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Assessing changes in pial artery resistance and subarachnoid space width using a non-invasive method in healthy humans during the handgrip test

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The aim of this study was to assess the influence of the handgrip test (HGT) on: (1) pial artery pulsation (cc-TQ), (2) subarachnoid space (SAS) width (sas-TQ) and (3) the relationship between peripheral blood pressure (BP), heart rate (HR), cerebral blood flow velocity (CBFV), resistive index (RI), cc-TQ and sas-TQ. The study was performed on 29 healthy volunteers (11 men and 18 women) with a mean age of 29.3 ± SE 4.0. HGT was performed in the sitting position at 30% of maximal voluntary contraction. cc-TQ and sas-TQ were registered using near-infrared transillumination/backscattering sounding (NIR-T/BSS); BP and heart rate (HR) were measured using a Finapres monitor. CBFV and RI were recorded using a transcranial Doppler. A significant reduction in cc-TQ (−34.3%, $P<0.0001$) and sas-TQ (−12.9%, $P<0.001$) were observed, while mean arterial pressure and HR increased (+34.8%, $P<0.0001$ and +7.9%, $P<0.0001$, respectively). There was no significant change in CBFV (+1.0%) while RI increased (+12.0%, $P<0.05$). Correlation and regression analysis did not reveal any interdependencies between the investigated variables. HGT evoked a significant increase in pial artery resistance, with a simultaneous decrease in the width of the SAS. A decrease in pial artery compliance should be seen as protective mechanism against acute BP elevation, most likely mediated by sympathetic activation. NIR-T/BSS recordings allowed for non-invasive assessments of changes in pial artery compliance, and were consistent with data from the literature and physiological knowledge.

Key words: NIR-T/BSS, infrared radiation, subarachnoid space, pial artery pulsation, handgrip test

INTRODUCTION

There has been an ongoing scientific debate about the role of sympathetic innervation in the brain microcirculation. In the late 1970s, the concept was developed that sympathetic nerve activity (SNA) plays a vital protective role under conditions that threaten the integrity of cerebral blood vessels such as sudden increases in blood pressure (BP; Heistad and Marcus 1979). In parallel, it was proven in animal models that SNA stimulation leads to pial vein constriction and a decrease in cerebral venous outflow (Traystman and Rapela 1975, Ulrich and Kuschinsky 1985). The advent of transcranial Doppler technology (Aaslid et al. 1989) and the use of transfer function analysis (Zhang et al. 1998) has opened a new era in human research. Zhang and colleagues (2002) demonstrated that ganglion blockade with trimethaphan significantly affects static and dynamic autoregulation and therefore postulated that the autonomic system plays an important role in beat-to-beat cerebral blood flow regulation in humans.

The main disadvantage of transcranial Doppler technology is that the measurement is performed in large cerebral arteries, and reflects cerebral blood flow velocity (CBFV; Aaslid et al. 1989), while the regulation of cerebral blood flow (CBF) takes place in small arterioles (Kontos et al. 1978). To date, cranial window installation and microscopic examination remain the

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methods of choice to investigate the pial microvessels in vivo (Levasseur et al. 1975). Not surprisingly, such an approach cannot be applied to human research. However, the amplitude of cerebrovascular pulsation (CVP) can be measured non-invasively using near-infrared transillumination/backscattering sounding (NIR-T/BSS), a new method based on infrared radiation (IR) that has been developed in the last decade by our team (Plucinski et al. 2000, Plucinski and Frydrychowski 2007, Frydrychowski et al. 2001, 2002, 2009, Frydrychowski and Plucinski 2007). Contrary to near-infrared spectroscopy (NIRS), which relies on the absorption of IR by haemoglobin (Li et al. 2010, 2011), NIR-T/BSS uses the subarachnoid space (SAS) filled with translucent cerebrospinal fluid (CSF) as a propagation duct for IR. In addition, NIR-T/BSS allows for the assessment of changes in the width of the SAS, indicative of changes in CSF volume and intracranial pressure (Plucinski et al. 2000, Plucinski and Frydrychowski 2007, Frydrychowski et al. 2002, 2011a, Frydrychowski and Plucinski 2007). Due to its non-invasive character, ease of use and low cost, NIR-T/BSS potentially constitutes an ideal tool to monitor brain microcirculation over long periods of time.

It is widely accepted that the handgrip test (HGT) is associated with an SNA increase, and is used to study the effects of sympathetic stimulation (Ainslie et al. 2005, Ikemura et al. 2012). To the best of our knowledge, the effect of an SNA increase on pial artery pulsation has not been investigated yet in humans. The aim of this study was to assess the influence of HGT on: (1) the amplitude of CVP, (2) the SAS width and (3) the relationship between peripheral BP, heart rate (HR), CBFV, resistive index (RI), cc-TQ and sas-TQ.

METHODS

The study was performed on 29 healthy volunteers (11 men and 18 women) 25–40 years old, with a mean age of 29.3 ± SE 4.0. The volunteers were selected on the basis of a medical questionnaire, interview and blood pressure measurements. All of them gave informed consent to participate in the study. The experimental protocol was approved by the ethical committee of the Medical University of Gdansk. Subjects were free of any disorders and not taking any medications. No coffee, food or nicotine were permitted for 3 hours before the test. Two smokers were included in the study (1 female and 1 male). Additionally, prior to the test, the volunteers were asked to sit comfortably and rest for 30 minutes. Subjects were instructed to breathe normally in order to avoid apnoea's or Valsalva like manoeuvres. Tests were performed within the following scheme: (1) Rest sitting position (Baseline 1), (2) Bend Over Position Test (BOPT), subject bent forward at 45º angle between the trunk and the head (Fig. 1; Frydrychowski et al. 2002), (3) Rest sitting position for at least 30 minutes (Baseline 2), (4) HGT in sitting position, the subject performed 30% of maximal voluntary contraction during 2 minutes. A maximal voluntary contraction for each subject was measured before the trial. Each subject was studied once, with at least 30 minutes of rest after the study.

Changes in the amplitude of CVP and in the width of the SAS with NIR-T/BSS were recorded using head-mounted NIR-T/BSS sensor unit of our own design. The sensor unit consists of the emitter (E) and two photo-sensors located at various distances from the emitter. The NIR-T/BSS emitter is a light-emitting diode (LED). The proximal sensor (PS) is located close to the emitter, while the distal sensor (DS) is located further from the emitter. The stream of IR generated by the emitter penetrates the highly perfuse layer of the skin of the head, the skull bones and the subarachnoid space. The stream of radiation reflects from the surface of the brain and reaches the sensors, crossing the aforementioned layers of tissues in reverse order. Signals from the sensors undergo analogue-digital conversion in a specialised data acquisition system, and are recorded on a microcomputer's hard disk for subsequent analysis with on-line computer presentation.

Theoretical and practical foundations of the NIR-T/BSS method were provided in the earlier model studies (Pluciński et al. 2000, Frydrychowski et al. 2002, Frydrychowski and Plucinski 2007, Plucinski and

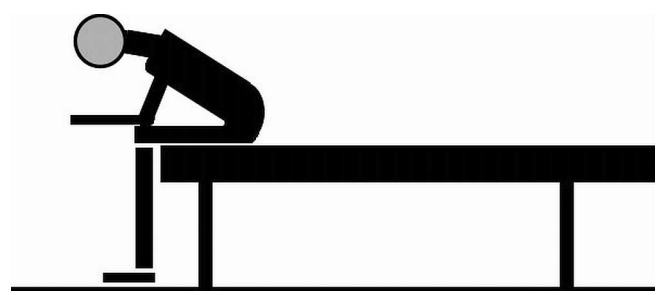

Fig. 1. Bend Over Position. At forward bend, the brain floats forward toward the inner surface of the frontal bones, and the SAS in the frontal region assumes its minimum value.

Frydrychowski 2007). Briefly, the signal received by the DS is divided over the signal received by the PS. Such division reduces the proportional factors which affect each of the two signals in an identical way, due to the fact that the quotient of these factors assumes the value 1. Both the dividend, i.e. the power of the DS signal, and the divisor, i.e. the power of the PS signal, are influenced by the width of the SAS as well as by any factor capable of changing that width. Therefore, the quotient of the two signals, hereafter called the transillumination quotient (TQ), is sensitive to changes in the width of the SAS. The oscillations of TQ have

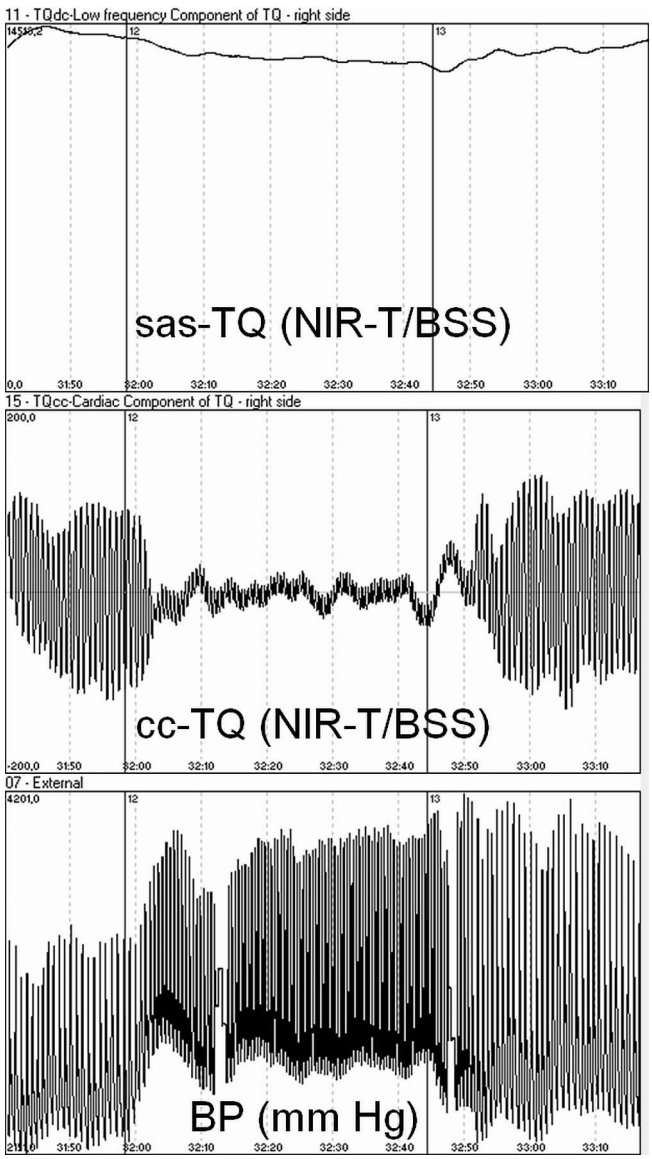

Fig. 2. Changes in the width of the SAS (upper tracing), pial artery pulsation (medium tracing) and mean arterial pressure (lower tracing) during the HGT. The start and end of the HGT are indicated with vertical lines.

their origin in different modulation of the PS and DS signals, namely in the modulation of the DS signal on its way through the SAS. This happens because only DS receives radiation propagated within the SAS. Propagation of IR in the skin and bone is much worse than in the clear, translucent CSF contained in the SAS, and with the DS placed far enough from the emitter, no radiation propagated in the superficial tissue layers can reach the DS (Plucinski et al. 2000, Frydrychowski et al. 2002). The power of the IR stream reaching the DS is directly proportional to the width of the SAS. The wider the SAS, or the propagation duct, the more radiation reaches the DS and the greater the signal from that sensor, which is the dividend in the calculation of the TQ (Plucinski et al. 2000, Frydrychowski et al. 2002).

Thus, in the transillumination quotient (TQ), three main components can be identified: (1) constant or non-pulsatile component, further referred to as sas-TQ, its value depending on the permeability for radiation of the skin and bones as well as on the width of the CSF-filled SAS, (2) slow-variable pulsation, further referred to as the subcardiac component (scc-TQ), mainly of respiratory origin, (3) fast-variable pulsation, further referred to as the cardiac component (cc-TQ), resulting from heart-generated arterial pulsation which is the cause of fast oscillations in the width of the SAS.

The first harmonic of the arterial pulsation-dependent oscillations of TQ is extracted through appropriate filtering, along with its modulation, for further analysis. Modulation of that harmonic is a fast-variable component (or cardiac component) of the principal, second and third harmonics of the cardiac component waveform, respectively. A detailed description of the method of signal analysis is presented in other papers (Plucinski et al. 2000, Plucinski and Frydrychowski 2007, Frydrychowski et al. 2002, Frydrychowski and Plucinski 2007).

Recording of changes in systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and HR were measured using a Finapres monitor (Finapres, Ohmeda, Englewood, CO, USA). The Finapres sensor was mounted to the middle finger of the non-dominant hand resting on the table. Beat-to-beat BP was transferred to a computer console continuously displaying SAP, DAP and HR. Mean arterial pressure (MAP) and pulse pressure (PP) were calculated from the following equations: MAP = DAP + 1/3 PP, PP = SAP – DAP.

Table I

Mean ± SE values of sas-TQ, cc-TQ, HR, SAP, DAP, PP and MAP during the BOPT and HGT

	n	Baseline 1	BOPT	Baseline 2	Handgrip test
sas-TQ	29	9918.70 ± 885.20	8000.11 ± 825.53 ***	9630.79 ± 972.05 ^{NS}	8388.59 ± 833.07 **
cc-TQ	29	56.77 ± 4.05	24.05 ± 2.73 ***	60.37 ± 4.89 ^{NS}	39.64 ± 3.59 ***
HR	29	77.79 ± 1.63	79.59 ± 2.27 ^{NS}	75.55 ± 1.25 ^{NS}	81.55 ± 1.49 ***
SAP	29	118.31 ± 2.27	125.76 ± 2.88 **	118.28 ± 2.40 ^{NS}	156.59 ± 3.85 ***
DAP	29	71.07 ± 1.91	75.59 ± 1.81 **	69.14 ± 1.77 ^{NS}	93.24 ± 2.62 ***
PP	29	47.41 ± 1.83	50.17 ± 2.57 *	49.14 ± 1.98 ^{NS}	64.54 ± 2.68 ***
MAP	29	86.49 ± 1.88	92.29 ± 1.86 **	84.80 ± 1.76 ^{NS}	114.35 ± 2.88 ***

*** $P<0.0001$, ** $P<0.001$, * $P<0.05$ *versus* baseline 1 and baseline 2, respectively; ^{NS} not statistically significant *versus* Baseline 1

Additionally, during the HGT transcranial Doppler (TDS4, Sonomed, Warsaw, Poland) measurement of CBFV and RI in the left anterior cerebral artery was performed. Pulse probe of 2 MHz was used and analysis of the results was carried out on a built-in IBM PC computer. To assure best reproducibility of the recordings, Doppler probe mounted on the head with a special stabilizing strip was used.

The Shapiro-Wilk, *U* Mann-Whitney and ANOVA tests were used for the analysis of differences between average values. Changes in BP (SAP, DAP, MAP and PP), HR, CBFV, RI, sas-TQ and cc-TQ responses were compared. Correlation and regression analysis was performed to assess interdependences between BP, HR, sas-TQ and cc-TQ. All statistical calculations were done using the Statistica for Windows 8.0 commercial package.

RESULTS

Figure 2 shows the typical time course of sas-TQ, cc-TQ and BP during HGT. It can be observed that changes in sas-TQ and cc-TQ follow the BP increase.

The BOPT evoked a decrease in sas-TQ (−19.3%) and cc-TQ (−57.7%), while SAP (+6.3%), DAP (+6.5%), MAP (+6.7%) and PP (+5.9%) slightly increased. HR did not change significantly during the BOPT (+2.2%). HGT produced a decrease in sas-TQ (−12.9%) and cc-TQ (−34.3%), with a considerable elevation in SAP (+32.4%), DAP (+55.0%), MAP (+34.8%) and PP (+31.3%) and a slight increase in HR (+7.9). The mean values of sas-TQ, cc-TQ, HR, SAP, DAP, PP and MAP are shown in Table I.

The transcranial Doppler recordings brought the following results: before start of the HGT, mean CBFV = 55.3 cm/s ± SE 4.4, RI = 0.6 ± SE 0.11; during the HGT, mean CBFV = 55.8 cm/s ± SE 6.9, RI = 0.72 ± SE 0.17. Increase in RI was statistically significant (+12.0%; $P<0.05$). The typical transcranial Doppler recordings are presented in Figure 3.

Correlation and regression analysis did not indicate any interdependencies between the investigated variables (data not shown).

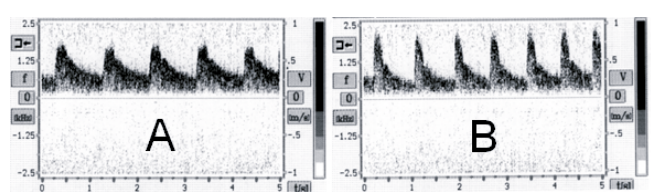

Fig. 3. Representative transcranial Doppler recordings before (A) and during (B) the HGT. CBFV remained unchanged, while RI increased.

DISCUSSION

To the best of our knowledge, NIR-T/BSS is the first portable and easy to use device to allow non-invasive measurement of the brain microvasculature and width changes in the CSF-filled SAS. There are two novel findings of this study: during HGT, (1) the width of the SAS decreases and (2) pial artery pulsation decreases.

The BOPT has been described earlier in detail (Frydrychowski et al. 2002). The aim of performing the BOPT first was to ensure that between-subject repeatability of the results was maintained. The BOPT evokes very typical changes in sas-TQ and cc-TQ due to physical brain movements. The brain, enclosed in the indistensible skull, is subject to gravitation and changes its position along with changes in the position of the head (Maier et al. 1994). At forward bend, the brain floats forward toward the inner surface of the frontal bones, and the SAS in the frontal region assumes its minimum value (unpublished Magnetic Resonance Imaging results). The observed decreases in sas-TQ and cc-TQ were associated with a very modest BP increase and unchanged HR. Therefore, we may assume that SNA did not increase significantly during the BOPT. Nevertheless, we allowed subjects to have 30 minutes rest before starting further experiments. The high within- and between-subject reproducibility and repeatability of NIR-T/BSS measurements have been also demonstrated earlier (Frydrychowski et al. 2001, 2002). NIR-T/BSS, like NIRS, allows for direct within-subject comparisons (Frydrychowski et al. 2002, Wagner et al. 2003). As long as changes from baseline values are analysed, high between-subject reproducibility is observed. So far, measurements using IR light (NIRS and NIR-T/BSS) do not allow for direct between-subjects comparisons due to differences in skull bone parameters (Frydrychowski et al. 2002, Wagner et al. 2003).

Zhang and coauthors (2002) suggested that sympathetic withdrawal after ganglion blockade may lead to a decrease in cerebrovascular resistance. The influence exerted by the HGT on CBFV measured with transcranial Doppler remains controversial. Ainslie and colleagues (2005) and Ikemura and others (2012) demonstrated that during the HGT, CBFV remains unchanged, while cerebrovascular resistance significantly increases, what is in line with our results. Sohn (1998) and Rasmussen and coworkers (2006) reported that CBFV increases during the HGT. We have previously shown that the amplitude of CVP (cc-TQ) reflects pial artery pulsation and may serve as a sensitive index of changes in microvessel compliance. cc-TQ increases were observed during acetazolamide and hypercapnic tests, acute hypoxia, papaverine and glucagon administration and electroconvulsive therapy, while cc-TQ decreases were recorded during the stabilisation period after the abovementioned procedures (Frydrychowski et al. 2002, 2009, 2011b,c). Therefore, the cc-TQ decrease observed during the HGT reflects an increase in pial artery resistance. Analysing cc-TQ, we cannot be certain if the decrease in pial artery compliance was due to an SNA increase or a myogenic response to HGT which induced an increase in BP. Cerebrovascular resistance can be also increased by other procedures that elevate BP, like phenylephrine infusion (Zhang et al. 2009). Nevertheless, during the HGT, Ainslie et al. (2005) observed a strong correlation between SNA increases in microneurography (MSNA) and cerebrovascular resistance which supports the hypothesis of sympathetically mediated vasoconstriction. Cassaglia and colleagues (2008) demonstrated in a very elegant study on the lambs that SNA recorded in superior cervical ganglion increases promptly and proportionally in response to acute BP elevation. Such data supports the suggestion that there is reflex augmentation of cerebral SNA in response to raised BP. The same team (Cassaglia et al. 2009) showed that SNA increases protect the brain against potentially devastating BP increases during periods of unstable hemodynamics during rapid-eye-movement (REM) sleep. Our results provide for the first time, to the best of our knowledge, direct evidence that in humans, the pial arteries can effectively protect the brain microcirculation against acute increases in BP.

It has been demonstrated earlier that sas-TQ is sensitive to changes in cerebral blood volume and/or intracranial pressure (Frydrychowski et al. 2002, 2011a, Frydrychowski and Plucinski 2007, Wszedybyl-Winklewska et al. 2011). The significant reduction in sas-TQ observed in our study is consistent with earlier evidence that cerebral blood volume increases during the HGT (Bhambhani et al. 2006). However, the study of Bhambhani and colleagues was mainly methodological in nature, and aimed at validating the NIRS technique for the evaluation of cerebral oxygenation and cerebral blood volume changes during motor function. Therefore, it is important to confirm the NIRS results with another

method, in particular since in the Bhambhani and others (2006) study, the SNA component of the HGT was not been even briefly mentioned. Ogoh and coworkers (2011) in a very recent study using the NIRS technique has shown that venous cerebral blood volume increases in healthy volunteers during phenylephrine infusion. sas-TQ decrease was observed as well in our lab during dopamine infusion (data not published). Thus, the increased cerebral venous blood volume may explain the potential mechanism of the reduction in the width of the SAS (sas-TQ). Ogoh and others (2011) suggested, that the discrepancy between arterial and venous blood flow may be explained by an increased contribution of vertebral artery blood flow. The differences in the density of β-adrenergic, cholinergic and serotoninergic innervations (Edvinsson et al. 1976) and responses to sympathetic activation between different arteries (Delp et al. 2001, Sato and Sadamoto, 2010) may support this hypothesis. Contrary to above presented reasoning, the animal studies indicated that SNA stimulation leads to pial vein constriction (Traystman and Rapela 1975, Ulrich and Kuschinsky 1985). Furthermore, Wilson and colleagues (2005) suggested that the cold pressor test may selectively decrease cerebral blood volume in grey matter. The study was performed on 8 volunteers; cerebral blood volume, mean transit time and cerebral blood flow were measured using the enhanced computed tomography procedure. The cold pressor test was performed in supine position for approximately 2 minutes, and the computed tomography scans occurred between sixtieth and ninetieth seconds. There might be some differences between the HGT and the cold pressor test, as well as, between the supine and sitting position which may explain the different responses. Finally, due to small number of subjects the Wilson and coauthors (2005) results should be viewed with caution. Nevertheless, Wilson and others (2005) also reported an increased cerebrovascular resistance during the cold pressor test. Further studies are needed to elucidate the influence of sympathetic activation on cerebral venous blood volume as to date results reported by various teams remain inconsistent. Disturbances in venous blood volume/outflow maybe potentially harmful if maintained over longer periods inducing local ischaemia and/or oedema, leading to leukoaraiosis (Brown at al. 2009) or promoting amyloid beta deposition (Nation et al. 2011).

We did not find any interdependencies between cc-TQ, sas-TQ and CBFV, RI or BP (SAP, DAP, MAP, PP). The lack of direct relationship between cc-TQ and BP might suggest that cerebral autoregulation was not jeopardised during HGT. This is in agreement with the classic concept of Lassen (1959). However, the classic concept of cerebral autoregulation (Lassen 1959) has been recently challenged by Lucas and coworkers (2010). Also, other authors have pointed out that the mechanisms of CBF maintenance are more complex, and include baroreceptors (Ogoh et al. 2010a, Tzeng et al. 2010) and mechanisms independent from blood pressure, such as flow-induced changes in pial artery compliance (Frydrychowski et al. 2011b). Ogoh and others (2010b) reported that dynamic autoregulation is not jeopardised during HGT. Unfortunately, we cannot provide any evidence with respect to changes in dynamic cerebral autoregulation. This is the main limitation of this study. The next step in NIR-T/BSS technology development is to synchronise beat-to-beat cc-TQ tracings with Finapres recordings, and include transfer function analysis as the standard modality. Such synchronisation will allow for precise, non-invasive assessment of changes in dynamic cerebral autoregulation in humans. Two smokers were included into the study. Chronic decrease in CBF was demonstrated in cigarette smokers (Kubota et al. 1983, Rogers et al. 1983). The results obtained from the two smoker volunteers included in this trial were within the study average what may confirm the intact pial artery reactivity. However, we did not collect any data regarding duration or exposure to smoking, such as number of packs of cigarettes smoked per day. Therefore we are not able to assess the potential influence of chronic smoking on the obtained results. Nevertheless, due to small number of smokers we believe that the impact on the final results was very limited. Nicotine exerts an acute effect on CBF, causing nitrergic dependent vasodilation (Si and Lee, 2002) and increasing CBFV (Silvestrini et al. 1996, Boyaijan and Otis, 2000), what is followed by a fall in CBF immediately after smoking, suggesting cerebral vasoconstriction (Terborg et al. 2002), and reduction in cerebrovascular reactivity (Silvestrini et al. 1996). To avoid acute effects of nicotine, nicotine use was not permitted for 3 hours before the test.

CONCLUSIONS

HGT evokes significant increase in pial artery resistance, with a simultaneous decrease in the width of the SAS. A decrease in pial artery compliance should be seen as a protective mechanism against acute BP elevation, which is most likely mediated by sympathetic

activation. NIR-T/BSS recordings allow for non-invasive assessments of changes in pial artery compliance, and are consistent with data from the literature and physiological knowledge.

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Conflicts of interest

Infrared sensor unit for NIR-T/BSS recording through intact scalp was filed at the World Intellectual Property Organization in Geneva (WO 96/25876) by the second author of this paper (A.F. Frydrychowski). Remaining authors declare that they have no competing interests.

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