

Diagnostic performance of contrast enhanced magnetic resonance angiography in detecting intracranial aneurysms in patients presenting with subarachnoid haemorrhage

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Abstract

Introduction: Most centres use computed tomographic angiography (CTA) as the primary diagnostic tool in patients presenting with a subarachnoid haemorrhage (SAH). Contrast enhanced magnetic resonance angiography (CEMRA) might be an alternative. In this study the ability to detect cerebral aneurysms with CEMRA in patients presenting with a SAH is investigated and compared with CTA. **Methods:** In 75 consecutive patients, two experienced neuroradiologists evaluated CEMRA and CTA images. Digital subtraction angiography (DSA) served as standard of reference. The diagnostic performance in detection of aneurysms was calculated for both modalities and a comparison was made between the two. **Results:** No significant difference was found between the two modalities for the detection of aneurysms: sensitivities for the two observers were 96.6 and 93.8 respectively for CEMRA and 90.8 and 92.3 respectively for CTA; specificities were 77.8 and 88.9 for CEMRA and 94.4 for both observers for CTA. Kappa values for interobserver variability were 0.82 for CEMRA and 0.85 for CTA. **Conclusion:** The diagnostic accuracy of CEMRA and CTA in the work-up of patients presenting with a SAH does not differ significantly. The choice to use either CEMRA or CTA depends on preference or availability.

Keywords: magnetic resonance angiography, intracranial aneurysm, subarachnoid haemorrhage, computed tomography, angiography

Abbreviations

Computed tomographic angiography (CTA)
Confidence intervals (CI's)
Contrast enhanced magnetic resonance angiography (CEMRA)
Digital subtraction angiography (DSA)
Magnetic resonance angiography (MRA)
Matched mask bone elimination (MMBE)
Maximum intensity projection (MIP)
National centre for patient related research (CCMO)
Phase contrast (PC)-MRA

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Subarachnoid haemorrhage (SAH)
Time-of-flight (TOF)-MRA

Introduction

Magnetic resonance angiography (MRA) has some advantages over computed tomographic angiography (CTA): no harmful ionising radiation or iodinated contrast agent and no image degradation arising from vascular calcifications and surrounding bony structures. Therefore, MRA might be a preferable diagnostic tool in the detection of intracranial aneurysms in patients presenting with a subarachnoid haemorrhage (SAH).

Few direct comparisons between the two modalities have been published. White et al. described the performance of CTA and MRA 10 years ago in a meta-analysis [1]. The results of their review did not allow direct comparison between CTA and MRA because few studies included patients who underwent both CTA and MRA.

In a prospective study White et al. [2] performed CTA as well as MRA in 142 patients. The diagnostic performance of both modalities did not differ significantly and was not better than in the earlier review performed by the same group. The sensitivity was low, especially for detection of small aneurysms: 57 % for CTA and 35 % for MRA for aneurysms smaller than 5 mm. It was expected that future improvements in scan technique would lead to better performance, and that the addition of contrast enhanced MRA especially would contribute to improved performance.

All MRA studies included in the review as well as their own study used non-contrast-enhanced sequences such as time-of-flight (TOF)-MRA or phase contrast (PC)-MRA.

First-pass or contrast enhanced magnetic resonance angiography (CEMRA) has shorter acquisition times than flow dependent MRA sequences and does not suffer from signal loss due to turbulent or slow flow or as a result from spin saturation in larger scan volumes [3-5]. It might therefore be advantageous in the depiction of intracranial aneurysms.

Only a few studies have evaluated the diagnostic performance of CEMRA in the detection of cerebral aneurysms [3-8], involving only small numbers of patients (4-41 patients) and aneurysms (4-25 aneurysms). The largest series was published by Nael et al. [7] with 25 aneurysms in 41 patients. In this study, CEMRA was compared with CTA for the detection and characterisation of cerebral aneurysms without digital subtraction angiography (DSA) as the reference standard. Therefore, the diagnostic accuracy of the two techniques could not be assessed. The performance of both techniques was excellent in terms of interobserver agreement and correlation between the two modalities. In the smaller studies of Metens et al. [5], Suzuki et al. [8] and Unlu et al. [3], both CEMRA and DSA were performed. All aneurysms in these 3 studies except for 1 small (2 mm) aneurysm [3] were detected by CEMRA. All 3 groups concluded that CEMRA performed better than TOF-MRA. Specificity could not be defined in these studies because only patients with at least 1 aneurysm were included, so no false positive scores were possible.

In view of the sparse data about the performance of CEMRA in the detection of cerebral aneurysms in patients presenting with a SAH, and the lack of data about the comparative accuracy of CEMRA and CTA, we undertook a study to assess the accuracy of CEMRA in comparison with CTA. We recognise that

diagnostic accuracy is not the only factor determining the practical utility of a technique in a demanding clinical situation. Because catheter DSA is an integral part of the coiling procedure and remains the standard of reference for the detection of cerebral aneurysms, DSA is used as gold standard in our study.

If CEMRA were to perform better than CTA in the detection of intracranial aneurysms this would be an argument to add CEMRA to the work-up protocol of patients presenting with a SAH.

Materials and Methods

Study design

Patients admitted with a diagnosis of non-traumatic SAH between 2004 and 2006 were included in the study. All patients underwent CTA for detection of a possible cerebral aneurysm. Diagnostic catheter DSA was performed as an additional diagnostic procedure in cases of an initially negative CTA study or where there was uncertainty about the preferred treatment strategy. Moreover, DSA is an essential part of the endovascular coiling procedure (see flow chart in Figure 1). If endovascular treatment was not considered feasible on the basis of the CTA images the patient was referred to the neurosurgeon. Diagnostic DSA was performed at the request of the neurosurgeon if more detailed information was required about the aneurysm and its surrounding arterial branches. Within 48 hours of CTA, patients meeting the inclusion criteria for the study underwent an additional CEMRA study before endovascular or surgical treatment.

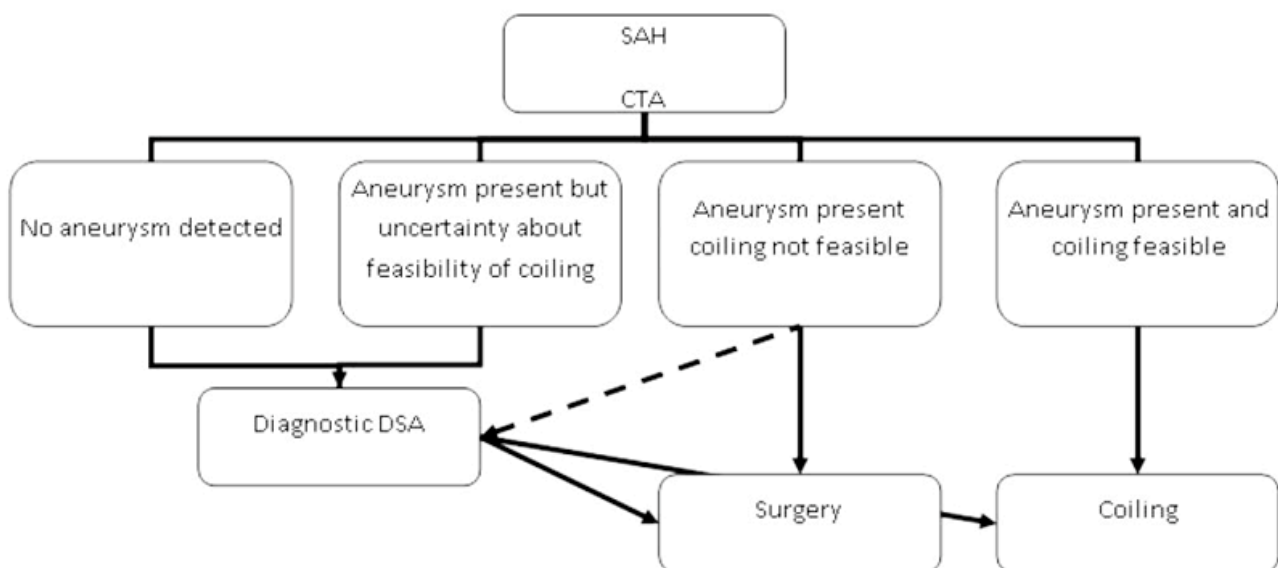


Figure 1. Flow chart of the work up of a patient presenting with a SAH.

However, performance of the additional CEMRA study did not delay treatment. Informed consent was obtained from all patients or, in unresponsive patients, from a legally responsible person. DSA served as reference standard in included patients.

The Institutional Review Board of our centre approved the study. Approval was also given by the National Centre for Patient Related Research (CCMO) because of the possible inclusion of patients who were unable to give informed consent.

Patients

All consecutive adult patients presenting with the diagnosis of a non-traumatic SAH were eligible to enter the study. The diagnosis SAH was established by CT or lumbar puncture.

Exclusion criteria were as follows: patients in whom there was a contraindication for MRI or in whom no further treatment was considered. A poor clinical condition was not considered a contraindication for inclusion, but if no reasonable chance of survival was expected by the treating physician, then no further diagnostic or treatment procedures would be undertaken and the patient was not included in the study.

Techniques

CTA

CTA was performed on a 2-slice (Elscent Dual, Elscint, Haifa, Israel) or on a 4-slice multidetector-row spiral CT scanner (Toshiba Aquilion, Toshiba, Tokyo, Japan). Scan parameters for the 2-slice scanner were: 120 kVp, 250 mAs, slice thickness 1.3 mm, pitch 0.7, FOV 250 mm, matrix 3402; and for the 4-slice scanner: 120 kV, 200 mAs, slice thickness 0.9 mm, pitch 0.67, FOV 230 mm, matrix 512. Reconstruction on both scanners to 0.5 mm slices. Contrast: iobitridol 350 mg/ml (Xenetix®, Guerbet, Villepinte, France), IV at 4 ml/s, total volume 125 ml, flushed with 40 ml NaCl 0.9 % at 4 ml/s. For the Elscint scanner a test contrast bolus of 20 ml was injected to determine the optimal interval between the start of contrast injection and the start of scan.

For the Toshiba scanner a detection slice through the internal carotid arteries was made; scanning began upon arrival of contrast in this slice. Scan direction in both scanners was from caudal to cranial.

In most cases a semi-automatic bone subtraction method, matched mask bone elimination (MMBE), was used. In this method a low dose-mask is acquired of the bony skull, after which the bone-containing voxels are extracted from the post-contrast images using a computer algorithm that compensates for movements between the scans [9-10]. In cases where the patient was too restless to undergo a mask CT scan before the contrast scan or in cases where the contrast scan could not be matched with the mask due to excessive movement between the scans, the contrast scan was evaluated using manual segmentation to remove the bony structures.

MRA

MRA was performed on a 1.5 Tesla Philips scanner using a dedicated head coil (Intera, Philips, Best, The Netherlands). The scan protocol included an ultra-short first-pass CEMRA with concentric k-space filling. The scan parameters were: parallel imaging (SENSE, factor 2), TR 5.4/TE 1.68 ms, flip angle 35 deg, FOV 256 mm (Rectangular FOV 65 %), matrix 512, slice thickness 0.4 mm, coronal orientation (parallel to basilar artery), one stack, 120 slices. Voxel size 0.5x0.8x0.4 mm. Contrast: gadopentetate dimeglumine (Magnevist®, Bayer Schering Pharma, Leverkusen, Germany) 35 ml IV, 3 ml/s (2 ml for a timing sequence and 33 ml for the CE-MRA sequence), flushed with 25 ml NaCl 0.9 % at 3 ml/s.

DSA

All patients underwent conventional catheter DSA technique (Integris, Philips Medical Systems, Best, The Netherlands). All four feeding arteries to the brain were catheterised and imaged with the exception of a few patients whom, due to patient unrest, only the vessel which contained the suspected aneurysm was catheterised. A 4 or 5F catheter system was used for diagnostic DSA and a 6F system in cases of immediate treatment. Automatic contrast injections were performed by a power injector (Medrad Inc., Warrendale, Pennsylvania, USA), of 9 ml iobitridol 350 mg/ml (Xenetix®, Guerbet, Villepinte, France) at 5 ml/s for the carotid arteries and 8 ml at 4 ml/s for the vertebral arteries. Internal carotid arteries were imaged in antero-posterior, lateral and oblique projections and the vertebral arteries in antero-posterior and lateral projections. Additional angiographic projections were obtained, if necessary, of the vessels that harbored an aneurysm, for better visualisation of the aneurysm, its neck and its surrounding arteries.

Image analysis and statistical analysis

The CTA and MRA studies were retrospectively evaluated by two independent observers on a dedicated workstation (Vitrea, Vital Images, Minnetonka, Minnesota, USA). Observers were able to use source images and interactively view volume rendered or maximum intensity projection (MIP) reconstructions. Observers evaluated both modalities in random order with an interval of at least 12 months between each modality. The DSA images were analysed by two independent observers; discordant results were settled by a third observer.

Scoring criteria included: quality of images, presence of aneurysm, size of aneurysm and diagnostic confidence. Quality of images and confidence in scoring were rated on a 3-point scale. Size was given in mm in two directions.

Sensitivity and specificity for the detection of aneurysms were calculated and compared with McNemar's test. ROC curves for the two modalities and two observers were calculated and the areas under the curve were compared. For ROC curve calculations the confidence scoring was transferred to a negative value if no aneurysm was found. The resultant values were used for cut-off points.

Cohen's Kappa was calculated for interobserver agreement.

Results

During an approximate 3-year period, a total of 189 patients entered our hospital with a SAH diagnosis. Of these 189 patients, 114 (60.3 %) were not included in the study for reasons set out in Table 1.

The characteristics of the total group of 189 eligible and of the 75 (39.7 %) included patients are given in Table 2. The parameters of the included patients did not differ significantly from the total group of eligible patients. All patients included in the study underwent DSA as part of their endovascular treatment or, sporadically, during diagnostic work-up, and these DSA studies were used as the standard of reference.

The quality of CTA images was rated as good in 62.7 % (47/75) by Observer 1 and 72 % (54/75) by Observer 2; CEMRA images were good in 82.7 % (62/75) by Observer 1 and 86.7 % (65/75) by Observer 2. The confidence rating of their final scoring per aneurysm (and per patient with no aneurysm) was "very

confident” in respectively 84.3 % (70/83, Observer 1) and 91.6 % (76/83, Observer 2) for CTA, and 88.0 % (73/83, Observer 1) and 94% (78/83, Observer 2) for CEMRA.

There were 18 patients without an aneurysm. Fifty patients had 1 aneurysm, 6 patients had 2 aneurysms and 1 patient had 3 aneurysms, making a total of 65 aneurysms. Locations of the aneurysms are given in Table 3.

Scoring results of the two observers for CTA and CEMRA are given in 2x2 (Tables 4a and 4b).

The sensitivity and specificity for the detection of an aneurysm by CTA and CEMRA with 95 % confidence intervals (CI's) are given in Table 5. There was no significant difference between the sensitivity and specificity of CTA and CEMRA tested with McNemar's test. Cohen's Kappa interobserver agreement in rating CEMRA and CTA was 0.82 and 0.85 respectively for the detection of an aneurysm. ROC curves are given in Figure 2. The areas under the curve (95 % CI) are 0.94 (0.90-0.99) and 0.96 (0.93-1) for CTA and 0.89 (0.79-0.99) and 0.91 (0.83-0.99) for CEMRA. The areas of CTA and CEMRA are not significantly different ($p=0.30$ for Observer 1 and $p=0.24$ for Observer 2).

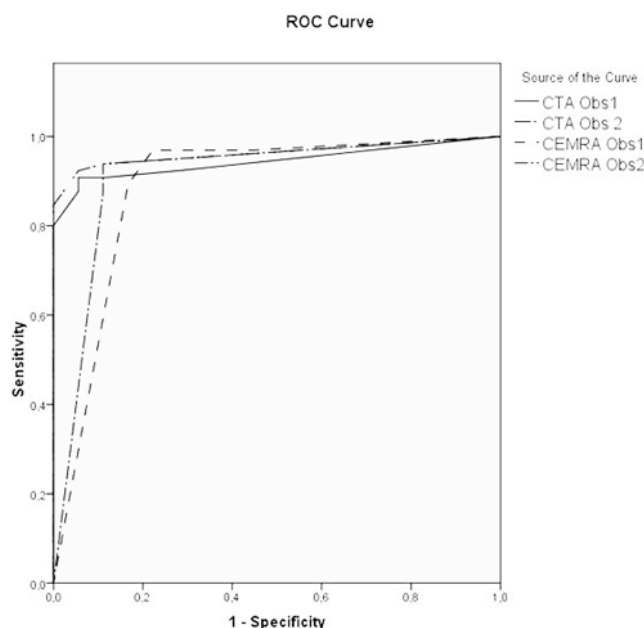


Figure 2. ROC curve for the detection of aneurysms by CTA and CEMRA by both observers.

No relation between aneurysm location and accuracy of detection was found.

One observer reported 4 aneurysms at CEMRA-all very small- that were not confirmed at DSA. One of these aneurysms, reported by both observers, appeared to be an infundibular widening of the origin of the left posterior communicating artery (Figure 3). One other aneurysm unconfirmed by DSA was (temporarily) thrombosed at the time DSA was performed. Because the study protocol states that DSA is the standard of reference, considering this finding a true aneurysm would be a violation of the study protocol. The other 2 aneurysms were seen only by Observer 1, located on the basilar tip (1.5x1.5 mm) and right middle cerebral artery (2x2 mm) respectively. These false positive findings represent either artifacts or irregularities of the vessel wall. None of 4 false positive aneurysms were registered by CTA. At CTA both

observers scored 1 false positive aneurysm, both located at the PICA, but in 2 different patients. In 1 of these 2 cases there was a dysplastic vertebral artery, rather than a true aneurysm. This was not considered as the bleeding source, but was reported by Observer 2 as an aneurysm. The other false positive PICA aneurysm reported at CTA was not seen on CEMRA or DSA.



Figure 3

(a) Lateral projection of a volume rendered reconstruction of the CEMRA scan of a patient presenting with an SAH. Both observers described a small left posterior communicating artery aneurysm.

(b) Lateral projection of the left internal carotid artery made by DSA of the same patient as in Figure 3a. It shows a posterior communicating artery with an infundibular widening.

In our study population 50.8 % (33/65) of the aneurysms were smaller than 5 mm and 18.5 % (12/65) were smaller than 3 mm. The sensitivities for detection of these small aneurysms are given in Table 6. For both observers sensitivity of detecting small aneurysms was slightly better with CEMRA than with CTA; however, this difference was not significant.

Discussion

This is the first report that directly compares the accuracy of CEMRA and CTA in the detection of cerebral aneurysms with a relevant number of consecutive patients. Scans of lesser quality due to patient movement or bolus timing problems were also included, reflecting the clinical situation.

We found no significant difference between CTA and CEMRA in the detection of intracranial aneurysms. In their meta-analysis, White et al. [1] calculated a pooled sensitivity and specificity (with 95 % CI) for detection of an aneurysm of 90 % (88-92) and 86 % (79-91) for CTA and 87 % (84-90) and 95 % (91-97) for MRA respectively. These results are in line with our study, even though our population contained a high percentage of small aneurysms (Figure 4 is an example of such a small aneurysm).

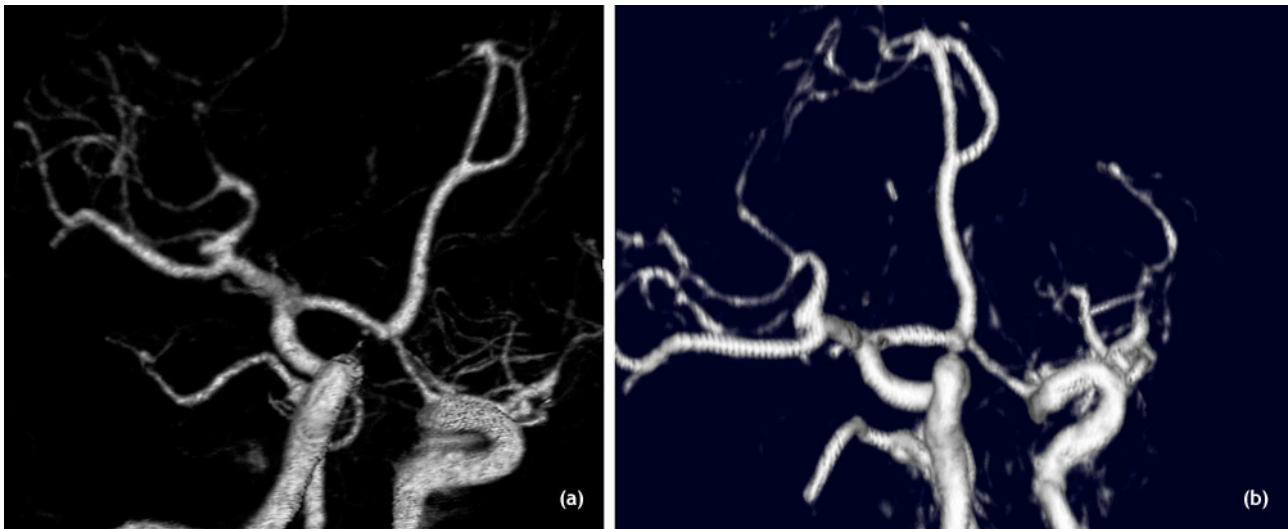


Figure 4

(a) Oblique projection of a volume rendered reconstruction of the CTA scan of a patient with a small right middle cerebral artery aneurysm. The aneurysm was properly described by both observers.

(b) Oblique projection of a volume rendered reconstruction of the CEMRA scan of the same patient as in Figure 4(a). The right middle cerebral artery aneurysm was not detected by both observers.

In the meta-analysis of White et al., sensitivity decreased to 61 % and 38 % for CTA and MRA respectively for aneurysms smaller than 3 mm. In their own prospective study, the sensitivity for small aneurysms was even lower: 57 % for CTA and 35 % for MRA for aneurysms smaller than 5 mm. In our series sensitivity for small aneurysms was considerably better for both modalities (Table 6).

Therefore, it seems that the improvement in scan techniques has led to better detection of small aneurysms, especially with MRA.

The sensitivity and specificity figures in our study are not as high as in previously published articles on the diagnostic performance of CEMRA in the detection of cerebral aneurysms [3-8], but because all acquisitions performed were included (no exclusions because of poor quality (Figure 5), it likely reflects a more realistic expression of the performance of CEMRA in daily clinical practice. It shows that the performance of CEMRA is not significantly different from that of CTA; moreover, it appears to be better than in the published studies using TOF-MRA [1-2].

In clinical practice where patients with negative CTA or CEMRA will undergo diagnostic DSA, specificity is of more importance than sensitivity. A false positive result may ultimately lead to an unnecessary surgical intervention [11] or a DSA examination at the start of a coiling procedure which is aborted when no aneurysm is found. In our series the specificity for CEMRA is lower than for CTA, although not significantly so.

In most hospitals MRI is less readily available than CT. Transporting the patient from the CT scanner, where the diagnosis of SAH is ideally made, to the MRI scanner for aneurysm detection and classification by CEMRA, is cumbersome, and patient monitoring is more difficult in the MRI room.

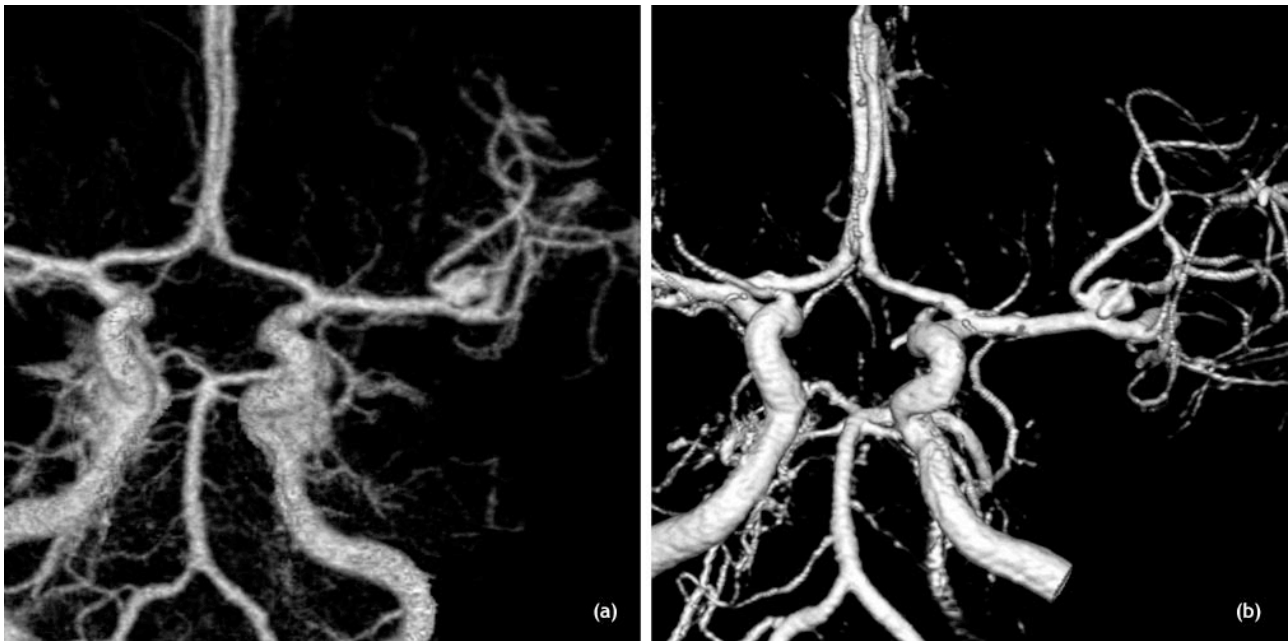


Figure 5

(a) Anteroposterior projection of a volume rendered reconstruction of the CTA scan of a patient with a left middle cerebral artery aneurysm. Despite suboptimal image quality due to venous contamination and movement artefacts both observers correctly described the aneurysm.

(b) Anteroposterior projection of a volume rendered reconstruction of the CEMRA scan of the same patient as in Figure 5a. The left middle cerebral artery aneurysm was properly described by both observers.

Furthermore, patient motion is more likely to degrade image quality with MRI than with CT. In our population only 6 patients were too restless to go into the MRI scanner, though they had already been able to undergo CTA. Contraindications such as pacemakers, intraocular metal fragments and claustrophobia will exclude another group (10 patients in our population). These MRI drawbacks make this modality less popular even though it has the advantage of not employing iodinated contrast media and ionising radiation [12].

The use of gadolinium chelates as a contrast agent for CEMRA involves the risk of inducing nephrogenic systemic fibrosis [13]. In the patient population included in our study this is normally not an issue: most SAH patients are relatively young and healthy and the risk of contrast-induced nephropathy from iodinated contrast media is higher [14]. In our population there were no patients with severe renal insufficiency. Additionally, the risk of other adverse reactions is higher with iodinated contrast material than with gadolinium based contrast agents [14].

Study limitations

Only 39.7 % of all eligible patients presenting during the study period were finally included, mainly due to logistical problems (lack of time for the informed consent procedure and performance of the additional CEMRA study). The patient characteristics and the prevalence of aneurysms, however, did not differ significantly between the total group of 189 presenting patients and the 75 included patients.

When patient inclusion for this study commenced it was not yet common practice to employ 3D rotational DSA. Therefore, we decided to use conventional 2D DSA as the standard of reference in all patients. In our practice, all patients with non-perimesencephalic and non-traumatic SAH, in whom the DSA study does not show an aneurysm, are studied by a second or even a third DSA. In the study population, these repeat DSA studies were performed with the knowledge of the CTA and CEMRA findings but no additional aneurysms were found with these repeat DSA studies (except for the 1 case described above where the thrombosed aneurysm was revealed on a second DSA some days later). Although this is not a guarantee that no additional aneurysms would be found if 3D DSA was used, this would not lead to difference in performance between CTA and CEMRA.

1.5T MRI scanners are still the systems mostly used. The use of 3T scanners has led to better results in the follow-up of coiled aneurysms [15-16], but this improvement has not yet been confirmed for the detection of aneurysms in patients presenting with a SAH.

The evolution in CT technique, on the other hand, from the 2- and 4-detector-row scanners used in our study to 16-, 64- and even 320-detector-row scanners, has definitely led to improved accuracy in the detection of intracranial aneurysms [17-20]. It is therefore likely that at the present time CTA with state-of-the-art CT-scanners performs significantly better than MRA in the detection of intracranial aneurysms.

Conclusion

Using the techniques available at the time of the study, our results indicate that CEMRA does not appear to provide superior diagnostic performance compared to CTA for the detection of cerebral aneurysms in this patient population. Improvements in CTA technique make it unlikely that with present state of the art equipment CEMRA will gain preference over CTA.

Conflict of interest

We declare that we have no conflict of interest.

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Tables

Table 1 - Reason for exclusion.

Table 1	N
- Not enough time between CTA and treatment to perform MRA	57
- Declined additional MRA	22
- Condition too poor to plan further treatment	11
- Contra-indication for MRI	10
- Patient distress, MRA not possible	6
- Died before MRA	4
- No informed consent before treatment (no MRA made)	2
- Died before DSA and treatment, after MRA	1
- Transferred to other hospital for treatment	1
Total excluded	11

Table 2 - Characteristics of the total group of eligible patients and the included patients.

Table 2	Total eligible pt	Included pt	P-value
N	189	75	
Female (%)	138 (73)	54 (72)	0.88
Mean age	54.5	54.0	
SD age	13.9	15.1	
Pt without aneurysm (%)	40 (21.2)	18 (24.0)	0.62
Total aneurysms	189	65	

Table 3 - Location of the aneurysms.

Table 3	N
Internal carotid artery, including posterior communicating artery, carotid tip and ophtalmic artery	14
Anterior cerebral artery, including anterior communicating artery	19
Middle cerebral artery	20
Vertebrobasilar complex (basilar tip)	12 (8)

Table 4a - 2 x 2 table of both observers assessing the CTA images.

^[a] Number of patients without an aneurysm. ^[b] Total number of aneurysms.

			CTA			
			Observer 1		Observer 2	
			-	+	-	+
DSA	18 ^a	-	17	1	17	1
	65 ^b	+	6	59	5	60
		Total	23	60	22	61

Table 4b - 2 x 2 table of both observers assessing the MRA images.

^[a] Number of patients without an aneurysm. ^[b] Total number of aneurysms.

			MRA			
			Observer 1		Observer 2	
			-	+	-	+
DSA	18 ^a	-	14	4	16	2
	65 ^b	+	2	63	4	61
		Total	16	67	20	63

Table 5 - Sensitivity and specificity (95% CI) of CTA and CEMRA for the detection of aneurysms.

Table 5		CTA	CEMRA
Sensitivity	Obs 1	90.8 (81.0 - 96.5)	96.9 (89.3 - 99.6)
	Obs 2	92.3 (83.0 - 97.5)	93.8 (85.0 - 98.3)
Specificity	Obs 1	94.4 (72.7 - 99.9)	77.8 (52.4 - 93.6)
	Obs 2	94.4 (72.7 - 99.9)	88.9 (65.3 - 98.6)

Table 6 - Sensitivity of CTA and CEMRA for the detection of small aneurysms

Table 6		All (n=65)	<5mm (n=33)	<3mm (n=12)
CTA	Obs1	90.8	84.8	75
	Obs2	92.3	84.8	75
CEMRA	Obs1	96.9	96.9	91.7
	Obs2	93.8	90.9	83.3