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Changing cerebral blood flow velocity by transcranial Doppler during head up tilt in patients with diabetes mellitus

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Abstract

Objective: Diabetes mellitus is an independent risk factor for poor prognosis in patients with ischemic stroke. It is known that diabetes mellitus directly affects cerebral vasculature as a secondary, long-term complication of cerebral circulation, and causes cerebral blood flow abnormalities. The abnormalities of cerebral autoregulation also poorly affects the prognosis of ischemic stroke. In this study, we aimed to show the cerebral autoregulation with transcranial Doppler (TCD) ultrasound in diabetic patients with autonomic nervous system abnormalities, determined with electrophysiological studies.

Material and method: Twenty healthy controls and 39 patients, who had at least 2 years of diabetes mellitus, were evaluated (age ranges: 42–75 years). The patients were divided into two groups according to sympathetic skin response and R–R interval variation studies: (1) patients with autonomic neuropathy; (2) patients without autonomic neuropathy. Blood flow velocities were measured during supine position and after the patients were raised upright position on head up tilt table. Arterial blood pressures and heart rates were also evaluated.

Results: Mean blood flow velocities of diabetic patients with autonomic neuropathy were found more decreased at 90 s after the patients were raised upright position.

Discussion: Autonomic neuropathy due to diabetes mellitus affects cerebral autoregulation, and by this way cerebral perfusion loses protection against hemodynamical changes.

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Keywords: Transcranial Doppler; Diabetes mellitus; Cerebral autoregulation; Autonomic neuropathy; Cerebral blood flow

1. Introduction

Cerebral autoregulation (CA) is defined as the intrinsic ability of the brain to maintain constant cerebral blood flow (CBF) during changes of cerebral perfusion pressure [1]. It is known that CBF is sensitive to the changes in carbon dioxide levels of blood. However, under the conditions the stability in carbon dioxide levels allow the other mechanisms such as heart rate and peripheric circulation to operate in controlling the CBF [2]. After standing up, vascular and muscular tonus regulated especially by sympathetic nervous system, maintains the normal CBF [3].

Impairment of cerebral functions and syncope may be seen in patients who had insufficiency of CA [3–5]. It is known that autonomic nervous system is primarily affected in patients with multisystem atrophy and secondarily affected in patients with diabetes mellitus, thus insufficiency of CA is commonly seen in patients with such diseases [6–9].

Diabetes mellitus is known as an independent poor prognostic factor for ischemic stroke [10]. In diabetic patients, the direct abnormalities of CBF and the insufficiency of CA affect the prognosis of ischemic stroke [11].

In recent studies, it is shown that transcranial Doppler ultrasound (TCD) monitoring of mean blood flow velocity during head-upright tilt can allow testing of cerebral autoregulation [12–14]. In this study, we used TCD to show the insufficiency of CA in diabetic patients with autonomic nervous system dysfunction determined with electrophysiological studies.

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2. Material and methods

Thirty-nine (age ranges 42–75 years) patients who had type 2 diabetes mellitus, diagnosed more than 2 years ago, and 20 age matched controls were included in the study. All the subjects were free from cardiac disease, stroke, chronic obstructive lung disease, anemia and polycythemia. The patients who had initial blood pressures higher than 190/100 mmHg or the patients who had history for hypertension were excluded. The patients under the medication of alpha or beta blockers, calcium channel blockers, anti-arithmic agents, and tricyclic antidepressants were also excluded. Subjects avoided caffeine-containing products, nicotine, and alcohol for at least 12 h before the transcranial Doppler study. All of the diabetic patients were from inpatient clinic of the endocrinology department because of uncontrolled glucose levels and receiving subcutan insulin. Arterial blood gas evaluation of all the patients were performed before the study, and the patients who had PaO_2 lower than 95% and $PaCO_2$ higher than 40% were not included.

3. Transcranial Doppler study

Blood flow velocities, pulsatility and resistance indexes of both internal carotid arteries were achieved before the tilt table test, and the patients who had carotid stenosis more than 50% were excluded. After a resting time of at least 10 min in the supine position, TCD evaluation was performed with transcranial Doppler machine (Multidop X4/TCD8, DWL Electronische Systeme GmbH, Sipplingen). The 2 MHz TCD probes were fixed bilaterally over the temporal bone windows with elastic head bandages. The blood flow velocity of the middle cerebral artery was monitored at the depth of 50–60 mm. Systolic, diastolic and mean blood flow velocities of MCAs and pulsatility indexes were measured five times within 10 min during supine position. The formulation described by Gosling "systolic blood flow velocity − diastolic blood flow velocity/mean blood flow velocity" was used for the measurements of pulsatility indexes [15]. Blood pressure and heart rate measurements were also performed five times within the 10 min during the supine position. Then, the tilt table raised to the upright position approximately 80°. The systolic, diastolic, and the mean blood flow velocities, pulsatility indexes, heart rate and blood pressures were measured again five times within the following 10 min during upright position.

4. Electrophysiological investigation

4.1. R–R interval variation (RRIV)

RRIV was performed during quiet and deep breathing. Active and reference recording electrodes were placed on the chest, a ground electrode was placed around one wrist. Recording was performed on Medelec Synergy EMG machine (Oxford Instruments, England). Sweep velocity was 100–200 ms/div, sensitivity was 200–500 μV/div, frequency band was 10–100 Hz. Using the triggering mode and delay line, oscilloscope display is adjusted by the trigger sensitivity and sweep speed so that two QRS complexes are displayed on the screen. Since the first QRS complex is the triggering potential, the variation of timing of the second QRS complex represents the variation in the R–R interval. Twenty traces were recorded and superimposed. Five groups of 20 sweeps were recorded during quiet breathing, and two groups of 20 sweeps were recorded during forced deep breathing at 6 breaths/min. The R–R interval variation was expressed as a percentage of the average R–R interval using the following formula: $(R\text{–}R_{max} - R\text{–}R_{min}) \times 100/R\text{–}R_{mean}$.

4.2. Sympathetic skin response analysis (SSR)

The active recording electrode was placed on palm, 3 cm proximal to the second web space and the reference electrode on the distal phalanx of the third digit for the analysis of SSR. The ground was placed at the wrist proximal to the recording electrodes. Ten consecutive electrical stimuli with 20 mA intensity and 0.2 ms duration were applied to the contralateral median nerve at the wrist, the cathode is placed proximally. The interval of the stimuli was more than 15 s. Band pass was set between 2 and 5000 Hz. Sweep velocity was 300–500 ms/div, sensitivity was 200–500 μV/div. The SSR latency was measured from stimulus onset to the negative peak of the action potentials.

A healthy age matched control group (20 patients) was used to determine the 5–95% confidence intervals for R–R interval variation. The lower limits were found as 11% during rest and 16% during forced deep breathing. As reported by Kucera et al. [16], we used only the absence of SSR as an indicator of autonomic neuropathy because of the SSR amplitude is notoriously variable. The patients were divided into two groups as patients with and without autonomic neuropathy according to electrophysiological investigations. Autonomic neuropathy was diagnosed based on the pathological responses of both tests (RRIV and SSR) and there was no patient with only one abnormal test (either SSR or RRIV) in the group of autonomic neuropathy. The patients were also evaluated for polyneuropathy with electrophysiological investigation.

5. Statistical analyses

No statistical significant difference was found for MBFV between the both MCAs of the patients with Mann–Whitney *U*-test. For this reason, the values of MBFV of bilateral MCAs were evaluated together. 'Repeated measure analysis of variance' test was used for comparison of the changes in MBFV, mean blood pressure and heart rate while patients lying in supine position and upright position, and the same test was

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