Clinical validation of an automated vessel-segmentation software of the extracranial-carotid arteries based on 3D-MRA: A prospective study


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Available online 15 August 2008

SUMMARY

Objectives. — To determine the accuracy of automated vessel-segmentation software for vessel-diameter measurements based on three-dimensional contrast-enhanced magnetic resonance angiography (3D-MRA).

Method. — In 10 patients with high-grade carotid stenosis, automated measurements of both carotid arteries were obtained with 3D-MRA by two independent investigators and compared with manual measurements obtained by digital subtraction angiography (DSA) and 2D maximum-intensity projection (2D-MIP) based on MRA and duplex ultrasonography (US). In 42 patients...
undergoing carotid endarterectomy (CEA), intraoperative measurements (IOP) were compared with postoperative 3D-MRA and US.

**Results.** Mean interoperator variability was 8% for measurements by DSA and 11% by 2D-MIP, but there was no interoperator variability with the automated 3D-MRA analysis. Good correlations were found between DSA (standard of reference), manual 2D-MIP ($r_P = 0.6$) and automated 3D-MRA ($r_P = 0.8$). Excellent correlations were found between IOP, 3D-MRA ($r_P = 0.93$) and US ($r_P = 0.83$).

**Conclusion.** Automated 3D-MRA-based vessel segmentation and quantification result in accurate measurements of extracranial-vessel dimensions.

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**Introduction**

The overall quality of carotid endarterectomy (CEA) is not only determined by the perioperative occurrence of neurological complications, but also depends on the quality of the reconstruction of the stenosed bifurcation. It has been shown that restenosis after CEA occurs in 6 to 36% of patients [1—4] and the majority of restenoses occur within the first two years [5]. In addition to systemic-cardiovascular risk factors, technical factors of vessel reconstruction could account for residual disease and early restenosis [3,6,7]. Therefore, systematic postoperative imaging of the reconstructed carotid bifurcation is important for surgical quality control and could also help to define morphological prognostic criteria for the risk of restenosis. For such an investigation of the postoperative result, invasive methods, such as digital-subtraction angiography (DSA) are not appropriate. Ultrasonography (US) is limited by its small field of view and the lack of postprocessing possibilities. With improvements in both hardware and software, gadolinium-enhanced magnetic-resonance angiography (MRA) has become the method of choice for the investigation of extra- and intracranial vessels. MRA has three major advantages over DSA [8]:

- it is noninvasive;
- its patients are not exposed to ionizing radiation;
- it uses a non-nephrotoxic paramagnetic contrast agent.

It has also been shown that MRA is preferred by the majority of patients [9].

The most widely used postprocessing technique for MRA is two-dimensional (2D) maximum intensity projection (MIP), which results in the loss of three-dimensional (3D) information in the source images. It is well known, however, that lower-intensity regions of the vessel may be lost on the MIP image and, thus, may lead to underestimation of vessel width [10—12]. The interpretation is carried out by either visual inspection or by caliper measurements [13,14]. Considerable intra- and interobserver variability may occur that will decrease the accuracy and value of quantitative MRA. An observer-independent and quantitative evaluation method based on MRA would therefore be desirable.

de Koning et al. [15] have presented a novel approach for quantitative vessel analysis of MRA images. Their approach uses knowledge of the image acquisition procedure to accurately determine vessel boundaries. The technique operates on the fully 3D dataset and not on the 2D projections. The aim of the current study was to validate the accuracy of this new 3D-MRA-analysis software before its routine clinical application. We performed multiple correlative analyses between 3D-MRA, DSA and US. We also compared 3D-MRA with direct measurements of the common carotid artery (CCA) and internal carotid artery (ICA) diameters obtained intraoperatively during CEA.
Methods

Study design: patient selection and treatment characteristics

All patients in the present study had high-grade carotid-artery stenosis as defined by the NASCET method [16] and had been admitted to the Department of Neurosurgery for CEA as recommended by the randomised controlled trials [17]. The study had been approved by our institution’s review board.

The study consisted of retrospective and prospective parts. Data for the retrospective part was obtained from a prior study in which DSA and first-pass gadolinium-enhanced 3D-MRA were performed [18]. Complete datasets for 10 patients (20 carotid arteries imaged: six men and four women, mean age: 63 years) were randomly selected by a technician who had no involvement in the study. These datasets were used to assess vessel measurement accuracy on DSA (standard of reference) and compared with 2D-MIP and automated 3D-MRA.

For the prospective part of the study, a consecutive series of 42 patients (30 men and 12 women, mean age: 68 years) who underwent CEA for high-grade carotid-artery stenosis were included. CEA was performed on the left side in 20 patients and on the right side in 22 patients under general anaesthesia. Intraoperative neuromonitoring with transcranial Doppler sonography, mild hypothermia and propofol were used as neuroprotective measures during cross-clamping. After removal of the plaque, the arteriotomy was closed with a running 6-0 Prolene suture without patch (Fig. 1). Intraoperative carotid-artery measurements (IOP) were performed using a Vernier caliper. After obtaining meticulous hemostasis, the external diameters of 42 CCA and 42 ICA were measured at a distance of 10 mm proximal and distal of the carotid bifurcation (see below). All patients were routinely imaged, using 3D-MRA and US, within four days of the surgery. Statistical analyses between IOP-, 3D-MRA- and US-based vessel measurements were done.

Imaging techniques

Magnetic-resonance angiography

Technical details of contrast-enhanced MRA acquisition have already been described [18]. In brief, all MRA investigations were performed on a 1.5-T imaging system equipped with a gradient overdrive (Magnetom Vision, Siemens Medical System, Erlangen, Germany). The maximum achievable gradient amplitude was 25 mT/m and the slew rate was 180 T/m/s. Spoiled 3D fast low-angle shot (FLASH) MR angiography was performed using a 4 × 2 circularly polarized phased-array neck coil. The sequence was performed with 32–36 coronal partitions, each one 1.94–2.5 mm thick, 2.84–3.15 ms repetition time TR, 1.03–1.11 ms echo time TE, 35–40° flip angle, 70 mm × 140 mm × 280 mm FOV by 36 × 92 × 256 image matrix and a scan time of 9–9.5 s [18]. Four consecutive 3D images were taken, starting at approximately 3 s after the start of a bolus injection of 0.1 mmol/kg of gadodiamide (Omniscan, Hafslund Nycomed, Oslo, Norway).

Digital-subtraction angiography

Biplane DSA was performed routinely in the anteroposterior and lateral projections with a 33-cm field of view and a 1024 × 1024 matrix on a CAS 500 biplanar angiographic system (Toshiba, Tokyo, Japan). Selective cerebral DSA was performed via the femoral artery, starting routinely with imaging of the aortic arch and followed by selective injections of contrast material [iopamidol (Iopamiro 300); Bracco, Milan, Italy] into both the common carotid and subclavian arteries and at least one vertebral artery. The injected volume of contrast medium was 5–8 mL. The spatial resolution was 0.32 × 0.32 mm. The system-integrated software, which allows real-diameter measurement of vessels positioned in the center of the image, has been previously described [19,20].

Duplex color-coded sonography

Sonographic examinations were performed using a 128 XP/10 duplex ultrasound scanner (Acuson, Mountain View, CA) with 7.5-MHz B-mode and 5-MHz Doppler linear-array transducers. Diameters of the CCA and ICA were measured bilaterally by experienced sonographers.

Data analysis

Automated segmentation and analysis of MRA images

Technical details of the software structure and segmentation algorithms have been described by de Koning et al. [15]. In brief, the user defines a start and end point on the
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Correlation of automated 3D-MRA analysis with 2D-MIP and DSA. All manual measurements were taken by two independent, experienced investigators (R.G. and L.R.) who were blinded to the clinical data and MRA/DSA findings. Readings of MRA and DSA were done in two separate sessions. Manual measurements on the 2D-MIP images (anteroposterior and lateral views) were made using a DICOM Viewer (GE-View, GE Medical Systems, Milwaukee, WI, USA), with signal thresholds set by the investigator. Measurements on the DSA images were also taken in the anteroposterior and lateral views, using a previously described software package [19,20]. Diameters of the left and right CCA and ICA were measured at a distance of 10 mm, proximal and distal, of the carotid bifurcation (Fig. 2). Automated measurements on the 3D-MRA images were made using the new segmentation and analysis software.

Correlation of automated 3D-MRA analysis with intraoperative carotid artery measurements. Intraoperative carotid artery measurements were taken by the senior author (A.B.) using a Vernier caliper. The external diameters of the 42 CCA and 42 ICA were measured at a distance of 10 mm from the carotid bifurcation. All patients routinely underwent contrast-enhanced 3D-MRA within four days of surgery. The automated measurements on the 3D-MRA images were done using the new segmentation and analysis software.

Statistical analysis

Commercially available software (GraphPad InStat 3.05, GraphPad Software, San Diego, California, USA) was used for the statistical analyses. Results are given as means plus or minus standard error of the mean (S.E.M.). All data were evenly distributed to conform to the Kolmogorov—Smirnov test (p < 0.01). One-way ANOVA followed by the Newman—Keuls test were used to compare the means. For correlations, the Pearson correlation test was used with two-tailed p values. The statistical significance level was set at p < 0.05 with a confidence interval (CI) of 95%.

Results

Correlation of automated 3D-MRA analysis with 2D-MIP and DSA

A total of 20 CCA from 10 patients were available for analysis. The mean-interoperator variability for cross-sectional diameter measurements on DSA was 8% (range: 0 to 22%). For measurements on 2D-MIP images, the mean-interoperator variability was 11% (range: 1 to 19%). There was no interoperator variability with the use of the new 3D-MRA-analysis software. The mean diameters (± S.E.M.) for the CCA and ICA as measured by the three modalities (DSA, 3D-MRA and 2D-MIP) shown in Fig. 3. All correlations were performed using the DSA data as the gold standard. The Pearson correlation factor for DSA–3D-MRA measurements was rP = 0.81.
Bar plot showing the mean diameter (in mm) of 20 common carotid arteries (CCA) and 20 internal carotid arteries (ICA) as measured by 3D-MRA (new automated software), 2D-MIP (manual) and DSA (manual). No statistically significant differences were found.

Diagramme montrant le diamètre moyen (en mm) de 20 artères carotides communes et 20 artères carotides internes mesurées sur l’angio-IRM 3D avec le nouveau programme automatique, en MIP-2D (mesure manuelle) et en angiographie conventionnelle (mesure manuelle). Il n’a pas été retrouvé de différence statistiquement significative.

for CCA and \( r_P = 0.78 \) for ICA. The Pearson correlation factor for DSA–2D-MIP measurements was \( r_P = 0.58 \) for CCA and \( r_P = 0.6 \) for ICA.

Correlation of automated 3D-MRA analysis with US

A total of 42 CCA was available for analysis. The mean diameters (± S.E.M.) of the CCA as measured by 3D-MRA and US are shown in Fig. 4. On US, two different diameter measurements were performed: the first diameter (outer) comprised the whole vessel; the second diameter (inner) was the distance from intima to intima. A highly-significant correlation (\( r_P = 0.83 \)) was obtained between the outer diameter as measured by sonography and the diameter measured by 3D-MRA (Fig. 5). However, a statistically-significant difference was found between the sonographically-determined inner diameter compared with the diameter on 3D-MRA (\( p < 0.001 \)) (Figs 2 and 4).

Correlation of automated 3D-MRA analysis with Intraoperative-carotid artery measurements

No patient experienced any adverse effects from the intraoperative vessel measurements or postoperative radiological investigations. A total of 42 CCA and 42 ICA were available for analysis. The mean diameters (± S.E.M.) of the CCA and ICA as measured by 3D-MRA and intraoperatively are shown in Fig. 6. These measurements were highly correlated, with factors of \( r_P = 0.75 \) for CCA and \( r_P = 0.81 \) for ICA. The overall (CCA + ICA) Pearson correlation coefficient was \( r_P = 0.93 \) (\( p < 0.0001 \)) (Fig. 7).

Discussion

MRA has become a routine method for diagnostic evaluation of the extracerebral circulation as well as to follow patients after treatment of carotid-artery stenosis. There are, however, only a few studies assessing whether or not contrast-enhanced MRA gives accurate quantitative vessel...
measurements and these were done on the abdominal and peripheral vessels [22,28].

Systematic imaging of the extracerebral–carotid arteries after carotid endarterectomy is necessary for surgical quality control. Based on morphological and quantitative analyses of the treated vessel, the prognostic criteria for long-term prevention of restenosis could potentially be defined. Along with a morphological description, carotid-artery diameter measurement at the site of revascularization could offer a quantitative assessment of the surgical result. Few studies, however, have reported on the measurement of vessel diameter using contrast-enhanced MRA and, again, these were done for the abdominal and peripheral vessels [22,28].

Technical considerations

DSA with a 1024 matrix is still considered to be the gold standard for imaging of supra-aortic vessel disease. Therefore, in our study and in the studies in vitro by de Koning et al. [15], MRA results were initially compared with DSA. To determine the accuracy of the new automated software, de Koning et al. [15] undertook a series of measurements on phantoms, comparing contrast-enhanced 3D-MRA with X-ray DSA. They found that vessel diameters quantified by the new segmentation software did not differ by more than 1% from comparable measurements with X-ray DSA. To translate these findings into clinical application, we performed measurements on DSA images from patients planned for CEA and correlated these with measurements on 2D-MIP and 3D-MRA images. Automated measurements of carotid diameters were highly correlated with manual measurements on DSA. This was true for both CCA and ICA, with a Pearson correlation factor of 0.81 and 0.78, respectively. Greater discrepancies were found with manual measurements on 2D-MIP, which can be explained by the variability of manual measurements ($r = 0.58$ for CCA and $r = 0.6$ for ICA) in the setting of threshold levels.

A major problem of manual vessel-diameter measurements based on MRA is variability in the definition of threshold levels in the image settings. In our study, each observer set the signal threshold visually before performing the diameter measurement on 2D-MIP images. The estimated vessel diameter on MRA can depend greatly on the threshold levels in the image settings. We found a mean interobserver variability of 11% (range: 4.1 to 22%) for 2D-MIP measurements. Westenberg et al. [22] demonstrated that changing the threshold values from 10 to 60% led to variation in the estimation of vessel diameter of approximately 35%. In the Westenberg et al. study, the best threshold level was found to be 30% of the maximum signal [22]. Based on this work, de Koning et al. [15] applied a threshold level of 30% in the settings of the new 3D-MRA analysis software used in our study, thus, eliminating the interobserver variability caused by thresholding.

Color-coded duplex sonography is another noninvasive imaging modality widely used for evaluation of carotid-artery pathology [23,24]. All of our carotid endarterectomy patients undergo routine postoperative carotid-duplex sonography. One question was: how do vessel diameters measured by 3D-MRA compare with diameters measured by US? We performed two diameter measurements on US: the intima-to-intima (inner or endoluminal) diameter and the total (outer) diameter. Interestingly, 3D-MRA diameters of the CCA did not differ from the sonographically measured outer diameters, whereas a significant difference was found with the inner diameters. MRA is based either on the time-of-flight technique, which uses the intrinsic contrast of excited corpuscles or the first-pass effect of intravenously injected gadolinium (Gd-DTPA). The contrast agent, usually Gd-DTPA, leads to a $T_1$ shortening during its first pass inside the vessel. In other words, luminography is performed similar to DSA. We hypothesized that the 3D-MRA-vessel diameter would correspond to the inner diameter as measured by sonography. Instead, there was a consistent overestimation by 3D-MRA of 19% of the intima–intima distance as measured by US (Figs. 2 and 4). A strong correlation was found, however, between outer-diameter measurements on US and 3D-MRA ($r = 0.93$) (Figs. 2 and 5). Two parameters could account for this observation. Setting the threshold limits at 30% could slightly overestimate vessel diameter. The partial-volume effect, a well-known phenomenon of MR imaging, could furthermore account for the discrepancy. If the vessel segment extends into an adjacent pixel, the signal intensity would be averaged over the two outer pixels and would appear to be part of the lumen. Thus, the lumen would be represented by one additional pixel, leading to an overestimation of the vessel diameter.

We also compared the real-vessel diameter (including the vessel wall) to the diameter obtained on 3D-MRA. We performed direct intraoperative measurements of the CCA and ICA during carotid-endarterectomy surgery. We confirmed that vessel diameters measured on 3D-MRA were well correlated ($r = 0.93$) with the total vessel diameter as measured intraoperatively (Figs. 3 and 7). This was true for both CCA ($r = 0.75$) and ICA ($r = 0.83$).

Clinical application

An objective observer-independent automated method to analyze blood vessels would be useful for following progressive pathologies, such as carotid-artery stenosis, carotid-artery dissection and fibromuscular dysplasia. The main advantage of this new postprocessing method is its capability of performing an unbiased quantitative analysis of vessel morphology based on 3D-MRA. We have demonstrated...
that highly accurate user-independent vessel measurements can be obtained. In addition, this method is not limited to the extracranial-carotid artery system, but may also be applied to the intracranial vasculature as well as the peripheral circulation.

We have applied this new method to the study of the extracranial-carotid artery as part of a study on postcardiot endarterectomy quality control. Indeed, there is a lack of objective evaluation of postoperative results after CEA. Most studies of CEA have used US, which has the disadvantage of a small field of view, a lack of postprocessing capacity and interobserver variability [25].

Another possible application of the new method would be to better quantify vessel enlargement after CEA. There is still considerable debate over whether routine patch angioplasty or primary closure should be performed after CEA [26,27]. Patch angioplasty is thought to result in fewer cases of residual disease and early restenosis in comparison to primary closure. Techniques for primary vessel closure can, however, vary considerably (for example, microsurgical primary closure using an operating microscope versus closure using the eversion method). Without objective values, scientific comparison of results is difficult. Systematic postoperative 3D-MRA with unbiased objective analysis of vessel diameter at the site of vessel reconstruction would help to allow comparisons of the results of different investigators and different surgical techniques.

Conclusion

In conclusion, quantitative analysis of contrast-enhanced 3D-MRA data using the new segmentation software is reproducible and highly accurate in terms of clinical patient data. Measurements by DSA, US and 3D-MRA as well as direct Intraoperative-vessel measurements and 3D-MRA are all highly correlated. Moreover, interobserver variability is eliminated because vessel segmentation and diameter measurement is automated. This approach could be invaluable for the systematic and objective evaluation of vascular disease, vascular treatment results and surgical quality assessment following carotid endarterectomy.

References

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