Ultrasound in Med. & Biol., Vol. ■■, No. ■■, pp. ■■–■■, 2017

0301-5629/$ - see front matter

https://doi.org/10.1016/j.ultrasmedbio.2017.08.1880

● *Original Contribution*

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

Eline J. Vinke,* Jens Eyding,† Chris L. de Korte,‡ Cornelis H. Slump,§ Johannes G. van der Hoeven,* and Cornelia W. E. Hoedemaekers*

* Department of Intensive Care, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; † Department of Neurology, Sana-Klinikum Remscheid and Universityhospital Knappschaftskrankenhaus, Ruhr University, Bochum, Germany; ‡ Department of Radiology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; and § MIRA Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, The Netherlands

(*Received* 21 *June* 2017; *revised* 14 *August* 2017; *in final form* 20 *August* 2017)

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).

Address correspondence to: Cornelia W. E. Hoedemaekers, Department of Intensive Care, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB Nijmegen, The Netherlands. E-mail: Astrid.Hoedemaekers@radboudumc.nl

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