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Featured Article

Poor cerebrovascular function is an early marker of cognitive decline in healthy postmenopausal women

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Abstract

Introduction: Impairment of cerebrovascular function becomes evident after menopause. No study has yet explored relationships between deficits in cerebrovascular function, cognitive performance, and mood in postmenopausal women.

Method: Cerebrovascular function was assessed in 80 healthy postmenopausal women by monitoring blood flow velocity (BFV) in the middle and posterior cerebral arteries using transcranial Doppler ultrasound at rest, following a hypercapnic challenge, and during performance of a cognitive test battery; the latter assessed domains of memory and executive functions. Various measures of mood (i.e., Profile of Mood States and Center for Epidemiological Studies Depression Scale) were also assessed.

Results: Cerebral artery elasticity and BFV responsiveness to cognitive tests (neurovascular coupling) correlated with cognitive performance but not with depressive symptoms or mood states. Mood deficits were related to poor cognitive performance.

Conclusion: These results highlight the importance of adequate cerebral perfusion for optimized cognitive function in healthy postmenopausal women. Preventative strategies to attenuate accelerated cognitive decline should also consider restoring cerebrovascular function.

Keywords: Menopause; Cerebrovascular function; Pulsatility index; Depression; Mood; Cognition

1. Introduction

Complaints of decreased mental clarity and mood swings are common during the menopausal transition [1]. Although these symptoms may be situational at this time of life, for example, health issues, stress of caring for aging parents, or "empty nest syndrome", we cannot ignore that the prevalence of Alzheimer's disease, most common form of dementia, is higher in elderly women than men [2]. Although the biological basis for this heightened risk in women remains to be established, basic and clinical evidence indicate that the rapid decline in estrogen at onset of menopause has adverse consequences, particularly for the brain [3,4]. Higher endogenous estrogen has been shown to be associated with better cognitive function in postmenopausal midlife women (~60 years old), particularly for semantic and verbal memory [5].

From a vascular perspective, estrogen can also bind to estrogen receptors on the endothelium of cerebral arteries, causing vasodilatation and thereby increasing perfusion of brain regions in response to need [6]. Hence, estrogen deficiency after menopause rather than aging *per se* is thought to contribute to the large reduction in cerebral vasodilator responsiveness (CVR) in postmenopausal women compared with premenopausal women and elderly men [7]. Evidence of associations between impaired CVR and cerebral arterial stiffness and severity of dementia is well established [8,9]. Impaired CVR is evident in those with major depression, suggesting that optimal cerebrovascular function may be critical for optimal brain function independent of sex

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hormones [10]. With the increased life expectancy in the aging population, extension of the postmenopausal period may result in reduced quality of life in latter years, due to prolonged cerebral hypoperfusion, thereby adversely affecting cognitive abilities and mood [11].

Recovery from depression is possible by improving cerebral perfusion [12]. However, no studies have yet explored relationships between CVR to physiological or cognitive demands and either mood states or cognitive performance in postmenopausal women. Understanding if such relationships exist can help tailor early interventions to attenuate these deficiencies so as to assist older women achieve quality of life.

We are currently investigating whether a 14-week dietary supplementation with a phytoestrogen, viz., resveratrol, can improve cerebral perfusion and thereby enhance cognitive performance and mood in postmenopausal women who are not taking HRT (Clinical Trial Registration no: ANZCTR12615000291583). Assessments of cerebrovascular function, cognitive performance in specific cognitive domains implicated in mood states, and depressive symptoms in postmenopausal women were obtained at baseline to examine the relationships between cerebrovascular function, cognitive function, and mood in this cohort.

2. Method

All potential volunteers gave written informed consent before attending the Clinical Nutrition Research Centre, University of Newcastle, for the assessments of outcomes at baseline (see [13] for details of study protocol and description of the assessments). Arriving at the center after a 1-hour fast, they undertook the Australian version of the modified Mini-Mental State Examination (3MS) to exclude those with suspected dementia (score of <78/100). Their 3MS scores were also used as a measure of global cognition as administration of this assessment does not require high level of training and frequently used in clinical settings [14]. Menopausal symptoms were quantified using the Menopausal Rating Scale [15] and used as a covariate in this exploratory analysis as they have been shown to affect mood and cognitive function [16]. The order of assessments was conducted as follows with at least a 2-minute interval between each test.

2.1. Basal cerebral hemodynamics

Transcranial Doppler ultrasound (Doppler-Box X, Singen, Germany) is a noninvasive technique to assess blood flow velocity (BFV) in the brain. Using an adjustable headpiece, the middle and posterior cerebral arteries (MCA and PCA, respectively) on both the left and right sides were isolated using the transtemporal window as this provides the least interference during insonation [17]. A 30-s continuous recording of basal BFV (maximum, mean, minimum) in the MCA and the PCA was obtained before hypercapnic provocation and before the start of each cognitive test. The Gosling pulsatility index (PI) and Pourcelot resistive index (RI) reflecting intracranial vessel stiffness and the basal mean BFV were determined by averaging the last 10 s of the 30-s basal recording. PI and RI are calculated as follows: PI = (maximum BFV − minimum BFV)/mean BFV; RI = (maximum BFV − minimum BFV)/maximum BFV. Although PI and RI are linearly correlated and reflect intracranial vascular resistance [18], RI is arguably a better reflection of resistance as it combines vascular compliance in the arterial waveform, which is modifiable by blood pressure (BP), age, and medication use [19]. The PI/mean BFV ratio (multiplied by 100 for ease of reporting) was also determined; it is a recognized index of intracranial vascular disease [20].

2.2. Cerebrovascular responsiveness

Increases in BFV in the cerebral vessels in response to physiological (i.e., hypercapnia) or cognitive stimuli are indirect measures of cerebrovascular responsiveness (CVR); they reflect the extent of vasodilator capacity in downstream vascular beds [21]. To assess CVR to hypercapnia, volunteers inhaled a carbogen gas mixture (5% CO_2, 95% O_2) through a two-way nonrebreathing mouthpiece for 180 seconds, which elicited an acute increase in BFV. The ultrasound probes were kept in position throughout the cognitive assessments to determine CVR to cognitive stimuli in the MCA during each cognitive task. CVR to hypercapnia or cognitive stimuli is calculated as the peak increase in mean BFV, expressed as a percentage of the mean BFV recorded under basal conditions.

2.3. Cognitive performance

In addition to the 3MS, we also used a neuropsychological test battery that is more sensitive to capture deficits in cognitive domains known to be negatively affected in postmenopausal women, namely semantic [22], verbal [1], and visual spatial working memory [23], as well as executive function, shown to decline with age irrespective of gender [24]. The battery consisted of the Rey Auditory Verbal Learning Test [25], the Cambridge Semantic Memory Battery [26], the Double Span [27], and the Trail Making Task [28]. Performances on each test were converted to Z scores and were summated to determine their overall cognitive performance.

2.4. Assessment of mood

Participants' mood states were assessed using two different indices, the Profile of Mood States version 2, and the Center for Epidemiological Studies Depression Scale. The Profile of Mood States questionnaire assessed how the participant was feeling over the last week (including the day of the visit) through 65 adjectives that the participant rated on a 5-point Likert scale (1 being "not at all" and 5

being "extremely"). This has proven to be an excellent measure of mood states and their fluctuations. A calculated score denoting "total mood disturbances" was used to determine overall mood state [29]. The depression scale is a commonly used tool to characterize depressive symptoms in the general population [30]; its sensitivity is ideal for detecting depressive symptoms in postmenopausal women [31].

2.5. Statistical analysis

Statistical analyses were performed using SPSS, version 21.0 (SPSS by IBM Inc., Chicago, IL). Pearson's correlations were used to determine the relationships between basal cerebral hemodynamics, CVR to hypercapnia and cognitive stimuli, global cognition (3MS), overall cognitive performance, depressive symptoms, and total mood disturbances. Age was entered as a covariate in all the analysis. Menopausal symptoms, years of menopause, and years of formal education were considered as covariates if they correlated significantly with the outcome assessments. The level of significance was set at $P = .05$, and no adjustments were made for multiple comparisons in this exploratory analysis.

3. Results

3.1. Participant characteristics

Participant characteristics are detailed in Table 1. The 80 postmenopausal women assessed were normotensive but slightly overweight, and their mean waist circumference of >80 cm is consistent with postmenopausal fat redistribution.

Table 1
Participant characteristics of 80 postmenopausal women obtained at baseline

Characteristics	Mean ± SEM
Age (y)	61.5 ± 0.8
Years since onset of menopause	11.4 ± 0.9
Education years	15.5 ± 0.5
3MS (% accuracy)	96.1 ± 0.4
BMI (kg/m^2)	26.71 ± 0.57
Waist circumference (cm)	87.0 ± 1.4
Systolic BP (mm Hg)	125.3 ± 1.5
Diastolic BP (mm Hg)	70.9 ± 1.0
MCA	
Basal mean BFV (cm/s)	49.36 ± 1.39
Pulsatility index (PI)	0.83 ± 0.02
Resistive index	0.55 ± 0.01
PI/mean BFV	1.76 ± 0.08
CVR to hypercapnia (%)	51.33 ± 1.60
PCA	
Basal mean BFV (cm/s)	41.14 ± 1.52
Pulsatility index (PI)	0.93 ± 0.02
Resistive index	0.59 ± 0.01
PI/mean BFV	2.34 ± 0.11
CVR to hypercapnia (%)	56.32 ± 2.31

Abbreviations: BP, blood pressure; MCA, middle cerebral arteries; BFV, blood flow velocity; CVR, cerebral vasodilator responsiveness; PCA, posterior cerebral arteries.

Their 3MS scores and years of formal education were indicative of a high level of cognitive functioning. One quarter of the cohort (n = 20) had previously taken HRT for an average of 9.8 ± 1.2 years. Eight had been hysterectomized due to prolapse. However, no further data on their surgical history or whether these women had oophorectomy were collected.

In the MCA, their basal PI was 0.83 ± 0.02, which was lower than values of 0.87–0.97 for 60-to-80-year-old healthy women reported in the literature [15]. In the PCA, the PI of 0.93 ± 0.02 was similar to values previously reported [15].

None of the women were clinically diagnosed or medicated for depression, yet 12 women had a depressive symptom score of ≥16, suggestive of depression [32].

3.2. Relationships between assessments of cerebrovascular function in anterior and posterior arteries

There were no bilateral differences for basal MBFV, RI, PI, PI/mean BFV, and CVR to hypercapnia in the MCA and PCA (data not shown); thus, values were averaged from left and right arteries to give a combined value (Table 1).

The vessel stiffness (PI, RI, and PI/mean BFV) and BFV of the MCA correlated positively with those in the PCA (PI: r = 0.574; RI: r = 0.609; PI/mean BFV: r = 0.582; Basal BFV: r = 0.703, $P < .001$; n = 40).

There was a positive correlation between CVR to hypercapnia obtained in the MCA and in the PCA (r = 0.551, $P < .001$, n = 41). CVR to cognitive stimuli correlated positively with CVR to hypercapnia in the PCA (r = 0.446, $P = .003$ n = 41) but not in the MCA (r = 0.109, $P = .401$, n = 62).

3.3. Cognition and mood

Years of education did not correlate with 3MS scores (r = 0.093, $P = .414$) or overall cognitive performance (r = 0.152, $P = .177$) hence was not used as a covariate in this correlational analysis. Menopausal symptoms have an influence on mood (depressive symptoms: r = 0.639, $P < .001$; total mood disturbances: r = 0.618, $P < .001$) but not on 3MS (r = −0.203, $P = .072$) or overall cognitive performance (r = −0.067, $P = .556$). Years since menopause did not correlate with 3MS (r = 0.034, $P = .766$) or overall cognitive performance (r = −0.056, $P = .621$) or with depression scores (r = −0.120, $P = .294$) or total mood disturbances (r = 0.00, $P = .999$). Thus, only menopausal symptoms were controlled for in the correlational analysis relating to mood.

Volunteers' performance on the 3MS (global cognition) correlated with their overall performance on the cognitive test battery (r = 0.589, $P < .001$). Overall cognitive performance but not 3MS scores was related to depression scores (3MS: r = −0.206 $P = .076$; overall cognitive performance: r = −0.275, $P = .016$; n = 74). Similarly, overall performance on the cognitive test battery also correlated with total

mood disturbances (r = −0.330, P = .004, n = 74). Total mood disturbances did not correlate with 3MS (global cognition; r = −0.106, P = .362, n = 74).

3.4. Cerebrovascular function and cognitive function

Table 2 shows the correlations between cerebrovascular function in the MCA and PCA and cognitive function before and after controlling for age and menopausal years. After adjustments, PI/mean BFV in both the MCA and the PCA correlated negatively with 3MS score and overall cognitive performance on the test battery. High PI and RI in the MCA and PCA also negatively correlated with global cognition. Only higher basal mean BFV measured in the PCA predicted better overall performance on the test battery. Overall cognitive performance on the test battery was dependent on CVR in the MCA during task activation. In contrast, CVR to hypercapnia in the MCA correlated negatively with global cognition.

3.5. Cerebrovascular function and mood

Table 3 shows the correlations between cerebrovascular parameters in the MCA and PCA and mood, with and without controlling for age, menopausal years, and symptoms. High PI and RI in the MCA correlated with depression score and total mood disturbances but disappeared after controlling for these covariates.

4. Discussion

Our cross-sectional findings provide evidence of a plausible link between cerebrovascular function and both mood and cognitive performance in postmenopausal women. After controlling for age, menopausal years, and symptoms, it appears that basal cerebral BFV, intracranial artery elasticity, and CVR to a cognitive test battery are associated with cognitive performance but not depressive symptoms or mood states. Cognitive performance was affected by mood deficits.

Performance on the cognitive test battery was dependent on basal BFV and intracranial artery elasticity, whereby lower basal BFV and greater stiffness were associated with poorer cognitive performance. We observed that in both the MCA and PCA, PI/mean BFV was a better predictor of performance on the 3MS, a crude measure of global cognition, and on a comprehensive neuropsychological test battery than PI or RI alone. The combination of low BFV and high PI (represented by PI/mean BFV) has been associated with diffuse stenosis of intracranial arterioles in stroke patients and can lead to chronic hypoperfusion [33]. Over time, the ischemic environment may lead to loss of neuronal function [34], which may explain previous neuroimaging evidence of cerebral hypoperfusion in dementia patients [35]. Our observation that high PI/mean BFV is associated with poor cognition in healthy postmenopausal women independent of age provides evidence linking intracranial vessel stiffness to cognitive impairment. Emerging evidence also indicates that postmenopausal women with poor metabolic profile have significantly lower cognitive function compared with healthy women [36]. Adults with type 2 diabetes have lower BFV in the MCA and elevated PI [37] and have greater risk of accelerated cognitive impairment in later life [38].

CVR to hypercapnia is reflective of the global compensatory dilatory capacity of cerebral vessels to a physiological stimulus. Impairment of CVR to hypercapnia has been implicated in the severity of cognitive impairment in patients

Table 2
Correlations between cerebrovascular parameters collected in the MCA and in the PCA and cognition before and after controlling for age and menopausal years

	Global cognition (3MS scores)		Overall cognitive performance on test battery		Global cognition (3MS scores)		Overall cognitive performance on test battery	
	Unadjusted				Adjusted			
Cerebrovascular parameters	r	P	r	P	r	P	r	P
MCA								
Basal mean BFV	0.233	.058	0.291	.017*	0.137	.310	0.240	.072
Pulsatility index (PI)	−0.212	.085	−0.292	.016*	−0.319	.019*	−0.219	.102
Resistive index	−0.175	.156	−0.244	.046*	−0.264	.047*	−0.142	.291
PI/mean BFV	−0.303	.013*	−0.448	<.001*	−0.273	.040*	−0.393	.003*
CVR to hypercapnia	−0.289	.020*	−0.162	.194	−0.341	.036*	−0.163	.224
CVR to cognitive test battery	0.251	.045*	0.301	.016*	0.194	.148	0.316	.017*
PCA								
Basal mean BFV	0.106	.516	0.218	.177	0.134	.430	0.379	.021*
Pulsatility index (PI)	−0.527	<.001*	−0.280	.080	−0.514	.001*	−0.210	.212
Resistive index	−0.498	.001*	−0.122	.453	−0.533	.001*	−0.073	.660
PI/mean BFV	−0.336	.034*	−0.318	.046*	−0.327	.048*	−0.380	.020*
CVR to hypercapnia	−0.010	.948	0.079	.622	−0.068	.688	0.072	.674

Abbreviations: BP, blood pressure; MCA, middle cerebral arteries; BFV, blood flow velocity; CVR, cerebral vasodilator responsiveness; PCA, posterior cerebral arteries.

*P < .05.

Table 3
Correlations between mood and cerebrovascular function in the MCA and in the PCA after controlling for age, menopausal years and symptoms

	Without adjustment				Adjusted			
	Depression score		Total mood disturbances		Depression score		Total mood disturbances	
Cerebrovascular parameters	r	*P*	r	*P*	r	*P*	r	*P*
MCA								
Basal mean BFV	−0.131	.294	−0.054	.665	0.008	.956	0.037	.791
Basal PI	−0.305	.013*	−0.182	.144	−0.101	.463	−0.026	.849
Basal RI	−0.306	.012*	−0.199	.110	−0.098	.479	−0.044	.750
PI/mean BFV	−0.094	.451	−0.047	.706	−0.123	.372	−0.101	.463
CVR to hypercapnia	−0.211	.092	−0.229	.066	−0.134	.330	−0.172	.209
CVR to cognitive stimuli	−0.067	.602	−0.187	.143	0.078	.573	−0.094	.495
PCA								
Basal mean BFV	−0.094	.564	−0.108	.509	0.124	.466	0.034	.841
Basal PI	0.004	.980	0.015	.929	−0.049	.773	−0.026	.880
Basal RI	−0.053	.744	−0.081	.619	−0.128	.452	−0.164	.331
PI/mean BFV	0.084	.608	0.073	.653	−0.186	.272	−0.141	.406
CVR to hypercapnia	−0.146	.361	−0.117	.467	−0.115	.498	−0.058	.735

Abbreviations: MCA, middle cerebral arteries; BFV, blood flow velocity; CVR, cerebral vasodilator responsiveness; PCA, posterior cerebral arteries; RI, resistive index.
*$P < .05$.

with Alzheimer's disease, who are at the end-stage of dementia [8]. It was surprising to observe that enhanced CVR to hypercapnia in the MCA correlated with poorer 3MS scores in our analysis. However, this correlation did not exist with the CVR to hypercapnia in the PCA or with overall cognitive performance on the test battery. Although the 3MS is used routinely in clinics to screen for suspected dementia in those with subjective cognitive complaints, it is relatively insensitive for detecting subtle cognitive changes in normal functioning adults [39]. Considering that the 3MS was administered as part of our study inclusion screening protocol before the cognitive test battery, some participants might perform poorly due to anxiety associated with the uncertainty of whether they qualify for the intervention, independent of their cerebrovascular function. Furthermore, our restrictive study inclusion criteria meant that relatively healthy women without overt vascular dysfunction or cognitive impairment were enrolled in the intervention. Therefore, we cannot draw meaningful interpretations with the association between 3MS scores and cerebral vasodilator responsiveness to hypercapnia from our cohort.

Instead, we found that their overall cognitive performance was directly related to CVR to cognitive test battery that has greater specificity to detect cognitive deficits in aging women and sensitivity to detect changes in local blood flow velocities. In the brain, dynamic regulation of oxygen and glucose to match the metabolic demands of active neurons is achieved through concerted signaling actions by neurons, glial cells, and the endothelium. They form a neurovascular coupling unit to regulate local blood flow through endothelium-dependent vasodilatation [40]. The compliance of cerebral vessels is crucial for delivering sufficient blood to regions of the brain on demand. Thus, the impairment of CVR to cognitive stimuli may signify the beginning of a chain of events leading the progressive decline in brain metabolism, cognition, and tissue pathology that characterizes dementia [41]. Perhaps, the deficits in neurovascular coupling are better predictors of cognitive decline in healthy women. Interestingly, a higher basal mean BFV in the PCA, but not in the MCA, was linked to better overall cognitive performance on test battery. Most of the tests in our cognitive test battery assess the memory domain subserved by the hippocampus. Given that the hippocampal artery arises from the PCA [42], this observation warrants further evaluation of CVR to various cognitive tests in different vessels, notably in the PCA. In this study, we only explored the global dilatory responsiveness to hypercapnia in the PCA but not the local blood flow changes in the PCA during cognitive testing. No studies have evaluated the association between CVR to cognitive stimuli in the PCA and the neurovascular coupling capacity derived from neural activity. Elucidating the mechanisms that underpin associations between cognitive function and efficacy for cerebral perfusion are vital for deriving interventions to assist postmenopausal women in preserving brain health. Taken together, the integrity of the neurovascular coupling unit is more critical for achieving optimal performance in healthy, dementia-free older adults.

We found that 3MS scores were unrelated to depressive symptoms. This was probably due to the lack of range in the severity of depressive symptoms in our cohort of non-clinically depressed postmenopausal women or that the subjective ratings for depression failed to account for an individual's life situation at time of data collection. Instead total mood disturbances, which better quantifies the day-to-day fluctuations of various mood states in nondepressed individuals, were negatively affecting overall cognitive performance. This is somewhat consistent with existing literature of an association between depressive symptoms and

cognitive decline in older adults [43]. In a PET imaging study, as predicted, adult men and women with depression performed poorly on a verbal fluency test compared with nondepressed controls. Interestingly, there was no difference between depressed and nondepressed groups in cerebral perfusion at rest or during the verbal fluency tests, suggesting a neural activity mismatch may be involved in the pathophysiology of mood deficits rather than a simple reduction in neural activity [44].

We also did not find any relationships between reduced basal cerebral BFV and severity of depressive symptoms and total mood disturbances in our sample of postmenopausal women. In fact, none of our cerebrovascular function parameters correlated with depression scores or total mood disturbances. Again, the lack of association may be attributable to the inclusion criteria for this study whereby our participants are not clinically depressed and without overt vascular dysfunction. One study has also shown that in cognitively intact but depressed postmenopausal women, there was no difference in basal cerebral blood flow between women with and without depression. However, the authors observed a blunted rise in cerebral blood flow during the Wisconsin Card Sorting Task (WCST; CVR to cognitive task), which correlated with poorer scores on the Mini-Mental State Examination, one measure of global cognition, but not with WCST performance [45]. Alleviating depressive symptoms early in menopause may be crucial for reducing the risk of dementia in women later in life. Analysis of the Women's Health Initiative Memory Study predicts that depression in postmenopausal women >65 years old doubles their chances of developing dementia within 5 years [46]. Although the integrity of the neurovascular coupling unit is important for maintaining adequate cerebral blood flow, the underlying pathophysiology of mood deficits remains unclear. Nonetheless, Yao et al showed that the responsiveness of the neurovascular coupling unit could be restored with hormone therapy, and this was accompanied by improvements in cognitive function but it did not alleviate depressive symptoms in postmenopausal women, suggesting that cognitive deficits differ from mood disorders in their neuropathologic mechanisms, particularly for women [47].

In conclusion, our exploratory analysis of the relationships between cerebrovascular function, cognitive performance, and mood have identified associations between adequate cerebral perfusion both at rest and during cognitive demands and the resultant cognitive performance in healthy postmenopausal women. Although cognitive performance is negatively affected by mood disturbances, mood deficits appear unrelated to the integrity of cerebrovascular function, at least in our sample of healthy, nondepressed postmenopausal women.

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RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using PubMed and Web of Science databases for articles describing mechanisms that link cerebral perfusion to cognition and depression in postmenopausal women.
2. Interpretation: While there is an association between depression and dementia risk and the severity of cognitive impairment has been attributed to poor cerebral perfusion, there is a lack of evidence to link poor cerebrovascular function to cognitive deficits and depressive symptoms in otherwise healthy postmenopausal women. Impairment of cerebrovascular function that becomes evident following menopause is partly due to the loss of beneficial effects of estrogen on vascular function.
3. Future directions: Our analysis of baseline data from a clinical trial in postmenopausal women indicates direct relationships between intracranial arterial elasticity, integrity of the neurovascular coupling unit and cognitive performance in healthy postmenopausal women. As such, early interventions to maintain optimal function may help attenuate accelerated cognitive decline.

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