Original articles

Usefulness of the acceleration time ratio in the diagnosis of internal carotid artery origin stenosis

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Short title: The acceleration time ratio for diagnosis of internal carotid artery origin stenosis

Abstract

Purpose: Acceleration time (AcT) ratio on internal carotid artery (ICA) is increased in ICA stenosis. However, there are few reports that directly compared AcT ratio to digital subtraction angiography (DSA) findings.

Methods: We evaluated 177 vessels with DSA and carotid artery ultrasonography. AcT ratio was calculated as AcT of ICA (ICA-AcT)/AcT of the ipsilateral common carotid artery (CCA). We evaluated the correlation of DSA-NASCET stenosis with the origin of ICA or the peak systolic velocity (ICApsv) in the stenotic region, ICApsv/peak systolic velocity of CCA (CCApsv), ICA-AcT and AcT ratio. Sensitivity and specificity for stenosis ≥ 70% were calculated based on the ICApsv, ICApsv/CCApsv, ICA-AcT, and AcT ratio.

Results: Using NASCET criteria, 34 vessels had 70% or greater stenosis. DSA-NASCET showed a significant positive correlation with ICApsv, ICApsv/CCApsv, ICA-AcT and AcT ratio ($p < 0.0001$). When the cut-off value for ICApsv was set at 176 cm/s, ICApsv/CCApsv at 2.42, ICA-AcT at 0.095 s, and the AcT ratio at 1.35, the sensitivity was 97.1%, 97.1%, 82.4%, and 97.1%, and the specificity was 94.4%, 91.0%, 83.2%, and 83.2%, for DSA-NASCET ≥ 70%, respectively.

Conclusion: AcT ratio is a beneficial parameter for evaluating ICA stenosis as well as ICApsv and ICApsv/CCApsv.

Keywords

Acceleration time ratio, peak systolic velocity, Internal carotid artery stenosis, digital subtraction angiography, acoustic shadow

Introduction

A management of atherosclerotic risk factors and medications such as statins are considered for asymptomatic extracranial internal carotid artery (ICA) stenosis but carotid artery stenting (CAS) and carotid endarterectomy (CEA) are also considered for patients with an expected long-term prognosis**[1]**. For symptomatic extracranial ICA stenosis, CAS and CEA are considered in addition to best medical treatment for cases of severe stenosis of 70% or more based on the North American Symptomatic Carotid Endarterectomy Trial (NASCET)**[2]**. Therefore, from the viewpoint of primary and secondary prevention of ischemic stroke, non-invasive and simple diagnosis of extracranial internal carotid artery (ICA) stenosis is important, and carotid artery ultrasonography is widely used for diagnosing extracranial ICA stenosis by carotid artery ultrasonography.

Peak systolic velocity (PSV) is widely used for the diagnosis of extracranial ICA stenosis by carotid artery ultrasonography. When PSV is 125 cm/s or higher, stenosis of 50% or more is suspected, but when PSV is 230 cm/s or higher, stenosis of 70% or more is indicated based on the North American Symptomatic Carotid Endarterectomy Trial (NASCET)**[3]**. In addition, ICA to common carotid artery (CCA) PSV ratio is also useful for diagnosis of extracranial ICA stenosis according to NASCET criteria**[4]**.

However, acoustic shadows will appear on ultrasonography when there is calcification, making observation of that region difficult. Therefore, diagnosis of stenosis becomes impossible by directly measuring PSV when there is circumferential calcification of the carotid arteries.

Conversely, it is known that the acceleration time (AcT) on the peripheral artery is extended where is stenosis and the usefulness of diagnosing of extracranial ICA stenosis has been suggested**[5-7]** in addition to diagnosis of restenosis after CAS**[8]**. However, there are a limited number of subjects in whom AcT to findings of cerebral angiography were directly compared **[7]** and, moreover, only one study has been conducted to directly compare the AcT ratio, which is calculated by dividing the AcT of ICA by the AcT of the ipsilateral CCA, and cerebral angiography**[8]**. However, in their study, only subjects receiving CAS was included.

Therefore, we examined the usefulness of the AcT ratio for diagnosing extracranial ICA stenosis, especially ICA origin stenosis.

Methods

The subjects were 97 consecutive patients (mean age: 68.4 years, SD: ±10.8, 76 men) that were hospitalized in the Department of Neurology, Dokkyo Medical University, for atherothrombotic cerebral infarction and received both carotid artery ultrasonography and digital subtraction angiography (DSA) between April 1, 2014 and March 31, 2017. Seventeen vessels were excluded because the internal carotid arteries were obstructed at their origins; therefore, 177 vessels were retrospectively analyzed.

HT, YT, KI, AI, HI, AS, and MO performed carotid artery ultrasonography using SSA-770A (Toshiba, Japan). Ultrasound imaging was performed with the subject lying supine, the head turned away from the side being scanned and the neck extended.

Measurement of pulsed-wave Doppler of CCA was carried out approximately 2 cm from the carotid sinus using a linear-array probe (5–11 MHz). Pulsed-wave Doppler of ICA was performed in the region approximately 3.5 cm (3.50 ± 0.92 cm) from the ICA bifurcation using a convex-array probe (1.9–6 MHz). The sample volume of the pulsed-wave Doppler was set at 1/2 or longer than the vessel diameter, and the Doppler insonation angle against the direction of jet flow or the blood vessel direction was 60 degrees or smaller. Additionally, power or color Doppler was used to observe the origin of the ICA and the PSV (ICApsv) was measured after setting the sample volume in a way that sufficiently covers the stenotic lesion for cases in which stenosis was present. We measured the ICApsv at the origin of the ICA in cases in which stenosis was not present. We measured the PSV that was higher around the acoustic shadow in cases in which the point at which stenosis was most severe was unclear due to calcification. The ICApsv/CCApsv is calculated as ICApsv/(PSV of the ipsilateral CCA). The measurements of ICApsv and CCApsv were performed by pulsed-wave Doppler at the maximum peak of the waveform **[4]** **(Fig. 1)**.

Measurement of AcT was carried out in accordance with the report by Takekawa et al.**[6]** **(Fig. 1)**. More specifically, we showed the monomodal peak pattern and defined AcT as the time up to PSV for cases where there was no distinct inflection point. We showed the monomodal peak pattern and defined AcT as the time up to the inflection point when there was a distinct inflection point. When there were bimodal peaks, AcT was defined as the time up to the first peak. AcT, defined as time from initiation of the upstroke to the first maximum peak of the waveform, was measured by the average of five heartbeats. We calculated the AcT for ICA (ICA–AcT) and CCA. The AcT ratio is calculated as ICA−AcT/(AcT of the ipsilateral CCA).

ICA origin stenosis diagnosed via DSA was evaluated by NT using the NASCET method (DSA-NASCET).

We evaluated the correlation of DSA-NASCET with ICApsv, ICApsv/CCApsv, ICA-AcT and AcT ratio using the Pearson correlation coefficient, and examined whether DSA-NASCET was predictable based on each item using single regression analysis. Also, we calculated the sensitivity and specificity for DSA-NASCET ≥ 50% and ≥ 70% based on the ICApsv, ICApsv/CCApsv, ICA-AcT, and AcT ratio using a receiver operating characteristic (ROC) curve. Then, positive predictive value (PPV), negative predictive value (NPV) and accuracy for these parameters were calculated.

Also, we calculated the inter-rater reliability for the ICA-AcT, AcT ratio, ICApsv and ICApsv/CCApsv of five blood vessels using the intraclass correlation coefficients (ICC). IBM SPSS (ver. 24.0, Tokyo, Japan) was used for statistical processing and plotting, and $p < 0.05$ was considered statistically significant.

HT, KS and HK were involved in overseeing the entire study.

Results

1. All vessels

There were 55 blood vessels (31.1%) with DSA-NASCET ≥ 50% and 34 blood vessels (19.2%) with DSA-NASCET ≥ 70%. No patient underwent CAS. The ICCs for ICApsv, ICApsv/CCApsv, ICA-AcT and AcT ratio were 0.988, 0.996, 0.888 and 0.842, respectively.

DSA-NASCET showed correlations with ICA-AcT ($r = 0.647$, $p < 0.0001$), AcT ratio ($r = 0.744$, $p < 0.0001$), ICApsv/CCApsv ($r = 0.670$, $p < 0.0001$) and with ICApsv ($r = 0.833$, $p < 0.0001$). Furthermore, we could predict DSA-NASCET based on the ICApsv, ICApsv/CCApsv, ICA-AcT, and AcT ratio using simple linear regression analysis **(Fig. 2a, b, c, d)**. Also, when we excluded the vessel showing the left ICApsv/CCApsv of 28.6 (left carotid artery, Fig. 1b dotted arrow) in an 86-year-old male patient, the correlation coefficient between ICApsv/CCApsv and DSA-NASCET increased to 0.788.

On observing the diagnostic yield for DSA-NASCET ≥ 50% on the ROC curve, the area under the curve (AUC) of ICApsv was 0.985, ICApsv/CCApsv was 0.970, ICA-AcT was 0.861, and the AcT ratio was 0.958, indicating increased usefulness of the ICApsv, ICApsv/CCApsv and AcT ratio (**Fig. 3a**). When the cut-off value of ICApsv was set at 112 cm/s, ICApsv/CCApsv at 1.95, ICA-AcT at 0.085 s, and AcT ratio at 1.31, the sensitivity was 94.5%, 87.3%, 80.0%, and 94.5%, and the specificity was 93.4%, 96.5%, 82.0%, and 91.0%, respectively. Meanwhile, the AUC for DSA-NASCET ≥ 70% was 0.978 for ICApsv, 0.963 for ICApsv/CCApsv, 0.888 for ICA- AcT, and 0.945 for the AcT ratio (**Fig. 3b**). Additionally, when the cut-off value for ICApsv was set at 176 cm/s, ICApsv/CCApsv at 2.42, ICA-AcT at 0.095 s, and the AcT ratio at 1.35, the sensitivity was 97.1%, 97.1%, 82.4%, and 97.1%, and the specificity was 94.4%, 91.0%, 83.2%, and 83.2%, respectively.

2. The diagnostic accuracy of the combined parameters of AcT and PSV

The diagnostic yield of DSA-NASCET ≥ 50% had slightly lower sensitivity and NPV compared with ICApsv; However accuracy in the setting of ICApsv ≥ 112 cm/s and AcT ratio ≥ 1.31 showed highest (97.2%) (**Table 1**).

In contrast, the diagnostic yield of DSA-NASCET ≥ 70% were highest in the setting of 1) ICApsv ≥ 176 cm/s or 2) ICApsv ≥ 176 cm/s and AcT ratio ≥ 1.35 (94.9%). The diagnostic yield of combination of ICApsv and AcT ratio had slightly lower sensitivity and NPV, but showed higher specificity and PPV, compared to that of ICApsv only (**Table 1**).

3. Vessles with calcification-related acoustic shadow

We identified 30 vessels with calcified plaque-related acoustic shadow which hampered a direct measurement of ICApsv. Among them, 17 vessels (56.7%) had DSA-NASCET ≥ 50% and 10 vessels (33.3%) had DSA-NASCET ≥ 70%. Median calcification length was 0.9 cm (range, 0.6-1.6). DSA-NASCET showed correlations with ICApsv ($r = 0.661$, $p < 0.0001$), ICApsv/CCApsv ($r = 0.683$, $p < 0.0001$), ICA-AcT ($r = 0.639$, $p < 0.001$) and AcT ratio ($r = 0.670$, $p < 0.0001$).

In contrast, on observing the diagnostic yield for DSA-NASCET ≥ 50% on the ROC curve, the AUC of ICApsv was 0.516, ICApsv/CCApsv was 0.914, ICA-AcT was 0.839, AcT ratio was 0.887 (**Fig.3c**). Meanwhile, the AUC for DSA-NASCET ≥ 70% was 0.648 for ICApsv, 0.895 for ICApsv/CCApsv, 0.753 for ICA-AcT, and 0.860 for the AcT ratio (**Fig. 3d**). However, the AUCs for DSA-NASCET ≥ 50% or DSA-NASCET ≥ 70% for ICApsv , ICApsv/CCApsv , ICA-AcT and

AcT ratio in the 30 vessels with acoustic shadow were smaller compared to those in all 177 vessels. Particularly, the AUC for ICApsv was smaller in these vessels.

Discussion

The present study focused on atherothrombotic cerebral infarction, and compared DSA-NASCET to carotid artery ultrasonography, that is, ICApsv, ICApsv/CCApsv, ICA- AcT, and the AcT ratio, to examine the usefulness of these items in diagnosing the level of stenosis. Our results showed that DSA-NASCET had a significantly positive correlation with ICApsv, ICApsv/CCApsv, ICA- AcT, and AcT ratio. Based on the AUC of the ROC curve, ICApsv and ICApsv/CCApsv had the highest utility, followed by AcT ratio. Among vessels with calcified lesions, we showed utility of ICApsv/CCApsv and AcT ratio. Furthermore, when these parameters were combined with ICApsv and AcT ratio, the diagnostic yield might be significantly improved.

Measuring the PSV in the stenotic region by pulsed-wave Doppler is known to be effective and is widely used for prediction of DSA-NASCET stenosis **[3]**. It has been reported that PSV >125-150 cm/s predicts NASCET 50–69% stenosis and PSV > 200-230 cm/s predicts NASCET 70–99% stenosis **[3,10]**. The utility of ICApsv/CCApsv has also been reported. ICApsv/CCApsv of 2-4 indicates NASCET 50–69% stenosis and ICApsv/CCApsv > 4 indicates NASCET 70–89% stenosis **[4]**. However, in our study, we determined the cut-off values lower than the previous studies. In order to measure PSV, it is essential to correct the Doppler insonation angle so that it is equal to or smaller than 60 degrees**[11]**. However, the blood flow direction at the stenotic lesion is not always parallel to the blood vessel direction. Because of this, there are differences in the PSV and percent stenosis depending on whether the Doppler insonation angle is used as a reference or the blood vessel direction is used as a reference**[12]**. Therefore, we believe that cut-off values for percent stenosis diagnosis by ICApsv may vary from study to study. Similarly, cut-off values for ICApsv/CCApsv using ICApsv may differ depending on the studies. In fact, in our study, we did not have a fixed rule as to whether the Doppler insonation angle should be corrected in accordance with the blood vessel direction or the jet flow direction. Also, we used the ICApsv that was higher around the acoustic shadow for cases where the point with the most severe stenosis was unclear due to calcification. Therefore, it cannot be ruled out that we obtained cut-off values for ICApsv or

ICApsv/CCApsv similar to those in previous studies because we used the ICApsv at the point with the most severe stenosis.

Conversely, a few studies have reported the diagnostic yield of AcT or AcT ratio on ICA stenosis (**Table 2**). A part of the study by Tamura et al **[7]** and the study by Kamiya et al **[8]** directly compared AcT or AcT ratio and DSA-NASCET. However, the study by Kamiya et al [8] included only the vessels in which CAS was performed. Comparing to the previous reports, the cut-off value of ICA-AcT predicting stenosis was lower in our study. In general, AcT often refers to the time required to reach PSV. However, we defined AcT as the time up to the inflection point in cases with monomodal peak pattern with a distinct flection point and we defined AcT as the time up to first peak in cases with bimodal peaks. Therefore, it is possible that shorter cut-off values for ICA-AcT were obtained in previous studies than those in the present study.

In the study by Tamura et al **[7]**, DSA was performed in 11 vessels, and among the vessels with DSA-NASCET $\geq$ 10% mean ICA-AcT was 138.5$\pm$26.3s. However, AcT ratio was not shown in those vessels. DSA-NASCET and AcT ratio have not been compared in large sample studies. Takekawa et al**[6]** have compared AcT ratio and diameter stenosis used in the criteria of the European Carotid Surgery Trial**[14]** using carotid artery ultrasonography. However, the cut-off value for AcT ratio was lower in our study. An accurate evaluation of the vascular lumen is possible with DSA but it is difficult to evaluate the vascular adventitia and the vascular endometrium without plaques. Therefore, the possibility cannot be ruled out that there was an error in the evaluation using the NASCET method, which makes use of the ratio of a normal vascular diameter and the vascular diameter of the stenotic region.

Although in a small sample size (30 vessels), we suggest the usefulness of ICA-AcT and AcT ratio as well as ICApsv/CCApsv in vessels with calcification-related acoustic shadow which interfered with direct measurement of ICApsv in the stenotic lesions. Our observation from the usefulness of ICA-AcT and AcT ratio in cases with the median length of calcified lesions of 0.9cm suggests ICA-AcT and AcT ratio could be also useful in cases with long calcified lesions.

There are several limitations to the present study. One is that there was no fixed rule for the correction of the Doppler insonation angle. Moreover, there are cases where the ICApsv cannot be measured at the point where stenosis is most severe. Additionally, because evaluation using TTE was not conducted, we were unable to verify whether the influence of valvular heart disease and EF was excluded from the AcT ratio. Furthermore, the influence of ICA kinks was not evaluated. In the future, detailed investigation that takes these factors into consideration is required. Nevertheless, our study suggests a combined use of AcT ratio and other parameters will enable us to make an accurate diagnosis of stenosis rate. We believe the usefulness of the AcT ratio as shown in the present study will be valuable in cases where the ICApsv in the stenotic region cannot be measured directly because no study has directly compared the DSA-NASCET and the AcT ratio.

Conclusions

We compared ICApsv, ICApsv/CCApsv, ICA-AcT, and the AcT ratio to DSA-NASCET. Our results showed that the AcT ratio as well as ICApsv and ICApsv/CCApsv is highly useful. We believe that the AcT ratio is a useful evaluation method for diagnosing stenosis in cases where the ICApsv or ICApsv/CCApsv in the stenotic region cannot be measured owing to acoustic shadows caused by calcification.

Compliance with ethical standards

All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all subjects prior to study inclusion. The Institutional Review Board of Dokkyo Medical University Hospital approved this study.

Conflict of Interest

There are no financial or other relations that could lead to a conflict of interest.

References

1. Schenone AL, Cohen A, Shishehbor MH. Asymptomatic carotid artery disease: A personalized approach to management. Cleve Clin J Med 2015;82:855-63.

2. North American Symptomatic Carotid Endarterectomy Trial C, Barnett HJM, Taylor DW, et al. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991;325:445-53.

3. AbuRahma AF, Srivastava M, Stone PA, et al. Critical appraisal of the Carotid Duplex Consensus criteria in the diagnosis of carotid artery stenosis. J Vasc Surg 2011;53:53-9; discussion 9-60.

4. Oates CP, Naylor AR, Hartshorne T, et al. Joint recommendations for reporting carotid ultrasound investigations in the United Kingdom. Eur J Vasc Endovasc Surg 2009;37:251-61.

5. Takekawa H, Asakawa Y, Lee T, et al. Usefulness of acceleration time for assessment of stenosis in the extracranial internal carotid artery. Neurosonology 2009;22:79-82.

6. Takekawa H, Suzuki K, Takada E, et al. Acceleration time ratio for the assessment of extracranial internal carotid artery stenosis. J Med Ultrason (2001) 2014;41:63-7.

7. Tamura H, Akaiwa Y, Onda K. Usefulness of acceleration time for internal carotid artery origin stenosis. Ann Vasc Dis 2013;6:590-5.

8. Kamiya Y, Mori M, Kuriki A, et al. Evaluation of restenosis after carotid artery stenting using acceleration time in carotid ultrasonography. Neurosonology 2015;28:54-8.

9. Eckstein HH, Kuhnl A, Dorfler A, et al. The diagnosis, treatment and follow-up of extracranial carotid stenosis. Dtsch Arztebl Int 2013;110:468-76.

10. Koga M, Kimura K, Minematsu K, et al. Diagnosis of internal carotid artery stenosis greater than 70% with power Doppler duplex sonography. AJNR Am J Neuroradiol 2001;22:413-7.

11. The Joint Committee of the Japan Academy of Neurosonology and the Japan Society of Embolus Detection and Treatment on Guideline for Neurosonology. Carotid Ultrasound Examination. . Neurosonology 2006;19:49-67.

12. Igarashi H, Okabe R, Okamura M, et al. Influence of Doppler angle on peak systolic velocity for diagnosis of internal carotid artery stenosis. Neurosonology 2017;30:8-12.

13. Naylor AR, Lin PH, Chaikof EL. Carotid artery disease. In: Davies AH, Brophy CM, editors. Vascular surgery. London: Springer; 2010. p. 155-80.

14. European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998;351:1379-87.