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Vascular Alterations Associated With Cognitive Deficits in Geriatric Individuals With Peripheral Arterial Disease

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Abstract

Peripheral arterial disease is associated with cognitive impairments and carotid intima-media thickness alterations, but little is known about the relationship between intima-media thickness and cognition in geriatric patients with peripheral arterial disease. We conducted a cross-sectional study comparing 26 geriatric individuals with peripheral arterial disease and 26 controls. Both groups had a similar composition in terms of age and gender. Both groups were referred for a detailed clinical examination, assessing the ankle-brachial index and intima-media thickness, as well as neuropsychological testing, using Digit Span, Controled Oral Word Association Test letters (FAS) and Wisconsin Card Sorting Test. Geriatric patients with peripheral arterial disease showed a set of cognitive impairments regarding attention, working memory, and mental flexibility. Moreover, lower values of the ankle-brachial index were independently associated with a lower level of abstract thinking. When adjusted further for intima-media thickness, no differences in cognitive performance or associations with ankle-brachial index remained significant. Therefore, the role of this marker could be crucial to explain our results. Further and prospective studies are required however to disentangle the real role of intima-media thickness on cognition, especially in geriatric patients with PAD.

Keywords: Ankle-Brachial Index; Cognition; Intima-Media Thickness; Peripheral Arterial Disease; Neuropsychological Tests

Abbreviations

PAD – Peripheral Arterial Disease;
ABI – Ankle-Brachial Index;
IMT – Intima-Media Thickness;
MMSE – Mini-Mental State Examination;

DF – Digit Forward (Digit Span Test);
DB – Digit Backward (Digit Span Test);
COWAT – Controlled Oral Word Association Test;
WCST – Wisconsin Card Sorting Test

Introduction

Cognitive decline is a common characteristic among the elderly [1, 2]. The prevalence of dementia from all causes is 5-10% of individuals over 65 years of age [3], of which 19% might be due to vascular dementia [4]. Peripheral arterial disease (PAD) may contribute to the development of vascular dementia, since it is an important manifestation of atherosclerotic disease [5], and also affects a considerable portion of the elderly. Evidence shows that more than 20% of the population over 65 years of age is affected by PAD [5, 6], which represents an increased risk for cognitive loss [7]. In fact, PAD has been associated with cognitive deficits, either in cohort or cross-sectional studies [8]. For example, studies have shown that a lower ankle-brachial index (ABI) – which is the most widely utilized test for the diagnosis of PAD [9] – is associated with a higher prevalence of cognitive decline and dementia [10, 11] and that an altered ABI may predict worse cognitive functioning after 10, 11, and 15 years [10-12].

As we said, many studies have shown cognitive impairments in geriatric patients with PAD [10, 13,14] and this is true even for asymptomatic individuals [15]. Moreover, a previous study conducted by our group has shown that impaired executive cognitive functions among geriatric patients with PAD are associated with functional impairments in daily life tasks, [16] showing the relevance of studies on cognitive and executive abilities for these patients. However, most studies on cognitive functions in PAD have utilized an ABI cut point of 0.90 to detect PAD [17]. They do not include individuals presenting ABI values of 0.91 to 0.99, that should be considered "borderline" according to the latest version of the Guideline for the Management of Patients With Peripheral Artery Disease [9]. Dementia and atherosclerotic disease might start silently, before they manifest clinically, and they can still affect cognition[18] and vascular function [19], respectively. Thus, here we hypothesize that borderline values of ABI can also be associated with cognitive impairments, and should be included in the group under investigation.

Moreover, an increase of carotid intima-media thickness (IMT), a marker of subclinical atherosclerosis, has been separately associated with PAD [20] and with cognitive deficits in individuals without clinical vascular disease [21]. The Edinburg Artery Study verified that the presence of PAD was significantly associated with an increased carotid IMT in symptomatic and asymptomatic patients [15]. On the other hand, a cohort study conducted with elderly women showed that an increased IMT at baseline could predict an increased risk for cognitive impairments, especially on memory and cognitive speed [21]. However, to the best of our knowledge, there are no studies investigating the impact of IMT alterations on cognitive functions of patients with PAD.

Continuing the investigation of cognitive performance in patients with PAD might contribute to a more detailed pathophysiological explanation of the role of atherosclerotic disease on cognitive impairment. Therefore, the main aim of our study was to evaluate cognitive functions, more specifically attention and executive function, of a group of patients with PAD, using an ABI cut point of 1.00, and comparing them with a geriatric group of individuals without PAD, and to investigate the association between ABI and cognitive performance. A secondary aim of our study was to analyze the role of carotid IMT in the cognitive performance of our sample of geriatric individuals with and without PAD.

Methods

Participants

We evaluated 52 geriatric individuals, divided into two groups: 26 patients with PAD and 26 individuals without PAD. Patients were recruited from the Vascular Ambulatory of the Clinics Hospital, in Sao Paulo, Brazil, from April to August/2011. The inclusion criterion for the group of geriatric patients was an ABI value <1.00. The group without PAD was similar to the group with PAD in age (range of ± 1 year) and gender, and was recruited during the same period, from August/2011 to September/2012, from elderly community groups. The inclusion criterion for the geriatric group without PAD was an ABI value >1.00. The exclusion criteria for both groups were refusal to participate in the study, history of epilepsy, delayed neurodevelopment, traumatic brain injury, and presence of major mental disorders (DSM-IV/Axis I), collected during a clinical interview (self-report) with the patient.

Ethical aspects

All the subjects were informed about the purpose of the study and agreed to participate. All patients filled out and signed a written informed consent form. The research protocol satisfied the Helsinki Declaration and it was approved by the University of Sao Paulo Review Board (CAPPesq), number 006/05.

Clinical examination

Subjects were invited to attend an interview and examination session at the hospital. Information about age, gender, years of education, history of myocardial infarction, diabetes, and smoking (either former or current smokers were considered smokers) were collected. Subjects' height and weight were measured and their Body Mass Index (BMI) were calculated as the ratio weight/square of their height. Systolic and diastolic blood pressure as well as heart rate were collected with an

electronic instrument (Omron HEM 741C, Omron Healthcare Inc., China), while subjects were in the supine position. Carotid IMT high-resolution B-mode ultrasonography was measured utilizing a linear-array, 4-13MHz transducer (Vivid i, GE Healthcare Inc.), on the left and right common carotid artery, while the subjects were still in the supine position, with their head rotated 45° to the opposite side of the artery under examination. The transducer was placed 2 cm below the carotid bifurcation and the device calculated the IMT (distance between the lumen/intimal interface and the medial/adventitial interface) of the far arterial wall based on a dynamic image. The ABI was measured using a sphygmomanometer, a cuff, and a Vascular Portable Doppler (DV 610, Med mega, SP, Brasil), with the subjects remaining in the supine position. Systolic pressure for both arms and both ankles was measured, and the ratio of arm/ankle was calculated for both legs. The lowest value was considered the subject's ABI. The Mini-Mental State Examination (MMSE), [22] which has been shown to detect the occurrence as well as the severity of dementia, was used to screen for the presence of the disease [23-25].

Cognitive assessment

The neuropsychological battery focused on attention and executive functioning. It was composed of three instruments: 1) The Digit Span Test, [26] which consists of two subtests: Digit Forward (DF) and Digit Backward (DB). The subjects were asked to repeat the sequences of numbers separately, one by one, first forwards and then backwards. The score is based on the number of correct sequences. This test was used to evaluate attention span (DF) and working memory (DB). 2) The Controlled Oral Word Association Test (COWAT): the subjects were asked to say words beginning with the letters "F", "A" and "S", and they had one minute for each letter [27]. The score was calculated based on the total number of correct words, the number of correct words for each letter, and the total number of errors. This test was used to evaluate verbal fluency. 3) The Wisconsin Card Sorting Test (WCST): it has four key cards with colored geometric figures and the subjects were asked to match other 64 cards to these key cards, either by color, shape, or number, depending on the specific criteria. The criteria, however, were not given to the subjects. The only information given to them by the examiner was feedback if a combination was "right" or "wrong". The score was calculated based on the number of completed categories, the number of failures to maintain set, and the number of perseverative errors [28]. These subtests were used to evaluate abstract thinking, sustained attention, and mental flexibility, respectively. The Neuropsychological battery took about 15 to 20 minutes to be completed.

Statistical Analysis

Statistical analysis was carried out using the statistical package SPSS-19 (SPSS, Inc., Chicago, IL). The raw scores for each test or subtest were registered for each group, and then the means were calculated. Kolmogorov-Smirnov test was performed for each variable to test normality. The comparison of cognitive performance between groups was performed using Analysis of Covariance controlling for the effect of the confounding variable "years of education" and further for the variable "right carotid IMT" to investigate the role of this marker in the comparison. Associations between ABI values and cognitive functions were analyzed for the whole sample using the Pearson correlation for parametric variables and the Spearman correlation for non-parametric variables. Partial correlations were then performed to eliminate the effect of the confounding variable "years of education" and to verify the role of right IMT on the associations found (left IMT mean was similar in between the groups).

Results

Of the 32 patients with PAD that agreed to participate in the study, 27 actually came to the examination, and one was excluded due to a high ABI value. The remaining group of 26 geriatric subjects with PAD was similar in age and gender to the other group of 26 individuals without PAD (see table 1).

Sociodemographic and clinical characteristics of the samples are presented in Table 1. Male gender was more frequent for both groups, but there were no statistically significant differences among the samples. Patients with PAD had fewer years of education than individuals without PAD. The groups had a similar performance on the MMSE and were also similar for systolic blood pressure, diastolic blood pressure, heart rate, and BMI, and diabetes and smoking were more frequent in the PAD group. The mean IMT was similar at the left side for both groups and was higher at the right side for the geriatric group with PAD. As expected, the mean ABI value was lower for the geriatric patients with PAD than for the geriatric individuals without PAD.

Geriatric patients with PAD showed impaired performance related to attention, working memory, and mental flexibility after adjusting for years of education (Table 2 – Adjusted[a]). Furthermore, as shown in Table 3 (Unadjusted), the ABI value was associated with attention, working memory, abstract thinking, and verbal fluency - both with total score for letters F.A.S. and with the specific scores for letters A and S. After adjusting for years of education, the ABI value remained associated with abstract thinking (Table 3 – Adjusted[a]).

Since IMT is usually associated both with PAD and cognition, [20, 21] we further adjusted the comparisons and the asso-

ciations for right IMT, to verify the influence of this factor on the cognitive deficits of geriatric patients with PAD. After the adjustment, differences between the group with PAD and the group without PAD on cognitive performance were no longer significant, neither was the association between ABI and abstract thinking (Tables 2 and 3 – Adjusted[b]).

Table 1. Comparison of demographic and clinical characteristics between groups.

Variable	Non-PAD (mean±SD)	PAD (mean±SD)	P-value
Age			
Mean (years)	68.11 (±7.82)	68.57 (±8.34)	0.838[a]
Gender (%/n)			
Male	65.4% (n=17)	65.4% (n=17)	1.000[b]
Female	34.6% (n=9)	34.6% (n=9)	1.000[b]
Education (years)	12.15 (±4.54)	8.30 (±4.76)	**0.005**[c]
MMSE	28,58 (±1,46)	27,41 (±1,76)	0.075[d]
SBP (mmHg)	136.30 (±21.76)	147.05 (±22.93)	0.190[a]
DBP (mmHg)	79.00 (±10.24)	80.20 (±12.68)	0.777[a]
HR (bpm)	63.69 (±10.94)	63.78 (±10.36)	0.910[c]
BMI (kg/m^2)	25.00 (±3.49)	25.81 (±4.65)	0.494[a]
Left IMT (mm)	0.71 (±0.13)	0.81 (±0.17)	0.057[a]
Right IMT (mm)	0.70 (±0.14)	0.86 (±0.26)	**0.020**[a]
ABI	1.10 (±0.08)	0.63 (±0.19)	**0.001**[a]

[a]Student T Test;

[b]Qui-square Test;

[c]Mann-Whitney Test;

[d]Analysis of covariance adjusted for "years of education".

SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; IMT: intima-media thickness; ABI: ankle-brachial index.

Finally, we also conducted a sub analysis comparing the subjects with borderline ABI values (originally included in the geriatric group with PAD) to the geriatric group without PAD and to the rest of the geriatric group with PAD, in order to verify their cognitive performance. As a result, we observed that the borderline subjects performed worse than the geriatric group without PAD and similar to the geriatric group with PAD on verbal fluency – letter F (data not shown).

Table 2. Comparison of the neuropsychological tests and subtests, including and excluding adjustment for years of education and IMT.

Variable	Non-PAD (mean±SD)	PAD (mean±SD)	P-value adjusted[a]	P-value adjusted[b]
Digit Span	10.95 (±2.99)	8.70 (±1.80)	**0.019**	0.164
DF	5.72 (±1.77)	4.80 (±1.19)	0.082	0.389
DB	5.22 (±1.63)	3.90 (±1.20)	**0.019**	0.129
WCST				
Categories	2.10 (±1.14)	1.27 (±1.12)	0.107	0.073
Failure to maintain set	0.68 (±1.05)	0.44 (±0.70)	0.298	0.404
Perseverative errors	12.42 (±7.29)	21.27 (±13.31)	**0.048**	0.680
COWAT	37.30 (±15.36)	26.92 (±10.12)	0.123	0.400
Letter F	12.65 (±5.30)	9.15 (±4.20)	0.104	0.218
Letter A	12.53 (±5.33)	8.73 (±3.72)	0.127	0.485
Letter S	12.11 (±5.63)	9.03 (±3.25)	0.278	0.705
Errors	0.34 (±0.68)	0.34 (±0.62)	0.671	0.751

[a]Analysis of covariance adjusted for years of education;

[b]Analysis of covariance adjusted for years of education and IMT.

DF: Digit Forward

DB: Digit Backward

WCST: Wisconsin Card Sorting Test

COWAT: Controlled Oral Word Association Test

Table 3. Association between cognition and ABI, including and excluding adjustment for years of education and IMT.

Variable	Unadjusted	Adjusted[a]	Adjusted[b]
Digit Span	0.342*	0.282	0.289
DF	0.238	0.193	0.241
DB	0.415**	0.298	0.259
WCST			
Categories	0.329*	0.338*	0.304
Failure to maintain set	0.115	0.286	0.081
Perseverative erros	-0.260	-0.233	0.149
COWAT	0.325*	0.135	0.019
Letter F	0.266	0.154	0.066
Letter A	0.362**	0.106	-0.029
Letter S	0.288*	0.111	0.010
Errors	0.040	0.065	-0.204

*p<0.05; **p<0.01.

[a]Partial correlation adjusted for years of education;

[b]Partial correlation adjusted for years of education and IMT.

DF: Digit Forward

DB: Digit Backward

WCST: Wisconsin Card Sorting Test

COWAT: Controlled Oral Word Association Test.

Discussion

In our study, geriatric patients with PAD showed reduced cognitive performance, compared to geriatric individuals without PAD. The most impaired domains were attention, working memory, and mental flexibility, independent of years of education. The ABI value was independently associated with abstract thinking, reinforcing the relationship between PAD and cognitive functioning. However, after further adjustment for right IMT, no differences in cognitive functions or associations between variables remained significant, suggesting that this marker might be playing an important role in the results we found. Furthermore, patients with borderline values of ABI showed impaired performance on verbal fluency, when compared to the geriatric individuals without PAD.

Our findings contribute to the growing body of evidence indicating that cognitive functions are generally impaired in geriatric patients with PAD, in this case including patients with borderline values of ABI. Rao et al. [13] found similar results in tasks measuring executive functions and memory among geriatric patients with different cardiovascular diseases (PAD x stroke). The Whitehall II Study, [12] a cohort study based on the British civil service, found that the occurrence of PAD in elderly individuals was associated with deficits in executive functions, memory, and language after 11 years of follow-up.

Mangiafico et al. [15] also detected cognitive impairments in patients during the early stages of PAD. They evaluated a group of asymptomatic patients with PAD, over 55 years old, comparing them to a control group without PAD, and detected deficits on executive functions, memory, and visuoconstructive abilities. Our findings reinforce these results and go further, because our group of patients with PAD included individuals with borderline values of ABI and some differences between subgroups could still be detected. Thus, it demonstrates the presence of early manifestations of cognitive decline in patients with PAD.

The cognitive impairment in this population has been attributed to the presence of generalized atherosclerosis, [15, 29, 30] though the exact mechanism leading to this association is still unknown. Two possibilities have been given: atherosclerosis that could contribute directly to the deficits, through its inflammatory and ischemic processes, or indirectly, through events related to cerebral ischemia such as stroke and myocardial infarction. [10] Our findings point to direct associations between PAD and cognitive deficits, because, when adjusting for IMT, differences between the performances of the groups were no longer significant. In other words, our findings suggest that cognitive impairments in these patients may be explained, at least in part, by the underlying atherosclerotic mechanism present both in PAD and carotid IMT. To our knowledge, this is the first study associating carotid IMT with cognitive functioning in patients with PAD.

Executive cognitive deficits have been frequently detected in patients with cardiovascular diseases and risk factors [31]. However, data regarding the presence of language deficits among this group of patients are not as consistent as the findings on executive functions. While one study observed verbal deficits on PAD patients (in areas of verbal reasoning, verbal recognition and verbal comprehension) [10] another investigation found that deficits in verbal fluency were no longer significant after adjusting for premorbid cognitive function [12]. In our study, we did not observe independent differences between the control group and the group with PAD in verbal fluency. However, in a sub analysis, we detected worse verbal fluency performance among subjects with borderline ABI, when directly compared to the control group. Yet, the reason for this controversy is still unclear, suggesting that this cognitive function should be targeted in further studies assessing PAD and cognition.

One of our limitations, however, is the absence of neuroimaging data. This information could help to better explain the observed relationship between PAD and cognition by investigating the presence of small infarcts and ischemia in brain tissue and its influence on cognitive performance. A second limitation of our study was the restricted sample size, which may have biased the results. However, we performed adjusted analyses and our results remained significant, reinforcing the validity of our findings, even though we did not consider cardiovascular risk factors in this adjustment, which might be a limitation in itself. A third limitation was the difference between groups based on the variable "years of education", which is a determinant variable when we assess cognitive functions, and should be considered more closely in future studies. Nonetheless, our data analysis controlled for this variable, and the results described remained significant after this adjustment.

The implications of our findings are relevant. Cognitive impairments in older people are always a concerning finding. Executive functions, more specifically aspects of frontal lobe functioning, are important functions involved in behavior adaptation and treatment adherence. [32] Thus, patients with executive deficits are at greater risk of not engaging in treatments that are usually necessary at this age. Furthermore, any cognitive deficit contributes to the development of dementia and loss of independence, [33, 34] which means that geriatric patients at risk for PAD and/or increased IMT should be targeted when we think about preventive strategies.

Conclusion

In conclusion, our study found a relevant association between carotid IMT and cognitive deficits in geriatric individuals with PAD, suggesting that IMT might play an important role in the relationship between cognition and PAD. Other prospective studies, however, should further investigate these associations using other strategies such as the measure of carotid flow and neuroimaging techniques.

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Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

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