

BMJ Open Addition of arterial spin-labelled MR perfusion to conventional brain MRI: clinical experience in a retrospective cohort study

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ABSTRACT

Objective The usage of arterial spin labelling (ASL) perfusion has exponentially increased due to improved and faster acquisition time and ease of postprocessing. We aimed to report potential additional findings obtained by adding ASL to routine unenhanced brain MRI for patients being scanned in a hospital setting for various neurological indications.

Design Retrospective.

Setting Large tertiary hospital.

Participants 676 patients.

Primary outcome Additional findings from ASL sequence compared with conventional MRI.

Results Our patient cohorts consisted of 676 patients with 257 with acute infarcts and 419 without an infarct. Additional findings from ASL were observed in 13.9% (94/676) of patients. In the non-infarct group, additional findings from ASL were observed in 7.4% (31/419) of patients, whereas in patients with an acute infarct, supplemental information was obtained in 24.5% (63/257) of patients.

Conclusion The addition of an ASL sequence to routine brain MRI in a hospital setting provides additional findings compared with conventional brain MRI in about 7.4% of patients with additional supplementary information in 24.5% of patients with acute infarct.

INTRODUCTION

Neuroimaging constitutes a significant portion of hospital-based imaging both for CT and MRI.^{1–3} Although most acute hospital-based neurological encounters can be assessed with CT, MRI offers an attractive alternative due to the lack of ionising radiation and superior soft tissue contrast that is extremely useful for a detailed evaluation of brain tissue. In fact, the Appropriateness Criteria of the American College of Radiology list MRI as the desired imaging modality for most neurological symptoms, including headache, focal neurological deficits, altered mental status, ataxia, seizure and vision loss.⁴ A conventional brain MRI consists of several weightings and is often constructed

Strengths and limitations of this study

- To our knowledge, this is the first study to assess additional findings from arterial spin labelling (ASL) MRI compared with conventional MRI for a variety of neurological pathology seen in routine clinical practice.
- The study consists of a relatively large patient cohort, which strengthens the validity of the study.
- There was only one observer in the study, which limits the assessment of reproducibility.
- This is a retrospective cohort study, which limits the determination of the effect of ASL images on clinical management.
- The 1.5 T is not a preferred magnetic field for ASL, which may suggest that additional findings may be underestimated in this study.

with at least five sequences including T1, T2, Fluid-attenuated inversion recovery (FLAIR), gradient-recalled-echo (GRE) and diffusion-weighted imaging (DWI).^{5 6}

Arterial spin labelling (ASL) is a contrast-free MR perfusion technique that uses magnetically labelled water as a freely diffusible tracer to measure cerebral blood flow (CBF).^{7–9} Twenty-five years after its introduction and with significant advances in sequence design, hardware technology and postprocessing techniques, ASL has become readily available for routine clinical practice in recent years.^{10 11} In particular, ASL has shown promising results in the assessment of acute neurological disorders such as stroke,^{12–16} transient ischaemic attack (TIA),^{17 18} seizure,^{19 20} migraine headaches,²¹ as well as various neuropsychiatric diseases such as major depressive disorder,^{22 23} Alzheimer's dementia^{24–26} and Parkinson's disease.^{27–30} In this study, we aimed to investigate additional findings from ASL imaging

compared with routine unenhanced brain MRI scan in a hospital setting.

MATERIALS AND METHODS

Study population

This is a single-centre retrospective study. Patients who presented to our inpatient and emergency department from January 2015 to September 2018 were included if they had concurrent ASL imaging obtained with a routine unenhanced brain MRI scan. A total of 5676 brain MRIs were performed in our hospital (inpatient and emergency department) of which 700 patients had MRI with concurrent ASL imaging that met our inclusion and exclusion criteria. Contrast-enhanced brain MRIs did not have ASL and therefore were not included in this study. Indications for these studies included a variety of neurological indications seen in routine clinical settings such as headaches, altered mental status, neurological deficits and seizures. Specific protocols, for example, epilepsy protocol, multiple-sclerosis protocol, internal auditory canal protocol and brain tumour protocol, did not have ASL imaging routinely included and were excluded from the study. Paediatric patients were excluded. Patients were excluded if the ASL images were severely limited by motion artefact or insufficient tagging. This yielded a total of 700 cases with concurrent ASL imaging. Of which, 24 were excluded due to various reasons: motion artefact and insufficient tagging (n=14), inability of the patient to complete the ASL sequence (n=6) and susceptibility artefacts (n=4). This resulted in the inclusion of a total of 676 patients in our study.

Image acquisition

Imaging protocol for brain MRI included the acquisition of sagittal T1, axial T2, axial GRE, axial FLAIR, axial DWI and axial ASL. Image acquisition was performed using two 1.5T clinical MRI units (GE Optima MR450w; GE Medical Systems, Milwaukee) with an eight-channel head coil for signal reception. Three-dimensional (3D) pseudocontinuous ASL with a fast spin-echo stack-of-spiral readout with eight interleaves was used with each spiral arm including 512 sampling points. The following parameters were applied: repetition time (TR)/echo time (TE): 4525/11 ms; field-of-view (FOV): 24×24 cm, matrix size: 64×64mm, 30 slices each 4mm thick; and number of excitation (NEX)=3. Pseudocontinuous spin labelling was performed for 1.5s before postlabelling delay of 2s. Background suppression was achieved by applying inversion pulses on the volume to be imaged, allowing for the increase in the sharpness of the bolus.³¹ This setting resulted in the acquisition of a 3D voxel size of 3.8×3.8×4mm³ during 4:30min. Scanner software was used for online image reconstruction. Pairwise subtraction between label and control images was obtained and averaged to generate the mean difference and converted to CBF maps based on a previously published model.¹⁰ After automated reconstruction by the scanner software, digital

imaging and communications in medicine (DICOM) CBF maps along with all other anatomical imaging were sent to picture archiving and communication system (PACS) and were available for interpretation.

Image analysis

For the purpose of this study, ASL images were retrospectively evaluated by one board-certified neuroradiologist for the detection of regional hypoperfusion or hyperperfusion. The observer was blinded to the final diagnosis to avoid bias. 'Additional diagnostic findings' were noted in the context of conventional images and final diagnosis. For example, in a patient with a diagnosis of TIA, for additional findings to be counted, initial ASL analysis (blinded to TIA diagnosis) must have been recorded as regional hypoperfusion. In a review of conventional imaging for this case, there should be no evidence of acute infarction. Image analysis was performed on a PACS (Centricity, GE Healthcare, Chicago, Illinois, USA) station without any additional software. Additional findings were noted if the ASL finding (1) suggested a new diagnosis, (2) helped narrow the differential or (3) prompted further imaging/workup, which would not have been considered with conventional imaging only.

In patients with acute infarct, the diagnosis was made by DWI and therefore ASL findings if any were considered supplementary and not as an 'additional finding'. In patients who had multiple regions of perfusion abnormality or a mixture of hypoperfusion and hyperperfusion, the most acutely relevant ASL finding was regarded as the predominant perfusion pattern. For example, in a patient with an acute infarct with associated luxury hyperperfusion and a chronic infarct elsewhere with corresponding hypoperfusion, the hyperperfusion related to acute infarction was included in the data analysis.

Final diagnoses were extracted from patients' discharge summary and patients were categorised into two groups: acute infarction and non-infarction. Percentages of ASL abnormalities were calculated and subdivided in each category.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

Patient cohort

Our final cohort included 676 patients. The mean±SD of age (years) was 62±18 with a median of 64. Among our cohort, 312 were men and 364 were women. CBF analysis of the cohort revealed 79 patients with hyperperfusion, 250 with hypoperfusion and 347 with normal perfusion.

Group with acute ischaemic infarction

A total of 257 of 676 (38.0%) patients had acute infarcts (109 with small vessel infarcts and 148 with large vessel

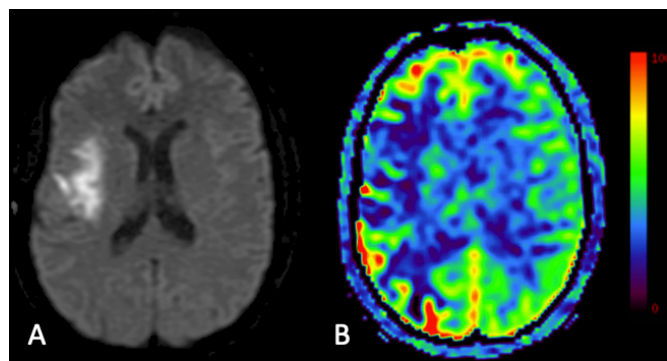


Figure 1 Patient presented to the emergency department with sudden left facial and arm weakness and underwent a standard stroke protocol with non-contrast brain MRI. DWI (A) and ASL-CBF (B) are shown. There is restricted diffusion in the right middle cerebral artery (MCA) territory involving the anterior and posterior portion of right insula. ASL demonstrated corresponding and larger hypoperfusion around the infarction bed suggesting persistent hypoperfusion of ischaemic territory ('penumbra'). ASL, arterial spin labelling; CBF, cerebral blood flow; DWI, diffusion-weighted imaging.

infarcts). ASL provided supplementary information in 3 of 109 (2.8%) patients with small vessel infarcts and 60 of 148 (40.5%) patients with large vessel infarcts. Among 63 patients with acute infarct in whom ASL showed supplementary information, 47 patients had luxury perfusion of infarction bed representing infarct reperfusion (figure 1) and 16 patients had corresponding and larger hypoperfusion around the infarction bed suggesting persistent hypoperfusion of ischaemic territory (figure 2). ASL's additional findings in these patients are summarised in table 1.

Group without acute infarction

Out of 419 patients who did not have an acute ischaemic infarct, additional findings were observed on ASL in 31

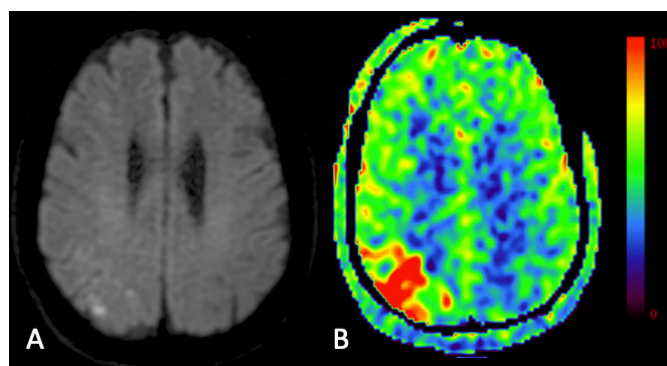


Figure 2 Patient presented to the emergency department with altered mental status. DWI (A) and ASL-CBF (B) are shown. There are several foci of restricted diffusion in the right middle cerebral artery (MCA) / posterior cerebral artery (PCA) border zone. ASL demonstrated corresponding hyperperfusion around the infarction bed representing luxury perfusion. ASL, arterial spin labelling; CBF, cerebral blood flow; DWI, diffusion-weighted imaging.

Table 1 Supplementary information provided by ASL in patients with acute infarction

Category	No of patients	Additional findings	Yield of ASL (%)
Acute infarct	257 (52/148)	63 (47/16)	24.51
Small vessel infarct	109 (0/109)	3 (0/3)	2.80
Large vessel infarct	148 (52/96)	60 (47/13)	40.50

Data presented within parenthesis represent the number of hyperperfusion and number of hypoperfusion on ASL. ASL, arterial spin labelling.

patients (7.4%) (table 2). In these cases, ASL helped diagnose certain stroke mimics that otherwise would not have been as conspicuous or easily diagnosed on conventional MR sequences. Hypoperfusion on ASL was observed in patients with TIA or unsuspected vascular stenosis (n=12) (figure 3). Hyperperfusion was seen for infection/encephalitis (n=7), postictal state (n=4) (figure 4), hyper-vascular masses (n=4) (figure 5), posterior reversible encephalopathy syndrome (n=2), migraine (n=1) and Wernicke encephalopathy (n=1).

DISCUSSION

Due to its non-invasive nature and ability to measure cerebral perfusion, ASL can provide important physiological information that would not be available through conventional MRI. With recent technical advances including fast imaging tools and automated postprocessing, ASL can be performed routinely in clinical practice with minimal burden on acquisition time or radiologists' workflow while providing valuable physiological information.

In this study, we showed that ASL can be added successfully to routine unenhanced brain MRI protocol in a hospital setting and provide valuable diagnostic and

Table 2 Additional diagnostic findings from ASL for patients in the non-infarct cohort

	Patients (n)	Additional findings	Yield of ASL (%)
Non-infarct/Other	419	31	7.40
TIA/vascular stenosis		12	
Infection		7	
Seizure		4	
Tumour/mass		4	
PRES		2	
Migraine		1	
Wernicke		1	

ASL, arterial spin labelling; PRES, posterior reversible encephalopathy syndrome; TIA, transient ischaemic attack.

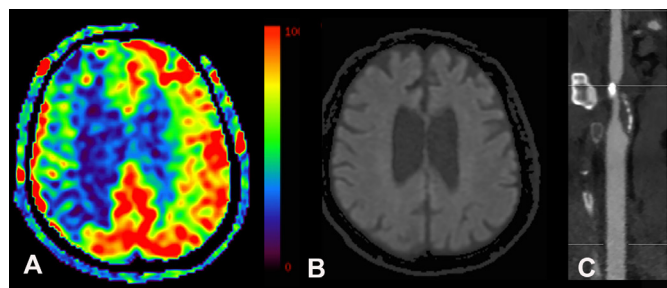


Figure 3 Patient presented with recurrent episodes of syncope and unresponsiveness. ASL-CBF (A) showing significantly decreased perfusion in the right hemisphere along the right anterior cerebral artery (ACA) and middle cerebral artery (MCA) distributions suggesting underlying carotid stenosis. Axial DWI (B) showing no acute infarction. Based on these findings, a CT angiogram of the head and neck was recommended and performed, which revealed approximately 93% stenosis at the right internal carotid artery (ICA) origin (C) due to mixed atherosclerotic plaque. The patient was diagnosed with symptomatic high-grade carotid stenosis and was subsequently scheduled for carotid endarterectomy. ASL, arterial spin labelling; CBF, cerebral blood flow; DWI, diffusion-weighted imaging.

prognostic findings that would not be available through conventional MRI. In particular, we highlight two findings.

First, in a subset of patients without acute infarction, ASL provided additional diagnostic findings in 31 (7.4%) patients. These included patients with diagnoses of seizure, migraine, central nervous system (CNS) infection, haemodynamic impairment, such as TIA or underlying vascular stenosis, or hypervascular mass lesions.

Migraine and seizure (postictal) both have been reported as common stroke mimics.^{32–34} Identifying a mimic from a stroke is critical in regard to the financial burden and avoiding the subsequent unnecessary medical management of these patients. These include direct and indirect hospital costs of occupying a stroke bed and tissue plasminogen activator (tPA) administration, not

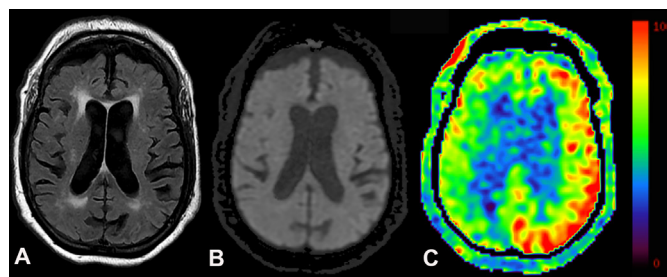


Figure 4 Patient presented to the emergency department with altered mental status and unexplained loss of consciousness and underwent a routine non-contrast brain MRI. Axial FLAIR (A), DWI (B) and ASL-CBF (C) are shown. There is regional hyperperfusion involving the left cerebral hemisphere without associated FLAIR hyperintensity or restricted diffusion. Seizure and postictal status were correctly suggested based on increased non-territorial hyperperfusion. ASL, arterial spin labelling; CBF, cerebral blood flow; DWI, diffusion-weighted imaging.

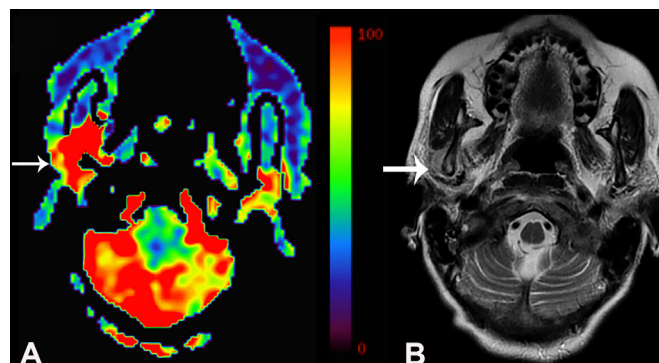


Figure 5 Patient presented with a severe headache and underwent routine brain MRI in the emergency department. Axial ASL-CBF (A) showing hyperperfusion in the right masticator space and around the mandibular condyle (arrow). This led to a closer inspection of the other sequences and the axial T2 image (B), showing thickening of the right temporomandibular joint capsule and abnormal signal in the mandibular condyle (arrow). Further workup led to the diagnosis of multiple myeloma. ASL, arterial spin labelling; CBF, cerebral blood flow.

to mention the financial burden on the patient after discharge such as the effect on driving and medical insurance premiums that are often not considered. In our study, we showed that non-territorial hyperperfusion on ASL-CBF is helpful in the correct diagnosis of patients with migraine and seizure in the postictal state (figure 4) as has been reported previously.^{19–21} Prior ASL studies in postictal states have shown hyperperfusion in the epileptogenic grey matter surrounding parenchyma in a non-vascular territory.³⁵ There were four cases in our study where additional findings were observed on ASL compared with conventional MRI.

Vascular disorders were the most common type of pathology where additional diagnostic findings were observed from ASL images in the non-infarct group. The most common of these were in identifying territorial hypoperfusion with areas of stenosis that were or were not known but identified on MRI based on locally decreased CBF along a vascular territory (figure 3). Perfusion deficit has also been reported in patients with TIA and in fact up to 30% of patients with DWI-negative TIA can have regional perfusion abnormalities.^{36–38} We correctly identified seven patients with TIA in our cohort as having territorial hypoperfusion. One last case among the vascular disorder group was a patient with a very small dural arteriovenous (AV) fistula identified by hyperperfusion on ASL, which otherwise would have been a more challenging diagnosis to make on routine MRI. The usage of ASL for dural AV fistula has also been described in the prior literature.³⁹

CNS infection, such as lept meningitis or encephalitis, was another subgroup of patients in whom additional diagnostic findings were observed on ASL imaging compared with conventional MRI. The diagnosis was suggested based on the areas of leptomeningeal FLAIR hyperintensity with associated elevated CBF. Typically, the

history in these patients was non-specific such as headache and not all patients presented with high fever or nuchal rigidity. Observing subtle sulcal FLAIR signal abnormality particularly in the occipital lobes is not uncommon in a high-volume inpatient setting. The clinical significance of this finding is not always easily determined, especially in patients with an ambiguous clinical presentation. When such a finding is observed in conjunction with elevated CBF, the interpreting radiologist may suggest further workup with lumbar puncture and cerebrospinal fluid analysis to confirm the diagnosis of meningitis.⁴⁰ In one case, ASL also helped diagnose hyperperfusion secondary to phlegmonous changes in the parapharyngeal space in a patient with recent neck surgery. The last group of patients for whom we found additional diagnostic findings from ASL was for hypervascular mass lesions (n=4) that otherwise would have been difficult to identify on an unenhanced MRI (figure 5).

The second finding we would like to highlight in this study is that in a subset of patients with acute infarct, ASL provided supplementary information to conventional MRI with potential prognostic or therapeutic implications. The authors decided to categorise these patients separately as diagnosis of infarction is made with high confidence by DWI images and ASL information will have a negligible value from additional findings. However, ASL can provide supplementary physiological information about the infarction bed with prognostic and therapeutic value. Having ASL hypoperfusion associated with the ischaemic territory in patients with acute infarction has been reported to worsen functional outcome and infarct growth.¹¹ The so-called DWI-ASL mismatch, where ASL defect is larger than a DWI lesion (figure 1), has been used for clinical decision making in prior studies,^{38 41} however, this should be interpreted with caution as ASL can notoriously overestimate the extent of hypoperfusion due to problem associated with sluggish blood flow and arterial transit delay.^{42 43} Patients with subjectively large areas of mismatch were interpreted as having hypoperfusion around a core infarct, which may guide the treating physician in medical management.

Having ASL hyperperfusion associated with ischaemic bed in patients with acute ischaemic stroke can be valuable (figure 2), especially with large vessel involvement.¹¹ Prior studies have shown that hyperperfusion on ASL within or around DWI lesions is associated with hypertension^{16 44} or developing parenchymal haemorrhage.¹⁶ Thus, identification of hyperperfusion may encourage clinicians to ensure closer monitoring and tighter blood pressure regulation to avoid complications such as parenchymal haemorrhage. In contrast, it has been shown that focal hyperperfusion early after thrombolysis is associated with a smaller final infarct volume and with the improved functional outcome at 24 hours and 3 months even despite having a higher chance of parenchymal haemorrhage.^{45 46} It should be emphasised that some of this presumed hyperperfusion may indeed represent arterial transit delay related to sluggish flow and collateral vessels

in particular considering applied 1.5 T imaging in our study.¹⁷

Our study has several limitations. First, this was a retrospective cohort study, which limited the determination of the effect of ASL images on clinical management. A prospective study would have allowed us to assess for clinical implications and outcomes based on these additional findings from ASL imaging. Second, these additional findings were inherently based on the diagnostic interpretations of the conventional MR sequences and may be operator dependent. For example, depending on the experience of the radiologist, the interpretation from conventional sequences may differ, which would affect the determination of what was considered an additional finding on ASL imaging. Additionally, we acknowledge that the patient population in our study is not representative of the general population as our cohort consisted of patients from inpatient and emergency settings and additional findings on ASL may vary in a different clinical scenario. Lastly, we acknowledge that ASL image acquisition at 1.5 T in our study is suboptimal as ASL is best optimised for 3 T MR scanners. Although this is a limitation, it is plausible that the additional findings from ASL may have been underestimated by our study.

In conclusion, the addition of an ASL sequence to routine brain MRI provides additional diagnostic findings compared with conventional brain MRI in about 7.4% of patients with additional supplementary information in 24.5% of patients with acute infarct. The additional findings observed on ASL may aid in the differential diagnosis of neurological processes such as TIA, important stroke mimics, such as seizure and migraine, and hypervascular lesions.

Contributors Guarantor of integrity of the entire study: PB, SK, PP and KN. Study concepts and design: PB, PP and KN. Literature research: PB, SK, FP, PP, GC and KN. Clinical studies: PB, FP, PP, GC and KN. Experimental studies/data analysis: PB, SK, FP and KN. Statistical analysis: PB, SK and KN. Manuscript preparation: PB, SK, PP and KN. Manuscript editing: PB, SK, PP and KN.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. All data are included in the manuscript. No additional data are available.

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