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Citation for published version (APA):

Wong, S. M., Jansen, J. F. A., Zhang, C. E., Staals, J., Hofman, P. A. M., van Oostenbrugge, R. J., Jeukens, C. R. L. P. N., & Backes, W. H. (2017). Measuring subtle leakage of the blood-brain barrier in cerebrovascular disease with DCE-MRI: Test-retest reproducibility and its influencing factors. *Journal of Magnetic Resonance Imaging*, 46(1), 159-166. <https://doi.org/10.1002/jmri.25540>

Document status and date:

Published: 01/07/2017

DOI:

[10.1002/jmri.25540](https://doi.org/10.1002/jmri.25540)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

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Measuring Subtle Leakage of the Blood–Brain Barrier in Cerebrovascular Disease with DCE-MRI: Test–Retest Reproducibility and Its Influencing Factors

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Purpose: Increased blood–brain barrier (BBB) permeability has been shown to play a significant role in the pathophysiology of cerebrovascular disease and it may provide an early functional marker of progression or treatment effects. The aim of the study was to investigate the test–retest reproducibility and influencing factors of dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) in measuring subtle leakage in patients with cerebrovascular disease.

Material and Methods: DCE-MRI (3T) was performed on two separate days in 16 patients (age 66 ± 9 years) with cerebrovascular disease, prospectively. The leakage rate was quantified for white matter (WM) and gray matter (GM) using the Patlak graphical approach with individual vascular input functions (VIFs). Furthermore, the influence of session-averaged VIFs, the average of the VIFs obtained on two days, and shorter scan times (range 5–25 minutes) on the reproducibility were evaluated in WM and GM.

Results: Coefficients of variation (CV) $\leq 14.4\%$ (WM and GM), intraclass correlation coefficients (ICCs) of 0.77 (WM) and 0.49 (GM), were observed for the leakage rate. Session-averaged VIFs hardly affected these results (CV $\leq 13.4\%$). The repeatability coefficients (RCs) of the leakage rate decreased from $2.7 \cdot 10^{-3}$ to $0.4 \cdot 10^{-3} \text{ min}^{-1}$ in WM ($P < 0.01$) and $4.4 \cdot 10^{-3}$ to $0.9 \cdot 10^{-3} \text{ min}^{-1}$ in GM ($P < 0.01$) with increasing scan time (range 5–25 minutes).

Conclusion: Based on the moderate CVs and moderate-to-excellent ICCs, we demonstrate that measuring subtle BBB leakage using DCE-MRI is moderate-to-excellent reproducible. Longer scan times improve the reproducibility. The provided RCs at various scan times may assist future clinical studies investigating BBB leakage using DCE-MRI.

Level of Evidence: 2

Technical Efficacy: Stage 2

J. MAGN. RESON. IMAGING 2017;46:159–166

Dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) of the brain is often employed in the clinic to determine the leakage of a contrast medium through a disrupted blood–brain barrier (BBB) in tumors.^{1–4} Knowledge of the degree of BBB breakdown is used for tumor characterization that can assist in tumor grading and in evaluating treatment response. Recently,

DCE-MRI is increasingly applied to estimate subtle leakage of the BBB in cerebrovascular and neurodegenerative diseases (e.g. cerebral small vessel disease [cSVD] and Alzheimer's disease).^{5–7} These studies have found increased leakage of the BBB, which confirmed the role of the breakdown of this barrier in the pathophysiology. BBB leakage might represent a quantitative functional marker of

View this article online at wileyonlinelibrary.com. DOI: 10.1002/jmri.25540

Received Aug 10, 2016, Accepted for publication Oct 19, 2016.

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cerebrovascular or neurodegenerative disease that signals pathophysiological changes related to disease progression or treatment response, prior to the appearance of structural effects (e.g. white matter hyperintensity lesions).^{7,8}

However, measuring this leakage is challenging, as the magnitude of subtle leakage ($10^{-4} - 10^{-3} \text{ min}^{-1}$) is more than one order lower than observed in (high-grade) tumors (10^{-2} min^{-1}). To enable a future clinical application of DCE-MRI in cerebrovascular diseases, knowledge of its reproducibility is a prerequisite. In addition, it can aid the investigation of long-term gadolinium deposition in the brain.⁹

Various sequences of DCE-MRI and pharmacokinetic models¹⁰ have been employed to determine BBB leakage. In this study, dual temporal resolution DCE-MRI was used to measure BBB leakage.⁸ This sequence consists of two sequences, where the first sequence has a high temporal resolution (i.e., 3.2 sec) for a short period and the second sequence has a relatively lower temporal resolution (i.e., 30.5 sec) for a long period. The first sequence with high temporal resolution enables accurate sampling of the bolus passage and the subsequent second sequence with the lower temporal resolution samples the rather slow extravasation of the contrast agent. For dynamic image analysis, the Patlak graphical approach was used, which was previously shown to provide accurate determination of subtle BBB leakage.¹¹

Several studies using different DCE-MRI methods have already investigated the reproducibility in tumors and reported good results.^{2,3} However, a study on the reproducibility of the subtle BBB leakage in non-tumorous tissue is lacking. This study aims to determine the test-retest reproducibility of the BBB leakage measurement in terms of pharmacokinetic measures using dual temporal resolution DCE-MRI in patients with cerebrovascular disease. In addition, potential factors that may influence the reproducibility, such as the vascular input function (VIF), T_1 relaxation rate mapping, and the scan duration are explored.

Materials and Methods

Study Population

The study population had mixed cerebrovascular pathologies to obtain a range in leakage rate values and consisted of patients with cerebrovascular disease ($n = 17$) including patients with cSVD, cortical stroke, or intracerebral hemorrhage. Patients were scanned twice on separate days.

Patients with cSVD ($n = 11$) were defined as 1) those with symptoms of transient stroke attack (TIA)¹² and cSVD-related abnormalities on MRI (i.e. extensive white matter hyperintensities combined with microbleeds and/or lacunes); or 2) those with lacunar stroke, which was defined as an acute stroke syndrome accompanied with a recent small subcortical infarct on brain MRI or using established clinical lacunar stroke criteria.^{13,14}

Patients with cortical stroke ($n = 5$) were defined as those with an acute cortical syndrome (i.e. monoparesis [face, arm, or

leg] or hemiparesis with one or more of the following symptoms: aphasia, neglect, hemianopia, apraxia) and confirmed on brain computed tomography (CT).¹² Patients with intracerebral hemorrhage ($n = 1$) were defined as those with a nontraumatic intracerebral hemorrhage confirmed on brain CT.¹²

To potentially obtain some variation in leakage values, patients were divided into two groups: 1) patients who were scanned within 6 weeks of the event, and 2) patients who were scanned after 8 weeks of the event. Patients who received their first scan within 6 weeks, in whom we expect the leakage value may change quickly, were scanned on subsequent days. Furthermore, it was aimed to scan patients who received their scan 8 weeks after the event, in whom we expect little change in leakage, on subsequent days; if that was not possible, at most 4 weeks was allowed between subsequent scans.

Patients were recruited on either the Transient Ischemic Attack outpatient service or the Stroke Unit of the Department of Neurology of the hospital.

Standard Protocol Approvals, Registrations, and Patient Consent

This study was approved by the Medical Ethical Committee of our institution. All participants were included after written informed consent was obtained.

Imaging Protocol

Brain MRI was performed for all participants on a magnetic resonance system (3T, Achieva TX, Philips Healthcare, Best, the Netherlands) using a 32-element head coil suitable for parallel imaging. For structural imaging a T_1 -weighted sequence (TR/TI/TE = 8.3/800/3.8 msec; field of view [FOV] $256 \times 256 \times 160 \text{ mm}^3$; 1.0 mm^3 cubic voxel) and a T_2 -weighted FLAIR sequence (TR/TI/TE = 4800/1650/299 msec; FOV $250 \times 256 \times 180 \text{ mm}^3$; 1.0 mm^3 cubic voxel) were used.

For dynamic imaging dual temporal resolution DCE-MRI was used, as described by van de Haar et al.⁸ The sequence consisted of two saturation recovery gradient-recalled sequences: 1) the fast sequence, with a short dynamic scan time (DST), (DST 3.2 sec, TR/TE/TD = 5.6/2.5/120 msec, FOV: $256 \times 200 \text{ mm}^2$, acquisition matrix: 128×67 , reconstruction matrix: 256×256 , 10 slices with 5 mm thickness, centric k -space ordering, SENSE factor 2, 29 volumes, scan time 1:33 min), and 2) the slow sequence with a relative longer DST (DST 30.5 sec, TR/TE/TD = 5.6/2.5/120 msec, FOV: $256 \times 256 \text{ mm}^2$, acquisition matrix: 128×128 , reconstruction matrix: 256×256 , 50 slices with 2 mm thickness, centric k -space ordering, SENSE factor 2, 45 volumes, scan time 22:53 min). The sequences were integrated as follows: first, precontrast scans were acquired: 1) three precontrast scans using the slow sequence, followed by 2) nine precontrast with the fast sequence. Then the contrast medium (gadobutrol, 0.1 mmol/kg) was injected in the antecubital vein at a rate of 3 ml/s. Thereafter, postcontrast volumes were acquired: 1) first 20 postcontrast volumes with the fast sequence, then 2) 42 postcontrast volumes using the slow sequence. The sequences did not overlap in time.

T_1 -mapping¹⁵ was performed to convert the contrast-enhanced signal intensity to concentration in tissue and was performed prior to dynamic imaging.

FIGURE 1: Schematic representation of sessions 1 and 2. For sessions 1 and 2, the signal intensity–time curves of both the tissue and vascular input function (VIF) was converted to concentration–time curves using $T_{1,0}$ mapping and a calibration curve obtained from phantoms, respectively. Both concentration–time curves were used in a two-compartment model, where infinite flow and no back flux can be assumed, to calculate the leakage rate (K_i) and blood plasma volume (v_p) by means of the Patlak graphical approach. Reproducibility of the leakage rate and blood plasma volume using the outcome values of session 1 and session 2 was assessed. To study the effect of VIFs and $T_{1,0}$ maps, both were averaged over two sessions and the leakage rate and blood plasma volume were recalculated. Subsequently, the reproducibility was reassessed.

Data Analysis

All dynamic images were registered to the same reference image, which is the average image of the precontrast images obtained with the slow sequence, to correct for head displacements. To calculate the leakage rate and blood plasma volume the Patlak graphical approach¹⁶ was used. This approach considers a two-compartment model where no back flux and infinite flow is assumed, so that the leakage rate approximates the product of vessel permeability (P) and surface area (S), P-S per unit mass of tissue. For the Patlak graphical approach, input from both tissue and the VIF is needed (Fig. 1). Therefore, a $T_{1,0}$ -map was generated,¹⁵ which was used in the linear conversion of small intensity changes in tissue over time to concentrations. Signal intensity changes were also calculated to select voxels, which were enhanced due to the contrast agent. Furthermore, the VIF was calculated by selecting a region of interest (ROI) in the superior sagittal sinus. The sagittal sinus has a sufficiently large cross-section, from which voxels can be selected with minimal partial volume effects. To calculate the concentration over time of the VIF, the relative signal intensity change and a calibration curve obtained with an in vitro concentration series phantom (data not shown) were used. This was necessary since T_1 values in blood could not be calculated accurately due to inflow artifacts. Hereafter, both inputs were used to generate a scatter (Patlak) plot to perform linear regression, where the slope of the regression line represents the leakage rate K_i (min^{-1}) (assuming a tissue density of 1 g/mL) and the intercept the blood plasma volume v_p . Note that the tissue density might not be the same between different regions

(i.e. white and gray matter), but it should not affect the reproducibility evaluation.

K_i and v_p were calculated in a voxelwise manner. Total white matter (WM) (i.e. normal-appearing WM and WM hyperintensities), gray matter (GM) (i.e. cortical and deep GM), and vascular lesions (VLs) (i.e. infarcts or hemorrhage) were chosen as ROIs in the FOV of the fast DCE-MRI scan, which was at the periventricular level. The volume of the total number of analyzed voxels (mean $\pm$ SD) in the WM and GM are $250 \pm 50 \text{ cm}^3$ and $240 \pm 20 \text{ cm}^3$, respectively. The visible VLs ($n = 5$) were manually delineated by an experienced neuroradiologist (>20 years of experience). For patients ($n = 7$) with an acute infarct or hemorrhage, only the contralateral hemisphere was considered for analysis for the WM and GM to avoid acute changes in leakage rate. For these patients, the volume of total number of analyzed voxels (mean $\pm$ SD) in the WM and GM are $130 \pm 30 \text{ cm}^3$ and $130 \pm 20 \text{ cm}^3$, respectively.

The outcome measures per ROI were defined as the mean of the v_p values and the 75th percentile of the K_i values, hereafter referred to as v_p or blood plasma volume and K_i or leakage rate, respectively. The 75th percentile of the K_i values was chosen to avoid a large part of the K_i distribution that is close to zero, which represents noise to some extent (Fig. 2). Thresholding of K_i is assumed to be more representative for the actual leakage rate.⁶

Reproducibility Assessment and Statistical Analysis

K_i and v_p were calculated for two sessions and compared between the sessions to assess the test–retest reproducibility (Fig. 1) by

FIGURE 2: Normalized histograms representing leakage value distributions and corresponding 75th percentiles for one patient in various regions of interest (ROIs): white matter (light gray), gray matter (dark gray), and one vascular lesion (red). For all regions, high fractions can be seen for low K_i values, which are indicative of noise. 75th percentiles were calculated to apply a measure less sensitive to noise. It can be appreciated that the 75th percentiles are indicative of values in the tail of the leakage rate distributions for all three ROIs.

means of a number of different measures¹⁷: 1) The coefficient of variation (CV) measures the relative within-subject variation with respect to the mean. It is defined by the average within-subject population standard deviation (SD_{ws}) averaged over two sessions divided by the overall mean. CV is expressed as a percentage value and low CVs are indicative of good reproducibility. Please note that CV values for certain measures (such as K_i and v_p) become unstable, as the denominator in calculating the CV is very small. 2) The repeatability coefficient (RC) may therefore provide a more suitable measure. The RC was calculated as $1.96 \cdot \sqrt{2} \cdot SD_{ws}$.¹⁸ Differences between two measurements in the same patient are expected to be less than the RC in 95% of the observations.¹⁸ 3) The intra-class correlation coefficient (ICC) was used to evaluate the part of the total variance ascribed to biological variation (SD_{bs}^2) (variation over the average values of both sessions over all patients), rather than test–retest error (SD_{ws}^2), and is defined by $SD_{bs}^2 / (SD_{bs}^2 + SD_{ws}^2)$. Low test–retest error will lead to ICC values towards 1. The following cutoffs were used to evaluate the reproducibility: poor: $ICC < 0.40$; moderate: $0.40 \leq ICC < 0.60$; good: $0.60 \leq ICC < 0.75$; and excellent: $0.75 \leq ICC \leq 1.00$.¹⁹ Furthermore, Bland–Altman plots were depicted to explore any correlation between the magnitude and the differences between sessions of the K_i and v_p .²⁰ In the Bland–Altman plots, limits of agreement are plotted, which are defined as mean differences $\pm 1.96 \cdot \sqrt{2} \cdot SD_{diff}$, where SD_{diff} is the population SD over the differences between the two sessions over all patients. The (Pearson) correlation of the Bland–Altman plot was calculated using robust linear regression.

Influencing Factors of Reproducibility

Three factors potentially contributing to the test–retest reproducibility of the K_i and v_p were studied. Since the concentration time-series from both tissue and blood are required to calculate these measures, variations in both affecting the reproducibility of measuring BBB leakage were investigated. The effect of T_1 -mapping, required for the calculation of tissue concentration, was explored

by calculating a session-averaged $T_{1,0}$ -map, which is the average over the $T_{1,0}$ -maps calculated on two separate days. Furthermore, to investigate the effect of the VIF on the reproducibility, a session-averaged VIF was calculated, which was obtained by taking the average over VIFs calculated on two days. Both session-averaged $T_{1,0}$ -map and VIF were separately applied to recalculate the K_i and v_p for the two sessions. Subsequently, the obtained CV values were compared with the values acquired using individual session-specific $T_{1,0}$ -maps or VIFs.

To accurately measure subtle leakage, a long scan time (≥ 15 min) has been recommended.²¹ However, it is not known yet how the scan duration influences the reproducibility of K_i . Therefore, the reproducibility of K_i for varying scan time was investigated. Data samples at the end of the measurement were omitted to mimic reduction of total scan time.

The effect of decreasing scan time on reproducibility was studied using adjusted CV and RC. The adjusted CV was defined as a CV adjusted for the biased K_i value at shorter scan time by dividing the average SD_{ws} with the mean magnitude of K_i at 25 minutes scan time instead of the magnitude of K_i at a corresponding scan time.²¹ Furthermore, the RC was used since it is independent of the magnitude of the K_i . The differences in RCs obtained with 5 and 25 minutes were tested using a paired t -test.

Results

For this study, 17 patients were scanned. One patient with cortical stroke did not complete both sessions of MRI. This resulted in 16 patients (14 males and 2 females, mean age 66 ± 9 years) who were suitable for analysis. Thirteen patients received their scans on subsequent days. For three patients with cSVD, who received their first scan 8 weeks after the event, the time between subsequent days ranged from 3–8 days.

FIGURE 3: Bland-Altman plot of the leakage rate values in the WM (white circles) and GM (gray lozenges) showing the limit of agreements (mean $\pm 1.96 \cdot \sqrt{2 \cdot SD_{diff}}$) in blue (WM: dashed; GM: straight) and the mean difference between two sessions in red (WM: dashed; GM: straight).

The ranges of K_i ($0.6\text{--}3.6 \cdot 10^{-3} \text{ min}^{-1}$) and v_p ($0.9\text{--}6.1 \cdot 10^{-2}$) values are shown in the Bland-Altman plots (Figs. 3, 4). No correlations between the magnitude and intersession differences were found for the K_i ($r = 0.05$, $P = 0.74$) or v_p ($r = -0.06$, $P = 0.52$).

Tables 1 and 2 show the magnitude values and reproducibility values of K_i and v_p , respectively. For K_i , CVs of $\leq 14.4\%$ in WM and GM, moderate-to-excellent ICCs (WM: 0.77; GM: 0.49), and RCs of $0.4 \times 10^{-3} \text{ min}^{-1}$ (WM) and $0.9 \times 10^{-3} \text{ min}^{-1}$ (GM) were found when using individual VIFs and $T_{1,0}$ -maps. For the v_p , CVs of $\leq 10.9\%$ in WM and GM, moderate ICCs (WM: 0.47; GM: 0.50), and RCs of 0.7×10^{-2} (WM) and 1.4×10^{-2} (GM) were found. Excellent ICC (0.88) and a CV of 25.4% were observed in the VLs (Fig. 5) for somewhat higher K_i ($4.6 \pm 3.1 \cdot 10^{-3} \text{ min}^{-1}$), whereas for v_p ($2.0 \pm 1.0 \cdot 10^{-2}$) the ICC (0.18) was poor and the CV was 28.2%.

Table 2 also shows that using session-averaged VIFs instead of individual VIFs, quite lower CVs were seen for the v_p (5.9%) in both the WM and GM, but not for K_i ($\leq 13.4\%$). Similar CVs were observed for both the K_i and

FIGURE 4: Bland-Altman plot of the blood plasma volume values in the WM (white circles) and GM (gray lozenges) showing the limit of agreements (mean $\pm 1.96 \cdot \sqrt{2 \cdot SD_{diff}}$) in blue (WM: dashed; GM: straight) and the mean difference between two sessions in red (WM: dashed; GM: straight).

TABLE 1. Table K_i and v_p Obtained With Individual VIF and $T_{1,0}$

	Region	Mean(SD) ^a
K_i	WM	1.3 (0.5)
	GM	2.2 (0.7)
	VL	4.6 (3.1)
v_p	WM	2.2 (0.8)
	GM	4.7 (1.3)
	VL	2.0 (1.0)

^aUnits: $\times 10^{-3} \text{ min}^{-1}$ (K_i); $\times 10^{-2}$ (v_p). WM = white matter; GM = gray matter; VL = vascular lesion.

v_p using session-averaged $T_{1,0}$ -maps compared with individual $T_{1,0}$ -maps.

Figure 6 shows that K_i decreases as a function of scan duration. In Figure 7 it can be seen that with increasing scan duration (i.e. 5 to 25 min) the RCs decrease: from $2.7 \cdot 10^{-3}$ to $0.4 \cdot 10^{-3} \text{ min}^{-1}$ ($P < 0.01$) in WM and $4.4 \cdot 10^{-3}$ to $0.9 \cdot 10^{-3} \text{ min}^{-1}$ in GM ($P < 0.01$). The adjusted CV (Fig. 8) shows a similar trend compared with the RC as a function of scan duration: the values decrease from 72.9% to 10.0% in WM and 69.3% to 13.6% in GM.

Discussion

This study explored the test-retest reproducibility of DCE-MRI for measuring subtle BBB leakage in patients with cerebrovascular disease, which is essential for the interpretation of BBB leakage measurements and for future clinical application. The results showed that the CVs for the leakage rate, K_i , were $\leq 14.4\%$ and ICCs were moderate to excellent (0.47–0.77). Longer scan times further reduce the RC of the leakage rate.

The leakage rates observed in this study were in accordance with values found in a previous study in patients with white matter pathology⁶ ($\sim 2.0 \cdot 10^{-3} \text{ min}^{-1}$) and a study in patients with mild cognitive impairment⁷ ($\sim 1.0 \cdot 10^{-3} \text{ min}^{-1}$), despite differences in image acquisition and analysis methods. The fairly low CVs and moderate to excellent ICCs observed in this study indicate that the reproducibility of measuring subtle leakage is moderate to excellent. Furthermore, compared with previous reproducibility studies^{2,3} investigating DCE-MRI in brain tumors (root mean square CVs: 0.08), our CV values (root mean square CVs: 0.14 [WM]; 0.16 [GM] [calculated for comparison]) are slightly higher, but still fairly low despite the fact that measurement of subtle leakage is likely more affected by noise. Possible factors contributing to the signal-to-noise ratio (SNR) are: 1) the lower magnitude of subtle leakage compared with that found in tumors, and 2) the larger ROI, which was

TABLE 2. Reproducibility Values of K_i and v_p With Individual VIF and $T_{1,0}$, Session-Averaged VIF or $T_{1,0}$

	Region	RC ^a	ICC	CV(%)	CV(%)	CV(%)
					Averaged VIF	Averaged $T_{1,0}$
K_i	WM	0.4	0.77	11.6	13.4	12.9
	GM	0.9	0.49	14.4	12.7	15.3
v_p	WM	0.7	0.47	10.9	5.9	10.8
	GM	1.4	0.50	10.2	5.9	9.9

^aUnits: $\times 10^{-3} \text{ min}^{-1}$ (K_i); $\times 10^{-2}$ (v_p). WM = white matter; GM = gray matter; VIF = vascular input function.

purely the tumor in their study, in contrast with the periventricular WM or GM in our study. Moreover, the VLs in our study, which are more comparable in size and leakage rate values with tumors, showed excellent reproducibility according to the high ICC for the leakage rate. The sample size for VL was low ($n = 5$), and more subjects with visible VLs are needed to explore its reproducibility, which is beyond the scope of this study.

The reproducibility of the leakage rate was better for the WM than the GM (lower CV and higher ICC), despite the lower magnitude in the WM. In general, partial volume effects might affect values of the leakage rate and hence increase the test–retest variability. Especially, the cortical GM is more prone to partial volume effects (PVEs) of (pericortical) macrovessels and CSF than the WM.

In our study, observed from the ICCs, somewhat more than half of the test–retest variability can be ascribed to biological variation rather than a test–retest difference for both the leakage rate and blood plasma volume. To explore the nature of the test–retest difference, three factors were explored.

First, variations in the VIF notably affect the blood plasma volume and when reducing these variations, better reproducibility was obtained. This was observed by the

CVs, which were almost twice as small for the blood plasma volume using session-averaged VIFs compared with individual VIFs. On the contrary, it was thought that using individual VIFs would decrease the test–retest variability, since individual VIFs might compensate for physiological variations (e.g. intersession changes induced by kidney function or cardiovascular function in the same patient).²² An explanation for this discrepancy is that less variable and a more representative VIF can be obtained by sampling the VIF more than once. Using the average of two VIFs produces more reproducible blood plasma volume values.

Second, variations in the $T_{1,0}$ -maps hardly affected the test–retest variability of both the leakage rate and blood plasma volume. This can be concluded from the comparable results between session-averaged $T_{1,0}$ -maps and individual $T_{1,0}$ -maps. Further investigation indicated that T_1 -mapping (data not shown) is highly reproducible, which likely explains the small effect it has on the reproducibility of the calculation of both measures.

Third, the effect of the scan duration on the reproducibility of the leakage rate was studied. The RCs and adjusted CVs decreased for longer scan times, implying that scanning longer yields better reproducibility of the leakage rate. A possible explanation is that a longer scan time provides

FIGURE 5: Example of a FLAIR image (A), leakage rate map (B), and blood plasma volume map (C) from a patient with intracerebral hemorrhage. The lesion is marked with a white arrow. Note that white regions in (B,C) originate from the underlying hyperintensities of the FLAIR image (A). For (B,C), the core of the lesion is nonenhanced since here the data were not suitable for analysis, but the rim of the lesion is hyperpermeable on the leakage rate map (B) and shows low blood plasma volumes on the blood plasma volume map (C).

FIGURE 6: The leakage rate in the WM (white) and GM (gray) plotted versus the scan duration. Decreasing leakage rate values are observed for increasing scan durations.

more data samples, a more reliable fit of the Patlak plot, which was also shown by Cramer and Larsson,²¹ and possibly a higher concentration of contrast medium concentration outside the vascular lumen. Although longer scan times might lead to more motion artifacts, in our analysis it seems that the benefits of increased SNR due to more scans outweigh the disadvantages of motion artifacts. Moreover, a long scan time might not be easily achievable in the clinic, but the presented RC values provide information on the minimal change needed for a certain scan time, that can be considered as biological change rather than a test–retest difference.

This study provides values (e.g. CVs and RCs) that might aid in investigating the role of BBB in the pathophysiology of cerebrovascular and neurodegenerative diseases. Abnormalities in the BBB are subtle and can exist even before structural damage (e.g. WM hyperintensities and microbleeds) becomes visible.^{7,8} Therefore, it may be employed as a functional biomarker to study disease progression or treatment response in, for instance, clinical trials. For such studies knowledge of reproducibility is required.

The strengths of our study include the fact that we investigated patients for whom the technique is relevant, rather than subjects without any pathology. This enables the direct application of the new acquired information from

FIGURE 7: Repeatability coefficients (RCs) of the leakage rate plotted versus the scan duration for the WM (white) and GM (gray). Decreasing RCs can be observed with increasing scan durations.

FIGURE 8: Adjusted coefficients of variation (CVs) of the leakage rate plotted versus the scan duration for the WM (white) and GM (gray). Decreasing CVs can be observed with increasing scan durations.

this study to these patients in whom subtle leakage of BBB using DCE-MRI is investigated. More specifically, our findings can be used to interpret results in (future) longitudinal studies. In addition, we included a heterogeneous group of patients with cerebrovascular disease in order to obtain a range in relevant leakage rate values. This provides a more accurate calculation of the ICC. We also explored factors that might have an influence on the reproducibility of the leakage rate and blood plasma volume in this study to enable an efficient study design.

There are also a number of limitations to our study. More accurate reproducibility values can be obtained when scanning would be performed more than two times, which was not done in consideration of patient burden. Furthermore, only a small FOV was scanned instead of the whole brain to enable a high temporal resolution to sample the arrival and initial circulations of the contrast medium. The periventricular level was chosen, as it is the most vulnerable region in these patients.²³ The reproducibility evaluation was not likely influenced by potential changes in the biological status of the patients, as the period between two subsequent scans is very short (typically only 1 day), during which no substantial changes are expected. Moreover, for those who had a lacunar, cortical infarct, or intracerebral hemorrhage, only the contralateral hemisphere was selected for analysis. In addition, a previous study showed that patients with Binswanger disease, which is a progressive form of SVD, did not show significant changes in BBB permeability between baseline and 16.5 months after the baseline.²⁴ Furthermore, the Patlak approach uses a model that assumes an arterial instead of venous input function. For our analysis, the superior sagittal sinus was selected. A venous input function can have a more dispersed and lower peak compared with an arterial input function, which might affect (bias) K_i and v_p .²⁵ However, Ewing et al. validated the use of the sagittal sinus as the arterial input function and pointed out that using the sagittal sinus results in fewer partial volume effects and inflow artifact.²⁶ Moreover, this should not influence the reproducibility evaluation since the

same type of input function is used for both sessions. Lastly, only one metric, the 75th percentile K_i and mean v_p , was calculated to describe the K_i and v_p distribution, respectively. More descriptive metrics (e.g. skewness and kurtosis) can be calculated to further detail the properties and reproducibility of the distribution.

In conclusion, measuring subtle leakage of the BBB using DCE-MRI is moderate-to-excellent reproducible, despite the fact that the method is prone to noise due to the low values of the BBB leakage rate. The reproducibility was found to improve by longer scan times. The reproducibility values of this study may assist future clinical studies investigating BBB leakage using DCE-MRI.

Acknowledgments

Contract grant sponsor: 'Academisch Fonds' of Maastricht University Medical Centre and 'Stichting de Weijerhorst' foundation (to S.M.W.)

The authors thank Harm van de Haar and Frank van Bussel (Radiology and Nuclear Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands) for their participation in experiments supporting the data analysis. We also thank Marc Geerlings and Jos Slenter (Radiology and Nuclear Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands) for their support in hardware and software.

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