



Functional transcranial doppler sonography

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Abstract

Functional transcranial Doppler sonography constitutes a complementary perfusion-sensitive neuroimaging tool measuring cerebral perfusion changes due to neural activation. The method is based on the close linkage between local neural activity and regional cerebral blood flow changes. It also provides high temporal resolution, which allows the assessment of the fast changes in flow parameters resulting from change in neural activity. Additional advantages of the technique are its noninvasiveness, low cost, and mobility, which makes it ideal for follow-up investigations in adult and pediatric patients or healthy subjects. Recent advantages in the technique have produced a large number of fTCD studies on the organization of different motor, sensory, endothelial, vasomotor and cognitive functions in the brain. In this article the scientific and clinical applications of fTCD of our research group are presented.

INTRODUCTION

Functional transcranial Doppler sonography (fTCD) constitutes a complementary perfusion-sensitive neuroimaging tool measuring cerebral perfusion changes due to neural activation. It has been established since the first demonstration of noninvasive Doppler ultrasound pericranial recordings of the cerebral blood flow velocities (CBFv) in the basal cerebral arteries by Aaslid *et al* was demonstrated (1). Like functional magnetic resonance imaging and positron emission tomography, fTCD is based on the close linkage between local neural activity and regional cerebral blood flow (rCBF) changes (2). Regional cerebral blood flow changes result in CBFv alterations in the supplying basal cerebral arteries, which can be continuously monitored by fTCD. This method provides high temporal resolution, which allows the assessment of the fast changes in flow parameters resulting from change in neural activity. Additional advantages of the technique are its noninvasiveness, low cost, and mobility, which makes it ideal for follow-up investigations in adult and pediatric patients or healthy subjects. One major disadvantage is the limited spatial resolution of the technique which is restricted to the vascular territories of the insonated vessels. Additionally, about 5 % of the healthy population exhibits an insufficient temporal ultrasound window, when the ultrasound beam cannot penetrate the skull due to an increase bone thickness (3).

Recent advantages in the technique have produced a large number of fTCD studies on the organization of different motor, sensory, endothelial, vasomotor and cognitive functions in the brain.

The scientific and clinical applications of fTCD from our research group are presented in this article.

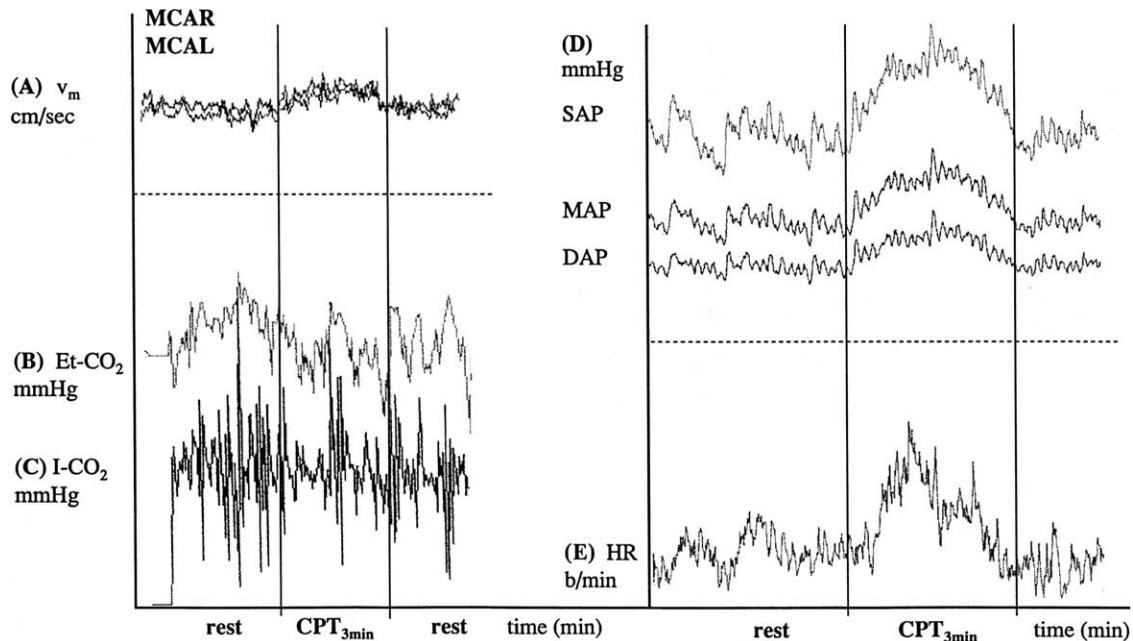


Figure 1. A typical response of blood velocity in both middle cerebral arteries and systemic parameters to CPT. (A) – mean blood velocity (v_m) in the both middle cerebral arteries (MCA); (B) – end-tidal CO_2 (Et- CO_2), (C) – instantaneous CO_2 signal (I- CO_2), (D) – systolic (SAP), mean (MAP), diastolic arterial pressure (DAP) and (E) – heart rate (HR) during rest and cold pressor test (CPT).

INFLUENCE OF THE COLD PRESSOR TEST ON THE MIDDLE CEREBRAL ARTERY CIRCULATION

A lot of research has been done on the regulatory mechanisms of CBF response to different types of stimuli (4, 5, 6, 7, 8).

It is well known that cerebral vessels receive innervation from cervical sympathetic nerve fibers. The importance of neural, i.e., sympathetic, regulation of cerebral circulation is still controversial. Sympathetic innervation probably mediates vasoconstriction and modulates the limits of autoregulation in the human cerebral circulation (9). The influence of the sympathetic nervous system (SNS) on the cerebral circulation in humans was noninvasively studied by TCD (4, 8, 10, 11). Some authors found an increase of mean arterial velocity (v_m) in the middle cerebral artery (MCA) in humans after electric stimulation of the sympathetic cord at the upper thoracic level (10) while others used the cold pressor test (CPT) for activating the sympathetic efferent branch of the autonomic nervous system (4, 8, 11). However, the results of these studies in healthy subjects were contradictory.

Cold pressor test evokes generalized activation of the sympathetic nervous system (SNS). To determine the response of SNS, our group studied the v_m during CPT. Thirty-four healthy volunteers, 13 female and 21 male (mean age 34 ± 9.5 years, range 18 to 55 years) participated in our study. The experiment consisted of a 5-min baseline period followed by a 3-min immersion of the

right hand in ice water. Blood velocity in both MCA's was monitored by bitemporal 2 MHz probes by using a Multi-Dop X4. Mean arterial pressure (MAP) and heart rate (HR) were measured simultaneously by a Finapres non-invasive blood pressure monitor and a computerized ECG system. End-tidal CO_2 (Et- CO_2) was measured with an infrared capnograph. To determine v_m over a chosen time interval the TCD-8 software was utilized. The results showed that during CPT v_m , MAP, and HR increased significantly ($P < 0.01$) for 9.8%, 18.5%, and 3.6%, respectively. Et- CO_2 did not change significantly ($P > 0.05$). The increase of v_m was also significantly higher in the stimulated hemispheres ($P = 0.005$) regarding to unstimulated ones. The increase of v_m during CPT was not gender dependent. To establish the association between variables the models of multivariate regression were used. Multiple regression CPT model was significant ($P < 0.01$) and fitted data moderately well ($r^2 = 0.28$). MAP and Et- CO_2 were significant in the model ($P < 0.01$). We conclude that the activity of the intracranial SNS is detectable by measuring v_m by using TCD during CPT. The method could be useful for studies of diseases with impaired intracranial SNS (8).

Figure 1 shows a typical response of v_m of both MCA's to CPT started immediately without latency after immersion of the right hand in ice water with stepwise increase, reached maximum between the first and second minutes of the test, then it stepwise decreased and stopped without obvious recovery time. Similar trends of responses to CPT were observed for HR, SAP, MAP and DAP. Et CO_2 was not influenced by CPT.

Effect of generalized sympathetic activation by cold pressor test on cerebral hemodynamics in diabetics with autonomic dysfunction

In this study we examined the effects of the CPT on the cerebral circulation in diabetics with autonomic dysfunction without orthostatic hypotension using TCD (12). Twenty diabetics with autonomic dysfunction and 19 age-matched healthy controls participated in the study. The mean arterial blood velocity was measured in the MCA during CPT together with MAP. The mean arterial blood velocity significantly ($P < 0.01$) increased during the 1st, 2nd, and 3rd min of the CPT by 10.6, 14.1, and 13.4%, respectively, in the control subjects and by 5.8, 7.2, and 6.8%, respectively, in the diabetics. Simultaneously, MAP significantly ($P < 0.01$) increased by 12, 26, and 23%, respectively, in the controls and by 9.4, 12.4 and 12.9%, respectively, in the diabetics. The increases in the vm as well as in the MAP were significantly higher in the controls than in the diabetics ($P < 0.01$). The change in the MAP related significantly to the change in the vm both in the controls ($P < 0.01$, $R = 0.76$) and in the diabetics ($P < 0.01$; $r = 0.59$). The slope of the regression line was significantly steeper in the controls ($b = 0.42$, $SE = 0.05$) as compared with the diabetics with autonomic dysfunction ($b = 0.27$, $SE = 0.05$; $P = 0.02$). Moreover, also the relative increase in the cerebrovascular resistance index was higher in the controls than in the diabetics ($P < 0.05$). These findings in the diabetics with autonomic neuropathy, but without orthostatic hypotension, suggest a failure in the cerebral autoregulation due to impaired cerebrovascular neurogenic control.

THE EFFECT OF AGE ON CEREBROVASCULAR REACTIVITY TO COLD PRESSOR TEST AND HEAD-UP TILT

We also studied the CPT and head-up tilt (HUT) responses of the older and younger healthy individuals by TCD (13). Forty healthy volunteers were divided into two age groups (18-39 years, 40-69 years). Mean blood velocity in both MCAs was monitored during CPT and HUT. Mean arterial blood pressure, HR and Et-CO₂ were measured simultaneously. The vm increased by 7.1% during CPT and decreased by 10.1% during HUT. The vm responses were significantly lower in the older group ($P < 0.01$). Linear regression analysis showed a significant effect of age on Δvm during both CPT ($P < 0.01$) as well as HUT ($P < 0.01$). We concluded that the age affected the vm responses to CPT and HUT in the group of older subjects.

The middle cerebral artery flow velocities during head-up tilt testing in diabetic patients with autonomic nervous system dysfunction

The mean flow velocity in the MCAs was examined in patients with diabetes mellitus during HUT (14). The

study was performed in 20 patients, 9 females and 11 males (mean age 51 \pm 12 years) with an average 17-year history of insulin-dependent diabetes mellitus type I or II and a dysfunction of the autonomic nervous system confirmed by cardiocirculatory tests (Valsalva maneuver, deep breathing test, handgrip test, orthostatic test and spectral analysis of HR variability), and 19 age-matched healthy volunteers, 9 females and 10 males (mean age 48 \pm 6.8 years). The mean flow velocity was measured by TCD monitoring system during a 5-min baseline period, followed by a 5-min HUT in the upright position (90 degrees). Mean arterial blood pressure, HR and Et-CO₂ were monitored concomitantly. In healthy volunteers, vm decreased stepwise during the first minute of HUT, reaching a minimum during the last 2 min of the test vm: basal 63.0 \pm 11.7 cm/s, 1st min 57.6 \pm 12.2 cm/s, 2nd min 55.9 \pm 12.6 cm/s, 3rd min 53.4 \pm 12.6 cm/s, 4th min 52.1 \pm 12.7 cm/s, 5th min 51.3 \pm 13.5 cm/s. In the supine position, vm recovered and reached the resting vm values. It declined gradually during HUT and less steeply in diabetic vm: basal 54.4 \pm 10.1 cm/s, 1st min 51.96 \pm 9.3 cm/s, 2nd min 50.7 \pm 11.6 cm/s, 3rd min 50.5 \pm 11.4 cm/s, 4th min 49.5 \pm 10.7 cm/s, 5th min 48.8 \pm 11.5 cm/s, than in healthy subjects. Mean velocity differed significantly ($P = 0.00$) between rest and HUT in both groups. The differences in MAP, HR and Et-CO₂ during rest and HUT between the groups were not statistically significant ($P \Delta MAP = 0.36$, $P \Delta HR = 0.86$, $P \Delta Et-CO_2 = 0.97$). The results of the analysis of variance of vm for repeated measurements between the two groups of subjects were highly significant ($P = 0.00$). The model of linear regression analysis was significant ($P = 0.007$). Diabetes was significant in the model ($P = 0.00$), while ΔMAP , ΔHR and $\Delta Et-CO_2$ were not. These findings may indicate that vasomotor responses during HUT testing are decreased in diabetic patients.

EFFECT OF VISUAL CONTRAST ON VISUAL EVOKED FLOW POTENTIALS AND DOPPLER SIGNAL

The neural activity can be changed during visual stimulation with different contrasts. In one of the study has been shown that activity in the primary visual cortex (V1) increases when subjects have perceived a higher contrast pattern and decreases when they have perceived a lower contrast pattern (15).

Transcranial Doppler could be used to evaluate the visually evoked cerebral blood flow responses (VEFRs) during graded visual cortex activity. In one of our study we evaluated the effects of visual contrasts on VEFR. The records were made from 30 healthy volunteers aged 38.0 \pm 9.6 years. The stimulus was a black-and-white checkerboard with visual contrasts of 1%, 10% and 100%. The VEFRs were measured in the posterior cerebral artery using TCD. We found that the VEFRs at 100% visual contrast were 36% higher than those at 10% visual contrast ($P < 0.01$). The VEFRs at 10% visual contrast were 81% higher than those at 1% visual contrast ($P < 0.01$). The linear regression showed significant relationships

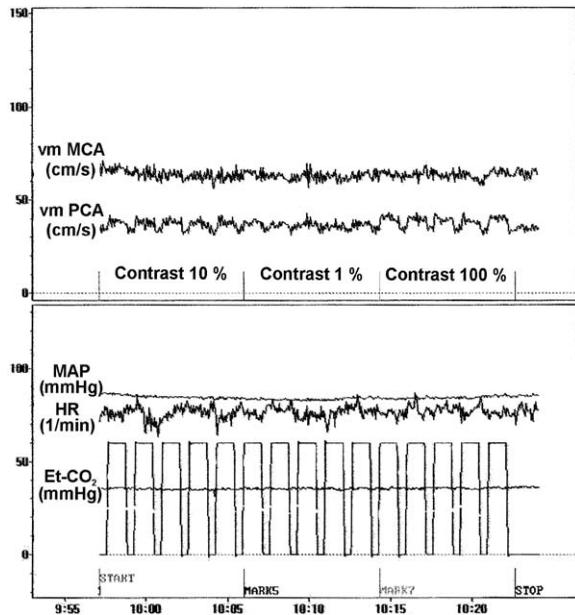


Figure 2. Multimodal recording of *vmMCA*, *vmPCA* (upper box) and *MAP*, *HR*, and *Et-Co2* (lower box) at three different visual contrasts. During each visual contrast five consecutive on and off periods are seen.

between the visual contrast and the VEFR ($r = 0.61$, $P < 0.01$). We have concluded that TCD monitoring of VEFR detects the changes of the blood flow in the visual cortex and that TCD could allow an assessment of neurovascular coupling (16).

The investigation of electrophysiological response to visual contrast has shown that higher visual contrast produces higher amplitudes of visual evoked potentials (VEP) (17). In addition, TCD allows a simultaneous measuring of VEP, the electrophysiological response of visual cortex activity. In this study of our research group we tested VEFR and VEP to different visual contrasts

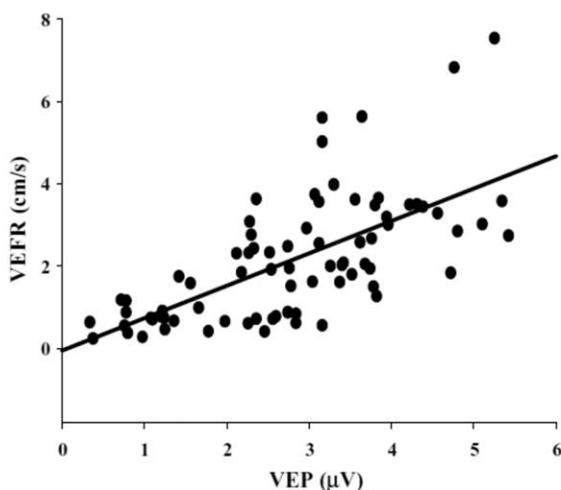


Figure 3. The scatter plot of visually evoked cerebral blood flow responses (VEFR) vs. visual evoked potentials (VEP). The correlation coefficient is $r = 0.69$ with significance $P < 0.01$.

and analysed the relationship between them. The records were made from 35 healthy volunteers aged 38.6 ± 10.1 years. The stimulus was a black-and-white checkerboard with visual contrasts (VC) of 1%, 10% and 100% (Figure 2). The VEFR were measured in the posterior cerebral artery using transcranial Doppler, and the VEP were recorded from the occipital leads. We found the relationship between visual contrast and VEFR ($r = 0.79$, $P < 0.01$) as well as between visual contrast and VEP ($r = 0.71$, $P < 0.01$). We also found moderate association between the VEP and the VEFR ($r = 0.69$, $P < 0.01$) (Figure 3). The analysis of the regression slopes between two different age subgroups ($P < 0.01$) did not show a significant difference ($P = 0.020$). We concluded that a simultaneous recording of VEFR and VEP to visual contrasts could allow an assessment of neurovascular coupling in humans (17).

Age-related changes in the relationship between visual evoked potentials and visually evoked cerebral blood flow velocity response

In one of our study we evaluated neurovascular coupling during normal aging using VEPs and VEFRs. The recordings were made from a group of healthy younger and older subjects. The stimulus was a black and white checkerboard with visual contrasts of 1%, 10% and 100%. The VEFRs were measured in the posterior cerebral artery using TCD simultaneously with VEPs from occipital leads. A significant increase in the VEFRs and VEPs in response to graded visual contrasts ($P < 0.01$) was found in both groups. Linear regression analysis showed a significant positive association between the VEPs and the VEFRs in the younger ($r = 0.66$, $P < 0.01$) and older subjects ($r = 0.74$, $P < 0.01$). We also found significant differences in neurovascular coupling index (VEFR/VEP) between both groups at each visual contrast ($P < 0.01$). We concluded that simultaneous recording of VEFRs and VEPs at graded visual contrasts indicated attenuated neurovascular coupling in older subjects.

TESTING OF CEREBRAL ENDOTHELIUM FUNCTION WITH L-ARGININE

In the last decade, cerebrovascular reactivity to L-arginine (L-A), measured by TCD, has become an established method for evaluation of the cerebral endothelial function (4, 19, 20). Exogenous L-A induces vasodilatation through enhanced production of nitric oxide in the cerebral endothelium. It has been convincingly shown that intravenously administrated L-A increases cerebral blood flow velocities through the large cerebral arteries, which is a consequence of cerebral vasodilatation of associated arterioles (4, 19, 20).

Endothelial dysfunction in stroke patients

Endothelium-dependent vasodilatation could be impaired during hypoperfusion. L-A, a precursor of nitric



Figure 4. Testing of cerebrovascular reactivity to L-arginine with transcranial Doppler sonography in our Neurosonology laboratory.

oxide, is able to elicit endothelium-dependent vasodilation. To determine cerebral vascular endothelial function in the early stages after ischemic stroke, we studied cerebrovascular reactivity to L-A with TCD (Figure 4). The study group consisted of 15 patients with the middle cerebral artery syndrome, aged 57.6 ± 9.8 years. They were investigated on days 7 to 10 after ischemic stroke. The control group consisted of 15 healthy volunteers, aged 58 ± 10.7 years. All subjects received an intravenous infusion of L-A over 20 min at a rate of 1.5 g/min. The mean arterial velocity was measured in both middle cerebral arteries by using a bitemporal monitoring TCD system. At the same time, MAP and HR were measured by Finapres and ECG. The Et-CO₂ was monitored by capnograph. The vm over 5-min intervals at rest and during the infusion of L-A was determined by using the DWL TCD8 software. We found that the vm significantly increased in both hemispheres of both groups ($P=0.00$). Vm differences between rest and L-A stimulation were lower in the ischemic hemispheres compared to the healthy ones ($P=0.00$), but did not differ between the ischemic hemispheres and hemispheres of the healthy group ($P>0.05$). MAP, HR and Et-CO₂ did not change during the infusion ($P>0.05$). We concluded that the cerebrovascular reactivity to L-A is impaired in patients with recent stroke. The amino acid could thus be useful in testing endothelium function both in healthy persons and in stroke patients since endothelium dysfunction seems to be an important factor in reperfusion injury (19).

Endothelial dysfunction in patients with lacunar infarction

It is well known that endothelial dysfunction plays an important role in the pathogenesis of many cardiovascular disorders. In this study was tested the hypothesis that specific, marked endothelial dysfunction of cerebral arteries is present in patients with lacunar cerebral infarctions. Cerebrovascular reactivity to L-A, which reveals the function of the cerebral endothelium, was investigated in patients with lacunar infarctions (20 patients, 11 male and 9 female, aged 60.9 ± 7.3 years), 21 age- and gender-matched asymptomatic patients with similar car-

diovascular risk factors (all patients had arterial hypertension) and 21 age- and gender-matched healthy controls. The vm in both MCAs was measured by TCD during a 15-min baseline period, a 30-min intravenous infusion of L-A and a 15-min interval after L-A infusion. Arterial blood pressure, HR and CO₂ were measured continuously. The measured vm increase during L-A infusion in the patients with lacunar infarctions ($13.4 \pm 9.1\%$) was significantly lower compared to the healthy controls ($20.5 \pm 9.9\%$) but similar to that obtained in the patients with cardiovascular risk factors ($11.5 \pm 8.9\%$). Our results showed that cerebrovascular reactivity to L-A, which demonstrates cerebral endothelial function, is significantly impaired in patients with cardiovascular risk factors. Importantly, we found that patients with lacunar infarctions do not show any additional impairment of cerebral endothelial function (20).

Associations between systemic and cerebral endothelial impairment

In this study the relationships between cerebral and systemic endothelial (dys)function and between cerebral (dys)function and intima-media thickness (IMT) of carotid arteries in patients and healthy volunteers have been investigated. In order to explore these issues, the authors performed a post hoc correlation analysis of cerebrovascular reactivity to L-arginine, a marker of cerebral endothelial function; flow-mediated dilatation (FMD) (Figure 5), a marker of systemic endothelial function; and IMT of the carotid arteries, a marker of the extent of atherosclerosis. Correlations were analyzed in a heterogeneous group consisting of 20 patients with lacunar infarctions (LIs) and extensively impaired endothelial function, 21 patients with similar risk factors (SRs), but without LIs, and 21 healthy controls. Cerebrovascular reactivity to L-A was determined by the TCD, FMD by ultrasound measurements of the brachial artery after hyperemia, and IMT by measurement of the common carotid arteries. Analysis of correlations in the group of 62 subjects revealed that L-A reactivity, which was diminished in LI and SR patients, did not correlate with



Figure 5. The systemic endothelial (dys)function in the physiological and pathological conditions are investigated by flow-mediated dilatation (FMD), a marker of systemic endothelial function, using color-coded Doppler sonography equipment.

FMD, which was also diminished in both LI and SR patients ($Rho = 0.10$ with $P = 0.458$). On the contrary, a significant negative correlation was found between L-A reactivity and IMT ($Rho = -0.30$ with $P = 0.015$). In conclusion, this study investigating relations between cerebral and systemic endothelial dysfunction showed that cerebral endothelial function, determined by L-A reactivity, correlates well with the degree of atherosclerosis determined by IMT but does not correlate with FMD, suggesting that cerebral and systemic endothelial function may not be closely associated (21).

Differences between cerebrovascular reactivity to L-arginine in the anterior and posterior cerebral circulation

Cerebral endothelial function might be different in distinct cerebrovascular territory, thereby making these areas more susceptible to ischemia and stroke. Higher incidence and prevalence of stroke in males suggest that gender could have a strong influence on this difference. In order to evaluate cerebral endothelial function, we compared cerebrovascular reactivity (CVR) to L-A in the anterior and posterior cerebral circulation in healthy young males and females. Thirty healthy subjects, 15 females (32.1 ± 7.1 years) and 15 males (32.2 ± 6.3 years), were included. The mean arterial velocity in the MCA and the PCA was measured by TCD before and after intravenous infusion of L-A, and CVR to L-A was then calculated. Cerebrovascular reactivity to L-A was significantly higher in PCA than in MCA in all subjects (19.2 ± 8.2 vs. $13.6 \pm 7.1\%$, $P = 0.01$). In addition, CVR to L-A was significantly more pronounced in females compared to males in PCA (22.7 ± 8.3 vs. $15.8 \pm 6.7\%$, $p = 0.01$) and MCA (16.8 ± 6.4 vs. $10.4 \pm 6.4\%$, $P < 0.05$). We concluded that lower CVR to L-A and therefore lower cerebral endothelial function in the anterior cerebral circulation and in males might be related to the higher incidence of ischemia and stroke in the anterior cerebral circulation, particularly in males (22).

Cerebral endothelial function in migraine patients

Evidence of migraine involvement in ischemic stroke is growing. Particularly migraine patients with aura (MwA) and young women are more prone to this kind of stroke (23, 24). Ischemic cerebral infarction preferentially affects the posterior cerebral artery distribution in migraine patients (23). In addition, focal ischemic and hypertensive, ischemic-like lesions have been found in the territory of the posterior circulation in migraine patients (24, 25). However, the precise etiology of these lesions, and the reasons why migraine patients seem to be more susceptible to this kind of lesions, remain unknown. On the other hand, evidence of endothelial dysfunction in migraine patients is growing (26). In this view, and according to the fact that pathogenetic mechanisms of stroke occurrence in migraine patients are still not explained, a possible endothelial dysfunction in the posterior cerebral circulation could be crucial in the pathophysiology of migrainous stroke. Mainly due to lack of appropriate

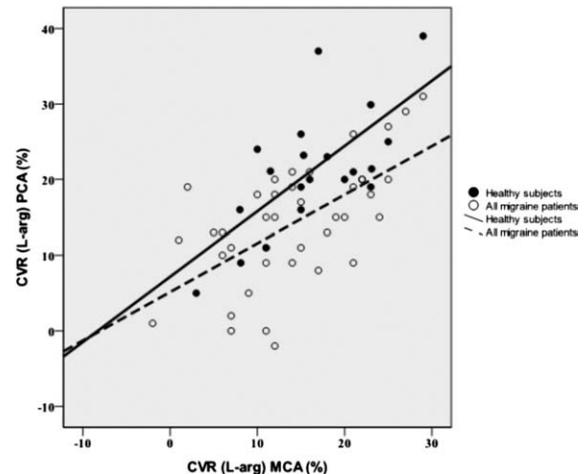


Figure 6. Correlation between cerebrovascular reactivity (CVR) to L-A in the middle cerebral artery (MCA) and the posterior cerebral artery (PCA) in all migraine patients ($P < 0.001$; $r^2 = 0.377$) and healthy subjects ($P < 0.001$; $r^2 = 0.481$).

methods, the evaluation of endothelial function in the posterior cerebral circulation has not been investigated extensively in MwA and without aura (MwoA). The results obtained from a few studies on endothelial dysfunction in migraine are controversial. It is well known that cerebral infarction preferentially affects the posterior cerebral artery distribution in migraine patients. To the best of our knowledge, CVR to L-A, measured by TCD, has not been previously used to determine the posterior cerebral endothelial function in MwA and MwoA. In our study we investigated forty migraine patients without comorbidities (20 MwA, 20 MwoA) and 20 healthy subjects (27). By employing strict inclusion criteria, we avoided the possible vascular risk factors. Mean arterial velocity in the MCA and the PCA was measured by TCD before and after infusion of L-arginine, and CVR to L-A was then calculated. All migraine patients had lower CVR to L-A in PCA ($P = 0.002$) and similar in MCA ($P = 0.29$) compared to healthy subjects. This difference was also present in MwA and MwoA compared to healthy subjects ($P = 0.003$). Lower CVR to L-A in PCA in migraine patients could associate migraine and cerebral infarcts that are more common in the posterior cerebral artery distribution. However, the relationship between cerebral and systemic endothelial function and the anterior and posterior cerebral endothelial function in migraine patients is still not clear. From this reason we compared in our next study cerebral and systemic endothelial function through post-hoc linear regression analysis of CVR to L-A between the MCA and FMD of the right brachial artery and the PCA and FMD in migraine patients without comorbidities and in healthy subjects. The anterior and posterior cerebral endothelial function was also compared using post-hoc linear regression analysis between CVR to L-A in the MCA and the PCA. No significant correlation was found between CVR to L-arginine in the MCA and FMD and in the PCA and FMD in MwA ($P = 0.880$ vs. $P = 0.682$), MwoA ($P = 0.153$ vs. $P = 0.179$) and in healthy subjects ($P = 0.869$ vs. $P = 0.662$). On the

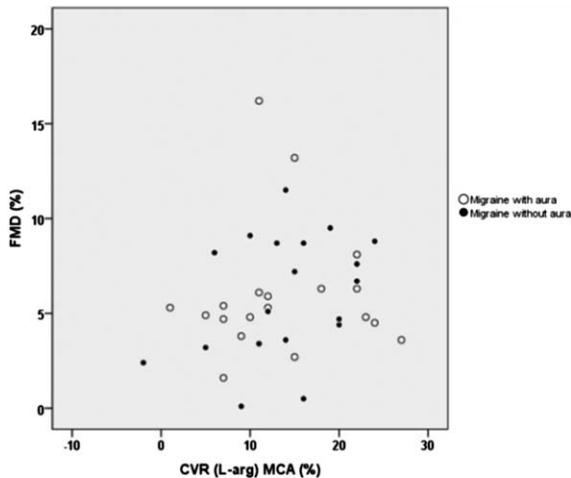


Figure 7. Scatter plot of comparison between CVR to L-A in the MCA and brachial artery FMD in migraine patients with and without aura ($P=0.287$; $r^2 = 0.031$).

other hand, we found a significant correlation between CVR to L-A in the MCA and PCA in MwA ($P=0.004$), MwoA ($P=0.001$) and in healthy subjects ($P=0.002$). Detailed analysis of the linear regression between all migraine patients and healthy subjects did not show any difference in the regression coefficient (slope) ($P=0.382$). However, a significant difference in curve elevation (intercept) was found ($P=0.002$).

Our study suggests that the endothelial function in the cerebral and systemic circulation might be different in migraine patients without comorbidities, while that of the anterior and posterior cerebral circulation might be coupled. These results could improve understanding of endothelial function in migraine patients without comorbidities.

CONCLUSION

Recent developments in fTCD have shown that the technique can assess different functions in the physiological and pathological conditions in humans in a scientific and clinical aspect.

This way, large cohorts of specific clinical and normal populations can be monitored to elucidate different influences of the brain.

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