Relationship between periventricular or deep white matter lesions and arterial elasticity indices in very old people

Daniel A. Duprez, Marc L. De Buyzere, Nele Van den Noortgate\textsuperscript{1}, Jan Simoens, Eric Achten\textsuperscript{2}, Denis L. Clement, Marcel Afschrift\textsuperscript{1}, Jay N. Cohn\textsuperscript{3}

Departments of Cardiology and Angiology, \textsuperscript{1}Geriatrics and \textsuperscript{2}Radiology, Ghent University Hospital, De Pintelaan 183, B-9000 Ghent, Belgium
\textsuperscript{3}Cardiovascular Division, Medical School of Minneapolis, Minneapolis, Minnesota, USA

Address correspondence to: D. A. Duprez. Fax (+32) 9 240 3462. Email: daniel.duprez@rug.ac.be

Abstract

Objective: to examine the relationship between the presence of cerebral white matter lesions and large and small artery elasticity indices in a population of healthy, very old subjects.

Methods: we studied 24 subjects (14 women, 10 men) with a mean age of 84±5 years, who were free from overt neurological, cardiovascular or psychiatric illness. We measured blood pressure and heart rate in supine and standing positions. Elasticity indices of the large arteries (C1) and small arteries (C2) were derived from radial artery pulse waves. Each subject had multi-slice spin-echo cerebral magnetic resonance imaging. The severity of white matter lesions was graded as 0, 1 or 2.

Results: cerebral white matter lesions on magnetic resonance imaging were common in very old apparently healthy subjects: grade 0 (n=4, C1=2.68±1.80 ml/mmHg and C2=0.045±0.017 ml/mmHg), grade 1 (n=7, C1=2.13±0.36 ml/mmHg and C2=0.040±0.016 ml/mmHg) and grade 2 (n=13, C1=1.12±0.36 ml/mmHg and C2=0.018±0.005 ml/mmHg). There was no significant association between elasticity indices and blood pressure.

Conclusion: in very old, apparently healthy subjects, both large and small artery elasticity indices were inversely related to the severity of cerebral white matter lesions on magnetic resonance imaging.

Keywords: arterial compliance, blood pressure, deep white matter lesions, large and small artery elasticity index, magnetic resonance imaging

Introduction

The prevalence of white matter lesions sharply increases with old age. Improvement of imaging techniques of the brain in the last two decades has allowed better characterization of these white matter lesions [1–3] and magnetic resonance imaging (MRI) has proved more sensitive than computed tomography in detecting them [4, 5].

Patients with a generalized abnormality of the white matter commonly have a history of stroke, hypertension or other risk factors for stroke [4, 6]. Van Swieten et al. [7] performed post mortem MRI on the brains of 40 patients aged over 60 who died from causes other than brain disease. They found periventricular lesions in 10% of those aged 60–69 and 50% in those aged 80–89. Their findings support the concept that extensive demyelination and/or gliosis causes the periventricular white matter lesions observed on MRI, and that arteriosclerosis precedes and probably causes the demyelination and loss of axons.

This group also compared the presence of lesions of the white matter in a group of 42 older hypertensive subjects with those of a normotensive control group of older people [8]. They found that the presence of lesions of the white matter was related to age and blood pressure level but not to the known duration of hypertension, nor to the presence of any other cardiovascular risk factor. This last result was in contrast to other studies, in which
cerebral white matter lesions seen on MRI scans of brains of older people were associated with a history of stroke and coronary heart disease and with cardiovascular risk factors [9–11], even after adjusting for smoking, hypertension and hyperlipidaemia.

Because of the association of cerebral white matter lesions seen on MRI and cardiovascular disease and vascular risk factors, Bots et al. [12] assessed the association of white matter lesions and atherosclerosis in a group of 111 subjects, aged 65–85 years, randomly sampled and stratified by age and sex from participants in the Rotterdam study. From this, they concluded that atherosclerosis—indicated by increased common carotid intima-media thickness and a lower ankle/brachial index—is related to cerebral white matter lesions.

The reported association between cerebral white matter lesions and arteriolosclerosis and atherosclerosis in older people prompted us to assess arterial compliance in this population. A non-invasive technique which can provide information about the functional behaviour of small and large arteries was used in a population of older people without clinically overt cerebrovascular or cardiovascular diseases. This pulse contour analysis method measures arterial elasticity, which is abnormally low in subjects with atherosclerotic disease [13–16].

In this study we aimed to examine the relationship between the presence of cerebral white matter lesions and large and small artery elasticity indices in a population of healthy, very old subjects.

Methods

Subjects

We enrolled 24 subjects (14 women, 10 men), mean age 84 ± 5 years (range 73–96), body mass index 23 ± 5 kg/m². The subjects were recruited from a geriatric department and had extensive screening. We excluded subjects with any serious current or previous illness, history of hypertension, nicotine or alcohol abuse, head injuries, obesity (body mass index > 30 kg/m²) or psychiatric illness or who were taking any medications influencing either the cardiovascular or central nervous system.

On their first visit, subjects were given a physical and mental status examination, including a complete health history, 12-lead electrocardiogram, blood examination and urine analysis.

Exclusion criteria included neurological (e.g. history of stroke, Parkinson’s disease or any serious involvement of the central nervous system), cardiovascular (e.g. congestive heart failure, myocardial infarction, history of coronary artery disease, atrial fibrillation or symptomatic ventricular arrhythmias), respiratory (e.g. symptomatic bronchospasm), renal (e.g. elevated blood urea, proteinuria), endocrine and major psychiatric or other disorders. Diabetes mellitus or glucose intolerance was also an exclusion criterion. Patients were excluded if their diastolic blood pressure was > 90 mmHg at any of three consecutive measurements.

All subjects gave informed consent before entering the study, and the study protocol was approved by the local medical ethical committee.

Study protocol

After an overnight fast, the patients were examined between 0830 h and 0930 h after a 30-min supine rest.

Blood pressure was measured at the brachial artery using an automatic blood pressure device (Dynamap) in supine position. Means of three measurements at 1-min intervals were taken as systolic and diastolic blood pressure. Mean arterial pressure was calculated as:

\[
\text{diastolic pressure + } 1/3 \text{ (systolic pressure – diastolic pressure),}
\]

while pulse pressure was calculated as systolic pressure–diastolic pressure. Heart rate was determined from the electrocardiogram.

We then recorded non-invasive radial artery pulse waves for analysis of the large and small artery elasticity indices (C1 and C2). The subjects were then asked to stand, and arterial blood pressure was again measured three times at 1-min intervals and these values averaged.

We collected a venous blood sample for the determination of total cholesterol, low-density lipoprotein and high-density lipoprotein cholesterol, triglycerides and blood urea.

Large and small artery elasticity indices

Research was conducted using the HDI/PulseWave CR-2000 Research Cardiovascular Profiling System (Hypertension Diagnostics, Eagan, MN, USA). This uses a non-invasive pulse pressure sensor to obtain waveforms at the radial artery. The tonometer sensor array adjusts itself automatically to obtain the optimal waveform and repeats its calibration until the waveform is stable. The blood pressure waveform used to derive the elasticity indices resulted from computer-based averaging of consecutive individual arterial blood pressure waveforms, collected non-invasively over a 30-s period.

Elasticity indices of the large arteries (C1, representative of the aorta and conduit arteries) and of the small arteries (C2, representative of the distal part of the circulation where oscillations and reflected waves are generated)—both in ml/mmHg—are derived from a third-order, four-element modified Windkessel model. This can reproduce arterial pressure waveforms including both exponential and oscillatory pressure decays.
Cerebral white matter lesions and arterial elasticity

Cerebral white matter lesions were graded as 0 in four subjects, 1 in seven and 2 in 13.

The anthropometric data, blood pressure, heart rate and MRI score for the different groups are shown in Table 1. There were no differences in age, body mass index, mean arterial blood pressure and pulse pressure or heart rate in the subgroups with different grades of cerebral white matter lesions on MRI.

Large (C1) and small (C2) artery elasticity indices are given in Table 2. C1 and C2 were significantly lower in the subgroup characterized by the most extensive cerebral white matter lesions on MRI (P<0.01).

Blood urea concentrations and levels of cholesterol and high- and low-density lipoprotein cholesterol did not differ significantly between the groups, while triglycerides were elevated in the subgroup with the most extensive white matter lesions.

Discussion

In our study we have shown for the first time that, in very old, apparently healthy subjects, the high prevalence of cerebral white matter lesions on MRI is associated with a significantly decreased large artery and small artery elasticity index. There is no significant correlation between elasticity indices and blood pressure or cholesterol.

Table 1. Anthropometric data, blood pressure and heart rate among the different grades of white matter lesions on magnetic resonance imaging

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<th>Measure</th>
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<td>Age, years</td>
<td>85 ± 5</td>
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<td>Height, cm</td>
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MAP, mean arterial blood pressure.
There were no significant differences between values for the different grades (ANOVA).

Table 2. Large artery (C1) and small artery (C2) elasticity index among the different grades of white matter lesions on magnetic resonance imaging

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*P<0.01.

Results

Postural changes from supine to standing position did not significantly change systolic, diastolic, mean arterial blood pressures or pulse pressures. On the contrary, there was a significant (P<0.05) increase in heart rate.

Statistical analysis

The anthropometric, haemodynamic and metabolic measures were averaged for the different groups along with their grade of white matter lesions and compared with ANOVA tests. Study indices in supine and standing position were compared using Student’s t-test. Differences in C1 and C2 in relation to the grade of white matter lesions were analysed by the MANOVA test. Significance was considered at the level of P<0.05.

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Adaptations in the arterial vasculature play a critical role in influencing cardiovascular haemodynamics with advancing age [17]. The generalized structural and functional changes in the arterial circulation contribute to alterations in regional blood flow, progression of atherogenesis and the microvascular abnormalities that occur during senescence [18, 19].

The consistent changes in the arterial pulse contour with ageing and disease contrast markedly with the conflicting results of previous studies. These have examined the influence of ageing and cardiovascular risk factors on local or segmental mechanical wall properties that influence pulsatile arterial characteristics [20–23]. Using local or segmental mechanical wall properties there was no clear distinction in local arterial compliance between early and more extensive atherosclerotic involvement of the arterial wall.

Barenbrock et al. [20] demonstrated that arterial compliance of the common carotid artery by multigate Doppler system assessment was only significantly altered in extensive atherosclerosis. Weber et al. [21], using high-resolution echo-tracking at the radial artery, could only demonstrate borderline decreased isobaric incremental elastic moduli in untreated hypertensive patients compared with matched controls.

Cardiovascular function can vary dramatically among older individuals. This reflects the inter-individual variability in age-, disease- and lifestyle-related effects on vascular haemodynamics. The relation between altered mechanical properties of blood vessels and atherosclerosis is complex and probably involves both structural and functional influences that have led to conflicting reports.

An understanding of the age-related physiological changes that occur in the arterial system is crucial in order to appreciate the influence of age on the occurrence of cardiovascular and cerebrovascular disease. Diagnostic procedures are currently designed to assess the extent and severity of vascular disease after the development of symptoms or when morbid events occur. The diagnostic challenge must be to detect abnormal structure and function in the vascular system before the development of symptoms or signs of cardiovascular and/or cerebrovascular disease [16]. By providing a direct assessment of abnormal structure or tone in the arterial vasculature, alterations in arterial compliance may improve risk stratification and identify individuals with early vascular damage who are predisposed to future development of cerebral white matter lesions.

The use of data from pulse contour analysis is dependent on the reliability and reproducibility of the measurement. Data on repeatability and reproducibility both at a single visit and on 3-weekly measurements show that such measurements are reproducible as other non-invasive measurements, such as heart rate and blood pressure [24].

Van Swieten et al. [7] reported that the anatomicopathological findings of the cerebral white matter lesions depicted by MRI are in favour of the notion that extensive demyelination and/or gliosis is the pathological correlate of periventricular white matter lesions seen on MRI. They also suggested that arteriosclerosis precedes and probably causes the demyelination and loss of axons, and that dilatation of perivascular spaces is a secondary event.

The small artery elasticity index (C2) may be a sensitive marker not only for the effect of the ageing process per se, but also for arteriosclerosis, which is linked to the presence of cerebral white matter lesions [25].

The population-based Rotterdam study of MRI scans of brains of elderly people provides evidence that a high prevalence of cerebral white matter lesions is associated with a more extensive and widely distributed atherosclerotic process as it was linked to a reduced ankle/brachial index and an increased common carotid intima-media thickness [12]. These two non-invasive measures are well-accepted as non-invasive markers of severity of atherosclerosis.

A decrease in large artery elasticity index (C1) is associated with more pronounced atherosclerosis of large arteries. The association between cerebral white matter lesions and large vessel atherosclerosis cannot be entirely attributed to confounding common cardiovascular risk factors, because there are no differences for cholesterol, mean arterial blood pressure or pulse pressure. This favours the hypothesis that the cerebral white matter lesions are partly a direct consequence of atherosclerotic vessel wall disease. However, triglycerides were significantly higher in the group with the highest prevalence of white matter lesions.

Breteler et al. [10] found that an increased prevalence of white matter lesions is associated with both increased fibrinogen and increased factor VIIc levels. This suggests that the coagulation system may be involved in the pathogenesis of white matter lesions of the brain.

Conflicting data have been published on the relationship between blood pressure levels and the prevalence of white matter lesions.

Cross-sectional studies have shown an association between elevated blood pressure and white matter lesions. De Leeuw et al. [26] studied the relation between blood pressure and white matter lesions in a cohort of subjects aged 60–90 years who were randomly sampled from two prospective population-based studies. One of the study groups had had blood pressure measurements 20 years before, the others 5 years before. Diastolic and systolic blood pressure levels assessed 20 years before were significantly associated with cerebral white matter lesions. The association between concurrent diastolic blood pressure and white matter lesions was linear in subjects without, and J-shaped in subjects with, a history of myocardial infarction. However, some limitations and methodological issues must be pointed out. The overall response of participation was 63%, leading to potential selection bias, especially among the oldest participants. In the subjects aged between 80 and 90, the response
was only 48%. In the total group, 861 subjects were enrolled without myocardial infarction, while 99 had a myocardial infarction.

Goldstein et al. [27] examined the relationship between casual, ambulatory blood pressure and heart rate and MRI assessments of cerebral white matter lesions in a group of healthy older individuals (aged 55–79). After adjustment for age and sex, individuals with the most severe MRI rating for white matter lesions had a higher casual, awake and sleep systolic blood pressure than individuals with less severe ratings, indicating that blood pressure is associated with subcortical brain lesions. Additional confirmation was found in the higher awake diastolic blood pressure, the greater awake systolic blood pressure variability and the smaller nocturnal falls in both systolic and diastolic blood pressure in the individuals with the highest ratings. However, these authors concluded that longitudinal studies are needed to further explore the relationship between white matter lesions and cardiovascular measures, as well as the significance of these lesions for cerebrovascular disease in healthy elderly people [27].

In the group of non-healthy elderly subjects, pathological changes in small blood vessels were associated with diffuse white matter changes and may have a distinct role in the genesis of vascular dementia [28]. White matter lesions have also been observed in dementia with Lewy bodies and in Alzheimer’s disease [29]. However, white matter lesions may contribute to cognitive decline in both non-demented and demented older subjects [30, 31].

In conclusion, we have shown by pulse contour analysis that a decrease in large and small artery elasticity indices in older individuals is associated with the highest prevalence of cerebral white matter lesions, independent of blood pressure level and cholesterol. These findings should stimulate further research to explore whether large and particularly small artery elasticity indices are markers for the risk of development of cerebral white matter lesions and whether they are correlated with behavioural changes in this older population.

**Key points**
- There is a high prevalence of cerebral white matter lesions (periventricular or deep white matter) in apparently healthy, very old subjects.
- Cerebral white matter lesions are associated with significantly decreased large and small artery elasticity indices.

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**References**


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