International Journal of Gerontology 15 (2021) 330–334
https://doi.org/10.6890/IJGE.202110_15(4).0007

International Journal of Gerontology

journal homepage: http://www.sgecm.org.tw/ijge/

Original Article

Intracranial Vascular Aging: Focusing on the Circle of Willis

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ARTICLE INFO

Accepted 15 March 2021

Keywords:
circle of Willis,
aging,
time-of-flight MR angiography

SUMMARY

Purpose: To determine whether the age-related change occurs in the arterial segments of the circle of Willis (CoW).
Materials and Methods: Patients (n = 100) who underwent time-of-flight MR angiography (TOF-MRA) were grouped according to age, 10–20 years old (n = 50) or 50–60 years old (n = 50). MRA images were retrospectively analyzed and the diameters of segments of the CoW were measured, and the patency of the CoW and the half circles was estimated. The CoW patterns according to the patency of each vessel segment were recorded.
Results: Most segments of the CoW in adult group revealed significant decrease in vessel diameter except for bilateral posterior communicating arteries. The number of vascular patterns of the CoW in the adult group was higher than in the adolescent group. There was significant decrease in the patency rate of the posterior, left, and right half-circles.
Conclusion: The CoW showed age-related change, resulting in markedly decreased vessel diameters in most segments.

1. Introduction

Aging affects multiple aspects of human anatomy and physiology, including organ structure and function. In the neurovascular system, normal aging and atherosclerosis lead to narrowing of the blood vessels in the circle of Willis (CoW), which may affect blood flow and eventually result in the dysfunction of the perfused area.[1] As the CoW is the main intracranial collateral system, understanding the age-related changes in the CoW is important for evaluating the vascular health of older individuals. While various studies have focused on the changes of the CoW in healthy adults,[2–7] few have been designed to evaluate age-related changes of the CoW.[4,5]

Compared to traditional digital subtraction angiography or computed tomography angiography, magnetic resonance angiography (MRA) is a non-invasive and efficient imaging modality that can be used to assess the CoW.[8–10] Furthermore, time-of-flight (TOF) MRA is a remarkable technique that features high spatial resolution, complete elimination of venous contamination, and short scan times. As such, this study uses TOF-MRA to compare the differences in vascular segments of the CoW between adults and adolescents, including the vessel diameter and patterns of patency. Based on the results, we attempt to clarify the effect of aging on the CoW, which may contribute to the development of strategies aimed at the improvement of cerebral development and cognitive health.

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2. Materials and methods

2.1. Patients

This study was approved by our institutional review board. We retrospectively collected and analyzed data from individuals who underwent brain magnetic resonance imaging (MRI) with MRA between January 1st, 2016, and December 31st, 2016. Inclusion criteria for the adult group were subjects 50–60 years old. To minimize the effect of confounding factors, only subjects from the health check-up database in our hospital who did not report any specific chief complaints were enrolled in the adult group. Inclusion criteria for the adolescent group were subjects 10–20 years old. Because there were very few subjects 10–20 years old registered in the health check-up database, we also enrolled subjects that were referred to the pediatric outpatient department in our hospital for any reason. We screened the images of all MRI sequences for all enrolled subjects in these two groups. Exclusion criteria included the presence of any notable intracranial pathological changes, such as marked encephalomalacic changes, intracranial tumors, arterial aneurysms, and arterial dissection. Subjects with congenital intracranial arterial variations, such as fetal origin of posterior communicating artery, azygos anterior cerebral artery, and triple anterior anterior cerebral artery……etc, were also excluded because we could not rule out the possibility that the arterial variation had an effect on the vascular diameters of the CoW. Finally, a total of 100 subjects were included in the present study, with 50 subjects in each group.

2.2. Imaging protocol and measurements

All subjects underwent three-dimensional TOF-MRA in a 3T MRI scanner (Achieva 3.0T, Philips Medical Systems, N.V.) with the following imaging parameters: 25 ms repetition time /3.455 ms echo time, 20° flip angle, 200 × 200 mm field of view, 444 × 249 matrix, 0.45 × 0.8 mm pixel resolution, 1.2 mm section thickness, and 0.6 mm section overlap. The total number of sections was 100; therefore, a volume of 60 mm in the caudocranial direction was covered (100 × 0.6 mm effective section thickness). A sagittal two-dimensional phase-contrast survey image was used to position the three-dimensional TOF stack. The target vessels for measurement were the seven arterial segments of the CoW, including the first segment of the bilateral anterior cerebral arteries (A1), the first segment of the bilateral posterior cerebral arteries (P1), the bilateral posterior communicating arteries (PCom), and the anterior communicating artery (ACom). The maximum diameters of these vessels were measured in the axial images of TOF-MRA in millimeters. If the arterial segment was not visible, the diameter was recorded as 0 mm. All measurements were performed by a senior radiologist resident under the supervision of a certificated radiologist who had specialized in neuroradiology for six years. Figures 1 and 2 demonstrate representative measurements of vessel diameters. Figure 1 shows a right A1 segment that was smaller in an adult subject compared to an adolescent subject, and Figure 2 shows an example of invisible bilateral PCom segments in an adult subject, but visible segments in an adolescent subject.

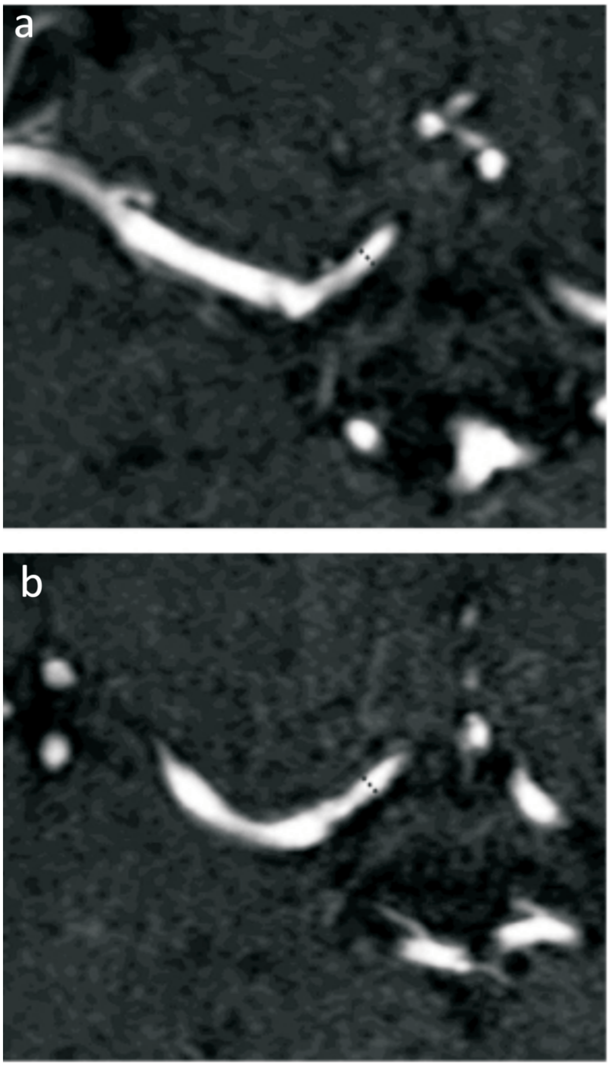

Figure 1. Differences in right A1 segment diameter between an adult and an adolescent. In a 57-year-old woman, the right A1 segment was 1.6 mm in diameter (dotted line in a), while it was 2.4 mm in a 12-year-old girl (dotted line in b).

2.3. Comparison between groups

The results of arterial measurements in the adult group were compared with those of the adolescent group. First, we compared the median diameter of each segment of the CoW in each group. The interquartile range (IQR), defined as the difference between the 75th and 25th percentiles of the vessel diameters in the group, was used to represent variation.

Next, all seven CoW segments for each subject were scored as either 'patent' or 'not patent', for three different thresholds defining

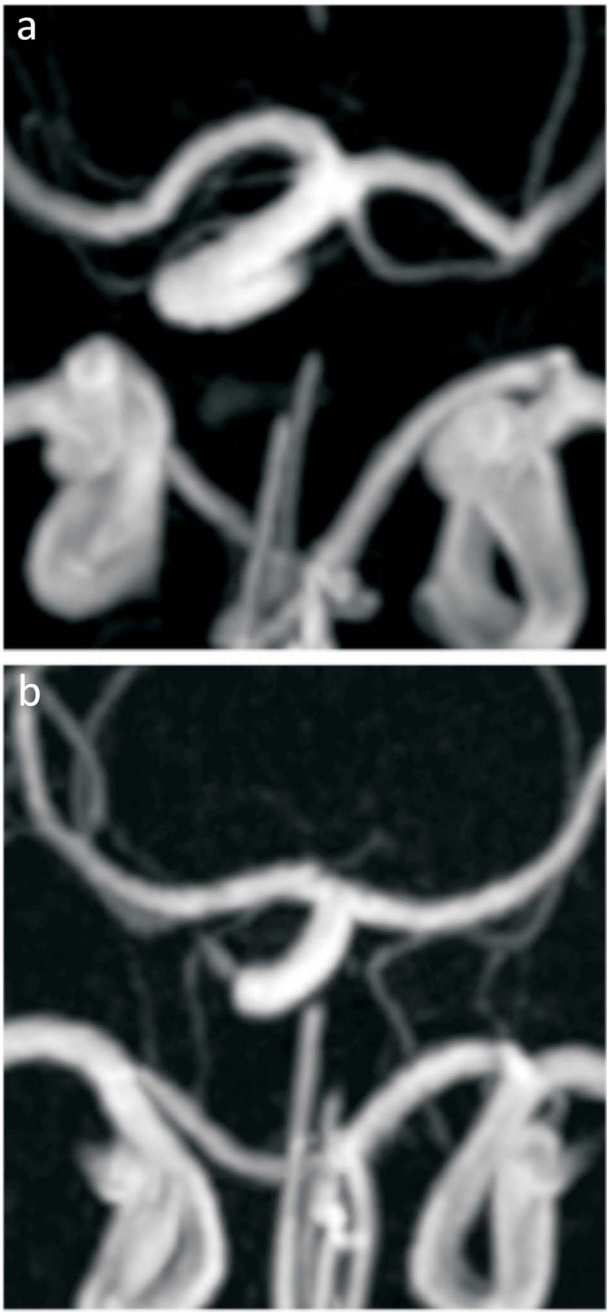

Figure 2. Bilateral PCom segments were not visible in an adult (a). However, bilateral PCom segments could be clearly delineated in an adolescent (b).

vascular patency: (1) visible on TOF-MRA, (2) at least 0.8 mm, and (3) at least 1 mm. Therefore, there were 128 theoretically possible patterns of patency for the CoW (2 levels of patency, calculated to the power of 7 CoW segments), for each of the three patency thresholds. We compared the patterns of patency in the CoW in the adult group with that in the adolescent group to investigate whether the aging process decreased vessel diameter or caused more occlusion of segments in the CoW. If aging affected vessel diameter or occlusion, more CoW patterns would be observed in the adult group than in the adolescent group.

We further recorded the patent counts in each vessel segment, and compared the patency rate of the anterior half-circle (bilateral A1 segments and ACom), the posterior half-circle (bilateral P1 segments and bilateral PCom segments), and the right and left half-circles (ipsilateral A1 segment, ipsilateral PCom segment, and ipsilateral P1 segment), between the adult and adolescent groups. Half-circles were recorded as patent only if all its segments were visible on TOF-MRA; if any segment was invisible, the respective half-circle was recorded as not patent.

2.4. Statistical analysis

SPSS 22 (IBM, Armonk, NY) was used to perform statistical analyses. The Mann-Whitney U test was used to detect the between-group differences in vessel diameters. Chi-square tests with Fisher's exact tests were used to detect the between-group differences in gender, the underlying atherosclerotic risk factors, and the patency rate of all half-circles. T-tests were used to evaluate the mean ages between the two groups. A p value < 0.05 was considered significant for all tests.

3. Results

3.1. Subject demographics

The details of subject demographics are given in Table 1. Male subjects comprised 56% of the total in both groups. The mean age in the adult group (54.48 ± 2.83 years) was significantly higher than the adolescent group (13.80 ± 2.49 years, $p < 0.001$). No subjects in the adolescent group had any underlying atherosclerotic risk factors, whereas there was significantly higher rates of hypertension (12%, $p < 0.05$), diabetes (8%, $p < 0.05$), and hyperlipidemia (22%, $p < 0.001$) in the adult group.

3.2. Diameter of vessel segments

The results from the measurement of CoW vessel segments are shown in Figure 3. The median diameter of CoW vessel segments in the adult group were as follows: right A1, 1.7 mm (0.6 mm); left A1, 1.7 mm (0.5 mm); ACom, 1.0 mm (1.1 mm); right PCom, 1.0 mm (1.6 mm); left PCom, 0.9 mm (1.4 mm); right P1, 1.7 mm (0.8 mm); left P1, 1.7 mm (0.8 mm). The median diameter of CoW vessel segments in the adolescent group were as follows: right A1, 2.0 mm (0.6 mm); left A1, 2.1 mm (0.6 mm); ACom, 1.2 mm (0.7 mm); right PCom, 1.2 mm (1.3 mm); left PCom, 1.2 mm (0.4 mm); right P1, 2.0 mm (0.6 mm); left P1, 2.0 mm (0.4 mm). Significant between-group differences were found for the right A1 ($p = 0.007$), left A1 ($p < 0.001$), ACom ($p = 0.046$), right P1 ($p < 0.001$), and left P1 segments ($p = 0.005$). The remaining two segments were not significantly different (right PCom, $p = 0.807$; left PCom, $p = 0.446$).

To exclude the underlying atherosclerotic risk factors in the adult group, a similar analysis of diameter of vessel segments was conducted again, without including individuals with hypertension, diabetes, and hyperlipidemia. Significant between-group differences were found for the right A1 ($p = 0.005$), left A1 ($p < 0.001$), right P1 ($p < 0.001$), and left P1 segments ($p = 0.008$). The remaining three segments were not significantly different (ACom, $p = 0.068$; right PCom, $p = 0.827$; left PCom, $p = 0.676$). The result after removing individuals with underlying atherosclerotic risk is similar to that including all subjects. Only ACom segment turned insignificant after excluding risk factors.

Table 1
Demographics of the two groups.

Group (case number)	Adult (50)	Adolescent (50)	p
Male (%)	28 (56%)	28 (56%)	1.000
Mean age (years)	54.48 ± 2.83	13.80 ± 2.49	< 0.001
Hypertension (%)	6 (12%)	0 (0%)	0.012
Diabetes (%)	4 (8%)	0 (0%)	0.042
Hyperlipidemia (%)	11 (22%)	0 (0%)	< 0.001

3.3. Patterns of CoW patency under different thresholds

With reference to the three thresholds used to define vessel patency in the CoW segments (i.e., visible on TOF-MRA, at least 0.8 mm, and at least 1 mm), the adult group showed 16, 18, and 20 different patterns of patency in the CoW, respectively, while the adolescent group showed 7, 8, and 8 different CoW patency patterns.

3.4. Patency of vessel segments and half-circles

Patency counts of each vessel segment are shown in Table 2. The patency rate of the anterior half-circle was not significantly different between the adult group (72%) and the adolescent group (86%) ($p = 0.086$). However, there were lower patency rates in the adult group than the adolescent group for the posterior half-circle (adult, 24%; adolescent, 60%; $p < 0.001$), the left half-circle (adult, 44%; adolescent, 82%, $p < 0.001$), and the right half-circle (adult,

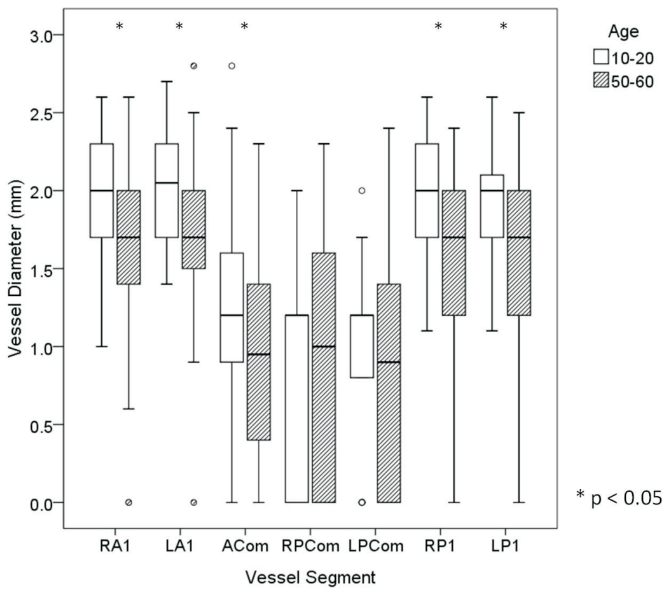

Figure 3. The comparison of the seven segments of the circle of Willis between the adolescent group (age: 10–20 years) and the adult group (age: 50–60 years). The adult group has significantly smaller right A1 (RA1) ($p = 0.007$), left A1 (LA1) ($p < 0.001$), ACom ($p = 0.046$), right P1 (RP1) ($p < 0.001$), and left P1 (LP1) ($p = 0.005$). There is no significant difference in the right Pcom (RPCom) and left Pcom (LPCom) segments.

Table 2
Patent counts in each vessel segments between the two groups.

	Adult (n)	Adolescent (n)
RA1	48	50
LA1	49	50
Acom	38	43
RPcom	30	36
LPcom	28	41
RP1	44	50
LA1	44	50

Table 3
The patency rates of the half circles between these two groups.

Half-circle	Adult (n, %)	Adolescent (n, %)	*p*
Anterior	36 (72%)	43 (86%)	0.086
Posterior	12 (24%)	30 (60%)	< 0.001
Left	22 (44%)	41 (82%)	< 0.001
Right	23 (46%)	36 (72%)	< 0.001

46%; adolescent, 72%; $p < 0.001$). The details of patency in the half-circles are listed in Table 3.

4. Discussion

The present study found that the diameter of the bilateral A1 segments, the ACom, and the bilateral P1 segments, but not the bilateral PCom segments, were significantly smaller in the adult group compared to the adolescent group. Further, the number of different patterns of the CoW was always higher in the adult group than in the adolescent group, whereas the patency rates of the posterior, left half-circle, and right half-circle were significantly lower in the adult group than in the adolescent group.

The results of smaller CoW segments in the adult are consistent with previous reports.[4,5] In a computational fluid dynamic simulation study, Alnæs et al. confirmed that differences in vessel radii and the angle of bifurcation influenced the magnitude of the wall shear stress,[11] which is a significant factor in vessel remodeling and in the development of vascular pathogenesis.[12,13] Additionally, atherosclerotic stages in the medium and small arteries of the CoW, such as the ACom and PCom segments and the anterior cerebral arteries, have been shown to differ from the large arteries, such as the internal carotid arteries (ICA), the basilar artery and the vertebral arteries.[14] The authors posit that the lower degree of plaque accumulation observed in medium and small arteries, compared to large arteries, is a consequence of the lower blood pressure in the small vessels, which activates the intrinsic mechanism of atherosclerosis to a lesser degree. The communicating arteries play a major role in maintaining collateral supply, and their direction of flow depends on the blood pressure of their main supplying arteries; therefore, another possible explanation is that the collateral flow in the CoW is affected by the large in-flow arteries.[15] In the ACom, hemodynamic alterations in the ICA cause a reversal of flow direction in order to maintain sufficient arterial perfusion, for example, when blood pressure and lumen diameter are not symmetrical. The interaction between various hemodynamic factors, with wall shear stress playing a major role, eventually leads to a general reduction in vessel radius. In our study, the vessel diameter of the bilateral PCom segments were not significantly different, but a similar study comparing CoW vessel diameters between various age groups revealed no significant differences in the ACom and the left PCom segments.[5] The observed inconsistencies can be explained by the unique hemodynamics of the communicating arteries, wherein flow direction depends on the pressure in the connecting vessels. The resulting alterations in wall shear stress on the endothelium generates variable remodeling conditions in the communicating arteries;[16] however, this process appears to have no significant relationship with age.

Surprisingly, despite a decrease in vessel diameter, the patency rate of the anterior half-circle was not significantly different between the two groups. Separate patency counts of the segments comprising the anterior half-circle (Table 2) showed fewer patent ACom segments and the bilateral PCom in the adult group than the adolescent group, whereas patency in bilateral P1 segments were comparable between groups. However, most bilateral A1 segments were patent, and only three were not visible in the adult group, while all were visible in the adolescent group. The higher rate of patency in the bilateral A1 compared to the other segments comprising the anterior half-circle in the adult group might have resulted from differences in histopathology between the anterior and the posterior circulation during aging. Specifically, posterior brain arteries show greater concentric intima thickening than their anterior counterparts.[17] This leads to differences in hemodynamics between the anterior and the posterior half-circle, which in turn affect wall shear stress, blood pressure, blood flow, vessel morphology, and geometry.

In a large study analyzing the brain arterial diameters by the TOF-MRA, participants with a higher difference of luminal diameters as compared to average individuals have a higher incidence of vascular events.[18] It comes as no surprise that those with the smallest diameters have a higher rate for death, vascular death, vascular events, and ischemic stroke. Our study demonstrates aging effect patterns of vascular patency and vessel diameter of CoW, which predispose a higher risk of ischemic stroke and other vascular events in the older age group. In a previous study, Chuang et al. suggest that PCom hypoplasia alone, even with patent ICA, contributes to a higher risk of ischemic stroke, i.e., a “low flow” infarction in the thalamus.[19] Similarly, in surgical contexts, an incomplete CoW predisposes patients undergoing a transient closure of the carotid artery to cerebral ischemia.[20] Our findings demonstrate age-related changes in the CoW, which may pose a threat of ischemic insult caused by compromised cerebral blood flow, especially in older adult patients.

The relatively small sample size of our study poses a limitation, and a larger study might be necessary to obtain more representative results. Although we excluded individuals with neurovascular disease and neoplasms, a detailed clinical history that includes information such as current medication was not fully accessible. In addition, a limitation of using TOF-MRA is that slow flow cannot span the entire volume before complete saturation, which results in signal loss artifacts that may be misinterpreted.[21] An alternative to TOF-MRA is phase-contrast MRA, which is also capable of determining flow direction and is much more sensitive to flow velocities, but at the price of longer acquisition times.

5. Conclusion

In conclusion, the CoW vessels change with age, resulting in markedly decreased vessel diameters in most segments.

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