Brain Perfusion; How & Why

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Introduction

Cerebral perfusion is defined as the steady-state delivery of nutrients and oxygen via blood to brain tissue parenchyma per unit volume and is typically measured in milliliters per 100 g of tissue per minute. In perfusion MR imaging, however, the term ‘perfusion’ comprises several tissue hemodynamic parameters (cerebral blood volume – CBV, cerebral blood flow – CBF, and mean transit time - MTT) that can be derived from the acquired data. In the evaluation of intracranial mass lesions, however, CBV appears to be the most useful parameter.

Perfusion MR imaging methods take advantage of signal changes that accompany the passage of tracer (most commonly gadolinium based MR contrast agents) through the cerebrovascular system. Perfusion imaging can be performed with techniques based on dynamic susceptibility contrast (DSC) or based on vascular permeability. DSC imaging allows the acquisition of T2* values and significant signal loss. Curves showing intensity changes based on the concentration of gadolinium over time can be generated. The concentration of gadolinium is a direct representation of the capillary density. From this, the relative cerebral blood volume (rCBV) can be determined, which corresponds to the volume of blood within brain tissue. rCBV mirrors the neovascularization associated with tumor angiogenesis; in adults with glial tumors, angiogenesis is highly correlated to tumor grade, and the rCBV of most high-grade glial tumors is greater than that of low grade tumors. Perfusion MR imaging is increasingly being used as a diagnostic and research tool that provides maps of the regional variations in cerebral microvasculature of normal and diseased brains. However, short imaging and data processing times and the use of a standard dose of contrast agent, perfusion MR imaging is a promising tool that can easily be incorporated as part of the routine clinical evaluation of intracranial mass lesions. Although still investigational, MR imaging allows the measurement of cerebral blood volume - CBV, cerebral blood flow - CBF, and mean transit time - MTT that can be derived from the acquired data. In the evaluation of intracranial mass lesions, however, CBV appears to be the most useful parameter. In the future, perfusion MR imaging may become useful in the monitoring of treatment, and its results may also potentially serve as an arbiter when determining the efficacy of novel therapeutics, especially antiangiogenic therapy. The DSC-MRI measurements can help investigate hemodynamic abnormalities associated with inflammation, lesion reactivity and vascular compromises. Even a non-enhancing lesion may show high perfusion which suggests inflammatory reactivity that cannot be seen on conventional MR. Although brain perfusion has been around for while [2] and its uses and advantages known for more than a decade [2–4], it is not yet widely performed. This could be due to the following reasons:

1. The interpretation/quantification is not well established (or accepted) among radiologists.
2. The post-processing of the images is not yet automated and still needs someone with expertise to perform all or part of the post-processing.
3. The technologists and radiologists assume that it is hard to integrate into the usual protocol.

Methodology

Scanning

All the brain perfusion studies have been acquired on Siemens MRI scanners and have been post-processed on a Siemens Multimodality Work Place (MMWP), with Siemens perfusion evaluation software. The scanners used were:

- MAGNETOM Symphony with Quantum gradients (software version syngo MR A25 and syngo MR A30),
- MAGNETOM Symphony a Tim System (syngo MR B15 and syngo MR B17),
- MAGNETOM Sonata (syngo MR A25),
- MAGNETOM Avanto (syngo MR B15 and syngo MR B17), all 1.5 T
- the 3T MAGNETOM Verio (syngo MR B15 and syngo MR B17).

The perfusion was done as part of the routine (with contrast) brain examination for patients who were scheduled for surgery or at the request of a radiologist. Our routine brain exam consists of sagittal T1 (TSE), axial T2 (TSE), axial FLAIR (TSE), axial EPI diffusion and post-contrast axial MPRAGE T1. The perfusion series uses the sequence ep26_per that integrates the Siemens protocol tree under head-Advance-Diffusion & Perfusion. We modified the Siemens standard protocol slightly to suit the rest of our protocols to match primarily the slice thickness, slice gap and field-of-view (FOV).

The following are the steps to perform a brain perfusion study on a Siemens MR scanner:

1. Make sure the patient has a good intra-venous line (IV) with a needle gauge of 18 or 20. Use the antecubital veins and avoid more peripheral placement of the needle.
2. Hook the patient’s IV to an injector and set the injection rate to 4 ml per second. A normal contrast dose of 0.1 mM/kg should be used.
3. Press the Contrast button, select the contrast agent, and set the dose. Select the post-processing parameters and press run. The injection rate is 4 ml per second, and the dose is 0.1 mM/kg.
4. Start the contrast injection and set the injection rate to 4 ml per second. A normal contrast dose of 0.1 mM/kg should be used. In the future, perfusion MR imaging may become useful in the monitoring of treatment, and its results may also potentially serve as an arbiter when determining the efficacy of novel therapeutics, especially antiangiogenic therapy. The DSC-MRI measurements can help investigate hemodynamic abnormalities associated with inflammation, lesion reactivity and vascular compromises. Even a non-enhancing lesion may show high perfusion which suggests inflammatory reactivity that cannot be seen on conventional MR.
Make sure the IV is good and shows no resistance to flow.

Start the routine exam, and insert the perfusion procedure just before the post-contrast T1.

The perfusion imaging slices should have the same positioning, thickness and gap as the axial FLAIR or T2 sequences to facilitate a direct comparison of the perfusion results with other pre- and post-contrast images (Fig. 1).

Make sure that both the lesion and cortical white matter are covered.

The phase encoding direction needs to be anterior-posterior (A/P) to reduce susceptibility artifacts.

After the pre-contrast portion of the brain exam is done, be ready with the injection: start the scan and inject the contrast at the 8th measurement. The scan has 50 time points (measurements) of ~2 s each resulting in total time just below 2 min.

Send the main series to the workstation where you want to do the post-processing of the images.

**Post-Processing**

On the Siemens workstation (MMWP or Leonardo), open the perfusion application (Application-Perfusion).

Open the Patient Browser and load the main perfusion series into the Perfusion Page (Fig. 2).

Click on the images and page through to get to the slice where you can see the area of interest (tumors etc.).

Identify an artery on the same slice.

Click on the small AIF icon: A square appears on the image. Place the square on the artery (Fig. 3).

On the right side of the screen (Fig. 3), select AIF, by choosing the best time graphs, the ones with significant signal drop (highlighted squares). Do so for 4 or more time-points, hold the Ctrl-key while clicking with the left mouse-button.

When done, click on the second tab: Step 2: Set Time Ranges (Fig. 4). Move the three time-lines, so that the first one is at the start of the baseline, the second one at the beginning of the drop (Gad entry) and the third one at the peak of the recovery, as shown in Figure 4. Then click the check box ‘Confirm Time Ranges’.

Make sure the selector at the lower-right side of screen is on ‘All Maps’.

Click on the color calculator/brain icon at the bottom-right corner of the screen. If the icon is dimmed (grayed out) the time selection has not been done yet. The calculation takes about 20–30 seconds.

Once the calculation is done, the rCBV (relative cerebral blood volume) and rCBF (relative cerebral blood flow) color images are displayed in the 4th quadrant, of the screen, as shown in figure 5 (A and B). Toggle between series using the ‘4’ and ‘5’ keys on the numerical key pad (on right of keyboard). The third quadrant shows the MTT (mean transit time) and TTP (time-to-peak) maps. We don’t bother with these.
In the 4th quadrant, i.e. the bottom right segment, select series (right mouse button), adjust the windowing (center mouse button) and save as new series (from the top menu, File-Save As… (e.g. call them CBV_color or CBF_color depending on which one was selected)). These are just the color maps but the pixel values are arbitrary.

Normalization of pixel values
To normalize the values:
- Go to the Viewing card (right side tabs) and open the series ‘CBV_color’.
- Scroll to the top of the brain where you can see the cortical white matter without any distortions.

Typical region selection for the cortical white matter tissue, to find the average healthy white matter intensity.

Using the free hand drawing (right side panel), draw an enclosure (Fig. 6), which only contains healthy white matter, one on each side, if possible, and on two slices if possible.
- Read the mean signal values and calculate their average (avg) mean value (adding all the values and divide by the number of samples used).
- Select the whole series (right mouse button). From the top menu choose ‘Evaluation-Dynamic Analysis – Divide…’.

In the new window (Fig. 7) enter the mean value (avg from above) as the constant and rename the final series to CBV_normalized_avg under ‘Result Series Description’. Press ok.
- Open the browser and select the ‘CBV_color’ series.
- From the Application tab, choose: MR – DICOM – Save as RGB. This creates a series automatically named ‘CBV_color_RGB’, adding ‘_RGB’ to the original series name. This makes the CBV_color series RGB-color coded so that it can be seen in color on PACS workstations.
- Do the same for ‘CBF_color’.  

The rCBV is displayed in the fourth quadrant (lower right) and the MTT is displayed in 3rd quadrant (lower left).

The dialog box which opens for dividing the whole rCBV by a number (average Cortical WM).

Typical region selection for the cortical white matter tissue, to find the average healthy white matter intensity.
Case reports

To illustrate the usefulness of perfusion imaging in clinical practice, here are four clinical examples from our practice:

**Case 1**
A 64-year-old female with a history of brain tumor received radiation and chemotherapy treatment a few months prior to our examination. The initial MRI showed abnormal signal on FLAIR (IR T2), but the T1w post-contrast showed no enhancement. This pointed to a low grade tumor. A follow-up MR with perfusion was performed, which again showed abnormal hyperintensity on FLAIR (Fig. 8A) and no gadolinium enhancement (Fig. 8B), but the perfusion images (rCBV) (Fig. 8C) showed highly perfused tissues pointing to a high grade neoplasm, which was subsequently resected. Histology confirmed high grade astrocytoma.

**Discussion**
Following the above procedure we have done many brain perfusion studies and have used them to grade tumors. The idea of having the color maps and the normalized version is that the normalized version appears only in gray scale on PACS stations, but its pixel intensities have CBV values normalized to white matter. By simultaneously displaying and correlating the color CBV images with the normalized ones, the radiologist is able to see the tissues color coded and can read the corresponding perfusion values with respect to healthy white matter (normalized value). In the literature describing a few studies with an aggressive tumor the perfusion ratio (with respect to white matter) was above 2.5 [5]. By using this method a radiologist can evaluate and grade a tumor more quantitatively.

**Case 2**
A 60-year-old female with history of metastatic lung cancer, presented with metastatic nodule in the left occipital lobe. She underwent craniotomy followed by postoperative radiotherapy to the surgical bed. The one year follow-up brain MRI showed minimal enhancement on post-contrast MRI. The two year follow-up showed a nodular mass, which further grew on short term follow-up. The diagnosis could be either new tumor growth or radiation necrosis. The low signal of rCBV in her perfusion examination pointed toward radiation necrosis rather than tumor re-growth. The enhancing part was subsequently excised and pathology confirmed radiation necrosis.
Case 3
The routine MRI of a 48-year-old right-handed man showed a lesion at the right thalamus suspected of low grade glioma. Subsequent imaging showed a lesion involving the right posterolateral thalamus posterior to the periventricular white matter, which had features suggestive of tumoricidal multiple sclerosis (MS), but the possibility of primary brain neoplasm could not be excluded, especially as the MR spectroscopy (MRS) showed elevated choline signal. The perfusion protocol was performed and both the rCBV and rCBF showed low values (close to those of normal white matter). That pointed to MS with a low possibility of an additional primary brain neoplasm.