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● *Review*

POTENTIAL OF CONTRAST-ENHANCED ULTRASOUND AS A BEDSIDE MONITORING TECHNIQUE IN CEREBRAL PERFUSION: A SYSTEMATIC REVIEW

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Abstract—Contrast-enhanced ultrasound (CEUS) has been suggested as a new method to measure cerebral perfusion in patients with acute brain injury. In this systematic review, the tolerability, repeatability, reproducibility and accuracy of different CEUS techniques for the quantification of cerebral perfusion were assessed. We selected studies published between January 1994 and March 2017 using CEUS to measure cerebral perfusion. We included 43 studies (bolus kinetics n = 31, refill kinetics n = 6, depletion kinetics n = 6) with a total of 861 patients. Tolerability was reported in 28 studies describing 12 patients with mild and transient side effects. Repeatability was assessed in 3 studies, reproducibility in 2 studies and accuracy in 19 studies. Repeatability was high for experienced sonographers and significantly lower for less experienced sonographers. Reproducibility of CEUS was not clear. The sensitivity and specificity of CEUS for the detection of cerebral ischemia ranged from 75% to 96% and from 60% to 100%. Limited data on repeatability, reproducibility and accuracy may suggest that this technique could be feasible for use in acute brain injury patients. (E-mail: Astrid.Hoedemaekers@Radboudumc.nl)

Key Words: **Contrast-enhanced ultrasound, Cerebral blood flow, Acute brain injury, Ischemia, Perfusion.**

INTRODUCTION

An adequate supply of blood containing oxygen and nutrients is crucial for the recovery and survival of brain tissue. Monitoring of cerebral perfusion is essential in prevention of secondary brain damage in patients with acute brain injury. The severity of the brain injury frequently obscures clinical changes and limits the reliability of clinical neurologic examination. Direct monitoring of the cerebral perfusion enables the detection of changes in brain perfusion at a stage before irreversible damage has occurred. In addition, the effects of therapeutic interventions can be monitored to evaluate and adjust therapy (Dagal and Lam 2011).

Contrast-enhanced ultrasound (CEUS) has been suggested as a new method to measure cerebral perfusion in patients both with acute brain injury at the ICU and in the acute state of cerebral ischemia. Ultrasound is an attractive technique because it is non-invasive, has high temporal resolution and can be used at the bedside. Ultrasound contrast agents (UCAs) are used for visualization of the cerebral vasculature to overcome the restricted level of acoustic intensity caused by the physical obstacles of the skull and leading to a limited signal-to-noise ratio. For CEUS, three different approaches can be used to measure cerebral perfusion (Meairs and Kern 2015). These approaches are based on bolus, refill (replenishment) and depletion kinetics. After a bolus injection, microbubbles enter the insonation field, and the acoustic intensity in this plane increases. The amount of non-linear scattering or microbubble concentration can be represented by a time–intensity curve (TIC). Different parameters of the TIC can be extracted for quantification of parenchymal perfusion. Refill kinetics are based on the reappearance of UCA after complete destruction of the microbubbles. By destroying the contrast agent within the scanning plane using high-mechanical-index (MI)

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flashes, an absence of contrast is created locally, and new microbubbles enter the plane. Depletion kinetics are based on the destruction of contrast agent at a constant frame rate with a high MI. The perfusion status is analyzed by destruction curves and the difference in acoustic intensity before and after the destruction of UCA (Seidel and Meyer-Wiethe 2007).

Several CEUS methods have been used to monitor cerebral perfusion in acute brain injury. Main differences between the methods are differences in kinetics used and differences in contrast imaging modes. The aim of this systematic review was to assess the tolerability, repeatability, reproducibility and accuracy of the different CEUS techniques for the quantification of cerebral perfusion.

METHODS

We performed a systematic review in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al. 2000).

Search strategy and study selection

An online literature search was conducted by E.J.V. and A.J.K. on 1 March 2017 using the electronic database Medline *via* PubMed. The search terms included are listed in Table 1. To be included, studies had to involve human adults, had to report original data published in English between 1994 and 2017 and had to have used transcranial CEUS to measure cerebral perfusion or related parameters. CEUS studies merely reporting blood flow velocities in the cerebral arteries, characterization and visualization of tumors, visualization and characterization of vasculature (*e.g.,* aneurysms) and determination of stenotic or occluded arteries were excluded. Only studies reporting semiquantitative or quantitative CEUS parameters were included. Reviews and general discussion papers not reporting original data were excluded. For all studies cited, informed consent had been obtained from each study participant, and the protocol had been approval by an ethics committee or institutional review board.

Manual selection was performed by selecting relevant references from the reference list of included articles. Two reviewers (E.J.V. and A.J.K.) checked the titles and abstracts identified by the search strategy and examined any publication that potentially met the inclusion criteria. Final inclusion/exclusion decisions were made after independent duplicate examination of the full articles of selected references.

Table 1. Search terms

	AND	
OR	Cerebral blood flow	Contrast-enhanced ultrasound
	Cerebral circulation	Contrast enhanced ultrasound
	Brain perfusion	Contrast-enhanced ultrasonography
		Contrast enhanced ultrasonography
		Contrast ultrasound
		Ultrasound perfusion imaging
		Ultrasound contrast agent
		Ultrasound contrast agents

Outcome measures

To compare tolerability, repeatability, reproducibility and accuracy of the different ultrasound techniques, the studies were categorized according to the underlying kinetic principles used: bolus kinetics, refill kinetics and depletion kinetics. For each category, the execution and data analysis characteristics were compared. Execution characteristics included operator, study population, UCA type, UCA dosage, duration of measurement and insonation approach. Data analysis characteristics, including reference method, ultrasound method, acquisition time, temporal and spatial resolution and outcome parameters, were recorded.

Tolerability was assessed by registration of side effects of both the UCA and application of high mechanical indexes (>1.0). Repeatability was defined as the variation in repeat measurements in the same subject by the same operator under identical conditions (Bartlett and Frost 2008). Reproducibility referred to the variation in measurements in the same subject under changing conditions (mainly inter-operator agreement). The accuracy of CEUS was assessed by comparison of this technique with a gold standard.

RESULTS

Study characteristics and population characteristics

We identified 407 publications in our primary search and added 9 articles by review of references. After exclusion of 373 publications, 43 publications were eligible for review. Main reasons for exclusion were subject, lack of perfusion parameters, measurement of flow velocity, stenosis/occlusion characterization, visualization or characterization of cerebral arteries or tumor or the fact that the CEUS measurements were not performed transcranially (Fig. 1).

The 43 studies were categorized into studies using the bolus kinetics (n = 31), refill kinetics (n = 6) and depletion kinetics methods (n = 6) (Table 2). A total of 861 patients were included (395 healthy control patients and 466 patients). In 309 (78.2%) healthy control patients, bolus kinetics was used; in 26 (7.0%) patients, refill kinetics; and in 60 (15.2%) patients, depletion kinetics. Most patients were studied after ischemic stroke.

Most studies assessed the diagnostic potential of the technique (23/43), mostly by comparing the technique directly with computed tomography (CT) or magnetic resonance imaging (MRI) (15/43). Other studies assessed feasibility of the technique in the healthy brain