IMAGING OF BRAIN ARTERIOVENOUS MALFORMATIONS - COMPARING SILENCE MAGNETIC RESONANCE ANGIOGRAPHY WITH THREE-DIMENSIONAL TIME-OF-FLIGHT MAGNETIC RESONANCE ANGIOGRAPHY AND DIGITAL SUBTRACTION ANGIOGRAPHY

THESIS

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CERTIFICATE

This is to certify that the work incorporated in this thesis titled ***"Imaging of Brain Arteriovenous malformations – comparing Silence Magnetic resonance angiography with Three-dimensional Time-of-flight magnetic resonance angiography and Digital subtraction angiography."*** *for the degree of* ***DM NEUROIMAGING AND INTERVENTIONAL NEURORADIOLOGY*** *has been carried out by* ***Dr.Jospaul Lukas*** *under our supervision and guidance. The work done in connection with this thesis has been carried out by the candidate himself and is genuine.*

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DECLARATION

I hereby declare that this thesis titled "Imaging of Brain Arteriovenous malformations – comparing Silence Magnetic resonance angiography with Three-dimensional Time-of-flight magnetic resonance angiography and Digital subtraction angiography ." has been prepared by me under the supervision and guidance of Dr.Santhosh Kumar K (Associate Professor) , Dr Jayadevan E R (Additional Professor), Dr Bejoy Thomas (Professor), Dr.Kapilamoorthy TR (Professor), Department of Imaging Sciences and Interventional Radiology, and Dr Mathew Abraham (Professor and HOD, Neurosurgery), Sree Chitra Institute for Medical Sciences and Technology, Trivandrum.

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CONTENTS

INTRODUCTION

INTRODUCTION

Brain arteriovenous malformations (AVM) are an intriguing disease entity involving the intracranial vasculature where arteries and veins are interconnected through a low resistance dysplastic nidus bypassing the normal intervening capillary network. (1)

Digital subtraction angiogram (DSA) is the gold standard in definitive diagnosis and therapeutic planning of brain arteriovenous malformations. However, as a technique digital subtraction angiography is incommodious due to its associated invasiveness. All the more brain arteriovenous malformation patients are destined to require multiple "invasive" DSAs as part of diagnostic work up, therapeutic process and in their follow up phase.

Digital subtraction angiography has a reported complication rate of only <1%. But these range from puncture site complications to the more perilous complications like stroke which can contribute to significant morbidity. Apart from this added problems of imaging with DSA include radiation exposure, requirement for an operative suite, higher cost, requirement for admission, especially in situations of anticipated difficult femoral punctures or complications and need for a trained interventional neuroradiologist with the requisite skill set. Hence there exists a need for a reliable and non-invasive imaging technique in the work up, management and follow up of Brain arteriovenous malformations.

Magnetic resonance angiogram with Three-dimensional Time-of-flight (3D TOF) or contrast enhanced magnetic resonance angiogram are modalities that may be used for this purpose. However, the clinical studies in this regard have always shown unparalleled superiority of Digital subtraction angiography. Contrast enhanced angiography apart from the problems of contrast induced nephropathy and nephrogenic systemic fibrosis has additional issues with cerebral parenchymal contrast deposition which recent studies have brought to light. Hence newer techniques and improvements of non-contrast imaging techniques are a requirement for

alternative to DSA in cerebrovascular imaging, especially in entities like AVMs which require multiple imaging sessions and follow up.

Silence magnetic resonance angiography (Silence MRA) is a new technique of non-magnetic resonance angiogram which employs of ultra-short echo-time imaging and is based on arterial spin labelling (ASL) technique. This is a proprietary technique developed by GE health care. (2,3) Silent MR angiography technique has several advantages as opposed to the conventional TOF imaging such as better background suppression and lower sensitivity to susceptibility artefact, which may be particularly useful in the setting of Brain AVM to elucidate its various angioarchitectural aspects. This study aims to compare usefulness of the non-contrast Silence magnetic resonance angiography with Three-dimensional Time-of-flight angiogram sequence in the evaluation and follow up of Brain arteriovenous malformations. The findings are assessed in comparison to Digital subtraction angiography.

AIMS AND OBJECTIVES

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- To compare Silence magnetic resonance angiography and Three-dimensional Time-of-flight angiogram sequence in the evaluation of Brain arteriovenous malformations in comparison with Digital subtraction angiography to determine the angiomorphology of Brain arteriovenous malformations.
- To study the utility of these noninvasive magnetic resonance angiography techniques in treatment planning and follow up.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

INTRODUCTION

Cerebral arteriovenous malformations (AVM) is an intriguing vascular disease entity where a cerebral arteriovenous interconnection occurs through an intervening dysplastic nidus with absence of normal intervening capillary network in between the arterial tree and the venous drainage. The reported incidence of Brain AVM is 1.34/100,000-person years and the prevalence is 10 -18/100,000. Brain AVM is the disease entity responsible for about 2% of haemorrhagic strokes. (4)

ETIOLOGY

The exact etiologic nature of cerebral arteriovenous malformations is still a question of debate with both congenital and acquired origins being attributed as the cause. The presence of most AVM at the border zone region of arterial territories have speculated the timing of development of these lesions to be around 29 weeks of gestation and thus attributing a congenital causation(4,5). But the relative paucity of in utero detection of Brain AVM on antenatal imaging is a deterrent to definite acceptance of the congenital nature of these lesions.

ANGIOMORPHOLOGY OF CEREBRAL AVM

The feeding arteries to cerebral AVM are usually from the anterior or posterior intracranial circulation and arise depending upon the location on the AVM. The arterial feeders can evolve through different morphological alterations such as vascular hypertrophy, development of feeding artery aneurysms, and vascular ectasia depending upon the AVM haemodynamics and resultant stresses on the feeding vasculature. Depending upon its type of supply to the AVM, the feeding arterial branch is classified as terminal where it directly ends

in the AVM nidus or as enpassage where the AVM is supplied by an artery through a perpendicular branch but the primary target of the vessel is parenchyma beyond the AVM(6).

The AVM nidus is categorised as compact or diffuse / sparse depending upon the presence of intervening brain parenchyma within and the definition on the AVM boundaries. Another categorisation of the nidus depending upon the rate of flow and calibre of the AV shunt sizes is into plexiform and fistulous categories.

On the venous side, the nidus can be drained by a single or multitude of veins. And the drainage can be into deep venous system or to the superficial system, a characteristic which is primarily dependant on the location of the AVM. The drainage venous channel in addition can also undergo several morphological alteration such a venous occlusion, stenosis and ectasia(7).

In addition an AVM may harbour multiple aneurysmal sacculations. These located within or adjacent to the nidus, are termed intranidal and perinidal aneurysms. These aneurysms are usually of arterial origin. Venous ectasia can also contribute to venous aneurysms or pseudoaneurysms. Apart from the aneurysms directly related to the nidus there also exists an increased propensity of the AVM feeders to undergo aneurysmal changes resulting in feeding artery aneurysms, that often resolve once the AVM is treated. Coincidently arterial territory unrelated to the AVM can also harbour an aneurysm(8,9).

In addition to the morphological alteration in the vascular make-up of the AVM the adjacent brain parenchyma can also show evidence of gliosis, prior or recent haemorrhage, atrophy and other dystrophic changes like calcifications.

CLINICAL PRESENTATION

The most common clinical presentation of Brain AVM is with ICH, with reported annual risk of bleed amounting to 2-4% per year. Other presentations include seizure, neurological deficit or headache. Incidental detection of AVMs on neuroimaging constitute is only 0.05%. Prior bleed significantly increases the propensity to subsequent haemorrhage with reported risk of re-bleed in the first year rising to between 6 -18%. In subsequent years the risk for bleed returns to the base line of 2-4% per year(10). Patients who present with haemorrhage have significant 10% mortality and 20-30% morbidity (11) making intervention imperative.

CLASSIFICATION

The most widely accepted classification scheme was the one proposed by Spetzler and Martin in 1986 and is primarily a directive for the surgical management of AVM. This classification compartmentalises cerebral AVM into 6 grades on the basis of the size, venous drainage and eloquence(12) and has become entrenched as a common parlance among all stake holders in AVM management. Another notable classification was by Houdart et al who classified AVM into 3 types, arteriovenous, arteriolovenous and arteriolovenulous to provide a guide for the endovascular management of AVM. They suggest arterial route of endovascular management for arteriolovenulous type of AVM while the option of arterial or venous side embolization is feasible in the other two types(13).

IMAGING OF ARTERIOVENOUS MALFORMATIONS

Cross sectional imaging with either CT or MRI holds the fort in initial detection of cerebral arteriovenous malformations. But despite the wide availability and increase in spatial resolution of these technique the age old digital subtraction angiography is still considered gold standard in the definite imaging work up, treatment and follow up of AVM. This is because till date MR or CT imaging has not been able to surpass the high spatial and temporal

resolution available on DSA. Also coupled with this is the advantage of selective injections and study of multiple compartments within an AVM(14).

CONVENTIONAL CT AND MRI

The initial detection of AVM is often on conventional CT or MRI in patients evaluated for headache, seizures, or other focal neurological deficit from haemorrhage or vascular steal and resultant ischemia. Imaging depicts the nidus as tortuous entangled cluster of hyperdense serpiginous structures on CT or as flow voids on MRI. Often the feeding artery and draining vein may also be seen on these plain studies to a fair extent as well as the venous drainage if ectatic. Larger the AVM easier is the detection on the plain studies unless there is evidence of bleed which would increase conspicuity even in small lesions.

CT Angiogram

CTA provides excellent demonstration of Brain AVM with separation of the feeding artery, nidus and draining venous anatomy to a great detail. Over and above conventional CTA is the technique of dynamic CTA where temporal information is also available and improves the delineation of AVM components (15). But increased radiation exposure and availability of alternative techniques like MRA makes the routine use of CTA or Dynamic CTA in AVM imaging less appealing.

MRA

A multitude of angiographic techniques are possible with MRI and several of these have been employed in evaluation of cerebral AVM. Both non-contrast techniques and contrast techniques are available. The most prominent of the non-contrast technique are the 3D TOF MRA, the PC MRA, the novel Silence MRA one being primarily evaluated in this study and new advances like 4D FLOW MRI techniques. On the contrast angiographic platter include routine CEMRA, dynamic technique like keyhole MRA techniques.

Non-contrast MRA

The primary non-contrast MRA techniques available are Phase contrast MRA and 3D TOF MRA.

Phase contrast MRA

3D Phase contrast MRA which utilises velocity induced phase shifts in moving spins to depict flow in the cerebral vasculature and a subtraction technique to cancel out the stationary tissues. But in case of non-laminar and vortex flows which are often found in cerebral vascular pathology like aneurysms and AVM significant signal loss is seen on phase contrast technique rendering it suboptimal(16). As 3D TOF is not subject to such gross artefactual loss of signal, this is preferred one among non-contrast MRA in cerebrovascular pathologies.

3D TOF MRA

TOF techniques rely on the saturation of the imaging slab of interest and detection of signal from the unsaturated protons flowing into the imaging slab depicted as high intravascular signal. TOF as a technique provides excellent demonstration of the arterial anatomy within a reasonable time of acquisition(17). 3D TOF MRA on a 3 Tesla clearly depicts even small cortical arteries that are larger than 1mm, with excellent quality. Normal veins are not simultaneously imaged on MR TOF angiogram but the early draining veins in cerebral AVM are relatively well depicted. This makes TOF an ideal sequence in non-contrast imaging of cerebral AVM. But an inherent defect in TOF imaging is, being direction dependent the artefactual venous contamination occurring at site of cranially directed venous flow in proximal Superior sagittal sinus and Vein of Galen may contaminate the arterial signal. Also, being a T1 weighted imaging technique, blood as bleed in the vicinity of the vascular malformation and thrombosis within the venous sacs or draining veins can impair the image quality in TOF MRA imaging presenting with high signal.

Several studies have evaluated the TOF MRA imaging in AVM. Studies by Heidenreich et al have proved the robustness of 3T MRI in TOF MRA imaging as compared to CE TOF imaging on 1.5T(18). In a comparison of dynamic MRA imaging by Sonlin et al 3D TOF MRA outperformed dynamic 4D Flow technique in AVM architectural elucidation(19). Hence TOF is often part of the routine vascular imaging protocol in many institutions.

SILENCE MRA.

Silence MRA is a novel angiographic technique is a distinctive novel sequence, primarily for its almost none to minimal noise generation on being endowed with algorithm for Silent scan technique by GE healthcare and also for its excellent vascular depiction cum background suppression in virtue of being an ASL based subtraction technique incorporating an ultrashort TE(20–22). In this sequence the vascular tree is explored by subtraction between a control image and a labelled image acquired after a cervical level labelling pulse. The Ultrashort TE also aids in minimising the phase dispersion of the labelled blood and likewise decreasing the susceptibility effects. Prior studies have evaluated for ASL based silence MRA technique mostly in comparison with the other prominent TOF angiographic imaging – TOF MRA. Kokzoglu et al evaluated 3D ASL MRA in assessment of Carotid stenosis using carotid vascular phantom which revealed its superiority 3D TOF in hemodynamically significant carotid stenosis(23). In studies by Irie at al and Takano et al the silence MRA technique was assessed in follow up of aneurysms post stent assisted coiling. Both authors were able to demonstrate the robustness of Silence MRA over TOF. Reports of Silence Technique in AVM evaluation per se are limited. Some of the very first anecdotal reports on the utility in AVM in vascular lesions and AVM were available from Suzuki et al (24) and in a case report by Jin II Moon et al. (21)

CONTRAST ENHANCED MRA

CE MRI coupled with CE MRA techniques are versatile in probing the angiomorphology of cerebral AVM and overcome to some extend the flow related artefacts seen on non-contrast MR imaging. Adding temporal resolution above the static images of the nidus and its connections is possible on MRI with dynamic MRA techniques. Further improvement is possible with subtraction of the angiogram from mask non contrast MRI data set christened as MR DSA technique(25). Time resolved angiography the key hole imaging further improves upon the temporal resolution of dynamic MRA imaging methodologies. These have been variability used in imaging of cerebral Arteriovenous malformations. But inherent to all the contrast enhanced techniques is the prime requirement for Gadolinium based contrast agents. With the recent studies providing telling evidence of GBCA causing cerebral parenchymal deposition, predominantly in dentate nucleus and Globus pallidus recommendations for limiting the use of GBCA and limiting the dose, frequency and altering to a macrocyclic compounds when required have been advocated by statutory bodies. Hence in case of lesions like AVM where non contrast technique are a possibility CEMRA is bound to play a lesser role now on(26)(27,28).

DSA

Among imaging techniques for cerebral AVM, Digital subtraction angiography still rules the roost in spite of the multitude of imaging techniques made available on MRI both contrast enhanced and non-contrast. The temporal and spatial resolution afforded by DSA is unparalleled till date and it is still the gold standard in imaging of cerebrovascular lesions. But digital subtraction angiography is limited by invasiveness, longer procedure time, higher cost, requirement for admission as per hospital protocols or on patient status, use of iodinated contrast and above all radiation exposure.(29–31) Hence a potential need for a non-invasive,

non-contrast, non-radiating technique of imaging with improved spatial and temporal resolution is a prominent unmet need in cerebral AVM diagnosis and management.

TREATMENT

The treatment of unbled AVM is debatable to varying extend with the major trial in AVM management, ARUBA(32) showing favourable outcome in untreated patients. But several criticisms were levelled against the planning and orchestration of the trial and still a haze of indecision overlies the optimum management decision in unbled subset of AVM (33). But in those patients with history of prior bleed, a re-bleed is an ever present risk that argues in favour of treatment(33,34). The available options include surgical, endovascular and radiation therapy(10,35). Substantial difference in management decisions exist from institution to institution and treatment is most often delivered in an individualised manner with less rigid compartmentalisation of treatment algorithms. In general, an AVM if completely curable and surgically amenable is tackle so. In larger lesions and deep-seated lesions where surgical risks are substantial, an endovascular first approach may be employed with progressive embolization of the AVM over multiple sittings and the residue if any tackled by radiation. In cases with substantial endovascular and surgical risks, prima facie radiotherapy by stereotactic radiosurgery or gamma knife surgery may be the option.

POST TREATMENT IMAGING EVALUATION AND FOLLOW UP

The treated AVM is one that requires follow up both clinically and with imaging. And often patients are subjected to multiple MRI evaluations and repeat DSA. The reason being possibility of a residual nidal components exist even in an AVM where the best complete resection has been attempted. In endovascular management of AVM, embolization of one segment of the nidus can bring in varying morphological changes to the remaining vessels due to altered haemodynamics. And in those lesions treated by radiotherapy, often the

treatment response occurs in a protracted manner over one or more years. Therefore, post treatment imaging of AVM, is one requiring a definite DSA to localise small nidal elements that may be elusive on MRI techniques.

THE UNMET NEED IN AVM

There are several morphological aspects of Brain arteriovenous malformation that need to be assessed prior to planning therapeutic approach and intervention. These include determining the location, feeding arteries, draining veins, nidus and size of the lesion. (36) The presence of feeding artery, intranidal and perinidal aneurysms, venous pouches, venous dilatations, fistulas, venous stenosis, venous thrombosis and collateral circulation are the other factors that need elucidation and which could necessitate therapy in brain arteriovenous malformations. (37,38). An ideal imaging modality should reliably reveal these parameters. Digital subtraction angiography as already described reliability depicts these varied parameters at the cost of its invasiveness, associated radiation exposure and other procedural risks.

Another requirement is follow up imaging of brain arteriovenous malformation treated by surgical or endovascular techniques or stereotactic radiosurgery(39). The presence of residual nidus is a risk for haemorrhage and therefore optimal follow up with an imaging modality as robust as digital subtraction angiography is required to document obliteration of brain arteriovenous malformations(38). Prior studies in this regard have demonstrated the inferior sensitivity of Magnetic resonance angiography to Digital subtraction angiography in detecting the residual nidus. (29,30)

Hence the extent of magnetic resonance angiography as a modality in brain arteriovenous malformation imaging is often limited to an initial diagnosis of brain arteriovenous malformations or to an early imaging follow up to evaluate for a residual nidus in a large

brain arteriovenous malformations. (18,29,30). In this regard either TOF MRA or CEMRA techniques are primarily used.

Silence Magnetic resonance angiography now available on GE 3T MRI machines is yet be formally assessed for this purpose (20). The advantages accorded by arterial spin labelling(ASL) and ultra-short echo-time techniques including lower susceptibility effects better background suppression (40) may be advantages on the part of Silence MRA for AVM angiomorphological evaluation. This study intends to probe this question for a future of better imaging and less invasive follow up of our Brain AVM patients.

MATERIALS AND METHODS

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INTRODUCTION

This was a prospective study conducted after obtaining the institutional ethics committee approval from October 2016 to June 2018. Informed written consent was obtained from all the participants who were part of this study.

Consecutive patients with brain arteriovenous malformations presenting to the SCTIMST neurosurgery, neurology and interventional radiology clinics by direct referrals and consultations from other departments were considered for inclusion. These patients underwent magnetic resonance imaging as per below stated protocol. Digital subtraction angiography was also done as per standard guidelines followed in the institution. Magnetic resonance imaging and Digital subtraction angiography were obtained within a gap of 2 weeks. For the purpose of the study magnetic resonance imaging and Digital subtraction angiography images were obtained from picture archiving and communication system (PACS), anonymised and stored separately in numbered folders.

These images were analysed by a radiologist with experience in interpreting diagnostic and interventional neurovascular imaging studies. The 3D TOF MRA image datasets, Silence MRA Data sets, DSA images and Three-Dimensional Rotational angiogram or Computed Tomography image sets were provided to the participating radiologist separately. The images sets were read with a time gap of at least 2 weeks to exclude memory bias. The AVM nidal parameters were analysed for the image quality cum diagnostic confidence and graded on a 4-point scale.

The images were independently assessed for following parameters: the location of the arteriovenous malformation, number of feeding arteries to the arteriovenous malformations, identification of the feeding arteries, the identification of the type and measuring the size of

nidus, associated aneurysms including intranidal, perinidal and feeding artery aneurysms, identifications of fistulas, venous pouches/ dilatations, any identifiable venous stenosis. After data collection, statistical analysis was done to generate inferences.

INCLUSION CRITERIA

- All consecutive patients with Brain arteriovenous malformations presenting to SCTIMST neurosurgery, neurology or radiology clinics.
- Patients treated with surgery, radiosurgery or embolization, who needs Digital subtraction angiography to assess completion of treatment.
- Patients who are not evaluated with prior magnetic resonance angiogram or Computed tomography angiogram at SCTIMST/elsewhere.
- Patients whose angiographic images are suboptimal or of poor interpretable quality and needs further or repeat imaging studies at SCTIMST.
- Minors and pregnant women was also planned for inclusion with strict compliance with the international protocol related to the radiation protection and MR imaging norms.

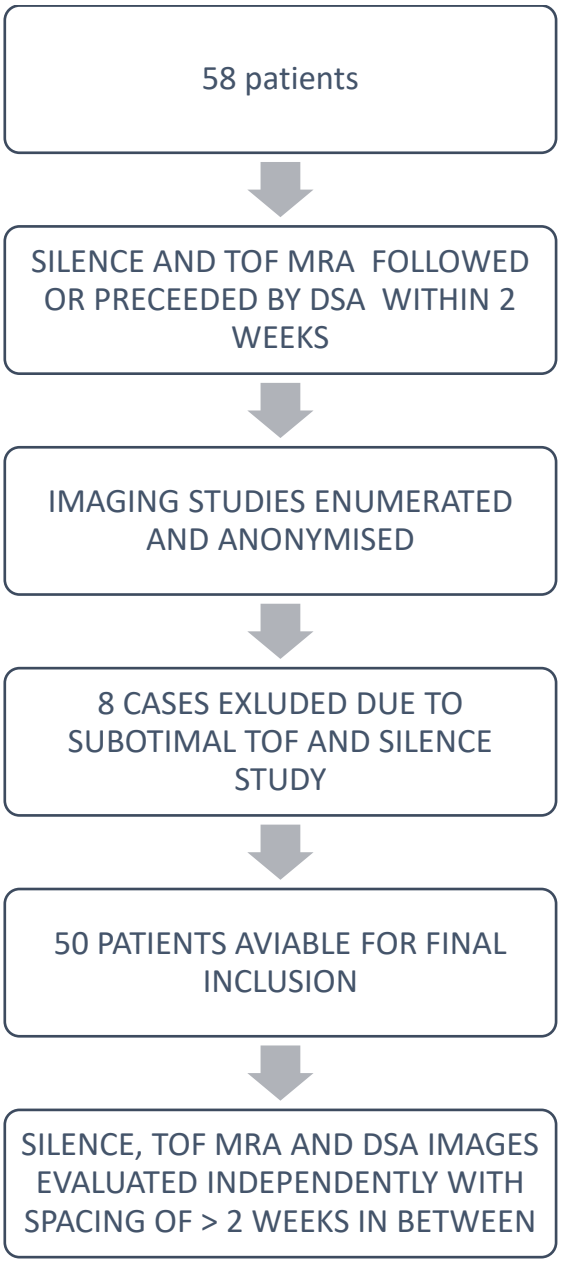
EXCLUSION CRITERIA

- Patient or relatives who declined consent.
- Patient who was already evaluated elsewhere with magnetic resonance angiogram or Computed tomography angiogram that reveal Brain arteriovenous malformation pathology.
- Claustrophobic patients, patients with 3 Tesla incompatible metallic implants, pacemakers or cochlear implants.
- Brain vascular lesions other than arteriovenous malformations was also excluded.

STUDY DESIGN

The recruitment of subjects for the prospective study was be done by the principal investigator from consecutive patients with Brain arteriovenous malformations presenting to SCTIMST neurosurgery, neurology or radiology clinics from the month of October 2016 to June 2018. Patients diagnosed of Brain arteriovenous malformations and planned for initial Digital subtraction angiography or who have undergone embolization or stereotactic radiosurgery and admitted for a check Digital subtraction angiography and Magnetic resonance angiogram were included in the study. Consent for inclusion in the study was obtained from appropriate persons or guardians. No inclusion of person incompetent to give informed consent, normal/healthy volunteer, Prisoner, student/staff of the institute was done.

FLOW CHART OF STUDY DESIGN



STUDY PROTOCOLS AND PARAMETERS – MRI AND DSA

Consecutive patients with Brain arteriovenous malformations considered for inclusion underwent Digital subtraction angiography and Magnetic resonance imaging as per the below stated protocol.

The Digital subtraction angiography was done in Interventional Radiology Suite at SCTIMST on General Electric Innova biplane 1313 and Magnetic resonance was done on General Electric Discovery 750E 3.0Tesla machine as per the routine protocol.

The MRI protocol for the Study was inclusive of the following sequences, apart from the routine MR imaging workup followed in the institution for brain AVM cases.

1. 3DTOF MR angiogram (TR/TE, 19/2.9 msec; flip angle, 15°; field of view, 200×200 mm; matrix, 416×192; section thickness, 1.2 mm; NEX, 1; band width, ±41.7 kHz; acquisition time, 3 min 31 s.)
2. Silence MR angiogram (TR/TE, 1116.4/0.016 msec; flip angle, 5°; field of view, 180×180 mm; matrix, 150×150; section thickness, 1.2 mm; number of excitations (NEX), 1.5; band width, ±20 kHz; acquisition time, 7 min 40 s.)

The MRI and Digital subtraction angiography images were then obtained from PACS, anonymized and stored separately in numbered folders and analysed independently.

Statistical analysis of the data was performed by the principal investigator using Graph pad Prism 6 statistical analysis software. Wilcoxon signed rank test (41)for assessment of the difference in assigned diagnostic scores and Bland and Altman analysis(42,43) to assess agreement between TOF s DSA and SILENCE MRA vs DSA in elucidation of the AVM components was done. The sensitivity and specificity of TOF and SILENCE MRA was also assessed for quantitative comparison between the two modalities.

RESULTS

RESULTS

DEMOGRAPHICS

Among the 50 consecutive patients included in this study of Cerebral arteriovenous malformations, from October 2016 till June 2018, the sex distribution was balanced with 22 female and 28 male patients.

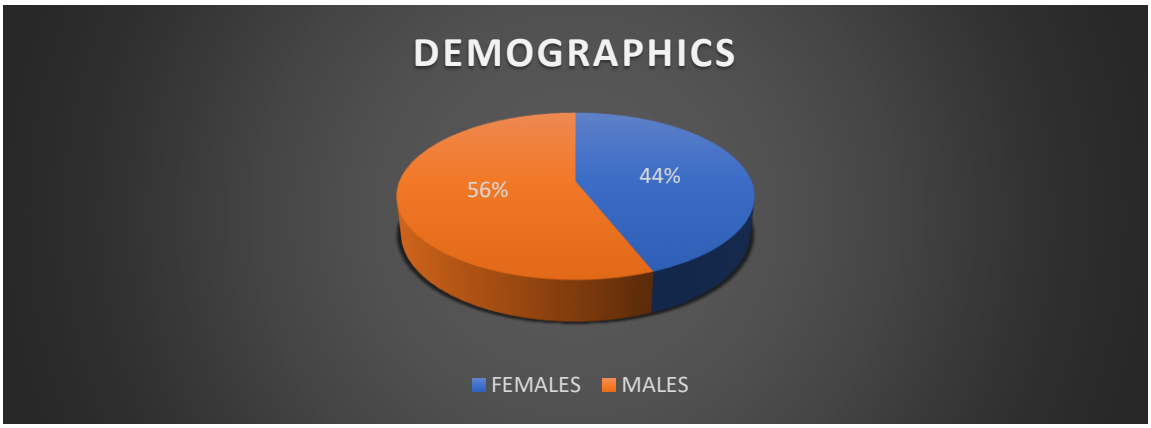


Figure No:1 – male to female distribution in this study

All the 50 patients were consecutively included without bias towards, age or sex.

CLINICAL PROFILE

AGE RANGE	FREQUENCY	PERCENTAGE
0 to 9	1.00	2%
10 to 19	12.00	24%
20 to 29	15.00	24%
30 to 39	12.00	24%
40 to 49	3.00	6%
50 to 59	6.00	12%
60 to 69	1.00	2%
TOTAL	50.00	100%

Table No: 1 –AVM location wise distribution.

The mean age of the study group was 29.9yr and ranged between 8 to 63 years. The group was a predominantly young cohort with 74% being < 40 years. 29 cases forming 58% had evidence of prior bleed and 21 cases 42% were unbled AVM.

ANGIOGRAPHIC FEATURES

DSA was done in the 50 patients confirming AVM in all the cases. The 50 cases were initially assed for various morphological features on DSA including, arterial feeders, presence of arterial hypertrophy, presence of AVM nidus related aneurysms, venous drainage pattern including superficial and deep, venous stenosis or ectasia if any.

AVM LOCATION and LATERALISATION

AVM LOCATION	FREQUENCY	PERCENTAGE
FRONTAL	9	18.00%
PARIETAL	7	14.00%
TEMPORAL	7	14.00%
PARIETOOCCIPITAL	6	12.00%
CEREBELLAR	5	10.00%
OCCIPITAL	3	6.00%
FRONTOPARIETAL	3	6.00%
PARIETOTEMPORAL	2	4.00%
OCCIPITOTEMPORAL	2	4.00%
CORPUS CALLOSAL	2	4.00%
CHOROIDAL	2	4.00%
THALAMIC	1	2.00%
PONTINE	1	2.00%
TOTAL	50	100.00%

Table No: 2.A –AVM location wise distribution.

Frontal AVM accounting for 18% of the AVM cases made up the commonest location of AVM in the present series, followed by parietal, temporal, parietooccipital and cerebellar regions constituting the majority of the arteriovenous malformation locations.

LESION SIDE	FREQUENCY	PERCENTAGE
RIGHT	18	36%
LEFT	29	58%
MIDLINE	3	6%
TOTAL	50	100%

Table No: 2.B –AVM nidus lateralisation.

Of the 50 patents included in the study 58% ie. 29 cases had left lateralisation of their arteriovenous malformations, 36% cases were lateralised to right side and 3 cases were midline in location.

AVM GRADING

SM GRADE	FREQUENCY	PERCENTAGE
GRADE 1	5	10%
GRADE 2	16	32%
GRADE 3	16	32%
GRADE 4	11	22%
GRADE 5	2	4%
GRADE 6	0	0%
TOTAL	50	100%

Table No: 3–SM grade wide distribution.

Of the 50 cases, 74% has Spetzler Martin Grades of 3 or less, and only 13 cases amounting to 26% had SM grades of 4 or more. None of the patients were assigned a SM grade of 6.

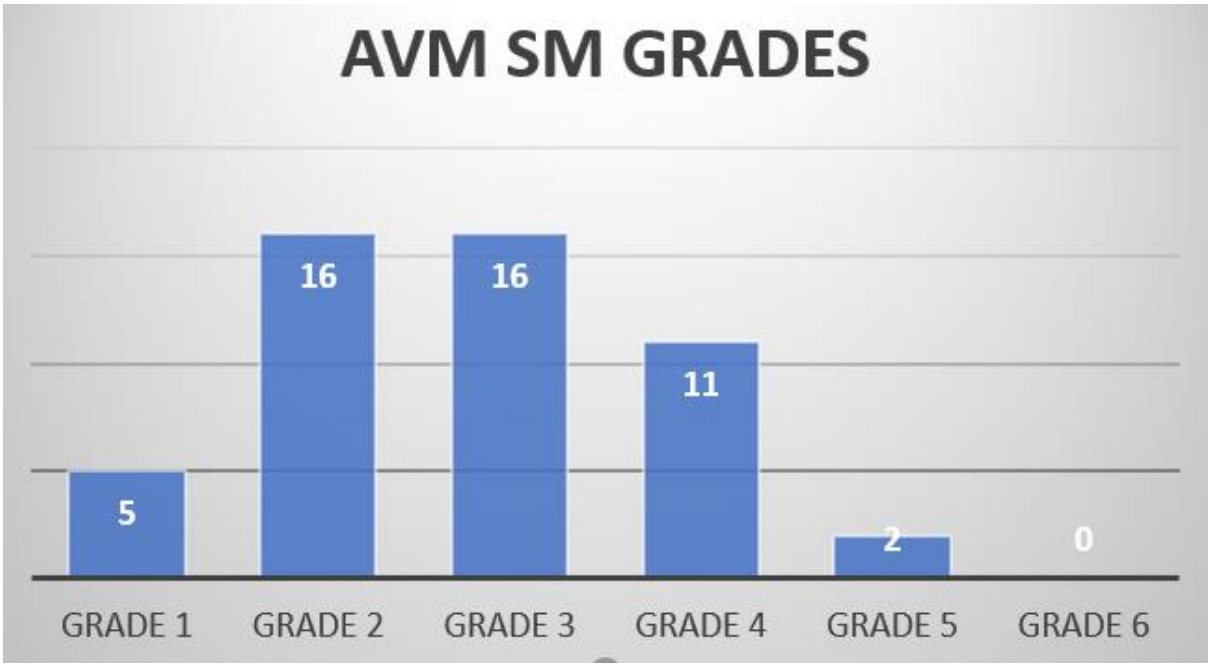


Figure No: 2–SM grade wise distribution of cases.

AVM NIDAL TYPE

The nidal characterization on DSA revealed, 28 of the 50 cases, 56% to have a compact nidal type, 16 cases (32%) had a diffuse morphology to the nidus and sparse nidus morphology was seen in 6 of the 50 patients (12%).

AVN NIDAL TYPE	FREQUENCY	PERCENTAGE
COMPACT	28	56%
DIFFUSE	16	32%
SPARSE	6	12%
TOTAL	50	100%

Table No: 4–AVM nidus type.

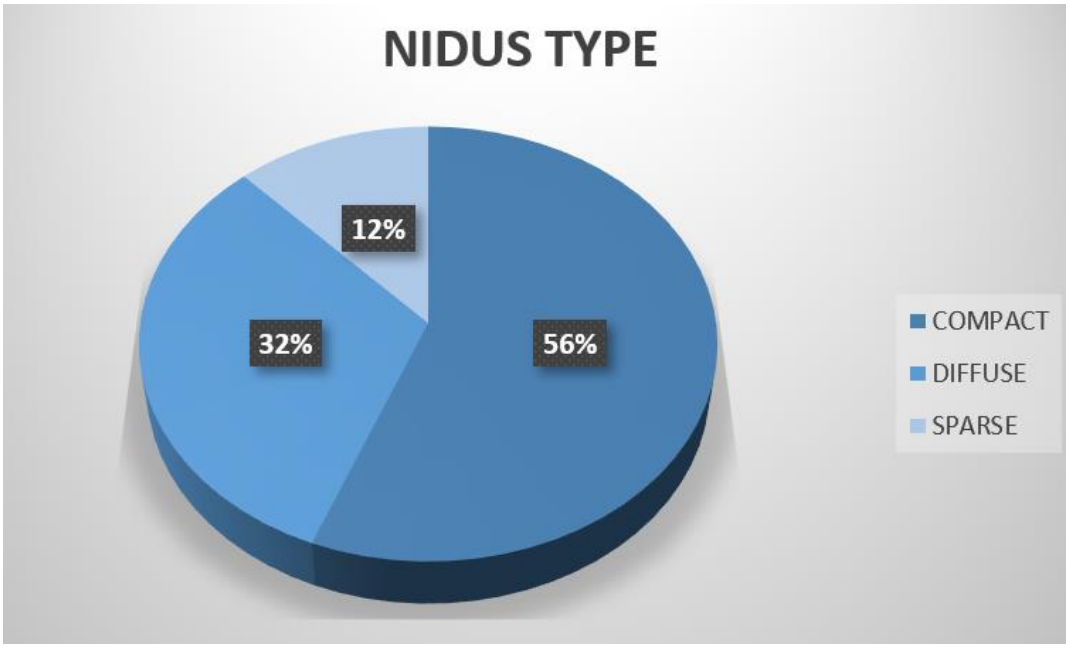


Figure No: 3–Distribution of AVM nidus type.

INTERMODALITY COMPARISION BETWEEN SILENCE, TOF MRA and DSA

The angiomorphology of the 50 AVM cases were assessed and compared across SILENCE and TOF MRA and against DSA which was the gold standard under consideration in this study.

AVM SIZE

The comparison of AVM nidus size across the three measured dimensions revealed, that some degree of overestimation of the nidal size was seen both on SILENCE and TOF MRA in anteroposterior and transverse dimensions. In the cranio-caudal direction SILENCE MRA revealed, overestimation of the nidal size, TOF recorded underestimation of the measured dimensions as to DSA.

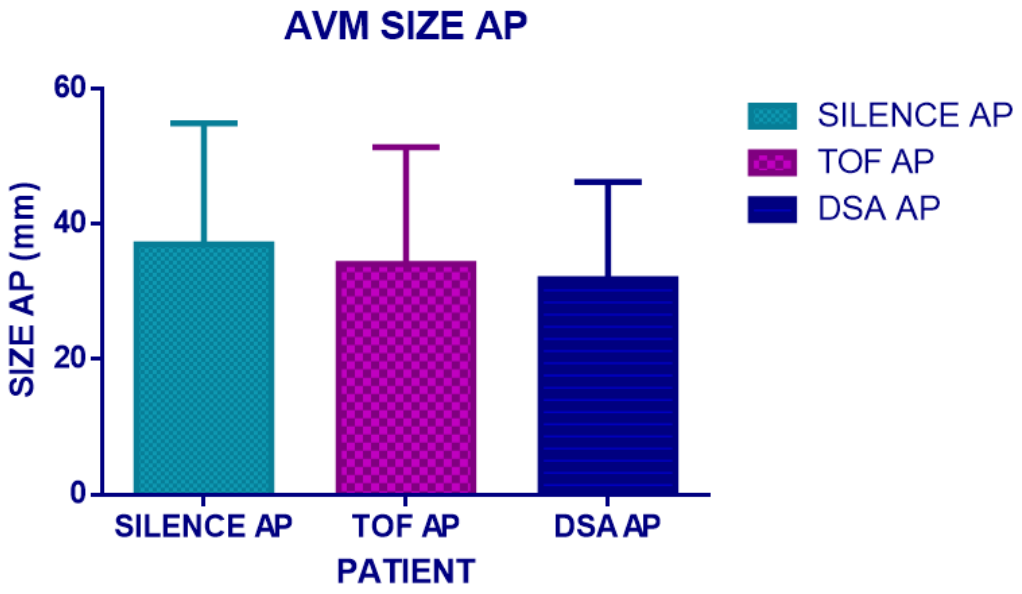


Figure No: 5–AVM size in anteroposterior dimension on the three modalities.

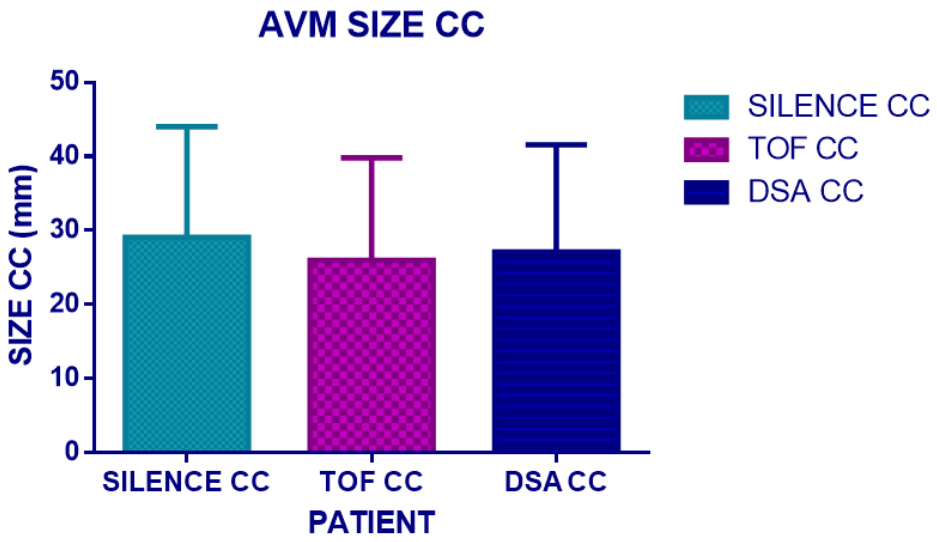


Figure No: 6–AVM size in craniocaudal dimension on the three modalities.

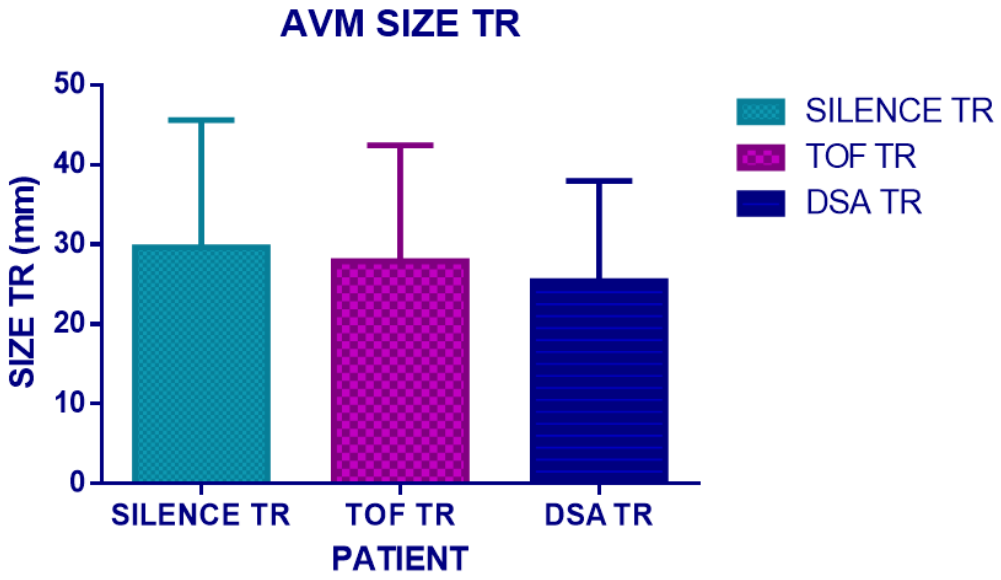


Figure No: 7–AVM size in transverse dimension on the three modalities.

On computing the AVM volume across modalities, and analysis by Bland and Altman method, the AVM volumes on SILENCE and TOF MRA differed more from the DSA recorded volumes for AVM with larger sizes. Volumes assessed by SILENCE MRA was

more different as to the analysis on TOF MRA. However, for AVM of smaller sizes the AVM sizes matched more closely with the measures on DSA.

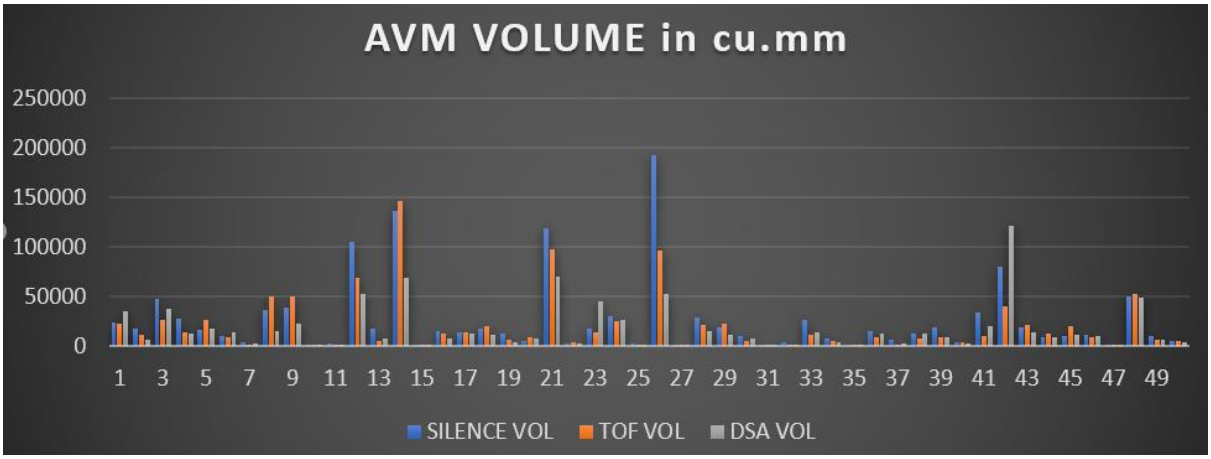


Figure No: 7–Frequency distribution of AVM volume across the three imaging modalities.

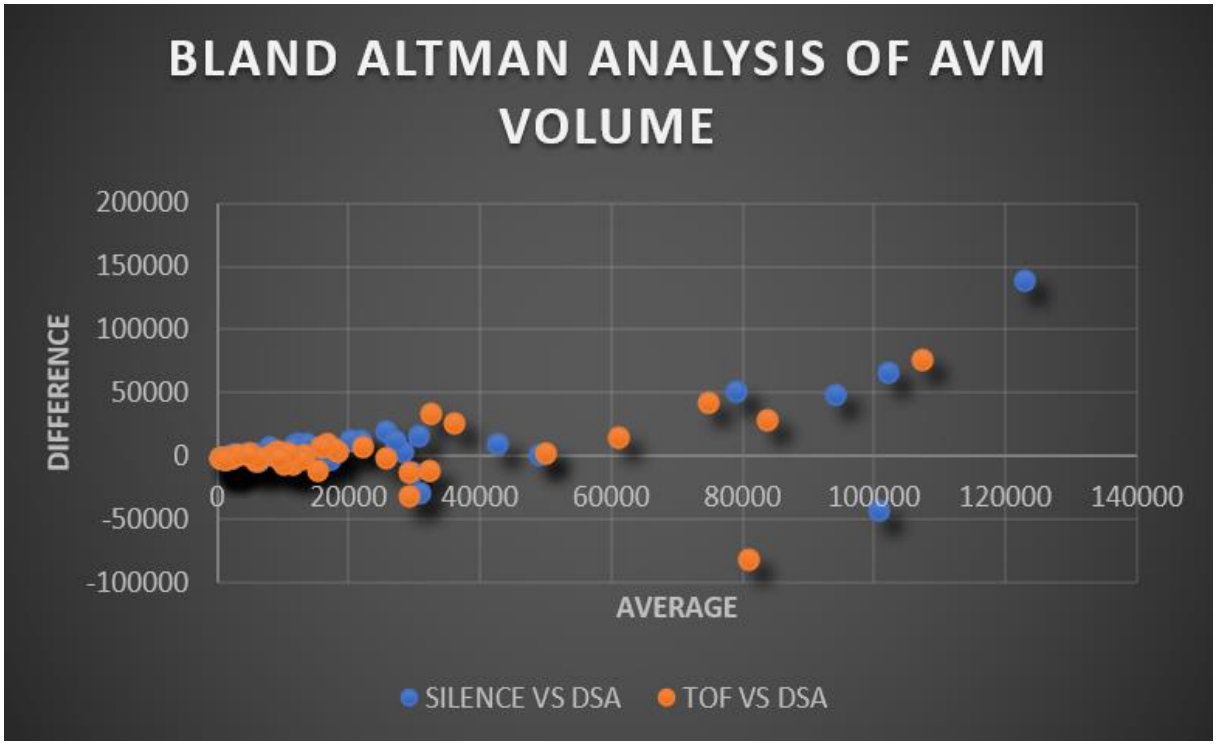


Figure No: 8– Bland Altman analysis plot of the AVM volume comparing between Silence MRA vs DSA and TOF MRA vs DSA

ARTERIAL FEEDER CHARECTERISATION AND DETECTION

Both SILENCE and TOF correctly identified 80%, 143 of the 177 arteries which were feeding the AVM and confirmed on DSA. The percentage of feeding arteries which were missed were similar on SILENCE and TOF being 21% for SILENCE (38 feeders) and 20% (36 feeders) for TOF. The number of misinterpreted vessels were larger on TOF angiogram as compared to SILENCE, 13.5%(24) on TOF as to 8.4%(15) on SILENCE.

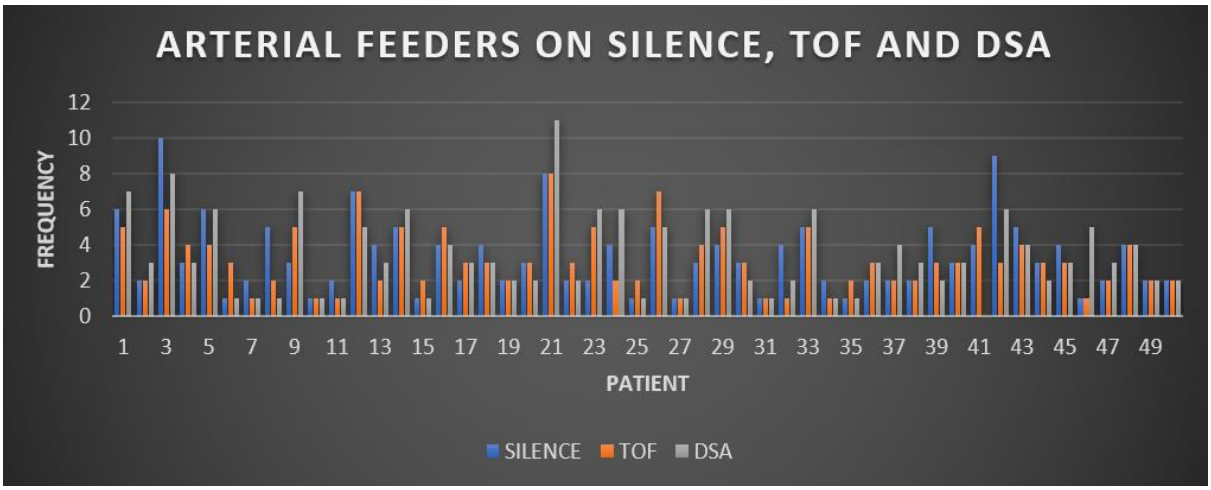


Figure No: 9–Frequency distribution of arterial feeders to the AVM nidus on silence MRA, TOF MRA and DSA.

ARTERIAL HYPERTROPHY

Presence of arterial hypertrophy was comparably detected both on SILENCE and TOF angiogram. Sensitivity and specificity of 87% and 81% and PPV and NPV of 78% and 94% for SILENCE as against sensitivity of 89% and Specificity of 30%, PPV of 79% and NPV of 83% for TOF MRA. The substantial decrease in specificity for arterial hypertrophy was attributed to the increased misinterpretation of vessel hypertrophy on TOF in comparison with DSA.

ARTERIAL HYPERTROPHY				
SILENCE	DSA			TOTAL
		Y	N	
	Y	34	2	36
	N	5	9	14
TOTAL		39	11	50

Table No: 5–ARTERIAL HYPERTROPHY ON SILENCE MRA.

DETECTION OF ARTERIAL HYPERTROPHY ON TOF VS DSA

ARTERIAL HYPERTROPHY				
TOF	DSA			TOTAL
		Y	N	
	Y	35	7	36
	N	4	3	14
TOTAL		39	11	50

Table No: 6–ARTERIAL HYPERTROPHY ON TOF MRA.

DETECTION OF AVM ASSOCIATED ANEURYSM

Evaluation for detection of intranidal and perinidal aneurysm revealed almost comparable but marginally better sensitivity for SILENCE MRA to TOF MRA which correctly identified aneurysm in 11/50 patients as compared to 10/50 patients in TOF MRA. The specificity was higher for TOF angiogram in comparison with SILENCE angiogram which was attributed to the increase in false positive identification of aneurysms on SILENCE. Obtained values of Sensitivity, specificity, PPV and NPV for SILENCE and TOF are 61%,78%, 61%, 78% and 55%, 90%, 76%, 78%.

INTRANIDAL ANEURYSM				
SILENCE		DSA		TOTAL
		Y	N	
	Y	11	7	18
	N	7	25	32
TOTAL		18	32	50

Table No: 7–INTRANIDAL ANEURYSM DETECTION ON SILENCE MRA.

INTRANIDAL ANEURYSM				
TOF		DSA		TOTAL
		Y	N	
	Y	10	3	13
	N	8	29	37
TOTAL		18	32	50

Table No: 8–INTRANIDAL ANEURYSM DETECTION ON TOF MRA.

VENOUS IDENTIFICATION

Totally 155 draining venous channels were identified on DSA in the 50 cases of AVM assessed in this study. Of these 66% were correctly identified on Silence MRA as to 53% identified on TOF. The misinterpretation rate was also substantially higher on TOF being 47% as to 34% on SILENCE MRA.

VENOUS IDENTIFICATION	SILENCE MRA	TOF MRA
CORRECT	103 (66.4%)	83 (53.5%)
MISSED	53(34%)	73 (47%)
MISINTERPRETED	5 (3.2%)	1 (0.6%)

Table No: 9–COMPARISION OF VENOUS VISUALISATION ON SILENCE AND TOF MRA.

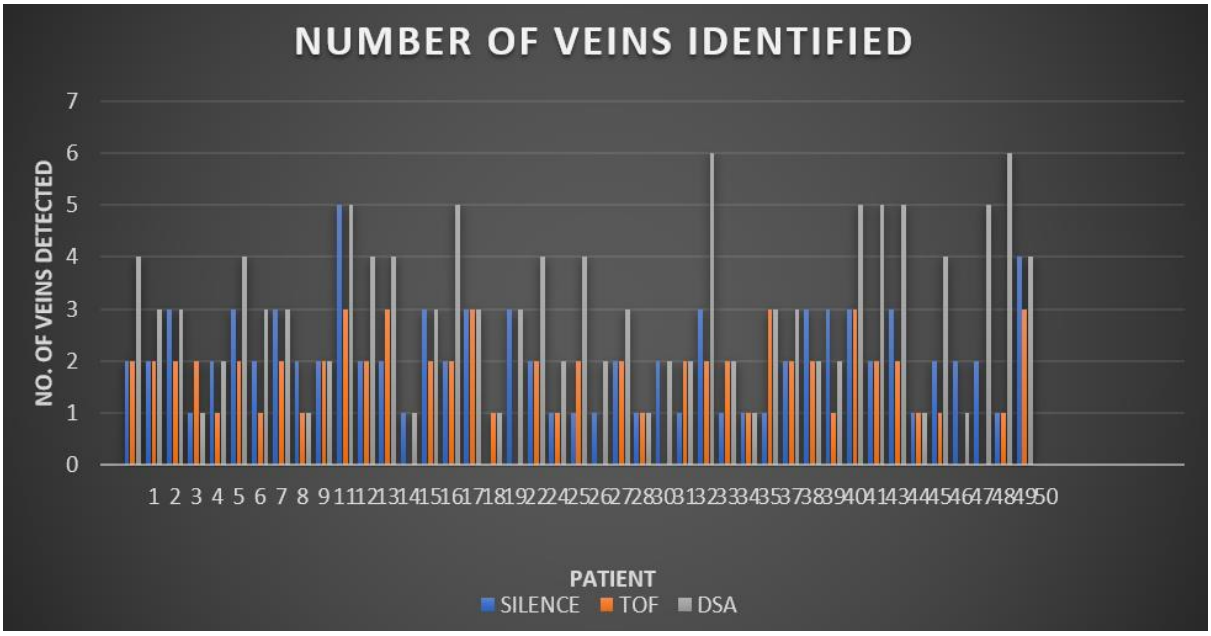


Figure No: 10–Frequency distribution of venous drainage from AVM nidus on Silence MRA, TOF MRA and DSA.

Bland and Altman analysis for the number of draining veins identified on the two modalities revealed, a tendency for lower detection of the draining veins on both the modalities comparing with DSA, however this was substantially more for TOF as compared to SILENCE angiogram.

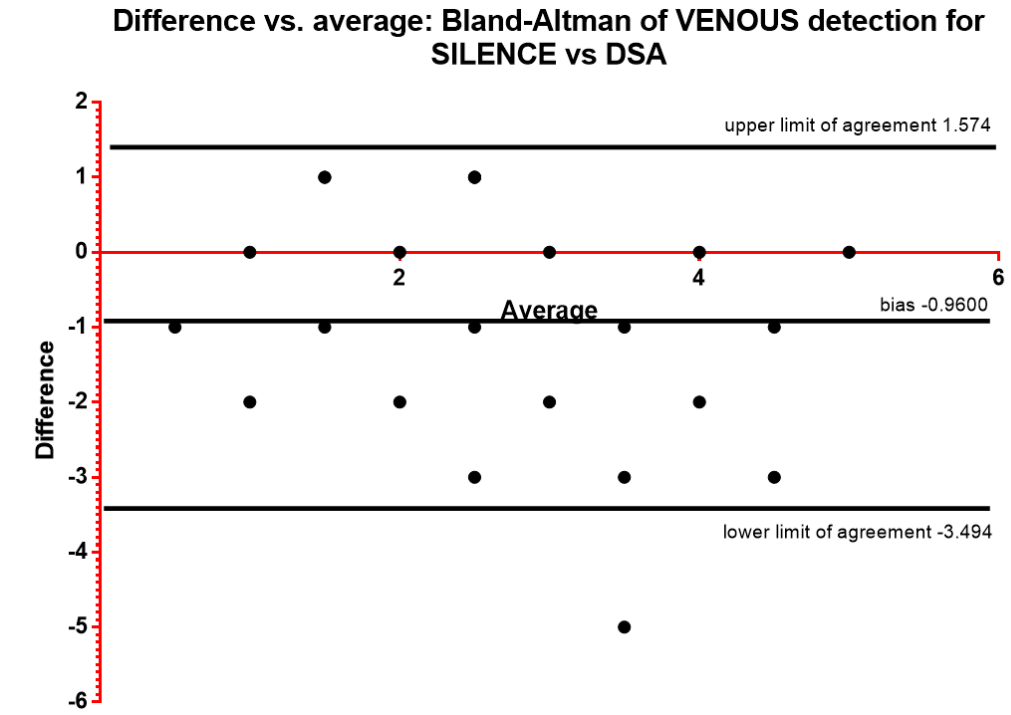


Figure No: 11–Bland Altman analysis plot of AVM venous drainage detection comparing Silence MRA vs DSA

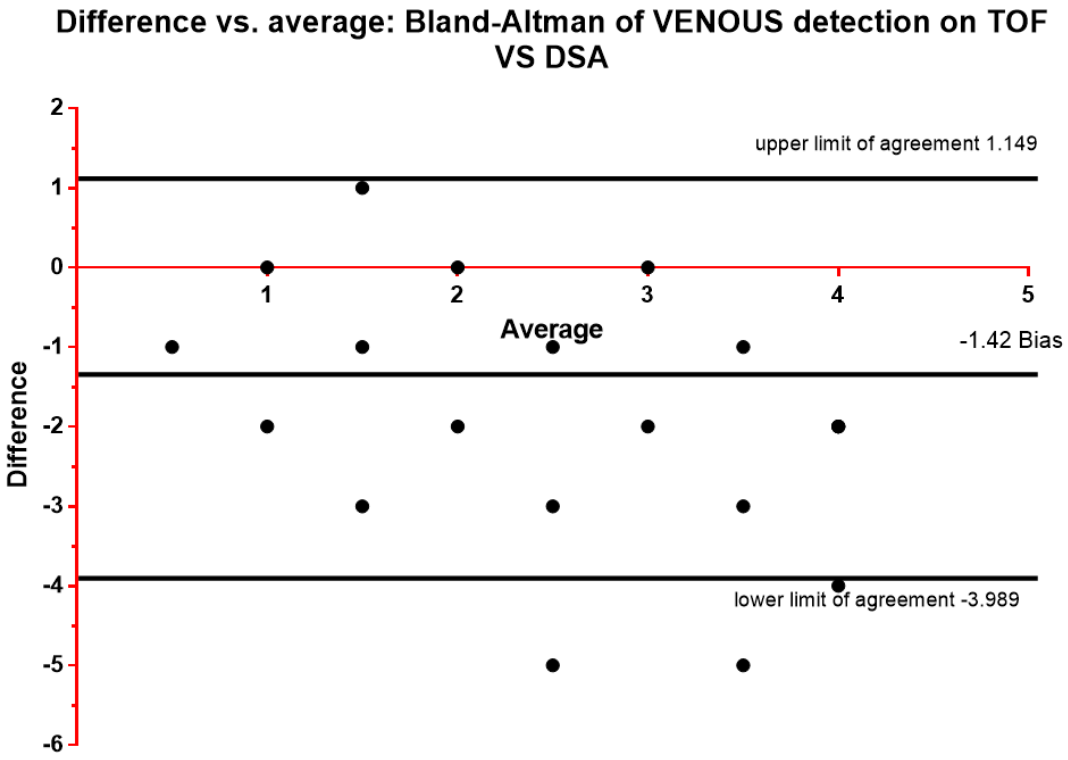


Figure No: 12–Bland Altman analysis plot of AVM venous drainage detection comparing TOF MRA vs DSA

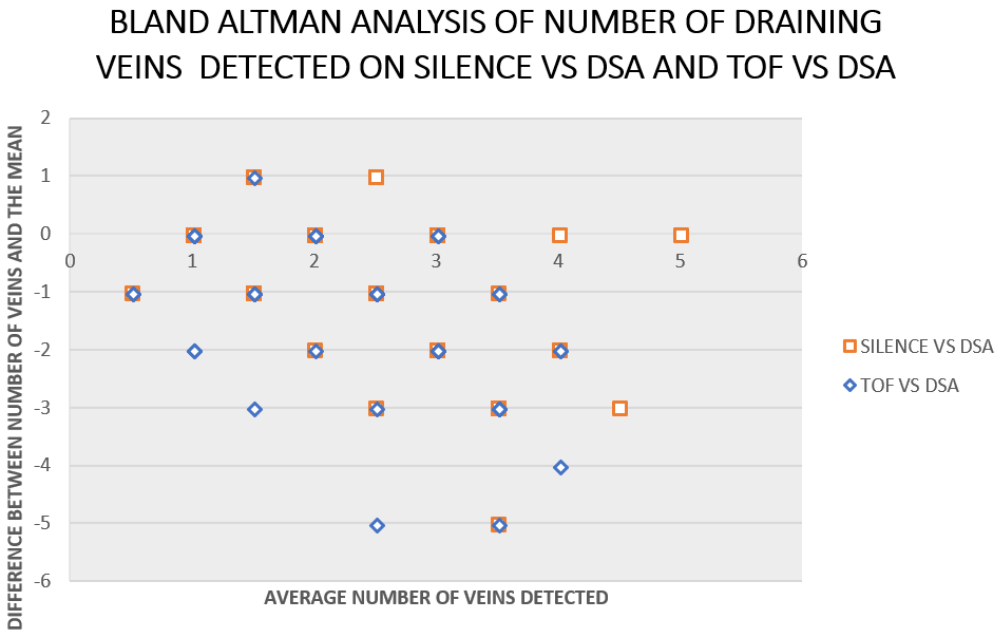


Figure No: 12–Bland Altman analysis plot of AVM venous drainage detection comparing Silence MRA vs DSA and TOF MRA vs DSA

SUPERFICIAL VENOUS DRAINAGE DETECTION

Silence MRA had a Sensitivity of 87.8%, specificity of 77.7%, PPV of 94.7% and NPV of 54.3% for the detection of superficial venous drainage from cerebral AVM on comparing with the gold standard DSA. TOF MRA had a Sensitivity of 67%, specificity of 90%, PPV of 96% and NPV of 40% for superficial venous drainage detection. This reveals that for initial screening of AVM and detection of superficial venous drainage SILENCE MRA would have an upper hand to TOF MRA.

SUPERFICIAL VENOUS DELINEATION				
SILENCE		DSA		TOTAL
		Y	N	
	Y	36	2	38
	N	5	7	12
TOTAL		41	9	50

Table No: 10–SUPERFICIAL VENOUS DRINAGE FROM AVM ON SILENCE.

SUPERFICIAL VENOUS DELINEATION				
TOF	DSA			TOTAL
		Y	N	
	Y	27	1	28
	N	13	9	22
TOTAL		40	10	50

Table No: 11–SUPERFICIAL VENOUS DRINAGE FROM AVM ON TOF.

DEEP VENOUS DRAINAGE DETECTION

Silence MRA with a sensitivity of 77%, specificity of 100%, PPV of 100% and NPV of 63% for the detection of deep venous drainage substantially outperformed TOF MRA which reported a sensitivity of 65%, specificity of 86%, PPV of 92% and NPV of 52% for deep venous drainage detection.

DEEP VENOUS DELINEATION				
SILENCE	DSA			TOTAL
		Y	N	
	Y	28	0	28
	N	8	14	22
TOTAL		36	14	50

Table No: 12–DEEP VENOUS DRINAGE FROM AVM ON SILENCE.

DEEP VENOUS DELINEATION				
TOF	DSA			TOTAL
		Y	N	
	Y	23	2	25
	N	12	13	25
TOTAL		35	15	50

Table No: 13–DEEP VENOUS DRINAGE FROM AVM ON TOF.

AVM ANGIOMORPHOLOGICAL PARAMETER	MODALITY	SENSITIVITY	SPECIFICITY	PPV	NPV	ACCURACY
ARTERIAL HYPERTROPHY	SILENCE	87.2	81.8	94.4	64.2	86
	TOF	89.7	30	83.3	42.8	77
ANEURYSM DETECTION	SILENCE	61.1	78.1	61.1	78.1	72
	TOF	55.5	90.6	76.9	78.3	78
SUPERFICAIL VENOUS IDENTIFICATION	SILENCE	87.8	77.7	94.7	58.3	86
	TOF	67.5	90	96.4	40.9	72
DEEP VENOUS IDENTIFICATION	SILENCE	77	100	100	63.4	84
	TOF	65.7	86.6	92	52	72

Table No: 14–comparison of Sensitivity, specificity, PPV, NPV and Accuracy for various AVM characteristics on Silence and TOF vs DSA.

EVALUATION OF DIAGNOSTIC CONFIDENCE SCORES AROSS MODALITIES

The DC scores was assessed for the different AVM characteristic including Feeding arteries, Nidus and Draining veins. The diagnostic confidence was grades as per a 4 point Likert scale which was defined as, Grade 1- non diagnostic images, 2 – faint visualisation and difficulty in diagnosis. 3 – moderate visualisation with some blurring due to artefacts but diagnostic, 4 – good quality images with definite diagnosis possible.

The difference in DC scores between Silence vs DSA and TOF MRA vs DSA was computed. Assuming the null hypothesis to be true with no statistically significant imaging quality difference between the modalities, the difference expected would be zero. The non

parameteric paired t test, Wilcoxon signed rank test, was used to determine if a statistically significant difference in image quality was present between the two modalities assessed. Statistical significance was assumed with a P value of <0.05.

	MODALITY	ARTERIAL VISUALISATION	NIDAL	VENOUS VISUALISATION
MEAN OF DC SCORES	SILENCE MRA	3.92	3.68	3.88
	TOF MRA	3.84	2.78	3.1
	DSA	3.98	3.96	4
Wilcoxon signed rank test, p value comparing difference in DC between DSA with Silence MRA and DSA with TOF MRA		0.0625	<0.0001	<0.0001
Mean of difference in DC between DSA and Silence MRA		0.06	0.28	0.12
Mean of difference in DC between DSA and TOF MRA		0.14	1.18	0.9

Table No: 15–comparison of diagnostic confidence scores across modalities for various AVM characteristics.

The mean of the Diagnostic confidence scores for feeding arterial detection was 3.92 for silence, 3.84 for TOF MRA and 3.98 for DSA. The DC score for nidus identification was 3.68 for Silence MRA, 2.78 for TOF MRA and 3.96 for DSA. The same was 3.88 for Silence MRA, 3.1 for TOF MRA and 4 for DSA.

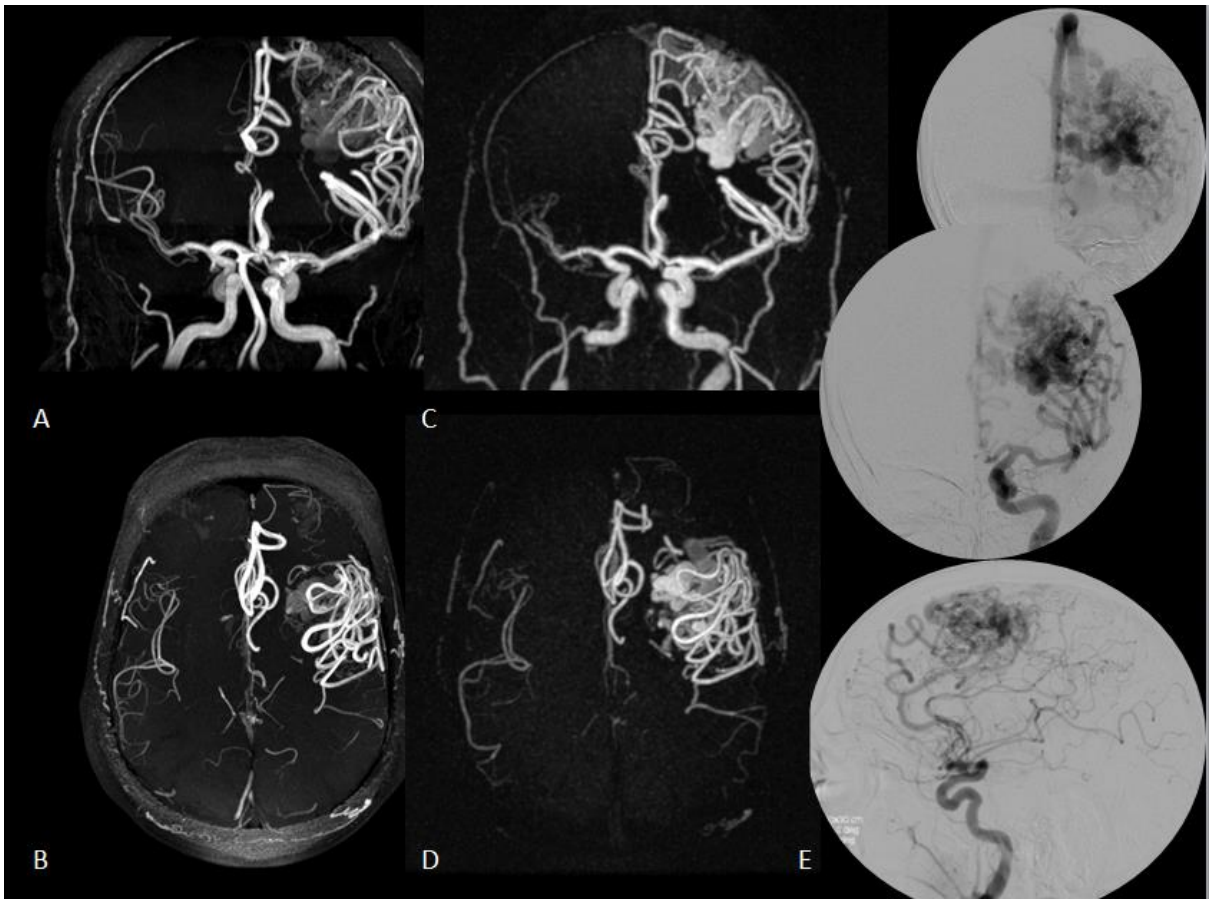
Wilcoxon signed rank test was assessed for difference in the diagnostic confidence in between Silence MRA from DSA and TOF MRA from DSA each of the AVM components.

The P value for arterial detection DC difference was 0.0625 and not statistically significant. Both the P values for nidal differentiation and venous visualisation DC difference was <0.0001 which was statistically significant. This indicated that while arterial identification was similar on Silence and TOF MRA, Silence was better for nidal differentiation and venous visualisation.

ILLUSTRATIVE CASES

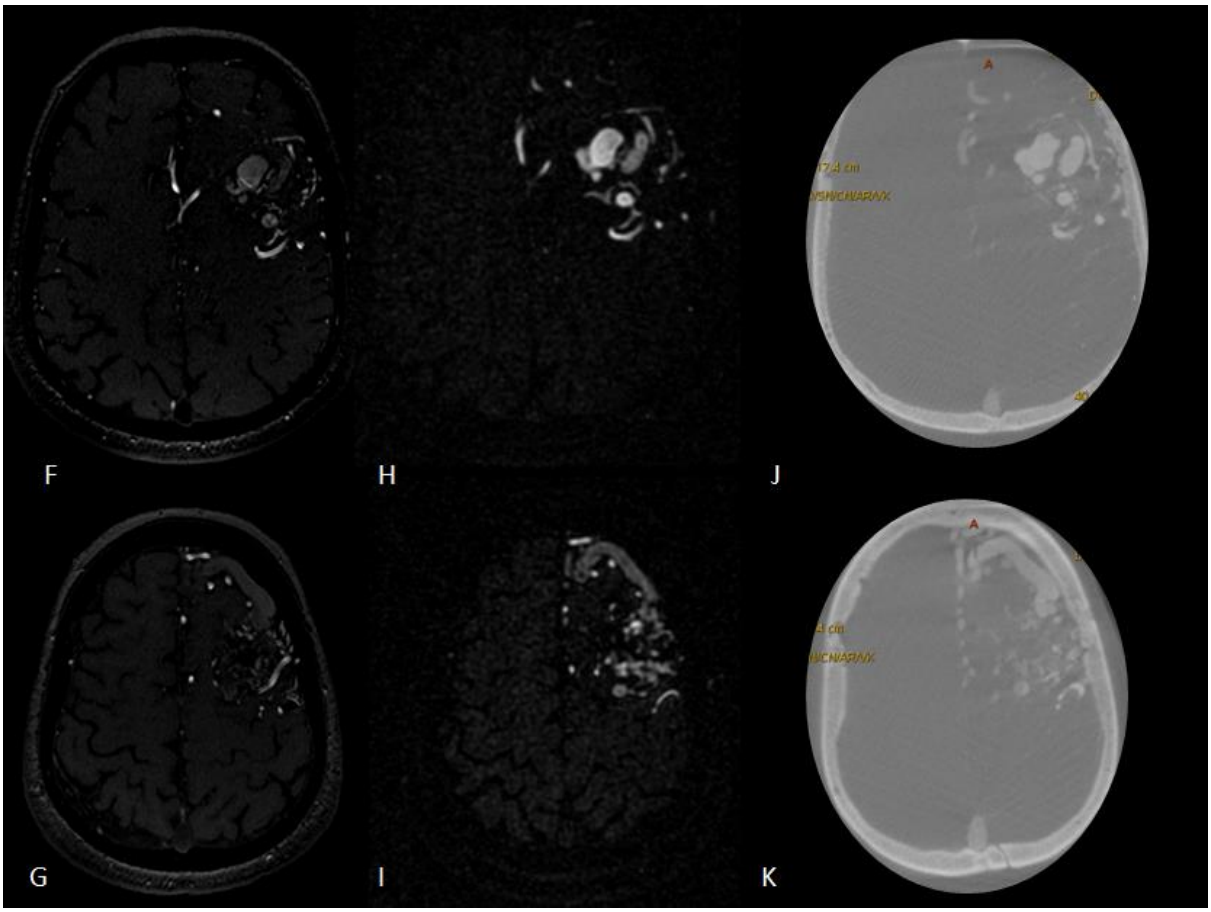
ILLUSTRATIVE CASES

CASE 1



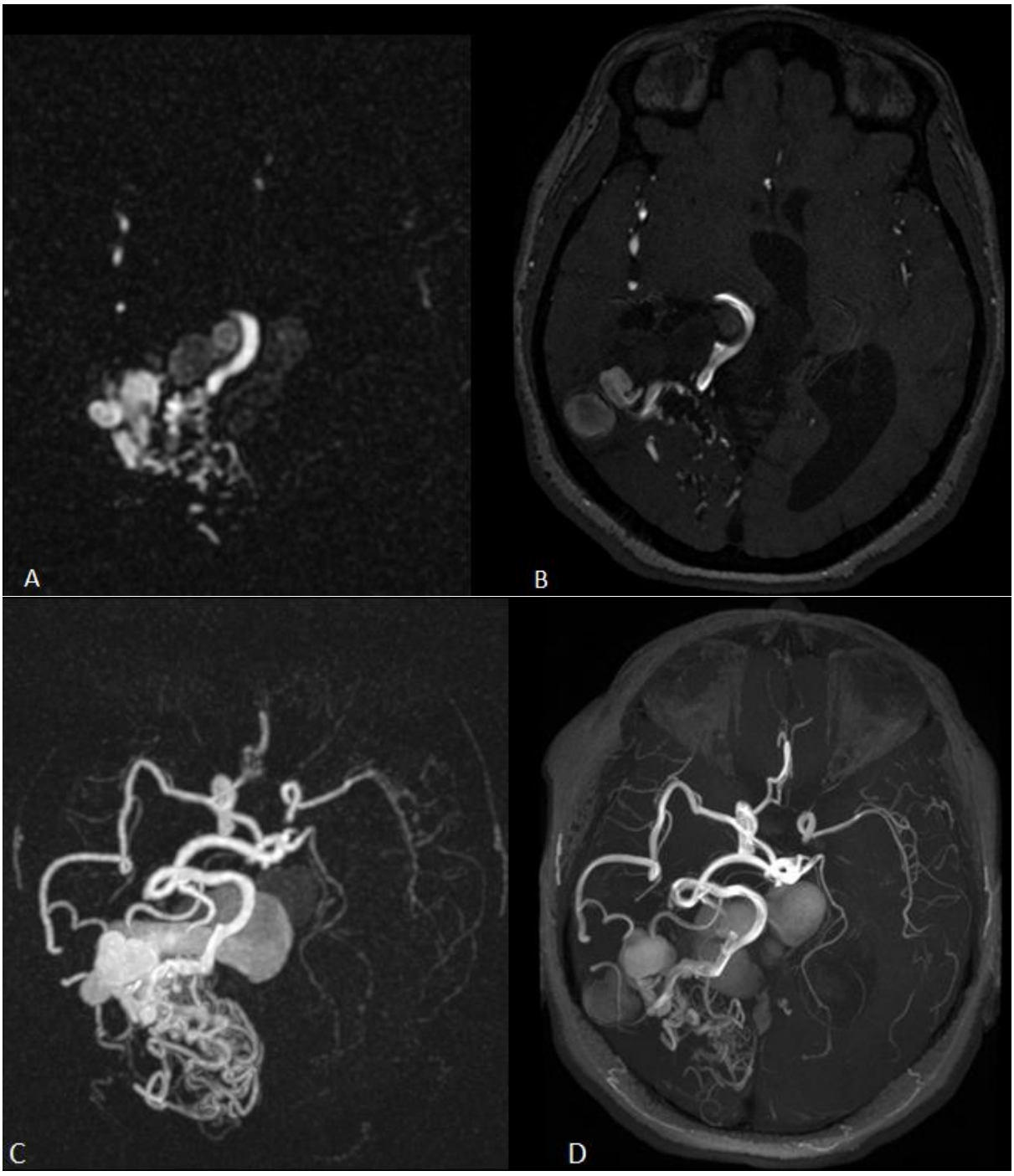
Case 1. Figure I: 53 year male patient, case of left frontal insular region AVM. (A,B- TOF MRA MIP images; D,C-SILENCE MRA MIP images; E – DSA). The arterial feeders are well depicted on both the TOF and MRA MIP images. But the nidal visualisation is better on SILENCE MRA. The draining vein is also well visualised on the SILENCE MRA as compared to TOF. DSA due to its inherent temporal resolution is able to segregate the AVM components in the best possible manner.

CASE 1



Case 1. Figure II: 53 year male patient case of left frontal insular region AVM. (F,G- TOF MRA axial images; H,I-SILENCE MRA axial images; J,K – 3D CT). Corresponding axial locations are presented on the 3 modalities (F,G,H – lower insular level through the inferior to mid part of the AVM nidus and G,I,K – through the superior aspect of the nidus where the major draining veins is located). The arterial feeders are similarly depicted on both the TOF and MRA images almost in a manner similar to the 3D CT images. But the nidal visualisation as in the MIP images is also better on SILENCE MRA though slightly inferior to the 3D CT images. The superficial draining vein depiction on SILENCE MRA almost comparable to that on the 3D CT images but is much lower in signal on TOF. But the vein margins are well depicted on TOF by the improved spatial resolution possible with TOF MRA.

CASE 2



Case 2.Figure I,II. 34 year female patient, case of right temporo occipital region AVM. (A-SILENCE MRA axial images; B- TOF MRA axial images; C-SILENCE MRA MIP images; D- TOF MRA MIP images).Corresponding axial locations show excellent visualisation of the large venous sacs associated of this AVM and relatively high signal within the fistulous

component on SILENCE MRA. This could have utility in localisation of fistula within AVM from the static SILENCE images. The deep venous drainage is also similarly better depicted on SILENCE MRA. The arterial feeders are similarly depicted on both the MRA.

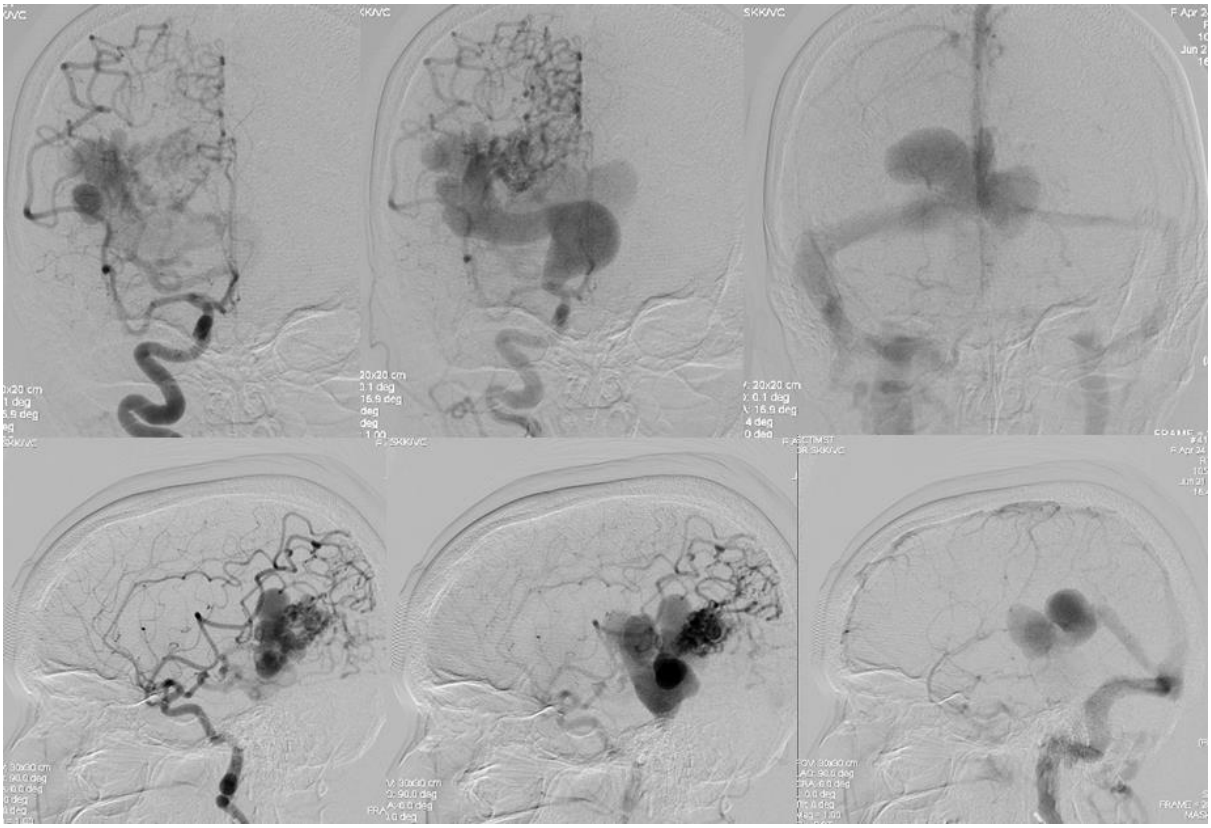
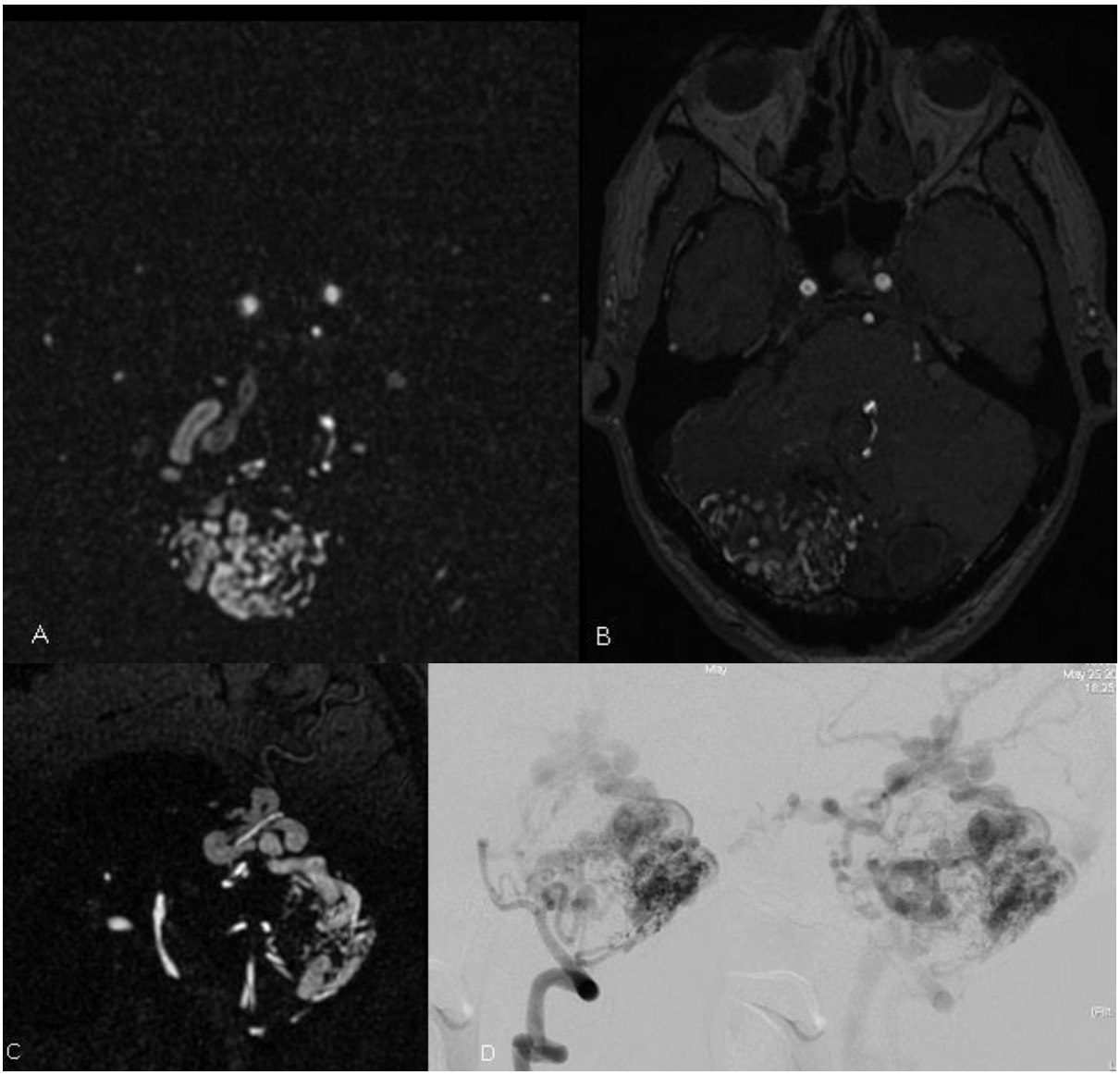


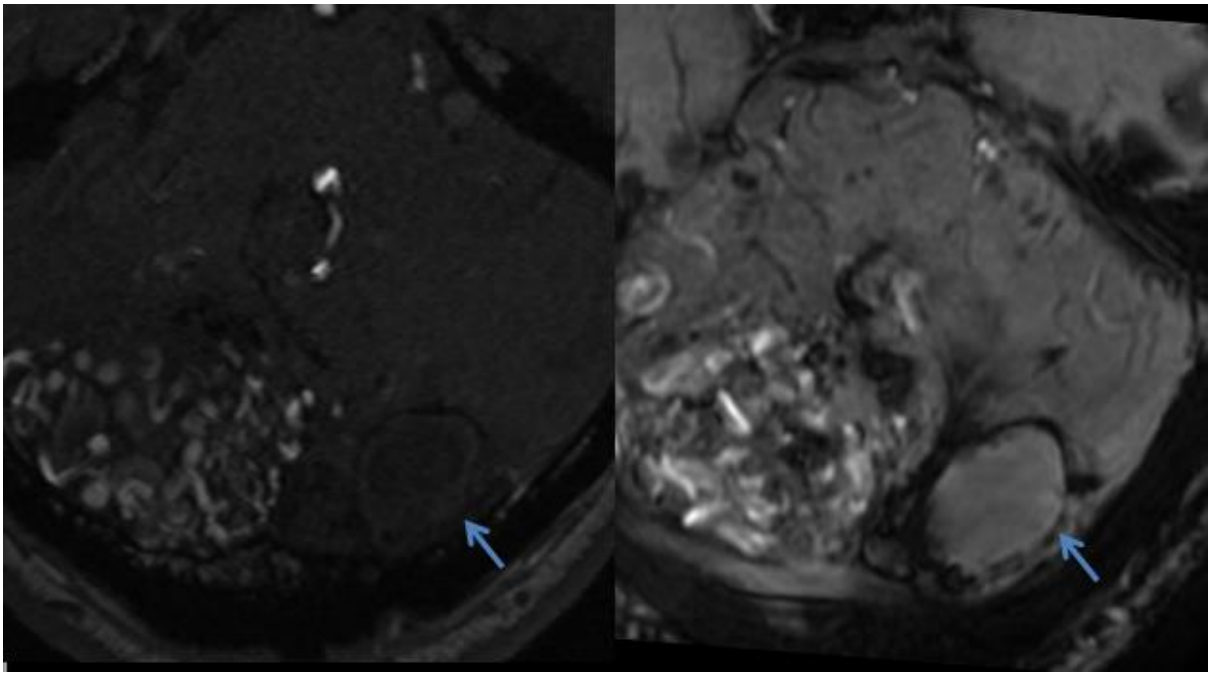
Figure 2.III DSA images of the same 34 year female patient with the temporo occipital AVM and predominant fistulous component. The AVM nidus per se appears much smaller as compared on the DSA images. Corresponding TOF and SILENCE MRA have some degree of overestimation of the nidal size, more so on SILENCE MR angiogram. The deep venous visualisation on SILENCE is almost comparable to the DSA images.

CASE 3



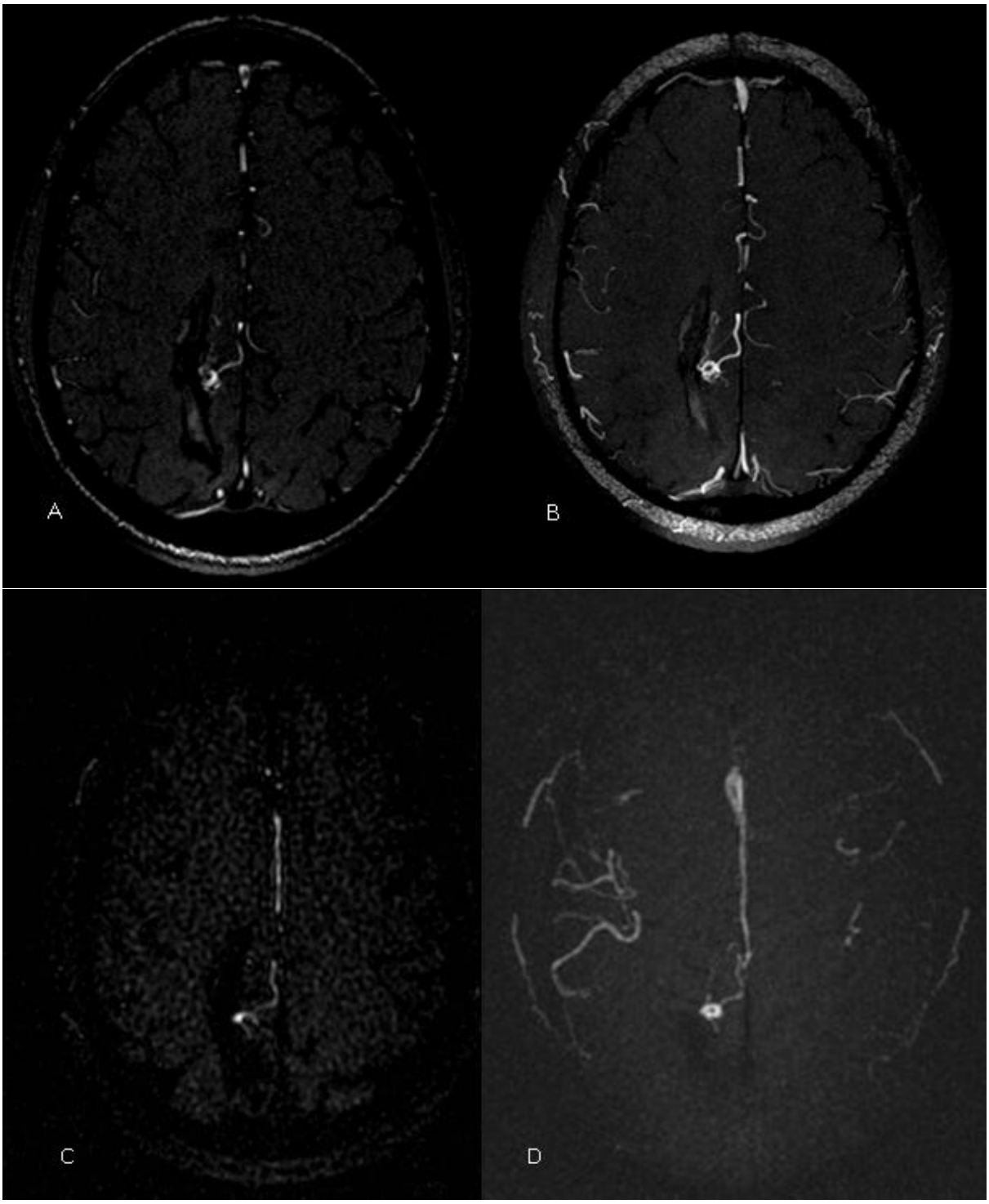
Case 3. Figure I: 50 year male patient case of cerebellar region AVM. (A,C -SILENCE MRA axial and sagittal images; B- TOF MRA axial images; D – DSA arterial feeder and venous phases of the AVM). Patient previously diagnosed with cerebellar AVM incidentally, now presenting with left cerebellar hemispheric bleed which is faintly seen on TOF Images. However due to the increased background suppression by subtraction of labelled and control datasets for SILENCE MRA there is no evidence of the bleed. The sagittal SILENCE MRA image shows both the predominant deep venous drainage as well as the venous drainage via a paramedian occipital vein egressing into the SSS(C). The VA injection images on DSA

revealing the plexiform nature of this compact AVM and multitude of associated veins with reflux and venous egress from the deep system into the SSS. These are only fairly depicted on Silence and with almost no visualisation on TOF.



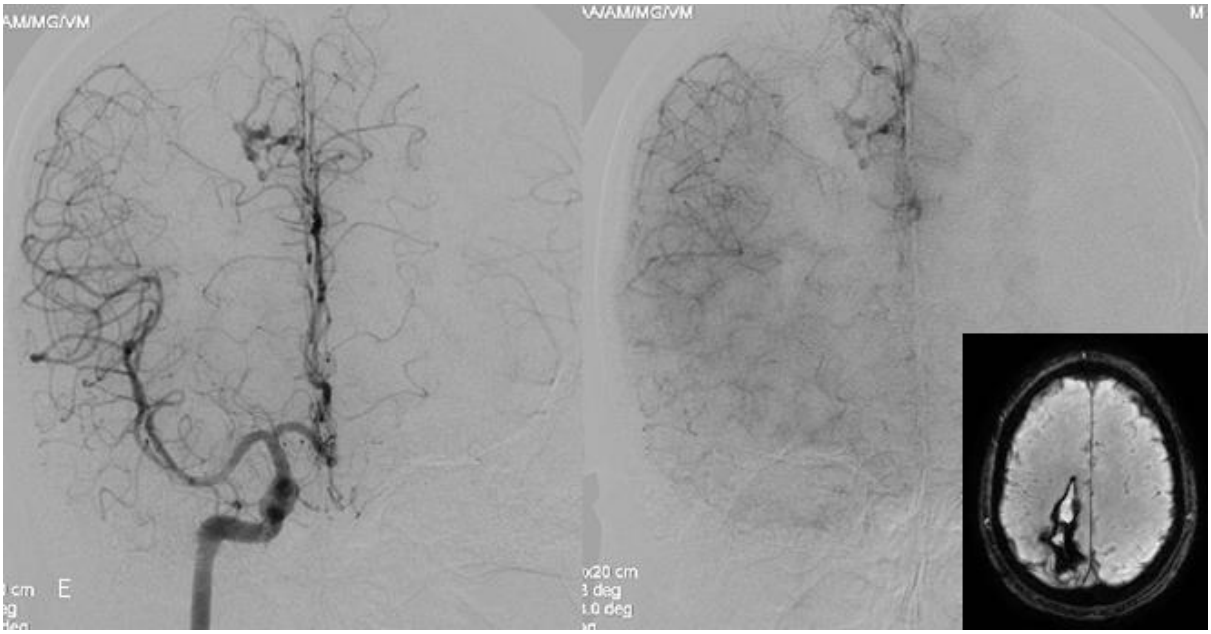
The evidence of the bleed on TOF in left cerebellar hemisphere and corresponding SWI axial image.

CASE 4



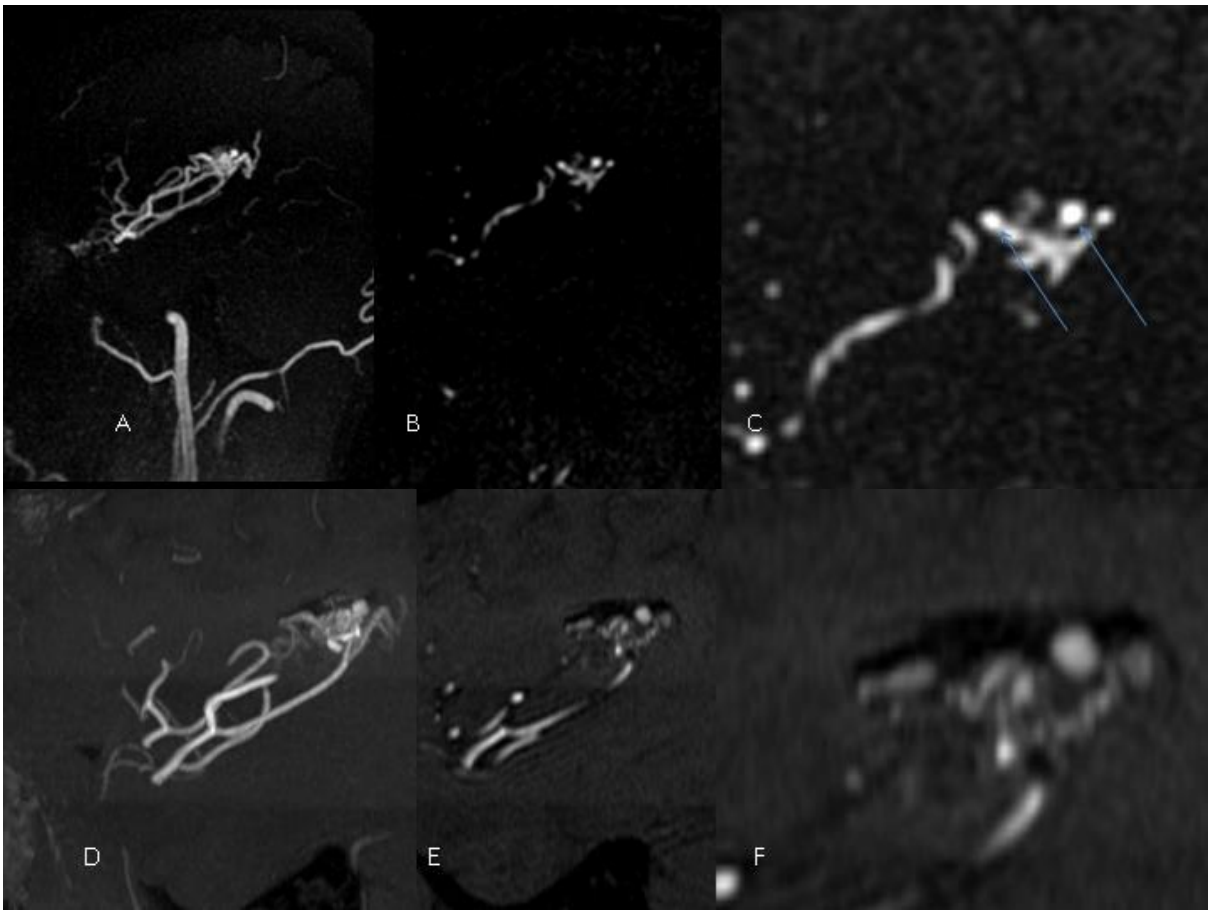
Case 4. Figure I,II: 28 year male patient case of bled right parietal region micro AVM. (A,B-TOF MRA axial and MIP images; C,D -SILENCE MRA axial and MIP images; D – DSA arterial feeder and venous drainage with SWI images inset). Both SILENCE and TOF MRA

images depicts the arterial feeders and micro-AVM nidus to a similar extent. But both techniques are lacking in depiction of its relatively less profuse venous out flow. This case illustrates the pit fall of non-contrast static MR angiographic images where the low velocity flow impairs vessel visualisation

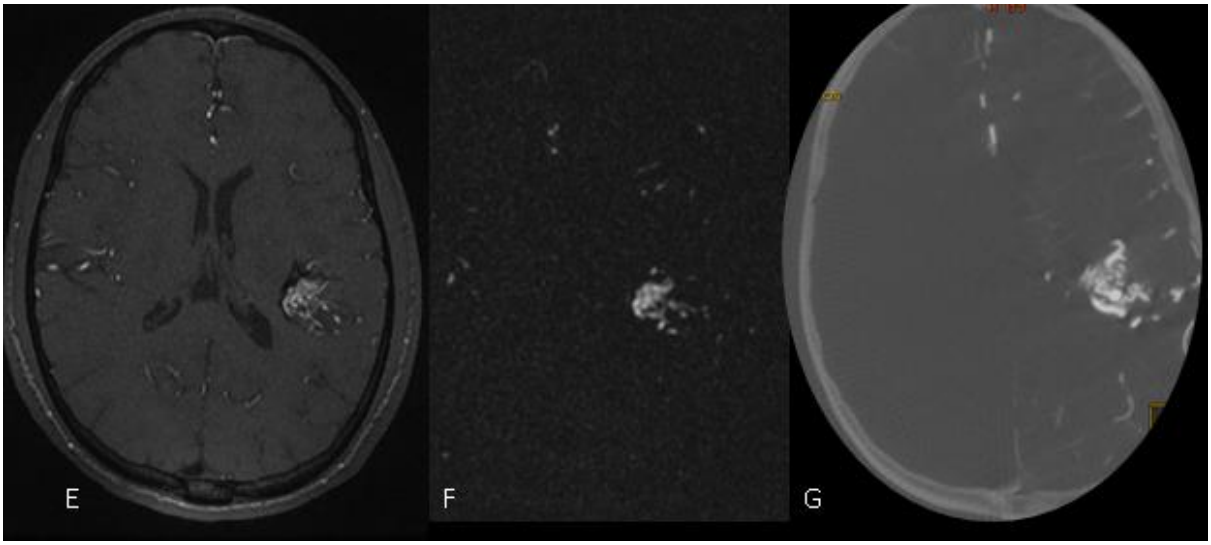


Case 4.Figure III. DSA images of this patient shows the sparse micro nidus and the superficial venous drainage form the nidus. Evidence of prior Bleed is as depicted by blooming on SWI.

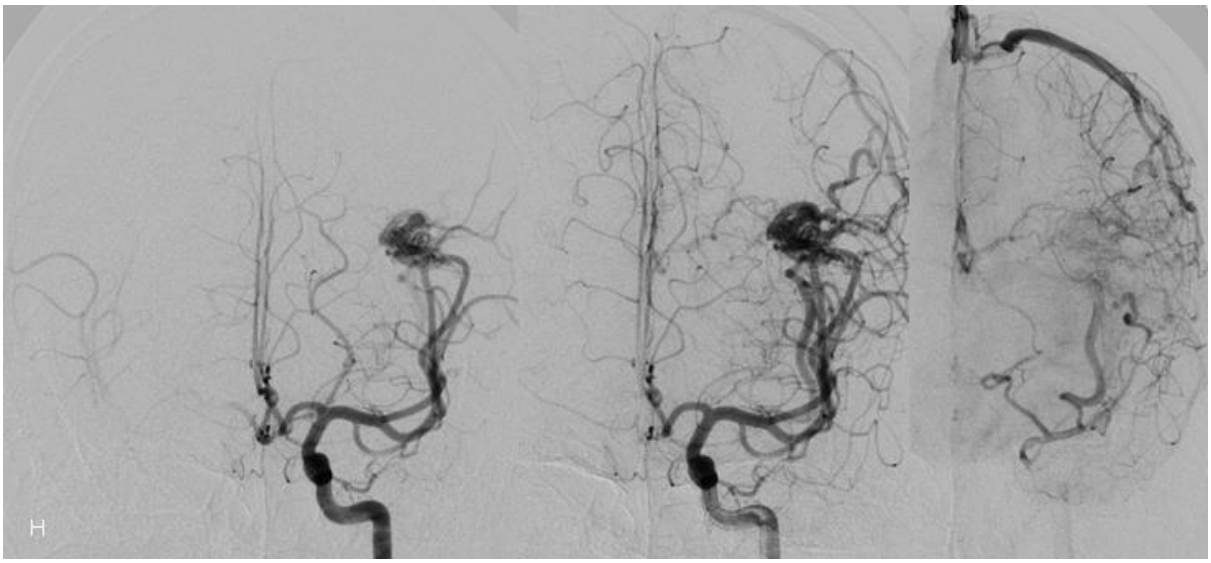
CASE 5



Case 5. Figure I,II: 22 year male patient case of bled Left fronto pareital region compact nidus AVM. (A,B,C- Silence MRA Sagittal MIP, Sagittal and zoomed sagittal images;,D,E,F -TOF MRA Sagittal MIP, Sagittal and zoomed sagittal images) The intranidal aneurysm is seen both on SILENCE and TOF MRA but the relatively higher signal intensity in the SILENCE MRA images makes delineation of the AVM easier as compared to TOF. Here the Aneurysm detection is relatively easier for the fact that it is almost near the superior edge of the nidus and is more or less free of nidal signal per se, which can impair the aneurysm detection in AVM MRA.



Case 5.Figure III,: E,F,G- axial TOF MRA, SILENCE MRA and 3DCT reveal almost comparable depiction of the AVM angiomorphology.



Case 5. Figure IV: H- DSA of the same patient depicting the nidus and associated aneurysm.

DISCUSSION

DISCUSSION

Cerebral arteriovenous malformations are vascular aberrations that require multiple imaging studies throughout the sequence of their treatment and follow up which might span over several months to years depending on the mode of treatment. The modality of choice in the definite diagnosis, treatment planning, treatment and follow up of this cerebrovascular disease entity is digital subtraction angiogram. But the multitude issues that can possibly be associated with DSA, including invasiveness, radiation, and risk of morbidity and mortality from a stroke, makes the question of an alternative very relevant. Despite the multitude of other option available such as contrast enhanced MRA techniques as well as non-contrast techniques, none have till date presented enough mettle to replace the superior spatial and temporal resolution accorded by DSA. But at least a modality that will reliability do away with the requirement of repeated DSA studies or limit number of DSA studies in an AVM patient would add significant respite. With the risk of brain GBCA deposition in patients who received prior IV GBCA for contrast enhanced MRI, recently coming into the limelight, the advantage of CE MR angiographic methods for this purpose have received a serious setback and non-contrast methods have gained a lead. Among the non-contrast methods one particular technique, the Silence non-contrast MRA technique holds promise.

This study of cerebral arteriovenous malformations compared, the novel Silence MRA technique against TOF MRA using DSA as the benchmark. From October 2016 after clearing the institutional ethics committee approval, till June 2018, 58 patients were recruited consecutively and underwent imaging by Silence and TOF MR angiogram in addition to their routine imaging work up for cerebral AVM. Of these 8 patients were excluded due to the suboptimal imaging that was not interpretable or was incomplete. The 50 cases were finally available was evaluated independently for the AVM components on Silence MRA, TOF MRA and DSA with a minimum interval of 2 weeks between the three different modalities.

The various angiomorphological characteristics of AVM were compared across the three modalities and statistically analysed in this study. No prior such studies were available on literature search on evaluation of AVM with Silence MRA except for a case report on use of silence in AVM(21). This is the first study addressing this novel imaging entity. Most of the prior studies available on MRA in AVM have compared 3T TOF with 1.5T TOF MRA(12) or utility of various static and dynamic contrast enhanced or key hole imaging based MRA against TOF MRA in AVM(44,45). Recently there has also been an increased interest in the utility of 4D FLOW based non contrast techniques in elucidation of the AVM architecture(19).

Recent studies addressing utility of Silence MRA, in aneurysms treated by stent assisted coiling in the anterior circulation by Irie et al and basilar tip aneurysms treated by Y stenting by Takano et al (3,46) have revealed superiorly of Silence in assessing the remnant neck and instent flow. The authors mainly attributed this to the ability of silence MRA in overcoming the susceptibility effects impairing image quality in TOF. This information can also considered relevant in AVM imaging which can have significant susceptibility effects from associated bleed or prior surgical or endovascular treatment.

DEMOGRAPHICS

The demographic profile of this study was a substantial improvement over prior studies comparing AVM with inclusion of a consecutive study sample of 50 patients. Also, the sex distribution among the recruited cases was well balanced with male to female ratio of 1.27.

Regarding the location of AVM, there was relatively fair distribution of lesions throughout the cerebral circulation.

AVM VOLUME

Both Silence and TOF MRA differed in measured volumes, in comparison to DSA. For AVM of smaller volumes, the volumes were relatively better matched to those measured on Silence and TOF MRA. With increasing size of AVM, the measured volumes showed significant difference from the actual DSA measured volumes both on Silence and TOF. There was more overestimation on Silence as compared to TOF. This can be partly accounted for the better venous visualisation on Silence MRA as to that on TOF and possible inclusion of the juxta nidal venous part of the AVM in the study. TOF mildly fared better in this regard. In comparison a prior study by Heidenreichet al (18) comparing 1.5T TOF vs 3T TOF MRA in AVM revealed an underestimation of the AVM size with increasing actual AVM size. In this study that assessed 3T TOF the authors noticed that the modality reported higher AVM volume compared to 1.5T and they attributed it to increased field distortion and susceptibility artefacts to be the contributing cause.

FEEDING ARTERY EVALUATION

The arterial feeder identification rate was similar for both Silence MRA and 3D TOF MRA with 80% of the arteries being correctly identified. The percentage of missed vessels was similar on both modalities, but misinterpretation on arterial feeders was more on Silence. Prior studies have revealed, arterial feeder identification at a rate of 73% on 3T TOF in study by Heidenreichet al (18). In another study by Cuong et al(47) 3T TOF could identify only 63% of the arterial feeders.

FEEDING ARTERY HYPERTROPHY

Detection of feeding artery hypertrophy was better on Silence with sensitivity and specificity of 87.2 and 81.8% compared to 3D TOF MRA which had a high sensitivity of 89.7% but low specificity of 30%.

ANEURYSM DETECTION

The sensitivity and specificity for intranidal and perinidal aneurysm detection was 61% and 78% for Silence MRA and 55.5% and 90% for TOF MRA. This indicates the marginally increased ability of silence MRA to detect AVM associated aneurysm. On comparing the images form Silence and TOF this higher sensitivity of Silence was attributed to the increased signal intensity within aneurysms on Silence MRA compared to the adjacent nidus. We attribute this to lower velocity vortex flow within aneurysm causing increased stasis of the tagged blood within the sac compared to the parent vessel(48). The lower specificity for silence can similarly attributable to the relatively higher nidal and juxta nidal venous signal which can lead to overestimation by misinterpretation of venous pouches as aneurysms.

VENOUS DRAINAGE IDENTIFICATION

Silence MRA was better in identification of both superficial and deep venous drainage with sensitivity of 87.8% and 67.5% for silence and TOF for superficial venous visualisation and 77% vs 65.7% for deep venous visualisation. The sensitivity was higher for superficial venous drainage on TOF MRA with 90% and 77.7% specificity for Silence MRA. In deep venous detection silence MRA was 100% specific and TOF MRA reported a specificity of 86.6%. The higher sensitivity of silence MRA could again be attributable to the high venous signal intensity and greater venous visualisation. The lower venous detection on TOF especially for deep venous visualisation was probably related to multislab acquisition of TOF. This would result in some degree of signal loss in intervening regions between the acquisition slabs corresponding to level of the deep venous system in most of our cases.

DIAGNOSTIC CONFIDENCE SCORES FOR AVM COMPONENTS

The mean diagnostic confidence score for the 50 cases were lower on TOF than Silence MRA as compared to DSA. But the Wilcoxon signed rank test revealed no significant difference

between the diagnostic scoring for arterial detection for both silence and TOF MRA indicating both to have a similar robustness in arterial feeder identification in AVM.

However, the difference between the scores for nidal delineation and venous recognition was statistically significant with reported difference in the mean score from DSA of only 0.28 on silence as to 1.18 for TOF in nidal differentiation and 0.12 for silence and 0.9 for TOF for venous visualisation.

LIMITATIONS

Interrater variability was an entity not assessed in this study, which would have assess the reliability in assessment of angiomorphology in each of these modalities. This is being currently undertaken by the investigators and would be part of the publication of this study.

The utility of the modalities in post treatment patients of AVM is also a requirement which was not fulfilled in this study. Investigation along these lines would supplement the requirement in imaging follow up in cerebral AVM. This is also a needs to be further addressed in further studies.

CONCLUSION

CONCLUSION

This study which compared the utility of the novel sequence, Silence MRA in angiomorphological elucidation of cerebral AVM in comparison to TOF and DSA revealed the following conclusions.

Both Silence and TOF MRA tend to overestimate aneurysm nidus size, slightly more so with Silence as to TOF. This can be attributed to the better venous visualisation on silence MRA.

The arterial feeder identification was similar on both the modalities, but with better identification of arterial hypertrophy on Silence as to TOF.

Silence MRA has a higher sensitivity for detection of intranidal aneurysm compared to TOF MRA due to the higher intra aneurysmal signal. But there is marginally lower specificity due to the possible erroneous detection of venous pouches as aneurysms due to the significantly higher venous signal on Silence MRA.

For both deep and superficial venous detection Silence MRA outperformed TOF MRA, by virtue of the better venous visualisation on Silence.

Comparing Diagnostic confidence scoring, both Silence and TOF MRA were similar for arterial feeder evaluation. But Silence MRA scored over TOF MRA in nidal characterisation and venous drainage visualisation.

But despite the better performance of Silence in characterisation of several AVM angiomorphological features, the diagnostic confidence in Silence was lower compared to DSA retaining the later as still the last say in AVM imaging.

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ANNEXURES

INFORMATION SHEET

TITLE OF THE STUDY: Imaging of Brain Arteriovenous malformations – comparing Silence Magnetic resonance angiography with Three-dimensional Time-of flight magnetic resonance angiography and Digital subtraction angiography .

Study number:

Participant's name: _____

Date of Birth / Age (in years): _____

Son/daughter of _____

You have been informed that there is an abnormal communication between the arteries and veins (Arterio venous malformation), within your brain parenchyma. For this you will have undergone or will be undergoing a digital subtraction angiography (DSA) test and Magnetic Resonance Imaging (MRI) as a part of clinical evaluation of your disease. This is to plan the treatment or for follow up your disease.

You are requested to participate in a study to evaluate the role of a new Magnetic Resonance Imaging sequence called Silence MR angiogram in arteriovenous malformations. While participating in this study, only the imaging data from the MRI and DSA investigations you have undergone for your treatment purpose will be used. Participating in this study will in no way influence your treatment decisions. The benefit that you may incur from this study is, if this new MRI technique is found useful, during subsequent reviews/ follow up your further imaging follow up can be limited to just an MRI rather than performing an invasive evaluation like DSA.

What are DSA and MRI and do they have any harmful effects?

DSA (Digital subtraction angiography) test is an advanced imaging technique where the blood flow to your brain will be evaluated by injecting a dye into the arteries to the brain through a small tube which will be inserted through the artery in your thigh. X-Rays will be obtained during the procedure which will clearly show the abnormal connections between arteries and veins if they exist. You will not experience much pain as an injection will be given on your thigh prior to the procedure to make it numb. You will not feel any pain during the rest of the procedure. In rare cases some people may have allergic reaction to the dye. There is also a very small risk of injury to the blood vessel and slight chance of bleeding at site of puncture. This test is vital in diagnosis of your condition and is also the means of treatment if planned subsequently.

MRI is an advanced imaging technique which uses certain waves and magnetic fields to image body part. It does not involve any ionizing radiation. There will be no administration of any type of drug or medicine during the study. Some patients may develop claustrophobia (Fear of closed spaces etc.) due to closed space and noise. This investigation is not to be done for patient with metallic implants, pacemakers. This MRI is being done as a part of clinical evaluation of your disease; however certain data from this study will be used for research purpose to compare with the DSA study which you have already undergone/ will undergo shortly.

If you take part what will you have to do?

This study will only analyse the results of the routinely ordered imaging investigations you will undergo during treatment and follow up of your illness. You will not be required to do anything apart from the regular follow up that will be advised to you.

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

What will happen if you develop any study related injury?

This study only analyzes the results of your investigation and treatment details and thus we do not expect any injury to happen to you but if you do develop any side effects or problems due to the study, these will be treated at this institute by the experienced team of medical professionals. We are unable to provide any monetary compensation, however.

Will you have to pay for the study?

The study will only analyse the results of the investigations and treatment which you will undergo in natural process of your treatment for AVM at this institute and no extra cost will be borne by you for this particular study.

What happens after the study is over?

You may or may not benefit from this study. If the study is found useful then during subsequent reviews you can be evaluated just by non invasive MRI rather than undergo a more invasive DSA.

Will your personal details be kept confidential?

The results of this study may be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

Will the study have any adverse effects on pregnancy if the patient is pregnant?

Both the DSA and MRI will be done only for a patient who require these studies as part of their treatment or follow up.

There is risk related to ionizing radiation in DSA study which can be harmful to the fetus. Regarding safety of MRI in pregnancy, to date there has been no indication that the use of clinical MRI during pregnancy has produced deleterious effects. However these investigations will be done in a pregnant patient only in situation where the mother's life is in danger and she requires treatment or an immediate follow up study is warranted. For these tests to be done she has to give her informed written consent.

Moreover this study is a comparison of the imaging data from the DSA and MRI tests you have or is about to undergo as part of the treatment. You are not undergoing these tests for the study per se.

If you have any further questions, please ask Dr. Jospaul Lukas (tel: 9400733593) or email: jospaul_lukas@sctimst.ac.in

IEC Member Secretary
Dr. Mala Ramanathan
Phone Number : 0471 2524234

CONSENT FORM

TITLE OF THE STUDY: Imaging of Brain Arteriovenous malformations – comparing Silence Magnetic resonance angiography with Three-dimensional Time-of flight magnetic resonance angiography and Digital subtraction angiography.

Study number:

Participant's name: _____

Date of Birth / Age (in years): _____

Son/daughter of _____

(Please tick boxes) •

I declare that I have read the above information provided to me regarding the study – "Imaging of Brain Arteriovenous malformations – comparing Silence Magnetic resonance angiography with Three-dimensional Time-of flight magnetic resonance angiography and Digital subtraction angiography"-- and have clarified any doubts that I had. [ ]

I understand that my participation in this study is entirely voluntary and that I am free to withdraw the permission to continue my participation at any time without affecting my usual treatment or my legal rights. [ ]

I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access. [ ]

I understand that my identity will not be revealed in any information released to third parties or published [ ]

I voluntarily agree to take part in this study [ ]

I have received a copy of this signed consent form [ ]

Name: _____

Signature:_____

Date:_____

Name of witness:_____

Relation to participant:_____

Date: _____

(Person Obtaining Consent) I, _____ attest that the requirements for informed consent for the medical research project described in this form have been satisfied. I have discussed the research project with the participant and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

_____ _____

Name and Signature of Person Obtaining Consent

INFORMATION SHEET – FOR GUARDIANS OF MINORS

TITLE OF THE STUDY: Imaging of Brain Arteriovenous malformations – comparing Silence Magnetic resonance angiography with Three-dimensional Time-of flight magnetic resonance angiography and Digital subtraction angiography .

Study number:

Participant's name: _____

Date of Birth / Age (in years): _____

Son/daughter of _____

You have been informed that there is an abnormal communication between the arteries and veins (Arterio venous malformation), within your child's brain. Your child will have undergone or will be undergoing a digital subtraction angiography (DSA) test and Magnetic Resonance Imaging (MRI) as a part of clinical evaluation of the disease to plan treatment or for follow up of disease.

You are requested to allow your child to participate in a study to evaluate role of a new Magnetic Resonance Imaging sequence called Silence MR angiogram in arteriovenous malformations. While participating in this study, only the imaging data from the MRI and DSA investigations your child has undergone for treatment purpose will be used. Participating in this study will in no way influence the treatment decisions. The benefit that your child may incur from this study is, if this new MRI technique is found useful, during subsequent reviews/ follow up further imaging can be limited to just an MRI rather than an invasive test like DSA.

What are DSA and MRI and do they have any harmful effects?

DSA (Digital subtraction angiography) test is an advanced imaging technique where the blood flow to brain is evaluated by injecting a dye into the arteries of the brain through a small tube inserted through an artery in the thigh. X-Rays obtained during the procedure will clearly show the any abnormal connections between arteries and veins. The patient will not experience much pain as an injection will be given on thigh prior to the procedure to make it numb. No pain will be felt during the rest of the procedure. In rare cases some people may have allergic reaction to the dye. There is also a very small risk of injury to the blood vessel and slight chance of bleeding at site of puncture. This test is vital in diagnosis of your condition and is also the means of treatment if subsequently planned.

MRI is an advanced imaging technique which uses certain waves and magnetic fields to image body part. It does not involve any ionizing radiation. There will be no administration of any type of drug or medicine during the study. Some patients may develop claustrophobia (Fear of closed spaces etc.) due to closed space and noise. This investigation will not be done in patients with metallic implants or pacemakers.
MRI and DSA will be done as a part of clinical evaluation of your child's disease. This study will require image data from the tests that your child will undergo as part of disease evaluation.

If you take part what will your child have to do?

This study will only analyse the results of the routinely ordered imaging investigations your child will undergo during treatment and follow up of your illness. Your child will not be required to do anything apart from the regular follow up that will be advised to you.

Can your child withdraw from this study after it starts?

Your child's participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your child's usual treatment at this hospital in any way.

What will happen if your child develops any study related injury?

This study only analyses the results of investigation and treatment details and thus we do not expect any injury to happen to you but if you do develop any side effects or problems due to the study, these will be treated at this institute by the experienced team of medical professionals. We are unable to provide any monetary compensation, however.

Will you have to pay for the study?

The study will only analyse the results of the investigations and treatment which your child will undergo in natural process of your treatment for AVM at this institute and no extra cost will be borne by you for this particular study.

What happens after the study is over?

Your child may or may not benefit from this study. If the study is found useful then during subsequent reviews evaluation can be limited to just a non invasive MRI rather than more invasive DSA.

Will your child's personal details be kept confidential?

The results of this study may be published in a medical journal but your child will not be identified by name in any publication or presentation of results. However, the child's medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further questions, please ask

Dr. Jospaul Lukas (tel: 9400733593) or email: jospaul_lukas@sctimst.ac.in

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I understand that the study staff and institutional ethics committee members will not need my permission to look at my child's health records even if I withdraw from the trial. I agree to this access. [ ]

I understand that my child's identity will not be revealed in any information released to third parties or published [ ]

I voluntarily agree to take part in this study [ ]

I have received a copy of this signed consent form [ ]

Name: _____

Signature:_____

Date:_____

Name of witness:_____

Relation to participant:_____

Date: _____

(Person Obtaining Consent) I, _____ attest that the requirements for informed consent for the medical research project described in this form have been satisfied. I have discussed the research project with the participant and guardian and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

_____ _____

Name and Signature of Person Obtaining Consent

Study Title: Imaging of Brain Arteriovenous malformations – comparing Silence MR angiogram with 3D TOF angiogram and DSA.

Brain AVM reporting Format for 3DTOF MRA ; SILENCE MRA and DSA.

a) Image identification number: ……..
b) Presentation : incidental / hemorrhage / seizure / headache / others
   - Date of presenting event:…….....
   - Any recent clinical events ; if so date and nature of event:…….
c) Prior treatment if any with date and embolic material used: …….
d) Study / Sequence evaluated : MRI – (3DTOF MRA ; SILENCE MRA) / DSA……...
e) Investigator analyzing study:…… Date of Image analysis:……
f) Time required for interpretation : ……..
g) Reformations required: Axial / Sagittal / coronal
h) Quality of image: four-point scale score*: ……

- **Imaging Findings:**

1. Lesion side : Right / Left
2. BAVM size (mm).....(CC x TR AP)
3. BAVM location : ……
4. BAVM eloquence : (Yes/No)……
5. BAVM - presence of gliosis (Yes / No) if yes location : perinidal / nidal
6. BAVM border with adjacent brain (on DSA) : Compact (sharp) / Diffuse……
7. BAVM hemorrhage
   a. Evidence of hemorrhage (yes/no)
   b. Age of hemorrhage (acute / subacute / chronic)
   c. Hemorrhage location : Ventricular / Parenchymal / Subarachnoid
   d. Hemorrhage size (mm) …….(CC x TR x AP)
8. Venous drainage
   a. Superficial vs deep venous drainage [#]: Both / Superficial only / Deep only
   b. Number of draining veins leaving nidus (count)……..
   c. Number of veins reaching sinus (count)……..
   d. Venous stenosis [$] (yes / no; degree of stenosis)……..
   e. Venous ectasia (dilatation) (yes/no)
   f. Venous reflux (yes/no)
   g. Sinus thrombosis/occlusion (number; percentage, where 100% occlusion)
9. Arterial supply : Feeding arteries : (number…….; Name the arteries:……)
10. Arterial aneurysms:
    i. Location : Nidal ; Proximal / Distal /
    ii. Type : Flow-related / Not flow-related
    iii. Number of arterial aneurysms ……
    iv. Angiomorphological alterations in the aneurysm……..
    v. Evidence of bleed from the aneurysm…….
11. Pial-to-pial collateralization : within Same territory / Between territories / None visible
12. Spetzler martin Grade : ……

*Categorization of various parameters are followed based on the definitions provided in Appendix X

(PTO)

Appendix X

The details within the box - image identification number and the details of presentation and prior treatment details if any including embolization; surgery or radiotherapy will be prefilled.

h. The quality of the image is evaluated considering overall quality of distal vessel identification, visualization of the nidus vascular signal intensity and motion artifact. This is graded on a *Four point scale score : 4 excellent quality; 3, adequate quality for diagnosis; 2, less than adequate quality for diagnosis; 1, nondiagnostic.

3. The location of the BAVM is described as : Cortical ; Subcortical / Frontal / Temporal / Parietal / Occipital / Basal ganglia /Internal capsule / Ventricular / Intraventricular / Corpus callosum / Cerebellar hemisphere / Vermian (paramedian) / Deep cerebellar nuclei / Brain stem

4. AVM location with respect to eloquence of the involved area is described. The eloquent area include : Internal capsule / Sensorimotor cortex / Cerebellar peduncle / Visual cortex / Deep cerebellar nuclei / Language cortex / Brain stem /Thalamus/hypothalamus/basal ganglia / Other eloquent areas / NOT eloquent

8. [#]Venous drainage into the deep / superficial venous system. Deep venous system is constituted by the ventricular group of veins and cisternal group of veins formed by the Basal vein of Rosenthal and its tributaries. [$]The degree of venous stenosis is described as Mild moderate an severe .

9. The feeder to the AVM is named from : Anterior choroidal a./Posterior choroidal a./Anterior cerebral a. cortical branches /Anterior cerebral a. penetrators /Middle cerebral a. cortical branches /Middle cerebral a. penetrators /Posterior cerebral a. cortical branches/Posterior cerebral a. penetrators /Superior cerebellar a./Anterior inferior cerebellar a./Posterior inferior cerebellar a./Basilar a. penetrators /Vertebral a. penetrators /Vertebral a. branches/ Internal carotid a. penetrators /Other internal carotid a. branches / External carotid a. branches/ Other a.

10. Aneurysm: Angiomorphological alterations in the aneurysm such as tit, lobulations , daughter aneurysms are to be noted.

12. For Spetzler martin grade is assessed considering the imaging findings numbered 2, 4 and 8a. [Size of nidus : Small (<3cm) = 1; medium (3-6cm) = 2 ; large (>6cm) = 3; Eloquence of brain area : Non eloquent = 0; eloquent = 1 ; Venous Drainage : Superficial only = 0; deep = 1.] The scores of these three criteria are added to get a grade between 1 to 5.

ABBREVIATIONS

AVM- Arteriovenous Malformation

CT- Computed Tomography

CTA- Computed Tomography Angiography

MRI- Magnetic Resonance Imaging

MRA- Magnetic Resonance Angiography

DSA- Digital Subtraction Angiography

SWI- Susceptibility Weighed Imaging

ASL- Arterial Spin labelling

SCTIMST- Sree Chitra Tirunal Institute for Medical Sciences and Technology

ICH- Intra Cerebral Haemorrhage

TOF- Time Of Flight

PATIENT NUMBER	SILENCE	TOF	DSA	SILENCE	TOF	DSA	SILENCE	TOF	DSA	VOL	VOL	VOL	VOL	VOL	VOL	VOL
	Sz- AP	Sz- AP	Sz- AP	Sz-CC	Sz-CC	Sz-CC	Sz-TR	Sz-TR	Sz-TR	SILENCE VOL	TOF VOL	DSA VOL	Average S/D	Difference S/D	Average T/D	Difference T/D
1	38	38	45	40	31	42	31	39	37	23560	22971	34965	29262.5	-11405	28968	-11994
2	45	28	24	30	29	22	26	27	25	17550	10962	6600	12075	10950	8781	4362
3	70	46	47	47	40	33	29	29	48	47705	26680	37224	42464.5	10481	31952	-10544
4	40	32	34	29	21	28	47	39	27	27260	13104	12852	20056	14408	12978	252
5	38	53	35	27	31	39	32	32	26	16416	26288	17745	17080.5	-1329	22016.5	8543
6	40	37	24	22	23	44	22	20	26	9680	8510	13728	11704	-4048	11119	-5218
7	29	11	24	14	14	12	16	16	14	3248	1232	2016	2632	1232	1624	-784
8	44	36	30	32	51	33	51	54	30	35904	49572	14850	25377	21054	32211	34722
9	58	61	40	30	31	26	45	53	42	39150	50111.5	21840	30495	17310	35975.75	28271.5
10	7	11	10	9	15	7	5	7	7	157.5	577.5	245	201.25	-87.5	411.25	332.5
11	23	23	18	13	9	10	19	15	11	2840.5	1552.5	990	1915.25	1850.5	1271.25	562.5
12	67	58	47	60	39	49	52	61	46	104520	68991	52969	78744.5	51551	60980	16022
13	45	26	34	35	18	20	22	19	21	17325	4446	7140	12232.5	10185	5793	-2694
14	57	52	61	78	78	59	61	72	38	135603	146016	68381	101992	67222	107198.5	77635
15	8	10	12	5	5	7	6	15	10	120	375	420	270	-300	397.5	-45
16	47	40	26	22	20	24	30	30	22	15510	12000	6864	11187	8646	9432	5136
17	37	37	23	23	25	41	33	29	26	14041.5	13412.5	12259	13150.25	1782.5	12835.75	1153.5
18	42	40	41	30	30	23	28	33	23	17640	19800	10844.5	14242.25	6795.5	15322.25	8955.5
19	24	32	25	40	16	15	26	24	17	12480	6144	3187.5	7833.75	9292.5	4665.75	2956.5
20	15	20	20	22	25	23	28	36	32	4620	9000	7360	5990	-2740	8180	1640
21	70	64	56	53	51	62	64	60	40	118720	97920	69440	94080	49280	83680	28480
22	15	16	17	18	22	13	14	19	17	1890	3344	1878.5	1884.25	11.5	2611.25	1465.5
23	35	36	39	38	25	40	26	30	57	17290	13500	44460	30875	-27170	28980	-30960
24	36	42	30	35	39	43	48	31	40	30240	25389	25800	28020	4440	25594.5	-411
25	16	20	17	24	13	11	15	12	11	2880	1560	1028.5	1954.25	1851.5	1294.25	531.5
26	83	87	63	54	49	42	86	45	40	192726	95917.5	52920	122823	139806	74418.75	42997.5
27	17	11	9	5	4	4	9	7	8	382.5	154	144	263.25	238.5	149	10
28	47	31	28	31	40	40	39	34	27	28411.5	21080	15120	21765.75	13291.5	18100	5960
29	43	46	36	25	28	24	34	34	26	18275	21896	11232	14753.5	7043	16564	10664
30	28	13	26	22	25	19	33	29	29	10164	4712.5	7163	8663.5	3001	5937.75	-2450.5
31	12	20	20	13	12	10	10	11	18	780	1320	1800	1290	-1020	1560	-480
32	20	11	21	13	13	13	27	7.5	8	3510	536.25	1092	2301	2418	814.125	-555.75
33	45	33	33	44	29	33	27	24	25	26730	11484	13612.5	20171.25	13117.5	12548.25	-2128.5
34	27	23	24	25	24	21	21	19	17	7087.5	5244	4284	5685.75	2803.5	4764	960
35	15	18	20	10	6	6	13	11	5	975	594	300	637.5	675	447	294
36	28	28	41	28	24	28	38	27	21	14896	9072	12054	13475	2842	10563	-2982
37	28	16	20	26	16	23	16	14	10	5824	1792	2300	4062	3524	2046	-508
38	25	17	24	27	28	30	38	33	34	12825	7854	12240	12532.5	585	10047	-4386
39	42	46	35	24	16	16	38	25	29	19152	9200	8120	13636	11032	8660	1080
40	48	47	32	16	15	18	9	12	8	3456	4230	2304	2880	1152	3267	1926
41	52	55	46	43	20	28	30	19	31	33540	10450	19964	26752	13576	15207	-9514
42	76	56	85	58	33	52	36	43	55	79344	39732	121550	100447	-42206	80641	-81818
43	32	39	35	42	37	36	28	29	22	18816	20923.5	13860	16338	4956	17391.75	7063.5
44	29	28	24	20	33	22	32	27	33	9280	12474	8712	8996	568	10593	3762
45	27	40	36	23	36	23	31	28	28	9625.5	20160	11592	10608.75	-1966.5	15876	8568
46	32	35	28	30	18	28	24	29	24	11520	9135	9408	10464	2112	9271.5	-273
47	33	18	30	6	5	10	4	10	10	396	450	1500	948	-1104	975	-1050
48	66	70	50	35	40	55	43	37	35	49665	51800	48125	48895	1540	49962.5	3675
49	28	26	26	33	23	29	22	19	17	10164	5681	6409	8286.5	3755	6045	-728
50	23	23	23	24	23	19	19	19	17	5244	5025.5	3714.5	4479.25	1529.5	4370	1311

SILENCE	TOF	DSA	TOF	TOF	TOF	SILENCE	SILENCE	SILENCE	TOF	DSA	ECTASIA S/D	ECTASIA T/D	TOF	SILENCE	SILENCE	DSA	DSA	SM GR S/D	SM GR T/D	SILENCE	TOF	DSA	SILENCE	TOF	DSA	SILENCE	TOF	DSA
ARTERIAL NO	ARTERIAL NO	ART NO	CORRECT	MISSED	WRONG	CORRECT	MISSED	MISINTERPRE	ECTASIA	ECTASIA	1-MATC	1-MATC	SM GR	eloquence	SM GR	eloquence	SM GR	1-MATC	1-MATC	ART EFEDE	ART EFEDE	ART EFEDE	DC-VENOU	DC-VENOU	DC-VENOU	DC-NIDUS	DC-NIDUS	DC-NIDUS
6	5	7	5	2	0	6	1	0	Y	Y	1	1	2	N	2	N	3	0	0	4	4	4	4	3	4	4	3	4
2	2	3	2	1	0	2	1	0	N	Y	1	0	1	N	2	Y	2	0	1	4	4	4	3	4	4	3	3	4
10	6	8	6	2	0	8	0	2	N	N	1	1	4	Y	5	Y	4	1	0	4	4	4	4	2	4	4	3	4
3	4	3	3	0	1	3	1	0	Y	Y	1	1	4	Y	4	Y	4	1	1	4	4	4	4	3	4	4	2	4
6	4	6	4	2	0	6	0	0	Y	Y	1	1	3	N	3	N	3	1	1	4	3	4	4	3	4	4	3	4
1	3	1	3	0	2	1	0	0	N	N	0	1	3	N	3	N	3	1	1	4	3	4	4	2	4	4	3	4
2	**1**	1	1	0	0	1	0	1	Y	N	1	0	3	Y	3	Y	3	1	1	4	4	4	4	4	4	4	4	4
5	2	1	1	0	1	1	0	4	Y	Y	1	1	4	Y	4	Y	4	1	1	4	3	4	4	3	3	4	3	4
3	5	7	5	2	0	3	4	0	Y	Y	1	1	4	N	3	N	3	0	1	4	4	4	2	3	4	4	3	4
1	1	1	1	0	0	1	0	0	N	N	0	1	1	N	1	N	1	1	1	4	3	4	1	3	4	4	2	4
2	1	1	1	0	0	1	1	0	N	N	1	1	1	Y	2	N	1	1	0	4	4	4	4	2	4	4	4	4
7	7	5	5	0	2	5	0	2	N	Y	1	0	4	Y	5	Y	4	1	0	4	4	4	4	2	4	4	2	4
4	2	3	2	1	0	3	1	0	N	Y	1	0	3	N	2	Y	3	1	0	4	4	4	4	4	4	4	4	4
5	5	6	5	1	0	5	1	0	Y	Y	1	1	4	Y	5	N	4	1	0	4	4	3	4	2	4	4	2	4
1	2	1	1	1	0	1	0	0	NA	N	1	0	NA	N	1	N	2	0	0	3	3	4	1	1	4	2	2	4
4	5	4	4	0	1	4	0	0	N	Y	1	0	3	N	3	N	2	0	0	4	4	4	4	2	4	4	3	4
2	3	3	3	0	0	2	1	0	Y	Y	1	1	2		2	N	3	0	0	4	4	4	4	3	4	4	3	4
4	3	3	3	0	0	3	0	1	N	Y	1	0	4	Y	4	Y	4	1	1	4	4	4	4	3	4	4	3	4
2	2	2	2	0	0	2	0	0	N	N	1	1	3	N	2	Y	2	0	1	4	4	4	1	4	4	3	4	4
3	3	2	2	0	1	2	0	1	N	Y	0	0	3	Y	2	N	2	0	1	4	4	4	4	4	4	4	4	4
8	8	11	8	3	0	8	3	0	Y	Y	1	1	5	Y	5	Y	5	1	1	4	4	4	4	4	4	4	3	4
2	3	2	2	0	1	2	0	0	NA	N	1	0	NA	N	2	N	3	0	0	4	4	4	4	1	4	4	4	4
2	5	6	5	1	0	2	4	0	N	Y	0	0	3	N	2	Y	3	1	0	4	4	4	4	3	4	4	4	4
4	2	6	2	4	0	4	2	0	N	Y	0	0	3	Y	3	Y	4	0	0	4	4	4	4	2	4	4	3	4
1	2	1	1	1	0	1	0	0	N	N	1	1	2	N	1	N	1	0	1	4	4	4	4	4	4	4	3	4
5	7	5	5	0	2	5	0	0	N	Y	0	0	4	Y	4	Y	3	0	0	4	4	4	2	3	3	4	2	4
1	1	1	1	0	0	1	0	0	NA	N	1	0	NA	N	2	N	2	0	1	3	3	4	3	0	4	3	3	4
3	4	6	4	2	0	3	3	0	Y	Y	1	1	4	N	3	Y	4	1	0	4	4	4	4	3	4	4	3	4
4	5	6	5	1	0	4	2	0	N	Y	1	0	2	N	2	N	2	1	1	4	4	4	4	3	4	4	3	4
3	3	2	2	0	1	2	0	1	N	N	1	1	1	N	2	Y	2	0	1	4	4	4	4	3	4	4	3	4
1	1	1	1	0	0	1	0	0	N	N	0	1	1	N	1	N	1	1	1	4	4	4	4	1	4	4	4	4
4	1	2	1	1	0	2	0	2	N	Y	0	0	2	N	1	N	2	1	0	3	4	4	3	2	4	3	2	4
5	5	6	5	1	0	5	1	0	Y	Y	1	1	3	Y	4	Y	4	0	1	4	4	4	4	4	4	4	4	4
2	1	1	1	0	0	1	0	1	N	Y	1	0	1	N	2	N	1	1	0	4	4	4	4	4	4	4	4	4
1	2	1	1	0	1	1	0	0	N	N	1	1	2	N	2	N	2	1	1	4	4	4	4	4	4	4	4	4
2	3	3	3	0	0	2	1	0	Y	Y	1	1	3	N	3	Y	3	1	1	4	4	4	4	3	4	4	2	4
2	2	4	2	2	0	2	2	0	N	N	1	1	2	N	2	N	2	1	1	4	4	4	4	4	4	4	4	4
2	2	3	2	1	0	2	1	0	N	Y	1	0	3	N	2	N	3	1	0	4	4	4	4	4	4	4	3	4
5	3	2	2	0	1	2	0	3	Y	Y	1	1	3	N	3	N	3	1	1	4	4	4	4	3	4	4	4	4
3	3	3	3	0	0	3	0	0	N	N	1	0	3	N	3	N	3	1	1	3	4	4	4	2	4	4	3	4
4	5	6	5	1	0	4	1	0	N	Y	1	0	3	N	3	Y	4	0	0	4	4	4	4	3	4	4	3	4
9	3	6	3	3	0	6	0	3	N	Y	0	0	3	Y	5	Y	5	0	1	4	4	4	4	3	4	4	3	4
5	4	4	4	0	0	4	0	1	Y	Y	1	1	2	Y	3	N	3	0	1	4	4	4	4	3	4	4	3	4
3	3	2	2	0	1	2	0	1	N	Y	0	0	3	Y	4	Y	4	0	1	4	4	4	4	3	4	4	3	4
4	3	3	3	0	0	3	0	1	N	N	0	1	3	N	3	N	2	0	0	4	4	4	4	3	4	4	3	4
1	1	5	1	4	0	1	4	0	NA	N	1	0	3	N	3	N	2	0	0	4	3	4	4	1	4	4	3	4
2	2	3	2	1	0	2	1	0	NA	N	1	0	1	N	3	N	2	0	0	4	3	4	4	1	4	4	2	4
4	4	4	4	0	0	4	0	0	Y	Y	1	1	3	Y	4	N	3	1	0	4	4	4	4	2	4	4	3	4
2	2	2	2	0	0	2	0	0	N	Y	0	0	2	N	1	Y	2	1	0	4	4	4	4	4	4	4	3	4
2	2	2	2	0	0	2	0	0	N	N	1	1	2	N	1	N	2	1	0	4	4	4	4	4	4	4	4	4

ABBREVIATIONS IN MASTERCHART

Y – PRESENT

N – ABSENT

SZ - SIZE

CC- CRANIOCAUDAL

AP – ANTEROPOSTERIOR

TR- TRANSVERSE

VOL – VOLUME

DC- DIAGNOSTIC CONFIDENCE SCORE

S/D – COMPARISION OF SILENCE VS DSA

T/D – COMPARISION OF TOF VS DSA

NA – NOT APPLICABLE

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STUDY DESIGN The recruitment of subjects for the prospective study was be done by the principal investigator from consecutive patients with Brain arteriovenous malformations presenting to SCTIMST neurosurgery, neurology or radiology clinics from the month of October 2016 to June 2018. Patients diagnosed of Brain arteriovenous malformations and planned for initial Digital subtraction angiography or who have undergone embolization or stereotactic radiosurgery and admitted for a check Digital subtraction angiography and Magnetic resonance angiogram were included in the study.

Consent for inclusion in the study was obtained from appropriate persons or guardians. No inclusion of person incompetent to give informed consent, normal/healthy volunteer, Prisoner, student/staff of the institute was done. FLOW CHART OF STUDY DESIGN STUDY PROTOCOLS AND PARAMETERS - MRI AND DSA Consecutive patients with Brain arteriovenous malformations considered for inclusion underwent Digital subtraction angiography and Magnetic resonance imaging as per the below stated protocol.

The Digital subtraction angiography was done in Interventional Radiology Suite at SCTIMST on General Electric Innova biplane 1313 and Magnetic resonance was done on General Electric Discovery 750E 3.0Tesla machine as per the routine protocol. The MRI protocol for the Study was inclusive of the following sequences, apart from the routine MR imaging workup followed in the institution for brain AVM cases.

1. 3DTOF MR angiogram (TR/TE, 19/2.9 msec; flip angle, 15°; field of view, 200×200 mm; matrix, 416×192; section thickness, 1.2 mm; NEX, 1; band width, ±41.7 kHz; acquisition time, 3 min 31 s.) 2. Silence MR angiogram (TR/TE, 1116.4/0.016 msec; flip angle, 5°; field of view, 180×180 mm; matrix, 150×150; section thickness, 1.2 mm; number of excitations (NEX), 1.5; band width, ±20 kHz; acquisition time, 7 min 40 s.)

The MRI and Digital subtraction angiography images were then obtained from PACS, anonymized and stored separately in numbered folders and analysed independently. Statistical analysis of the data was performed by the principal investigator using Graph pad Prism 6 statistical analysis software. Wilcoxon signed rank test (41)for assessment of the difference in assigned diagnostic scores and Bland and Altman analysis(42,43) to assess agreement between TOF s DSA and SILENCE MRA vs DSA in elucidation of the AVM components was done.

The sensitivity and specificity of TOF and SILENCE MRA was also assessed for quantitative comparison between the two modalities. RESULTS RESULTS DEMOGRAPHICS Among the 50 consecutive patients included in this study of Cerebral arteriovenous malformations, from October 2016 till June 2018, the sex distribution was balanced with 22 female and 28 male patients.

Figure No:1 - male to female distribution in this study All the 50 patients were consecutively included without bias towards, age or sex. CLINICAL PROFILE AGE RANGE FREQUENCY PERCENTAGE 0 to 9 1.00 2% 10 to 19 12.00 24% 20 to 29 15.00 24% 30 to 39 12.00 24% 40 to 49 3.00 6% 50 to 59 6.00 12% 60 to 69 1.00 2% TOTAL 50.00 100% Table No: 1 -AVM location wise distribution. The mean age of the study group was 29.9yr and ranged between 8 to 63 years.

The group was a predominantly young cohort with 74% being < 40 years. 29 cases forming 58% had evidence of prior bleed and 21 cases 42% were unbled AVM. ANGIOGRAPHIC FEATURES DSA was done in the 50 patients confirming AVM in all the cases. The 50 cases were initially assed for various morphological features on DSA including, arterial feeders, presence of arterial hypertrophy, presence of AVM nidus related aneurysms, venous drainage pattern including superficial and deep, venous stenosis or ectasia if any.

AVM LOCATION and LATERALISATION AVM LOCATION FREQUENCY PERCENTAGE FRONTAL 9 18.00% PARIETAL 7 14.00% TEMPORAL 7 14.00% PARIETOOCCIPITAL 6 12.00% CEREBELLAR 5 10.00% OCCIPITAL 3 6.00% FRONTOPARIETAL 3 6.00% PARIETOTEMPORAL 2 4.00% OCCIPITOTEMPORAL 2 4.00% CORPUS CALLOSAL 2 4.00% CHOROIDAL 2 4.00% THALAMIC 1 2.00% PONTINE 1 2.00% TOTAL 50 100.00% Table No: 2.A -AVM location wise distribution.

Frontal AVM accounting for 18% of the AVM cases made up the commonest location of AVM in the present series, followed by parietal, temporal, parietooccipital and cerebellar regions constituting the majority of the arteriovenous malformation locations. LESION SIDE FREQUENCY PERCENTAGE RIGHT 18 36% LEFT 29 58% MIDLINE 3 6% TOTAL 50 100% Table No: 2.B -AVM nidus lateralisation.

Of the 50 patents included in the study 58% ie. 29 cases had left lateralisation of their

arteriovenous malformations, 36% cases were lateralised to right side and 3 cases were midline in location. AVM GRADING SM GRADE FREQUENCY PERCENTAGE GRADE 1 5 10% GRADE 2 16 32% GRADE 3 16 32% GRADE 4 11 22% GRADE 5 2 4% GRADE 6 0 0% TOTAL 50 100% Table No: 3-SM grade wide distribution. Of the 50 cases, 74% has Spetzler Martin Grades of 3 or less, and only 13 cases amounting to 26% had SM grades of 4 or more.

None of the patients were assigned a SM grade of 6. Figure No: 2-SM grade wise distribution of cases. AVM NIDAL TYPE The nidal characterization on DSA revealed, 28 of the 50 cases, 56% to have a compact nidal type, 16 cases (32%) had a diffuse morphology to the nidus and sparse nidus morphology was seen in 6 of the 50 patients (12%).

AVN NIDAL TYPE FREQUENCY PERCENTAGE COMPACT 28 56% DIFFUSE 16 32% SPARSE 6 12% TOTAL 50 100% Table No: 4-AVM nidus type. Figure No: 3-Distribution of AVM nidus type. INTERMODALITY COMPARISION BETWEEN SILENCE, TOF MRA and DSA The angiomorphology of the 50 AVM cases were assessed and compared across SILENCE and TOF MRA and against DSA which was the gold standard under consideration in this study.

AVM SIZE The comparison of AVM nidus size across the three measured dimensions revealed, that some degree of overestimation of the nidal size was seen both on SILENCE and TOF MRA in anteroposterior and transverse dimensions. In the cranio-caudal direction SILENCE MRA revealed, overestimation of the nidal size, TOF recorded underestimation of the measured dimensions as to DSA.

Figure No: 5-AVM size in anteroposterior dimension on the three modalities. Figure No: 6-AVM size in craniocaudal dimension on the three modalities. Figure No: 7-AVM size in transverse dimension on the three modalities. On computing the AVM volume across modalities, and analysis by Bland and Altman method, the AVM volumes on SILENCE and TOF MRA differed more from the DSA recorded volumes for AVM with larger sizes. Volumes assessed by SILENCE MRA was more different as to the analysis on TOF MRA.

However, for AVM of smaller sizes the AVM sizes matched more closely with the measures on DSA. Figure No: 7-Frequency distribution of AVM volume across the three imaging modalities. Figure No: 8- Bland Altman analysis plot of the AVM volume comparing between Silence MRA vs DSA and TOF MRA vs DSA ARTERIAL FEEDER CHARECTERISATION AND DETECTION Both SILENCE and TOF correctly identified 80%, 143 of the 177 arteries which were feeding the AVM and confirmed on DSA.

The percentage of feeding arteries which were missed were similar on SILENCE and

TOF being 21% for SILENCE (38 feeders) and 20% (36 feeders) for TOF. The number of misinterpreted vessels were larger on TOF angiogram as compared to SILENCE, 13.5%(24) on TOF as to 8.4%(15) on SILENCE. Figure No: 9-Frequency distribution of arterial feeders to the AVM nidus on silence MRA, TOF MRA and DSA.

ARTERIAL HYPERTROPHY Presence of arterial hypertrophy was comparably detected both on SILENCE and TOF angiogram. Sensitivity and specificity of 87% and 81% and PPV and NPV of 78% and 94% for SILENCE as against sensitivity of 89% and Specificity of 30%, PPV of 79% and NPV of 83% for TOF MRA.

The substantial decrease in specificity for arterial hypertrophy was attributed to the increased misinterpretation of vessel hypertrophy on TOF in comparison with DSA. ARTERIAL HYPERTROPHY SILENCE DSA TOTAL Y N Y 34 2 36 N 5 9 14 TOTAL 39 11 50 Table No: 5-ARTERIAL HYPERTROPHY ON SILENCE MRA. DETECTION OF ARTERIAL HYPERTROPHY ON TOF VS DSA ARTERIAL HYPERTROPHY TOF DSA TOTAL Y N Y 35 7 36 N 4 3 14 TOTAL 39 11 50 Table No: 6-ARTERIAL HYPERTROPHY ON TOF MRA.

DETECTION OF AVM ASSOCIATED ANEURYSM Evaluation for detection of intranidal and perinidal aneurysm revealed almost comparable but marginally better sensitivity for SILENCE MRA to TOF MRA which correctly identified aneurysm in 11/50 patients as compared to 10/50 patients in TOF MRA. The specificity was higher for TOF angiogram in comparison with SILENCE angiogram which was attributed to the increase in false positive identification of aneurysms on SILENCE. Obtained values of Sensitivity, specificity, PPV and NPV for SILENCE and TOF are 61%,78%, 61%, 78% and 55%, 90%, 76%, 78%.

INTRANIDAL ANEURYSM SILENCE DSA TOTAL Y N Y 11 7 18 N 7 25 32 TOTAL 18 32 50 Table No: 7-INTRANIDAL ANEURYSM DETECTION ON SILENCE MRA. INTRANIDAL ANEURYSM TOF DSA TOTAL Y N Y 10 3 13 N 8 29 37 TOTAL 18 32 50 Table No: 8-INTRANIDAL ANEURYSM DETECTION ON TOF MRA. VENOUS IDENTIFICATION Totally 155 draining venous channels were identified on DSA in the 50 cases of AVM assessed in this study.

Of these 66% were correctly identified on Silence MRA as to 53% identified on TOF. The misinterpretation rate was also substantially higher on TOF being 47% as to 34% on SILENCE MRA. VENOUS IDENTIFICATION SILENCE MRA TOF MRA CORRECT 103 (66.4%) 83 (53.5%) MISSED 53(34%) 73 (47%) MISINTERPRETED 5 (3.2%) 1 (0.6%) Table No: 9-COMPARISION OF VENOUS VISUALISATION ON SILENCE AND TOF MRA.

Figure No: 10-Frequency distribution of venous drainage from AVM nidus on Silence MRA, TOF MRA and DSA. Bland and Altman analysis for the number of draining veins identified on the two modalities revealed, a tendency for lower detection of the

draining veins on both the modalities comparing with DSA, however this was substantially more for TOF as compared to SILENCE angiogram.

Figure No: 11-Bland Altman analysis plot of AVM venous drainage detection comparing Silence MRA vs DSA Figure No: 12-Bland Altman analysis plot of AVM venous drainage detection comparing TOF MRA vs DSA Figure No: 12-Bland Altman analysis plot of AVM venous drainage detection comparing Silence MRA vs DSA and TOF MRA vs DSA SUPERFICIAL VENOUS DRAINAGE DETECTION Silence MRA had a Sensitivity of 87.8%, specificity of 77.7%, PPV of 94.7% and NPV of 54.3% for the detection of superficial venous drainage from cerebral AVM on comparing with the gold standard DSA.

TOF MRA had a Sensitivity of 67%, specificity of 90%, PPV of 96% and NPV of 40% for superficial venous drainage detection. This reveals that for initial screening of AVM and detection of superficial venous drainage SILENCE MRA would have an upper hand to TOF MRA. SUPERFICIAL VENOUS DELINEATION SILENCE DSA TOTAL Y N Y 36 2 38 N 5 7 12 TOTAL 41 9 50 Table No: 10-SUPERFICIAL VENOUS DRINAGE FROM AVM ON SILENCE.

SUPERFICIAL VENOUS DELINEATION TOF DSA TOTAL Y N Y 27 1 28 N 13 9 22 TOTAL 40 10 50 Table No: 11-SUPERFICIAL VENOUS DRINAGE FROM AVM ON TOF. DEEP VENOUS DRAINAGE DETECTION Silence MRA with a sensitivity of 77%, specificity of 100%, PPV of 100% and NPV of 63% for the detection of deep venous drainage substantially outperformed TOF MRA which reported a sensitivity of 65%, specificity of 86%, PPV of 92% and NPV of 52% for deep venous drainage detection.

DEEP VENOUS DELINEATION SILENCE DSA TOTAL Y N Y 28 0 28 N 8 14 22 TOTAL 36 14 50 Table No: 12-DEEP VENOUS DRINAGE FROM AVM ON SILENCE. DEEP VENOUS DELINEATION TOF DSA TOTAL Y N Y 23 2 25 N 12 13 25 TOTAL 35 15 50 Table No: 13-DEEP VENOUS DRINAGE FROM AVM ON TOF. AVM ANGIOMORPHOLOGICAL PARAMETER MODALITY SENSITIVITY SPECIFICITY PPV NPV ACCURACY ARTERIAL HYPERTROPHY SILENCE 87.2 81.8 94.4 64.2 86 TOF 89.7 30 83.3 42.8

77 ANEURYSM DETECTION SILENCE 61.1 78.1 61.1 78.1 72 TOF 55.5 90.6 76.9 78.3 78 SUPERFICAIL VENOUS IDENTIFICATION SILENCE 87.8 77.7 94.7 58.3 86 TOF 67.5 90 96.4 40.9 72 DEEP VENOUS IDENTIFICATION SILENCE 77 100 100 63.4 84 TOF 65.7 86.6 92 52 72 Table No: 14-comparison of Sensitivity, specificity, PPV, NPV and Accuracy for various AVM characteristics on Silence and TOF vs DSA.

EVALUATION OF DIAGNOSTIC CONFIDENCE SCORES AROSS MODALITIES The DC scores was assessed for the different AVM characteristic including Feeding arteries, Nidus and Draining veins. The diagnostic confidence was grades as per a 4 point Likert scale which was defined as, Grade 1- non diagnostic images, 2 - faint

visualisation and difficulty in diagnosis. 3 - moderate visualisation with some blurring due to artefacts but diagnostic, 4 - good quality images with definite diagnosis possible.

The difference in DC scores between Silence vs DSA and TOF MRA vs DSA was computed. Assuming the null hypothesis to be true with no statistically significant imaging quality difference between the modalities, the difference expected would be zero. The non parameteric paired t test, Wilcoxon signed rank test, was used to determine if a statistically significant difference in image quality was present between the two modalities assessed. Statistical significance was assumed with a P value of <0.05.

MEAN OF DC SCORES MODALITY ARTERIAL VISUALISATION NIDAL VENOUS VISUALISATION SILENCE MRA 3.92 3.68 3.88 TOF MRA 3.84 2.78 3.1 DSA 3.98 3.96 4 Wilcoxon signed rank test, p value comparing difference in DC between DSA with Silence MRA and DSA with TOF MRA 0.0625 <0.0001 <0.0001 Mean of difference in DC between DSA and Silence MRA 0.06 0.28 0.12 Mean of difference in DC between DSA and TOF MRA 0.14 1.18 0.9

Table No: 15-comparison of diagnostic confidence scores across modalities for various AVM characteristics. The mean of the Diagnostic confidence scores for feeding arterial detection was 3.92 for silence, 3.84 for TOF MRA and 3.98 for DSA. The DC score for nidus identification was 3.68 for Silence MRA, 2.78 for TOF MRA and 3.96 for DSA. The same was 3.88 for Silence MRA, 3.1 for TOF MRA and 4 for DSA.

Wilcoxon signed rank test was assessed for difference in the diagnostic confidence in between Silence MRA from DSA and TOF MRA from DSA each of the AVM components. The P value for arterial detection DC difference was 0.0625 and not statistically significant. Both the P values for nidal differentiation and venous visualisation DC difference was <0.0001 which was statistically significant.

This indicated that while arterial identification was similar on Silence and TOF MRA, Silence was better for nidal differentiation and venous visualisation. ILLUSTRATIVE CASES ILLUSTRATIVE CASES CASE 1 Case 1. Figure I: 53 year male patient, case of left frontal insular region AVM. (A,B- TOF MRA MIP images; D,C-SILENCE MRA MIP images; E - DSA). The arterial feeders are well depicted on both the TOF and MRA MIP images.

But the nidal visualisation is better on SILENCE MRA. The draining vein is also well visualised on the SILENCE MRA as compared to TOF. DSA due to its inherent temporal resolution is able to segregate the AVM components in the best possible manner. CASE 1 Case 1. Figure II: 53 year male patient case of left frontal insular region AVM. (F,G- TOF MRA axial images; H,I-SILENCE MRA axial images; J,K - 3D CT).

Corresponding axial locations are presented on the 3 modalities (F,G,H - lower insular level through the inferior to mid part of the AVM nidus and G,I,K - through the superior aspect of the nidus where the major draining veins is located). The arterial feeders are similarly depicted on both the TOF and MRA images almost in a manner similar to the 3D CT images.

But the nidal visualization as in the MIP images is also better on SILENCE MRA though slightly inferior to the 3D CT images. The superficial draining vein depiction on SILENCE MRA almost comparable to that on the 3D CT images but is much lower in signal on TOF. But the vein margins are well depicted on TOF by the improved spatial resolution possible with TOF MRA. CASE 2 Case 2.Figure I,II.

34 year female patient, case of right temporo occipital region AVM. (A-SILENCE MRA axial images; B- TOF MRA axial images; C-SILENCE MRA MIP images; D- TOF MRA MIP images).Corresponding axial locations show excellent visualization of the large venous sacs associated of this AVM and relatively high signal within the fistulous component on SILENCE MRA. This could have utility in localisation of fistula within AVM from the static SILENCE images.

The deep venous drainage is also similarly better depicted on SILENCE MRA. The arterial feeders are similarly depicted on both the MRA. Figure 2.III DSA images of the same 34 year female patient with the temporo occipital AVM and predominant fistulous component. The AVM nidus per se appears much smaller as compared on the DSA images.

Corresponding TOF and SILENCE MRA have some degree of overestimation of the nidal size, more so on SILENCE MR angiogram. The deep venous visualisation on SILENCE is almost comparable to the DSA images. CASE 3 Case 3. Figure I: 50 year male patient case of cerebellar region AVM. (A,C -SILENCE MRA axial and sagittal images; B- TOF MRA axial images; D - DSA arterial feeder and venous phases of the AVM).

Patient previously diagnosed with cerebellar AVM incidentally, now presenting with left cerebellar hemispheric bleed which is faintly seen on TOF Images. However due to the increased background suppression by subtraction of labelled and control datasets for SILENCE MRA there is no evidence of the bleed. The sagittal SILENCE MRA image shows both the predominant deep venous drainage as well as the venous drainage via a paramedian occipital vein egressing into the SSS(C).

The VA injection images on DSA revealing the plexiform nature of this compact AVM and multitude of associated veins with reflux and venous egress from the deep system into the SSS. These are only fairly depicted on Silence and with almost no

visualisation on TOF. The evidence of the bleed on TOF in left cerebellar hemisphere and corresponding SWI axial image. CASE 4 Case 4.

Figure I,II: 28 year male patient case of bled right parietal region micro AVM. (A,B- TOF MRA axial and MIP images; C,D -SILENCE MRA axial and MIP images; D - DSA arterial feeder and venous drainage with SWI images inset). Both SILENCE and TOF MRA images depicts the arterial feeders and micro-AVM nidus to a similar extent.

But both techniques are lacking in depiction of its relatively less profuse venous out flow. This case illustrates the pit fall of non-contrast static MR angiographic images where the low velocity flow impairs vessel visualisation Case 4.Figure III. DSA images of this patient shows the sparse micro nidus and the superficial venous drainage form the nidus.

Evidence of prior Bleed is as depicted by blooming on SWI. CASE 5 Case 5. Figure I,II: 22 year male patient case of bled Left fronto pareital region compact nidus AVM. (A,B,C- Silence MRA Sagittal MIP, Sagittal and zoomed sagittal images;,D,E,F -TOF MRA Sagittal MIP, Sagittal and zoomed sagittal images) The intranidal aneurysm is seen both on SILENCE and TOF MRA but the relatively higher signal intensity in the SILENCE MRA images makes delineation of the AVM easier as compared to TOF.

Here the Aneurysm detection is relatively easier for the fact that it is almost near the superior edge of the nidus and is more or less free of nidal signal per se, which can impair the aneurysm detection in AVM MRA. Case 5.Figure III,: E,F,G- axial TOF MRA, SILENCE MRA and 3DCT reveal almost comparable depiction of the AVM angiomorphology. Case 5.

Figure IV: H- DSA of the same patient depicting the nidus and associated aneurysm. DISCUSSION DISCUSSION Cerebral arteriovenous malformations are vascular aberrations that require multiple imaging studies throughout the sequence of their treatment and follow up which might span over several months to years depending on the mode of treatment.

The modality of choice in the definite diagnosis, treatment planning, treatment and follow up of this cerebrovascular disease entity is digital subtraction angiogram. But the multitude issues that can possibly be associated with DSA, including invasiveness, radiation, and risk of morbidity and mortality from a stroke, makes the question of an alternative very relevant.

Despite the multitude of other option available such as contrast enhanced MRA techniques as well as non-contrast techniques, none have till date presented enough mettle to replace the superior spatial and temporal resolution accorded by DSA. But at least a modality that will reliability do away with the requirement of repeated DSA

studies or limit number of DSA studies in an AVM patient would add significant respite.

With the risk of brain GBCA deposition in patients who received prior IV GBCA for contrast enhanced MRI, recently coming into the limelight, the advantage of CE MR angiographic methods for this purpose have received a serious setback and non-contrast methods have gained a lead. Among the non-contrast methods one particular technique, the Silence non-contrast MRA technique holds promise.

This study of cerebral arteriovenous malformations compared, the novel Silence MRA technique against TOF MRA using DSA as the benchmark. From October 2016 after clearing the institutional ethics committee approval, till June 2018, 58 patients were recruited consecutively and underwent imaging by Silence and TOF MR angiogram in addition to their routine imaging work up for cerebral AVM.

Of these 8 patients were excluded due to the suboptimal imaging that was not interpretable or was incomplete. The 50 cases were finally available was evaluated independently for the AVM components on Silence MRA, TOF MRA and DSA with a minimum interval of 2 weeks between the three different modalities.

The various angiomorphological characteristics of AVM were compared across the three modalities and statistically analysed in this study. No prior such studies were available on literature search on evaluation of AVM with Silence MRA except for a case report on use of silence in AVM(21). This is the first study addressing this novel imaging entity. Most of the prior studies available on MRA in AVM have compared 3T TOF with 1.5T TOF MRA(12) or utility of various static and dynamic contrast enhanced or key hole imaging based MRA against TOF MRA in AVM(44,45).

Recently there has also been an increased interest in the utility of 4D FLOW based non contrast techniques in elucidation of the AVM architecture(19). Recent studies addressing utility of Silence MRA, in aneurysms treated by stent assisted coiling in the anterior circulation by Irie et al and basilar tip aneurysms treated by Y stenting by Takano et al (3,46) have revealed superiorly of Silence in assessing the remnant neck and instent flow.

The authors mainly attributed this to the ability of silence MRA in overcoming the susceptibility effects impairing image quality in TOF. This information can also considered relevant in AVM imaging which can have significant susceptibility effects from associated bleed or prior surgical or endovascular treatment.

DEMOGRAPHICS The demographic profile of this study was a substantial improvement over prior studies comparing AVM with inclusion of a consecutive study sample of 50 patients. Also, the sex distribution among the recruited cases was

well balanced with male to female ratio of 1.08. Regarding the location of AVM, there was relatively fair distribution of lesions throughout the cerebral circulation.

AVM VOLUME Both Silence and TOF MRA differed in measured volumes, in comparison to DSA. For AVM of smaller volumes, the volumes were relatively better matched to those measured on Silence and TOF MRA. With increasing size of AVM, the measured volumes showed significant difference from the actual DSA measured volumes both on Silence and TOF.

There was more overestimation on Silence as compared to TOF. This can be partly accounted for the better venous visualisation on Silence MRA as to that on TOF and possible inclusion of the juxta nidal venous part of the AVM in the study. TOF mildly fared better in this regard. In comparison a prior study by Heidenreichet al (18) comparing 1.5T TOF vs 3T TOF MRA in AVM revealed an underestimation of the AVM size with increasing actual AVM size.

In this study that assessed 3T TOF the authors noticed that the modality reported higher AVM volume compared to 1.5T and they attributed it to increased field distortion and susceptibility artefacts to be the contributing cause. FEEDING ARTERY EVALUATION The arterial feeder identification rate was similar for both Silence MRA and 3D TOF MRA with 80% of the arteries being correctly identified.

The percentage of missed vessels was similar on both modalities, but misinterpretation on arterial feeders was more on Silence. Prior studies have revealed, arterial feeder identification at a rate of 73% on 3T TOF in study by Heidenreichet al (18). In another study by Cuong et al(47) 3T TOF could identify only 63% of the arterial feeders.

FEEDING ARTERY HYPERTROPHY Detection of feeding artery hypertrophy was better on Silence with sensitivity and specificity of 87.2 and 81.8% compared to 3D TOF MRA which had a high sensitivity of 89.7% but low specificity of 30%. ANEURYSM DETECTION The sensitivity and specificity for intranidal and perinidal aneurysm detection was 61% and 78% for Silence MRA and 55.5% and 90% for TOF MRA.

This indicates the marginally increased ability of silence MRA to detect AVM associated aneurysm. On comparing the images form Silence and TOF this higher sensitivity of Silence was attributed to the increased signal intensity within aneurysms on Silence MRA compared to the adjacent nidus.

We attribute this to lower velocity vortex flow within aneurysm causing increased stasis of the tagged blood within the sac compared to the parent vessel(48). The lower specificity for silence can similarly attributable to the relatively higher nidal and juxta nidal venous signal which can lead to overestimation by misinterpretation of

venous pouches as aneurysms.

VENOUS DRAINAGE IDENTIFICATION Silence MRA was better in identification of both superficial and deep venous drainage with sensitivity of 87.8% and 67.5% for silence and TOF for superficial venous visualisation and 77% vs 65.7% for deep venous visualisation. The sensitivity was higher for superficial venous drainage on TOF MRA with 90% and 77.7% specificity for Silence MRA.

In deep venous detection silence MRA was 100% specific and TOF MRA reported a specificity of 86.6%. The higher sensitivity of silence MRA could again be attributable to the high venous signal intensity and greater venous visualisation. The lower venous detection on TOF especially for deep venous visualiastion was probably related to multislab acquisition of TOF.

This would result in some degree of signal loss in intervening regions between the acquisition slabs corresponding to level of the deep venous system in most of our cases. DIAGNOSTIC CONFIDENCE SCORES FOR AVM COMPONENTS The mean diagnostic confidence score for the 50 cases were lower on TOF than Silence MRA as compared to DSA.

But the Wilcoxon signed rank test revealed no significant difference between the diagnostic scoring for arterial detection for both silence and TOF MRA indicating both to have a similar robustness in arterial feeder identification in AVM. However, the difference between the scores for nidal delineation and venous recognition was statistically significant with reported difference in the mean score from DSA of only 0.28 on silence as to 1.18 for TOF in nidal differentiation and 0.12 for silence and 0.9 for TOF for venous visualisation.

LIMITATIONS Interrater variability was an entity not assessed in this study, which would have assess the reliability in assessment of angiomorphology in each of these modalities. This is being currently undertaken by the investigators and would be part of the publication of this study. The utility of the modalities in post treatment patients of AVM is also a requirement which was not fulfilled in this study.

Investigation along these lines would supplement the requirement in imaging follow up in cerebral AVM. This is also a needs to be further addressed in further studies. CONCLUSION CONCLUSION This study which compared the utility of the novel sequence, Silence MRA in angiomorphological elucidation of cerebral AVM in comparison to TOF and DSA revealed the following conclusions. Both Silence and TOF MRA tend to overestimate aneurysm nidus size, slightly more so with Silence as to TOF.

This can be attributed to the better venous visualisation on silence MRA. The arterial

feeder identification was similar on both the modalities, but with better identification of arterial hypertrophy on Silence as to TOF. Silence MRA has a higher sensitivity for detection of intranidal aneurysm compared to TOF MRA due to the higher intra aneurysmal signal.

But there is marginally lower specificity due to the possible erroneous detection of venous pouches as aneurysms due to the significantly higher venous signal on Silence MRA. For both deep and superficial venous detection Silence MRA outperformed TOF MRA, by virtue of the better venous visualisation on Silence. Comparing Diagnostic confidence scoring, both Silence and TOF MRA were similar for arterial feeder evaluation.

But Silence MRA scored over TOF MRA in nidal characterisation and venous drainage visualisation. But despite the better performance of Silence in characterisation of several AVM angiomorphological features, the diagnostic confidence in Silence was lower compared to DSA retaining the later as still the last say in AVM imaging.