Abstract—It has been demonstrated that internal jugular vein (IJV) compression aggravates headache intensity in patients of migraine. We hypothesized that patients with migraine may have veins that are less distensible; consequently, these veins are more likely to develop and transmit venous hypertension caused by the increased venous blood volume during IJV compression. We used ultrasonography to measure the extent of venodilatation and distensibility of IJV in response to increased transmural pressure, which was produced by a Valsalva maneuver. The extent of venodilatation were compared between 23 migraine patients (5 men, 18 women; mean age: 40.22 ± 12.71 years, range: 27–7 years) and 23 age- and gender-matched normal individuals (5 men, 18 women; mean age: 40.23 ± 12.04 years, range: 27–7 years). In the result, the venodilatation of IJV in response to each level of Valsalva pressure in patients with migraine was significantly less than that in normal individuals. Our results suggest that patients with migraine have less compliant IJVs, which makes them susceptible to cerebral venous hypertension. Further studies are needed to elucidate the clinical implications of decreased venous distensibility in migraine patients.

Key Words: Migraine, Venous compliance, Internal jugular vein.

INTRODUCTION AND LITERATURE

Previous studies have shown that internal jugular vein (IJV) compression (Queckenstedt’s maneuver) aggravates headache intensity in patients with migraine (Chou et al. 2004; Doep et al. 2003). Because IJV is the major drainage route for the cerebral venous system in the supine position (Schaller 2004), IJV compression would impair cerebral venous outflow, increase venous blood volume accumulation and, then, increase venous pressure (Klabunde 2004). The pressure can retrogradely transmit to the cerebral venous system, resulting in venous hypertension in the intracranial veins and sinuses and eventually cerebral venous congestion (Chung et al. 2006; Yamazaki and Hirayama 1990). Therefore, the findings of these studies support the fact that cerebral venous congestion and venous hypertension might play a role in the generation of pain in migraine patients.

A greater blood volume represents a higher venous pressure in the IJV (Klabunde 2004; Mohrman and Heller 2003). In our previous study, we have found that greater venous blood volume in the IJV would bring a higher pump-back pressure during a Valsalva maneuver (VM) (Chung et al. 2007). Besides increased venous blood volume, venous back pressure is also likely to be transmitted by a decrease in venous compliance (Hirakawa et al. 1993; Klabunde 2004; Mohrman and Heller 2003). Vessel compliance describes the extent of the volume changes (∆V) in response to a given change in transmural pressure (∆P) (Hirakawa et al. 1993; Klabunde 2004; Mohrman and Heller 2003). Transmural pressure is the difference between the internal and external pressure on the vessel walls. A compliant vein would accommodate the increased venous pressure, for example, from increased venous blood volume, by distending to maintain a normal venous pressure (Hirakawa et al. 1993; Klabunde 2004; Mohrman and Heller 2003). Therefore, we wonder if patients with migraine have greater venous volume and/or less venous distensibility and are, thus, more likely to develop and transmit venous hypertension caused by increased venous blood volume during IJV compression.

In the present study, we used ultrasonography to measure the change in the vessel-lumen area of the IJV
during different grades of VM in patients with migraine and normal individuals respectively. VM is defined as a forceful expiration against a closed glottis, resulting in an increase in intrathoracic pressure and a decrease in venous return to the heart (Attubato et al. 1994). Its effect on IJV is increased venous transmural pressure (Attubato et al. 1994). We hypothesize that patients with migraine, compared with normal individuals, have greater venous volume and/or less venous distensibility, which would be demonstrated by a lower degree of venodilation in response to VM.

MATERIALS AND METHODS

Subjects

We recruited 23 patients with migraine (5 men, 18 women; mean age: 40.22 ± 12.71 years, range: 27–67 years) and 23 age- and gender-matched normal individuals (5 men, 18 women; mean age: 40.23 ± 12.04 years, range: 27–67 years) into the study. The convenience sample of 23 patients was recruited when the patients visited our neurologic clinic for headache; all met the criteria for migraine (Olesen 2005). Their acute headache characteristics were recorded. None of them had other neurologic diseases, heart disease, hypertension, diabetes, hyperlipidemia or smoking history. There were no acute headache attacks and no medications for acute headache or headache prevention within the 72 hours preceding the study. For comparison, we recruited 23 age- and gender-matched normal individuals who were volunteers from our hospital staff or their families. None of them had had neurologic signs or symptoms before or at the present time. All migraine patients and normal individuals received ultrasonography. The institutional review board of this hospital approved the study proposal and we obtained written informed consent from all the participants.

Ultrasonography

Color-Doppler imaging was performed over right IJV in a head straight, flat supine position with a 7-MHz linear transducer (Sonos 5500; Hewlett Packard, Andover, MA, USA) after a 10-min quiet rest. The technician was blinded to patients’ clinical characteristics and study hypothesis. A luxury amount of ultrasound gel was used and great care was taken to avoid compression of neck veins during examination. VM was conducted by forced expiration from patients’ mouths into a flexible rubber tube connected to a manometer. Patients were asked to reach a certain Valsalva pressure and maintain it for at least 10 s. The monitor was frozen at the seventh second of VM (Berczi et al. 2005). A cursor on the screen was used to trace the cross-sectional area of IJV lumen and the area was computed by the software intrinsic to the duplex scanner (Fig. 1). The volume of IJV was expressed as a cross-section area of IJV lumen (volume per unit length, mm³/mm) measured at the level of 5 cm above the junction of the right IJV and brachiocephalic vein (Berczi et al. 2005). The measurements were obtained at baseline (0 mm Hg) and at 10, 20, 30 and 40 mm Hg of Valsalva pressure, respectively (Fig. 1). Each graded Valsalva pressure level was followed by 10-min quiet rest and several practices were performed before the measurement. We measured the volume of IJV at subject’s third attempt of VM of each Valsalva pressure for analysis. The workflow of our experiment is demonstrated in Fig. 2. Previous experiments from our laboratory showed that this measurement has a good reproducibility: In 20 subjects, the coefficients of variation of the measured JV volume at 20 mm Hg and 40 mm Hg (an interval of 2 h) were 9% and 6%, respectively.

Venodilatation measurement

The extent of venodilatation (ΔVn) in response to VM was analyzed by volume (volume per unit length) change at each Valsalva pressure level. ΔV_{10}, ΔV_{20}, ΔV_{30} and ΔV_{40} of each IJV were obtained using the equation $\Delta V_n \text{ (mm}^3/\text{mm}) = V_n - V_0$, where $V_n$ is the measured volume at each Valsalva pressure level and $V_0$ is the measured volume at baseline (0 mm Hg).

Statistical analysis

We used a Wilcoxon two-sample test to compare patients with migraine and normal individuals at baseline

![Fig. 1. Exemplary demonstration: right internal jugular vein (IJV) volume measurement at baseline (0 mm Hg); 20 mm Hg and 40 mm Hg of Valsalva pressure in one of our migraine patient.](image-url)
lumen and for the extent of the IJV venodilatation at different levels of Valsalva pressure. An alpha level of \( p < 0.05 \) (two-sided) was regarded as significant.

**RESULTS**

The clinical characteristics of migraine patients and normal individuals are listed in the Table 1. All patients met the criteria of migraine without aura. The trigger factors of acute migraine were stress (69.6%), sleep deprivation (69.6%), physical activities (26.1%) and menstruation (26.1%). During the ultrasonographic study, none of the patients or normal individuals developed acute headache.

In 10 individuals among the normal group, the coefficients of variation of the measured JV volume at 20 mm Hg and 40 mm Hg (an interval of 2 h) were 11% and 5%, respectively. The pressure-volume relationships of right IJV in patients with migraine and normal individuals are shown in Fig. 3. The baseline volume (mm\(^3/mm\), mean \( \pm SD \)) of the migraine group vs. the normal group in the right IJV were 78.26 \( \pm 34.88 \) vs. 64.48 \( \pm 25.55 \) (\( p = 0.13 \)). In both the migraine and normal groups, the extent of pressure-response venodilation surged at lower Valsalva pressures and was much less at higher Valsalva pressures.

The venodilatation of IJV in response to each level of Valsalva pressure in patients with migraine was significantly less than in normal individuals (Fig. 4). The volume change (\( \Delta V, \text{mm}^3/\text{mm}, \text{mean} \pm \text{SD} \); migraine group vs. normal group) in response to graded Valsalva pressure in IJV was 15.75 \( \pm 11.04 \) vs. 26.68 \( \pm 21.08 \) at 10 mm Hg (\( p = 0.04 \)), 17.12 \( \pm 12.48 \) vs. 45.05 \( \pm 32.05 \) at 20 mm Hg (\( p = 0.0004 \)), 18.05 \( \pm 12.69 \) vs. 54.01 \( \pm 39.84 \) at 30 mm Hg (\( p < 0.0001 \)), and 21.42 \( \pm 15.10 \) vs. 54.19 \( \pm 39.74 \) at 40 mm Hg (\( p = 0.0008 \)).

**DISCUSSION AND SUMMARY**

In the present study, we have found that, compared with normal individuals, patients with migraine have stiffer IJVs, which was demonstrated by a lesser degree of venodilatation in response to increased intramural pressure in the IJV. The greater baseline volume in the right IJV for the migraine group was nonsignificant (\( p = 0.13 \)).

Venous compliance was initially studied in vitro and in vivo by plethysmography (Neglen and Raju 1995). Using ultrasonography, a noninvasive method, to measure the venous volume change of large veins in relation to a variety of maneuvers or physiologic circumstances are currently conducted (Armstrong et al. 1994; Berczi et al. 2005; Botero et al. 2001; Duvvot et al. 1994; Lobato et al. 1998). Those previous in vivo and in vitro venous studies all agreed that large veins have a greater volume increment in response to increased transmural pressure (a greater distensibility) within a wide range of physiologic pressures and a decreasing distensibility with higher transmural pressures (Armstrong et al. 1994; Berczi et al. 1992, 2005; Botero et al. 2001; Dobrin et al. 1988, 1989; Duvvot et al. 1994; Hirakawa et al. 1993; Lobato et al. 1998; Neglen and Raju 1995). In our study, the pressure-volume relationship (Fig. 3) of IJV in normal individuals was consistent with this concept. However, the pressure-volume relationship of IJV in patients with migraine was different from that of normal individuals. The pressure-volume relationship of IJV in the migraine group showed an increased venodilatation at lower transmural pressures and a gradually decreasing venodilatation at higher transmural pressures but a mildly increased venodilatation at the highest transmural pressure of IJV.

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![Fig. 2. The workflow of our experiment.](image-url)
Although the definite pathophysiology is still unknown, most agree that migraine is a brain disorder with trigeminovascular involvement (Goadsby et al. 2002; Silberstein 2004). Several research findings support that the cerebral venous system dominates the cerebrovascular role in the mechanism of migraine (Chou et al. 2004; Dimitriadou et al. 1992; Doepp et al. 2003; Geppetti et al. 1990; Goadsby and Zagami 1991; Kaube et al. 1992; Strassman et al. 1996). A widely acceptable animal model of migraine has revealed preferential venules with inflammation and venous dilatation following trigeminal electrical stimulation (Dimitriadou et al. 1992; Geppetti et al. 1990). In our patients, frequent and similar trigger factors of migraine (69.6%) were also noted. Some of those frequently found trigger factors are known to alter sympathetic tone (Minson et al. 2000; Rozanski et al. 1999; Zhong et al. 2005). Acute stress would stimulate the sympathetic nervous system (Rozanski et al. 1999), acute sleep deprivation would increase sympathetic and decrease parasympathetic cardiovascular modulation (Zhong et al. 2005) and the menstrual cycle has been found to alter sympathetic outflow by hormonal fluctuation (Minson et al. 2000). Those trigger factors that increase sympathetic activity would increase venous pressure by increased venous tone (Klabunde 2004), which makes migraine patients with underlying less-compliant IJV subjective to more severe venous hypertension, which then leads to headache attacks. Recently, another research of migraine has found fewer migraine attacks at weekends and on days off (Alstadhaug et al. 2007), which might be explained by our finding. Days off might protect against migraine, which is susceptible to elevated cerebral venous pressure by getting rid of stress and its related elevated sympathetic tone.

Besides the sympathetic activity, the components and thickness of the venous wall also have an influence on venous compliance. More thickness and/or collagen proliferation of the venous wall contribute to decreased venous compliance (Hirakawa et al. 1993; Moody et al. 1995). Whether patients with migraine have a pre-existing, increased sympathetic activity or abnormal venous wall architectures, which decreases the venous compliance,
needs further investigation. There is another possible explanation for patients with migraine having less venodilation in response to increased transmural pressure in our study. The pressure-volume curve of a normal large vein reveals a larger venous volume and a decreased distensibility at higher venous pressures (Armstrong et al. 1994; Berczi et al. 1992, 2005; Botero et al. 2001; Dobrin et al. 1988, 1989; Duvekot et al. 1994; Hirakawa et al. 1993; Lobato et al. 1998; Neglen and Raju 1995). Since our patients with migraine have a larger volume of IJV at baseline, it is possible that they have a higher original IJV venous pressure at baseline, which leads to less distensibility. In patients with migraine, is there an underlying IJV venous hypertension that might be caused by proximal venous obstruction (Chung et al. 2006), pre-existing increased sympathetic activity, or other unknown factors? This also needs further study.

There are limitations in our study. We did not measure the definite transmural pressure in IJV, which might be a concern in studying IJV compliance. Since our studied individuals were relative young and absent of cardiovascular and chest diseases, and the normal venous pressure range of large veins within and near the thorax are narrow (Klabunde 2004; Mohrman and Heller 2003), we presumed the baseline transmural pressure of IJV were the same in each individuals. Furthermore, we measured the cross-section lumen area of IJV at the same height of IJV in each individual to ensure similar baseline transmural pressure and similar effect of increased intravascular pressure by VM. In our result, the baseline volumes of IJV in migraine and normal group were not significantly different, which further ensure the similar baseline intravascular pressure in the IJV (Klabunde 2004; Mohrman and Heller 2003). Therefore, the comparison of venodilatation at each Valsalva pressure between migraine group and normal group should be reasonable.

In summary, we found that patients with migraine have less compliant IJVs, which makes them susceptible to cerebral venous hypertension. Our results suggest that cerebral venous hypertension might be involved in the pathophysiology of migraine.

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