

● *Original Contribution***ASSESSMENT OF CEREBRAL AUTOREGULATION WITH TRANSCRANIAL DOPPLER SONOGRAPHY IN POOR BONE WINDOWS USING CONSTANT INFUSION OF AN ULTRASOUND CONTRAST AGENT**

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Abstract—Cerebral autoregulation is an important pathophysiological and prognostic parameter for a variety of neurologic conditions. It can be assessed quickly and safely using transcranial Doppler sonography (TCD). In elderly patients, poor insonation conditions decrease the number of examinable patients and can cause a systematic bias in autoregulation parameters. The aim of this study was to investigate whether a constant infusion of an ultrasound contrast agent (Levovist[®]) can counteract these effects. We examined two cohorts of unselected neurologic patients. In 45 patients with good insonation windows (cohort 1), we used a thin aluminium foil between the skin and the TCD probe to artificially decrease the insonation quality. We determined two parameters of cerebral autoregulation (phase difference [PD] and a cross-correlation coefficient [Mx]) in native patients, with aluminium foil and with aluminium foil and a constant infusion of Levovist[®]. In 30 patients with poor insonation windows (cohort 2), we measured the autoregulation twice, with and without an infusion of Levovist[®], to assess the reproducibility of the autoregulation parameters. In cohort 1, the foil model significantly decreased the Doppler signal quality, *i.e.*, the mean spectrum energy decreased from 33.9 ± 2.7 dB to 26.3 ± 2.4 dB ($p < 0.001$). This introduced a significant bias to all autoregulation parameters (PD: decreased from $38.2 \pm 10.0^\circ$ to $27.9 \pm 12.5^\circ$ ($p < 0.001$); Mx: decreased from 0.308 ± 0.170 to 0.254 ± 0.162 ($p < 0.01$)). Both effects were compensated largely by a constant infusion of Levovist[®] (300 mg/min). In cohort 2, infusion of the contrast agent at the same rate increased insonation quality, too, but to a lesser degree (27.4 ± 2.4 dB to 32.0 ± 3.7 dB, $p < 0.001$). This smaller increase did not cause a significant change in the autoregulation parameters, but the reproducibility of the PD was significantly improved (intraclass coefficient [ICC] 0.76, 95% confidence interval [0.59–0.87] in native poor bone window compared with ICC 0.90, 95% confidence interval [0.81–0.95] with infusion of the contrast agent). Our data show that constant infusion of an ultrasound contrast agent during the assessment of cerebral autoregulation can avoid potential bias introduced by poor insonation conditions. Furthermore, infusion of the contrast agent can improve reproducibility and contribute to the credibility of autoregulation assessment in the elderly. (E-mail: matthias.lorenz@em.uni-frankfurt.de) © 2008 World Federation for Ultrasound in Medicine & Biology.

Key Words: Transcranial Doppler sonography, Intracerebral arteries, Cerebral autoregulation, Temporal bone window, Ultrasound contrast agent.

INTRODUCTION

Cerebral autoregulation has high physiological and pathophysiological importance in many neurologic conditions. Impaired cerebral autoregulation has been shown in subarachnoid hemorrhage, cerebral ischemia, extra- and intracranial stenoses, hypertensive encephalopathy

and eclampsia (Haubrich 2003, 2004a, 2004b, 2005; Immink 2004, 2005; Lang 2001; Oehm 2003; Reinhard 2001, 2003a, 2003c; White and Markus 1997). A quick and noninvasive assessment of cerebral autoregulation can be performed with transcranial Doppler sonography (TCD). In elderly patient cohorts, the quality of the TCD signal is frequently impaired because of poor insonation conditions (Jarquin-Valdivia 2004; Marinoni 1997). Recently we have shown that cerebral autoregulation can be considerably biased by poor insonation conditions such as those observed in a poor bone window (Lorenz 2007). One possible reso-

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lution could be using a constant infusion of an ultrasound contrast agent to improve the TCD signal quality (Albrecht 1998). This approach has been shown to be effective for cerebral vasoreactivity (Rohrberg and Brodhun 2001).

The aim of the present study was to examine whether the continuous application of an ultrasound contrast agent was a feasible and effective way to counteract the changes in autoregulation parameters induced by a poor bone window.

MATERIALS AND METHODS

We studied two cohorts of patients. The first cohort was comprised of 45 consecutive patients with good insonation conditions that were examined in the cerebrovascular ultrasound laboratory of our clinic. A second cohort consisting of 30 consecutive patients with poor insonation conditions (class 2 according to Jarquin-Valdivia 2004) were also identified after routine cerebrovascular ultrasound. The exclusion criteria for both cohorts were as follows: known galactosemia, severe heart failure (NYHA III or IV), a history of myocardial infarction within the last six months, severe obstructive pulmonary disease or any other condition that interferes with the implementation of the study or may be a risk to the patient (*e.g.*, psychiatric conditions), impaired legal capacity, pregnancy, missing contraception in fertile women, lactation and participation in another clinical study. Patients from both cohorts gave written informed consent before the study started.

In cohort 1, we adjusted two 2-MHz transcranial Doppler probes (DWL[®] probe, DWL[®] Multidop L2; supplied by DWL, Sipplingen, Germany) to bilaterally insonate the median cerebral artery. To record a real-time arterial blood pressure (ABP) signal we used a Portapres[®] oscillometric device (TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands) on the right middle finger. We recorded the signals for 10 min while the patients rested in supine position. For a second recording we asked the patients to follow a breathing command with six cycles per minute, for a three-minute period. We then placed aluminium foil (10- μ m thick) between the probe and the skin on each side. Ultrasound gel was applied to both sides of the aluminium foils before insertion to ensure acoustic coupling. We then repeated the measurement protocol. A third identical measurement followed after a constant intravenous (IV) infusion of an ultrasound contrast agent (Levovist[®], Bayer Schering Pharma [formerly Schering], Berlin, Germany) was started. The infusion was assured by a high-speed infusion pump (Asena[®] GH, Alaris Medical Systems, Dublin, OH, USA) at a speed of 144 mL/min during the infusion of Levovist[®] (5g dissolved in 40 mL of 0.9% sodium chloride; final dose of 300 mg/min). Once the infusion had started, we waited for one minute before recording the measurements to attain a steady-state concen-

tration of Levovist[®]. The signal spectrum was stored before the start of every protocol.

In cohort 2, we assessed cerebral autoregulation for 10 min during rest and for three minutes with breathing commands. This assessment was repeated unchanged after a few minutes rest. Then the infusion of Levovist[®] (10g at 300 mg/min) was started and, after a steady-state concentration was attained, the autoregulation protocol was repeated twice. The study protocol for both cohorts is illustrated in Fig. 1.

During each recording in every patient, the settings of the ultrasound machine were held constant at the following values: 205-mW transmitter power, a TIC index of 3.5, an insonation depth of 50 mm and a 10-mm probe volume. These settings ensure the maximal signal quality and correspond to a signal energy of 570 mW/cm². The ultrasound spectra and the arterial blood pressure signal were stored digitally for subsequent off-line analysis.

Calculation of ultrasound parameters

With a MATLAB program (The MathWorks Inc., Natick, MA, USA) written by the first author, we calculated the average systolic, diastolic and mean blood flow velocities, and Gosling's (Gosling and King 1974) pulsatility index (PI) for every measurement.

Calculation of the phase shift in a transfer function analysis

This method has been described elsewhere in detail (Diehl 1998; Reinhard 2003b; Zhang 1998). Briefly, we performed a cross-spectral analysis over intervals of 10 min (during rest) or three minutes (breathing commands). The averaged phase angle shifts in degrees (phase difference [PD]) between the cerebral blood flow velocities (CBFV) and the ABP within the M-band (frequency range of 3–9/min or 0.05–0.15 Hz) were used as the resulting parameters for assessing autoregulation (Diehl 1998). The breathing commands with six cycles per minute produce a variation of the intrathoracic pressure and, therefore, the arterial blood pressure, within the M-band. This ensures a measurable amplitude of the signals, instead of relying on spontaneous blood pressure variations. Higher PD values represent better autoregulation. The calculations were made with a proprietary software tool (Domolyse V1.5, written by Thomas Jaeschke). The formulas used by the software tool are published by Diehl et al. (1996, 1998).

Calculation of the autoregulatory index, Mx

This method has been described previously (Czosnyka 1996; Piechnik 1999; Reinhard 2003a). The mean CBFV and ABP values were averaged over intervals of three seconds. We calculated Pearson's correlation coefficients between the CBFV and the ABP for 20 small intervals in a one-minute time period. The resulting coefficients were

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