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Accuracy and precision of pseudo-continuous arterial spin labeling perfusion during baseline and hypercapnia: A head-to-head comparison with ^{15}O H_2O positron emission tomography

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ABSTRACT

Measurements of the cerebral blood flow (CBF) and cerebrovascular reactivity (CVR) provide useful information about cerebrovascular condition and regional metabolism. Pseudo-continuous arterial spin labeling (pCASL) is a promising non-invasive MRI technique to quantitatively measure the CBF, whereas additional hypercapnic pCASL measurements are currently showing great promise to quantitatively assess the CVR. However, the introduction of pCASL at a larger scale awaits further evaluation of the exact accuracy and precision compared to the gold standard. ^{15}O H_2O positron emission tomography (PET) is currently regarded as the most accurate and precise method to quantitatively measure both CBF and CVR, though it is one of the more invasive methods as well. In this study we therefore assessed the accuracy and precision of quantitative pCASL-based CBF and CVR measurements by performing a head-to-head comparison with ^{15}O H_2O PET, based on quantitative CBF measurements during baseline and hypercapnia. We demonstrate that pCASL CBF imaging is accurate during both baseline and hypercapnia with respect to ^{15}O H_2O PET with a comparable precision. These results pave the way for quantitative usage of pCASL MRI in both clinical and research settings.

Introduction

Cerebral blood flow (CBF) measurements are important in the assessment of many brain disorders, ranging from acute stroke to Alzheimer's disease (Alsop et al., 2000; Chalela et al., 2000). While most techniques for CBF imaging rely on exogenous contrast-agent injection, arterial spin labeling (ASL) MRI employs magnetically labeled blood as endogenous "*contrast-agent*". This relative non-invasive nature of ASL offers the unique possibility for more extensive utilization of clinical and research CBF imaging in patients and normal adults, offering even the possibility of monitoring CBF fluctuations over time. This and the rapid technical improvements in image quality and precision over the past few years have propelled ASL into a promising CBF imaging technique ready for clinical and research usage (Golay and Guenther, 2012).

Various labeling methods have been developed over the years to efficiently generate the magnetically labeled bolus of blood (Dai et al., 2008; Detre and Alsop, 1999; Golay et al., 2005; Petersen et al., 2006; Wong et al., 2006). The pseudo-continuous ASL (pCASL) labeling method is currently regarded as the most reliable and robust technique for ASL imaging. However, the introduction of ASL and particularly of pCASL at a larger scale in research and routine clinical care awaits further evaluation of its accuracy and precision. ^{15}O H_2O positron emission tomography (PET) is currently regarded as the most accurate and precise method to measure CBF. A direct comparison of PET and pCASL-based measurements of the CBF would therefore give necessary information on both the accuracy and precision of pCASL.

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For this purpose, several studies have been performed in which ASL was compared head-to-head with ^{15}O H_2O PET (Bokkers et al., 2009; Henriksen et al., 2012; Kilroy et al., 2013; Van Golen et al., 2013; Xu et al., 2009; Ye et al., 2000). Significant correlations between ASL and ^{15}O H_2O PET based CBF estimates were found with r^2 values ranging from no gray matter region-of-interest (GM-ROI) correlation to a single slice whole brain voxel-wise correlation of 0.72. Yet, a one-to-one quantitative agreement was not observed indicating the presence of a possible bias in the ASL based CBF accuracy. An important reason could be the dependency on inter-modality differences in the CBF quantification modeling, the assumed quantification parameters, physiological fluctuations in CBF, and differences in image resolution, rendering a quantitative comparison of ASL with other perfusion imaging techniques particularly difficult (Donahue et al., 2006). In addition, CBF measurements were compared during rest, limiting the comparison to a restricted range of normal CBF values. Application of a cerebrovascular challenge will increase the range of CBF values included in the comparison, for an improved accuracy assessment. Furthermore, it would enable to evaluate the accuracy of the ASL-based cerebrovascular reactivity (CVR) measurements, which is a physiological parameter showing great clinical potential as a new hemodynamic marker (Bulte et al., 2009; Hajjar et al., 2010; Villien et al., 2013).

The precision of each modality per se has been studied in detail, by assessment of both intra-session and inter-session reproducibilities combined with the inter-subject variability. The intra-session and inter-session reproducibility indexes (RI) were estimated at 7.4% and 18% for ^{15}O H_2O PET and 11% and 22% for pCASL, respectively. Inter-subject coefficients of variation (CV) were reported at 13% for ^{15}O H_2O PET and 16% for pCASL (Bremmer et al., 2010; Chen et al., 2011; Coles et al., 2005; Gevers et al., 2011). To date, however, no head-to-head comparison of the precision of ^{15}O H_2O PET and pCASL has been performed.

The main aim of the present study was to assess the accuracy of quantitative pCASL CBF and CVR measurements by performing a head-to-head comparison with ^{15}O H_2O PET, based on quantitative CBF values under two different cerebrovascular conditions. A second aim was to compare the precision of both ^{15}O H_2O PET and pCASL by means of the intra- and inter-session reproducibilities.

Methods

Subjects and study protocol

This study was performed in compliance with regulations of the Local Institutional Review Boards of both participating centers. All MRI examinations were performed at the Amsterdam Medical Center on a Philips 3 T Intera system (Philips Healthcare, Best, the Netherlands), equipped with body coil transmission and an eight-channel SENSE receive head-coil. All PET examinations were performed at the VU University Medical Center on a Philips Gemini TF-64 PET/CT system (Philips Healthcare, Cleveland, TN, USA). Sixteen healthy volunteers (9 male, 7 female, age range 20–24 years) were included in this study and all gave written informed consent prior to inclusion. For both modalities, each volunteer underwent five CBF measurements distributed over two measurement sessions (a schematic overview of the study design is given in Fig. 1) resulting in a total of 10 CBF measurements over 4 measurement sessions. For comparability of the ASL and PET sessions, the interval between corresponding PET and MRI sessions was set at a maximum of 7 days. To avoid unnecessary exposure to radioactivity in the case of an incidental finding that would lead to exclusion of that subject, the first MRI session was always performed prior to the first PET scanning session, whereas for the second paired PET and ASL scanning sessions a random order was used.

For a full quantitative assessment of the CBF accuracy in two different cerebrovascular conditions with corresponding CVR, the CBF of each subject was measured under baseline (B) and hypercapnic (H) conditions (Fig. 1). The precision was assessed by comparing the intra- and inter-session reproducibilities of each modality. To this end, each subject received 3 baseline (B1, B2, B3, Fig. 1) and 2 hypercapnic (H1, H2, Fig. 1) CBF measurements. For the baseline intra-session reproducibility, two baseline CBF measurements were performed in a single imaging session (B1–B2), separated by 20 to 30 min. For the baseline inter-session reproducibility, a third baseline CBF measurement was performed in a second imaging session approximately 28 days after the first (B1–B3). The hypercapnic inter-session reproducibility was assessed in a similar manner (H1–H2).

Before each scanning session, subjects were fitted with an MRI-compatible mobile non-rebreather mask set-up for gas-delivery, which was identical at both imaging sites. During baseline, normal medical air (21% O_2, 79% N_2) was administered, while for the hypercapnic measurements the air delivery was switched to a pre-mixed gas mixture of 5% CO_2 and 95% air (70% N_2, 25% O_2) (Linde Gas Therapeutics, Munich, Germany). A delay of 2 min was included before the start of the measurement to allow for the subject to get accustomed to the challenge and to reach a new physiological steady state condition. A nasal side-stream capnograph was placed within the mask to measure the end-tidal CO_2 ($etCO_2$). At the end of each ^{15}O H_2O PET scan, arterial pH, arterial CO_2 pressure ($PaCO_2$) and arterial O_2 pressure (PaO_2) were additionally determined by means of arterial blood sampling.

MRI protocol

Acquisition

The MRI protocol consisted of a survey and a time-of-flight (TOF) angiogram for planning of the pCASL imaging- and labeling-planes, a T1-weighted scan for anatomical reference, the pCASL CBF scans (Dai et al., 2008), repeated phase contrast (PC)-velocity scans to measure the blood velocity in the brain feeding arteries (imaged directly after each pCASL scan), a T_1 mapping scan to determine the longitudinal relaxation rate of arterial blood (Varela et al., 2010), a multiple time point control-only pCASL scan for M_0 quantification and a vascular crushed pCASL scan (acquired once in the second imaging session) to study the effect of macrovascular crushing (imaging parameters for each scan can be found in Table 1). All pCASL scans were planned based on the survey and TOF scans, whereby the pCASL labeling plane was planned at an approximate distance of 90 mm from the anterior commissure–posterior commissure line, perpendicular to the labeling arteries. The corresponding PC-velocity measurement was planned at

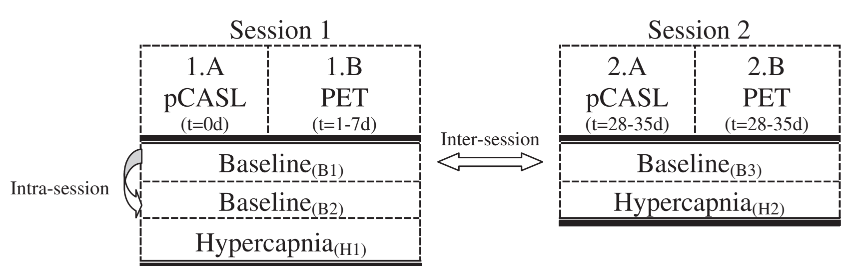

Fig. 1. Schematic diagram of the study design and imaging schedule.