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Carotid circumferential wall stress is not associated with cognitive performance among individuals in late middle age: The Maastricht Study

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ABSTRACT

Background and aims: Arterial remodelling aims at normalising circumferential wall stress (CWS). Greater CWS in the carotid artery has previously been associated with the prevalence and severity of cerebral small vessel disease, a major cause of ageing-related cognitive decline. Here we test the hypothesis that greater carotid CWS is associated with poorer cognitive performance.

Methods: We studied 722 individuals (60 ± 8 years, 55% men, 42.5% highly educated, blood pressure 137 ± 19/77 ± 11 mmHg, n = 197 with type 2 diabetes) who completed a neuropsychological assessment and underwent vascular ultrasound to measure the intima-media thickness (IMT) and interadventitial diameter (IAD) of the left common carotid artery at a plaque-free site. From IMT and IAD, lumen diameter (LD) was calculated. These structural measures were then combined with local carotid pulse pressure and brachial mean arterial pressure to obtain a measure of pulsatile ($CWS_{pulsatile}$) and average (CWS_{mean}) mechanical load on the vessel wall. Cognitive domains assessed were memory, executive function and attention, and processing speed.

Results: After adjustment for age, sex, and education, regression analyses showed that neither $CWS_{pulsatile}$ nor CWS_{mean} were associated with measures of cognitive performance (p-values ≥0.31). This null association did not differ by age or educational level, and was observed in both individuals with and without carotid plaque, diabetes and/or hypertension. In addition, none of the individual measures of carotid structure (i.e. IMT, IAD, and LD) was related to cognitive performance.

Conclusions: The present cross-sectional study shows that carotid CWS is not associated with cognitive performance, at least not among relatively highly educated individuals in late middle age with adequately controlled cardiovascular risk factors.

1. Introduction

Cognitive impairment and dementia are among the most feared conditions of old age [1] and their prevalence, with the ageing of the population, continues to grow [2]. Despite intensive research efforts, the mechanisms underlying age-related deterioration in

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cognitive performance remain incompletely understood. Vascular factors play an important role [3] and may include structural alterations of the carotid arteries, the main suppliers of blood to the brain.

As the vasculature ages [4], but also in response to haemodynamic and atherosclerotic stimuli [5], carotid arteries undergo structural changes. This process of structural changes is known as arterial remodelling and is characterised by diameter widening and wall thickening [5–7], resulting from a complex interplay between vasoactive molecules, extracellular matrix turnover, and inflammatory activity [5,6]. It is thought that arterial remodelling aims at normalising circumferential wall stress (CWS) [5]. Arterial remodelling is, however, not a uniform process [5–7] and can be maladaptive, resulting in greater CWS, as is, for example, the case in diabetes [5].

In theory, there are at least two mechanisms through which carotid CWS might influence cognitive performance. First, greater CWS has been related to the risk of plaque fissuring [8] and rupture [9] with consequential (micro)embolisation of plaque debris to the brain. Cerebral emboli cause neuronal ischaemia, which can ultimately lead to neuronal dysfunction and cell death. Alternatively, or simultaneously, greater CWS may induce endothelial dysfunction [10], even in the absence of carotid plaque, which at the level of the downstream microcirculation can contribute to blood-brain barrier disruption. Such disruption has been suggested to precipitate cerebral small vessel disease (CSVD) [11]. Collectively, CWS may thus be linked to cognitive performance through vascular damage of the brain. Indeed, previous studies have shown that circumferential wall tension [12] and stress [13] are associated with a greater prevalence of silent lacunar infarcts [12] and a greater volume of white matter hyperintensities (WMH) [13]. To date, however, data on the association of CWS with cognitive performance are lacking. We therefore tested the hypothesis that greater carotid CWS is associated with impairments of cognitive performance.

2. Patients and methods

2.1. Study population

In this study, we used data from The Maastricht Study, an observational prospective population-based cohort study enriched with individuals with type 2 diabetes. The rationale and design have been described previously [14]. In brief, the study focuses on the aetiology, pathophysiology, complications, and comorbidities of type 2 diabetes and is characterised by an extensive phenotyping approach. All individuals aged between 40 and 75 years living in the southern part of the Netherlands and sufficiently proficient in the Dutch language were eligible for participation. Participants were recruited through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings. For reasons of efficiency, recruitment was stratified according to known type 2 diabetes status.

For the present study, cross-sectional data from the first 866 participants were used who completed the baseline survey between November 2010 and March 2012. Each participant underwent all examinations within a time window of three months. We excluded participants with type 1 diabetes (n = 4), as well as those with missing data (n = 140) on cognitive performance (n = 21), CWS (n = 53), and/or one or more of the potential confounders (n = 80). The Maastricht Study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Netherlands Health Council under the Dutch “Law for Population Studies” (Permit 131088-105234-PG). All participants gave written informed consent.

2.2. Cognitive assessment

All individuals completed a concise (30 min) neuropsychological test battery to assess cognitive performance [14]. For conceptual clarity and to increase the robustness of the underlying cognitive construct, test scores were standardized and divided into three cognitive domains (i.e. memory function, executive function and attention, and information processing speed), as detailed in the Supplementary Data (see Extended methods, Supplementary Data). In short, memory function was evaluated using the Verbal Learning Test by averaging total immediate and delayed recall scores. The composite score for information processing speed was derived from the Stroop Colour Word Test Part I and II, the Concept Shifting Test Part A and B, and the Letter-Digit Substitution Test. Executive function and attention was assessed by the Stroop Colour Word Test Part III and the Concept Shifting Test Part C. Where necessary, individual test scores were inverted so that higher scores indicated better cognitive performance.

2.3. Circumferential wall stress

Carotid ultrasound examinations were performed by trained vascular technicians who were unaware of the participants' clinical characteristics. Measurements took place in a dark, quiet, and temperature-controlled room (21–23 °C) and were performed in supine position after a resting period of 10 min. Talking or sleeping was not allowed during the examination. Structural properties of the left carotid artery (at least 10 mm proximal to the carotid bulb) were determined with use of an ultrasound scanner equipped with a 7.5-MHz linear probe (MyLab 70, Esaote Europe, Maastricht, the Netherlands). This setup enabled the measurement of intima-media thickness (IMT) and interadventitial diameter (IAD), as described elsewhere [15,16] and detailed in the Supplementary Data.

Briefly, based on radio frequency multiple M-line analysis, mean IMT and IAD were calculated along a plaque-free segment of the left common carotid artery during end-diastole. IMT was defined as the distance between the lumen-intima and media-adventitia interfaces of the far (posterior) wall. IAD was defined as the distance between the media-adventitia interfaces of the near and far wall. The median IMT and IAD of three consecutive measurements were used in the analyses.

From IMT and IAD, lumen diameter (LD) was calculated using the following formula: LD = IAD-(2*IMT) in mm [5]. CWS was then calculated according to Laplace's law as P*(r/w), where P is transmural pressure, r is lumen radius and w is wall thickness. For the present study, both pulse pressure (PP) and mean arterial pressure (MAP) were used as representatives of transmural pressure in order to obtain a measure of pulsatile ($CWS_{pulsatile}$) and average (CWS_{mean}) mechanical load on the vessel wall. Local carotid PP was obtained from carotid pressure waveform calibration as specified in the Supplementary Data (see Extended methods, Supplementary Data). Brachial MAP was measured repeatedly during the vascular assessment at a 5-min interval with use of a commercially validated oscillometric device (Accutorr Plus, Datascope Inc., Montvale, NJ, USA), and the average of these measurements was taken. With PP and MAP as representatives of transmural pressure, $CWS_{pulsatile}$ and CWS_{mean} were calculated as (PP*(LD/2))/IMT and (MAP*(LD/2))/IMT, respectively, and expressed in kPa.

Reproducibility was assessed in 12 individuals (6 men; 60.8 ± 6.8 years; 6 with type 2 diabetes) who were examined by two observers at two occasions spaced one week apart. The intra- and inter-observer intra-class correlation coefficients were, respectively, 0.90 and 0.91 for IMT, and 0.98 and 0.95 for IAD.

Although IMT and IAD were measured at a plaque-free site, the