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Effects of poor bone window on the assessment of cerebral autoregulation with transcranial Doppler sonography – A source of systematic bias and strategies to avoid it

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ABSTRACT

Background: The consequences of poor insonation conditions on autoregulation parameters assessed with transcranial Doppler (TCD) are unclear.
Methods: We present two new complementary methods to assess the quality of a TCD signal. Inserting a thin aluminium foil between TCD probe and skin makes a simple model to artificially worsen a good insonation window. Validation studies are presented. We assessed insonation quality and cerebral autoregulation parameters with transfer function analysis and cross correlation in 46 healthy volunteers with and without the aluminium foil model. The same studies were operated on 45 patients with good insonation windows, naïve, after worsening the bone window and during constant infusion of an ultrasound contrast agent. For studying reproducibility, we assessed autoregulation twice in 30 patients with poor bone windows, with and without constant contrast infusion.
Results: Both methods to measure insonation quality are valid and reproducible. The aluminium foil model realistically simulates a natural poor bone window, reducing the signal quality (e.g. energy of the signal spectrum from 33.4 ± 3.5 to 26.2 ± 2.5 dB, $p<0.001$). Thereby, the autoregulation parameters are systematically biased (e.g. phase difference from $37.3 \pm 10.1°$ to $25.9 \pm 15.1°$, $p<0.001$); while with the use of an ultrasound contrast agent this can be largely compensated (phase difference $35.7 \pm 10.7°$, $p<0.001$). The reproducibility is significantly improved (ICC from 0.76 to 0.90, $p<0.05$).
Conclusions: Poor bone windows can cause considerable bias in TCD autoregulation parameters. This bias might be avoided by the use of ultrasound contrast agents, which may greatly improve the credibility of TCD autoregulation assessment in elderly patients.

1. Introduction

In many neurological conditions, cerebral autoregulation has pathophysiological implications or can give prognostic information [1–12]. Transcranial Doppler ultrasound (TCD) is an excellent method to assess cerebral autoregulation, as TCD combines high time-resolution with non-invasiveness and high availability at low costs. Multiple TCD protocols have been developed to assess cerebral autoregulation [e.g. 13–18]. Unfortunately, TCD assessment of autoregulation is dependent on high insonation quality, compared to most vasoreactivity tests. The fact that most patients with e.g. vascular dementia and a high proportion of stroke patients are elderly and age is a condition associated with poor ultrasound bone windows makes TCD autoregulation studies of these patient cohorts difficult. This is reflected in the fact that there are much more TCD vasoreactivity studies in vascular dementia or age-dependent white matter lesions [19–26] than studies using autoregulation [27], while autoregulation is considered of higher pathophysiological importance [28].

To illuminate the consequences of poor bone windows in TCD autoregulation studies, we need objective and fine scaled measuring techniques of insonation quality that have not been developed yet; the only tool we are aware of is a simple 3-step classification system introduced by Jarquin-Valdivia [29]: he defined class 1 as good TCD study, class 2 when only a partial study is possible, and class 3 as an impossible ultrasonic window. Moreover, an experimental model to simulate poor insonation conditions is lacking.

With this paper, we introduce two new complementary measuring methods of insonation quality, and a simple model of a poor bone window, and provide validation studies. With this instrumentarium,

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we studied one cohort of probands and two cohorts of patients to answer the following questions:

- Does a poor bone window influence the assessment of autoregulation parameters?
- If so, are these effects reproducible and clinically relevant?
- How can this influence eventually be eliminated?

We investigated two approaches to neutralize poor bone window effects. One is to model the biasing effects as a function of the insonation quality, and to develop a correction formula. The other is to use a constant infusion of an ultrasound contrast agent during the TCD recording. Both approaches are validated and valuated in this paper.

2. Methods

We studied one cohort of probands and two cohorts of patients. The first cohort was comprised of 46 healthy volunteers. Second, we examined 45 consecutive patients with good insonation conditions (class 1 according to Jarquin-Valdivia [29]) that were identified in the cerebrovascular ultrasound laboratory of our clinic. The third cohort comprised of 30 consecutive patients with poor insonation conditions (class 2 according to Jarquin-Valdivia [29]) who were screened during routine cerebrovascular ultrasound, too. The exclusion criteria for the patient cohorts were heart failure NYHA III or IV, history of myocardial infarction (within the last six months), severe obstructive pulmonary disease, known galactosemia, pregnancy, missing contraception in fertile women and lactation; exclusion criteria for all cohorts were any condition that may interfere with the study participation, like psychiatric conditions, impaired legal capacity and participation in another clinical study. All probands and patients gave written informed consent.

2.1. TCD recordings

In all cohorts, we measured cerebral autoregulation with three protocols. We therefore adjusted two 2 MHz transcranial Doppler probes (DWL® probe, Lam fixation, DWL® Multidop L2; all from DWL, Sipplingen, Germany) to insonate the middle cerebral artery (MCA) at a depth of 50 mm bilaterally. 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. After 10 min of supine rest, we recorded the Doppler and ABP signals for 10 min during rest. For a second recording, we asked the participants to follow a breathing command at a rate of six cycles per minute for 3 min.

2.2. Calculation of ultrasound parameters

These recordings were digitally recorded for later offline analysis. With a MATLAB® program (The MathWorks Inc., Natick, Massachusetts, USA) written by the first author, we calculated the average systolic and diastolic blood flow velocities for every measurement.

2.3. Calculation of autoregulation parameters

From both recordings (10 min at rest and 3 min following breathing commands) we calculated the phase shift between cerebral blood flow velocity (CBFV) and arterial blood pressure (ABP) in a transfer function analysis, as described elsewhere [15,16,18]. The resulting phase difference (PD) is a measure for autoregulation, where higher PD values represent better autoregulation. In the following, PD means PD in rest and PD during breathing commands is abbreviated 'PD bc'. We used the M-frequency band (0.05–0.15 Hz), the calculations were done with a proprietary software tool based on fast Fourier transformation (Domolyse V1.5, written by Thomas Jaeschke). The formulas used by the software tool are published by Diehl et al. [15,30].

From the first recording (10 min at rest), we additionally calculated another autoregulation index (Mx), as described by other authors [5,31,32]. The resulting index Mx represents basically Pearson's correlation coefficient between mean CBFV and mean ABP values. Higher values of Mx represent poorer autoregulation. The calculations were carried out using a program written by the first author in MATLAB®.

2.4. Measuring insonation quality

To assess an objective measure of the energy loss of the ultrasound signal on its way from the emitting ultrasound probe to the insonated vessel and back to the receiving probe, we calculated the power of the received ultrasound signal from the stored spectra. We kept all ultrasound emitter settings constant in all recordings (205 mW transmitter power, a TIC index of 3.5, and a 10 mm probe volume, corresponding to a signal energy of 570 mW/cm^2). We used a graphic output of the spectra stored by the monitoring software, where the power at every point of the spectrum is colour-coded. The graphic output was exported as a screenshot and opened with a MATLAB® program (written by the first author). The colour of every pixel along the spectrum was then converted back into power values in decibels (dB). The spectrum as a "region of interest" was defined manually via a graphic input routine. The program calculates the average power of the spectrum, after delogarithmizing the dB values into linear values. Since determining the region of interest includes a subjective factor, we calculated the inter-rater reproducibility of the analysis. We achieved an ICC 0.99 with a 95% confidence interval [0.98–0.99].

As a second measure of insonation quality, we assessed the effect of the power loss on the envelope algorithm of the monitoring software (MF monitoring software, Version 8.27c, DWL, Sipplingen, Germany). With decreasing signal quality, the algorithm starts to fail, producing artefacts with 'dips' of artificially low envelope values. To objectively assess the frequency of failures, we used a proprietary software tool (TCDQ V1.9, written by Stephan Theiss). The TCDQ outlier detection algorithm searches for narrow dips in the TCD envelope (<50 ms). The software counts the frequency of failures and calculates their average number per 10 s for every single measurement.

2.5. Aluminium foil model to simulate poor bone windows

As a simple model of a poor bone window, that can be easily introduced or removed, we placed a piece of 10 µm thick aluminium foil between the TCD probe and the skin of the proband or patient. Before insertion, ultrasound gel was applied to both sides of the aluminium foil to ensure acoustic coupling. The properties of this model and its effects on insonation quality was examined with the proband cohort and the good bone window patients, and compared to 'real' poor bone window patients.

2.6. Improving insonation quality with a constant infusion of Levovist®

In both patient cohorts (protocol see below) we attempted to improve the insonation quality by a constant infusion of an ultrasound contrast agent (Levovist®, Bayer Schering Pharma, formerly Schering, Berlin, Germany). The infusion was assured by a high-speed infusion pump (Asena® GH, Alaris Medical Systems, Dublin, Ohio, USA) at a speed of 144 ml/h, of 5 g Levovist® dissolved in 40 ml of 0.9% sodium chloride (equivalent to 300 mg/min). Once the infusion had started, we waited for 1 min before recording the measurements, to attain a steady-state concentration of Levovist®. One dosage of 5 g Levovist® sufficed for 16 min, in the second patient cohort (see below), two dosages were used per patient.