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● *Original Contribution*

REPEATABILITY OF BOLUS KINETICS ULTRASOUND PERFUSION IMAGING FOR THE QUANTIFICATION OF CEREBRAL BLOOD FLOW

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Abstract—Ultrasound perfusion imaging (UPI) can be used for the quantification of cerebral perfusion. In a neuro-intensive care setting, repeated measurements are required to evaluate changes in cerebral perfusion and monitor therapy. The aim of this study was to determine the repeatability of UPI in quantification of cerebral perfusion. UPI measurement of cerebral perfusion was performed three times in healthy patients. The coefficients of variation of the three bolus injections were calculated for both time- and volume-derived perfusion parameters in the macro- and microcirculation. The UPI time-dependent parameters had overall the lowest CVs in both the macro- and microcirculation. The volume-related parameters had poorer repeatability, especially in the microcirculation. Both intra-observer variability and inter-observer variability were low. Although UPI is a promising tool for the bedside measurement of cerebral perfusion, improvement of the technique is required before implementation in routine clinical practice. (E-mail: Astrid.Hoedemaekers@radboudumc.nl)

Key Words: **Ultrasound perfusion imaging, Contrast-enhanced ultrasound, Cerebral blood flow, Intensive care, Acute brain injury, Monitoring.**

INTRODUCTION

Ischemia is an important mediator of secondary brain insults in patients with acute brain injury. The main objective of intensive care management is optimization of cerebral perfusion and oxygenation by ensuring adequate blood flow to the brain. Early detection of ischemia and monitoring of therapeutic interventions are important aspects of the treatment of patients at risk for cerebral ischemia.

Ultrasound perfusion imaging (UPI) with microbubble contrast agents is a technique that can be used for quantification of tissue perfusion. Ultrasound is an attractive technique because it can be done at the bedside, is non-invasive and has high temporal resolution. With conventional Doppler ultrasound, the circulation in the larger cerebral blood vessels can be measured. With the use of ultrasound contrast agents, the microcirculation in the brain parenchymal areas can be visualized. So far, UPI has been applied mainly for the qualitative monitoring of the brain parenchyma, for instance, in neuro-oncologic surgery (He et al. 2008; Prada et al. 2014a, 2014b). More recently, a (semi)quantitative approach was developed for patients with neurovascular pathology such as acute stroke (Eyding et al. 2002; Federlein et al. 2000; Holscher et al. 2005; Rim et al. 2001; Seidel and Meairs 2009).

Injection of microbubbles as an intra-venous bolus results in an increase in acoustic intensity when the microbubbles are present in the insonation field. This increasing acoustic intensity over time by the in-wash of microbubbles can be represented by a time–intensity curve (TIC). From this TIC, different parameters can be extracted, including both volume-related parameters such as peak intensity (PI) and time-related parameters such as time-to-peak (TTP). These TIC-derived perfusion parameters correlate with perfusion parameters derived from magnetic resonance imaging (MRI)- and computed tomography (CT)-based perfusion studies (Krogias et al. 2010; Meves et al. 2002; Meyer-Wiethe et al. 2007; Reitmeir et al. 2017).

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The high variability of UPI is the key challenge of this technique. In general, sources of variability in UPI are related to scanner settings, patients and microbubble-related factors (Tang et al. 2011). The presence of the skull may be another complicating factor for quantification of cerebral blood flow. The thickness of the temporal bone window is heterogeneous between patients and within patients, resulting in increased inhomogeneity of the acoustic power distribution with a larger variance in perfusion parameters in the different parts of the brain (Kwon et al. 2006). The extent of the variability in UPI perfusion parameters in the quantification of cerebral perfusion has not been estimated yet.

For measurement of cerebral perfusion in a neurointensive care setting, repeated measurements are required to evaluate changes in cerebral blood flow and monitor therapy. No data are available on the repeatability of UPI for the quantification of cerebral perfusion. The aim of this study was to determine the repeatability of UPI in quantification of cerebral perfusion, compared with transcranial Doppler (TCD). Although no gold standard for the quantification of cerebral blood flow is used in this study, we present UPI and TCD data of repeated measurements within healthy patients.

METHODS

Study

We performed an observational study in 10 healthy volunteers. All participants gave written informed consent before entering the study. The study was approved by the ethics committee of the Radboud University Medical Center (NL 52854.091.15) and was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All measurements were performed by one operator (C.W.E.H.), and all analyses were performed by one analyst (E.J.V.). Interobserver agreement was assessed by another, less experienced, technical physician.

Population

The population consisted of 6 male and 4 female patients, between 18 and 35 y of age. Patients were screened by physical examination and electrocardiography. The main exclusion criteria were known hypersensitivity to the active substance(s) or to any of the excipients in SonoVue (Bracco International, Amsterdam, Netherlands); history, signs or symptoms of cardiovascular, pulmonary or neurologic disease; pregnancy; insufficient temporal bone window; and participation in another clinical trial within 3 mo before the experimental day.

Study protocol

Duplex and UPI measurements were performed on the patients at rest. Patients were placed in the supine position with the head in midline and elevated at 30°. Vital parameters including blood pressure, heart rate and oxygen saturation were monitored continuously. One-sided bilateral insonation was used to insonate both the ipsilateral and contralateral hemispheres.

The measurements consisted of bilateral pulsed wave (PW) Doppler imaging in duplex mode of middle cerebral artery (MCA) blood flow velocity (CBFV) followed by a UPI measurement using the bolus technique. PW Doppler imaging followed by UPI measurement of cerebral perfusion was performed three times. Intervals between examinations in one volunteer were at least 20 min to allow wash-out of the contrast agent.

Ultrasound protocol

A Philips iU22 ultrasound system was used (Philips Ultrasound, Bothell, WA, USA), equipped with a 2.5-MHz phased-array S5-1 probe for all duplex and UPI measurements. For the duplex measurements, the TCD preset was used with an imaging depth of 15 cm. In the contrast mode, a mechanical index of 1.09 with a gain of 76% was used. The imaging depth was also set to 15 cm, with a focus at 7.7 cm (range: 5.3–9.7 cm). The look-up table (LUT) and the automatic gain correction curve were experimentally derived from measurements of tissue phantoms to transform the gray levels into quantitative echo levels (Thijssen et al. 2008).

Ultrasound examinations were performed in contrast mode after manual intra-venous bolus injection of 2.4 mL of a sulfur hexafluoride dispersion (SonoVue), through an 18-gauge venous access into an antecubital vein, immediately followed by a rapid flush of 10 mL normal saline. Injection and data acquisition at a frame rate of 0.5 Hz started after the insonation plane was identified. An insonation plane was chosen by visualizing the MCA and other parts of the Willis circle to allow simultaneous analysis of the flow in the macrocirculation in the main arteries and the microcirculation within the parenchyma.

Data were then transferred to a personal computer and evaluated off-line.

Data analysis

For data analysis of the UPI measurements, in-house software was developed (MATLAB R2012 b; The MathWorks, Natick, MA, USA). The DICOM files were visualized, and the parameter images were calculated. Regions of interest (ROIs) were then selected from which time–intensity curves (TICs) were calculated and bolus curves were fitted (Postert et al. 2000).

One ROI was selected in the ipsilateral MCA at a depth of 4–5 cm (ROI_{MCA}), and three were selected in the parenchyma. One was at the ipsilateral side at a depth of 4 to 5 cm posterior to the ipsilateral MCA region, and one at the contralateral side at a depth of 9–10 cm at the same posterior level. The fourth region of interest was also

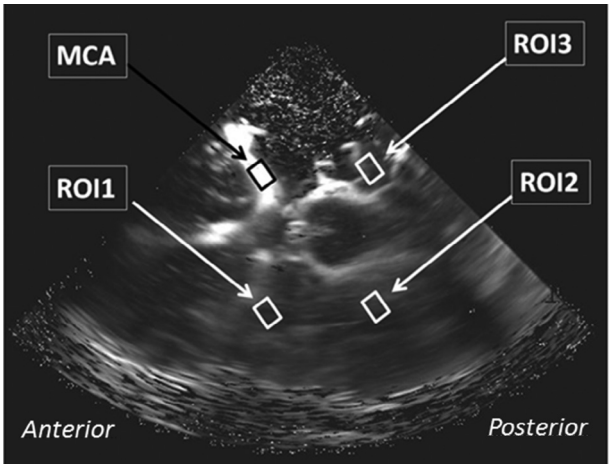

Fig. 1. Overview of the selection of the MCA region and the three parenchyma regions (ROI1, ROI2 and ROI3) for the data analysis, with MCA in the ipsilateral MCA region, ROI1 the anterior contralateral parenchyma region, ROI 2 the posterior contralateral parenchyma region and ROI3 the posterior ipsilateral parenchyma region. MCA = middle cerebral artery; ROI1; ROI2; ROI3 = regions of interest in the cerebral parenchyma.

selected at the contralateral side at a depth of 9–10 cm at the same anterior level as the ROI_{MCA} (Fig. 1). In case of reflections, large arteries, artifacts or poor fits, the position of the ROI was adjusted as close as possible to the original position.

To correct for the baseline ultrasound intensities before the contrast agent was administered, TICs were first normalized by subtraction of the first data point of the TIC, before extraction of perfusion parameters. The perfusion parameters of the bolus curve that were extracted included peak intensity (PI), defined as the maximum amplitude the curve reaches in the first 30 s of the measurement; time to peak intensity (T_{PI}), defined as the time from beginning of data acquisition to PI; and time to peak (TTP), defined as T_{PI} minus the start of the bolus curve. The start of the curve was identified at the time at which >2% of the PI was reached. Peak width (PW) was defined as the time at which the acoustic intensity was ≥90% of the PI. Full width at half of the maximum intensity increase (FWHM) was defined as the time at which the acoustic intensity was ≥50% of the PI. The AUC was calculated by a summation of all the acoustic intensities from the start of the bolus curve.

Curve fitting was performed using the method of least squares (SSE) with the model function as described previously (Eyding et al. 2003).

Statistical analyses

The repeatability of the three bolus injections of the UPI perfusion parameters and duplex measurements was determined by calculation of the coefficient of variation (CV). The CV was calculated as the standard deviation divided by the mean and expressed as a percentage of the mean.

The reliability of the off-line analysis of the bolus injections by one observer (intra-observer variability) was assessed with the intra-class correlation coefficient (ICC), using a two-way mixed model analysis of variance (ANOVA) (Zidan et al. 2015). During off-line analysis, the analyst selected the four ROIs and calculated the perfusion parameters three times, while blinded to previous results. The ICC was calculated as the proportion of variability between the off-line analysis and the total variability (variability between the objects and variability between the methods, with random measurement error variability). ICC values ranging from 0.00 to 0.10 represent virtually no agreement, 0.11–0.40 slight agreement, 0.41–0.60 fair agreement, 0.61–0.80 moderate agreement and 0.81–1.0 substantial agreement (Shrout 1998). Inter-observer agreement was also determined with an ICC between the analyst (E.J.V.) and a less experienced technical physician. Both analysts were blinded to the results of previous calculations.

All data were analyzed using a statistical software package (SPSS Version 22, IBM, Armonk, NY, USA). Results are expressed as median values with interquartile ranges. Differences between regions or perfusion parameters were assessed by calculation of a one-way ANOVA with the Bonferroni multiple comparison test or by a Friedman test with Dunn's test for multiple comparisons, depending on the Gaussian distribution. A p value < 0.05 was considered to indicate statistical significance.

RESULTS

Population and measurements

Ten healthy volunteers were included in the study. No adverse events occurred during the study; bolus injections of the ultrasound contrast agent were well tolerated. The data for the first subject could not be analyzed because of technical issues, mainly related to difficulties in imaging settings. In the remaining 9 patients, the UPI bolus and Duplex measurements could be analyzed. Baseline characteristics of the 9 patients are summarized in Table 1.

Table 1. Baseline characteristics of the patients (n = 9)*

Males	5 (56%)
Age (y)	21.3 ± 2.6
Mean arterial blood pressure (mm Hg)	87.2 ± 8.2
Heart rate (beats/min)	65.8 ± 12.3
Oxygen saturation >95%	9 (100%)
$EtCO_2$ (kPa)	5.4 ± 0.4
Mean CBFV MCA (cm/s)	61.7 ± 6.6

CBFV = cerebral blood flow velocity; $EtCO_2$ = partial pressure of CO_2 at the end of an exhaled breath; MCA = middle cerebral artery.

* Data are expressed as the number (%) or mean ± standard deviation.

Table 2. Coefficients of variation of the perfusion parameters in the different regions*

	Coefficient of variation			
Parameter	MCA	ROI1	ROI2	ROI3
T_{PI} (%)	6.8 [4.1–22.1]	10.4 [5.4–15.1]	8.2 [7.3–12.8]	6.1 [3.2–8.7]
TTP (%)	14.6 [8.5–22.0]	14.3 [10.1–27.3]	27.4 [14.0–35.0]	13.1 [7.1–21.0]
PI (%)	10.4 [3.2–15.4]	59.6 [37.1–62.4]	47.6 [12.7–69.8]	53.7 [32.0–62.8]
AUC (%)	19.5 [4.5–40.0]	61.1 [43.5–84.4]	68.0 [26.8–9033]	60.1 [40.4–80.0]
PW (%)	43.0 [17.1–60.3]	26.2 [6.3–28.2]	26.2 [14.3–34.8]	18.4 [9.6–27.8]
FWHM (%)	19.8 [9.7–36.1]	24.6 [8.5–30.3]	29.5 [18.8–36.5]	15.7 [13.6–32.0]

AUC = area under the curve; FWHF = full width half-maximum; MCA = middle cerebral artery; PW = pulse width; ROI1, ROI2, ROI3 = regions of interest in the cerebral parenchyma; T_{PI} = time to peak intensity; TTP = time to peak.

* Data are expressed as the median [interquartile range].

Repeatability of the three bolus injections

We assessed the repeatability of three different bolus injections under resting conditions using the CV (Table 2, Fig. 2). The CV of the time-related parameter T_{PI} was low for both the MCA and the parenchymal areas (MCA: 6.8% [4.1%–22.1%], ROI1: 10.4% [5.4%–15.1%], ROI2: 8.2 [7.3%–12.8%], and ROI3: 6.1% [3.2%-8.7%]), with no differences in repeatability between the different regions ($p = 0.1080$) (Fig. 2A). The CVs of the other time-related parameter TTP were higher: 14.6% (8.5%–22.0%) in the MCA, 14.3% (10.1%–27.3%) in ROI1, 27.4% (14.0%–35.0%) in ROI2 and 13.1% (7.1%–21.0%) in ROI3, with no significant differences between the regions ($p = 0.1524$) (Fig. 2B).

The volume-related parameter PI had a CV of 10.4% (3.2%–15.4%) in the MCA versus 59.6 (37.1%–62.4%) in ROI1, 47.6% (12.7%–69.8%) in ROI2 and 53.7% (32.0%–62.8%) in ROI3 ($p = 0.0026$) (Fig. 2C). Similarly, the CV of the AUC was 19.5% (4.5%–40.0%) in the MCA, versus 61.1% (43.5%–84.4%) in ROI1, 68.0% (26.8%–90.3%) in ROI2 and 60.1% (40.4%–80.0%) in ROI3 ($p = 0.0124$) (Fig. 2D).

The CV of the combined volume- and time-related parameter PW was 43.0% (17.1%–60.3) in the MCA, 26.2 (6.3%–28.2%) in ROI1, 26.2% (14.3%–34.8%) in ROI2 and 18.4% (9.6%–27.8%) in ROI3, with significant differences between the macro- and the microcirculation ($p = 0.0111$) (Fig. 2E). The FWHM had a CV of 19.8% (9.7%–36.1%) in the MCA compared with 24.6% (8.5%–30.3%), 29.5% (18.8%–35.6%) and 15.7% (13.6%–32.0%] in the three regions of the microcirculation ($p = 0.7002$) (Fig. 2F).

Immediately before each UPI measurement, the CBFV was measured by TCD. The CV of the mean CBFV was 8.0% (5.2%–16.4%), and the CV of the peak systolic velocity was 8.3% (2.2%–12.9%) (Fig. 3).

Changing the shape, position or size of the ROIs did not essentially change the CVs of the different parameters (data not shown).

Intra-observer variability

The reliability of the off-line analysis of the bolus injections by one observer (intra-observer variability) was assessed with the ICC (Table 3). The variability in the selection of ROIs, curve fitting and calculation of perfusion parameters from TICs was assessed. There was substantial agreement for all parameters and regions, except for PW in ROI1 (moderate agreement). The ICC of the TTP was significantly lower in all regions compared with the other perfusion parameters ($p = 0.0064$). There were no significant differences in ICCs between the macro- and microcirculation or between the different parenchymal regions.

Inter-observer variability

The reliability of the off-line analysis of the bolus injections between two analysts was also assessed with the ICC (Table 4). There was substantial agreement for all parameters and regions, except for FWHM in ROI3 (moderate agreement). There were no significant differences in ICCs between the macro- and microcirculation or between the different parenchymal regions.

DISCUSSION

For use in an intensive care setting, the repeatability of a diagnostic device must be high to detect clinically relevant changes in cerebral perfusion and to monitor the effects of therapy. In healthy control patients, the UPI time-dependent parameters T_{PI} and TTP exhibited overall the lowest CVs in both the macro- and microcirculation. The volume-related parameters PI and AUC had poorer repeatability, especially in the microcirculation.

Essential to the acceptance of a new method is determination of what CV is acceptable. In general, a new method is judged against a reference method. No gold standard is available for the measurement of cerebral perfusion in both the micro- and macrocirculation. When this new technique was compared with TCD, the CV of the mean CBFV and peak systolic velocity was approximately 8%. This is in agreement with a previous study that measured a CV of the mean CBFV in the MCA in healthy volunteers of 7%, using 5- to 15-min intervals of continuous data (C.H., unpublished results). A previous method

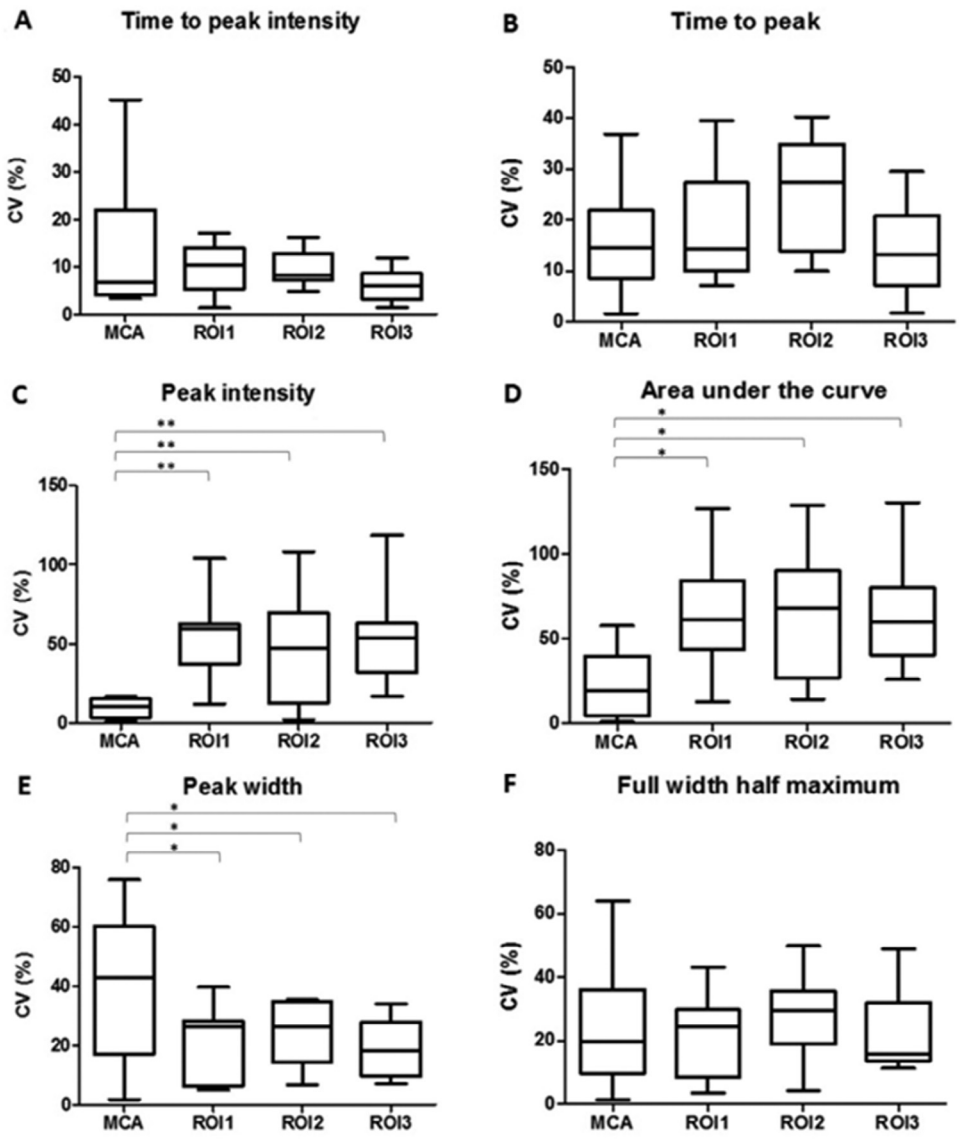

Fig. 2. Repeatability of the perfusion parameters in the different regions of interest, with MCA the macrocirculation region in the MCA and ROI1, ROI2 and ROI3 the three parenchyma regions. *$p < 0.05$. **$p < 0.01$. Data are expressed as medians with interquartile ranges. MCA = middle cerebral artery; ROI1, ROI2, ROI3 = regions of interest in the cerebral parenchyma.

estimated the acceptable agreement between two techniques (Critchley and Critchley 1999). Taking this method into account, acceptable agreement between TCD and a UPI parameter depends on the CV of PW Doppler. For example, when we state that a CV <10% is acceptable in the clinic, the quantified acceptable limit of agreement between the TCD and UPI measurement will result in a CV >10% because of the CV of 7% in duplex measurements. Assuming a CV of around 20%, as obtained for the time-dependent parameters (TPI and TTP), acceptable agreement with TCD would be a combined CV <21%.

The source of the variability in our measurements may be related to the normal physiologic variability of cerebral perfusion or to technical issues. Variation in cerebral perfusion is attributed to adaptive regulation of flow caused by perturbations in perfusion pressure or an intrinsic variation of perfusion *via* cerebral vasomotion (Fujii et al. 1990; Hudetz et al. 1992) or central control mechanisms (Newell et al. 1992; Zernikow et al. 1994). Previously we measured a CV of the CBFV in the MCA in healthy volunteers of 7%, suggesting that a normal variation in flow of 7% is likely, at least for the macrocirculation. Data on variability of flow in the microcirculation in healthy human patients are lacking.

Injection of the contrast bolus may be a major source of variability in our experiments. Although the contrast

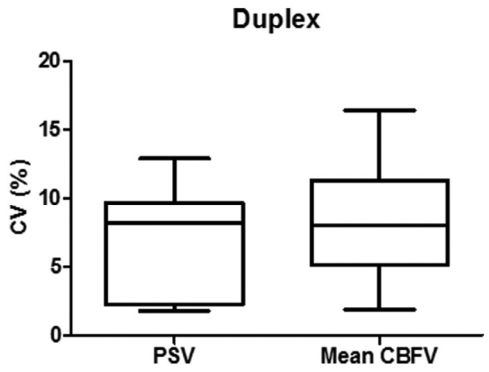

Fig. 3. Coefficient of variation (CV) of the Duplex measurements in the middle cerebral artery. Data are expressed as medians with interquartile ranges. CBFV = cerebral blood flow velocity; PSV = peak systolic velocity.

agent was prepared as instructed by the manufacturer, small differences in volume, sedimentation of the microbubbles in tubes and syringes and minor differences in injection speed and localization of the cannula strongly influenced bolus curve imaging. This is supported by the fact that the CVs of volume-dependent parameters such as PI and AUC were higher compared with those of T_{PI} and TTP, which are mainly time dependent.

Other factors may also account for variability in the measurements. The acoustic intensity in the MCA was higher than that in the parenchymal regions. We used a relatively large dose of contrast agent, which may result in a non-linear relationship between the concentration of microbubbles and signal intensity, especially in the MCA (Stride and Saffari 2005). High concentration of contrast can also reduce the signal intensity deeper in the brain, at longer distances from the probe (shadowing effect) (Seidel et al. 2001). Although we applied a correction for the automatic gain correction curve and the non-linear LUT, this correction cannot correct for the shadowing induced by high concentrations of contrast agent. Standardization of the image depth and titration of dose and optimization of the type and concentration of microbubbles may enhance the signal-to-noise ratio of the signal.

The heterogeneous thickness of the temporal bone window results in increased inhomogeneity of the acoustic power distribution with a larger variance in perfusion parameters in the different parts of the brain (Kwon et al. 2006). In addition, the imaging plane for visualization of the MCA in our experiments was in close proximity to the skull base, possibly causing additional artifacts and signal inhomogeneity compared with the more frequently used mesencephalic and diencephalic planes (Berg et al. 2008).

Variability may also arise from post-imaging analysis factors, including localization and size of the ROIs, calculation of the TIC and fitting of the bolus curves. Because the ICCs for intra- and inter-observer variability were high, construction of the TICs and calculation of perfusion parameters do not seem to contribute significantly to the variability.

T_{PI} was the most reliable parameter in this study, with a low CV. Comparison of T_{PI} with MRI perfusion parameters in different regions of the brain (relative to values of the anterior thalamus as a reference) indicated that this is a robust and reliable parameter for the quantification of cerebral blood flow in healthy volunteers (Meves et al. 2002) and, most recently, acute stroke patients (Reitmeir et al. 2017). This suggests that T_{PI} may be a promising parameter for the quantification of cerebral perfusion.

A number of adaptations are likely to improve the variability of UPI. Parameters related to acoustic intensity display relatively high variability compared to time-related parameters, most likely due to the unpredictable heterogeneity of the temporal bone which has to be penetrated. Parameters related to time are much more stable and reproducible. If they can be related to an intra-individual "normal value" as, for example, performed in the bilateral approach to the assessment of critically hypoperfused penumbral tissue in acute stroke patients, these parameters even have been proved to semi-quantitatively display perfusion deficits (Reitmeir et al. 2017). Automatic instead of manual bolus injection and improved stabilization of the microbubble suspension are expected to improve the repeatability of this technique to a large extent. Simultaneous ultrasound imaging of the internal carotid artery may serve as a reference point for intracranial bolus curve imaging (instead of time after injection

Table 3. Intra-observer variability

ICC	MCA	ROI1	ROI2	ROI3
PI	0.983	0.983	0.948	0.966
AUC	0.924	0.998	0.937	0.975
TPI	0.924	0.952	0.979	0.990
TTP	0.859	0.840	0.863	0.923
PW	0.838	0.711	0.936	0.951
FWHM	0.922	0.936	0.927	0.949

AUC = area under the curve; FWHF = full width half-maximum; ICC = intra-class correlation coefficient; PW = pulse width; ROI1, ROI2, ROI3 = regions of interest in the cerebral parenchyma; TTP = time to peak.

Table 4. Inter-observer variability

ICC	MCA	ROI1	ROI2	ROI3
PI	0.993	0.980	0.978	0.982
AUC	0.989	0.975	0.981	0.965
T_{PI}	0.980	0.993	0.987	0.981
TTP	0.954	0.965	0.871	0.952
PW	0.946	0.925	0.960	0.975
FWHM	0.992	0.881	0.965	0.786

AUC = area under the curve; FWHF = full width half-maximum; ICC = intra-class correlation coefficient; MCA = middle cerebral artery; PW = pulse width; ROI1, ROI2, ROI3 = regions of interest in the cerebral parenchyma; T_{PI} = time to peak intensity; TTP = time to peak.

of the bolus). Use of a headframe may facilitate repeated measurements in a single patient. A headband could also facilitate the use of a second transducer on the opposite side of the skull for contralateral data acquisition. Technical adaptations of the applied ultrasound beam may help to improve the quality of the signal that is received to be analyzed. Pulse inversion harmonic imaging techniques and other specific frequency filtering approaches may improve image quality. The effects of these adaptations on the repeatability of UPI need to be assessed.

The two major limitations of the study are the lack of a gold standard for the quantification of cerebral perfusion and the relatively small number of patients. In addition, the time between subsequent measurements was at least 20 min to ensure wash-out of the ultrasound contrast agent. Although vital parameters remained unchanged and patients were kept comfortably in the supine position, changes in cerebral perfusion pressure may have occurred, resulting in a change in cerebrovascular resistance and cerebral perfusion. TCD was chosen as a reference method because of its non-invasiveness and ease of use. With this technique, flow in the microcirculation was undetectable and could not be compared with UPI, and spontaneous variations in the parenchyma remained undetected.

CONCLUSIONS

Ultrasound perfusion imaging is a promising tool for the bedside measurement of cerebral perfusion. Time-related parameters have less variability compared with volume-related parameters. Adjustment of a number of factors, especially those related to injection of the contrast bolus, will likely reduce the variability of the results. Comparison with a currently accepted technique for flow measurement is needed before introduction of this technique into routine patient care.

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