Original article

Subtractive magnetic resonance angiography: description of a new diagnostic technique

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***SUMMARY:* AIMS.** *The most widely non-invasive technique used for the intracranial circulation's evaluation is magnetic resonance angiography. Particularly 3D time-of-flight sequences are the most useful because they are less susceptible to turbulent flow artefacts compared to phase contrast ones. time-of-flight sequences however have some limitations, among which one of the most important is that it's impossible to suppress the acute - subacute blood's signal. We have developed a technical improvement (denominated subtractive magnetic resonance angiography) of the time-of-flight sequences that will remove the blood's signal and improves intracranial vessels' contrast resolution. The aim of our work was to evaluate benefits and limitations of this new technique.*

MATERIAL AND METHODS. *We carried out a comparative evaluation between the conventional technique and the new technique both on twenty healthy volunteers and on twenty-two patients with intracranial vascular disease. Visually comparative evaluation between conventional and subtractive magnetic resonance angiography was carried out.*

RESULTS. *We showed that the subtractive technique improves the cerebral vessels' visualization especially when T1 hyperintense tissues are in the background (for example, blood debris or fat). Moreover, regarding the remaining normal or pathological vessels visualization, the resolution was the same as the conventional technique.*

CONCLUSIONS. *In conclusion, the subtractive technique may be usefully adopted for the intracranial circulation's evaluation especially during acute - subacute brain bleeding.*

KEY WORDS: *Angiography, Magnetic resonance, Technique, Time-of-flight sequences.*

INTRODUCTION

Intracranial circulation's MRA evaluation is usually carried out with TOF or PC sequences[15,19,24,27].
MRA is frequently adopted for intracranial vessels' evaluation, mainly for arterial stenosis and aneurysms visualization. Instead the AVM and dural fistulas' studies are difficult with both technique[1,6,18,21,29,30].
Intracranial aneurysms and arterial stenosis are properly displayed with 3D TOF technique because, unlike PC sequences, the former are less sensitive to spin dephasing effect resulting from turbulent flow[8,10,12,13,16].
Then the gold standard technique for noninvasive study of intracranial vessels is 3D TOF one.
We carried out a technical improvement applied to 3D TOF sequences and, in this study, its benefits and limits were evaluated.
One of the most important restrictions of TOF technique is the inability to fully saturate the static

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LIST OF ACRONYMS AND ABBREVIATIONS: **ACoA** = Anterior Communicating Artery; **AVM** = Arterio-Venous Malformations; **CTA** = Computed Tomography Angiography; **DSA** = Digital Subtraction Angiography; **FFE** = Fast Field Echo; **FISP** = Fast Imaging Steady Precession; **FLAIR** = Fluid Attenuated Inversion Recovery; **FOV** = Field Of View; **FSE** = Fast Spin Echo; **ICA** = Internal Carotid Artery; **MCA** = Middle Cerebral Artery; **MIP** = Maximum Intensity Projection; MR = Magnetic Resonance; **MRA** = Magnetic Resonance Angiography; **NEX** = Number Of Excitations; **PC** = Phase Contrast; **PD** = Proton Density; **PICA** = Posterior Inferior Cerebellar Artery; **SE** = Spin Echo; **T** = Tesla; **TE** = Time to Echo; **TOF** = Time-of-flight; **TR** = Time of Repetition; **VENC** = Velocity ENConding.

protons' signal. This limit is especially restrictive when short T1 tissues are in the background. Indeed, because in TOF sequences signal partly depends from T1 relaxation time, such tissues can mimic the signal flow making it impossible the correct vessels' identification[10,16,19,24,29].

Short T1 tissues can be detected in subacute bleeding or in cavernous angiomas (extracellular methemoglobin), in embolized aneurysms (ferromagnetic artefacts) and finally in any calcified or fatty lesion (neoplasms).

The technical improvement we found requires the acquisition, before conventional 3D TOF images, of a sequence exactly the same as diagnostic TOF but with complete flow signal's saturation. This sequence (without flow signal) was used as a "mask" for a digital subtraction process with the conventional TOF; the result was a complete deletion of the static protons' signal, similarly to digital angiography. To obtain the mask we simply acquired a conventional TOF sequence with a saturation pulse placed at the neck, to eliminate the arterial "inflow" signal (Figure 1). After achieving this mask was sufficient to carry out a digital subtraction with conventional sequence to obtain images only with flow signal, completely eliminating static tissues' signal, even if they were hyperintense (Figure 2).

Moreover the fully static protons' signal saturation increases the vessels resolution, thereby improving their visualization.

Aims. The aim of our work was to evaluate benefits and limitations of the new technique, in comparison to the conventional one, both on healthy volunteers and on patients with intracranial vascular disease.

□ MATERIALS AND METHODS

Twenty healthy subjects (12 males and 8 females with an age range between 25 and 68 years, average 43.85 years) and 22 patients with intracranial vascular disease (12 males and 10 females aged between 38 and 82 years, average 60.1 years) were studied in a comparative manner, evaluating the MIP reconstructions derived from subtraction images and those obtained from conventional ones.

As regards the pathological cases in 9 patients a cerebral aneurysm was found: two cases with giant not treated partially thrombosed aneurysm, one small size aneurysm originating from PICA studied after embolization treatment; the remaining six were not treated lesions: five small size aneurysms and one large size lesion; the five small aneurysms originated in two cases from the bifurcation of the MCA, in two cases from ACoA and in one case from the sovra-clinoid segment of the ICA. The large aneurysm originated from the basilar artery's apex.

We also studied: 5 patients with acute or subacute intra-axial cerebral hematomas, 2 patients with cavernous angiomas, a patient with previous cerebral ischemic stroke with dystrophic mineralization phenomena due to cortical laminar necrosis which appeared hyperintense in T1-weighted images, 5 patients with AVM, including 2 treated and 3 no and one patient with MCA stenosis.

A 1.5 T magnetic resonance equipment with 23 mt/m gradients (*Philips Gyroscan ACS-NT 3000*) was used for all healthy subjects' studies. The pathologic cases were studied with the 1.5 T unit and partly with a 3 T 45 mt/m gradients unit (*Siemens, Magnetom Verio*).

With both the equipment the following morphological sequences were acquired for each study: axial SE T1-weighted, axial FSE T2-weighted and PD, axial FSE FLAIR T2-weighted. Instead MRA sequences adopted in the 1.5 T studies were 3D TOF FFE (TR 25 ms, TE 6.9 ms, matrix 496x512, FOV 220 mm, 80 slices, 1 slab, thickness 0.7 mm, 1 NEX), while those used in the 3 T unit were 3D TOF FISP (TR 31 ms, TE 3.78 ms, matrix 486x512, FOV 190 mm, 40 slices, 4 slabs, thickness 0.4 mm, 1 NEX).

The volume acquired with angiographic 3D TOF sequences included the intracranial arteries from C3 segment of the ICA, up to A3 section of the anterior cerebral arteries. Thus, this volume includes the main intracranial arteries with exclusion of both PICA and the intracranial tract of vertebral arteries.

The venous signal's deletion has been obtained by a saturation pulse above the acquisition's volume.

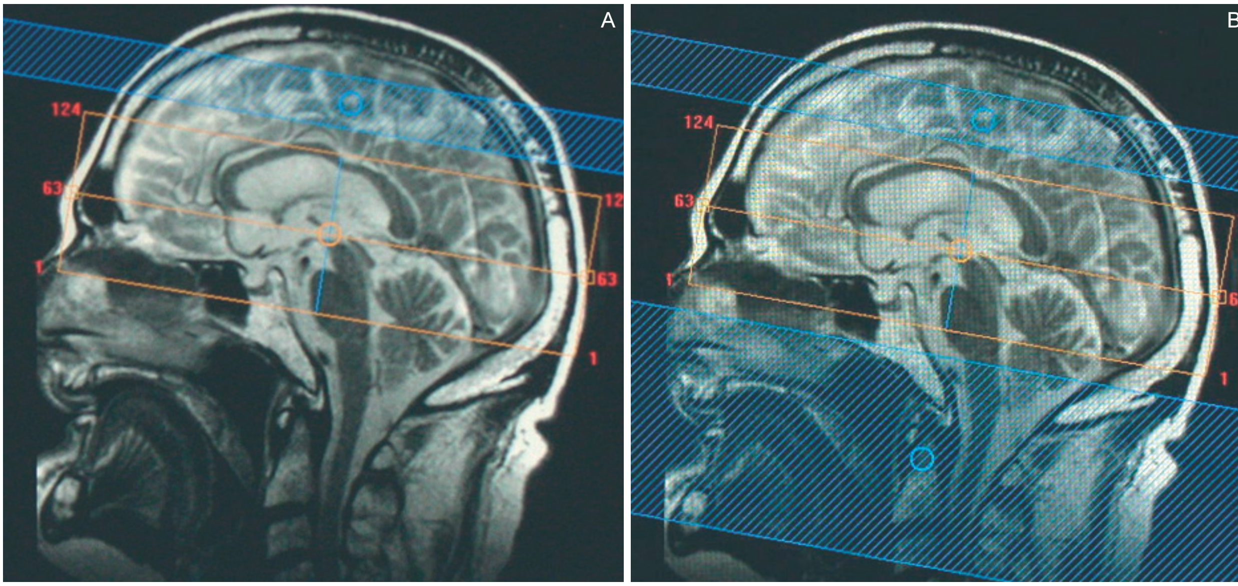


Figure 1. Description of the subtractive technique. Two identical sequences were acquired: the first with conventional technique (A) and the second with a saturation pulse at the bottom that removes the vascular flow's signal (B); the latter was used as a mask.

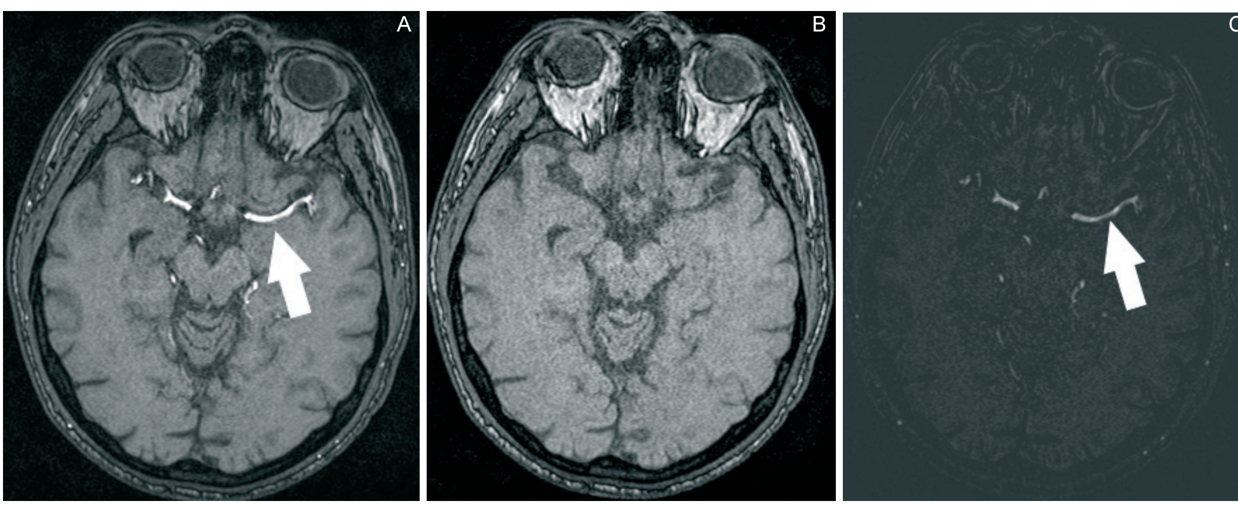


Figure 2. Description of the subtractive technique. A single partition of the conventional sequence (A), the same partition of the mask (B) without flow signal. The third image (C) is the result of the digital subtraction between A and B: only signal flow was displayed with complete removal of the background.

To achieve the mask we have acquired an identical sequence with at most a second saturation pulse below the acquisition volume. The two sequences were sequentially and randomly acquired.

None of the patient was excluded from the series for non-cooperation and therefore inaccurate overlapping of the two angiographic sequences.

Digital subtraction images were subsequently carried. Finally, both conventional and subtracted sequence, were elaborated by means MIP reconstruction, with at least 40 projections, using a dedicated work station (*Easy Vision, Philips*) by a single author.

All patients with cerebral hematoma, aneurysm or AVM were also studied with DSA.

Visually comparative evaluation of both MRA techniques was carried out by two authors. The inter-observer variability was assessed by calculating "inter-observer agreement index".

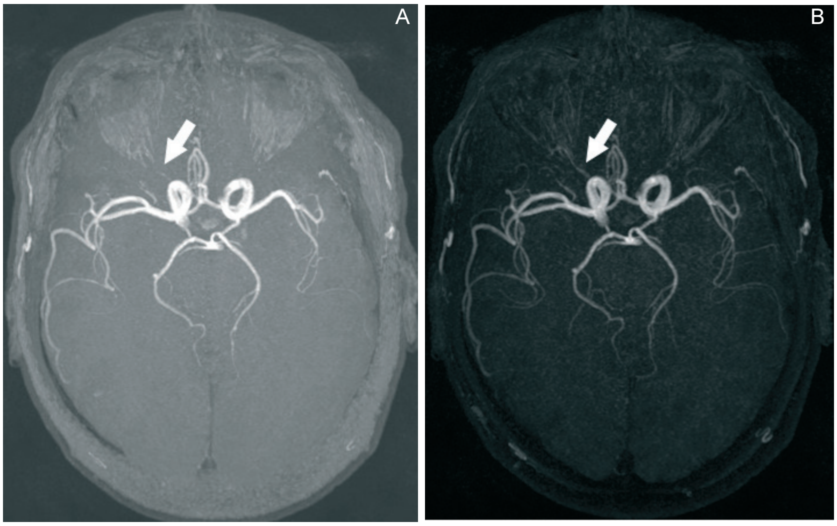


Figure 3. Ophthalmic artery (*arrow*) visualization with conventional (A) and subtractive technique (B). The latter image better displays the artery.

In normal controls number and length of the cerebral arteries displayed were evaluated.
In patients, in addition to the evaluation of normal brain arteries, made as in the controls, visualization of pathological vessels was assessed, always in a comparative manner between the two techniques.

□ RESULTS

Regarding the healthy subjects' evaluation a better visualization of ophthalmic artery with subtractive technique in 28 cases out of 40 was showed, since a large part of this artery's course occurs in orbital fat (Figure 3).
The remaining intracranial arteries were displayed with the same resolution with the two techniques.
Therefore in no case the conventional technique was superior to subtractive one.
Instead as it regards for the patients' evaluation, when background hyperintense tissues were present, it was possible to delete its, obtaining vascular images not disturbed.
This advantage has been achieved in the 5 acute/subacute cerebral hematomas (Figure 4), in the two thrombosed giant aneurysms (metahemoglobin) (Figure 5), in the two cavernous angiomas (metahemoglobin) (Figure 6), in embolized aneurysm, because Guglielmi's coils showed hyperintense signal (Figure 7) and in the patient with cortical laminar necrosis, spontaneously hyperintense in T1-weighted images too (Figure 8).
Regarding patients with small and large untreated aneurysms we founded in all 4 cases a similar lesions' visualization with both sequences without limitations for subtractive technique (Figure 9).
Even in patients with AVM we did not find significant differences between the two techniques (Figure 10).
Finally also in the patient with Sylvian artery's stenosis, we have not found differences between the two techniques as it concerns the lesion's visualization (Figure 11).
The "inter-observer agreement index" was 98.3.
In no case, therefore, the conventional technique proved better of subtractive one to show the pathological processes studied.

□ DISCUSSION

MRA is the method of choice for non-invasive study of intracranial arteries' pathological processes[12,23,27,29].
As we have seen above, two are the angiographic techniques which are used in MRA routine practice: the TOF and PC sequences.
Both are useful in providing good quality angiographic images, but differentiate between them for the acquisition way.
The TOF method is the better for different reasons: it is the most commercially widespread and then used the most, it is more suitable for the fast and turbulent flows (arterial) studies, has shorter acquisition times of that PC and it is characterized by a better spatial resolution each the other[19,24,28].
3D TOF sequences, on the other hand, have some

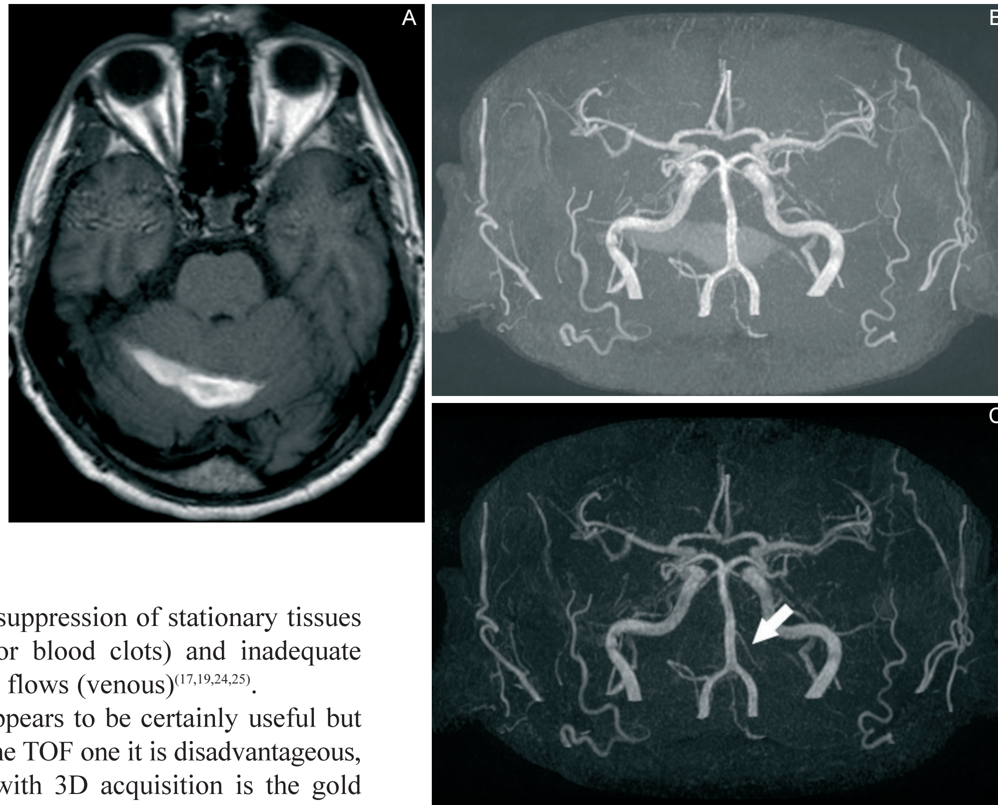


Figure 4. Intra-axial cerebellar haematoma. The lesion is hyperintense in T1-weighted image (A) due to extracellular methemoglobin; in conventional MRA (B) this tissue mimics flow signal, while in subtractive MRA (C) background signal is completely removed and left anterior-inferior cerebellar artery (*arrow*) is displayed. In this patients digital subtraction angiography examination don't show any vascular malformations.

limits: such as poor suppression of stationary tissues with short T1 (fat or blood clots) and inadequate visualization of slow flows (venous)[17,19,24,25].

The PC technique appears to be certainly useful but in comparison with the TOF one it is disadvantageous, and then the latter with 3D acquisition is the gold standard in arterial intracranial MRA studies.

In fact the PC technique although presents some advantages in comparison to TOF as: optimal slow flows visualization without signal's saturation (particularly suitable in intracranial venous circulation's studies) and complete stationary tissue saturation, on the other hand is limited by numerous restrictions than TOF as: long acquisition time, most sensitive to intravoxel dephasing and susceptibility artefacts and the need to optimise the VENC value as a function of the cardiac stroke[10,12,25,27].

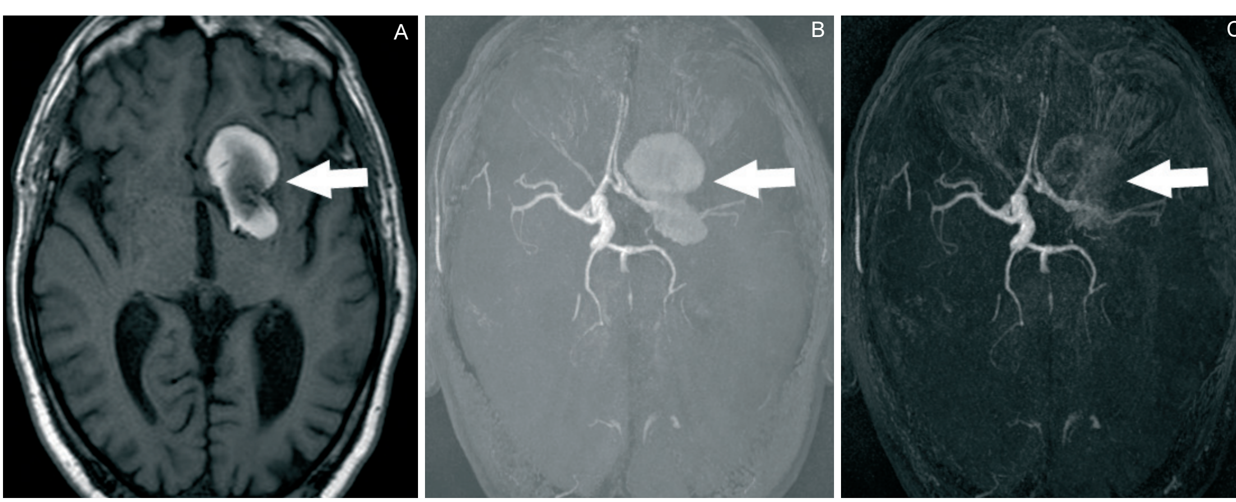
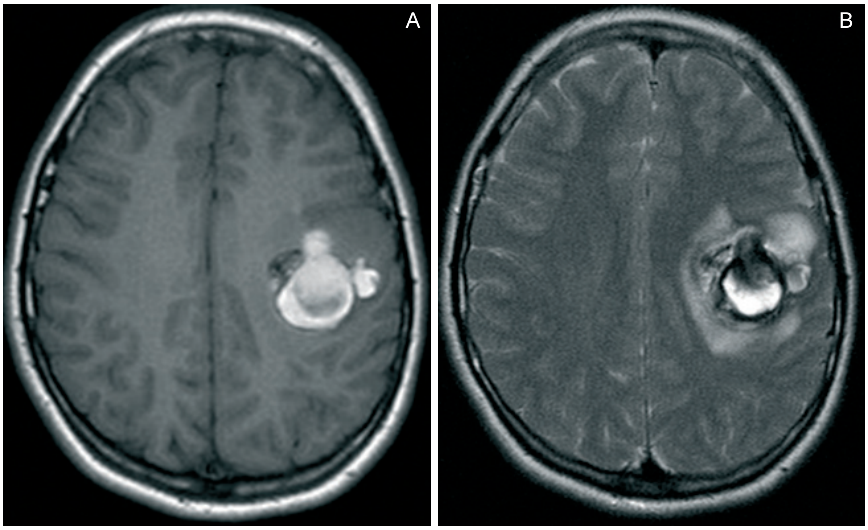


Figure 5. Left middle cerebral artery partially thrombosed giant aneurysm (arrow). The clotted blood shows in T1-weighted image (A) hyperintense signal and then, likewise to the figure 4 haematoma, conventional MRA image (B) is disturbed by extracellular methemoglobin, while subtractive MRA image (C) not.



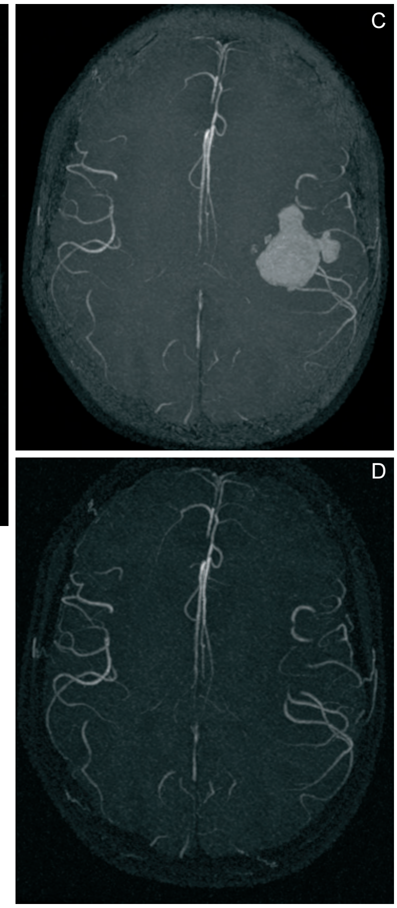


Figure 6. Cavernous angioma (surgically proved). In T1-weighted image (A) the lesion is predominantly hyperintense due to extracellular methemoglobin. In T2-weighted image (B) peripheral hemosiderin is showed. Likewise Figure 4 and 5 cases in conventional MRA (C) the hyperintense tissue overlaps vascular images, while in subtractive MRA (D) blood signal is removed.

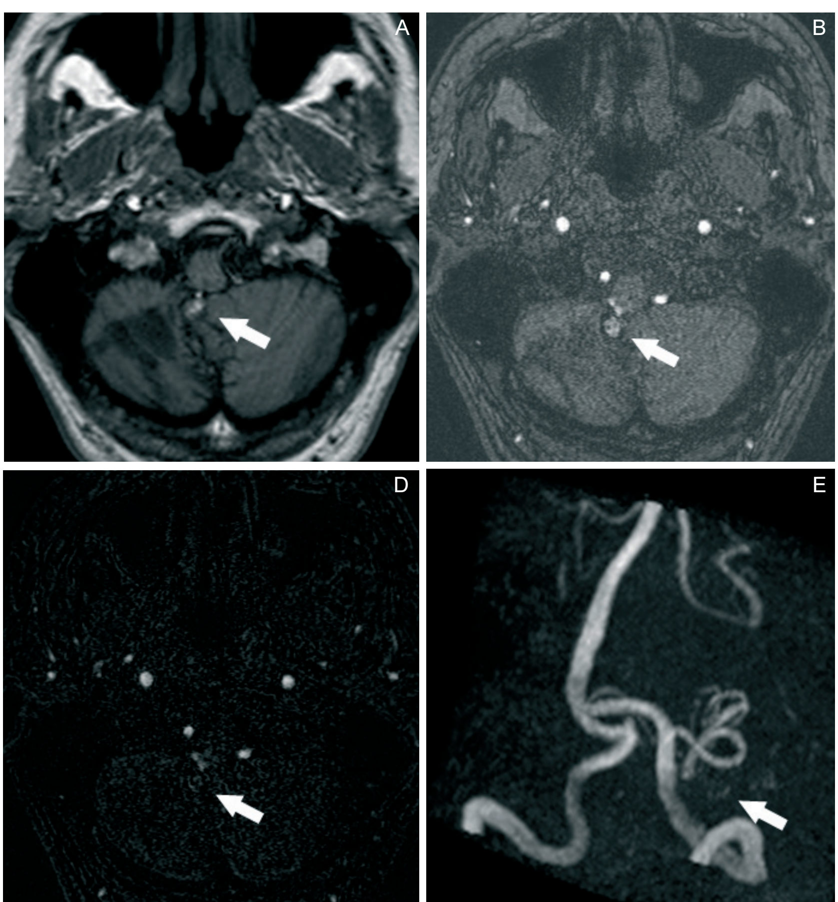
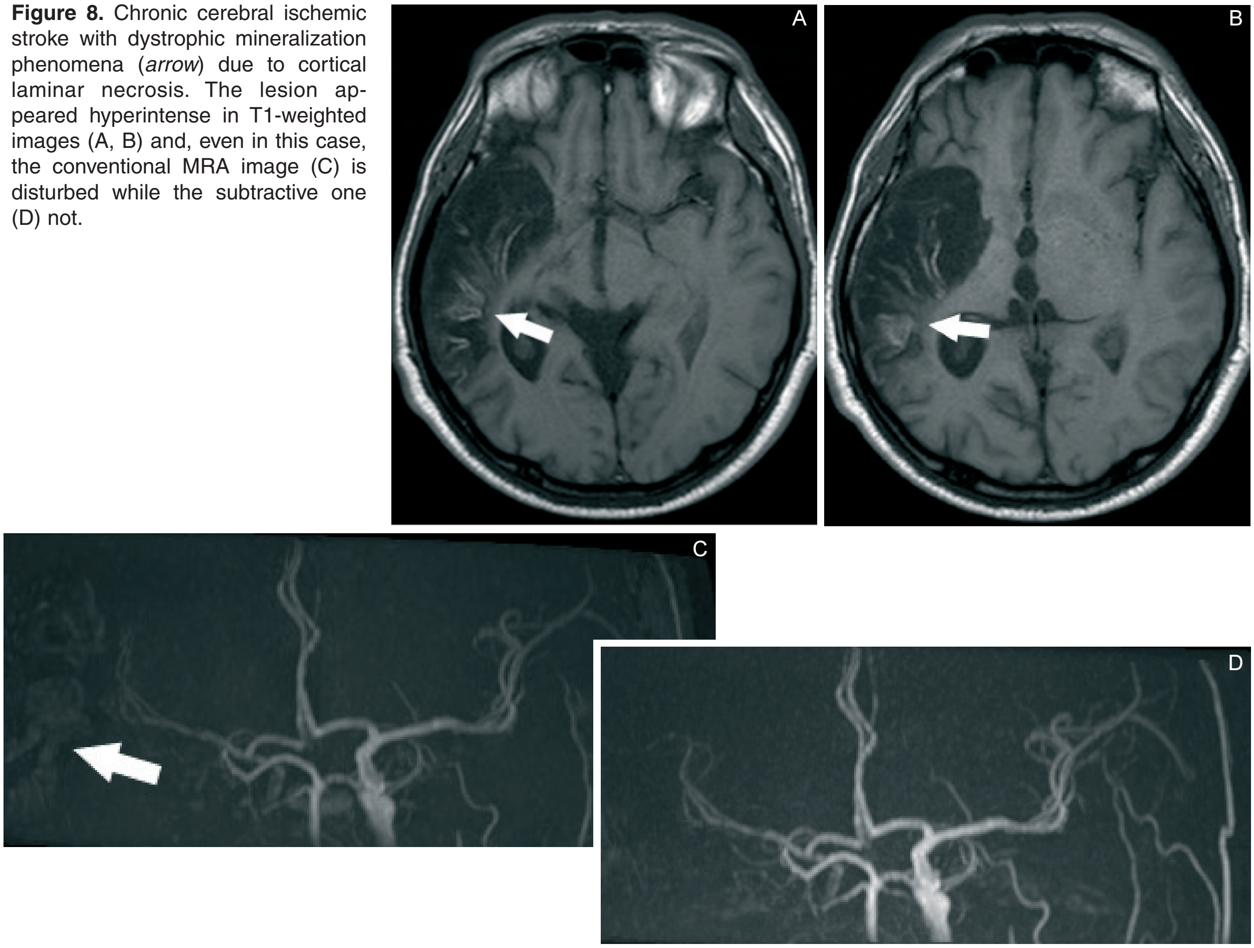


Figure 7. Embolized PICA aneurysm. In T1-weighted imaged (A) hyperintense ferromagnetic artefact (*arrow*) is showed. This artefact is visualized in conventional MRA too, both in single partition (B) and in MIP reconstruction (C); instead subtractive MRA is not disturbed (D: single partition, E: MIP reconstruction).

Figure 8. Chronic cerebral ischemic stroke with dystrophic mineralization phenomena (*arrow*) due to cortical laminar necrosis. The lesion appeared hyperintense in T1-weighted images (A, B) and, even in this case, the conventional MRA image (C) is disturbed while the subtractive one (D) not.



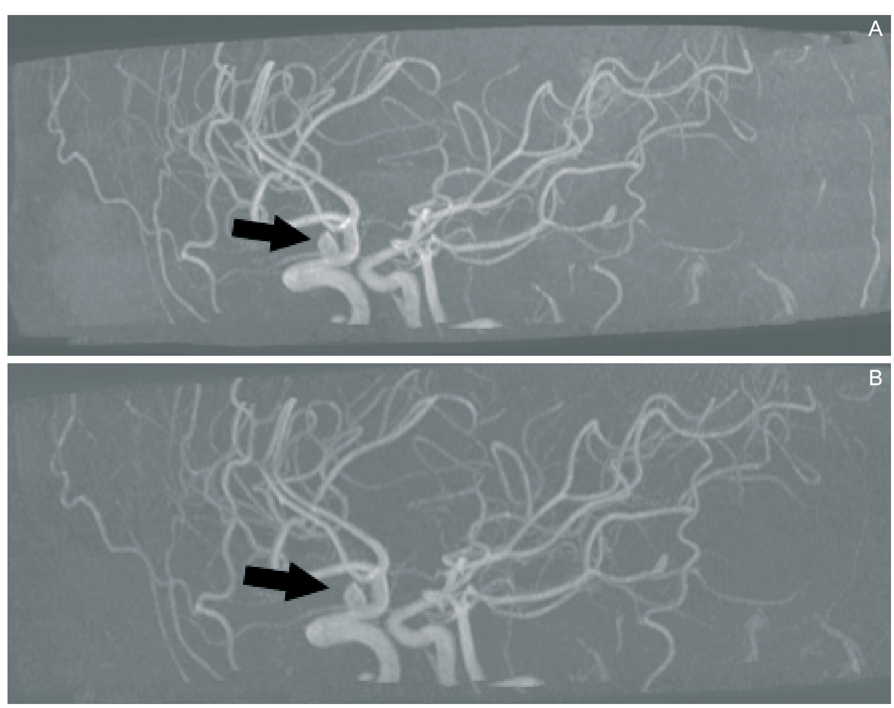


Figure 9. Not treated sovraclinoid internal carotid artery aneurysm (*arrow*). The lesion, both with conventional MRA (A) and with subtractive technique (B), is properly showed.

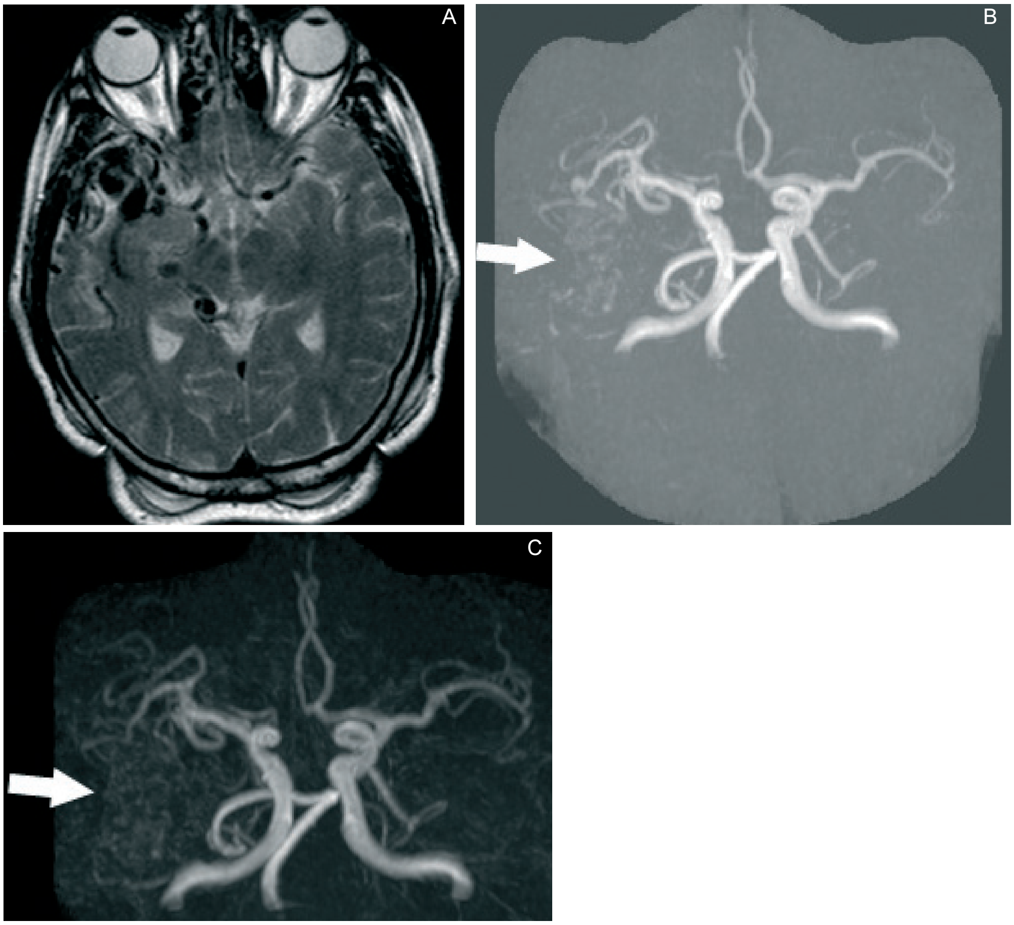


Figure 10. Not treated arterio-venous malformation (*arrow*). T2-weighted sequence (A) with typical signal void images. Also in this case both techniques (conventional: B and subtractive: C) properly showed the lesion.

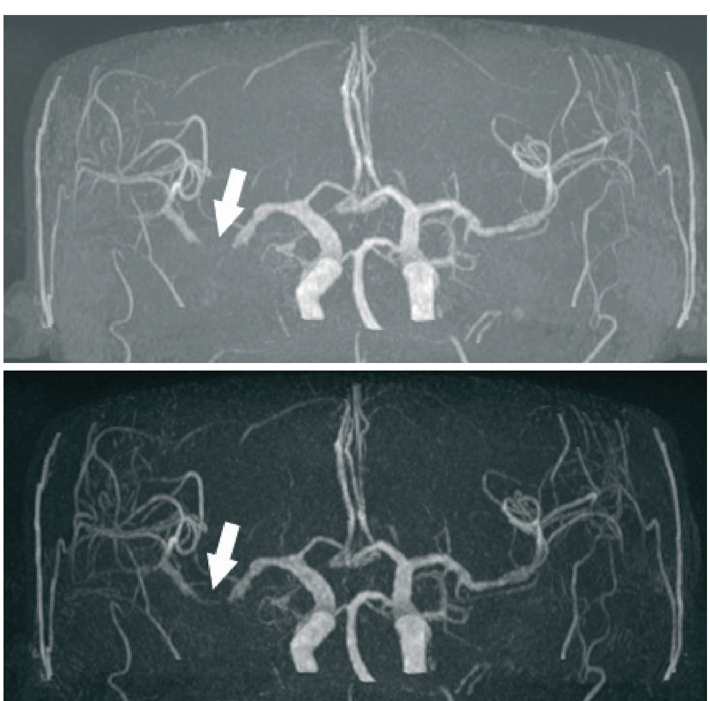


Figure 11. Right middle cerebral artery stenosis (*arrow*). The lesion visualization is the same both with conventional (A) and subtractive MRA (B).

Huston. et al.[11] have carried out a comparative evaluation between the two main techniques (TOF and PC) for the vascular intracranial diseases' evaluation. The study included 27 patients with aneurysms or vascular malformations. The TOF technique superiority for the evaluation of small and medium size aneurysms was demonstrated while the PC sequences were slightly better to evaluate high flow vascular malformations despite a resolution clearly worse respect DSA.

As regards the intracranial vascular stenosis' evaluation, Fujita. et al.[5] identified with high diagnostic sensitivity middle cerebral artery's stenosis with 3D TOF MRA in comparison with DSA, so showing that MRA can be used for a non-invasive evaluation of this pathology.

In recent years CTA, thanks to recent technological developments, enables intracranial circulation's evaluation with quality comparable to MRA.

However CTA has some important limitations such as: high ionizing radiation dose absorbed by the patient, the use of a contrast media presenting risks of adverse reaction and finally the vascular signal not always is dissociable from that of the hyperdense tissues (bone).

Several comparative studies between CTA and MRA confirmed this data[3,4,7,9,14,20,22]. In one of the first published studies Schwartz RB. et al. have shown that, in 21 patients with 30 aneurysms, the diagnostic sensitivity and specificity of the two techniques were similar, however, the MRA is preferred because less invasive[26].

Subtractive MRA was described in a previous our but only as a technical note on a few healthy volunteers and with low field MRI equipment[2].

Our new MRA technique has proven more useful than the conventional one.

Our method presents a significant advantage compared to that conventional: the fully short T1 tissues' signal elimination and particularly the signal of meta-hemoglobin, without the need for PC sequences, that are particularly unsuitable for the turbulent flows' evaluation (which are always present in aneurysms and in vascular stenosis).

This benefit allows an optimal evaluation of all patients suffering from vascular disease and presenting intracranial tissues hyperintense in T1, as long as the patient is collaborating since our method has an acquisition time longer than that of the traditional TOF.

We verified that, both in volunteers and in patients suffering from AVM, aneurysms and arterial stenosis, the visualization of normal and pathological vessels were similar both with conventional and subtractive MRA.

Therefore the subtractive technique has been shown to have a diagnostic potential equal to the conventional one, but with the advantage to be adopted for the intracranial circulation visualization also during cerebral bleeding in acute-subacute stage.

Our technique is simple to apply and presents further advantages.

First of all it can be used with any MRA sequence using the time of flight effect, with any MR equipment and with any field strength and magnet's type.

Moreover it can be used both for arteries or veins evaluation and to study each vascular district, even if we believe that probably the intracranial circle is the most suitable for subtractive method since in this district vessel's significant involuntary movements aren't usually present.

Finally, the subtractive technique enables to visualize the vessels with better contrast resolution respect the conventional one, without signal flow loss.

Our results shows that this novel technique allows to obtain diagnostic results as the conventional one, however, with respect to the latter it has the advantage of eliminating the blood's signal, that is characterized by a short T1 relaxation time, and therefore is equal to flow protons. This implies that, during bleeding, cerebral MRA study is poorly diagnostic because both the arteries and the hematoma are simultaneously displayed by overlapping the signal. Subtractive technique we have proposed removes this limitation because is possible to delete the signal of all the static protons, even those hyperintense in T1. Therefore it can be usefully adopted to eliminate the extracellular meta-hemoglobin's signal (parenchymal acute or subacute bleeding or cavernous angiomas), to remove dystrophic tissue hyperintense in T1 (for example, mineralization phenomena in previous laminar cortical necrosis after ischemia), to eliminate artefacts (for example, in aneurysms embolized with Guglielmi's coils) and finally to improve the visualization of vessels adjacent to adipose tissue (for example, the ophthalmic artery).

Finally it is a technique absolutely risk free and free of additional costs not being necessary to administer the contrast medium.

Only disadvantage is a relative long acquisition time, but acceptable by a cooperative patient. This may be a significant limitation and, for this reason, we don't recommend the extensive use of the new technique in all patients. Its indications are very robust when a bleeding in the subacute phase is found and thus in this case its adoption is strongly recommended. As for the elimination of ferromagnetic artefacts it can be taken only in cases where these are significant and inhibit a correct vessels' visualization. The optimally visualization of intra-orbital vessels is a minor advantage that can only be used in selected cases.

☐ CONCLUSIONS

In conclusion our subtractive technique enables to perform a non-invasive study of cerebral circulation in patients with acute-subacute bleeding with no artefacts or other limitations, which are instead present with conventional TOF technique. The subtractive technique also has other advantages, but of lesser clinical impact, over the conventional one (removal of metallic artefacts in embolized aneurysms and optimally visualization of the ophthalmic artery).

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Disclosure. *The Authors declare that they have no conflict of interest.*