus, further studies are needed to establish the sensitivity and specificity of using these measurements for the clinical screening of individuals with aMCI or early AD. In addition, a major limitation of these methods is their low spatial resolution for CBF and brain tissue oxygenation measurement. Using these methods, this study was only able to differentiate CBF between the ICAs and VAs (Table 2). Potential changes in more specific regional brain perfusion and metabolism may not be detectable either because of the presence of collateral blood flow and/or neuronal/vascular compensatory mechanisms [5,6]. Another limitation is the use of TOI as a surrogate of cerebral venous oxygenation for $CMRO_2$ calculation, which may lead to an underestimated or overestimated absolute $CMRO_2$. However, measurement of TOI was performed in the same way in aMCI patients as in the normal controls. Thus, a systematic bias, if it indeed existed, should have had less influence on the group differences observed in the study presented here. Of note, we also did not find any correlations between the measured LM scores (immediate and delayed recalls) and cerebral hemodynamics in this study (data not shown). Whether changes in cerebral hemodynamics in aMCI indeed are correlated with changes in cognitive function needs to be determined in longitudinal studies. In this regard, the cross-sectional nature of this study also limits its ability to draw conclusions regarding the cause-effect relationship between changes in cerebral hemodynamics and aMCI.

4.5. Summary of main findings

This study demonstrated for the first time that global brain perfusion and $CMRO_2$ were reduced and CVR was increased significantly in aMCI patients when compared with normal controls with similar age, sex, and education. Furthermore, we observed that global brain perfusion was correlated with $CMRO_2$ in the normal controls but not in aMCI, suggesting the presence of neurovascular decoupling in these patients. These findings collectively suggest that compromised cerebral hemodynamics and/or CBF dysregulation occur early at a prodromal stage of AD, which may contribute to AD onset or progression.

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RESEARCH IN CONTEXT

1. Systematic review: Previous studies showed that regional brain perfusion either was reduced or increased in patients with aMCI. Whether or not global brain perfusion and $CMRO_2$ are altered in aMCI is not clear. This study addressed this question by measuring global brain perfusion and $CMRO_2$ in patients with aMCI using advanced ultrasonography and NIR.
2. Interpretation: Global brain perfusion and $CMRO_2$ were reduced and CVR was increased in aMCI patients relative to the normal controls. In addition, brain perfusion was correlated with $CMRO_2$ in the normal controls but not in aMCI. These findings collectively suggest that cerebrovascular dysfunction occurs at a prodromal stage of AD.
3. Future directions: Future applications of these bedside-available methods into large population studies will determine the clinical significance of the findings presented here and unravel the role of cerebrovascular dysfunction in AD onset and progression.

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