

## Magnetic resonance techniques to measure distribution of cerebral blood flow

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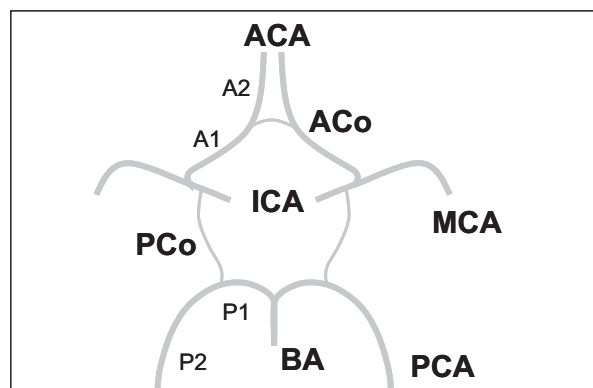
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### Introduction

The human arterial tree system is crucial for the delivery of oxygen and nutrients to the cells. For critical organs like the brain and the spinal cord the vascular system is designed in a way to ensure sufficient oxygen transportation to this particular tissue. This is usually achieved by having backup vessels (so-called collaterals) and connections (communicating arteries) between major arteries like in the circle of Willis at the base of the human brain. In equilibrium, only a small amount of blood is transported through those collateral and communicating vessels. But in case of an acute pressure drop in one region blood flow through this backup system will increase and ensure sufficient supply of the tissue. Even in case of non-acute changes of pressure relationships in cross-connected vessels this auto-regulation will adapt to the actual flow pattern and can help to level under-supply in certain regions.

Figure 1 shows a schematic drawing of the circle of Willis as it is commonly presented in educational books. However, this is not the whole truth. Although the human arterial tree is very similar in most individuals, there exist several variants, which differ in (sometimes important) details. Studies of the circle of Willis based on magnetic resonance angiography (MRA) have revealed a huge amount of variants (Krabbe-Hartkamp, van der Grond et al. 1998), where certain connecting vessels are missing or very small (hypo-plastic).

How can state-of-the-art techniques be employed for proper assessment of an individual's vascular tree anatomy and function? The obvious approach is to image the arterial tree of individuals to acquire knowledge about the actual realization of the vessel structure. As a non-invasive medical imaging technique, which does not employ ionizing radiation, magnetic



*Figure 1. Schematic diagram of the vessels that form the circle of Willis: The system is fed by left and right internal carotid arteries (ICA) and by the basilar artery (BA). "The pre-communicating segments (A1) of the right and left anterior cerebral arteries (ACA) and an anterior communicating artery (ACo) between them form the anterior part of the circle. The pre-communicating segments (P1) of the right and left posterior cerebral arteries (PCA) form the posterior part of the circle together with the right and left posterior communicating arteries (PCo). The right and left posterior communicating arteries originate from the right and left internal carotid arteries (ICAs). The post-communicating portions of the anterior and posterior cerebral arteries are A2 and P2, respectively. MCA = middle cerebral artery". (Krabbe-Hartkamp, van der Grond et al. 1998)*

resonance imaging (MRI) is a tool routinely used in such cases. Due to its flexibility and broad range of contrasts MRI enables a proper depiction of the arterial tree even without the use of endogenous contrast agents. This article will briefly summarize recent developments in noninvasive measurement of macro-

vascular blood flow and micro-vascular perfusion and show some results on imaging the cerebral vasculature.

## Methods

Magnetic Resonance Angiography (MRA) techniques to visualize blood vessels can be divided into two main categories: MRA with and without the use of intravenously injected contrast agents.

Contrast-enhanced MRA techniques (CE-MRA) (Marchal, Michiels et al. 1992; Warach, Li et al. 1992; Prince 1994) acquired during the passage of the contrast bolus can be used to produce high-quality angiograms and require approximately 20 seconds acquisition time. Contrast-enhanced MRA is capable of acquiring time-resolved MRAs by capturing the passage of the contrast agent through the vascular tree at several times. However, since this bolus passage only occurs over a period of several seconds, the time for acquisition is limited. Therefore, a tradeoff exists between image resolution, image quality and temporal resolution. The new technique of parallel imaging (Pruessmann, Weiger et al. 1999) can help, but a temporal resolution of less than 100 ms remains difficult. Anyway, a major drawback of CE-MRA continues to exist: tracer injection is needed.

There are several methods, which do not use contrast agent, including phase-contrast (PC-MRA) (Dumoulin and Hart 1986; Axel and Morton 1987; Dumoulin, Souza et al. 1989) Time-Of-Flight (TOF-MRA) (Dumoulin, Cline et al. 1989; Keller, Drayer et al. 1989; Ruggieri, Laub et al. 1989) and arterial spin labeling (ASL) techniques (Dixon, Du et al. 1986; Nishimura, Macovski et al. 1987; Wang, Nishimura et al. 1991; Edelman, Siewert et al. 1994). A good overview of MR angiography techniques (except for the ASL methods) is given by Price (Price, Creasy et al. 1992).

**Phase-contrast (PC) MRA** utilizes the fact that blood is flowing through the vessels. By switching magnetic gradient fields in a certain way allows differentiating moving from static spins and allows encoding of their velocity along this gradient. By varying the direction of the gradient field a complete picture of existing flow patterns can be gained. By subtracting a reference image without additional magnetic field gradients (i.e. without flow encoding) the vascular tree is separated.

**Time-of-Flight (TOF) MRA** also uses the feature of blood that it is flowing through the vessels. As opposed to PC-MRA TOF-MRA is based on constantly applied rf-pulses to the imaging slab. The signal of the static tissue will be decreased to a steady-state value which can be rather close to zero. The same will happen to the blood, which resides within the imaging for a while. However, fresh blood magnetization will flow into the imaging slab and in the beginning will have its full signal. Therefore, the blood signal within the vessels will appear bright against the diminished (saturated) background signal of the static tissue. The longer the blood travels through the imaging slab, it will experience more and more rf-pulses, thus, its magnetization is reaching the steady state value, which does not allow to distinguish it from the static tissue any more. The longer a vessel runs through the imaging slab the darker it will appear in TOF-MRAs.

Typically, the acquired angiographic data is static, i.e. no time dependent information is acquired, and unselective, i.e. all vessels are encoded the same way. As opposed to other MR angiography methods like conventional Time-Of-Flight (TOF) and phase-contrast (PC) schemes Arterial Spin Labeling (ASL) is also capable to acquire dynamic information of blood inflow (velocity and direction) through vessels at high temporal resolution as well as selectively tag spins in certain vessels.

### ASL basics

ASL techniques are capable of measuring flow and perfusion by magnetically labeling blood. Typically, the inflowing blood is labeled by inversion of its longitudinal magnetization followed by an image acquisition in a downstream slice of interest. Using acquisitions with and without inversion preparation (label and control image, respectively) after an inflow time  $T_I$ , the stationary tissue in the slice is nearly completely suppressed in the difference images, while signal of the inflowing blood is maintained (Spin Targeting with Alternating Radiofrequencies, **STAR** (Edelman, Siewert et al. 1994; Edelman, Siewert et al. 1994)). Therefore, the difference of images with a slice-selective as well as a non-selective, i.e. global inversion pulse is used (**Flow Alternating Inversion Recovery, FAIR** (Kim 1995)). By varying the time  $T_I$  between labeling and image readout various phases of the inflow of the labeled blood into the imaging slab can be acquired. For short inflow times  $T_I$  (~500-1000ms) the

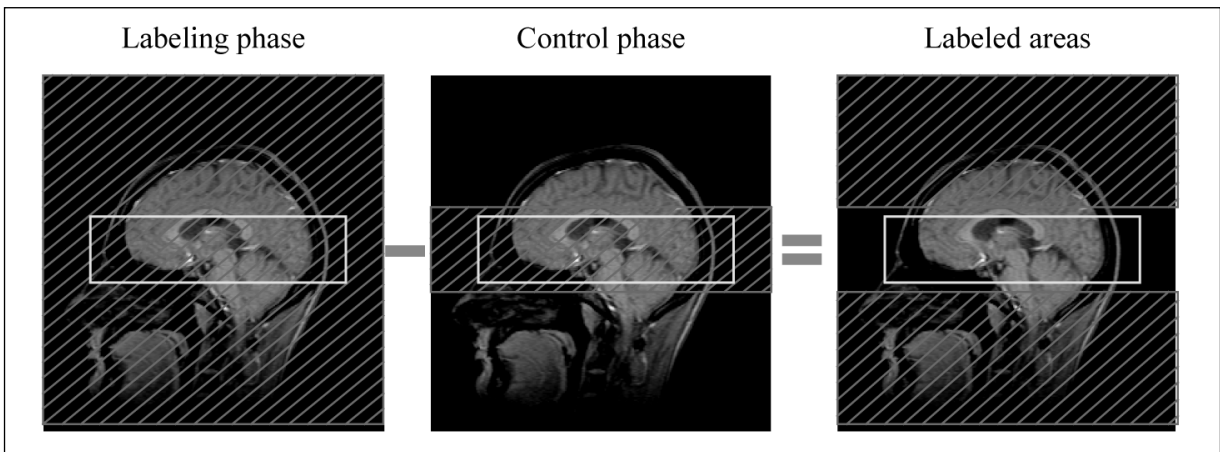


Figure 2. Arterial Spin Labeling (FAIR-Method): First, the blood is labeled using a non-selective, global inversion pulse. Second, a Control image is acquired with a spatially limited "selective inversion" pulse. By subtracting these two images, the stationary tissue and static blood within the image plane vanishes, while the blood inflowing from outside of the image slice becomes the only contribution to the image signal. Both arterial and venous blood is labeled and visualization is determined by their inflow speeds. Imaging slice = light grey, labeling region = cross-hatched

image will resemble an angiogram, since the labeled blood has not traveled much along the vascular tree between labeling and readout. For longer TIs (>1500s) the blood will have reached the capillary exchange site, thus, allowing to acquire micro-vascular perfusion. Measuring the blood signal at several different TI thus allows visualizing the temporal dynamics of flow as the labeled blood moves downstream in the arterial tree.

#### ASL measurement of inflow characteristic

Employing the conventional ASL acquisition scheme by acquiring data for only one image after each labeling pulse would be a very time consuming experiment, particularly when high spatial resolution is needed.

The method of ASL MRA, earlier called selective inversion recovery (Nishimura, Macovski et al. 1987; Wang, Nishimura et al. 1991) has been developed to acquire dynamic information of blood flow through vessels with both high temporal and spatial resolution. In this approach, a dynamic MRA sequence (dyn-MRA) with no injection of contrast agent is used to produce sub-millimeter cerebral angiographies at high temporal within clinically acceptable acquisition times, in under 5 minutes. This dynamic MRA method produces cine movies of cerebral blood flow in the Circle of Willis and cerebral arteries at high temporal

resolution that identifies normal cerebral vascular changes.

The basic idea of dyn-MRA is based on repetitive image acquisition to speed up the measurement of time series. Instead of acquiring a single inflow phase after labeling preparation the dyn-MRA sequence acquires multiple phases after each inversion pulse preparation. This technique was successfully employed for perfusion measurement (Gunther, Bock et al. 2001). It is based on the accelerated T1 measurement approach presented by (Look and Locker 1970), which samples the recovery curve of the longitudinal magnetization at multiple points instead of one single point.

However, only parts of the magnetization can be used for readout, leaving the rest for the later readouts. Therefore, only excitation flipangles smaller than  $90^\circ$  are allowed for image readout. Thus, any gradient-echo based 2D FT sequence including FLASH, EPI, spiral, or radial can be used for readout. Up until now, single-shot 2D-EPI (Gunther, Bock et al. 2001; Brookes, Morris et al. 2007), segmented 2D-EPI (van Osch, Hendrikse et al. 2006), segmented 3D-EPI (Günther, Warmuth et al. 2001), flash (Warmuth and Günther 2001; Günther, Warmuth et al. 2002) and spirals (Amann, Warmuth et al. 2002) were used.

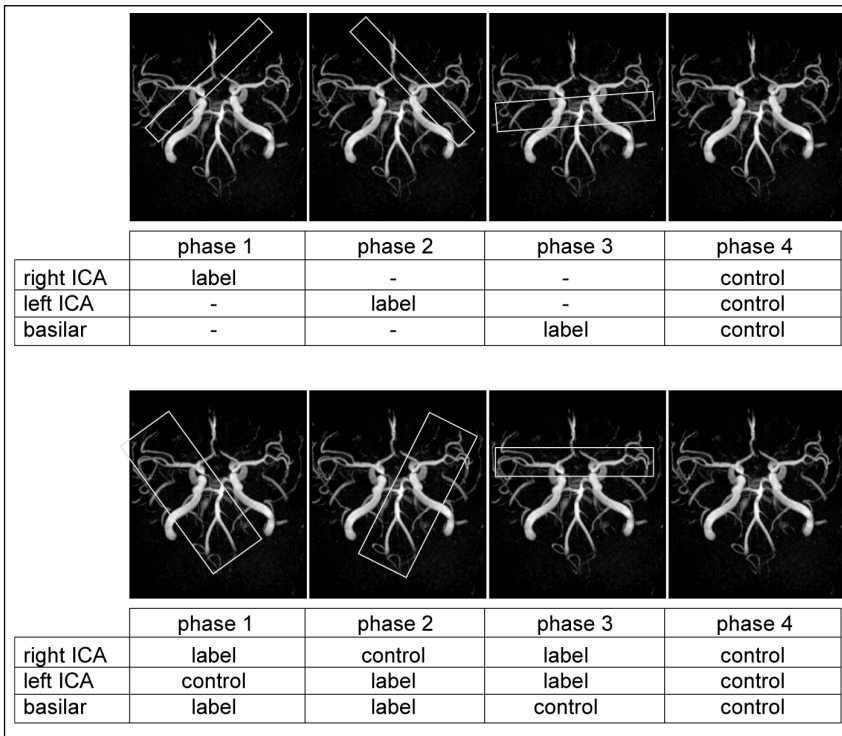


Figure 3. Demonstration of the positioning and orientation of labeling slabs on a high resolution 3D time-of-flight MR angiographic data set. Internal carotid arteries, the vertebral arteries, the basilar artery and the circle of Willis are shown. Due to the proximity of the vessels of interest careful slab positioning to avoid labeling bleed-over is necessary. Labeling scheme on top represents the single vessel approach (Hendrikse, van der Grond et al. 2004). The lower scheme describes the accelerated method of labeling different combinations of the vessels in a four pulse cycle, which allows separation of left and right ICA and basilar territory (Gunther 2006).

### ASL measurement of vascular territories

Imaging the vascular territories of cerebral vessels on a micro-vascular level has become feasible in the past years by employing selective ASL techniques. Instead of labeling in a non-selective manner as in the FAIR or STAR technique described above (i.e. labeling all blood spins flowing into the imaging slab), selective ASL techniques limit the tagging to certain vessels.

This is shown in Fig. 4. In the top row only one vessel is labeled at a time (Hendrikse, van der Grond et al. 2004). In the lower row different combinations of vessels are labeled in several phases (Gunther 2006) allowing to speed up the image acquisition. However, this combined vessel tagging cannot be applied in some vessel configurations due to difficulties in slab positioning. A more recent development is the vessel encoded approach based on continuous ASL (Kansagra and Wong 2008).

## Results

Figure 4 and 5 present typical results of the dynamic angiography technique described above for a healthy volunteer. The inflow of the labeled blood into the cir-

cle of Willis can be nicely seen. A high temporal resolution of 36ms is achieved within a total measurement time of 2 minutes.

Entirely complete circle of Willis configurations are typically found in only about 40% of the subjects (Krabbe-Hartkamp, van der Grond et al. 1998), with smaller numbers for elderly. An incomplete configuration prevalence of 16.7% was found in the same study. Other studies yielded similar findings with only 40-50% prevalence for a complete circle of Willis and about 10-20% prevalence for entirely incomplete configurations. Figure 6 summarizes some of these findings in the schematic diagram of the circle of Willis. Although these numbers are based on MRA techniques anatomical dissection studies in the 1950s revealed almost identical numbers of 52% for the existence of entirely complete configurations (Alpers, Berry et al. 1959).

A study by Lee et al. found in 2004, that the configuration of the collateral pathways of the circle of Willis can be a major risk factor for cerebral ischemia during carotid endarterectomy. In patients with contralateral ICA occlusion, incompleteness of the posterior part of the circle of Willis is a significant risk factor for development of ischemia during vascular clamping of the ICA (Lee, Choi et al. 2004).

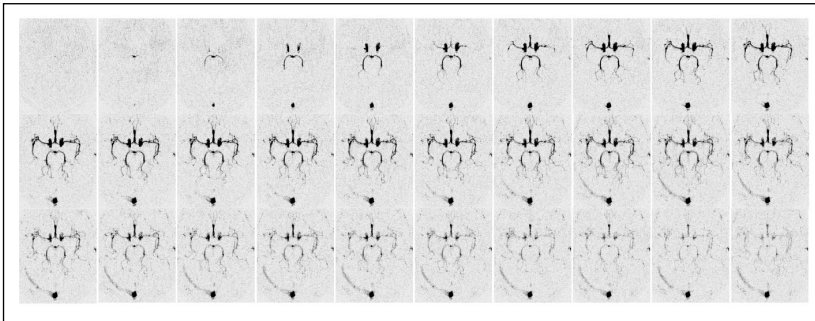


Figure 4. Dynamic Spin Labeling Cerebral 2D-Angiography of a normal person: All 30 phases of inflow of labeled blood with a temporal resolution of 36 ms are shown in inverted grayscale. The dynamic of blood flow can be depicted clearly. Total measurement time is 2.5 minutes.

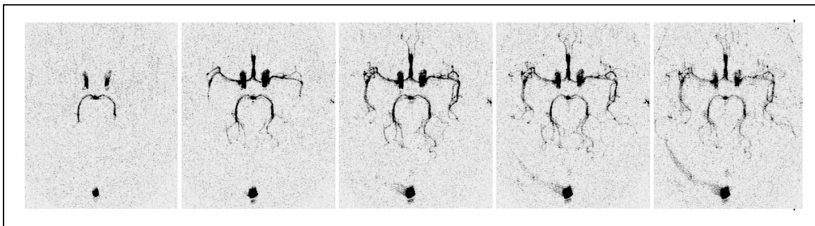


Figure 5: Dynamic MRA of normal subject, every 4th image at a two fold magnification shows smaller vessel branches visualized in the exam. Both PCoA appear to be missing in the dynamic image.

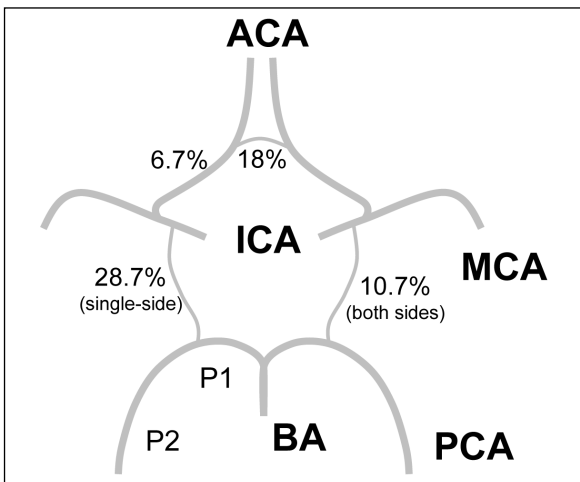


Figure 6. Prevalence of missing or hypo-plastic vessels of the circle of Willis according to a study by Krabbe-Hartmann et al. (Krabbe-Hartkamp, van der Grond et al. 1998). For example, the posterior and anterior circulation are not connected in 10.7% subjects (out of 150 subjects of the study), while 28.7% have one missing posterior communicating artery. No distinction is made between left and right side configurations.

Figure 7 shows typical results of vascular territory imaging on a 1.5T scanner. Total acquisition time was 2 minutes. Only one time step was acquired. However, this technique can easily be combined with inflow sampling yielding the inflow characteristic of the labeled blood as well as the information about the feeding vessel.

Vascular territory imaging is employed for several studies. An excellent overview on the technique and potential applications is provided in van Laar, van der Grond et al. (2008). Possible applications include carotid artery occlusion (van Laar, Hendrikse et al. 2007; van Laar, van der Grond et al. 2008), carotid endarterectomy (van Laar, van der Grond et al. 2006; Van Laar, Hendrikse et al. 2007) and bypassing (Golay, Hendrikse et al. 2005).

## Conclusion

Modern imaging techniques are capable of visualization of the vascular tree. Especially, MR techniques – often non-invasive – can help to assess vessel anatomy and function. Here, arterial spin labeling based techniques promise to yield a greater amount of information than was previously available. By sampling the inflow of blood into the vascular subtree of question with high temporal resolution as well as selectively imaging vascular territories even down to micro-vasculature new techniques have been introduced, which

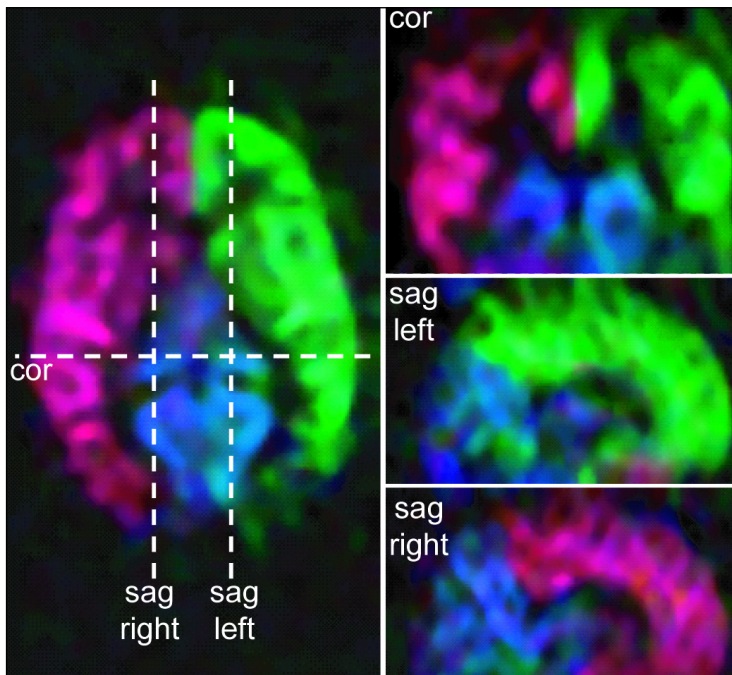


Figure 7. Transverse, coronal and sagittal views through median filtered 3D data set of 38 year old subject with symmetric ICA territories. Color coding separates the tissue of the different vascular territories (green = left ICA, red = right ICA, blue = basilar artery). Note the close proximity of blue and green on the lateral border of left thalamus matching exactly anatomical vascular supply territories in this border-zone region. Acquisition time of whole data set was two minutes. (Gunther 2006)

will (and already do) prove valuable in clinical application.

Multiple studies reveal the fact that no standard configuration of the circle of Willis exists or can be taken for granted. In fact, several variants exist, which are rather common. Therefore, before relying on connectivity between certain vessels or vessel systems a reliable measurement has to be performed. A positive result on this measurement is a viable indicator for functioning collateral flow. However, even in case of a negative result this does not mean that there will be no collateral flow. Since the depiction of vascular anatomy by MR techniques is primarily based on functional aspects at the current pressure distribution (i.e. equilibrium), the findings do not tell much about flow pattern for altered pressure distributions (i.e. disturbed equilibrium). Vessels, which appear hypo-plastic on MRAs, might prove to be fully functional vessels in case they are needed. However, this is true for almost all angiographic methods (not only MR-based), since existing flow within a vessel is assumed to make it visible (i.e. transport of contrast agent through the vessel).

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