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A new method for correcting middle cerebral artery flow velocity for age by calculating Z-scores

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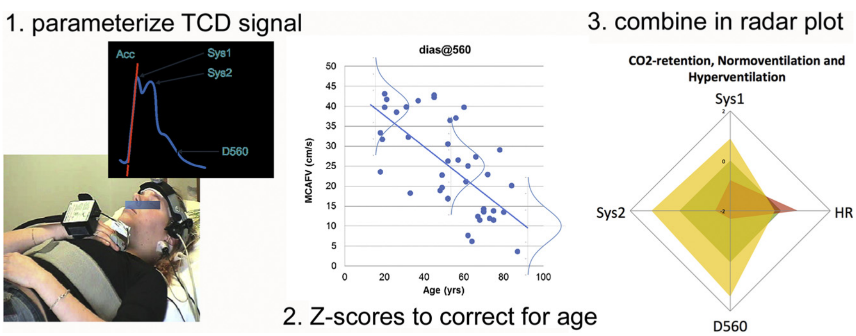
GRAPHICAL ABSTRACT



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ABSTRACT

Background: For the interpretation of middle cerebral artery flow velocity (MCAFV) measurements by transcranial Doppler clinicians should take normal aging into account.

New method: MCAFV measurements can be corrected for age by a transformation to Z-scores, expressing in standard deviations the distance of a measurement to the regression line as function of age. Z-scores for different parameters can be combined into a single plot in order to facilitate clinical interpretation.

Results: In a retrospective analysis 41 subjects were identified with normal autonomic responses, normal CO2-reactivity and satisfactory transcranial Doppler data. Age related changes were determined for: maximal change in flow velocity (FV) during stroke onset (Acc), maximal FV during the first (Sys1) and second phase (Sys2) of systole and mean diastolic FV 560 ms after stroke onset (Dias@560). Patients were supine and breathing normally. Sys1, Sys2 and Dias@560 decreased significantly with age: −0.58 cm/s/yr, −0.36 cm/s/yr. and −0.38 cm/s/yr., respectively. Sys1 decreased more rapidly than Sys2 and Dias@560 so that in the young the MCAFV signal is more Sys1 dominant, whereas in the elderly it becomes more Sys2 prevalent. The effect of CO2-reactivity was assessed by transformation to Z-scores and combining different parameters within a single radar plot.

Comparison with existing methods: In contrast to standard MCAFV measurements the calculation of Z-scores takes aging into account and standardizes the signal variation.

Abbreviations: a.u., arbitrary units; acc, acceleration (relative to Dias@560); Acc, absolute acceleration (cm/s2); CBF, cerebral blood flow; CS, cold submersion; DB, deep breathing; Dias@560, diastolic flow velocity over an interval of 80 ms centered around 560 ms (cm/s); ECG, electro-cardiography; EDFV, end diastolic flow velocity (cm/s); ETCO2, end-tidal carbon dioxide level; FV, flow velocity; MCA, middle cerebral artery; MCAFV, middle cerebral artery flow velocity; NIBP, non-invasive blood pressure; NR, normal response; PI, pulsatility index; POTS, postural orthostatic tachycardia syndrome; PSFV, peak systolic flow velocity (cm/s); SD, standard deviation; sys1, first systolic peak (relative to Dias@560); sys2, second systolic peak (relative to Dias@560); Sys1, absolute maximal flow velocity of the first systolic peak (cm/s); Sys2, absolute maximal flow velocity of the second systolic peak (cm/s); TCD, transcranial Doppler

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Conclusion: Graphically combining Z-scores for different MCAFV parameters makes the signal more accessible for rapid clinical interpretation.

1. Introduction

Transcranial Doppler (TCD) is a well-established non-invasive technique for studying intracranial hemodynamics under variable conditions both in healthy volunteers and in patients (Kirsch et al., 2013). Depending on the study population, TCD is not applicable in approximately 8–18% of normal subjects because of insufficient temporal windows (e.g. Krejza et al., 2007; Wijnhoud et al., 2008). Once found, the signal is difficult to interpret because it is influenced by many technical and physiological factors some of which are represented schematically in Fig. 1. To improve signal interpretation, some authors (e.g. Carey et al., 2001; Kasprowicz et al., 2012) have developed analytical strategies based upon a continuous co-registration with arterial blood pressure (ABP). Some have looked for new analytical strategies based upon the TCD signal alone (e.g. Crutchfield et al., 2004; Schaafsma, 2012).

The simultaneous analysis of ABP and TCD signals is challenging. A continuous non-invasive measurement of ABP can be achieved by a servo mechanism aiming at constant volume by varying the pressure in, for instance, a finger cuff. A mathematical approximation is required to reconstruct upper arm brachial blood pressure from finger pressures. Inaccuracy may occur due to arterial vaso-spasm. An invasive recording of ABP, for instance by means of a catheter in the radial artery, may be more stable but is not necessarily identical to the pressure measured in the basal arteries of the brain. Invasive recordings can be of use in clinical situations such as on an Intensive Care Unit, but are less practical in outpatient studies or studies in normal volunteers.

Therefore, new strategies for the analysis of the TCD signal alone are welcome. The detection of intracranial blood flow velocities based upon the Doppler shift within the reflected signal of an ultrasound beam is straightforward and requires no model assumptions. The signal has a high temporal resolution. Apart from the actual blood flow, the amplitude of the signal is mainly influenced by the angle of insonation and the vessel's cross-sectional area at the site of insonation (Fig. 1).

In 2012 Schaafsma proposed new parameters for the analysis of blood flow velocities recorded by TCD: the maximal change in flow velocity (FV) during stroke onset (acc), the maximal FV during the first (sys1) and second phase (sys2) of systole and the mean diastolic FV 560 ms after stroke onset (Dias@560). The acc, sys1 and sys2 were expressed relative to Dias@560 so that these parameters became unit free and independent from the angle of insonation and from the cross-sectional area at the site of insonation[1]. It is claimed that these parameters better describe intracranial hemodynamics in patients with carotid artery stenosis than traditional parameters such as peak systolic flow velocity, end diastolic flow velocity and pulsatility index.

The rationale behind distinguishing a first and second systolic peak is explained in a paper by Schaafsma (2014) where the theory of arterial acceleration is forwarded. This theory proposes that the first systolic peak is based upon a short lasting contraction within the arterial smooth muscle cells that spreads along the arterial tree as a peristaltic wave. Theoretically, such a mechanism would add force to the onset of the pressure wave allowing it to penetrate even in the most remote capillary systems of the body. The second systolic peak is due to actual stroke volume being ejected by the heart. How important it is to analyse both systolic components separately is illustrated by a recent study in sepsis patients (de Goede et al., 2017).

MCAFV is closely correlated with age. For instance, Ackerstaff et al. (1990) have measured mean MCAFV in 158 volunteers ranging from 14 to 70 yrs. Volunteers were in a reclined position and breathing normally. These investigators found a decrease in mean MCAFV of 0.41–0.45 cm/s/yr. The mean MCAFV was calculated over a period of 5 s including both systole as well as diastole. Similarly, Bakker et al. (2004) studied TCD data in a large prospective population-based cohort study of 7983 participants aged 55 years and over. In a subgroup of 1720 participants they found a decrease in mean MCAFV of 0.4-0.6 cm/s/yr.

In the present study it was investigated whether the decrease in MCAFV with aging was also measurable in the subcomponents Acc, Sys1, Sys2 and Dias@560. For this, a retrospective analysis was performed of TCD data collected in a group of subjects undergoing autonomic function testing. A subgroup of patients was identified who had normal results on all autonomic function tests, namely deep breathing, cold submersion, Valsalva and tilt table test, who had normal CO2-reactivity as determined by a CO2-retention and a hyperventilation test and who had sufficient quality TCD recordings for further analysis.

Regression lines were calculated for the different TCD parameters with respect to age. This allowed the transformation to Z-scores expressing how many standard deviations a given data point is smaller or larger than the mean value expected for that age by linear regression. Subsequently, the Z-scores for Sys1, Sys2, Dias@560 and HR could be combined into a single radar plot allowing the clinician to assess the most important signal characteristics at a twinkle of the eye. This is illustrated by plotting the differences in MCAFV occurring during CO2 reactivity testing.

2. Methods

A retrospective analysis was performed at this facility of all patients undergoing autonomic function tests during the study period (from January 1st 2014 till January 1st 2017). Patients were investigated with

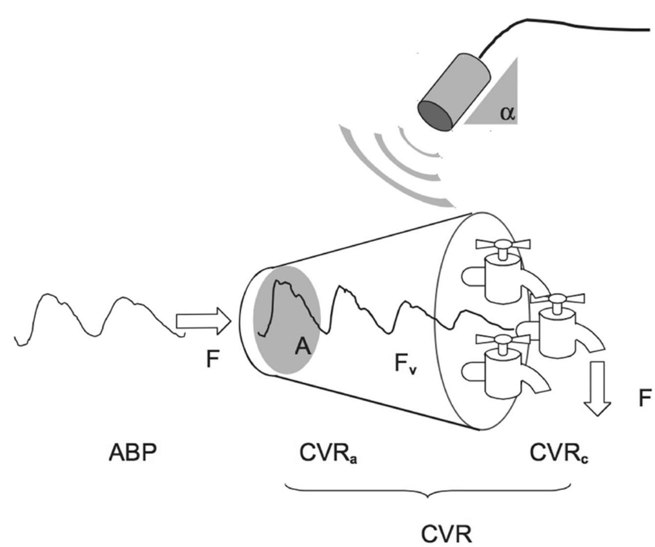

Fig. 1. Schematic representation of the most important determinants of the TCD signal (ABP: arterial blood pressure; CVRa: cerebrovascular resistance of the conducting arteries; CVRc: cerebrovascular resistance of the arterioles and capillaries; F: blood flow; A: cross-sectional area at the site of insonation and α: angle of insonation).

[1] In order to avoid confusion but remain consistent with the previous publication (Schaafsma, 2012) this paper will refer to absolute parameter values by parameter names starting with a capital and to values relative to Dias@560 by parameter names starting with a lowercase.