Measurement of Blood Flow in Arteriovenous Malformations before and after Embolization Using Arterial Spin Labeling

L. SUAZO¹, B. FOERSTER², R. FERMIN¹, H. SPECKTER¹, C. VILCHEZ¹, J. OVIEDO¹, P. STOETER¹

¹ CEDIMAT, Plaza de la Salud; Santo Domingo, Republica Dominicana; ² Philips Healthcare; Tamboré, Barueri, Brazil

Key words: embolization, arteriovenous malformations, shunt, arterial spin labeling

Summary

The assessment of shunt reduction after an embolization of an arteriovenous malformation (AVM) or fistula (AVF) from conventional angiography is often difficult and may be subjective.

Here we present a completely non-invasive method using magnetic resonance imaging (MRI) to measure shunt reduction. Using pulsed arterial spin labeling (PASL), we determined the relative amount of signal attributed to the shunt over 1.75 s and 6 different slices covering the lesion. This amount of signal from the shunt was related to the total signal from all slices and measured before and after embolization.

The method showed a fair agreement between the PASL results and the judgement from conventional angiography. In the case of a total or subtotal shunt occlusion, PASL showed a shunt reduction between 69% and 92%, whereas in minimal shunt reduction as judged by conventional angiography, the ASL result was -6% (indicating slightly increased flow) to 35% in a partially occluded vein of Galen aneurysm. The PASL method proved to be fairly reproducible (up to 2% deviation between three measurements without interventions). On conclusion, PASL is able to reliably measure the amount of shunt reduction achieved by embolization of AVMs and AVFs.

Introduction

Arteriovenous malformations (AVMs) and arteriovenous fistulas (AVFs) are characterized by a loss of the normal capillary bed,

which is replaced by a nidus of abnormally enlarged vessels in the case of AVMs or a direct connection between arteries and draining veins in the case of AVFs. In both instances, a fair amount of blood is shunted from the arterial to the venous side. Embolizations aiming to occlude these shunts are successful only in a minority of cases, but in most interventions only some reduction of the shunted blood volume is achieved. The “success” of such an intervention is usually expressed as percentage of nidus reduction as judged by conventional angiography taking into consideration the change in extension of the nidus as well as the change in flow. More than 20 years ago, the measurement of cerebral blood flow (CBF) in patients with AVMs by means of single photon emission tomography (SPECT) was mainly performed to investigate perinidal perfusion deficits and the pressure-break-through phenomenon¹⁻⁶. The same applies to studies using positron emission tomography (PET)^{7,8} or xenon-enhanced computed tomography^{9,10}. There are only a limited number of perfusion studies directed to the shunt itself, specifically to the reduction of shunted blood volume after occlusion or removal of the AVM, either by Doppler sonography¹¹, red blood cell scintigraphy¹², PET^{13,14}, or by more recent techniques as MR- and CT perfusion measurements depending on injection of contrast medium¹⁵⁻¹⁸. The completely non-invasive method of arterial spin labeling (ASL) has been applied as well to measure nidus/shunt perfusion¹⁹, but was used as a post-interventional control only in one AVM²⁰ and three dural AVFs²¹.

Here, we report the results of a prospective study of ASL perfusion measurements for estimation of shunt reduction before and after embolization of eight cerebral AVMs and two AVFs in 12 interventions.

Patients and Methods

Patients and Interventions

Embolizations were performed in eight patients with AVMs, in one dural AVF of the cavernous sinus fed by dural branches of the ophthalmic and middle meningeal artery, and in one case of a vein of Galen aneurysm (VOGA). Six of the eight AVMs and the VOGA were high-flow lesions, whereas the other two AVMs and the dural AVF were low-flow lesions. In six cases (five AVMs and the VOGA), a previous embolization had been carried out. Six of the eight AVMs were embolized once and two AVMs were embolized twice using a mixture of Histoacryl® and Lipiodol®. The reduction of the arteriovenous shunt after the intervention was estimated from the control angiography at the end of the procedure. According to these findings, we achieved a shunt reduction of 90 to 100% in two AVMs, of 30 to 50% in four AVMs (in two of them on the second intervention) and of ten to 20% in the other four AVMs. The dural AVF could be occluded to 90% by glue injection into the supplying branches of the middle meningeal artery, whereas in the VOGA, the shunt was reduced only by 10%. The interventions were tolerated well without clinical complications. Further details as age and gender of patients and Spetzler classification of the AVMs are listed in Table 1.

To test for reproducibility, we repeated the ASL measurement in one previously embolized patient with a low-flow AVM three times on the same day, once without and once after changing of his head position by taking him out from the magnet in between two measurements.

This prospective study had been approved by the national ethical committee.

MR imaging

Having received informed consent from the patients scheduled for an embolization, MR imaging was performed on a 3 Tesla system (Achieva, Philips Medical Systems, Best, Netherlands) one or two days before as well as one day after the intervention. Apart from the routine imaging which consisted of T2-weighted, T1-weighted (3D Turbo Field Echo (3D T1W TFE)) and diffusion-weighted scans as well as a time-of-flight angiography, we applied a Pulsed ASL sequence (GE-EPI) with the following parameters: TR/TE=3000/16 ms, flip angle 40°; 6 successive phases were acquired in a single multiphase ASL scan starting at a label delay of 500 ms with equally spaced 250 ms increments; for averaging purpose, 40 repetitions were measured (20 labeling scans plus 20 controls); six slices, slice thickness 5 mm, gap 8.2 mm, FOV 240 mm, measured voxel size 3.75 mm, reconstruction matrix 128). The labeling slabs (label thickness 200 mm, label gap 20 mm) were placed in a way that the nidus or AVF was covered completely by the area of measurement, and we took great care to apply the same positioning in both examinations. The subtraction images were calculated automatically by scanner software and were used for further post-processing.

Post-processing

The ASL signal amplitudes of AVMs or AVFs were reported as relative values compared to a normal reference to correct for any changes in baseline signal between the two scans. Following the suggestion of Wolf et al. (2008)²⁰, we recorded the signal attributed to the AVM or AVF as a percentage of the total signal, both collected over all phases and slices. All post-processing steps were performed using

Table 1 Patients included in the study and characterization of AVMs/AVFs.

	No. patients (f : m)	Age (mean, range)	Shunt (high: low flow)	Spetzler Grade				
				1	2	3	4	5
AVMs	8 (3 : 5)*	40 (15-51)	5 : 2	1	2	1	1	3
Dural AVF	1 (f)	37	1 (low flow)	not applicable				
VOGA	1 (f)	31	1 (high flow)	not applicable				

* 2 interventions in 2 pre-embolized high-flow AVMs (Spetzler grade 5)

the “Image J” (<http://rsb.info.nih.gov/ij>). The area attributed to the AVM/AVF was determined in a similar way as described by Wolf et al., taking the average (AV) and the standard deviation (SD) of the signal in a region of interest (ROI) placed into the territory of the contralateral middle and/or anterior cerebral artery not involved in the supply of the lesion. This measurement was taken in that image of the six phases where the arterial signal reached a maximum, and was repeated for every slice. Within one slice, a mask was used to suppress all voxels below a threshold S of $S=AV + (8*SD)$. This threshold was chosen empirically because it usually suppresses all signals not related to the shunt. Only rarely, could we identify voxels clearly not related to the lesion, which had escaped this relatively high suppression, by carefully checking the anatomic distribution of preserved voxels. On the other hand, not all voxels obviously belonging to a nidus “survived” this high suppression threshold. Having defined the ROIs attributed to the AVM/AVF on a pixelwise basis as described above in all six phases for one slice, the procedure was repeated for the other slices. Within a given ROI, the signal volume was measured (sum of mean signal amplitudes over time multiplied by number of voxels). Then, a ROI covering a total slice (brain section) was drawn allowing measure the total signal of that slice over all phases, and again this was done on all slices. Finally, the relative amount of signal attributed to the lesion in relation to the total signal was calculated from all slices and compared between the pre- and post-interventional scans.

In addition to the calculation of the relative amount of signal attributed to the lesion, we qualitatively assessed the time course of the signal and characterized it in three categories: (a) identical time to spin arrival (T0) and time to signal peak (TTP) before and after embolization,

(b) slight differences of one or both parameters of 250-500 ms between pre- and post-embolization and (c) completely different time courses.

Results

After all but one intervention, we saw a reduction of the relative amount of signal attributed to the AVMs or AVFs by an average of 36%, which was in fair agreement with the reduction of the shunt in case of AVMs or flow in case of AVFs as estimated by conventional angiography (Table 2): In cases with a shunt reduction of 90% - 100% as estimated by angiography, ASL showed a relative reduction of signal attributed to the lesion of 69% - 92% (Figure 1), whereas in cases of a shunt reduction of 10% - 20% according to the angiographic results, the ASL follow-up showed a slight increase of 6% in one AVM (the only post-interventional increase), but no change or a reduction of 5% to 14% in the other three AVMs (Figure 1B), and of 35% after the partial embolization of the VOGA.

The time course of the signal attributed to the shunt showed an unexpected similarity between both curves measured before and after embolization over all slices and cases (72 graphs all together). In 20 graphs however, one or both curves did not show any recordable signal and a meaningful comparison was not possible. In four out of the remaining 52 graphs, the time course was clearly different (category c) with an important flattening of the curve after the embolization in three and a new peak after the embolization in a forth one. These major differences were only seen in the two most proximal (two graphs) and most distal slices (two graphs), all in high-flow AVMs. The remaining 48 pairs of curves showed a very similar time course, with no shift of T0 or TTP (category a: 30 graphs), or a minor

Table 2 **Reduction of nidus/flow after intervention: comparison of results as estimated by angiography and as estimated by ASL.**

	Reduction of shunt as estimated by angiography	Number of interventions	Reduction of rel. amount of signal attributed to the AVM/AVF
AVMs	10% - 20%	4	- 6% (*) to 14%
	30% - 50%	4	25% to 60%
	80% - 100%	2	69% to 76%
Dural AVF	90%	1	92%
VOGA	10%	1	35%

*) increase in relative signal attributed to shunt of 6% after embolization.

Figure 1 A) Low-flow AVM (32-year-old male, after previous embolization). Angiography before (upper image) and after embolization (lower images) showing shunt filled with glue. Shunt reduction 100%. B) Same patient, shunt reduction as measured by ASL in slice 1 to 6. The over-all shunt reduction measured from all slices amounts to 76% in this case.

shift of TTP only (category b: 18 graphs), mainly in slice 2, and in the majority into the direction of a longer delay. Those 72 graphs representing the signal course of the rest of the slice without the lesion did not show any major differences, just a shift of the time-to-maximum of 250 ms in 15 and of 500 ms in 1 graph.

The reproducibility study showed relative shunt signals between 9.7% and 9.9% without and after changing of the head position.

Discussion

This is the first prospective study in which ASL was used to “measure” the result of an embolization of AVMs and AVFs in a group study of more than three patients. Although we still deal with a limited number of cases, the data are in accordance with the angiographic results and thus are regarded to somehow reflect the “success” of an embolization. Nevertheless, there are

still a number of points to be discussed. The first question is about the way how the measured signal is related to the AVM or AVF and if it represents more of its extension or flow. Because the evaluation is based on subtraction images all signal is supposed to be caused by labeled spins entering the volume of measurement. As a consequence, thrombosed veins or artifacts caused by embolization material should not contribute to the measured values. Because of the rather short T1 relaxation time of water, most of the signal due to labeling will decay during capillary perfusion in cases of normal or restricted arterial flow²²⁻²⁴. Under high-flow conditions as in arteriovenous shunts however, some signal will be transported to the venous side as in spin-tagging based MR angiographies^{25,26} and flow-sensitive alternating inversion recovery (FAIR) MR imaging²⁷. These transit effects resemble conditions after injection of a conventional contrast medium and afford consideration of an outflow function if true blood flow is aimed to

be determined. With our technique of nidus or shunt identification however, which suppresses all normal arterial and capillary signal, all parts of the nidus and draining veins are suppressed as well in which spins have already relaxed. Instead of measuring an average flow in the whole lesion, only signals from those parts with an increased flow are collected. Because the total signal volume of a given ROI (mean signal amplitude over time multiplied by number of voxels) is taken in consideration, our measurement results most probably represent the volume of the high-flow parts of a nidus or fistula including their feeding arteries and draining veins. As a consequence, we clearly underestimate the relative amount of blood flowing through the shunt when we relate the signal determined in this way to the signal measured from the total slice (brain section). This is in contrast to conventional perfusion-weighted imaging after injection of contrast medium where the AVM nidus was overestimated on most occasions¹⁶. The underestimation of the nidus or shunt inherent in our technique might be of importance if in the examination following the embolization, the relative amount of low-flow areas within an AVM/AVF has increased and thus these areas are still present, but no longer seen after mask suppression. But this caveat does not seem to be a major issue because the embolization results as reported by the ASL technique were usually below those estimated by conventional angiography. A similar "underestimation" of the embolization success has been reported in that one case followed with ASL by Wolf et al. (2008)²⁰ who found a reduction of the shunt fraction of 3% in an AVM with angiographically estimated flow reduction of 20%. A second argument supporting the comparability of the signals measured before and after the intervention is the rather similar course of the signal amplitude over time on a given brain section. This does not only apply to the signals measured from the non-affected parts of a brain section -this finding supports the reproducibility of the method- but also to those ones measured from the AVMs and AVFs. Only in four of all measured slices, was the signal course over time completely different with a flattening of the signal rise after embolization, which is easy to explain by a partial occlusion of the feeding arteries. In only one high-flow AVM, a new and early (after 750 ms) peak of signal was seen after an estimated embolization success of 20%. This peak was related to feeding branches of the anterior cerebral ar-

tery and elevated the relative amount of the shunt-related signal from 52% to 70% on that special slice. But taking into account the results from all other slices, the overall reduction of the shunt-related signal after embolization amounted to 14%. Nevertheless, this exception underlines the importance of a reproducible positioning of the labeling and measurement cuts. Another result of the recording of the signal course over time was the slight, but nevertheless present shift of the signal maximum between 250 and 500 ms in 10 AVMs and 15 rest-of-the-slice measurements. These maxima had been missed in case of a monophasic ASL sequence. This time-dependence of signal maxima in AVMs has also been found in case of continuous ASL (CASL) examinations using different delay times^{19,20} and stresses the necessity of applying multiphase ASL sequences in case of flow measurements in arteriovenous shunts²¹. As shown by our follow-up examination of an AVM without intermittent treatment, the reproducibility of our method is sufficiently high (2% difference of relative shunt signal between measurements) to enable a meaningful comparison of two studies within a short time interval. Nevertheless, there is one single case showing a relative increase of the shunt-related signal of 6% after the intervention which might be difficult to explain on a pathophysiological basis. We regard this result as an example pointing to the limits of the reproducibility of our technique. However, a similar lack of shunt reduction after an intervention was measured by Noguchi et al.²¹ in an early follow-up study using pulsed ASL (PASL) in one of their three dural AVFs. A second somehow unexpected finding is the inability to demonstrate a complete shunt occlusion which was achieved in one AVM according to conventional angiography. By ASL, shunt reduction was estimated to 76% only. If the angiographic finding is taken as gold standard, the remaining signal could be due to dilated proximal segments of previously feeding arteries in the surroundings of the lesions which sometimes remain dilated for several days. Noguchi et al.²¹ attributed their observation of a relatively high signal outside the previous shunt area which disappeared with time, to a reduction in the upward shift in autoregulation. Because our technique uses a high suppression of signals which are not shunt-related, these effects of a moderately increased brain perfusion should not be visible. For the same reason -the signal suppression above normal arterial level- we did not try to assess the perfusion

Figure 2 A) High-flow AVM (36-year-old male, after previous embolization). Angiography before (upper images) and after embolization (lower images) showing partial occlusion. Estimated shunt reduction 20%. B) Same patient, shunt reduction as measured by ASL in slice 1 to 6. The over-all shunt reduction measured from all slices amounts to 14% in this case.

in the neighbourhood of the lesions or comment on possible steal effects or the risk of malignant hyperperfusion. As far as reproducibility between measurements is concerned, one source of error could be a change of scanner performance during the interscan interval due to alterations of the magnetic field, gradients, etc. and efficiency of labeling²⁸. By relating the signal attributed to the shunt to the signal of the total brain section of the actual scan, we have tried to minimize these influences. Another problem affecting reproducibility could arise in case of an important shift of high flow channels into more proximal or distal slices after a partial occlusion

of shunts. In this case, T1 relaxation effects might influence the signal amplitude. Our technique of sampling the total “volume” of signal from all slices over time, however, may compensate to some extent for this shift.

Conclusion

We consider our ASL technique rather robust and fairly reproducible. It is able to quantify the reduction of shunts achieved by an intravascular intervention at least as reliably as the non-quantitative inspection of conventional angio-

graphic controls which sometimes do not include all feeding territories and in high-flow conditions, have difficulties to see remaining low flow parts of the nidus. Nevertheless, some caveats have to be made such as the inability to predict a post-interventional hyperperfusion, the underestimation of the amount of shunt in

relation to total cerebral flow volume, and the limited capability to demonstrate a 100% shunt occlusion. In this respect, a larger number of studies comparing conventional angiography and ASL techniques before and after embolization in different shunt conditions and long-term follow-ups are clearly needed.

References

- 1 Homan RW, Devous MD Sr, Stokely EM, et al. Quantification of intracerebral steal in patients with arteriovenous malformation. *Arch Neurol*. 1986; 43: 779-785.
- 2 Batjer HH, Devous MD Sr, Meyer YJ, et al. Cerebrovascular hemodynamics in arteriovenous malformation complicated by normal perfusion pressure breakthrough. *Neurosurgery*. 1988; 22: 503-509.
- 3 Takeuchi S, Abe H, Nishimaki K, et al. Cerebral haemodynamic changes after endovascular treatment of arteriovenous malformations: evaluation by single-photon emission CT. *Acta Neurochir (Wien)*. 1994; 127: 142-150.
- 4 Hacein-Bey L, Nour R, Pile-Spellman J, et al. Adaptive changes of autoregulation in chronic cerebral hypotension with arteriovenous malformations: an acetazolamide-enhanced single-photon emission CT study. *Am J Neuroradiol*. 1995; 16: 1865-1874.
- 5 Nakagawa I, Kawaguchi S, Iida J, et al. Postoperative hyperperfusion associated with steal phenomenon caused by a small arteriovenous malformation. *Neurol Med Chir (Tokyo)*. 2005; 45: 363-366.
- 6 Nocuń A, Szajner M, Obszańska K, et al. Changes of brain perfusion after endovascular embolization of intracranial arteriovenous malformations visualized by ^{99m}Tc-ECD SPECT. *Nucl Med Commun*. 2008; 29: 1073-1080.
- 7 Okazawa H, Yonekura Y, Sadato N, et al. Delayed data acquisition for optimal PET activation studies with oxygen-15-water in cerebral arteriovenous malformation. *J Nucl Med*. 1995; 36: 2149-2153.
- 8 Iwama T, Hayashida K, Takahashi JC, et al. Cerebral hemodynamics and metabolism in patients with cerebral arteriovenous malformations: an evaluation using positron emission tomography scanning. *J Neurosurg*. 2002; 97: 1314-1321.
- 9 Brawanski A, Meixensberger J, Holzschuh M, et al. CBF studies with Xenon-133 in arteriovenous malformations: a methodological study. *Neurosurg Rev*. 1992; 15: 51-55.
- 10 Van Roost D, Schramm J, Solymosi L, et al. Presence and removal of arteriovenous malformation: Impact of regional cerebral blood flow, as assessed with xenon/CT. *Acta Neurol Scand Suppl*. 1996; 166: 136-138.
- 11 Harders A, Bien S, Eggert HR, et al. Haemodynamic changes in arteriovenous malformations induced by superselective embolization: transcranial Doppler evaluation. *Neurol Res*. 1988; 10: 239-245.
- 12 Aigner RM, Leber K, Nicoletti R, et al. Semi-quantitative scintigraphic follow-up studies of cerebral arteriovenous malformations after radiosurgical treatment. *Nucl Med Commun*. 1996; 17: 877-883.
- 13 Guo WY, Wu YT, Wu HM, et al. Toward normal perfusion after radiosurgery: perfusion MR Imaging with independent component analysis of brain arteriovenous malformations. *Am J Neuroradiol*. 2004; 25: 1636-1644.
- 14 Kaminaga T, Hayashida K, Iwama T, et al. Hemodynamic changes around cerebral arteriovenous malformation before and after embolization measured with PET. *J Neuroradiol*. 1999; 26: 236-241.
- 15 Cronqvist M, Ramgren B, Geijer B, et al. Diffusion- and perfusion-weighted MRI in therapeutic neurointerventional procedures. *Neuroradiology*. 2001; 43: 662-671.
- 16 Cronqvist M, Wirestam R, Ramgren B, et al. Endovascular treatment of intracerebral arteriovenous malformations: procedural safety, complications, and results evaluated by MR imaging, including diffusion and perfusion imaging. *Am J Neuroradiol*. 2006; 27: 162-176.
- 17 Saliou G, Krings T, Rutgers DR, et al. PWI-MRI and contrast extravasation in brain AVM help to estimate angiogenic activity. *Neuroradiology*. 2011; 53: 793-800.
- 18 Kim DJ, Krings T. Whole-brain perfusion CT Patterns of brain arteriovenous malformations: a pilot study in 18 patients. *Am J Neuroradiol*. 2011; 32: 2061-2066.
- 19 Lüdemann L, Jedrzejewski G, Heidenreich J, et al. Perfusion imaging of cerebral arteriovenous malformations: a study comparing quantitative continuous arterial spin labeling and dynamic contrast-enhanced magnetic resonance imaging at 3 T. *Magn Reson Imaging*. 2011; 29: 1157-1164.
- 20 Wolf RL, Wang J, Detre JA, et al. Arteriovenous shunt visualization in arteriovenous malformations with arterial spin-labeling MR imaging. *Am J Neuroradiol*. 2008; 29: 681-687.
- 21 Noguchi T, Irie H, Takase Y, et al. Hemodynamic studies of intracranial dural arteriovenous fistulas using arterial spin-labeling MR imaging. *Interv Neuroradiol*. 2010; 16: 409-419.
- 22 Chalela JA, Alsop DC, Gonzalez-Atavales JB, et al. Magnetic resonance perfusion imaging in acute ischemic stroke using continuous arterial spin labeling. *Stroke*. 2000; 31: 680-687.
- 23 Parkes LM, Tofts PS. Improved accuracy of human cerebral blood perfusion measurements using arterial spin labeling: accounting for capillary water permeability. *Magn Reson Med*. 2002; 48: 27-41.
- 24 Buxton RB. Quantifying CBF with arterial spin labeling. *J Magn Reson Imaging*. 2005; 22: 723-726.
- 25 Essig M, Engenhart R, Knopp MV, et al. Cerebral arteriovenous malformations: improved nidus demarcation by means of dynamic tagging MR-angiography. *Magn Reson Imaging*. 1996; 14: 227-233.
- 26 Yan L, Wang S, Zhuo Y, et al. Unenhanced dynamic MR angiography: high spatial and temporal resolution by using true FISP-based spin tagging with alternating radiofrequency. *Radiology*. 2010; 256: 270-279.
- 27 Noguchi K, Kuwayama N, Kubo M, et al. Flow-sensitive alternating inversion recovery (FAIR) imaging for retrograde cortical venous drainage related to intracranial dural arteriovenous fistula. *Neuroradiology*. 2011; 53: 153-158.
- 28 Wang Y, Saykin AJ, Pfeuffer J, et al. Regional reproducibility of pulsed arterial spin labeling perfusion imaging at 3T. *Neuroimage*. 2011; 54: 1188-1195.

Peter Stoeter, MD
Department of Radiology - CEDIMAT
Plaza de la Salud - Santo Domingo, Dominican Republic
E-mail: peter.stoeter@gmx.de