Original Article

Semi-automatic computed tomography angiography quantification assessment is an alternative method to digital subtraction angiography in intracranial stenosis: a multicenter study

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Background: The recent randomized controlled trials studying intracranial atherosclerotic stenosis (ICAS) have used digital subtraction angiography (DSA) to quantify stenosis and enroll patients. However, some disadvantages of DSA such as invasive features, contrast agent overuse, and X-ray radiation overexposure, were not considered in these studies. This study aimed to explore whether computed tomography angiography (CTA) with semi-automatic analysis could be an alternative method to DSA in quantifying the absolute stenotic degree in clinical trials.

Methods: Patients with 50–99% ICAS were consecutively screened, prospectively enrolled, and underwent CTA and DSA between March 2021 and December 2021 at 6 centers. This study was registered at www.chictr.org.cn (ChiCTR2100052925). The absolute stenotic degree of ICAS on CTA with semi-automatic analysis was calculated by several protocols using minimal/maximum/mean diameters of stenosis and reference site from a semi-automatic analysis software. Intraclass correlation coefficient (ICC) was used to evaluate the reliabilities of quantifying stenotic degree on CTA. The optimal protocol for quantifying ICAS on CTA was explored. The agreements of quantifying ICAS in calcified or non-calcified lesions and 50–69% or 70–99% stenosis on CTA and DSA were assessed.

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Results: A total of 191 participants (58.8±10.7 years; 148 men) with 202 lesions were enrolled. The optimal protocol for quantifying ICAS on CTA was calculated as (1 – the minimal diameter of stenosis/the mean diameter of reference) × 100% for its highest agreement with DSA [ICC, 0.955, 95% confidence interval (CI): 0.944–0.966, P<0.001]. Among the 202 lesions, 80.2% (162/202) exhibited severe stenosis on DSA. The accuracy of CTA in detecting severe ICAS was excellent (sensitivity =95.1%, positive predictive value =98.1%). The agreements between DSA and CTA in non-calcified lesions (ICC, 0.960 *vs.* 0.849) and severe stenosis (ICC, 0.918 *vs.* 0.841) were higher than those in calcified lesions and moderate stenosis.

Conclusions: CTA with semi-automatic analysis demonstrated an excellent agreement with DSA in quantifying ICAS, making it promising to replace DSA for the measurement of absolute stenotic degree in clinical trials.

Keywords: Computed tomography angiography (CTA); digital subtraction angiography (DSA); intracranial atherosclerotic stenosis (ICAS); semi-automatic quantification

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Introduction

Quantifying intracranial atherosclerotic stenosis (ICAS) on digital subtraction angiography (DSA) by the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) method represents the gold standard (1). In the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) and the China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS) trials, focusing on endovascular treatment compared to medical treatment for reducing the recurrent stroke in symptomatic ICAS, DSA has been implemented to measure ICAS for deciding whether the patient fulfilled severe stenosis (70–99%) (2,3). However, in addition to its invasiveness, diagnostic DSA has other pitfalls including excess cost, contrast media use, time-consuming nature, and radiation exposure (4,5). Considering that clinical trials comparing the safety and efficacy of medical treatment and stenting in high-risk patients with ICAS are still needed, looking for a noninvasive diagnostic modality to measure ICAS is imperative to their success.

Noninvasive imaging modalities are frequently utilized for the evaluation of intracranial stenosis diseases (5-7). Computed tomography angiography (CTA) is a fast, cost-effective imaging modality for evaluating the severity of ICAS (diagnosed as mild, moderate, and severe stenosis) and has less contrast media volume and less radiation exposure compared with diagnostic DSA (8,9). However, measuring the absolute degree of ICAS on CTA has not been widely regarded as an alternative to DSA, due to small lumen diameter, vessel tortuosity, and calcification occurrence in intracranial arteries, based on various CTA reconstruction methods, including maximum intensity projection (MIP), multiplanar reconstruction (MPR), and volume rendering (VR) (10-15). With the development of computer-aided analysis, semi-automatic vessel stenosis evaluation methods (for example, Advanced Vessel Analysis software from GE medical systems; GE Healthcare, Chicago, IL, USA) based on multiple reconstructed images (including VR, curved MPR, oblique MPR, and lumen images) have been proposed. The accuracy and reproducibility of such methods have been successfully demonstrated in carotid and peripheral artery stenosis measurement compared with diagnostic DSA (16,17); however, they have not been implemented and validated in the quantification of ICAS compared with DSA.

The ongoing Drug Eluting Stenting and Aggressive Medical Treatment for Preventing Recurrent Stroke in Intracranial Disease (DREAM-PRIDE) trial (18) enrolled 70–99% of ICAS patients using the semi-automatic method on CTA. In the present study, we aimed to evaluate the reliability of measuring absolute stenotic degree of ICAS by a semi-automatic method on CTA compared with the DSA approach, and to determine the optimal protocol for quantifying ICAS on CTA. We present this article in accordance with the STARD reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1343/rc).

Methods

Study design and participants

This study is a prospective, multicenter, and hospital-based study which was registered at www.chictr.org.cn (ChiCTR2100052925). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University (No. KY2019-083-01). All participating hospitals/institutions were informed and agreed with the study. Written informed consent was provided by all participants or their legally authorized guardians. Patients with ischemic stroke ascribed to symptomatic moderate-to-severe ICAS (50–99%) from 6 centers were consecutively and prospectively enrolled between March 2021 and December 2021. All enrolled participants underwent both CTA scan and DSA procedure within 7 days after enrollment. The inclusion criteria were as follows: transient ischemic attack (TIA) or ischemic stroke due to intracranial internal carotid artery (ICA), the M1 segment of middle cerebral artery (MCA), basilar artery (BA), or intracranial vertebral artery (VA) moderate-to-severe stenosis suspected by CTA (≥50% on MIP or VR image) or magnetic resonance imaging (MRA; focal signal loss with the presence of a distal signal). The exclusion criteria were as follows: patients with a stenotic degree <50% confirmed on DSA; non-atherosclerotic disease including Moyamoya disease, intracranial artery dissection; total occlusion of the responsible artery; in-stent restenosis; or images with various artifacts that impact the measurements of ICAS.

Stenosis and reference sites selection

Selection of stenosis and reference sites at the responsible artery was based on the WASID method (1). After reviewing the responsible artery on CTA (VR mode) and DSA, the stenosis and reference sites were consistently identified on CTA and DSA by 2 experienced neurologists (with >10 years of experience) with consensus.

Quantification of ICAS by CTA

The details of CTA scan parameters and contrast agent methods of 6 centers are shown in the Table S1. The axial images were reconstruction by using the standard algorithm. The CTA axial raw data from 6 centers were loaded on a semi-automated vessel analysis software (GE Advantage Workstation, version AW4.7, GE Healthcare) and reformatted (*Figure 1A*,*1B*). A 3-dimensional (3D) VR image was created on the workstation (*Figure 1C*). The operators selected the starting and ending points of the interested vessel lumen by browsing the VR image (the vessel lumen of interest needed to cover at least the stenosis site and the proximal and distal reference site). A central lumen line was then automatically performed by the software (*Figure 1D*, green line), and the selected vessel lumen was meanwhile displayed to the operators as the curved MPR, axial MPR, oblique MPR (axial vessel view oriented perpendicular to the central lumen line), and lumen MPR (i.e., stretched vessel view). The window width and level were set to 700 and 200 Hounsfield units (HU), but the width/level setting were allowed to be adjusted to best visualize the contrast filled lumen. If the automatically generated central lumen line tracked the lumen poorly, a manual vessel tracking was conducted on the curved MPR, in which the necessary angle adjustment was allowed to best display the lumen center (*Figure 1D*, red line).

The region of interest (ROI) indicator (*Figure 1E*, green coil) was then automatically rendered by the software on the oblique MPR at each tracking site, outlining the true cross-sectional area of contrast filled lumen. The minimal diameter and maximal diameter of the generated ROI indicator at the tracking site were automatically measured and displayed on the oblique MPR (*Figure 1E*), and its mean diameter was automatically measured and displayed on the lumen MPR (*Figure 1E*). If the ROI indicator of the stenosis site on the oblique MPR was visually estimated to fall outside the range of the actual vessel lumen, manual correction was applied to rectify measurement generated from automatic recognition. All operations on the oblique MRP were performed at the maximum zoom factor that could be achieved.

The diameters of stenosis site and reference site, measured automatically on the semi-automated vessel analysis software, were used to calculate the absolute stenotic degree. The absolute stenotic degree was calculated as (1 – the diameter at the stenosis site/the diameter at the reference site) × 100% (1). Considered minimal, maximal, and mean diameters generated both in stenosis site and reference site (*Figure 2*), there were 9 permutations of the absolute stenotic degree calculated by CTA.

The software identifies calcifications in the arteries within a ROI in every slice as areas with density >130 HU. At least 3 contiguous pixels with HU >130 is registered as calcification (19).

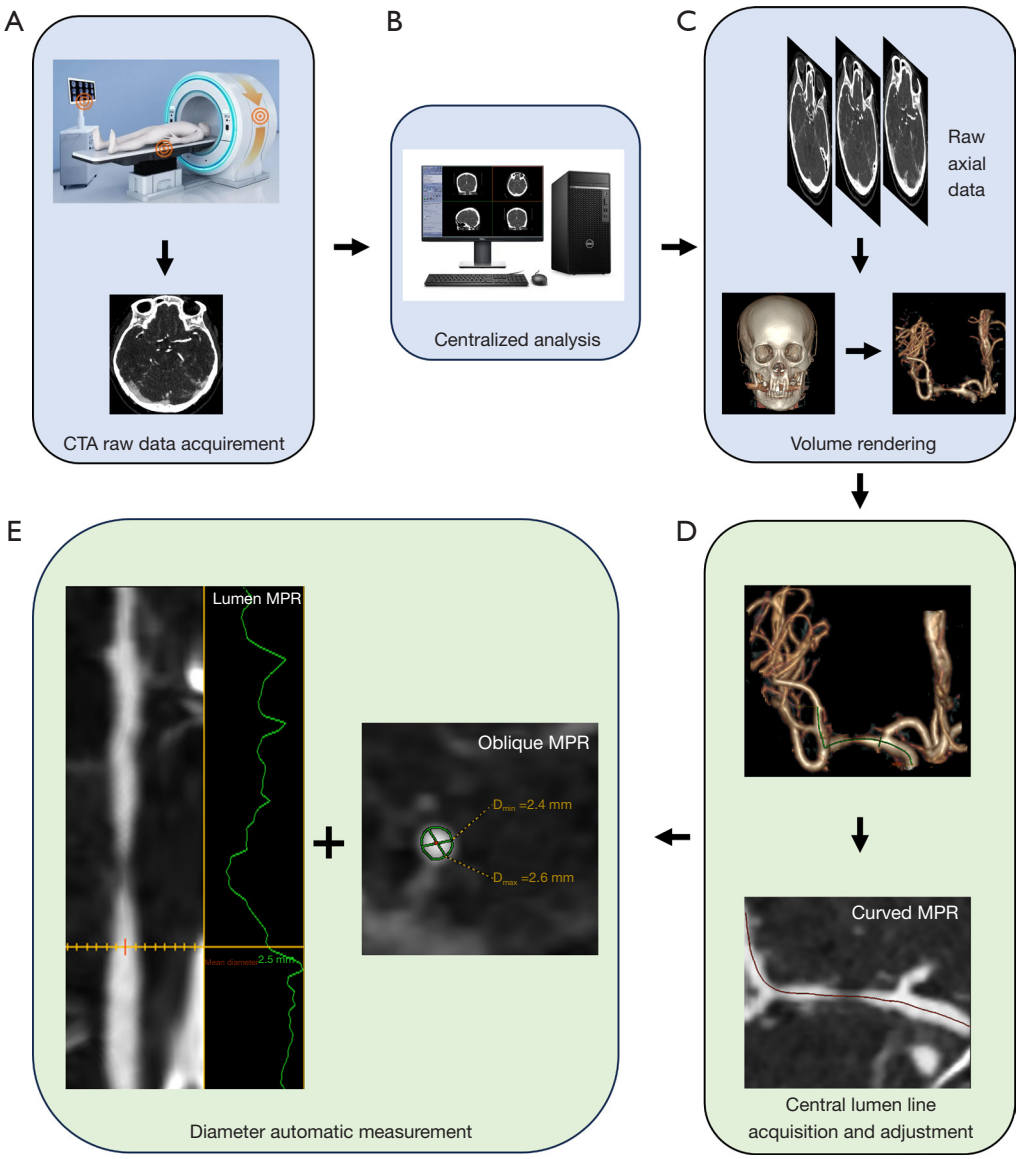

Figure 1 Process framework of imaging data generation and analysis. (A) CTA axial raw data were acquired from 6 centers; (B) imaging data from 6 centers were centrally analyzed by a semi-automated vessel analysis software (Advantage Workstation). The steps of centralized analysis were as followed: a volume rendering image was created from the raw axial data (C); a central lumen line was automatically acquired and manually adjusted (D); diameters (including minimal diameter, maximal diameter, and mean diameter) of stenosis site and reference site were automatically measured (E). CTA, computed tomography angiography; MPR, multiplanar reconstruction.

The degree of ICAS was independently semi-automatedly measured by 2 experienced neurologists (with >10 years of experience), using 1 display (MVCD-1619 AW GE) with identical resolution, contrast, color gamut, and colorimetric. Then, the average of their measuring was calculated and recorded. At 1 month after the first measurement, the CTA raw data of the first 30 patients were analyzed and measured by the same neurologist for a second time to verify intra-observer reproducibility.

Quantification of ICAS by DSA

After transfemoral artery puncture under either local or general anesthesia, angiography was performed in all

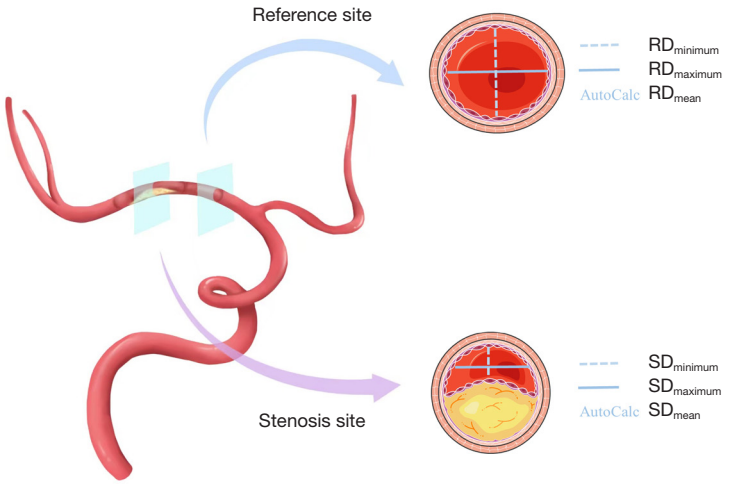

Figure 2 Schematic diagram of the stenosis degree calculated by CTA. The degree of stenosis was calculated as (1 – the diameter at the stenosis site/the diameter at the reference site) × 100%. Considering the minimal, maximal, and mean diameters obtained from semi-automatic vessel analysis software in every site, there were 9 permutations of the degree of stenosis by CTA. RD, reference diameter; SD, stenosis diameter; CTA, computed tomography angiography.

cases. To ensure a comprehensive assessment of the culprit lesion, anteroposterior, lateral, and oblique projections were obtained in all cases, and in some instances, additional rotational DSA was performed. DSA raw data were post-analyzed using RadiAnt Dicom Viewer (Medixant, Poznan, Poland) software. The quantification process of ICAS by DSA was the same as that of the WASID method (1): the absolute stenotic degree was calculated as $(1 - D_{stenosis}/D_{normal}) \times 100\%$, and $D_{stenosis}$ referred to the narrowest diameter at the culprit lesion. The quantitative measurements were performed by the same 2 experienced neurologists independently, and the average of their measurements was recorded.

All measurements with disagreements greater than 10% were reviewed by a third experienced reader (with >20 years of experience), who determined the quantification result from the 2 previous measurements. If the measurements of the stenosis site were unavailable due to a gap sign (i.e., the vessel lumen was not visible at the stenosis site, but contrast media filling was noted in the distal vessel of the stenosis site) on CTA or DSA, a 99% stenosis was defined (*Figure 3*) (1).

Algorithm of radiation exposure from CTA and DSA

Radiation doses from head CTA and DSA were collected from the first 20 participants in this study. The dose-length product (DLP) from head CTA and dose-area product (DAP) during DSA were recorded. The formula for calculating effective dose (ED) of head CTA and DSA were as follows, respectively: ED (mSv) of CTA = DLP (mGy·cm) × conversion factor (mSv/mGy·cm); ED (mSv) of DSA = median DAP (Gy·cm^2) × conversion factor (mSv/Gy·cm^2). According to previous studies, the conversion factors of head CTA and DSA were set as 0.0021 mSv/mGy·cm and 0.04 mSv/Gy·cm^2, respectively (20,21).

Statistical analysis

The sample size was calculated according to the suggested formula (22). The minimum required sample size was calculated to be 187 participants, with a 95% confidence level, a 10% width of confidence level, and an expected intraclass correlation coefficient (ICC) of 0.810 (23). Categorical data were expressed as frequencies and percentages. Normally distributed continuous data were expressed as the means and standard deviations (SDs), whereas nonnormally distributed continuous data were expressed as the median and interquartile range (IQR). Either Student's *t*-test or Mann-Whitney U test was used to compare the degree of stenosis and ED of radiation exposure between CTA and DSA. ICC was used to evaluate the reproducibility of intra-observer and inter-observer quantification of ICAS on CTA through a single

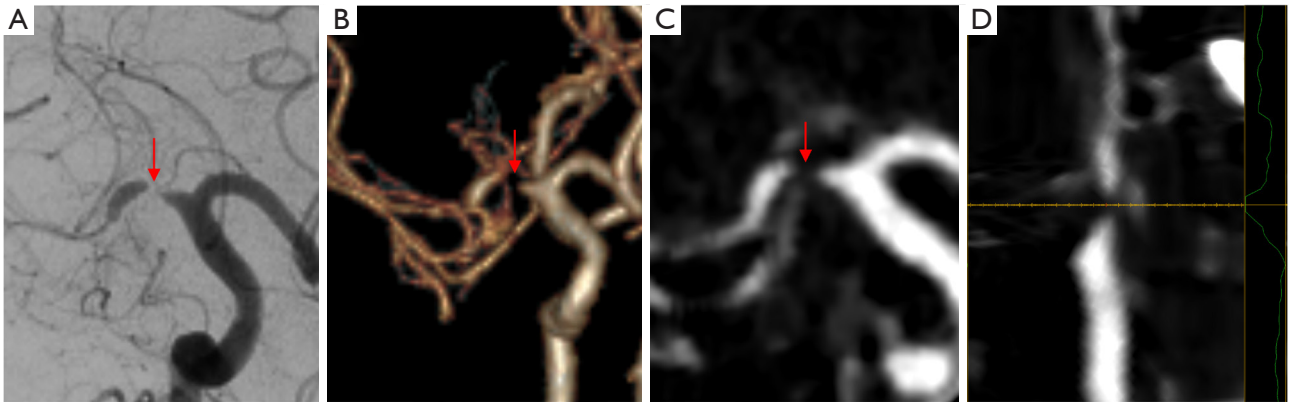

Figure 3 An example of 99% stenosis. An adult patient with a symptomatic right middle cerebral artery stenosis. The 99% stenosis showed a gap sign (red arrows) on DSA (A), CTA (B) and semi-automatic vessel analysis software (C,D). DSA, digital subtraction angiography; CTA, computed tomography angiography.

measurement, absolute agreement, 2-way mixed effects model. The reliability of quantification of ICAS on CTA, as well as the agreements of quantification of ICAS in various lesion location, calcification or not, and stenosis severity on CTA and DSA were estimated by ICC based on a mean-rating (κ=2), consistency, 2-way randomized effects model (24). An ICC value <0.5, 0.5–0.75, 0.75–0.9, and >0.9 was considered poor, moderate, good, and excellent agreement, respectively (24). A sensitivity analysis to further confirm the reliability for quantifying ICAS on CTA was performed by excluding the lesions with a 99% stenosis. Sensitivity, specificity, positive predictive values, negative predictive values, κ statistic, and receiver operating characteristic (ROC) curve for the identification severe (70–99%) stenosis on CTA with the optimal protocol were calculated using DSA as reference standard. A 2-tailed P<0.05 was considered a statistically significant difference. All statistical analyses were performed using the software SPSS 24.0 (IBM Corp., Armonk, NY, USA).

Results

Participant baseline characteristics

From March 2021 to December 2021, 242 patients met the inclusion criteria. Finally, after excluding 51 patients due to various reasons, 191 participants were consecutively enrolled (flow chart shown in Figure S1). The mean age was 58.8±10.7 years, and among them, 148 of 191 participants (77.5%) were male. The main qualifying events included ischemic stroke in 51.3% (98/191) and TIA in 48.7% (93/191) of the participants.

Among the 191 participants, 11 (5.8%) had intracranial tandem lesions, so a total of 202 lesions were evaluated. These lesions included 22 lesions (10.9%) at the ICA, 88 lesions (43.6%) at the MCA, 43 lesions (21.3%) at the VA, and 49 lesions (24.3%) at the BA (*Table 1*). None of them had extracranial tandem stenosis. Calcified ICAS was found in 8.4% (17/202) of the lesions, including 9 of 17 at the ICA (52.9%), 6 of 17 at the VA (35.3%), and 2 of 17 at the BA (11.8%). The median of stenotic degree was 78.5% (IQR: 71.2–85.0%) on DSA. On DSA, 80.2% (162/202) lesions were identified as severe stenosis [including 10.9% (22/202) lesions with a 99% stenosis] and 19.8% (40/202) as moderate stenosis. The median time interval from CTA scanning to DSA was 1 day (IQR, 1–1 day).

Comparison of ED of CTA and DSA radiation

The median DLP and ED from head CTA were 1,390.85 mGy·cm (IQR, 1,388.30–1,394.41 mGy·cm) and 2.92 mSv (IQR, 2.92–2.93 mSv), respectively. The median DAP and ED during DSA were 219 Gy· cm^2 (IQR, 187–271.25 Gy·cm^2) and 8.76 mSv (IQR, 7.48–10.85 mSv), and the ED during DSA was higher than that from CTA (P<0.001).

Reproducibility of intra-observer and inter-observer quantification of ICAS on CTA

The reproducibility of intra-observer quantification [ICC, 0.905; 95% confidence interval (CI): 0.731–0.964, P<0.001]

Table 1 Patients baseline characteristics of including participants (n=191, lesions =202)

Characteristics	Total (n=191, lesions =202)
Age (years)*	58.8±10.7
Male, n (%)	148 (77.5)
Risk factors, n (%)	
Diabetes mellitus	65 (34.0)
Hyperlipidemia	30 (15.7)
Hypertension	123 (64.4)
Smoking history	76 (39.8)
Qualifying events, n (%)	
Transient ischemic attack	93 (48.7)
Ischemic stroke	98 (51.3)
Location of target lesions, n (%)	
Intracranial internal carotid artery	22 (10.9)
Middle cerebral artery	88 (43.6)
Basilar artery	49 (24.3)
Intracranial vertebral artery	43 (21.3)
Time interval from CTA to DSA (days)†	1 (1–1)

Unless otherwise indicated, data are numbers of participants, and data in parentheses are percentages. *, data are means ± SDs; †, data are reported as the medians, with the IQRs in parentheses. CTA, computed tomography angiography; DSA, digital subtraction angiography; SDs, standard deviations; IQRs, interquartile ranges.

and inter-observer quantification (ICC, 0.933; 95% CI: 0.911–0.950, P<0.001) of ICAS on CTA were excellent.

Reliabilities of quantification of ICAS on CTA and DSA

The reliabilities of quantifying ICAS on CTA and DSA were excellent ranging from 0.906 (95% CI: 0.876–0.929, P<0.001) to 0.955 (95% CI: 0.944–0.966, P<0.001) (*Table 2*). The ICC of the stenotic degree calculated as $(1 - D_{min\text{-}stenosis}/D_{mean\text{-}normal}) \times 100\%$ was the highest among the 9 permutations generated from semi-automatic CTA (*Table 2*). The sensitivity analysis after excluding lesions with 99% stenosis indicated similar results (Table S2). Thus, the $(1 - D_{min\text{-}stenosis}/D_{mean\text{-}normal}) \times 100\%$ was used as the standard CTA measurement protocol for quantifying ICAS in the present study. Typical examples of measurement by

Table 2 Reliability of semi-automated quantitation of ICAS by 9 different combinations on CTA

Measurement protocols	ICC	95% CI	P value
$(1 - D_{min\text{-}stenosis}/D_{max\text{-}normal}) \times 100\%$	0.953	0.937–0.964	<0.001
$(1 - D_{min\text{-}stenosis}/D_{min\text{-}normal}) \times 100\%$	0.943	0.925–0.957	<0.001
$(1 - D_{min\text{-}stenosis}/D_{mean\text{-}normal}) \times 100\%$	0.955	0.944–0.966	<0.001
$(1 - D_{mean\text{-}stenosis}/D_{max\text{-}normal}) \times 100\%$	0.933	0.911–0.949	<0.001
$(1 - D_{mean\text{-}stenosis}/D_{min\text{-}normal}) \times 100\%$	0.906	0.876–0.929	<0.001
$(1 - D_{mean\text{-}stenosis}/D_{mean\text{-}normal}) \times 100\%$	0.934	0.913–0.950	<0.001
$(1 - D_{max\text{-}stenosis}/D_{max\text{-}normal}) \times 100\%$	0.937	0.917–0.952	<0.001
$(1 - D_{max\text{-}stenosis}/D_{min\text{-}normal}) \times 100\%$	0.913	0.885–0.934	<0.001
$(1 - D_{max\text{-}stenosis}/D_{mean\text{-}normal}) \times 100\%$	0.937	0.917–0.952	<0.001

ICAS, intracranial atherosclerotic stenosis; CTA, computed tomography angiography; ICC, intraclass correlation coefficient; CI, confidence interval; D, diameter.

CTA and DSA are presented in *Figures 4,5*. In order to assess the impact of different CT devices on image quality, we respectively calculated the agreements of quantification of ICAS on CTA and DSA in the 6 centers. The results are presented in Table S3.

Agreements of quantification of ICAS in various lesion location, calcification or not, and stenosis severity on CTA and DSA

The agreement of CTA and DSA in quantifying BA (ICC, 0.969; 95% CI: 0.945–0.983; P<0.001), MCA (ICC, 0.959; 95% CI: 0.938–0.973; P<0.001), and intracranial VA (ICC, 0.946; 95% CI: 0.901–0.971; P<0.001) was excellent, but was good in quantifying intracranial ICA (ICC, 0.881; 95% CI: 0.714–0.951; P<0.001) (*Table 3*). The agreement of quantification of non-calcified ICAS on CTA and DSA was excellent (ICC, 0.960; 95% CI: 0.946–0.970; P<0.001), but that of calcified ICAS was good (ICC, 0.849; 95% CI: 0.583–0.945; P<0.001). Similar results were found when excluding lesions with 99% stenosis (Table S4).

The agreements of quantifying severe stenosis (ICC, 0.918; 95% CI: 0.889–0.940, P<0.001) on CTA and DSA was higher than that of moderate stenosis (ICC, 0.841; 95% CI: 0.700–0.916, P<0.001). However, when excluding lesions with 99% stenosis, the agreement of severe stenosis (ICC, 0.786; 95% CI: 0.702–0.847, P<0.001) reduced (Table S4).

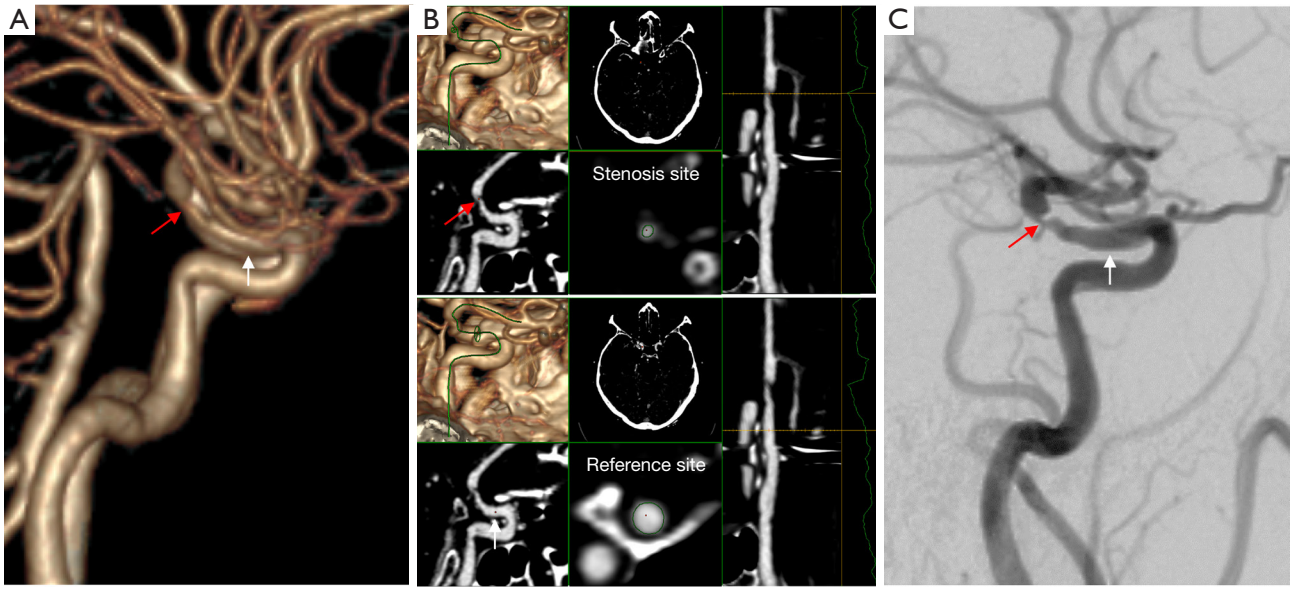

Figure 4 An example of measurement in ICA stenosis. An adult patient with a symptomatic ICA stenosis. The stenosis (red arrow) and reference (white arrow) sites were decided on CTA (A). The degree of stenosis was calculated as (1 – the minimal diameter at the stenosis site/the mean diameter at the reference site) × 100%, and the degree of stenosis was 71.9% on semi-automatic method (B) (red arrow indicates stenosis site; white arrow indicates reference site). The degree of stenosis was 77.0% on DSA (C) (red arrow indicates stenosis site; white arrow indicates reference site). ICA, internal carotid artery; DSA, digital subtraction angiography; CTA, computed tomography angiography.

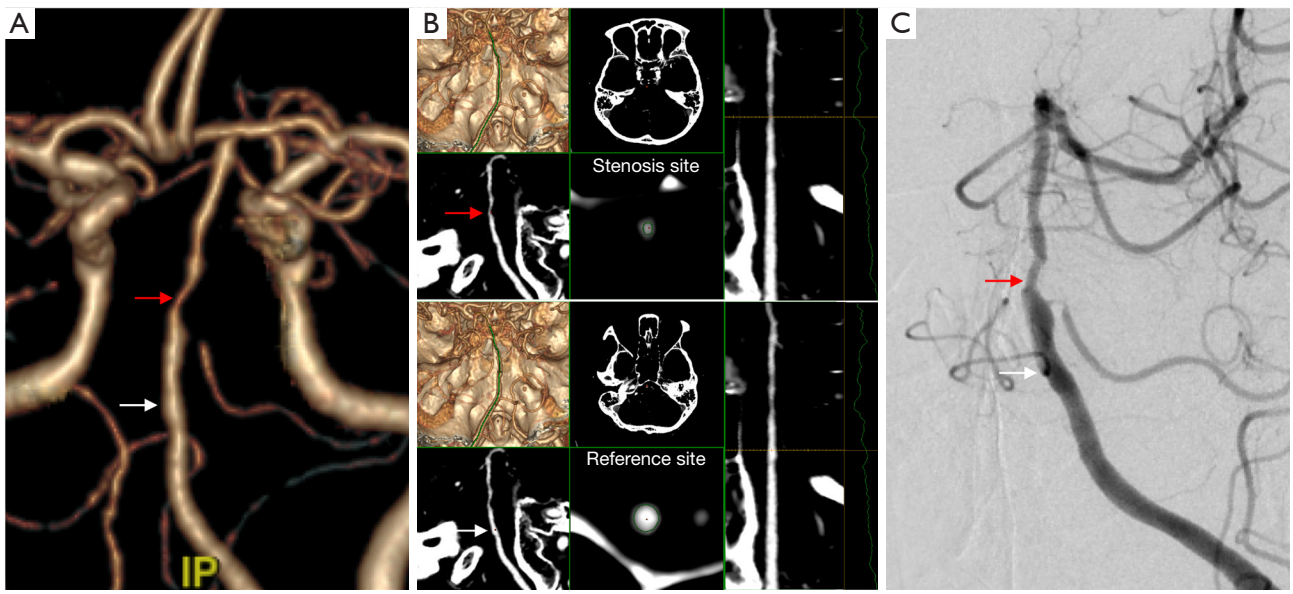

Figure 5 An example of measurement in basilar artery stenosis. An adult patient with a symptomatic BA stenosis. The stenosis (red arrow) and reference (white arrow) sites were decided on CTA (A). The degree of stenosis was calculated as (1 – the minimal diameter at the stenosis site/the mean diameter at the reference site) × 100%, and the degree of stenosis was 56.5% on semi-automatic method (B) (red arrow indicates stenosis site; white arrow indicates reference site). The degree of stenosis was 55.1% on DSA (C) (red arrow indicates stenosis site; white arrow indicates reference site). IP, inferior posterior; BA, basilar artery; CTA, computed tomography angiography; DSA, digital subtraction angiography.

Table 3 Agreements of semi-automated quantitation of ICAS on CTA with DSA based on various lesion location, calcification or not, and different stenosis severity

Characteristics	ICC	95% CI	P value
Lesion location			
Intracranial internal carotid artery	0.881	0.714–0.951	<0.001
Middle cerebral artery	0.959	0.938–0.973	<0.001
Basilar artery	0.969	0.945–0.983	<0.001
Intracranial vertebral artery	0.946	0.901–0.971	<0.001
Calcified plaque			
Non-calcified plaque	0.960	0.946–0.970	<0.001
Calcified plaque	0.849	0.583–0.945	<0.001
Stenosis severity			
≥70% stenosis	0.918	0.889–0.940	<0.001
50–69% stenosis	0.841	0.700–0.916	<0.001

ICAS, intracranial atherosclerotic stenosis; CTA, computed tomography angiography; DSA, digital subtraction angiography; ICC, intraclass correlation coefficient; CI, confidence interval.

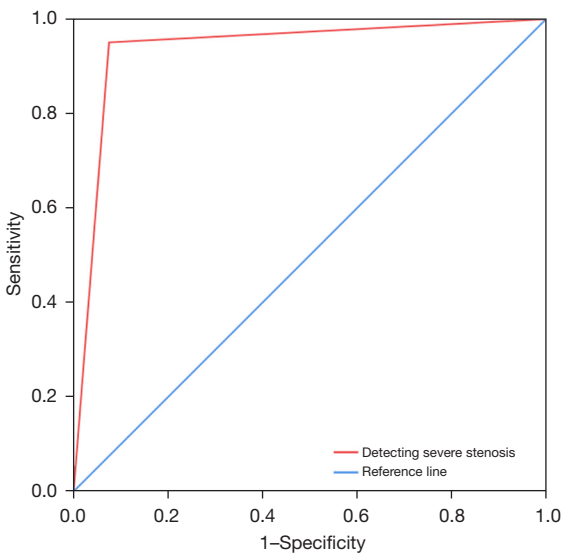

Figure 6 Receiver operating characteristic curve for the identification of severe stenosis on CTA. The area under curve was 0.938 (95% CI: 0.887–0.989, P<0.001). CTA, computed tomography angiography; CI, confidence interval.

Accuracy of CTA compared with DSA in detecting severe (70–99%) or 99% stenosis

For the 202 lesions, the median of stenotic degree was 77.8% (IQR: 71.1–83.6%) on CTA. There was no difference in stenotic degree measured on CTA and DSA (P=0.70). On CTA, 77.7% (157/202) of lesions had severe [stenosis including 11.4% (23/202) of lesions with a 99% stenosis], and 22.3% (45/202) had moderate stenosis.

CTA with semi-automatic method detected severe ICAS with a sensitivity of 95.1%, a specificity of 92.5%, a positive predictive value of 98.1%, and a negative predictive value of 82.2% (Table S5). The κ value was 0.836 (95% CI: 0.742–0.930, P<0.001), and the area under the ROC curve (AUC) (*Figure 6*) was 0.938 (95% CI: 0.887–0.989, P<0.001). CTA detected 99% of ICAS with a sensitivity of 95.5%, specificity of 98.9%, positive predictive value of 91.3%, and a negative predictive value of 99.4%.

Discussion

The present study found that the semi-automatic quantification of ICAS on CTA has an excellent agreement compared with DSA (ICC, 0.955, P<0.001), and the optimal measurement protocol was calculated as (1 – the minimal diameter of stenosis/the mean diameter of reference) × 100%. After excluding lesions with 99% stenosis, the sensitivity analysis indicated that the results were robust. Besides, the agreements of the semi-automatic CTA with DSA in quantifying non-calcified lesions and severe stenosis were higher than that in calcified lesions (ICC, 0.960 *vs.* 0.849, P<0.001) and moderate stenosis (ICC, 0.918 *vs.* 0.841, P<0.001). These findings demonstrated that CTA using the semi-automatic method may be a reliable alternative to DSA for quantifying ICAS.

Previous studies on measuring ICAS with CTA have primarily focused on the classification of stenotic degree, with only a few addressing the comparison of absolute stenotic degree. A large-scale study that compared the accuracy of CTA, using visual inspection on MIP images, to DSA in diagnosing ICAS, demonstrated moderate accuracy in detecting both moderate stenosis (sensitivity =61%, predictive value =84.6%) and severe stenosis (sensitivity

=78%, predictive value =81.8%) (25). A following study revealed a high sensitivity (98%) and positive predictive value (93%) of CTA in the classification of ICAS (26). Although previous studies involving absolute stenotic degree reported similar agreement between CTA and DSA, compared with our study (ICC, 0.98, 95% CI: 0.98–0.99; 0.96, 95% CI: 0.95–0.97, respectively) (27,28), it must be noted that both of these studies utilized a digital caliper or ruler respectively for diameter measurement which may be inconvenient for clinical practice. Our study utilized the semi-automated vessel analysis software that can identify the lumen boundary according to intensity discrepancies and ensure consistency by selecting the same point in the halo in both the stenosis site and reference site to measure ICAS, which may decrease reader bias when measuring vessel diameters (16,29). The finding supported that CTA can be an alternative imaging modality for DSA in measuring the absolute stenotic degree of ICAS.

Among 9 permutations from the semi-automatic software in our study, the $(1 - D_{min\text{-}stenosis}/D_{mean\text{-}normal}) \times 100\%$ was found to be the optimal combination for the quantifying the stenotic degree. The underlying explanation may be that at the stenosis site, the minimum diameter in the axial reconstruction image on CTA is probably consistent with the diameter measured at the narrowest value on the tangential projection of DSA. When measuring the reference site, the projection of DSA was the same with that at the stenosis site. Considering that the lumen outline at the reference site is quasi-circular shaped, the diameter measured on DSA was more likely to be a value ranging from minimum to maximum diameter of the lumen. Mean diameter generated from CTA is more likely to be consistent with the diameter measured on DSA, but not maximal or minimal diameter form CTA. The previous studies about semi-automated measurement of carotid stenosis used minimum diameter generated from CTA alone (16,17,23). Our study may fill this gap and innovatively provide a practicable and accurate measurement protocol on CTA for ICAS in clinical practice.

Previous studies have demonstrated that evaluating the classification of stenotic degree in the intracranial segment of ICA on CTA had a lower accuracy compared with other lesion locations (25,30). The reasons were as follows: (I) curved course; (II) bone and calcification influence. Similarly, the agreement of CTA and DSA in quantifying intracranial ICA in our study was the lowest among all lesion locations. However, its value (ICC =0.881) still showed a good agreement, which may be attributed to multiple image reconstruction techniques displayed from the semi-automated vessel analysis software, including VR, curved MPR, oblique MPR, and lumen MPR (10-12,14,15). By combining these techniques, it is possible to effectively reconstruct and accurately measure intracranial ICA after careful tracking editing and section editing (10,15).

In the current study, calcified plaque did not demonstrate an excellent agreement compared with non-calcified plaque. The blooming artifacts caused by calcified plaque restricted the delineation of lumen boundary, resulting in reduced measurement accuracy, especially when calcification occurs in small, curved intracranial arteries (30). Not only for intracranial calcified lesions, a similar result was also observed in a study focusing on the measurement of coronary arterial stenosis with high calcium score (31). A study reported that dual-energy CT using a modified algorithm can remove calcified plaque to improve the diagnostic accuracy for calcified stenosis, but iodine in the vessel lumen was concurrently removed (32). Further research is needed to establish the effectiveness of this new method. DSA may be still necessary for severe calcified plaque in the evaluation of ICAS.

In our study, the ICC between CTA and DSA in quantifying severe ICAS was higher than that in moderate stenosis (ICC, 0.918 *vs.* 0.841), possibly owing to the high sensitivity (95.5%) and specificity (98.9%) between CTA and DSA in assessing the 99% stenosis. Considering that the definition of 99% stenosis (22/202, 10.9%) was a gap sign on CTA or DSA rather than via precise measurement (1), we conducted a sensitivity analysis by excluding lesions with 99% stenosis, and the results presented an attenuated agreement (ICC, 0.786) in quantifying severe stenosis. However, compared with DSA, CTA still has a high sensitivity (95.1%) and positive predictive value (98.1%) in detecting severe stenosis, which suggested the reliability of semi-automatic CTA in diagnose severe ICAS.

The major trials studying ICAS, including SAMMPRIS, WEAVE, and CASSISS, have historically enrolled patients with 70–99% stenosis as evaluated by DSA (2,33,34). Noticeably, the result of our study reveals that the radiation exposure during DSA is higher than that from CTA (median ED, 2.92 *vs.* 8.76 mSv), which is in line with a previous study (5). These findings supported using CTA as an alternative diagnostic modality to DSA to confirm severe ICAS (70–99%), which can give DSA a pure role focusing on endovascular treatment for the culprit artery. Adverse events related to DSA owing to its invasive features (such as iatrogenic embolization), contrast agent overuse, and X-ray

radiation overexposure may decrease (35).

Our study had limitations. Firstly, our study only enrolled patients with moderate or severe ICAS, excluding those with normal vessel and mild stenosis, which may cause a selection bias and restrict the generalizability of our findings to a broader population. Secondly, ICAS located at the anterior cerebral artery, posterior cerebral artery, and so on, was not evaluated in the present study, which may hinder the comprehensiveness of our study findings. Thirdly, as none of the enrolled patients had extracranial tandem stenosis, the potential impacts of stenosis at the initial segment of the ipsilateral internal carotid artery or VA on the measurement of the target intracranial arterial stenosis could not be evaluated.

Conclusions

CTA with semi-automatic analysis demonstrated an excellent agreement with DSA in quantifying ICAS, making it a promising option to replace DSA for the measurement of absolute stenotic degree in clinical trials.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-1343/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1343/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University (No. KY2019-083-01) and performed in accordance with the Declaration of Helsinki (as revised in 2013). All participating hospitals/institutions were informed and agreed with the study. Written informed consent was provided by all participants or their legally authorized guardians.

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