Systemic and cerebral hemodynamics in response to cardiovascular challenges : the heart-brain connection

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CHAPTER 5

Using high field magnetic resonance imaging to estimate distensibility of the middle cerebral artery

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Neurodegener Dis 2016; 16:407–410
DOI: 10.1159/000446397

ABSTRACT

Background: Although cerebral arterial stiffness may be an important marker for cerebrovascular health, there is not yet a measurement that accurately reflects the distensibility of major intracranial arteries. Herein we aim to non-invasively measure distension of the human middle cerebral artery (MCA).

Methods: Ten healthy volunteers (age: 30.3±10.8 years) underwent ultra-high field (7 Tesla) MRI scanning. Time of flight angiography and phase contrast flow imaging were used to locate the M1 segment of the middle cerebral artery (MCA) and to determine the occurrence of systole and diastole. High resolution cross-sectional cardiac triggered T_2-weighted images of the M1 segment of the MCA were acquired in systole and diastole.

Results: The average distension of the middle cerebral artery area from diastole to systole was 2.58% [min-max range: 0.08%–6.48%]. There was no significant correlation between MCA distension and the pulsatility index, calculated from the phase contrast flow velocity profiles.

Conclusion: These results lead to the first non-invasive image-based estimation of distensibility of the MCA (approximately 3×10^{-4} $mmHg^{-1}$) and demonstrate that ultra-high field MRI could be a promising tool for investigating distensibility of intracranial arteries in relation to cerebrovascular pathology.

Key words
Arterial Stiffness; Arterial Structure and Compliance; Cerebral Small Vessel Disease; Ultra-high field MRI; Middle Cerebral Artery

INTRODUCTION

Healthy cerebral arteries are able to smooth out the pulsatile blood flow originating from the heart into an almost continuous flow into the capillary bed of the brain [1]. If the cerebral arteries stiffen, the pulsatile blood flow propagates further into the arterial tree, where the pulsatile shear stress can induce damage to the walls of the small vessels [2,3]. This process has been linked to severe pathologies, including cerebral small vessel disease (SVD) and vascular cognitive decline [2,3], and highlights the potential value of a measure of cerebral arterial stiffness as a marker of cerebrovascular health.

Measuring stiffness (or its inverse: distensibility) in extracranial arteries is commonly done by assessing changes in diameter occurring with changes in pressure occurring at the same site [4]. The skull complicates such measurements for intracranial arteries, and therefore explains the absence of an accurate measurement of cerebral arterial stiffness. However, volume changes of approximately 5% occurring throughout the cardiac cycle in the middle cerebral artery (MCA) have recently been measured with computed tomography (CT) angiography [5].

In contrast to CT, magnetic resonance imaging (MRI) can be used non-invasively to measure the cross-sectional area of the MCA.[6] Based on the volume changes found by CT angiography [5], distention of the MCA through the cardiac cycle is expected to be small (0.05–0.1 mm). Non-invasive imaging of such small geometrical changes requires high resolution measurements, which currently is only feasible with ultra-high field MRI [6].

In this proof-of-principle experiment we aimed to measure distension of the MCA by using ultra-high field MRI and by synchronizing the image acquisition to the cardiac cycle. In addition, we assessed the pulsatility index as a combined measure of cerebrovascular resistance and stiffness. To the best of our knowledge, this is the first non-invasive assessment of cerebral arterial distension in humans.

MATERIAL AND METHODS

Ten healthy participants were recruited for this experiment (6 females, all non-smoking, average age 30.3±10.8 years). Informed consent was obtained from all volunteers. This study was performed under approval of the institutional review board of the Leiden University Medical Center according to the Declaration of Helsinki and in accordance with the guidelines for Good Clinical Practice (CPMP/ICH/135/95).

Image acquisition

MRI scans were performed at 7 Tesla (whole body Philips Achieva, Philips Healthcare, Best, The Netherlands) and similar to a previously described protocol[6]. All image acquisition parameters

are stated in the online data supplement. A 3-dimensional time-of-flight (TOF) angiogram was performed to identify the MCA and for planning of an imaging plane perpendicular to the M1 segment. Care was taken to select a straight portion of the MCA and exclude branching arteries. Planning of this imaging plane was guided by additional reconstructions of the TOF scan to better visualize the course of the MCA in all directions. The position and orientation of the imaging plane were copied to the quantitative flow scan to assess the flow velocity waveform through the MCA. Directly after acquisition, a circular region of interest in the centre of the MCA was used to determine to flow velocity profile at the level of M1, which was used to determine the time points at which peak-diastole and peak-systole occurred and to calculate the post-trigger acquisition delay times for the cardiac triggered T2-weighted images. High resolution and cardiac triggered T2-weighted images were acquired at 4 time points in the cardiac cycle in pseudo-random order: 200 (t_1) and 100ms (t_2) preceding peak-diastole, and 50 ms before (t_3) and 50 ms after (t_4) peak-systole. These time points were chosen because in the carotid artery peak flow velocities have been shown to closely follow systolic and diastolic pressure [7]. An example of a high resolution structural image can be seen in Figure 5.1a. Throughout all scans pulse oximetry at the finger was used to measure the cardiac pulse.

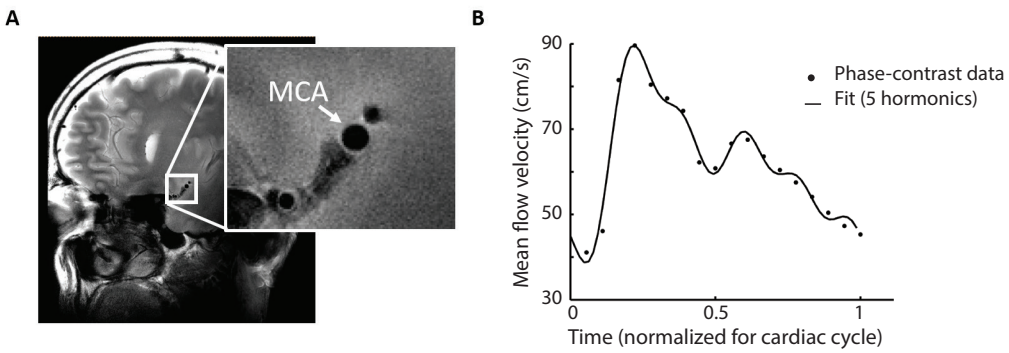

Figure 5.1 | A. Example of T_2-weighted high-resolution structural image of the cross-sectional area of the M1 segment of the MCA. **B**. Example of phase contrast flow velocity data (dots) measured at the same location as A. The flow velocity waveform was approximated by fitting the first five harmonics of a Fourier sequence (solid line), from which the pulsatility index was calculated. MCA = middle cerebral artery, Sys = systole, Dia = diastole.

Image analysis

Two observers, blinded to participant and cardiac phase of the images, manually drew elliptical regions of interests on the T_2-weighted images to delineate the internal wall of the MCA. Each observer repeated this process once, and the average of all 8 measurements (two scans per time point and two observers who delineated the MCA twice) per time point was used to calculate MCA cross-sectional area. Paired t-tests were used to investigate whether the MCA area at time points t_1, t_3, and t_4 were significantly different than at t_2 (triggered closest to peak-diastolic velocity).

To investigate the consistency within and between observers the intraclass coefficient of correlation for consistency (ICC(C,1), ICC(C,k)) was calculated with Matlab (R2012b, MathWorks, Natick, Massachusetts, USA).

The quantitative flow scan was also used to calculate a commonly used cerebral arterial stiffness index based on the blood flow velocity waveform through the MCA, the pulsatility index (PI) [8]. A linear regression was performed (*robustfit* in Matlab) between the distention of the MCA between peak-diastole and peak-systole (t_2 and t_3) and the PI.

RESULTS

There was high consistency in MCA area measurements within observer ($ICC(C,1)_{Obs.1}$ = 0.89, $ICC(C,1)_{Obs.2}$ = 0.92) and between observers (ICC(C,k) = 0.91), justifying the averaging of all 8 MCA area measurements per time point.

There was a significant increase in MCA area between diastole and systole of 2.58% [min-max range: 0.08%–6.48%] (*t*-test, p<0.01), see Figure 5.2a.

The group average PI was 0.80 ± 0.12, and was not significantly correlated with the change in MCA area between systole and diastole (r^2 = 0.13, p = 0.35), see Figure 5.2b.

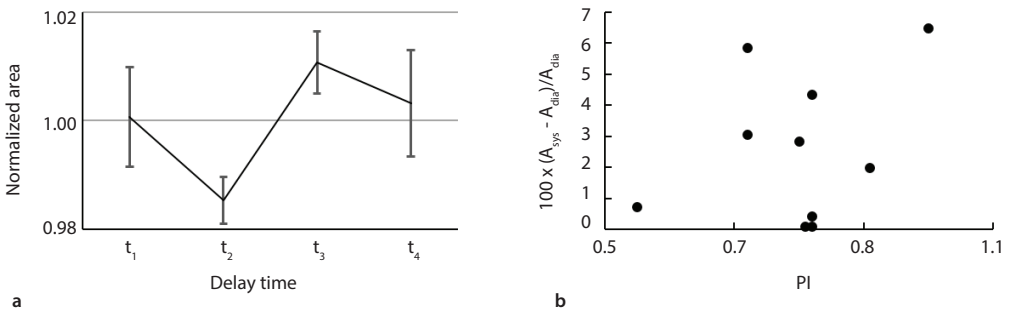

Figure 5.2 | A. Group average (N = 10) cross-sectional area of the MCA for 4 different delay times. Data was normalized per participant by dividing by the average MCA cross-sectional area of each individual. Note that t_2 is the delay time closest to peak-diastole and t_3 the delay time closest to peak-systole. There was a significant difference (* p<0.05, paired *t*-test) between the diastolic and systolic area. The errorbars indicate the standard error of the mean. **B**. The increase in area from diastole to systole plotted against the pulsatility index for all 10 participants. (No significant correlation, r^2 = 0.13, p = 0.35). MCA = middle cerebral artery.

DISCUSSION

In the current study it is shown for the first time that ultra-high field MRI can be used to non-invasively measure distention of the MCA occurring through the cardiac cycle, which is a prerequisite for measurement of cerebral arterial stiffness. When combined with reference values for central pulse pressure in healthy participants (45 mmHg [9]), the estimated average MCA distensibility is approximately 3.0×10^{-4} $mmHg^{-1}$.

This level of distensibility in the MCA is plausible, as the significant change in MCA area of 2.58%±2.4% through the cardiac cycle falls within the range of volume changes in the MCA measured with CT.[5] Furthermore, the resulting estimation of MCA distensibility follows the expectation that intracranial arteries are less distensible than extracranial arteries, e.g. reported distensibility in the carotid artery ranges from 0.5×10^{-3} to 5.8×10^{-3} $mmHg^{-1}$ [4].

There was no correlation between the distention of the MCA cross-sectional area and PI. Although in a small cohort, this finding highlights that in addition to local arterial stiffness, other factors such as stiffness and resistance of the downstream vascular bed shape the blood flow velocity waveform [10]. Furthermore, this illustrates the need for investigation of the relationship between cerebral arterial distensibility and the formation of blood flow velocity waveforms, which is an important step in understanding the mechanisms that link increased arterial stiffness to cerebrovascular pathologies, such as SVD [11] and vascular cognitive decline [3]. Future studies investigating these mechanisms should include participants with a wide range of expected cerebral arterial distensibilities, e.g. young and elderly individuals or patients with SVD.

A limitation of this study is that no blood pressure measurements were included and therefore only an estimation of MCA distensibility was feasible. However, underlying pulse pressures are not expected to show large deviations from reference values [9], because only healthy and non-smoking volunteers were recruited. Future work should include blood pressure measurements, such that cerebral arterial stiffness can be quantified in terms of distensibility or compliance [1,12]. Although measuring local pulse pressure would be a requirement for accurate estimation of arterial distensibility [4], we recommend using a non-invasive measurement of blood pressure (e.g. brachial blood pressure [12]) in studies for which it is not feasible to invasively assess intracranial blood pressure.

In summary, we have shown that ultra-high field MRI can be used to non-invasively measure cerebral arterial distensibility and that this is a promising tool for future research into the relationship between cerebral arterial stiffness and cerebrovascular pathology.

REFERENCE LIST

1. Hall JE, Guyton AC (2006) Vascular distensibility and functions of the arterial and venous systems. Textbook of medical physiology, 11th edn. Elsevier Inc, Philadelphia
2. Mitchell GF, van Buchem Ma, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson O, Garcia M, Aspelund T, Harris TB, Gudnason V, Launer LJ (2011) Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility - Reykjavik Study. Brain 134:3398-3407. doi:10.1093/brain/awr253
3. O'Rourke MF, Safar ME (2005) Relationship Between Aortic Stiffening and Microvascular Disease in Brain and Kidney: Cause and Logic of Therapy. Hypertension 46:200-204. doi:10.1161/01.HYP.0000168052.00426.65
4. O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE (2002) Clinical applications of arterial stiffness; definitions and reference values. Am J Hypertens 15:426-444. doi:S0895706101023196 [pii]
5. Kuroda J, Kinoshita M, Tanaka H, Nishida T, Nakamura H, Watanabe Y, Tomiyama N, Fujinaka T, Yoshimine T (2012) Cardiac Cycle-Related Volume Change in Unruptured Cerebral Aneurysms: A Detailed Volume Quantification Study Using 4-Dimensional CT Angiography. Stroke, vol 43. doi:10.1161/STROKEAHA.111.626846
6. Verbree J, Bronzwaer A, van Buchem M, Daemen M, van Lieshout J, van Osch M (2016) Middle cerebral artery diameter changes during rhythmic handgrip exercise in humans. Journal of Cerebral Blood Flow & Metabolism:0271678X16679419. doi:10.1177/0271678X16679419
7. Hirata K, Yaginuma T, O'Rourke MF, Kawakami M (2006) Age-related changes in carotid artery flow and pressure pulses: Possible implications for cerebral microvascular disease. Stroke 37:2552-2556. doi:10.1161/01.STR.0000242289.20381.f4
8. Bouvy WH, Geurts LJ, Kuijf HJ, Luijten PR, Kappelle LJ, Biessels GJ, Zwanenburg JJM (2015) Assessment of blood flow velocity and pulsatility in cerebral perforating arteries with 7-T quantitative flow MRI. NMR in biomedicine. doi:10.1002/nbm.3306
9. Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, Levy D (2004) Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: The Framingham Heart Study. Hypertension 43:1239-1245. doi:10.1161/01.HYP.0000128420.01881.aa
10. Bude RO, Rubin JM (1999) Relationship between the resistive index and vascular compliance and resistance. Radiology 211:411-417. doi:10.1148/radiology.211.2.r99ma48411
11. Webb AJS, Simoni M, Mazzucco S, Kuker W, Schulz U, Rothwell PM (2012) Increased Cerebral Arterial Pulsatility in Patients With Leukoaraiosis: Arterial Stiffness Enhances Transmission of Aortic Pulsatility. Stroke 43:2631-2636. doi:10.1161/STROKEAHA.112.655837
12. Warnert EAH, Murphy K, Hall JE, Wise RG (2015) Noninvasive assessment of arterial compliance of human cerebral arteries with short inversion time arterial spin labeling. Journal of Cerebral Blood Flow & Metabolism 35:461-468. doi:10.1038/jcbfm.2014.219