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MRI-based Investigation on Outflow Segment of Cerebral Venous System under Increased ICP Condition

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Abstract
Objective: Increased intracranial pressure (ICP) is responsible for causing most nervous system diseases to progress seriously, till death. Recently, volume-targeted therapeutic strategy against increased ICP, which works by releasing excessive intracranial liquid especially from the venous compartment, attracted a great deal of attention. Previous research by us found a structurally special "outflow segment cuff" that is located at the juncture of superior sagittal sinus (SSS) and the brain-bridging veins in porcine model. Sequential observation demonstrated that this special structure appeared to have functional abnormalities. Based on these findings, it was proposed to try and prove a further hypothesis that there exists a similar structure in human beings that might be of importance for cerebral venous system to intervene in volume-initiated ICP regulation. Meanwhile, the diameters of bridging veins under either increased or normal ICP are compared by means of magnetic resonance imaging (MRI).
Method: Forty patients who presented with increased ICP were selected to undergo 2D time of flight (TOF) venography and ten normal volunteers were taken as the control group. Increased intracranial pressure status was evaluated by using flash visual evoked potential (fVEP) technique. All the patients and volunteers underwent 2D-TOF MRI imaging for the following parameters: repetition time/echo time, 50/4.9 milliseconds; flip angle, 45°; field of view, 250×250 mm; matrix, 256×256 pixels; section thickness, 1.5 mm. Syngo fastview imaging system was used to process and analyze the targeted brain-bridging venous section.
Results: By using 2D-TOF method in vivo, most bridging venous profiles as well as SSS and vicinal cortical veins could be clearly visualized. A short and narrow section, as previously described, obviously emerged because of MRI signal weakness even disappearing at the juncture of SSS and bridging veins in increased ICP patients. In combination with previous animal morphological findings we believe that this section with abnormal MRI signal could stand for the human counterpart of "outflow segment cuff" in porcine. Such a special structure could be observed within a majority of increased ICP patients (32/40 cases), whereas only one case presented the existence of similar imaging signal weakness. Furthermore, the diameters of the bridging veins in increased ICP group are statistically larger than the control group.
Conclusion: Intracranial venous compartment occupies about 70 to 80% blood volume inside the inflexible cranial cavity. Following volume-targeted rationale, ICP can be regulated effectively by the fluctuation of venous blood volume based on different aspects of morphology, biomechanics, and hemodynamics. In the present study, the coincidence of animal model and human venography in vivo offers strong evidences to support the hypothesis that venous hemodynamics, although passively, influences intracranial pressure environment through a possible key regulator – outflow segment narrow structure. The fact that this narrow formation and proximal vascular dilation appears more in patients under high ICP condition rather than in patients with normal pressure. Both narrow formation and proximal vascular dilation indicate its significant contribution to intracranial venous congestion, resulting from difficult drainage and the close relationship between intracranial venous volume and ICP.

Key words: Increased ICP; Cerebral venous system; Brain-bridging veins; MR venography

Introduction

Raised intracranial pressure (ICP) always accounts for deteriorating conditions of patients with neurological or neurosurgical disabilities, even leading to death. Till date, it still remains the most challenging task to relieve ICP effectively, and lots of researches on involved mechanisms continuously excite interests in the neuroscience field. Based on the rationale that relief of ICP can be obtained by drawdown of volume from within the closed and changeless compartment of the skull cavity, "volume-targeted" strategy thus provides a potential management to treat intracranial hypertension preclinically and clinically. For example, Grande P.O et al. made a significant attempt to unify the principles behind both surgical and nonsurgical therapies by putting forward the "Lund concept", which focused on the physiological volume regulation of the intracranial compartments [1]. To general knowledge,

intracranial vascular system is the most inconstant part for allowing the passage of blood liquid to or from an enclosed cavity. More than 70% of the cerebral blood volume, which constitutes approximately 6% of the brain volume under normal conditions, is located in the venous vascular bed. The inflow and outflow of venous blood volume may be of clinical importance. However, the venous hemodynamics remains more elusive. The brain-bridging veins (BBVs) are situated at the final common path of cerebral venous system (CVS) by which intracranial venous blood volume is drained into sinuses and further flow out of cranial cavity. Besides being in an important anatomical situation, the classic three-layer hierarchies of blood vessel wall shifts to dual sinus, formed by a single-layer tube structure. These characteristics of BBVs may indicate certain special importance to hemodynamics of CVS. In the present study, the BBVs and adjacent sinuses are presented using magnetic resonance (MR) venography technique to observe morphology. By investigating and comparing the morphological differences of BBVs under raised or normal pressure, the validity of the hypothesis that pathologically raised ICP could lead to blood congestion inside cerebrovenous bed is demonstrated, which in return even worsens the pressure status by increasing intracranial volume. The results may open a new window for further research on significant relationship between CVS and ICP.

Clinical Materials and Methods

Patient Population

From November 2005 to October 2007 40 patients were examined. The patient population suffering from raised ICP consisted of 28 males and 12 females ranging in age from 22 to 55 years with an average age of 40.2 years. Causes of intracranial hypertension include trauma, tumor and successive hydrocephalus (Table 1). Considering the possibility that congenital venous defects could be complicated by vascular diseases, the patient population excluded all kinds of diseases originating from intracranial vascular system, such as aneurysm, arteriovenous malformation, and so on. Ten volunteers with normal pressure were selected as the control group. All patients and volunteers participated in this study under protocol approved by the Human Subject Committee/Institutional Review Board of Shandong University (Jinan, China).

Monitoring of ICP

All patients in this study had undergone ICP monitoring that was performed using NIP-200 noninvasive ICP monitor (HaiWeiKang Medical Instrument Co. Ltd, ChongQing, China). Flash visual evoked potentials (fVEP) tests were performed according to the technical instruction from the company. The latency of the fVEP wave response was used as a mark to pick out the candidates who met the study criteria (larger than the published range of adult normal values using the same technique (i.e. 119 to 137 milliseconds)) [2].

MRI Procedure

MRI equipment

The Magnetom Sonata 1.5 T clinical research system (Siemens) was used, which offers a maximum amplitude of 40 mT/m in each axis (maximum effective amplitude: 69 mT/m) with a minimum rise time of 200 s, a maximum slew rate of 200 T/m/s (maximum effective slew rate: 346 T/m/s), and standard quadrature head coil.

MRI protocol

Fast spin echo (FSE) T1- and T2-weighted sequences were applied to obtain general MRI information. T1 parameters: TR = 700ms, TE = 14ms. T2 parameters: TR = 3700ms, TE = 96ms. Common parameters: NEX = 1, thickness = 5mm, FOV = 250mm×250mm, matrix = 256×256. 2D TOF sequence was performed immediately after T1 and T2 scans: TR = 50ms, TE = 4.9ms, flip angle = 45, thickness = 1.5mm, FOV = 250mm×250mm, matrix = 256×256, NEX = 1. The presaturation region was set up to suppress arterial signals. MRI vascular contrast agent was not used.

Imaging analysis and diameter analysis

The configuration of original CVS images was reconstructed using maximum intensity projection (MIP). Syngo fastview image processing software (Siemens) was used to classify and analyze the obtained data. All images were reviewed by two experienced radiologists based on a common standard to yield consistent impression.

The site for measuring diameter was located 5mm away from the wall of ipsilateral venous sinus. The 5mm distance was decided for two reasons: First, the signal from the bridging veins fades out along with the increase in the distance from sinus, thus influencing the accuracy of estimating the diameter value; second, a 5mm measurement site from the sinus can be situated away from the possible narrow part, which has been demonstrated in the present study. After deciding the site for measurement, the region of interest in every image and scale were both amplified in the same proportion to reduce possible error when drawing the measuring line manually. The highlighted length in the vertical direction on the wall of the bridging vein was expected to represent the diameter value, whereas the

Table 1. Causes of increased ICP.

Causes	Tumor	Trauma	Traumatic SAH	Abscess	Benign increased ICP
N	15	10	7	5	3
With hydrocephalus	7/15*	4/10*	5/7*	0/5*	0/3*

* Left number represents the patients with hydrocephalus, right one represents total enrolment

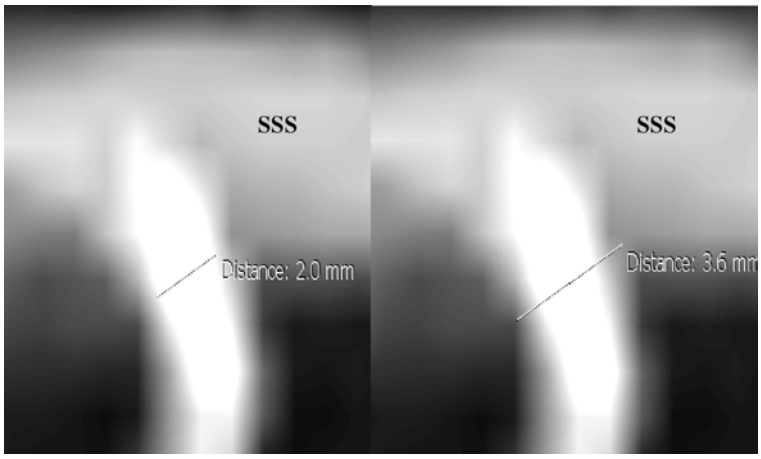

Fig. 1. The diameters of BBVs are calculated based on the highlighted part in venography images (left) rather than the partially lighted part (right).

surrounding region, that is, the partially lighted part was excluded (Fig. 1).

Results

Radiological Features of BBVs

About 8 to12 pairs of BBVs can be visualized. They line bilaterally along the corresponding sinuses in each image (Fig. 2). All of them directly enter into the sinuses without visible tributary veins. On the middle sagittal image, the following characteristics of BBVs are exhibited: Not all the bridging veins are arranged symmetrically at both sides of sinuses; most bridging veins take smooth routes into sinus, whereas some twist; neither the angle between the route and venous sinus trend remain same for different BBVs, nor the distance distribution between each pair of bridging veins at both sides. Each pair may stagger along both sides or join the sinus by the same corresponding entrance. In some cases, two adjacent bridging veins first form an enlarged ampulla-like structure ipsilaterally before joining the sinus through a short but distended vein trunk. In some images pseudomorphy was displayed and was marked by two cross veins before their entrance. Such an image distortion disappeared if the view position was rotated. The false appearance is produced because of the MRI signal overlapping on one side of the BBV and its opposite counterparts, rather than really being crossed blood vessels. The MRI signals of veins tail away gradually till it disappears along the distal-end direction of bridging and cerebral superficial veins. The venous sinuses can also be plainly visualized by venography images.

Formation of Narrow Segment

Subtotally, BBVs can and clearly be defined by 2D-TOF MRI technique along the visualized vessel path (Figs. 2, 3). However, MRI signals weaken and even

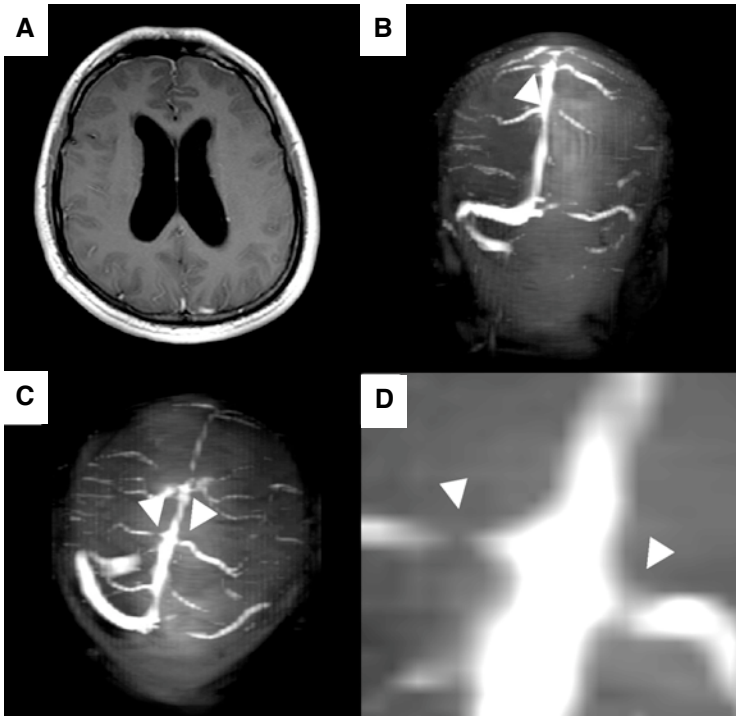

Fig.2. Dilated bilateral ventricles and surrounding interstitial edema, (A), the narrow segment of BBVs are seen just before their flowing into superior sagittal sinus through 2D-TOF method. Narrow part is amplified locally at D.

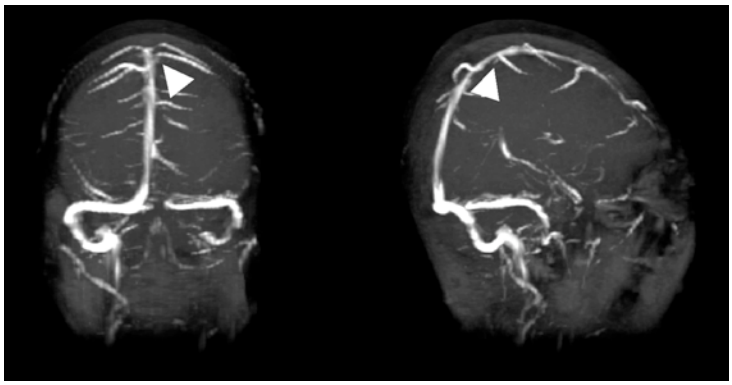

Fig. 3. The narrow segment seen resulted from signal attenuation on coronal MRI scan. Because the BBVs overlap partly with venous sinus, such a structural feature disappeared if the view position was rotated for the same patient.

Table 2. Diameter of BBVs under raised and normal ICP.

	N	Diameter value	Minimum value	Maximum value
Raised ICP group	40	2.65±0.10mm*	1.8 mm	4.0 mm
Control group	10	2.04±0.12mm*	1.4 mm	2.8 mm

The pair wise comparison was analyzed by t test. * P£°0.01

disappear when they approach close to the venous sinus wall. The phenomenon of signal weakness or disappearance could be seen in most venous images of patients. Such a signal abnormality shapes a radiological and morphological narrow part that locates the outflow segment of CVS near the sinus. In some cases the signals of BBVs reappeared or recovered right before their entrance to form a short venous trunk between the narrow part and the dual sinus. This narrow structure of outflow segment apeared in 32 cases suffering from increased ICP, whereas only one case presented the same narrow structure in the control group. In a single case, not all of outflow segments displayed similar signal abnormality, and part of them entered into the sinus with a continuous and constant diameter without visible radiological stenosis. There is one point that requires particular attention: If image viewing position is chosen differently, for example, rotated at an angle, the MRI signal of the narrow part might be overlapped onto the adjacent sinus so that they cannot be observed. The strength of such an imaging signal does not depend on the head position or standard plane of MRI scan. Combined with the results of our previous animal experimental study [3] we believed that there existed a similar narrow structure along the outflow segment of CVS in human beings that is of significant importance for venous hemodynamics under increased ICP condition.

Diameter Measurement of Brain Bridging Veins

The diameter of BBVs was 2.04±0.12 mm (95% confidence interval) under normal pressure status and 2.65±0.10mm (95% confidence interval) under increased ICP condition. The pairwise comparison was analyzed by t-test with SPSS 11.0 for Windows (Table 2, $p<0.01$)

Discussion

Till date, regulation of ICP still seems to be in a state that is not completely understood and needs urgent solution because of its mainly decisive importance to the prognosis. According to the classical "Kellie-Monroe" doctrine, volume increments in any single compartment of the skull, for example, the cerebrospinal fluid (CSF), tissue, and blood compartments, create a pressure gradient involving the other compartments. Based on this doctrine the volume-targeted strategy, which is expected to work by reducing the intracranial volume, excited interests [4, 5]. The principle of this strategy focuses on reducing the blood flow volume into the skull cavity by controlling systemic artery pressure, promoting reabsorption of fluid over the capillary membrane, suppressing CSF production or increasing its absorption, and so on. Even though these therapeutic methods, according to volume-targeted strategy, should be effective theoretically, they could possibly lead to aggravation by secondary brain injury rather than improvement of the patient's condition. Declination of cerebral perfusion pressure is the most common condition. Grande P.O et al. realized the importance of sufficient blood flow volume in treating increased ICP status and proposed the "Lund concept" [1] based on their research. This concept believes that a lasting reduction of intracerebral water content could be obtained by increased reabsorption of fluid without decreasing sufficient cerebral perfusion pressure. But, if venous blood cannot flow out of the venous compartment smoothly, the reabsorbed water just transfers from the capillary bed into the venous compartment. The fluid still stays inside the same closed skull cavity and fluid transfer can not sufficiently have an effect on decreasing interstitial space and targeted volume. So it possess the possible and significant importance how the flowing-out process of venous blood happens, and how much will be restrict-

ed by BBVs – the last common path of CVS. However, our knowledge of in vivo cerebral venous outflow is very limited. Hence we proposed a hypothesis that CVS could play an important, but unnoticed role to control blood volume. Regional venous stasis with no change in blood flow is described in the experimental data obtained during the early stages of ICP dysregulation [6]. In this study, CVS was considered as a possibly effective aspect of volume-targeted strategy for two reasons: (1) venous capacitance segment encompasses more than 70% of the complete cerebral vascular volume and has a more adjustable section. Larger volume has more effective volume-pressure effect of fluid shift. (2) The volume fluctuation of venous compartment does not interrupt required cerebral perfusion pressure from the artery system. If the hemodynamic characteristics of CVS and associated mechanisms on ICP regulation are thoroughly understood, it might be possible to demonstrate that venous blood-induced volume-targeted strategy could open a new window to treat increased ICP condition preclinically and clinically by draining venous blood out of skull cavity.

As the last drainage pathways of CVS, BBVs occupy important anatomical positions by connecting superficial brain veins and venous sinuses. Along this short distance the classic three-layer hierarchies (i.e. intimal, medial, and adventitial layer) of venous blood vessel wall alter to single-layer dura matter lined with only endothelial cells. These may have particular significance to venous blood channels draining away intracranial blood volume. Nakagawa [6] and Auer [7] have shown that the fall in intracranial venous pressure, that is, the so-called waterfall phenomenon, does not have a gradual steepness, but drops abruptly from the BBVs into the superior sagittal sinus. Based on "waterfall outflow phenomenon", the existence of an outflow orifice resistance, which is presumed to be at the venous side very close to the ve-nous outlet, was suggested to explain the regulation mechanism of the cerebral venous outflow during increased ICP. Piechnik [8] built up a conceptual model which described the venous outflow from the cranium mathematically, and emphasized the importance of venous flow as a source of pressure fluctuation. Our previous experiments [3] in pigs discovered a narrow and stiff outflow cuff segment between BBVs and superior sagittal sinus with different morphological and biomechanical properties when compared to other regions of BBVs. Autopsy studies indicated the absence of smooth muscle and differently arranged collagen fibers (In the outflow cuff segment the fibers are dense and circular, whereas they are loose and irregular in the venous wall) in pig BBVs. The behavior of bridging vein and outflow cuff segment was nonlinear and anisotropic with pronounced residual stresses. These observations convinced us that the outflow cuff segment played an important role in stabilizing cerebral venous outflow during changing venous outflow conditions. In our same series of experiment, similar abnormalities were proved in humans including absence in morphological three-layer structure and smooth muscle but presence of quantities of fiber component and fibroblasts (data not shown).

Brain bridging veins in patients suffering from increased ICP were observed using venography technique in this study. MRI signal of this piece of blood vessel weakened or even disappeared right at the near-end of the sinus and thus created a radiological stenosis. Combined with our previous experimental findings in pigs [3] and data of human BBVs morphologic abnormality, we believe that there exists a structurally and functionally narrow part at CVS outflow segment in humans. They have definite differences from other regions of BBVs, especially in morphological and biomechanical abnormalities that are consistent with data previously proved in pig model. These differences might determine venous vessels with narrow parts especially to be of substantial importance to the cerebral venous blood outflow regulation during physiological and pathophysiological conditions. More frequent appearance of such a special narrow part in patients with increased ICP rather than volunteers further provides a potential link with ICP environment, as also between venous blood volume and ICP. The change in ICP gives rise to an adaptive or compensatory morphological subsequence. Despite this fact, we still believe that the "abnormal" narrow part always exists at their place congenitally instead of being shaped by regional reactive vasoconstriction. The radiological stenosis shapes not because vascular smooth muscle cells initiate contraction but rather because of expansion of bridging veins away from sinuses passively. Under increased ICP condition venous bulk augments followed with blood congestion inside the cerebral vascular bed. Subsequently, the venous blood increment leads to the cerebral vascular bed being pressed and passive dilation of vascular wall and enlargement. At the same time, the stiff narrow part resulting from extensive fiber component and absent smooth muscle cells has only a finite dilation range. The disparity of both dilations should be the real cause for the narrow shape. Under normal pressure environment because the vascular wall resists smaller pressure and remains relatively relaxed, the diameter makes little difference inbetween the "abnormal" outflow and connected normal vessel. In the present study obtained data of the enlarged diameter of BBVs in cases with increased ICP offered a forceful support to the above explanation. This conclusion implies that this special structure actually restricts outflow of intracranial blood and thus results in increased capacity of CVS. This increased volume in the cranium further worsens intracranial hypertension making this a vicious circle: ICP increase – finite dilation of narrow part – limited blood outflow – worsening blood congestion – intracranial volume increase – further increase in ICP. This circle differs from other normally virtuous cycle in humans. All studies including the present one imply that an anatomical narrow part is located at the junction of BBVs and sinuses by which the cerebral venous system may play an important role in regulating ICP as a blood reservoir.

Increasingly,, developed MR angiography techniques provide more reliable and potentially multiple alternatives to investigate CVS in vivo. For example, contrast enhanced MRA can improve the vascular visualization [9] and phase-contrast MR angiography

[10] can be used to accurately evaluate velocity, flow direction of the cerebral venous system, and its presence, extent, and distribution. By such techniques the morphology, biomechanics, and hemodynamics of cerebral venous system could be explored in greater details. In literature, less space is devoted to the study of the cerebral venous system than that of the cerebral arterial system in regulatory mechanisms of ICP. This finding could drop a hint for future research on intracranial hypertension and open up a new preclinical or clinical field based on volume-targeted strategy. In addition, this theory may be of some importance for ICP autoregulation physiologically because it controls blood flow according to ICP fluctuation in such a way that a balanced resistance to venous outflow is provided.

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