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Assessing Vascular Changes Associated with Healthy Aging using 7T Magnetic Resonance Angiography

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Aging is known to produce changes in the cerebral vasculature and circulation. We aimed to quantitatively assess age-related changes in the morphology of small perforating vessels, lenticulostriate arteries (LSAs). LSA images were acquired using ultra-high field 7-Tesla magnetic resonance imaging (7T MRI) from 24 young healthy volunteers (young group: YG) and 25 old healthy volunteers (old group: OG). Vessel-related factors such as curvature and tortuosity were analyzed using two-dimensional images. Our quantitative results demonstrated a fewer in their branches and a significantly more pronounced curvature in the OG compared to the YG. These findings were further confirmed qualitatively using image analysis. Our study findings show that MR angiography utilizing ultra-high field MRI can provide high-resolution images that can identify morphological characteristics of small perforating vessels. Based on these features, it is possible to document age-induced changes in cerebral small vessels.

Keywords : 7T MRI, MRA, lenticulostriate artery, vascular aging, vessel curvature

1. Introduction

Aging is a universal phenomenon that causes various physical and functional changes over time. The pathomechanism of aging can be viewed as cumulative cell damage occurring over time [1, 2]. Although the onset and rate of aging vary between individuals, aging is a natural phenomenon that affects all organisms [3].

The brain receives oxygen from the blood circulation system to perform various functions, and a diminished oxygen supply causes a decline in function or malfunction of this vital organ [4]. Despite its relatively small size (the brain accounts for approximately 2% of the human body by volume), because of the various functions it performs, the oxygen requirement of the brain is > 20% [4, 5]. Therefore, cerebral vessels supplying oxygen to the brain play a key role in maintaining adequate blood circulation to this important organ. Changes in the amount of oxygen utilized by the brain determine the changes in blood flow to the brain (based on the principle of demand and supply); thus, vascular changes secondary to aging, particularly in the cerebral vessels, warrant close attention [5].

Age-related changes in the morphological characteristics of cerebral vessels can lead to vascular diseases that compromise brain function, such as stroke [6, 7]. Hematological changes can impair blood flow to the brain or affect oxygen transfer to neurons to cause hypoxia leading to cognitive dysfunction [8]. Based on these factors, it can be stated that pathology of cerebral small vessels (less than 1 mm) is known to cause cognitive dysfunction and neurodegeneration associated with aging [9-11]. Vascular pathologies such as fibrosis and vessel wall atrophy are known age-related phenomena, and it has been documented that aging causes cerebral arteriolar wall atrophy, reduced elasticity of cerebral arterioles, and blood flow

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changes [8, 12, 13], in addition to an increased blood flow resistance index and a significantly reduced mean blood flow. However, brain perfusion being maintained at a consistent level regardless of age in young people (19-40 years of age) and old people (65-85 years of age) indicates that blood pressure shows a compensatory increase to maintain blood flow in blood vessels that develop increased tortuosity secondary to aging [8, 14, 15]. The degree of increase in vascular tortuosity is significantly associated with various diseases such as hypertension and Alzheimer's disease, and it has been observed that in these cases, blood vessels show a relatively greater degree of curvature compared to vessels observed in those presenting with healthy aging [16].

However, not many modalities are available to examine the in vivo changes occurring in human cerebral vasculature. Magnetic resonance angiography (MRA) is a non-invasive method that enables visualization of vascular changes and is used as the standard method to assess vascular impairment such as formation of aneurysms or development of stenosis [17, 18]. A non-contrast-enhanced time-of-flight (TOF) MRA technique finds application in this context because using this technique, blood vessels are observed to generate stronger signals than surrounding tissues [18].

To date, morphology and characteristics of age-related changes in cerebral vessels have been studied only in major intracranial vessels, and the effects of aging on cerebral small vessels remain unclear [13]. The lack of studies pertaining to small vessels is related to limitations in available technology to acquire images of small vessels. Small vessel images can be obtained using imaging techniques such as digital subtraction angiography; however, this is an invasive method that requires injection of a contrast agent into vessels, which makes it unsuitable for studies on aging in healthy individuals [19]. Recent introduction of ultra-high field 7 Tesla magnetic resonance imaging (7T MRI) has enabled visualization of intracranial small vessels, which had been difficult to observe until this novel modality could be used [20, 21]. Using an ultra-high field MRI to acquire images of small vessels shows that the T1 relaxation time becomes longer and signal-to-noise ratio becomes higher than a normal high-field MRI, and thus, it provides greater vascular contrast and higher image resolution [22, 23]. Owing to such features, recent studies report the use of 7T MRA for angiographic imaging of small vessels such as the lenticulostriate arteries (LSAs), whose diameters range approximately 0.3 to 0.6 mm [22, 24, 25]. We aimed to observe changes in intracranial small vessels accompanying healthy aging.

2. Materials and Methods

2.1. Patient selection and MRI protocol

Our study participants comprised healthy individuals who were divided into two different age groups to clearly demonstrate age-based changes in small vessels. We analyzed 7T MRA images obtained from 24 members of the young group (YG: aged 21-34) and 25 of the old group (OG: aged 55-69). Blood pressure (BP) was measured, and a medical interview was conducted to obtain patient information including family history to determine whether variables in addition to age (e.g. use of medication that can affect blood vessels and/or family history confirming genetic predisposition to specific diseases) were relevant in individual cases. Informed consent was obtained from all study participants. The study was conducted using the TOF MRA study protocol (which was the same one that had been used in a previous study) and was approved by the Institutional Review Board (IRB) of the university and the Korean Food and Drug Administration (KFDA) [22, 25]. Images of LSA were acquired using 7T MRI (Magnetom, Siemens AG, Berlin, Germany) comprising a 90 cm superconducting magnet system (Magnex Magnet Technology, Oxford, UK). Imaging parameters used are shown in Table 1.

2.2. Data analysis

We focused on morphological changes in LSA to compare age-based changes in small vessels between the study groups. Images of major vessels including the anterior cerebral artery (ACA) and the middle cerebral artery (MCA) from which the LSAs originate were obtained to assess for anomalies in the morphological

Table 1. MR imaging parameters.

	3D TOF MRA
TR (msec)	15
TE (msec)	4.78
# of slices	104
Field of view (mm)	180 × 163
Flip angle, α (°)	15-25[a]
Acquisition matrix / pixel size (mm)	640 × 580 / 0.28
Slice thickness (mm)	0.36
Pixel bandwidth (Hz/Px)	90
Partial Fourier	6/8
Flow Compensation	Yes
GRAPPA (R=2)	ACS[b] = 38
TA (min:sec)	8:34

[a]Adjusted to be less than 70% of the limit of specific absorption rate during scan.
[b]ACS = auto-calibration scan.

structure of the vessels [26]. Morphological characteristics of LSA, primarily details pertaining to the stem, branches, distance, length, curvature, and tortuosity were quantified. Values obtained were categorized into the YG and OG groups and accordingly analyzed. Stems of LSA were defined as blood vessels originating from the ACA or MCA. Branches of LSA were defined as vessels originating from the stem, and a stem without any branch was defined as being a single branch [27, 28]. Curvature is a factor that indicates how much the vessels are curved and it was defined as the sum of the vertical angles of segments derived from the branch vessel, while tortuosity was obtained as the ratio of the measured distance and length values. Distance referred to the length between the origin and termination of a branch, while length referred to the actual measured length of the small vessel [27]. A matrix laboratory (MATLAB) based image signal processing program was used to obtain quantified values of LSA length, distance, curvature, and tortuosity utilizing two-dimensional maximum intensity projection (2D-MIP) images, and these were analyzed using coronal MIP images, which is the optimal image view for visualization of the LSA.

As shown in Fig. 1, prior to in vivo human vessel measurements, based on the shape and/or degree of angulation, changes in curvature and tortuosity were compared and analyzed via simulation. Equations for tortuosity and curvature were determined as follows:

$$\text{Tortuosity} = \frac{Length}{Distance}$$

$$\text{Length} = \sum_{i=1}^{n} \Delta L_i$$

$$\text{Curvature} = \sum_{i=1}^{n} \Delta C_i$$

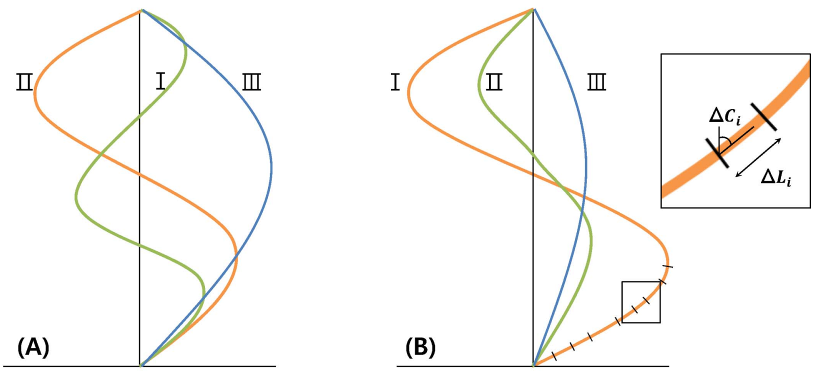
ΔL_i represents the length of the i^{th} segment of the small vessel, and ΔC_i was calculated by subtracting i^{th}-1 angle from the i^{th} branching angle (ANGLE) measured, meaning $\Delta C_i = \text{ANGLE}_i - \Delta C_{i-1}$, where ANGLE was defined with the angle between the normal vector and the z-axis.

2.3. Statistical analysis

Study participants were divided into the YG and OG for a comparison of small vessels based on age, and the t-test was performed using dependent variables in each group (e.g. tortuosity, and curvature, among others). Moreover, to achieve an in-depth analysis, the t-test was performed with each group divided into men and women participants. Statistical analysis was performed using SPSS 23.0 software with the statistical significance level set to P-value < 0.05.

3. Results

As shown in Fig. 1, differences in the shapes of blood



	Length (mm)	Distance (mm)	Curvature (degree)	Tortuosity
I	445.87	355.80	330.83	1.25
II	445.26	355.80	236.93	1.25
III	444.80	355.16	147.31	1.25

	Length (mm)	Distance (mm)	Curvature (degree)	Tortuosity
I	518.41	355.49	379.64	1.45
II	430.23	355.48	247.19	1.21
III	373.02	355.48	125.27	1.04

Fig. 1. (Color online) Differences in tortuosity and curvature based on shape of vessels. (A) shows that for vessels with the same length and distance, tortuosity showed the same values though curvature differed. (B) shows that for vessels where only distance remained the same, length, curvature, and tortuosity all showed different values. In (A), curvature change showed 147.31, 236.93, and 330.83 degree, respectively. In (B), as length increased to 373.02, 430.23, and 518.41 mm, curvature changed to 125.27, 247.19, and 379.64 degree, respectively, and tortuosity changed to 1.04, 1.21, and 1.45, respectively.

vessels might lead to differences in tortuosity and curvature. Thus, a basic blood vessel model was used to analyze the correlation between these two factors. Fig. 1 shows simulated images depicting tortuosity and curvature based on shape and degree of angulation. In Fig. 1(A), when both, length and distance of the vessels are observed to be the same, tortuosity is also observed to show the same value, although curvature is observed to be different. In Fig. 1(B), when only the distance remains the same, length, curvature, and tortuosity all show different values. Figure 1(A) represents an image that demonstrates how curvature shows a change based on the shape of the vessel, where I, II, and III represent angulation of the vessel once, twice and thrice, respectively. Values in I (330.83), II (236.93), and III (147.31) decreased by approximately 100, indicating that each time a bend occurred, curvature of the vessel was observed to increase. In Fig. 1(B), although the distance has remained the same, length, curvature, and tortuosity have changed based on the degree of angulation. As the length increased to 373.02, 430.23, and 518.41 mm, tortuosity was observed to increase to 1.04, 1.21, and 1.45, respectively, and curvaure was observed to increase to 125.27, 247.19, and 379.64 degree, respectively. Therefore, it is clear that a greater degree of curvature was associated with a greater occurrence of morphological changes in the vessels.

Table 2 shows the family history, medication use, and BP measurements in participants. Mean BP in the YG and OG was 90.0 ± 7.7 and 92.3 ± 6.1 mmHg, respectively and did not show a significant difference (P = 0.284). We ensured that participants did not manifest other symptoms related to vascular diseases, which could confound our results. Participants were selected judiciously based on age criteria. Thorough history taking and medical interview ensured that we chose only those with no history related to vascular diseases. Investigation regarding use of medication that could affect blood vessels showed that individuals belonging to the YG were administered medication for acid reflux and common cold, while those belonging to the OG were administered medication for hair loss, ulcers, muscle ache, as well as adrenal corticosteroids. We confirmed that other than these medications, no participant received any other drug that could affect blood vessels. The age difference between the individuals belonging to the study groups was > 30 years. Even in those presenting with a positive history of disease, only an association of the condition with vascular disease was checked. Moreover, use of medication for specific diseases that may affect blood vessels was checked, and BP

Table 2. Demographics of subjects.

Category	Young	Old
Age (mean ± SD)	27.04 ± 4.22	61.00 ± 3.61
Male	10 (42 %)	13 (52 %)
Female	14 (58 %)	12 (48 %)
Systolic BP	118.05 ± 10.78	120.85 ± 6.61
/ diastolic BP (mmHg)	/ 76.02 ± 7.12	/ 78.00 ± 6.43
MABP (mm Hg)[a]	90.03 ± 7.70	92.28 ± 6.06
Family history[b]	6	6
Drug record[c]	1	3

[a]MABP indicates mean arterial pressure, p = 0.284, not significant
[b]Family history indicates hypertension, diabetes, cerebral infarction, cancer
[c]Drug record : medicine for a cold, Gastric ulcer

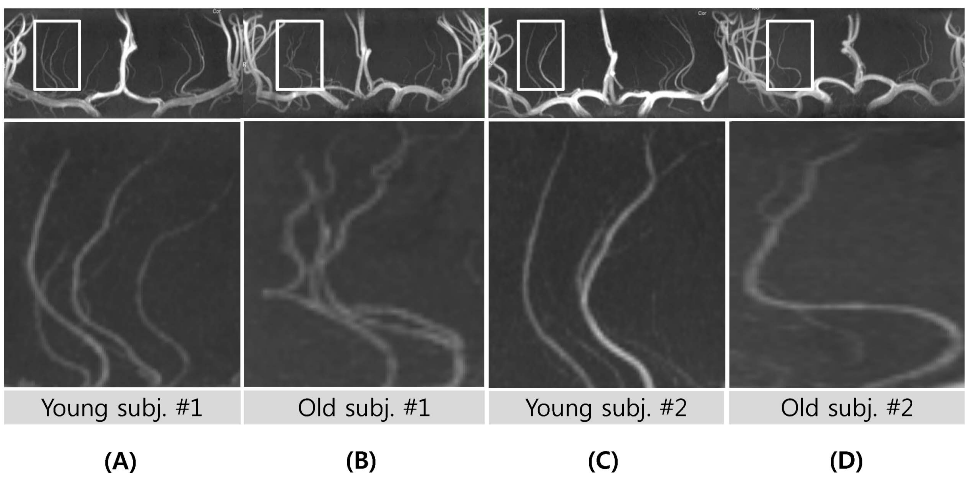


Fig. 2. Comparison of small vessel images acquired using 7T MRA. (A) and (B) represent images showing branches, while (C) and (D) represent images showing curvature. (A) is an image obtained from a 24-year-old individual belonging to the YG, (B) is an image obtained from a 67-year-old individual belonging to the OG, (C) is an image obtained from a 25-year-old individual belonging to the YG, and (D) is an image obtained from a 64-year-old individual belonging to the OG: old group; YG: young group.

Table 3. Comparison of quantified values of the lenticulostriate arteries (LSAs) between the young and old group (*P < 0.05).

	Young	Old	P-value
Stem (# of vessel)	2.45 ± 0.87	2.28 ± 0.90	0.323
Branch (# of vessel)	4.79 ± 1.55	3.88 ± 1.43	0.003*
Distance (mm)	20.98 ± 3.81	20.89 ± 3.82	0.911
Length (mm)	27.28 ± 4.28	28.08 ± 5.77	0.437
Curvature (degree)	474.97 ± 184.96	565.46 ± 234.26	0.037*
Tortuosity	1.31 ± 0.14	1.35 ± 0.20	0.317

values were used to indirectly confirm that BP did not interfere with vascular functions.

Figure 2 shows qualitative images of typical blood vessels of participants in the YG and OG, which were used to compare age-based changes in the number and shape of small vessels. Figure 2(A) and Fig. 2(B) represent images that show the difference in branches, while Fig. 2(C) and Fig. 2(D) represent images that show the curvature. Figure 2(A) is an image obtained from a 24-year-old individual from the YG group, Fig. 2(B) is an image obtained from a 67-year-old individual from the OG group, Fig. 2(C) is an image obtained from a 25-year-old individual from the YG, and Fig. 2(D) is an image obtained from a 64-year-old individual from the OG. Table 3 shows quantified values of stem, branch, distance, length, tortuosity, and curvature of LSA in individuals from the YG and OG. In the YG and OG, numbers of stem were 2.45 and 2.28, branch were 4.79 and 3.88, distance were 20.98 and 20.89 mm, length were 27.28 and 28.08 mm, curvature were 474.97 and 565.46 degree, and tortuosity were 1.31 and 1.35, respectively. Statistical analysis showed that significant differences were observed in terms of branch and curvature.

Table 3 shows quantified values of morphological characteristics of LSA (stem, branch, distance, length, tortuosity, and curvature) obtained from 2D coronal MIP images using the MATLAB-based image signal processing program. Table 3 and images in Fig. 2(A) and Fig. 2(B) show that the YG demonstrated a greater number of vessels than the OG indicating that the number of vessels decreases with aging. Table 3 and images in Fig. 2(C) and Fig. 2(D) show that the OG demonstrated a larger curvature of vessels compared to the YG indicating that curvature of vessels increases with age. The OG showed fewer branches and a larger curvature compared to the YG, which was confirmed using images.

4. Discussion

Using ultra-high resolution 7T MRA images, our study examined morphological characteristics of blood vessels in a healthy YG and OG to determine the effects of aging on small vessels. Blood vessels form a structural and functional component of the body that can only be identified using images. The development of ultra-high field 7T MRI has facilitated the acquisition of images of small vessels, which was not possible prior to the introduction of this novel technology, which we used to perform our study of LSAs [20-22, 24, 25]. Our study excluded those in the 35-55 age group because this period typically represents a transition period from an adult to an elderly individual, which is also viewed as a transition period for anatomical and/or physiological changes. Rapid changes are likely to occur in individuals belonging to the 35-55 age group, and significant differences could be expected even among those within the same age group. Therefore, these individuals were excluded for observation of definitive age-based changes. To ensure that our study participants differed only with respect to age, we conducted thorough medical interviews and obtained detailed medical history to examine variables other than age, such as concomitant diseases, use of medication that can affect blood vessels, and a family medical history of genetic predisposition to diseases. Based on results, participants who demonstrated an association with factors that can affect vascular diseases were excluded from the study.

In the same manner as was performed in previous studies, quantified values of morphological characteristics of LSA such as stem, branch, distance, length, tortuosity, and curvature were measured and analyzed utilizing 2D coronal MIP images using the MATLAB-based image signal processing program [27]. Aging is known to cause increased vascular curvature and tortuosity, and our study results confirmed that values of vascular curvature and tortuosity were higher in the OG compared to the YG. While curvature showed a significant difference, tortuosity did not, which indicates that with respect to tortuosity (calculated as length/distance), angulation of vessels was observed to increase without a significant change in length, and thus only the value for curvature showed a significant increase. Number of vessels is known to decrease with aging, and our study results confirmed that the number of vessels was decreased in the OG compared to the YG. While branches of LSA showed a significant decrease, the stem did not. Generally, blood vessels might demonstrate several branches originating from a single stem or just a single branch originating from a stem, where branches are smaller than stems. Aging causes atrophy of the walls of cerebral arteries, reduces elasticity in the cerebral arterioles, causes changes in the blood flow, and/or increases flow resistance index, whereby the mean blood flow is significantly decreased with a consequent reduction in cerebral blood flow to important areas of the brain.

Investigation of age-based vascular changes in healthy people using MRA showed clear quantitative and qualitative evidence of fewer branches and higher curvature in the OG compared to the YG. Previous studies have demonstrated clear differences between elderly and young individuals with respect to their large blood vessels; however, there are few or no earlier studies describing differences in small vessels. Therefore, our study focused on small vessels [13]. Regardless of the size of blood vessels (large or small), our study results were similar to those derived by previous studies-showing that elderly individuals demonstrate fewer blood vessels and/or greater vascular curvature compared to younger individuals [16, 27, 28].

Although our study is more advanced than previous studies, there are various limitations in our study [27, 28]. We must overcome these limitations and seek solutions that can be further developed. The limitations are as follows: 1) Our study acquired LSA images utilizing 7T MRA for 2D analysis via MATLAB. Because we used 2D, and not 3D image analysis, the relative accuracy of our results could be low. 2) 7T MRA provided images of small vessels with a maximum image size of only 230 μm. Thus, vessels smaller than this size could not be studied. 3) Due to the characteristics of TOF MRA that generates signals proportional to flow intensity, there were additionally a few limitations to the imaging technique. Therefore, we propose that vessels smaller than LSA should be studied using 3D and not 2D image analysis. Moreover, it is important to develop a technique to improve the quality of images.

5. Conclusion

Our study used 7T MRA to acquire and analyze LSA images from 24 healthy individuals in the YG and 25 healthy individuals in the OG. Previous studies have investigated changes observed only in major intracranial vessels; therefore, we focused on changes observed in small perforating vessels, and we could compare and demonstrate differences in small vessels between healthy young and elderly individuals. Our study confirmed that elderly individuals demonstrate fewer vascular branches and greater vascular curvature, and similar to previous studies, our study confirmed that a decreased number of vessels and increased tortuosity were associated with healthy aging. Our study utilized ultra-high field 7T MRA images to analyze vascular characteristics. We reckon that this could serve as a new method to analyze blood vessels and be used for future pathological studies on small vessels because it facilitates easy observation of vascular changes associated with healthy aging.

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