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INNOVATIONS IN CLINICAL MRI (F SCHICK, SECTION EDITOR)

Examination of Tissue Perfusion by Arterial Spin Labeling (ASL)

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Abstract Arterial spin labeling (ASL) is a non-invasive magnetic resonance technique for tissue perfusion quantification working without contrast media application. The method uses magnetically labeled blood protons as intrinsic tracer. Perfusion-weighted images are obtained by the signal difference between an image with proximal labeling of the arterial water protons and a control image. Initially designed for cerebral perfusion measurement, the ASL technique is increasingly being used for the evaluation of extracranial organs which might be attributed to the improvements in scanner, coil and sequence technology but also to the elaboration of postprocessing tools. In this review, the basic principles of ASL are explained. Technical difficulties in ASL sequence design are discussed. To illustrate the potential role of ASL in clinical research and diagnostics, comparison of ASL with other methods currently applied for perfusion assessment is performed. Finally, a variety of clinical applications of ASL is presented with respect to the current literature.

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Introduction

Perfusion represents a characteristic parameter that can be used to analyze vitality and function of tissue [1]. The analysis of perfusion has markedly contributed to the understanding of physiological and pathological processes in the human body. As an example, perfusion measurement allows to investigate the influence of metabolic and endocrine factors on tissue perfusion. On the other hand, analysis of tissue vascularization is important for the diagnosis, characterization and monitoring of inflammatory tissue changes. In malignant tumors, analysis of the lesion's perfusion pattern plays a crucial role as the degree of vascularity may correlate with tumor invasiveness [2]. Thus, there is strong clinical need for sensitive and robust techniques with the possibility of absolute quantification in order to assess the degree of vascularity of different tissues.

Definition of Perfusion

The term perfusion refers to the nutritive blood supply in the capillary tissue. For quantitative description of perfusion, different parameters have been introduced. In order to describe the blood supply to an organ, the blood volume flow in the feeding vessels per unit time can be given in ml/min. This parameter describes the *absolute perfusion* of the organ. If the perfusion is referred to the cardiac output, one obtains the *relative perfusion*. Finally, the perfusion can be referred to the organ volume as the *specific perfusion rate* given in ml/min/100 ml tissue.

MR-Based Perfusion Assessment

Among the MR perfusion imaging techniques, methods with and without i.v. contrast media injection exist. Contrast-enhanced perfusion MRI comprises dynamic contrast-enhanced (DCE) and dynamic susceptibility contrast (DSC) techniques. DSC is almost exclusively used in cerebral perfusion studies. The sequences used in contrast-enhanced MR perfusion imaging are either designed to be sensitive to the presence of contrast medium in the intra- and extracellular space (DCE; T1 or relaxivity based methods) or to the vascular phase of contrast medium delivery (DSC; T2* or susceptibility-based methods) [3]. As opposed to CT perfusion imaging, in DCE-MRI the relationship between the observed signal changes and the contrast media concentration is non-linear. Therefore, correction algorithms are necessary to convert the regional signal changes into contrast agent concentration time curves [4••]. Most Gadolinium-based contrast agents used for MR perfusion distribute in the extracellular space and are renally eliminated. Thus, compartment models can be used for the calculation of perfusion parameters as done in nuclear medicine and CT-based bolus techniques [5].

In MRI, perfusion assessment can also be performed without contrast media administration, such as in intravoxel incoherent motion (IVIM) or arterial spin labeling (ASL) approaches. The IVIM technique was first described by Le Bihan et al. [6]. IVIM means the translational microscopic motion of water molecules which is attributed to the following two components: one is the Brownian motion (diffusion) and the other is the blood flow in the capillary bed (perfusion). The water molecule motion can be assessed using diffusion-weighted imaging (DWI) and can then be separated mathematically in the two components of diffusion and perfusion. In the last years, this technique has been investigated in different organs such as liver, brain and placenta [7–11]. Extensive clinical application, however, has not yet been reached, probably because the method is relatively prone to artifacts and provides only limited dynamic range of perfusion assessment [12].

The ASL approach has first been described by Williams et al. and Detre et al. in the early 1990s [13, 14]. It has obtained broad experimental and partly clinical acceptance as a non-invasive technique in the assessment of cerebral blood flow. However, the technique can also be adapted for the application in extracranial organs.

ASL Perfusion Imaging and Quantification

The ASL method is based on the use of magnetically labeled blood protons serving as an intrinsic tracer. Volume selective labeling is performed by a radiofrequency pulse in a region proximal to the imaging slice (Fig. 1). Image acquisition is performed in a slice in which the inflowing, labeled blood protons cause a change in magnetization. The extent of magnetization change is measured by comparing a control image recorded without prior labeling and the labeled image [15]. The signal difference in the subtraction image reflects the amount of blood that has flown into the imaging slice and is related to the local blood flow. In practice, the signal difference depends on several additional factors such as the T1 relaxation time of blood and tissue, the efficiency of blood proton labeling, the transit time of blood that passes from the labeling to the imaging slice and the blood tissue partition coefficient λ (defined as the quantity of water per gram of tissue divided by the quantity of water per milliliter of blood) [16]. Therefore, for perfusion quantification, a model is required that considers all these parameters.

The quantification models described in the literature are based on the indicator dilution method proposed by Kety and Schmidt [17]. This method was adapted for ASL perfusion quantification by Detre and Williams [1, 14]. In the original model, one assumes that the blood protons are freely diffusible and immediately exchange with the water protons in the tissue. Therefore, the perfusion calculation can be performed based on a one-compartment kinetic model [18••]. This simplified model has been repeatedly modified: Calamante et al. [19] elaborated an approach that considered flow effects. Buxton et al. [20••] proposed a kinetic model in which transit time and bolus width could be taken into account.

There are two main approaches of ASL perfusion imaging which differ in the type of the applied labeling radiofrequency pulse: continuous ASL (CASL) and pulsed (PASL). In the following sections these two types are briefly described and both their advantages and shortcomings are explained.

CASL (Continuous ASL)

CASL was the first ASL method described for perfusion quantification [14]. In CASL, the blood is continuously labeled while it flows through a thin labeling slice by a relatively long (1–5 s) labeling pulse of low intensity. Because of continuous spin labeling, the signal in the imaging slice reaches equilibrium state. The signal in the image slice is recorded after the end of the labeling pulse. Perfusion signal is obtained by subtracting the perfusion-weighted image recorded after labeling from a control

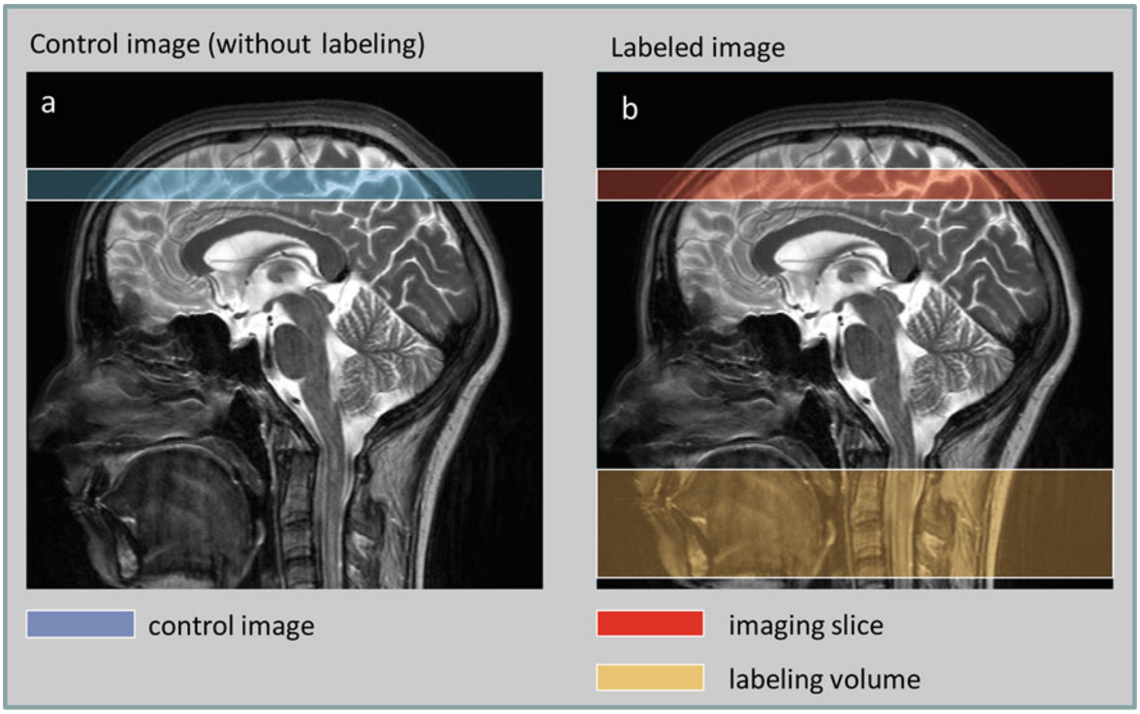

Fig. 1 Principle of ASL perfusion imaging. The ASL method is based on the use of magnetically labeled blood protons as an intrinsic tracer. Labeling is performed by a radiofrequency pulse proximal to the imaging slice. Image acquisition is performed in a slice in which the inflowing, labeled blood protons cause a change in magnetization. The extent of magnetization change is measured by comparing the control image without labeling and the labeled image. The signal difference reflects the amount of blood that has flown into the imaging slice and is related to the local blood flow

image without labeling. The obtained perfusion signal is proportional to the local blood flow [1, 14, 15].

PASL (Pulsed ASL)

The first scheme for a pulsed ASL sequence was proposed by Edelman et al. in 1994 [21]. In PASL, blood in a large blood volume (10–15 cm slab thickness) is labeled by a short (10 ms) radiofrequency pulse. The signal is recorded in the imaging slice after a defined time, which is termed the inversion time (TI). As in CASL, the perfusion signal is obtained by subtracting the perfusion-weighted image recorded after labeling from a control image. The subtraction image represents the amount of labeled blood flown into the target volume during the inversion time and is proportional to the local blood flow [15]. PASL techniques can be differentiated into two categories depending on the symmetry or asymmetry of the labeling localization in relation to the imaging region [18•, 22]. In PASL, the shape of the labeling pulse is very important and should be rectangular with no space between the imaging and the labeling region. However, due to the finite duration of the radiofrequency pulse, this is not feasible in practice. Thus, contamination can occur in the imaging slice due to proximity of the labeling region. To reduce this, imaging and labeling region are positioned apart with a certain gap in between. In CASL labeling, the pulse profile of the radiofrequency pulse is positioned at a greater distance from the imaging slice, so that the pulse profile is less of a concern [18••].

Although PASL and CASL are based on the same method, both approaches have their advantages and disadvantages. PASL has the important advantage of shorter measuring time. CASL, however, is easier to implement and provides higher signal gain as compared to PASL [18••]. On the other hand, in CASL, perfusion quantification can be falsified by magnetization transfer effects that occur due to the longer duration of the labeling pulse. Moreover, CASL is suffering from loss of spin labeling during the blood protons' transit from the labeling to the imaging slice [22]. Furthermore, the continuous high frequency pulse can transfer marked radiofrequency power to the patient exceeding the safety level of the specific absorption rate at higher field strengths [23••].

Technical Developments and Future Challenges

ASL has been developed in the early 1990s for cerebral perfusion quantification [13]. Since then, experimental and clinical application of ASL has gained increasing importance. As the perfusion signal in the subtraction image is rather low due to the relatively low signal difference between labeled and control image, the main goal in technical ASL research was to improve the signal to noise ratio [24]. This could be achieved by the introduction of high field scanners [25], the implementation of background suppression techniques [26, 27] and the design of dedicated surface coils with parallel imaging technique [28]. The increase in perfusion signal has allowed improving of the spatial resolution of ASL to a certain degree. However, the spatial resolution of ASL, especially for extracranial purposes, still remains to be improved.

In the past several years, so-called velocity-selective ASL (VS-ASL) has been introduced [29••]. VS-ASL is a pulsed ASL sequence in which the flowing spins are tagged based on flow velocity and not on spatial location [29••, 30]. The technique allows for improved perfusion measurement in scenarios with low blood flow.

Another promising development in ASL is the so-called selective ASL perfusion imaging, in which protons in defined blood vessels are labeled selectively, so that it is possible to measure perfusion components of primary territories or collaterals [31]. However, all of these approaches have to deal with a reduction of signal intensity.

An important step towards clinical application of ASL is the development of dedicated postprocessing software tools. Today, suitable software is commercially available for cerebral diagnostic applications, which allows for fast evaluation and reading of the perfusion data. Moreover, the introduction of the evaluation software has also facilitated data archiving. However, the development and official licensing of adapted software also for extracranial applications is a prerequisite to further integrate the ASL perfusion approach in routine scan protocols in the near future.

Technical Problems and Solutions in ASL

In the following section, technical limitations of the ASL approach and solutions to overcome remaining problems will be discussed.

Sensitivity to Motion

ASL as a subtraction method is sensitive to motion artifacts. Organ movement might be misinterpreted as perfusion and leads to overestimation of blood flow. The implication of registration or navigator techniques could reduce this problem, such as proposed by Wang et al. [32] for the assessment of myocardium perfusion. However, navigator techniques unfortunately lead to relatively low signal gain per measuring time.

Influence of Transit Effects

In ASL perfusion quantification systematic errors due to transit effects can occur. Transit effects arise because it takes a certain amount of time until the labeled blood flows from the labeling region to the imaging slice. Given the regional differences in blood flow velocity the transit time can vary so that the subtraction signal in the imaging slice can be altered independently from the perfusion rate. In pulsed ASL techniques, this effect is less prominent because in this sequence design the labeling volume and the imaging slice are positioned closer to each other. Pulsed ASL techniques which are insensitive for the variation in transit time have been developed, such as QUIPPS (Quantitative Imaging of Perfusion using a Single Subtraction). However, these techniques provide much lower signal gain per measuring time [33].

Intravascular Signal Contribution

Intravascular signal contribution in the imaged slice can lead to overestimation of tissue perfusion [33]. Different approaches have been proposed to reduce this effect. One is to increase the inversion time so that labeled blood in vessels with high flow velocity has already passed the imaging slice at the time of image acquisition. The increase of inversion time, however, leads to a marked signal loss in the perfusion image. A practical often used solution to the problem is to visually exclude macroscopic vessels in the analysis or to establish thresholds so that the contribution of macroscopic blood flow in vessels is reduced. These techniques, however, reduce the reproducibility of the method. The improvement of suppression techniques for the reduction of intravascular signal contribution seems to provide a more robust solution for this problem. Pell et al. [34] have reported on the implementation of a modified TurboFLASH sequence for FAIR imaging in which intravascular signal suppression was obtained by dephasing of fast flow in large vessels. This was achieved by using a modified preparation period with a combination of 90°–180°–90° radiofrequency pulses after the inversion time. The pulses turn the perfusion-prepared magnetization into the transverse plane where it experiences diffusion gradients before being returned to the longitudinal direction. Pell and co-workers [34] found that most of the intravascular signal could be suppressed using b values of 20–30 s/mm^2.

Influence of Slice Orientation

Perfusion quantification using ASL techniques is sensitive to the orientation of the imaging slice in relation to the course of the feeding vessels. Saturation effects can occur if the feeding vessels run within the labeling plane. This can lead to differences in perfusion values depending on the slice position chosen for each measuring experiment [35]. Therefore, slice orientation needs to be chosen with respect to vessel anatomy when the perfusion imaging study is planned.

Single- and Multi-Slice Techniques

Most of the initially presented ASL sequences were single slice techniques which require multiple acquisitions to cover a whole organ. In principal, all ASL sequences can be upgraded to multi-slice technique, by recording multiple image slices distal to the labeling volume. However, this leads to different transit times for different slices to be recorded and to a loss of labeling effectiveness which is linked to a loss of signal [33]. Further elaboration of multi-slice ASL techniques will be a primary step towards broader clinical acceptance of the ASL approach.

Comparison of ASL to Other Perfusion Imaging Methods

In comparative studies, ASL techniques led to results for cerebral blood flow according to oxygen 15 water positron emission tomography (PET) [36]. The advantage of ASL in contrast to the nuclear medicine and CT-based perfusion measurement approaches is obvious: First, ASL is completely non-invasive and works without contrast injection or radiation exposure. Second, in contrast to dynamic CT or MRI studies, ASL has the advantage of providing quantitative perfusion data. The bolus techniques available allow a more qualitative analysis with relative changes in blood flow or mean transit time and, therefore, may have difficulties to detect global hypo- or hyperperfusion [37••]. Third, the ASL approach comes closest to physiological perfusion of tissue because it measures the distribution of blood water protons and is not based on the observation of an extrinsic tracer or contrast agent. On the other hand, contrast-enhanced (CE) perfusion MRI provides perfusion assessment with higher spatial and temporal resolution and is working more robustly in organs with low perfusion rates. In CE MR perfusion imaging, exact timing of the measurement is mandatory which requires expertise of the examiner. In ASL, care has to be taken in order to position the imaging slice with respect to the feeding vessel anatomy. The most important advantage of ASL lies in the fact that this method provides quantitative perfusion data using a completely non-invasive approach that works without the need of contrast media application and therefore can be applied repetitively in patients with impaired renal function, especially with regard to the potential risk of nephrogenic systemic fibrosis (NSF) [38].

Clinical Applications of ASL

Neuroradiology

The most frequent clinical ASL application is the evaluation of cerebral perfusion patterns. It could be shown by ASL studies that perfusion values of the gray matter physiologically peak in the age of 5–15 years and then decrease until the age of 30 years. After then, a slow progressive decline is observed [37••].

The method has been proven useful in ischemic and neurodegenerative pathologies [39, 40]. In Alzheimer's disease, focal hypoperfusion was observed in certain cerebral areas [41]. In patients with temporal lobe epilepsy, ASL studies revealed local areas of cerebral hypoperfusion in the mesial temporal lobe [42]. In ASL studies of intra- and extraaxial tumors [37••] strong evidence was found that the perfusion characteristics of tumors can be correlated with the histologic grading in the majority of lesions [43]. Yamashita et al. [44] confirmed the usefulness of ASL imaging in differentiating primary central nervous system lymphoma from glioblastoma multiforme. Pollock et al. [37••] have reported that ASL perfusion imaging is helpful in the discrimination of toxoplasmosis versus lymphoma in immunocompromised patients. When analyzing the tumor's perfusion pattern by means of ASL, one has to be aware, that ASL imaging can be impaired in the presence of hemorrhage, metallic clips or calcification [37••]. Pollock et al. [37••] have given an excellent overview about neuroradiological ASL applications which is recommended to the interested reader.

Extracranial Applications

Initially designed to measure cerebral perfusion, the extracranial application of ASL has to face several challenges. First, in the brain, the vessel anatomy is ideal for ASL studies because all cervical vessels feeding the brain are running caudo-cranially in one direction. This simplifies slice positioning of the ASL experiment. Extracranial organs may have a more complex vessel anatomy with inflowing blood contributions coming from different directions which makes the ASL method challenging. Second, the brain is a relatively highly perfused organ and is, therefore, providing sufficient signal for ASL studies while extracranial organs may show lower primary signal due to low proton density and susceptibility effects (e.g. lung, neck) or may have markedly lower perfusion values (e.g. muscle). Third, perfusion assessment of thoracic or abdominal organs is difficult due to the inevitable organ movement in the cardiac or respiratory cycle. Therefore, registration methods or navigator techniques need to be adapted. However, one has to be aware that by applying such techniques signal is generally reduced while the measuring time is increased.

Kidney and Renal Transplants

Assessment of renal perfusion seems to be a promising application of ASL, especially in patients with impaired renal function in which the use of i.v. contrast media should be avoided. Renal perfusion measurement by ASL has been demonstrated by Martirosian et al. [45] in 2004 using a FAIR TrueFISP technique which combines a flow-sensitive alternating inversion recovery (FAIR) perfusion preparation and a true fast imaging with steady precession (TrueFISP) data acquisition strategy. In Fig. 2, a coronal ASL perfusion map of the kidneys obtained using the FAIR TrueFISP sequence is shown. Pedrosa et al. [46] reported the usefulness of ASL in the characterization of renal masses in patients with impaired renal function. Their results, based on the evaluation of 17 renal masses, indicate that the detection of tumor vascularity in renal masses is suggestive for the presence of neoplasia. Boss et al. [47] have shown the value of ASL perfusion analysis in the follow-up of patients after radiofrequency ablation of renal tumors. ASL perfusion has also been investigated in the monitoring of renal transplants and seems to be useful for the assessment of transplant rejection [48].

Lung

The assessment of lung perfusion is of clinical importance in the diagnosis of pulmonary pathologies such as pulmonary embolism, pneumonia or bronchial carcinoma. Pulmonary perfusion MR studies, particularly quantitative methods, would be desirable to avoid the radiation dose associated with classic radionuclide or CT perfusion studies [49]. ASL techniques offer the possibility of reliable, quantitative assessment of pulmonary perfusion as shown in previous studies in healthy volunteers [50] as well as in pulmonary embolism and lung transplantation patients [51]. The ASL method has also been proven helpful in the characterization of the pulmonary involvement in pediatric patients with cystic fibrosis [52].

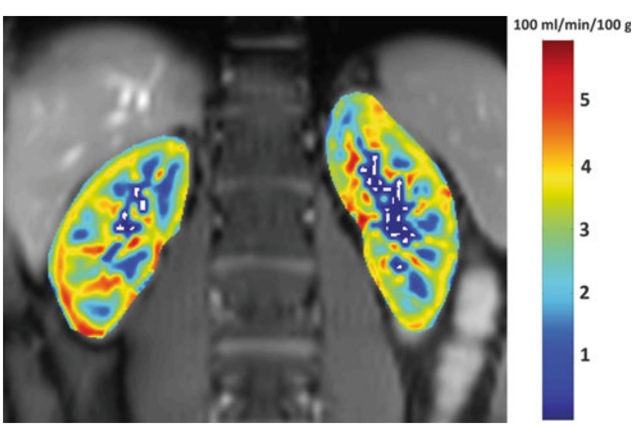

Fig. 2 ASL perfusion map of the kidneys Coronal ASL perfusion map of the kidneys obtained in a healthy young volunteer using a FAIR TrueFISP technique which combines a flow-sensitive alternating inversion recovery (FAIR) perfusion preparation and a true fast imaging with steady precession (TrueFISP) data acquisition strategy

Glands

Ultrasound and gamma scintigraphy are the key imaging modalities in the diagnosis of thyroid pathologies. However, certain thyroid pathologies, for example several forms of autoimmune thyroiditis, are known to be related with altered thyroid perfusion which cannot be absolutely quantified by the above named imaging modalities. In these cases, perfusion assessment of ASL has allowed to identify significant differences between Graves' disease, Hashimoto thyroiditis and normal glandular tissue [53]. In Fig. 3, an ASL perfusion map of the thyroid gland in a patient with Graves' disease shows marked hyperperfusion of the gland. Moreover, significant correlation between endocrine laboratory parameters and thyroid perfusion could be demonstrated.

Schwenzer et al. [54] investigated ASL perfusion imaging for the evaluation of functional changes in the parotid gland following gustatory stimulation and found a marked increase of parotid perfusion of 62 % after stimulation. The ASL technique could be used for disease monitoring in patients with affected saliva production (e.g. after radiotherapy or Sjögren's syndrome).

The feasibility of ASL perfusion imaging has been demonstrated for the pancreas in a clinically applicable measuring time of 15 min providing mean pancreatic perfusion values of 270 ml/min/100 g [55]. The assessment of pancreatic perfusion disorders may be useful in the diagnosis of inflammatory pancreatic pathologies, endocrine and exocrine pancreatic disorders, and in monitoring of pancreatic transplants.

In a recent study, the ASL technique has been reported to be feasible for the assessment of prostate perfusion by Li et al. [56]. Prostate perfusion might serve as an important pathophysiological marker for the disease monitoring or the assessment of the therapeutic response of prostate cancer.

Oncology

In several recent studies, the application of ASL techniques has been described for the assessment of tumor perfusion,

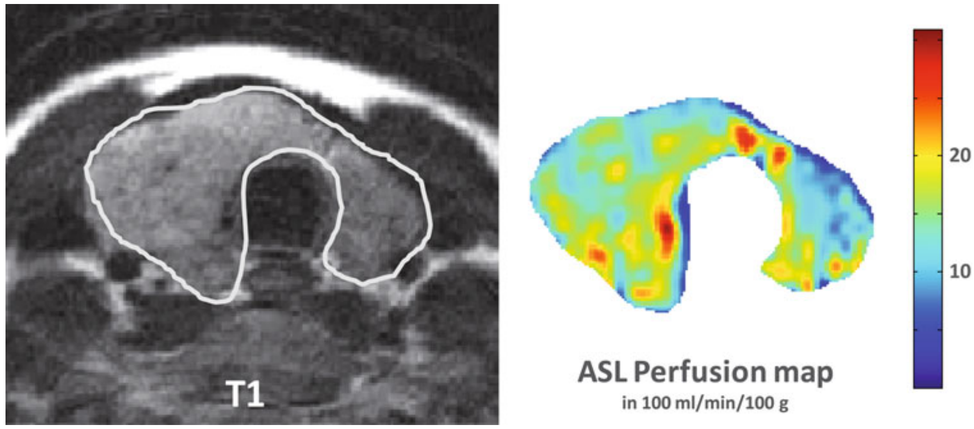

Fig. 3 ASL perfusion map of the thyroid Anatomical axial T1-weighted image (*left*) and perfusion map (*right*) of the thyroid gland obtained by ASL (FAIR TrueFISP). Significant hyperperfusion of the thyroid gland is observed in this 26-year-old male patient with Graves' disease

for example in renal cancer, breast cancer or multiple myeloma [44, 46, 57, 58]. The ASL technique provides important information for tumor characterization, such as in the evaluation of the lesion's vascularization pattern which may contribute to the evaluation of the degree of malignancy. Moreover, the ASL technique seems to be ideal for response monitoring of oncological patients especially in therapies targeting angiogenesis [59]. Fenchel et al. [60] have investigated the value of ASL perfusion in ten myeloma patients under anti-angiogenic therapy. They found that ASL in conjunction with DWI yielded clinically relevant information regarding tumor viability and could predict response already early after therapy onset. This underlines the potential benefit of ASL in the assessment of targeted, mainly anti-angiogenic treatment because the ASL method is completely non-invasive and offers the possibility of reproducible, objective, quantitative method of perfusion assessment.

Conclusion

Today, perfusion imaging using radiological techniques plays an important role in various clinical settings. Perfusion is used for characterizing neoplastic and inflammatory tissue alterations, performing functional central nervous system studies or monitoring treatment in oncology. ASL as an MRI technique provides a sophisticated approach for perfusion measurement working without the necessity of contrast media application or radiation exposure. ASL techniques were initially described and used exclusively for cerebral application. However, their potential for extracranial diagnostic applications has been recognized and its application is continuously expanded. Although ASL perfusion imaging has undergone considerable progress in the last years, the technique has not yet replaced classical invasive methods of perfusion assessment such as contrast-enhanced MR studies or PET. The reasons for this may be attributed to the limited access to ASL techniques on many clinical MR systems and to the lack of commercially available postprocessing software. A methodical disadvantage of ASL lies in the relatively low signal of the perfusion-weighted images which requires repetitive measurement and consecutively prolonged measuring time. However, this disadvantage is compensated by the complete non-invasiveness of the method in many applications. An important benefit of the method is the possibility to calculate absolute, quantitative perfusion values. This opens up a broad clinical application for ASL in the near future, especially in oncological research, where perfusion patterns are increasingly used to characterize neoplasm and to assess response to targeted treatment.

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Papers of particular interest, published recently, have been highlighted as:
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