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Cerebral Blood Perfusion is Improved Regionally After Shunt Surgery in the High-Pressure Hydrocephalic Brain

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ABSTRACT

AIM: To show the abnormal cerebral hemodynamics, in high-pressure hydrocephalic patients, could be restored by shunt surgery, and the tympanic membrane temperature (TMT) could be used to non-invasively monitor this recovery process.

MATERIAL and METHODS: One-hundred-and-four patients, with high-pressure hydrocephalus (spinal tap opening pressure >180 mmH_2O), were prospectively enrolled in our study. The computed tomography perfusion (CTP) was scheduled for 7-10 days pre- and post-shunt surgery. The TMT and Glasgow Coma Scale (GCS) scores were collected during the same session.

RESULTS: The CTP after the shunt surgery revealed a significant increase in cerebral blood volume (CBV) in both hemispheres ($p<0.05$). More specifically, this CBV increase was observed in the midbrain, cerebellum, basal ganglion, temporal lobe, and frontal lobe regions (all $p<0.05$). Simultaneously, patients' post-surgical TMT and GCS scores also increased compared to their pre-surgical scores since the first post-shunt follow-up ($p<0.01$). Notably, while the GCS scores continued to increase during the post-shunt follow-up, the TMT exhibited a fluctuation period after the shunt and required seven days to reach a steady state.

CONCLUSION: Our study revealed that a shunt could significantly increase cerebral perfusion in high-pressure hydrocephalic patients in a region-specific manner. During the perioperative period of hydrocephalus, TMT can be used to monitor cerebral hemodynamic changes.

KEYWORDS: Hydrocephalus, Ventriculoperitoneal shunt, Perfusion, Temperature, Tympanic membrane

ABBREVIATIONS: ACA: Anterior cerebral artery, **CBF:** Cerebral blood flow, **CBV:** Cerebral blood volume, **CSF:** Cerebrospinal fluid, **CTP:** CT perfusion, **iNPH:** Idiopathic normal pressure hydrocephalus, **GCS:** Glasgow Coma Scale, **ICP:** Intracranial pressure, **MCA:** Middle cerebral artery, **MEC:** The middle ear cavity, **MTT:** Mean transit time, **ROIs:** Regions of interest, **TCD:** Transcranial Doppler, **TMT:** Tympanic membrane temperature

INTRODUCTION

Hydrocephalus is a common but potentially life-threatening neurological condition (12). Although an excessive amount of cerebrospinal fluid (CSF) is found within the ventricular system, the mechanisms underlying hydrocephalus remain largely unknown. Previous studies proposed the cerebral blood flow (CBF) hypothesis, suggesting that a global CBF decrease is the major abnormality of hydrocephalus, and a shunt could prominently increase CBF and simultaneously relieve symptoms in patients with hydrocephalus (8,28,47). However, this observation is mainly based on studies focusing on idiopathic normal-

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pressure hydrocephalus (iNPH). Little is known about cerebral hemodynamics in high-pressure hydrocephalus. Additionally, CBF reduction is not a specific sign of hydrocephalus, as it has also been observed in other cerebral metabolism-related diseases (23). Thus, it remains unclear whether abnormal cerebral hemodynamics exist in patients with high-pressure hydrocephalus.

According to Pennes' bioheat equation, blood is the main heat transfer vehicle within the body, and tissue temperature is directly proportional to its blood flow (38). Thus, an increase in blood perfusion volume leads to an increase in the rate of heat transfer from the blood to the surrounding tissue. Previous studies have revealed a positive correlation between cerebral perfusion status and cerebral temperature in animals (41-43). In the neuro-intensive care setting, targeted cerebral temperature management, also known as therapeutic hypothermia, is an intentional therapeutic strategy to strictly control the cerebral temperature within a certain range (44). Thus, neurosurgeons can understand the cerebral perfusion status by monitoring cerebral temperature, which guides them to promptly adjust the therapeutic regimen and thus improves outcomes in patients with traumatic brain injury (TBI) and stroke (9,39). Because of the global CBF decrease (8,28,47), a hydrocephalic brain should maintain a relatively lower cerebral temperature and recover to a normal level after shunt surgery. However, nothing is known about changes in cerebral perfusion and temperature in the hydrocephalic brain, before and after shunt surgery.

The middle ear cavity (MEC) is a narrow air-filled space located in the petrous portion of the temporal bone. For descriptive purposes, the MEC is depicted as a rectangular room with four walls, a floor, and a ceiling. The ceiling of the MEC is called the tegmen tympani, which delimits it from the temporal lobe of the cerebrum. Additionally, a thin plate of bone consists of the MEC floor, which separates the MEC from the internal carotid artery anteriorly and the jugular bulb posteriorly (14). Since these heat sources (the temporal lobe, internal carotid artery, and jugular bulb) all neighbor the MEC and heat the MEC radiatively, the changes in the cerebral and MEC temperatures are synchronized. As the tympanic membrane forms the outer boundary of the MEC, these anatomical features create the foundation of the tympanic membrane temperature (TMT) to be used as an inference to cerebral temperature via the MEC. This hypothesis is well supported by the academic community (5,10,30,31,34), and TMT has been widely used to indicate the changes in cerebral temperature in animal studies (2,3).

Based on these studies, we hypothesized that high-pressure hydrocephalic patients suffer from abnormal cerebral hemodynamics, which could potentially be restored by shunt surgery. Since we have previously observed a simultaneous increase in cerebral perfusion and TMT after cranioplasty (20) as well as increased TMT after shunt placement (21), we further hypothesized that the restored cerebral perfusion by the shunt in the hydrocephalic brain could be captured by monitoring TMT.

MATERIAL and METHODS

The institutional ethics committee approved the research protocol before the study was conducted in our hospital's Neurosurgery Department. All patients were informed about the study procedures and provided written informed consent prior to enrollment. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and the Helsinki Declaration of 1975, as revised in 2008.

Patients' Information and Inclusion Criteria

All patients were referred by various clinical sources for the evaluation of communicating hydrocephalus due to their symptoms and imaging related to the diagnosis. The patients had to satisfy the following inclusion criteria:1) $\geq$18-years-old, 2) an intact cranial cavity (If the patient previously underwent a craniectomy, cranioplasty was required before enrollment); 3) a CT or MRI scan was required before a high-volume spinal tap test to confirm the communicating hydrocephalus diagnosis (All patients must have fulfilled the mandatory criterion of the Evans index); 4) a high-volume spinal tap (HiVol-ST) was required to identify the opening pressure [a.k.a. the intracranial pressure (ICP) >180 mmH_2O] as well as to achieve an increase in the Glasgow Coma Scale (GCS) 12 hours after HiVol-ST; 5) absence of any contraindication of the shunt surgery; 6) voluntary provision of written informed consent; and 7) all CSF laboratory parameters, including white blood cell, red blood cell, protein, glucose, and chloride concentrations, must have been in the normal range to minimize the risk of shunt malfunction. The HiVol-ST was performed slowly to ensure the safety of enrolled patients. Overall, we enrolled 104 patients in our study (55 males and 49 females). All 104 patients finished the TMT and GCS score collection while 34 cases finished two CTP tests.

All patients received a single ventriculoperitoneal shunt using either a Codman-Hakim programmable valve with a SIPHONGUARD (Codman, Johnson & Johnson, Raynham, MA, USA) or a MIETHKE proGAV® shunt system valve with **s**iphon compensating gravitational device (Braun, Tuttlingen, Germany). The valve pressure setting was determined from the closing pressure during HiVol-ST after the removal of 30 ml CSF.

Study Design

Cerebral perfusion studies using CTP were scheduled 7-10 days pre- and post-shunt. All patients underwent GCS evaluation and TMT acquirement 1-2 days prior to- and 2-3, 4-7-, and 8-10-days post-shunt surgery.

Brain CT Perfusion Study

All brain CTP examinations were carried out on the Philips 64-section CT scanner (Philips Healthcare, Cleveland, OH, USA). Five seconds after 35 ml of non-ionic contrast agent (Iomeron 300 mg/ml, Bracco Imaging SPA) was injected into the patient at a rate of 4 ml/s with a power injector (Medrad, Indianola, PA), CTP started to collect perfusion images. The CT scanner software automatically generated perfusion images

including CBF, mean transit time (MTT), and cerebral blood volume (CBV). The images were stored and subsequently analyzed by an independent technician. Perfusion parameters were collected from both pan-hemisphere regions and eight regions of interest (ROIs), including the frontal lobe, parietal lobe, occipital lobe, temporal lobe, thalamus, basal ganglia, mesencephalon, and cerebellum.

TMT Measurement and GCS Score Collection

The Braun ThermoScan PRO 4000 (Welch Allyn Braun ThermoScan®, Kaz USA, Inc.) was used to collect TMT. After we inspected the patients' ear canals to exclude any obstructions that could cause detection errors, patients were placed in the supine position for 5 min before TMT collection. The temperature from the forehead was also measured in the same follow-up session using a Braun Forehead Thermometer BFH175US (Welch Allyn Braun ThermoScan®, Kaz USA, Inc.). The GCS scores were collected during the same follow-up session, as previously described (52).

Statistical Analysis

All values are expressed as mean ± SD. GraphPad® Prism 8.0 (GraphPad Prism Software Inc, California, CA, USA) was used for data analysis. The significance of data differences was tested using pairwise comparisons of variables before and after shunt placement. Correlations among CBV, TMT, and GCS scores were verified using Pearson's correlation coefficient. Statistical significance was set at $p<0.05$.

RESULTS

Patient Demographics

We prospectively enrolled a total of 104 patients in our study. The 104 patients comprised 55 males and 49 females, with an average age of 57.3 ± 19.4. Among them, 50% (n=52) complained of a medical history of subarachnoid hemorrhage. TBI, intraventricular hemorrhage, and meningitis history had also been reported, accounting for 23.1% (24 cases), 10.6% (11 cases), and 5.8% (6 cases), respectively, of the entire study population. Of all the patients, 13.5% (14 cases) could not recall any significant medical history. The average opening and closing pressure of the HiVol-ST were 243.1 ± 29.4 and 139 ± 48.4 mmH_2O, respectively.

Brain CTP Examination

After shunt placement, no surgery-related complications or new neurological deficits were identified in any of the patients.

Overall, before shunt placement, cerebral blood perfusion was equal between the two hemispheres ($p>0.05$, Figure 1, Table I). At the post-surgical follow-up, the shunt resulted in significantly increased perfusion (CBV) in both hemispheres (both $p<0.05$). To better understand the regional impact of the shunt on the brain, we further investigated the hemodynamic changes in eight ROIs, which were divided into three groups based on their blood supply source (Tables I-III).

Before shunt placement, all ROIs supplied by the posterior cerebral circulation (PCA) showed no difference between the two hemispheres ($p>0.05$). After the shunt, an instant

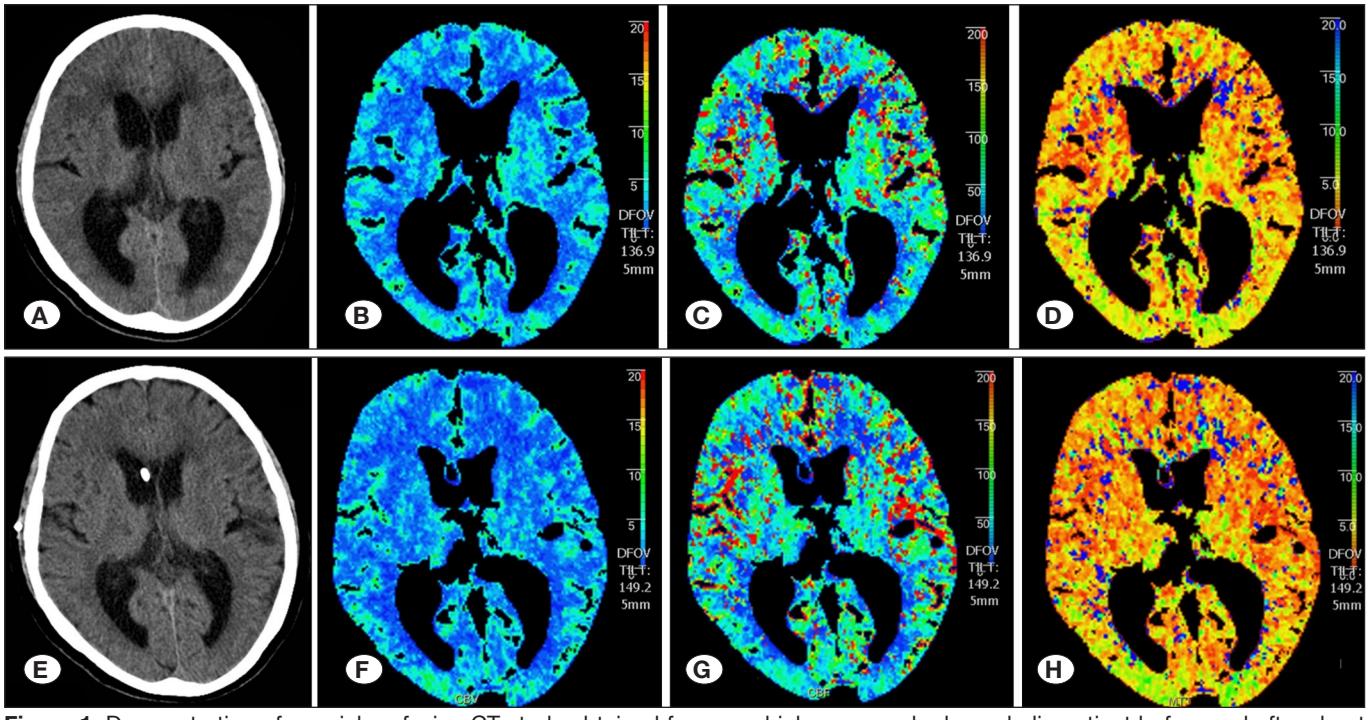

Figure 1: Demonstration of a serial perfusion CT study obtained from one high-pressure hydrocephalic patient before and after shunt surgery. Axial CT scans obtained images without contrast addition **(A & E)** and perfusion maps of CBV **(B & F)**, CBF **(C & G)**, and MTT **(D & H)** at the level of the foramen of Monro. Studies were obtained before the shunt (upper row) and 7 days (lower row) after a shunt.

elevated CBV was observed in two out of four ROIs in both hemispheres, the mesencephalon and cerebellum (both p<0.05). This was mainly due to the elevated CBF (p<0.05) and MTT (p<0.05) in those regions after the shunt. In contrast, the thalamus exhibited an apparently decreased CBV after a shunt was placed in both hemispheres (p<0.05), which was mainly due to the decrease in CBF and MTT at the shunt and contralateral sides, respectively (both p<0.05). During the entire testing period, the occipital lobe demonstrated constant CBV, CBF, and MTT (all p>0.05).

The middle cerebral artery (MCA)-perfused regions also responded to the shunt in a regionally specific pattern. First, shunt surgery predominantly elevated CBV and CBF in both the basal ganglion and temporal lobe in both hemispheres (p<0.01). After the shunt was placed, MTT was found to be

Table I: The Changes in Cerebral Blood Volume (CBV) at Shunt and Contralateral Sides Before and After Shunt Surgery. The Pre-and Post-Shunt Follow-Ups were Scheduled 7–10 Days Before and After Shunt, Respectively. The Asterisk Indicated Statistical Significance Existed in the Same Hemisphere Between Two Follow-Ups (* and ** indicated p<0.05 and <0.01, respectively)

Cerebral Blood Volume (ml/100g brain tissue)		Pre-shunt		Post-shunt	
		Shunt side	Contralateral side	Shunt side	Contralateral side
Pan hemisphere		2.95 ± 0.52	2.99 ± 0.46	3.11 ± 0.57 *	3.05 ± 0.61*
PCA	cerebellum	3.53 ± 0.28	3.8 ± 0.47	4.18 ± 0.37 *	4.3 ± 0.65 *
	mesencephalon	2.44 ± 0.34	2.33 ± 0.21	2.91 ± 0.63 *	3.11 ± 0.41 **
	thalamus	3.07 ± 0.53	3.2 ± 0.34	2.4 ± 0.01 *	2.58 ± 0.51 *
	occipital lobe	3.71 ± 0.43	3.22 ± 0.53	3.68 ± 0.86	3.13 ± 0.56
MCA	frontal lobe	3.14 ± 0.84	3.2 ± 0.86	2.65 ± 1 *	2.59 ± 0.87 *
	parietal lobe	3.45 ± 0.86	3.14 ± 0.61	2.99 ± 0.87 *	2.85 ± 0.89 *
	temporal lobe	2.46 ± 0.44	3 ± 0.64	3.46 ± 0.54 **	3.37 ± 0.74 *
	basal ganglion	3.01 ± 0.5	3.07 ± 0.37	3.46 ± 0.39 **	3.69 ± 0.13 **
ACA	frontal lobe	2.18 ± 0.43	2.25 ± 0.62	2.79 ± 0.48 *	2.42 ± 0.62
	parietal lobe	2.56 ± 0.64	2.75 ± 0.43	2.54 ± 0.43	2.41 ± 0.4

PCA: *Posterior cerebral circulation,* ***MCA:*** *Middle cerebral artery,* ***ACA:*** *Anterior cerebral artery.*

Table II: The Changes in Cerebral Blood Flow (CBF) at Shunt and Contralateral Sides Before After Shunt Surgery. The Pre-and Post-Shunt Follow-Ups Were Scheduled 7–10 Days Before and After Shunt, Respectively. The Asterisk Indicated Statistical Significance Existed in the Same Hemisphere Between Two Follow-Ups While the Pound Indicated Statistical Significance Existed Between the Opposite Hemispheres in the Same Follow-Up (*, **, and # indicated P < 0.05, <0.01, <0.05, respectively)

Cerebral Blood Flow (mL/100 g/min)		Pre-shunt		Post-shunt	
		Shunt side	Contralateral side	Shunt side	Contralateral side
PCA	cerebellum	50.42 ± 6.38	51.73 ± 7.08	52.96 ± 2.41	56.72 ± 11.18 *
	mesencephalon	42.67 ± 4.05	56.57 ± 7.47	52.22 ± 15.77 *	65.3 ± 5.39 *
	thalamus	64.63 ± 3.94	48.94 ± 7.61	56.74 ± 22.62 *	52.46 ± 14.94
	occipital lobe	51.67 ± 11.93	38.37 ± 17.95	48.14 ± 11.31	41.45 ± 9.06
MCA	frontal lobe	57.18 ± 26.14	60.62 ± 26.1	55.35 ± 9.9	62.38 ± 10.04
	parietal lobe	48.85 ± 14.7	52.14 ± 13.25	46 ± 10.15	64.28 ± 26.38
	temporal lobe	35.42 ± 9.1	46.93 ± 16.07	59.71 ± 9.53 **	72.81 ± 13.57 ** #
	basal ganglion	53.49 ± 14.3	71.06 ± 18.53	67.33 ± 8.07 **	85.53 ± 3.28 ** #
ACA	frontal lobe	45.8 ± 18.5	58.06 ± 18.9	51.34 ± 9.2 *	59.54 ± 8
	parietal lobe	36.12 ± 7.3	38.8 ± 6.22	41.67 ± 8.72 *	43. 28 ± 10.3

PCA: *Posterior cerebral circulation,* ***MCA:*** *Middle cerebral artery,* ***ACA:*** *Anterior cerebral artery*

Table III: The Changes in Meant Transit Time (MTT) at Shunt and Contralateral Sides Before and After Shunt Surgery. The Pre-and Post-Shunt Follow-Ups were Scheduled 7–10 Days Before and After Shunt, Respectively. The Asterisk Indicated Statistical Significance Existed in the Same Hemisphere Between Two Follow-Ups While the Pound Indicated Statistical Significance Existed Between the Opposite Hemispheres in the Same Follow-Up (*, **, and # indicated P < 0.05, <0.01, <0.05, respectively)

Mean Transit Time (second)		Pre-shunt		Post-shunt	
		Shunt side	Contralateral side	Shunt side	Contralateral side
PCA	cerebellum	4.18 ± 0.25	4.42 ± 0.18	4.67 ± 0.79 *	4.57 ± 0.23
	mesencephalon	3.75 ± 0.56	3.13 ± 0.58	4.14 ± 1.29 *	3.68 ± 0.53 *
	thalamus	3.82 ± 1.27	4.58 ± 0.43	3.64 ± 0.04	3.77 ± 0.37 *
	occipital lobe	5.02 ± 0.62	5.22 ± 0.78	5.181 ± 0.7	5.27 ± 0.61
MCA	frontal lobe	4.67 ± 1.18	4.4 ± 1.08	4.26 ± 0.82	3.63 ± 0.3 *
	parietal lobe	4.88 ± 0.72	4.36 ± 0.77	4.26 ± 0.48	3.39 ± 0.47 **
	temporal lobe	5.33 ± 0.6	4.87 ± 0.9	4.82 ± 0.47 *	3.66 ± 0.39 *#
	basal ganglion	4.32 ± 0.6	3.71 ± 0.63	3.6 ± 0.38 *	3.39 ± 0.21
ACA	frontal lobe	4.73 ± 1.12	4.7 ± 1.6	4.3 ± 0.8	3.6 ± 0.4 *
	parietal lobe	4.91 ± 0.68	4.75 ± 0.41	4.5 ± 0.45 *	4.42 ± 0.68

PCA: *Posterior cerebral circulation,* ***MCA:*** *Middle cerebral artery,* ***ACA:*** *Anterior cerebral artery.*

predominantly inhibited in the temporal lobe (p<0.05). In contrast, in the frontal and parietal lobes supplied by the MCA, both regions appeared to show downregulated CBV (p<0.05), indicating decreased perfusion in these regions post-surgery. The drop in MTT was also monitored in both regions after the shunt (p<0.05 for the frontal lobe, p<0.01 for the parietal lobe).

We further tested the frontal and parietal lobes next to the callosal sulcus, which was perfused by the anterior cerebral artery (ACA). Contrary to the regions supplied by the MCA, the frontal lobe supplied by the ACA exhibited a significant elevation in CBV and CBF (p<0.05). In contrast, compared to the pre-surgical perfusion status, the shunt did not change the CBV of the ACA-supplied parietal region (p>0.05) because CBF and MTT exhibited reversed shifting.

Using TMT to Assess the Cerebral Hemodynamic Changes

As described in our previous study, TMT could potentially be used to indirectly monitor cerebral blood perfusion status (20). Thus, to understand the effect of shunt surgery on modifying cerebral perfusion, the TMT was collected in all patients both pre- and post-surgery (Figure 2, Table IV). At the first post-surgical follow-up, patients' TMT of both ears were found to be significantly higher than those from the pre-surgical follow-up (p<0.01). Additionally, the TMT on the side of the ventricular drainage tube was significantly higher than that on the contralateral side (p<0.01). At the second post-surgical follow-up, while TMT remained predominantly increased compared to that from the pre-surgical follow-up (p<0.05), a significant drop in TMT was observed compared to that of the first post-surgical follow-up (p<0.05). Moreover, the difference between the TMT from the shunt and the contralateral side was insignificant (p>0.05). At the third post-surgical follow-up, the TMT mean values were not different from those from the second follow-up (p>0.05) and remained elevated compared to those of the pre-surgical follow-up (p<0.05). No differences were observed in bilateral TMT (p>0.05).

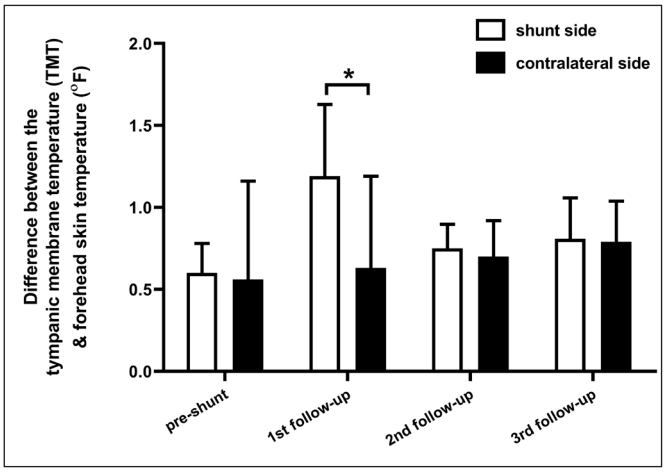

Figure 2: The difference between tympanic membrane temperature (TMT) and forehead skin temperature obtained from all shunt patients. Data were collected from four follow-ups, which were 1-2 days before and 2-3, 4-7, and 8-10 days after shunt surgery. The bilateral TMT showed volatility phases after the shunt as the TMT from the shunt side was higher than that of the contralateral side. This difference eventually disappeared, but the mean TMT remained higher than that of the pre-surgical ones. The asterisk indicated a significant difference between the two groups (p<0.05).

We further performed a correlation study between the shunt-induced variation in TMT and CBV of the temporal lobe and

Table IV: The Changes in Tympanic Membrane Temperature (TMT), TMT Difference, Patients' Glasgow Coma Scale (GCS) Score, and Body Temperature Before and After Shunt Surgery. The TMT Value was Presented in Fahrenheit Degrees (°F). The TMT Difference was Obtained by Using the Equation "TMT Difference = $TMT_{shunt\ side}$ - $TMT_{contralateral\ side}$". Different Letters Indicated Statistical Significance within the Same Hemisphere Among Different Follow-Ups (The Same Row) While the Asterisk Indicated Statistical Significance Between the Two Hemispheres in the Same Follow-Ups (the same column) (*** indicated p<0.001)

	Pre-shunt	1st post-shunt follow-up	2nd post-shunt follow-up	3rd post-shunt follow-up
TMT difference (°F)				
Shunt side	98.57 ± 0.7 [a]	99.62 ± 0.5 [b]	98.97 ± 0.46 [c]	98.97 ± 0.12 [c]
Contralateral side	98.58 ± 0.6 [a]	99.13 ± 0.77 [b ***]	98.79 ± 0.44 [c]	98.63 ± 0.35 [c]
Difference	-0.06 ± 0.55 [a]	0.49 ± 0.68 [b]	0.18 ± 0.26 [c]	0.22 ± 0.46 [c]
GCS	12.4 ± 2.2 [a]	13 ± 3.1 [ab]	13.6 ± 2.2 [bc]	13.7 ± 2.8 [c]
Body Temperature (°F)	98.26 ± 0.48	98.34 ± 0.57	98.3 ± 0.51	98.23 ± 0.39

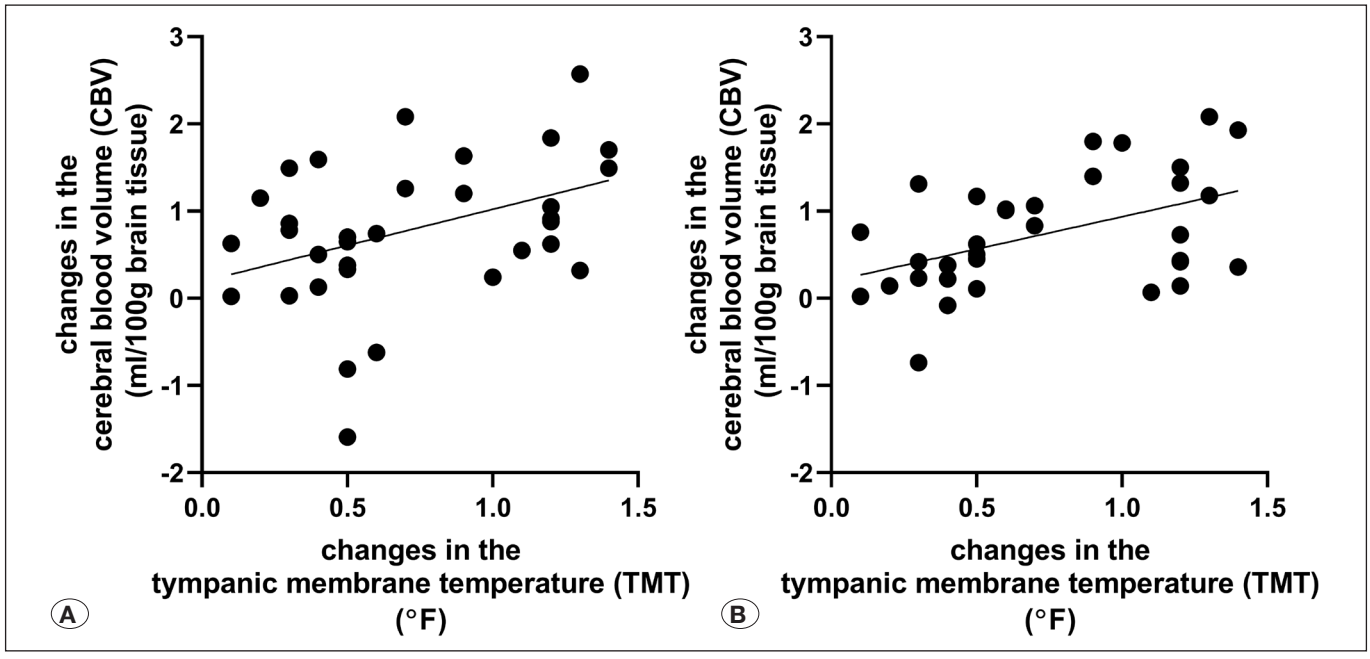

Figure 3: The correlation between the shunt-induced changes in tympanic membrane temperature (TMT) and cerebral blood volume (CBV) at the temporal lobe and mesencephalon on the shunt side. The differences of TMT and CBV were calculated from their corresponding pre-and post-shunt value. Our data demonstrated a tight correlation between changes of TMT and CBV in **(A)** the temporal lobe (slope = 0.83 ± 0.33, R^2 = 0.16, p=0.017) as well as **(B)** the mesencephalon (slope = 0.74 ± 0.25, R^2 = 0.22, p=0.005).

mesencephalon, whose temperatures were suggested to be reflected by the tympanic membrane based on their close anatomic loci toward the middle ear cavity (30) (Figure 3). Both TMT and CBV data were collected from the shunt side. Our data demonstrated a strong correlation between the variation of TMT and CBV in the temporal lobe (slope = 0.83 + 0.33, R^2 = 0.16, P = 0.017) as well as the mesencephalon (slope = 0.74 + 0.25, R^2 = 0.22, p=0.005).

During the entire perioperative period, the body temperature of all patients varied slightly from the normal range (Table IV). Contrary to the volatile phases of TMT, the GCS score showed a sustainable increase after shunt placement (Table IV).

DISCUSSION

Although the precise definition is controversial, hydrocephalus generally refers to a neurological disorder that has an abnormal CSF build-up, resulting in abnormal expansion of the cerebral ventricles that puts pressure on the cerebral tissue, resulting in a myriad range of neurological problems. Since the normal ICP is defined between 5 and 13 mmHg (70 – 180 mmH_2O) (16, 37), hydrocephalus can be further divided into iNPH and high-pressure subtypes. The iNPH is usually insidiously progressive, with cardinal symptoms, such as gait impairment, dementia, and urinary incontinence. Meanwhile, disproportionate widening of the ventricles (e.g., Evans index ≥ 0.3) is typically

manifested in neuroimaging. High-pressure hydrocephalus can be differentiated from iNPH based on its established pathogenesis. It is reported that the common causes of high-pressure hydrocephalus include subarachnoid hemorrhage, TBI, meningitis, and intraventricular hemorrhage (40). Under such circumstances, there is an inadequate passage of CSF from its point of production to its absorption site, which is typically accompanied by elevated ICP (>180 mmH_2O). Shunt surgery is the optimal intervention for iNPH, which has previously been shown to improve blood flow parameters in the MCA using transcranial Doppler (TCD) (1). However, to date, no study has focused on cerebral hemodynamics in high-pressure hydrocephalus in the deep brain structures before and after shunt surgery. Nor has any study reported a novel non-invasive and easy modality to keep tracking the status of cerebral perfusion and subsequent shunt status. In this study, we used CTP to monitor cerebral perfusion changes in various regions before and after shunt placement. Our data revealed that the shunt could rectify the inhibited CBV within 7-10 days, both pan-cerebrally and region-specifically. However, this improved CBV was not instantly achieved, as TMT revealed a bilateral volatile phase immediately after shunt surgery, which gradually reached a steady state. Our study indicated that impaired cerebral perfusion is one of the pathophysiological mechanisms of high-pressure hydrocephalus, which could be rectified by shunt surgery in 7-10 days.

First, we demonstrated that patients with hydrocephalus suffered from a pan-cerebral perfusion decrease, which agrees with the literature conclusions (8,24,51). Under physiological conditions, ICP remains constant, as the three components of the cranial cavity (intracranial blood volume, brain tissue, and CSF) remain in a balanced state. In the case of hydrocephalus, this balance is disrupted (25). When the normal CSF reserve is exhausted, increased ICP directly inhibits cerebral blood perfusion. This phenomenon has been observed in several previous studies. For example, Haubrich et al. (15) demonstrated that an increased ICP leads to a significant decrease in CBF. Tanaka et al. (45) reported that in patients with normal-pressure hydrocephalus, globally reduced CBF was observed in the pre- and post-shunting stages. These studies agree with our current study, as our data also demonstrated that impaired CBF in the hydrocephalic status was restored after shunt surgery. However, these studies relied on CBF measurements alone, which are not as sensitive as CBV (18,19). According to the literature, CBV is more prone to present perfusion reduction (22), which makes it more sensitive than CBF for identifying and assessing cerebrovascular risk factors (22). With respect to the limitations of CBF, the current study focused on CBV to study cerebral perfusion in high-pressure hydrocephalus. In our study, we not only observed increased CBF in hydrocephalic patients, but also found disagreements between CBV and CBF in certain cerebral regions after shunt placement. This was mainly due to the impact of MTT in modulating cerebral perfusion. According to the central volume principle, CBV is the product of CBF and MTT. Thus, we agree that CBV is a better indicator of cerebral perfusion than CBF, as the cerebral perfusion blood volume cannot simply be determined by the change in CBF alone.

Second, we demonstrated that the shunt-improved cerebral perfusion appeared to be region-specific. Shunt surgery has been suggested as the optimal therapy for hydrocephalus because it reflects a high improvement rate and acceptable complication rate (13,36). This is because the shunt corrects the low perfusion status of hydrocephalus (33,50,51), thus increasing cerebral metabolism (11,27). Previous studies have shown that the classic triads of hydrocephalic symptoms in iNPH patients were relieved as early as 7 days after shunt surgery (6,7), which agreed with the GCS score improvement in our study. However, studies on regional perfusion improvement are largely unknown. Among the limited literature, most studies have focused only on iNPH patients. For instance, Ziegelitz et al. (51) reported that CBF increase was found specifically in the periventricular white matter and the lentiform nucleus in iNPH patients. Kristensen et al. (24) demonstrated that CBF reduction occurred in the subcortical white matter and frontal-temporal cortical regions in iNPH patients. One study also compared the cerebral perfusion between non-hydrocephalic and acute hydrocephalic patients after subarachnoid hemorrhage (46). Although CBV did not reflect any difference, CBF was significantly lower, in the basal ganglia, in patients with hydrocephalus than in patients without hydrocephalus. To the best of our knowledge, our study is the first to extend the observation to a more detailed region-specific pattern in the brains of high-pressure hydrocephalic patients. In agreement with Kristensen's study (24), our data demonstrated that the frontal and temporal lobes exhibited decreased CBV in the hydrocephalic state. Moreover, our data regarding CBF improvement in the basal ganglia also matched those of van Asch et al. (46). Both improvements could explain the rectification of the GCS scores after shunt surgery. Most importantly, this study demonstrated for the first time that cerebral perfusion is also increased in the midbrain and cerebellum in a hydrocephalic state. This phenomenon could be related to the relief of dyskinesia (17,49). We believe that regional CBV improvement provides some evidence to explain the potential mechanisms of shunt surgery response.

Third, TMT could reflect CBV changes in hydrocephalic patients before and after shunt placement. The TMT has been proposed as a substitute indicator of cerebral temperature since 1956 (4). This hypothesis was proposed based on the anatomical location (29) and blood supply (48) of the tympanic membrane and is supported by solid evidence from both animal and human studies (5,10,30,31,34). In our previous study, a tight correlation was also detected between TMT and cerebral perfusion in the temporal lobe and mesencephalon in cranioplasty patients (20). Thus, we adopted similar research methods for hydrocephalic situations in this study. Our study revealed that the CBV variation of both the temporal lobe and mesencephalon matched the TMT changes, which also supported the "TMT-CBV correlation," as previously observed. Notably, we also found that the shunt could cause an unequal bilateral TMT fluctuation period. This fluctuation period disappeared seven days after shunt placement in our study. To the best of our knowledge, this is the first study report on this phenomenon. As stated in Pennes' bioheat equation, blood is the main vehicle for heat transfer within the body, and the

tissue temperature is proportional to its blood flow (38). Thus, fluctuating TMT could potentially indicate changes in cerebral perfusion status in the brain, especially in the temporal lobe and mesencephalon. As previously described by Nishiyama et al. (35), CSF dynamics tend to be stable within 1 week after endoscopic third ventriculostomy surgery. This conclusion is consistent with our finding, as the TMT reached a steady-state on the seventh day after shunt placement. Moreover, our study suggested that perfusion rebalancing is a dynamic process and is not equal between the two hemispheres, as there is a significant TMT difference between the two ears. This information could probably help neurosurgery to observe and help patients understand the post-shunt hemodynamics. Most importantly, we believe that TMT could be used to monitor cerebral hemodynamic changes in the hydrocephalic brain during the perioperative period. TCD is an inexpensive, non-invasive, real-time measurement of cerebral blood flow characteristics and cerebrovascular hemodynamics and has been adopted in various hydrocephalus studies (1,26). However, TCD is operator-dependent, which could result in registering inaccurate velocities due to miss operations and wrong insonation angles (32). As multimodality monitoring is of mainstay importance after shunt surgery, TCD alone may not be sufficient to follow progression or detect deterioration of hydrocephalus. Thus, based on the results of the current study, we believe that TMT could be used as a supplement and an alternative to TCD to monitor hemodynamics during the perioperative period for hydrocephalus.

The current study had some limitations. First, the small sample size reduced the reliability of the study and increased the variance of the results. Second, although we detected a novel correlation between TMT and cerebral hemodynamic changes, its clinical application still requires more evidence and further verification from clinical studies, as its reliability remains a disadvantage to all other non-invasive techniques. In future studies, we will enroll a larger pool of participants and use more reliable modalities, including invasive cerebral probes and imaging examinations, to refine the current results.

CONCLUSION

In conclusion, we found that shunt surgery could potentially rectify impaired cerebral perfusion in patients with high-pressure hydrocephalus. By monitoring TMT changes, the hemodynamics became stable after the seventh postoperative day. Additionally, we found that TMT correlated well with cerebral perfusion status. We believe that our findings could be used to evaluate the cerebral perfusion status of patients during the perioperative period of shunt surgery.

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AUTHORSHIP CONTRIBUTION

Study conception and design: YJ
Data collection: YJ
Analysis and interpretation of results: YJ
Draft manuscript preparation: YJ
Critical revision of the article: YJ, WH, XJW
Other (study supervision, fundings, materials, etc...): YJ, WH, XJW
All authors (YJ, WH, XJW) reviewed the results and approved the final version of the manuscript.

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