Arterial spin labeling perfusion MRI: Inter-vendor reproducibility and clinical applicability
Mutsaerts, H.J.M.M.

Citation for published version (APA):
Cerebral perfusion measurements in the elderly using arterial spin labeling

HJMM Mutsaerts
JW van Dalen
DFR Heijtel
PFC Groot
CBLM Majoie
E Richard
AJ Nederveen

In submission
Abstract

Purpose The current study assesses the feasibility and value of crushed cerebral blood flow (CBF\textsubscript{crushed}) and transit time (TT) estimations for large clinical imaging studies in the elderly.

Material and Methods Two pseudo-continuous arterial spin labeling (ASL) scans with (CBF\textsubscript{crushed}) and without flow crushers (CBF\textsubscript{non-crushed}) were performed in 186 elderly with hypertension, from which CBF and TT maps were calculated. Standard flow territory maps were subdivided into proximal, intermediate and distal flow territories, based on the measured TT. The coefficient of variation (CV) and physiological correlations with age and gender were compared between the three perfusion parameters.

Results There was no difference in CV between CBF\textsubscript{crushed} and CBF\textsubscript{non-crushed} (15-24%, \( p > 0.4 \)) but the CV of TT (4-9%) was much smaller. The total gray matter correlations with age and gender were most significant with TT (\( p = .016 \) and \( p < .001 \) respectively), in between for CBF\textsubscript{crushed} (\( p = .206 \) and \( p = .019 \)) and least significant for CBF\textsubscript{non-crushed} (\( p = .236 \) and \( p = .100 \)).

Conclusion These data show the feasibility and added value of combined measurements of both crushed CBF and TT for group analyses in the elderly. The obtained flow territories provide knowledge on normal vascular anatomy and can be used in future studies to investigate regional vascular effects.
Introduction

Perfusion as measured with arterial spin labeling (ASL) is a promising in vivo hemodynamic parameter to investigate the interplay between normal aging and neurodegenerative and cerebrovascular pathology. Parallel to the optimization of conventional ASL-based cerebral blood flow (CBF) measurements for clinical applications, advanced ASL methods have been developed that enable the acquisition of multiple perfusion parameters simultaneously.

One example is the acquisition of both CBF and the micro-vascular transit time (TT) by the flow-encoding arterial spin tagging (FEAST) method. FEAST is based upon the subdivision of an imaging voxel into macro- and micro-vascular compartments based on differences in blood flow velocity. By performing ASL with and without the application of a vascular crusher, FEAST separately acquires CBF of the micro-vascular compartment (CBF_{crushed}) and CBF of the macro- and micro-vascular compartments together (CBF_{non-crushed}) (Figure 1). The ratio of the perfusion signal of CBF_{non-crushed} over CBF_{crushed} is then proportional to the TT, which is defined as the time it takes for the labeled blood to travel from the labeling plane to the micro-vascular compartment of the imaging voxel.

Several advantages exist for the application of a vascular crusher and the estimation of TT using FEAST. CBF_{crushed} may be preferable to CBF_{non-crushed}, since micro-vascular CBF changes are generally assumed to reflect (patho-)physiological changes in neuronal activity and energy demand whereas macro-vascular CBF is believed to be dominated by cardiovascular fluctuation. TT has been shown to be able to provide additional diagnostic value to CBF measurements, especially in cerebrovascular pathology. However, these possible advantages may come at the cost of a decrease of reliability. Considering the often limited available scanning time, vascular crushing reduces the available SNR for the CBF measurement. Therefore, it has been recently agreed upon that crushing is currently not recommended in the individual subject. However, for group analyses, the feasibility and utility of crushed CBF or TT is still under debate.

The primary purpose of this study was to assess the feasibility and value of the combined measurement of CBF_{crushed} and TT for large clinical imaging studies in the elderly. To investigate the spatial distribution of these parameters, we used the estimated TTs to divide standard flow territory maps into proximal, intermediate and distal flow territories. We study the reliability of these perfusion parameters in terms of their population variation and physiological correlations with age and gender.
Figure 1. a) Schematic overview of the two-compartment perfusion model explains the FEAST technique, adapted from Wang et al. 6 b) shows raw perfusion-weighted maps and c) perfusion maps after post-processing for a representative subject. Note that the signal intensity is lower after crushing ($\Delta M'$) than before ($\Delta M$) and that crushed CBF (CBF$_{crushed}$) is weighted toward the micro-vascular CBF whereas non-crushed CBF (CBF$_{non-crushed}$) is weighted toward both micro- and macro-vascular CBF. $\propto$ = proportional to
Materials and methods

Subjects
195 community-dwelling elderly (46% male, mean age 77 years, range 72-80 years) with hypertension (systolic blood pressure higher than 140 mmHg) participating in the Pre-DIVA study were eligible for inclusion. Exclusion criteria were dementia and disorders or circumstances expected to interfere with successful follow-up. Nine subjects were excluded from analysis because of severe labeling or motion artifacts.

Ethics statement
All patients provided written informed consent and the study was approved by the institutional review board of the Academic Medical Center, Amsterdam.

Imaging protocol
All imaging was performed on a 3T system (Intera, Philips Healthcare, Best, The Netherlands) equipped with an 8-channel head coil. Foam padding was used to restrict head motion. A slightly adapted version of the original FEAST acquisition, which enables the simultaneous acquisition and quantification of CBF\textsubscript{crushed}, CBF\textsubscript{non-crushed} and TT within clinical scanning time, was added to a routine clinical dementia protocol. Two ASL scans were performed with (CBF\textsubscript{crushed}) and without (CBF\textsubscript{non-crushed}) flow-crushing gradients in three directions (velocity encoding 50 mm/s). Identical imaging parameters of the two consecutive gradient-echo single-shot EPI pseudo-continuous ASL (pCASL) sequences were: matrix = 64x64, FOV = 240 x 240 mm, 17 axial slices, slice thickness 7 mm, no gap, echo time/repetition time = 17/4000 ms, flip angle = 90 degrees, SENSE = 2.5, initial post-label delay (PLD) = 1525 ms; slice readout time = 34.9 ms; resulting PLD range for 17 slices = 1525-2080 ms, labeling duration = 1650 ms and two background suppression pulses at 1710 and 2860 ms after a pre-labeling saturation pulse. 20 label-control pairs were acquired - resulting in a duration of 2:40 minutes for each scan. The labeling plane was positioned parallel and 8.3 cm inferior to the center of the imaging volume. An isotropic 1 mm\textsuperscript{3} 3D T1-weighted scan was included in the imaging protocol for segmentation and registration purposes.

Quantification
The raw EPI control and label images were 3D motion corrected using SPM8 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, London, UK). After pair-wise subtraction, these
raw maps were converted to CBF with a single compartment model, assuming that the label decays with the T1 of blood \(^{10,13}\):

\[
CBF [mL/100g/min] = \frac{\Delta M e^{\frac{TE}{T_1a}}}{\rho M_0 a 2aa_{inv} T_1a (e^{-\frac{\delta}{T_1a}} - e^{-\frac{-\alpha-\tau}{T_1a}})}
\]  

where \(\rho\) is the density of brain tissue (1.05 g/mL) \(^{14}\), \(\Delta M\) is the difference between control and label intensities, TE is the echo time (17 ms), \(T_2^*\) is the transverse relaxation time of arterial blood (50 ms) \(^{15}\), \(M_0a\) is the equilibrium magnetization of arterial blood, for which an average scanner value was used \(^{16}\), calculated according to previously described methods \(^{17}\), \(\alpha\) is the labeling efficiency (0.85) \(^{12}\), \(a_{inv}\) is the correction for label loss due to background suppression pulses (0.83) \(^{18}\), \(T_1a\) is the T1 relaxation time of arterial blood (1650 ms) \(^{19}\), \(\omega = 1525\) ms + 34.9 ms/slice, \(\tau\) is the labeling duration (1650 ms) and \(\delta\) is the measured TT (averaged per subject for each flow territory, as described below) for CBF\(_{crushed}\), which is replaced by the PLD for CBF\(_{non-crushed}\).

TT was calculated based on the following two FEAST equations \(^6\):

\[
\Delta M = A (e^{-\frac{w}{T_1a}} - e^{(-w-\tau)/T_1a})
\]

\[
\Delta M' = A (e^{-\frac{\delta}{T_1a}} - e^{(-w-\tau)/T_1a})
\]

where \(A\) is a constant and \(\Delta M\) and \(\Delta M'\) represent the scans acquired without and with vascular crushing, respectively (Figure 1).

**Registration**

The 3D T1-weighted anatomical scans were segmented using SPM8 into gray matter tissue probability maps, on which the CBF and TT maps were rigid-body registered. The tissue probability maps were spatially normalized using the Diffeomorphic Anatomical Registration analysis using Exponentiated Lie algebra (DARTEL) algorithm and the resulting normalization fields were applied to the CBF and TT maps \(^{20}\).

**Flow territories**

The total cerebral gray matter was defined as tissue probabilities >70%. Standard flow territory templates (left and right combined) were used to investigate vascular territories supplied by the bilateral
Cerebral perfusion measurements in the elderly using ASL

Chapter 7

anterior, middle and posterior cerebral arteries (referred to as ACA, MCA and PCA respectively). Within each flow territory the TTS were ranked in tertiles, resulting in three proximal, three intermediate and three distal flow territories.

Statistics

Prior to all analyses, the distributions of investigated values were tested for normality using the Shapiro-Wilk test. Because most distributions of perfusion parameters deviated from normal, distributions were summarized by the median and mean absolute deviation (instead of mean and standard deviation). To compare variation between the perfusion parameters, the coefficient of variation (CV) was used, calculated as mean absolute deviation divided by the median. To test whether respectively the median or CV differed between CBF\textsubscript{crushed} and CBF\textsubscript{non-crushed}, the sign test and Brown-Forsythe test were used (comparable to Student's t-test and Levene's test but more robust in distributions that deviate from normality). To provide insight in the distribution of CBF and TT values in the ACA, MCA and PCA, median group-level histograms were generated from the histograms of individual maps (100 bins, smoothed with 2 bins full-width-half-maximum). To investigate physiological correlations, robust linear regression analyses were performed to model cross-sectional correlations between the predictors age or gender and the dependent variables CBF\textsubscript{non-crushed}, CBF\textsubscript{crushed} or TT, adjusted for total brain volume (defined as the combined volume of gray and white matter segmentations).

Results

Flow territories

The TT-based flow territories showed an almost entirely continuous sequence from anterior-inferior to posterior-superior (ACA), inferior to superior (MCA) and anterior-inferior to posterior-superior (PCA) (Figure 2).

![Flow territories](image)

**Figure 2.** Flow territories. ACA (green), MCA (red) and PCA (blue) refer to the standard flow territories perfused by the bilateral anterior, middle and posterior cerebral arteries respectively, whereas the
shadings represent their subdivision into proximal, intermediate and distal flow territories, based on transit times.

**Comparison perfusion parameters**

Figure 3 shows the median and CV maps of the perfusion parameters. The perfusion patterns in the median $\text{CBF}_{\text{crushed}}$ and $\text{CBF}_{\text{non-crushed}}$ maps had a similar appearance. Whereas the median $\text{CBF}_{\text{crushed}}$ differed in nearly all flow territories from the median $\text{CBF}_{\text{non-crushed}}$, there was no CV difference between $\text{CBF}_{\text{crushed}}$ and $\text{CBF}_{\text{non-crushed}}$ ($p>0.4$ all flow territories), both ranging from 15% to 20% (Table 1). The CV of TT was much smaller than the CV of $\text{CBF}_{\text{crushed}}$ or $\text{CBF}_{\text{non-crushed}}$, ranging from 4% to 9%. For all perfusion parameters, CV increased from proximal to distal flow territories (Table 1). All perfusion histograms appeared to approximate a normal distribution, except for the TT histogram in the PCA (Figure 3h).

**Figure 3.** a-b) median and c-d) coefficient of variation (CV) maps of non-crushed CBF and crushed CBF, e) median and f) CV maps of transit time (TT). g,h) median histograms of (non-)crushed CBF and transit time.
TT maps for the three vascular territories. ACA, MCA and PCA refer to the vascular territories perfused by the anterior, middle and posterior cerebral arteries respectively, corresponding to Figure 2.

<table>
<thead>
<tr>
<th></th>
<th>CBF\textsubscript{non-crushed} (CV)</th>
<th>CBF\textsubscript{crushed} (CV)</th>
<th>Difference</th>
<th>TT (CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[mL/100g/min]</td>
<td>[mL/100g/min]</td>
<td>median ∙∙ CV</td>
<td>[ms]</td>
</tr>
<tr>
<td>ACA proximal</td>
<td>48.4 ± 8.5 (17%)</td>
<td>52.8 ± 9.1 (17%)</td>
<td>Y ∙∙ N</td>
<td>1990 ± 90 (4%)</td>
</tr>
<tr>
<td>intermediate</td>
<td>53.8 ± 9.0 (17%)</td>
<td>58.0 ± 9.1 (16%)</td>
<td>Y ∙∙ N</td>
<td>2070 ± 100 (5%)</td>
</tr>
<tr>
<td>distal</td>
<td>46.8 ± 9.0 (19%)</td>
<td>49.6 ± 9.4 (19%)</td>
<td>Y ∙∙ N</td>
<td>2210 ± 130 (6%)</td>
</tr>
<tr>
<td>MCA proximal</td>
<td>53.5 ± 8.8 (17%)</td>
<td>57.8 ± 8.7 (15%)</td>
<td>Y ∙∙ N</td>
<td>1930 ± 80 (4%)</td>
</tr>
<tr>
<td>intermediate</td>
<td>54.8 ± 9.3 (17%)</td>
<td>58.5 ± 9.4 (16%)</td>
<td>Y ∙∙ N</td>
<td>2040 ± 110 (5%)</td>
</tr>
<tr>
<td>distal</td>
<td>53.9 ± 9.7 (18%)</td>
<td>55.7 ± 10.0 (18%)</td>
<td>Y ∙ N</td>
<td>2210 ± 140 (6%)</td>
</tr>
<tr>
<td>PCA proximal</td>
<td>45.2 ± 8.5 (19%)</td>
<td>46.8 ± 8.9 (19%)</td>
<td>Y ∙ N</td>
<td>1930 ± 140 (7%)</td>
</tr>
<tr>
<td>intermediate</td>
<td>45.9 ± 10.1 (22%)</td>
<td>46.7 ± 10.4 (22%)</td>
<td>Y ∙ N</td>
<td>2030 ± 170 (9%)</td>
</tr>
<tr>
<td>distal</td>
<td>46.8 ± 10.9 (23%)</td>
<td>46.3 ± 10.9 (24%)</td>
<td>N ∙ N</td>
<td>2290 ± 200 (9%)</td>
</tr>
<tr>
<td>Total gray matter</td>
<td>51.4 ± 8.6 (17%)</td>
<td>54.6 ± 8.9 (16%)</td>
<td>Y ∙ N</td>
<td>2080 ± 110 (5%)</td>
</tr>
</tbody>
</table>

Table 1. Distributions of perfusion parameters (n=186). Shown are the median ± mean absolute deviation from median (with the coefficient of variation (CV) between parentheses) of CBF and transit time (TT). ACA, MCA and PCA refer to the flow territories perfused by the anterior, middle and posterior cerebral arteries respectively, corresponding to Figure 2. Difference (4th column) shows whether the median or CV differed (Y) or not (N) \((p<0.01)\) between CBF\textsubscript{crashed} and CBF\textsubscript{non-crushed}.  

**Physiological correlations**

In all vascular territories, CBF\textsubscript{crashed} and CBF\textsubscript{non-crushed} decreased and the TT increased with age, although the changes with age were significant in some flow territories only (Table 2). In almost all flow territories, men had lower CBF and longer TTs compared to women. Generally, correlations were strongest with TT and slightly stronger with CBF\textsubscript{crashed} than with CBF\textsubscript{non-crushed}. The regression coefficients roughly suggested that both aging 10 years and being male decreases total gray matter CBF with 8% and increases total gray matter TT with 5%. For all perfusion parameters, correlation coefficients and \(p\)-values increased and decreased respectively from proximal to distal flow territories.
Cerebral perfusion measurements in the elderly using ASL

Chapter 7

Table 2. Regression coefficients for age and gender (n=186). For each ROI, estimated cross-sectional regression coefficients and p-values are shown. †p<0.01. ACA, MCA and PCA refer to the flow territories perfused by the anterior, middle and posterior cerebral arteries respectively, corresponding to Figure 2.

Discussion

The results of this study prove the feasibility of ASL-based CBF\textsubscript{crushed} and FEAST-based TT measurements within acceptable scanning time in an elderly population. These perfusion parameters showed stronger correlations with age and gender compared to conventional CBF measurements, demonstrating the potential value of CBF\textsubscript{crushed} and TT for group analyses. The observation that the variation of perfusion parameters within flow territories was comparable with the variation of the total gray matter, suggests that the reliability of crushing and FEAST within flow territories is sufficient on a
group level, and no further spatial averaging is required. For large clinical imaging studies in the elderly, therefore, there appears to be potential to study more perfusion parameters than CBF alone.

The TT maps comply with the trajectory of the cerebral vessels, with shortest TTs where the vessels enter the cerebrum and longest at the superior-posterior watershed area. The resulting TT-based flow territories can be used as ROIs in future studies if hypothesized perfusion effects are restricted to certain flow territories only, or if spatial averaging is required when an anatomical structure is too small considering ASL limitations in terms of SNR or spatial smoothing. Potential applications include the investigation of a vascular component to degeneration of the dementia-related regions precuneus and hippocampus, which are supplied by the distal ACA and PCA. The fact that distal flow territories demonstrated the largest variation and strongest correlations, could be due to the fact that these regions are most vulnerable to inadequacy of arterial supply due to cerebrovascular pathology. In addition, whole-brain vascular effects across the population can be envisioned to accumulate in the distal flow territories. This suggests that perfusion measurements in distal flow territories have the highest statistical power to detect vascular effects, even if these effects are expected to be distributed across the total brain.

The observed correlations of the perfusion parameters with age lie within the range of previously reported values, whereas the differences with gender were relatively small compared to previous values. These correlation differences with previous studies may result from our specific population of high age and hypertension, in which large and small vessel disease is expected to be highly prevalent.

The observation that the population variation of TT was much smaller than the variation of CBF could originate from the fact that the physiological perfusion fluctuations affect CBF more than TT. Methodologically, the measured physiological variation can be expected to be similar for $\Delta M'$ (CBF\textsubscript{crushed}) and $\Delta M$ (CBF\textsubscript{non-crushed}), and will thus not propagate into the FEAST-based TT measurement, which is derived from the ratio of the two perfusion scans (Figure 1). The smaller extent of random variation of TT could explain its stronger correlations with age and gender, indicating that TT measured by FEAST can be a more sensitive parameter for physiological correlations in the elderly than CBF.

Our study includes the following limitations. The main drawback for the quantification of TT using the FEAST method, is that the dichotomization of macro- and micro-vascular compartments is based on a single pre-defined velocity cutoff (Figure 1). We have employed a conservative velocity cutoff of 50 mm/s, which is required to retain sufficient SNR in the ASL readout of the CBF\textsubscript{crushed} measurement.
(Figure 1)\(^{10}\). The drawback of this high velocity cutoff is that CBF\(_{\text{crushed}}\) is more similar to CBF\(_{\text{non-crushed}}\), which is illustrated by the fact that the median images of both CBF parameters have a similar visual appearance. Consequently, the micro-vascular compartment is defined more proximal, resulting in TT-values that are more weighted towards the macro-vascular TT than would be the case with lower velocity cutoffs as implemented in the original FEAST method. Although it has been shown in young healthy volunteers that this penalty is not severe, it is advisable to perform multi-TI measurements in a small subset of subjects, for calibration of FEAST-based TT in the elderly\(^{6,32}\).

Another drawback of the FEAST method, is that its TT estimates depend on the selected PLD. A too long PLD will overestimate the TT, since the FEAST method cannot measure TTs that are shorter than the PLD\(^{6}\). On the other hand, a too short PLD leads to measurement errors if the labeled blood has not yet arrived in the imaging voxel at the time of imaging, which may lead to severe underestimation\(^{32}\). To satisfy PLD criteria for both CBF and TT measurements, we applied a PLD that is a trade-off between conventional CBF measurements and FEAST-based TT measurements. The penalty of this PLD trade-off seems small for the ACA and MCA, since their TT distributions appear close to normal. For the PCA, however, the distribution of TT values was more skewed to the left. This can be expected to result mainly from a too short PLD, considering the fact that TT are known to be longest in this region\(^{32}\). Therefore, the reliability of FEAST-based TT measurements in the elderly is limited for the PCA.

In conclusion, we have shown the feasibility and value of combined measurements of CBF and FEAST-based TT for large imaging studies in the elderly. The obtained flow territories can be used in future studies to identify regional vascular effects. On a group level, crushing can improve correlations with physiological parameters such as age and gender. The high physiological correlations of TT suggest that this perfusion parameter can be more relevant than conventional CBF measurements. However, the PLD should be carefully selected and one should account for the possible under- and overestimation of TT. These data encourage future clinical imaging studies in the elderly to investigate multiple MRI perfusion parameters, instead of focusing at CBF only.
Reference list


