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Correlation Between Trans-Stenotic Blood Flow Velocity Differences and the Cerebral Venous Pressure Gradient in Transverse Sinus Stenosis: A Prospective 4-Dimensional Flow Magnetic Resonance Imaging Study

BACKGROUND: The relationship between trans-stenotic blood flow velocity differences and the cerebral venous pressure gradient (CVPG) in transverse sinus (TS) stenosis (TSS) has not been studied.

OBJECTIVE: To evaluate the hemodynamic manifestations of TSS and the relationship between trans-stenotic blood flow velocity differences and the CVPG.

METHODS: Thirty-three patients with idiopathic intracranial hypertension (IIH) or pulsatile tinnitus (PT) and TSS who had undergone diagnostic venography using venous manometry were included in the patient group. Thirty-three volunteers with no stenosis and symptoms were included in the control group. All the 2 groups underwent prospective venous sinus 4-dimensional (4D) flow magnetic resonance imaging (MRI). The average velocity (V_{avg}) difference and maximum velocity (V_{max}) difference between downstream and upstream of the TS in 2 groups were measured and compared. Correlations between the CVPG and trans-stenotic V_{avg} difference/ V_{max} difference/index of transverse sinus stenosis (ITSS) were assessed in the patient group.

RESULTS: The differences in V_{avg} difference and V_{max} difference between the patient and control groups showed a statistical significance ($P < .001$). The V_{avg} difference and V_{max} difference had a strong correlation with CVPG ($R = 0.675$ and 0.701 , respectively, $P < .001$) in the patient group. Multivariate linear regression using the stepwise method showed that the V_{max} difference and ITSS were correlated with the CVPG ($R = 0.752$ and $R^2 = 0.537$, respectively; $P < .001$).

CONCLUSION: The trans-stenotic blood flow velocity difference significantly correlates with the CVPG in TSS. As a noninvasive imaging modality, 4D flow MRI may be a suitable screening or complimentary tool to decide which TSS may benefit from invasive venous manometry.

KEY WORDS: Blood flow velocity, Venous pressure, Hemodynamics, Idiopathic intracranial hypertension, Tinnitus, Magnetic resonance imaging, Manometry

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In recent years, transverse sinus (TS) stenosis (TSS) has attracted the interest of clinical researchers because of its association with idiopathic intracranial hypertension (IIH) and

venous pulsatile tinnitus (PT). TSS is consistently found in more than 90% of patients with IIH and is considered its most sensitive imaging indicator,¹ with 93% sensitivity and specificity.²

ABBREVIATIONS: 4D, 4-dimensional; CVPG, cerebral venous pressure gradient; IIH, idiopathic intracranial hypertension; ITSS, index of transverse sinus stenosis; PC, phase contrast; PT, pulsatile tinnitus; SS, sigmoid sinus; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; TS, transverse sinus; TSS, transverse sinus stenosis

PT may be one mode of presentation of IIH or may appear in patients without IIH, and the prevalence of TSS in PT patients is approximately 50%.^{3,4}

A growing body of evidence supports endovascular venous sinus stenting for patients with IIH and disabling PT secondary to TSS with an associated cerebral venous pressure gradient (CVPG).^{3,5,6} The gold standard for measuring the CVPG across TSS is cerebral venography with manometry, which is an invasive examination and often used to assess the indication for stenting.⁷

Four-dimensional (4D) flow magnetic resonance imaging (MRI) can provide volumetric quantification of the blood flow velocity throughout the imaging volume⁸ and visualization of complex blood flow patterns. The feasibility of 4D flow MRI applied to the dural venous sinus has been widely acknowledged, as well as its accuracy in blood flow velocity measurement.^{9,10} Because the blood flow velocity is directly related to the pressure gradient,¹¹ it may provide clearer and more precise evidence for the indication of venography with venous manometry.¹²

We conducted a prospective 4D flow MRI study investigating the blood flow pattern and blood flow velocity in the venous sinuses of 33 patients with TSS and 33 volunteers with no TSS and symptoms. Our goal was to evaluate the hemodynamic manifestations of TSS and analyze the correlation between the blood velocity and CVPG.

METHODS

Participants

This study was approved by the Institutional Review Board, and all the patients provided written informed consent for this study. A prospectively gathered database of 33 patients with IIH according to the diagnostic criteria by Friedman et al¹³ or unilateral venous PT between September 2018 and January 2020 was reviewed. All the patients had undergone diagnostic venography with venous manometry; the presence of TSS was confirmed, and its degree of severity was recorded. We recorded the demographic characteristics of the patients and performed prospective venous sinus 4D flow MR.

Thirty-three healthy volunteers were included in the control group, and the inclusion criteria were as follows: no history of tinnitus, IIH or other central nervous system symptoms; no abnormal manifestation on MR images; no TSS on MR venography; matched for age and gender with the patient group. The control group also underwent venous sinus 4D flow MR.

Diagnostic Venography With Venous Manometry

Cerebral venography (Innova 4100-IQ, GE Healthcare, Milwaukee, Wisconsin) was performed in a conscious state under local anesthesia in all the patients. First, the right femoral artery was accessed, and a 5F diagnostic catheter was positioned in the right and left internal carotid arteries, external carotid arteries, and vertebral arteries for conventional cerebral arteriography and venography to evaluate the presence of TSS and exclude other vascular diseases such as arteriovenous fistulae, arterial aneurysms, and cerebral venous sinus thrombosis. Indirect 2D digital subtraction angiography (DSA) images in the anteroposterior and lateral projections and 3D rotated DSA images of the venous sinuses were

TABLE 1. Acquisition Parameters Used for 4D Flow and 2D PC-MR Sequences

Parameter	4D flow	2D PC
TR (ms)/TE (ms)	8.5/3.9	10/5.8
FA (°)	20	10
Field of view (mm ³)	161 × 161 × 40	161 × 161
Matrix size	160 × 160 × 40	160 × 162
Acquired voxel size (mm ³)	1 × 1 × 1	1 × 1
Reconstructed voxel size (mm ³)	0.459 × 0.459 × 1	0.305 × 0.305
Slice orientation	Transverse	Perpendicular to target
Bandwidth (Hz/pixel)	193.4	192.4
Cardiac phases	13	13
Scan time	5'24"	1'23"

obtained. Next, the right femoral vein was accessed, and a 2.7 F coaxial microcatheter (Stride, Asahi) was navigated into the superior sagittal sinus from the internal carotid vein of the stenotic side to perform direct venography. A standard vascular pressure transducer (DPT-248, Yixinda) was calibrated and connected to the microcatheter, and manometry was attempted in the venous sinus segments downstream and upstream to the stenosis. The CVPG was calculated and recorded (mmHg). The results from the symptomatic side in PT patients and the dominant side in IIH patients were chosen for further analysis.

Venous Sinus 4D Flow MRI

Cerebral 4D-flow MRI was performed using a 3.0T MR scanner (Ingenia; Philips Healthcare) with a digital head coil. A retrospectively captured free-breathing electrocardiogram-gated multishot turbo field echo sequence was used with 3-direction velocity encoding. The velocity encoding was flexibly determined according to a preprocedural 2D phase contrast (PC)-MRI sequence with 1-direction velocity encoding in the through-plane direction at the levels of venous sinus segments downstream to the stenosis and perpendicular to the venous sinus. Velocity encoding of 2D PC-MRI was first set to 80 cm/s and then increased in steps of 20 cm/s (100, 120, 140 cm/s) if velocity aliasing was present in the images. The final velocity encoding of 2D PC-MRI without velocity aliasing was set as the velocity encoding of 4D flow MRI. The acquisition parameters are summarized in Table 1.

Data Analysis

GTFlow (version 2.2.17, GyroTools, Zurich, Switzerland) was used to perform preprocessing, visualization, and quantification of the 4D flow data. In the patient group, the symptomatic side in PT patients and the dominant side in suspected IIH patients were chosen. In the control group, the dominant side in dominant venous cases or either side in co-dominant venous cases was selected. Before data visualization and quantification, region masking, eddy current correction, possible velocity aliasing correction, and vessel segmentation were performed. For blood flow patterns, streamlines reconstructed by the software were used. Two expert radiologists who were blinded to the clinical data evaluated the presence of jet, turbulent, or vortex flow downstream to the stenosis by visual inspection. Regarding the quantitative measurement of blood flow velocity, 3 different planes of section (slice space: 1 mm) were created perpendicular to the venous sinus with a normal vessel diameter 5 mm downstream/upstream to the stenosis (downstream/upstream of the TS

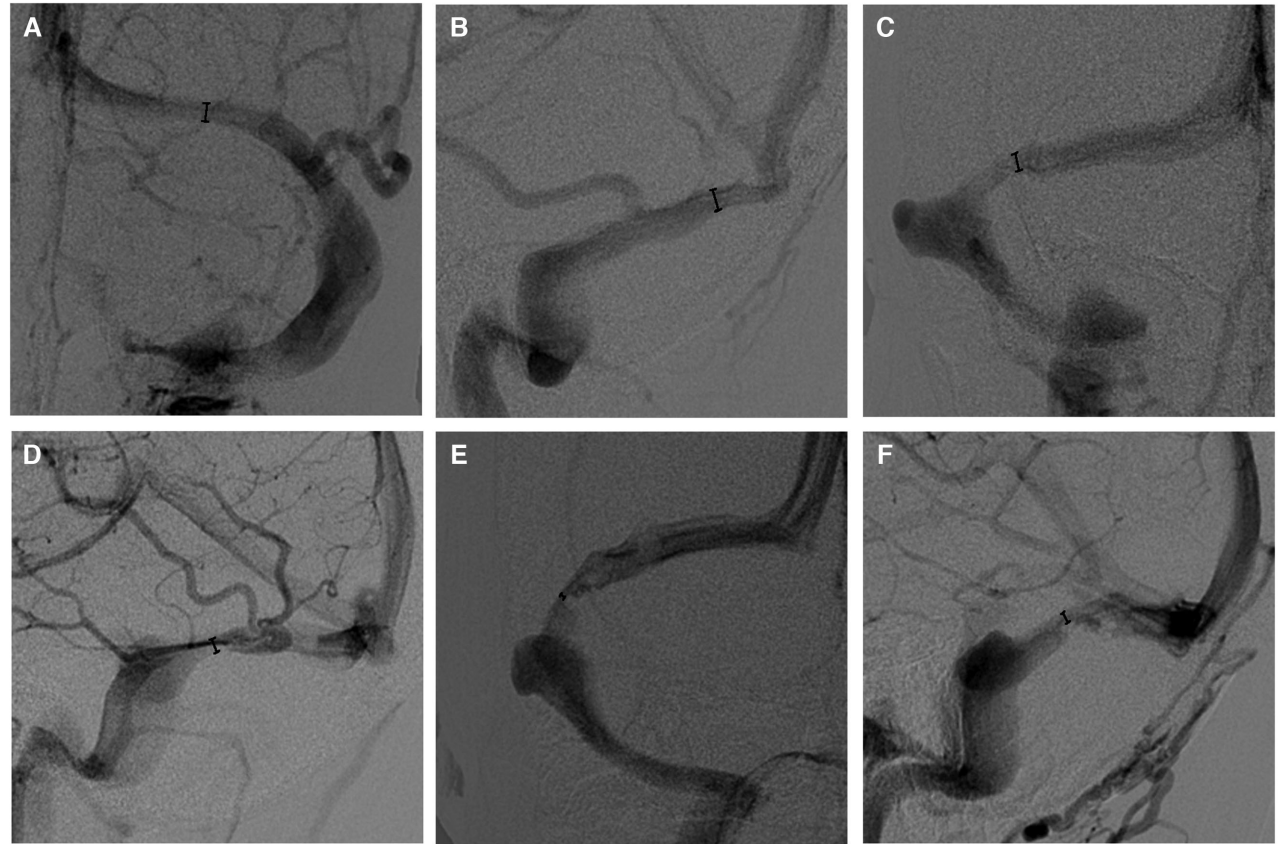


FIGURE 1. **A and B,** TS stenosis <33%, with a smooth tapered appearance. **C and D,** TS stenosis 33% to 66%, with segmental hypoplasia. **E and F,** TS stenosis >66%, with hyperplastic arachnoid granulations.

for the control group). A contour was drawn manually along the vessel wall in the plane of section, and the average velocity (V_{avg} , cm/s) and maximum velocity (V_{max} , cm/s) of flowing blood that passed through this contour in all 13 cardiac phases of 1 cardiac cycle were calculated automatically. The mean velocity of 3 contours was taken as V_{avg} and V_{max} . The V_{avg} difference and V_{max} difference were calculated according to the following formulas:

$$\begin{aligned} V_{avg} \text{ difference} &= V_{avg\text{-downstream}} - V_{avg\text{-upstream}} \\ V_{max} \text{ difference} &= V_{max\text{-downstream}} - V_{max\text{-upstream}} \end{aligned}$$

The index of transverse sinus stenosis (ITSS) was evaluated by combined 4D flow MRI and DSA and calculated according to the following formula according to Carvalho criteria¹⁴:

$$\begin{aligned} \text{ITSS} &= \text{degree of stenosis of the right TS} \\ &\quad \times \text{degree of stenosis of the left TS.} \end{aligned}$$

Statistical Analysis

All analyses were conducted using SPSS Statistics for Windows (version 26.0, IBM Corporation). Statistical significance was defined

as a 2-tailed $P < .05$. The study size was calculated by PASS (version 15.0, NCSS) according to the preliminary study. Inter-rater reliability was assessed by using the Cohen's kappa coefficient based on the visual inspection of the blood flow pattern by each expert radiologist to avoid observer reliability bias. The coefficient was interpreted as follows: almost perfect (0.81-1), substantial (0.61-0.80), moderate (0.41-0.60), fair (0.21-0.40), slight (0.01-0.20), or poor (≤ 0) reliability. The differences in $V_{avg\text{-upstream}}$, $V_{avg\text{-downstream}}$, $V_{max\text{-upstream}}$, $V_{max\text{-downstream}}$, V_{avg} difference, and V_{max} difference between the patient and control groups were compared using the independent t test. Pearson correlation analysis was performed to evaluate the correlation between the CVPG and V_{avg} difference/ V_{max} difference/ITSS, respectively, and the correlation was interpreted as follows: very strong (0.81-1.0), strong (0.61-0.80), moderate (0.41-0.60), or weak (0.21-0.40) correlation. The significant variables were subjected to the underwent multicollinearity test and further multivariate linear regression using the stepwise method.

Research Reporting Guideline and Data Availability

STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline was implemented in this study. The anonymized data analyzed during the current study that support the

TABLE 2. Differences in Variables Between Patients and Control Group

Variables (mean ± SD)	Patients group n = 33	Control group n = 33	P value
V _{avg} -upstream	18.42 ± 4.76 (95% CI 16.73-20.10)	18.17 ± 5.26 (95% CI 16.30-20.03)	P = .841
V _{avg} -downstream	41.45 ± 17.18 (95% CI 35.36-47.54)	22.37 ± 8.05 (95% CI 19.51-25.22)	P < .001
V _{avg} difference	21.53 ± 14.61 (95% CI 16.35-26.71)	4.20 ± 6.16 (95% CI 2.01-6.38)	P < .001
V _{max} -upstream	35.15 ± 9.28 (95% CI 31.86-38.44)	32.14 ± 8.98 (95% CI 28.96-35.33)	P = .186
V _{max} -downstream	163.42 ± 65.73 (95% CI 140.12-186.73)	49.46 ± 14.93 (95% CI 44.17-54.76)	P < .001
V _{max} difference	116.04 ± 61.24 (95% CI 94.32-137.75)	17.32 ± 13.28 (95% CI 12.61-22.03)	P < .001

findings are available from the corresponding author on reasonable request.

RESULTS

Participants

Of 33 patients (5 males and 28 females; age 39.7 ± 11.5 yr) who met the inclusion criteria, 5 cases had IIH and venous PT, and 28 cases had only venous PT. All 28 veins of the symptomatic side in PT patients and 5 veins of the dominant side in IIH patients were included in the present study, and all the contralateral sides were excluded. Two cases, 13 cases, and 18 cases showed stenosis <33%, 33% to 66%, and >66%, respectively (Figure 1). Regarding the morphology of the sinus stenosis, 2 cases showed stenosis with a smooth tapered appearance (Figure 1A and 1B), and 31 cases showed intrinsic stenosis (hyperplastic arachnoid granulations, 29 cases; segmental hypoplasia, 2 cases; Figure 1C-1F). The average CVPG was 7.2 ± 4.1 mmHg (range: 2.0-17.0).

Thirty-three veins (24 dominant venous cases and 9 co-dominant venous cases) of 33 volunteers (5 males and 28 females; age 36.8 ± 10.9 yr) were included in the control group according to the inclusion criteria.

Statistical Analysis

Differences in V_{avg}-upstream, V_{avg}-downstream, V_{max}-upstream, V_{max}-downstream, V_{avg} difference, and V_{max} difference between the patient and control groups are summarized in Table 2. A scatterplot of the V_{avg} difference/V_{max} difference and CVPG is displayed in Figure 2A and 2B. The results of unary linear regression between the CVPG and V_{avg} difference/V_{max} difference/ITSS are summarized in Table 3. After performing the multicollinearity test and adjusting the variables, multivariate linear regression using the stepwise method showed that the V_{max} difference and ITSS were correlated with the CVPG and yielded the following equation: $y_{CVPG} = 0.147 + 0.040x_{V_{max} \text{ difference}} + 0.421x_{ITSS}$ ($R = 0.752$, $R^2 = 0.537$, $P < .001$).

Observation of Blood Flow Patterns

For the assessment of poststenotic flow jets/complex flow patterns, the inter-reader reliability was almost perfect ($\kappa = 1.000/\kappa = 0.897$).

In all 33 cases in the patient group, a high-velocity flow jet was observed. The flow jet was oriented along the long axis of the sigmoid sinus (SS) in cases with only proximal TSS (54.5%, n = 18) (Figure 3A) and along the long axis of the TS in cases with mid-TSS with or without distal TSS (45.5%, n = 15) (Figure 3B). In all 33 control cases, no high-velocity flow jet was observed (Figure 3C).

In the patient group, 3 types of flow patterns were observed in the SS in 15 cases with mid-TSS: a flow jet with bilateral vortex flow (13.3%, n = 2) (Figure 4A), flow jet with medial vortex flow (46.7%, n = 7) (Figure 4B), and a flow jet with medial turbulent flow (40.0%, n = 6). Additionally, 3 types of flow patterns were observed in the SS in 18 cases with only proximal TSS: a flow jet with medial turbulent flow (66.7%, n = 12) (Figure 4C), a helical flow along the long axis of the SS (27.8%, n = 5) (Figure 4D) and a flow jet with lateral vortex flow (5.6%, n = 1) (Figure 4E).

DISCUSSION

We demonstrate for the first time that the V_{avg} difference and V_{max} difference were correlated strongly with the CVPG. The gold standard for measuring the CVPG across TSS is invasive cerebral venography with manometry.⁷ The velocity of blood flow is directly related to the CVPG,¹¹ and the accuracy of noninvasive 4D flow MRI for blood flow velocity measurement has been investigated¹⁰; thus, 4D flow MRI has the prospective value to provide quantitative evidence to indicate of venography. In our study, for every increase of 10 cm/s in the V_{avg} difference, the CVPG increased by approximately 2.0 mmHg; for every increase of 10 cm/s in the V_{max} difference, the CVPG increased by approximately 0.5 mmHg. Thus, the same CVPG may lead to a greater difference in V_{max} difference than V_{avg} difference.

Some researchers have found that patients with apparently severe TSS might have no CVPG, while those with mild TSS sometimes have a large CVPG that benefits from stenting.^{15,16} These findings agreed with our results that ITSS correlated moderately with the CVPG. The cause may be the compliance and complexity of the venous sinus anatomy and collateral pathways.¹⁷ Additionally, this study explored the multivariate linear regression correlation among V_{avg} difference, V_{max} difference, ITSS, and CVPG. Dinkin et al¹⁸ proposed that fixed intraluminal structures that alter venous flow dynamics, such as fenestration and embryological remnant, may have an important

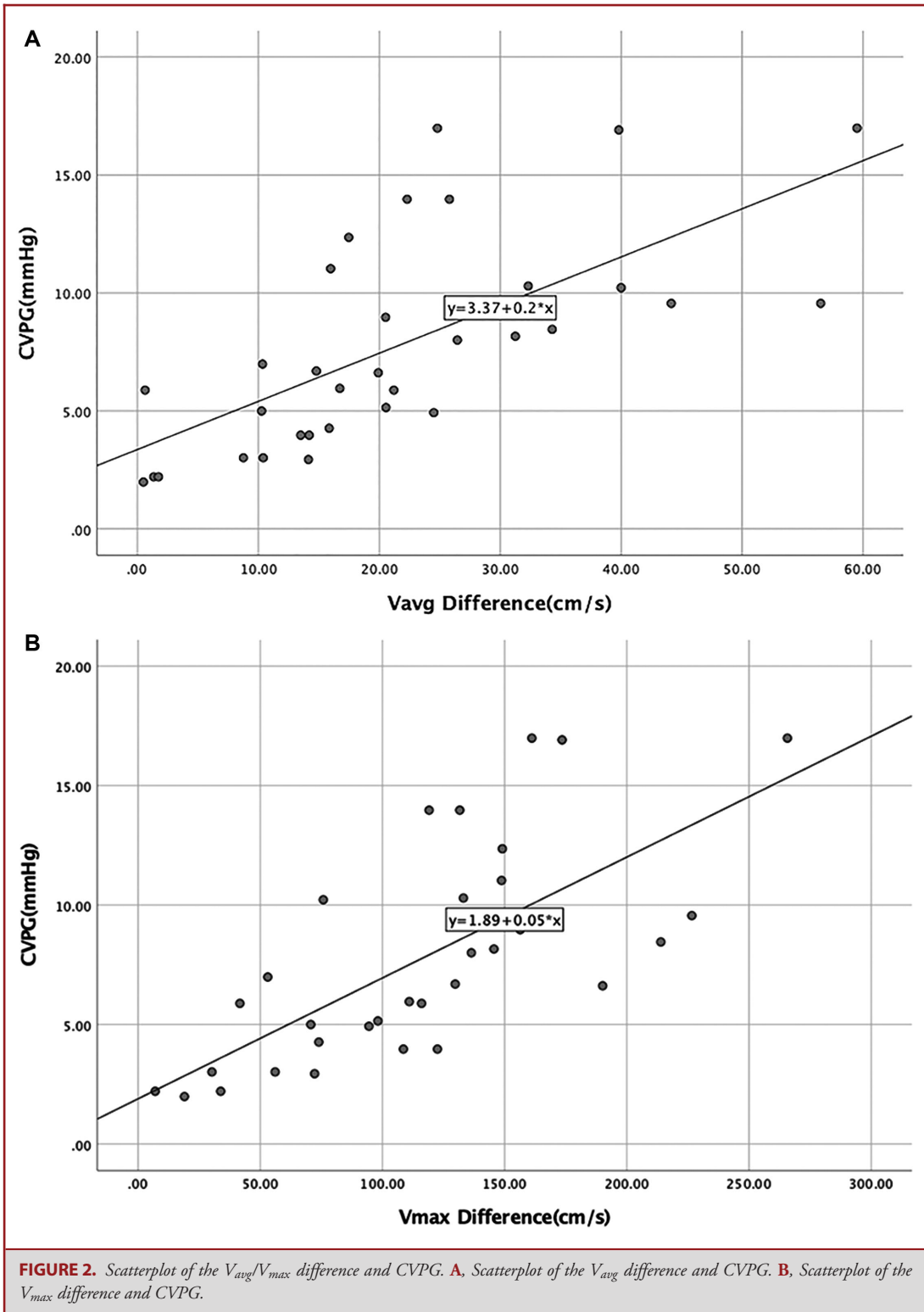


TABLE 3. Results of Unary Linear Regression Between CVPG and Variables

Variables	B	R	R ²	P value
V _{avg} difference	0.204	0.675	0.438	P < .001
V _{max} difference	0.051	0.701	0.475	P < .001
ITSS	0.781	0.575	0.309	P < .001

impact on clinical courses. In the study by Zhao et al,¹⁹ the length of ipsilesional TSS and alternative pathways were correlated with the CVPG. Considering these factors may be useful to improve the multivariate linear regression models. However, limited by the resolution of 4D flow MRI, we did not consider these factors in our study.

Visualization of the blood flow pattern can show the flow speed and direction directly. In our current study, all the subjects showed poststenotic flow jets. A flow jet in the poststenotic region, which indicates a high velocity, has been reported by some previous studies,^{8,20} and the results were consistent with ours. Haraldsson et al²¹ found that the flow jet velocity was reduced after cerebrospinal fluid drainage, which may be caused by the expansion of the stenosis after lumbar puncture. Because the flow jet is directly related to the pressure gradient, the color of the poststenotic flow jet according to the color scale can

reflect CVPG, with red coloration in the venous sinus potentially indicating a high CVPG.

Concerning other complex flow patterns, such as vortex flow, turbulent flow, and helical flow, some researchers have studied the complex flow pattern in the venous system in PT patients. Acevedo-Bolton et al²² found a helical flow pattern originating in the jugular bulb and propagating down the descending jugular in a PT patient. Amans et al²³ reported that strong components of the rotational blood flow were seen in 5 PT patients with SS diverticulum but not in control subjects. In the study by Li et al,¹⁰ 19 of 22 cases with PT showed vortex or turbulent flow. In our study, the 33 cases showed different types of complex flow patterns. We hypothesize that these patterns are all closely related to the poststenotic flow jet and may be instrumental in the development of PT sound, a topic that will be further discussed in our future work.

Limitations

This study has limitations. First, with data from only 33 cases, the study was not sufficiently powered to compare blood flow patterns and velocity between the IIH and PT groups. Second, the inclusion of 5 IIH patients and 28 PT patients in the cohort may introduce clinical symptomatic bias. Because PT can be one mode of presentation of IIH, and because both PT and IIH have close associations with TSS, we believe that certain types of PT and IIH

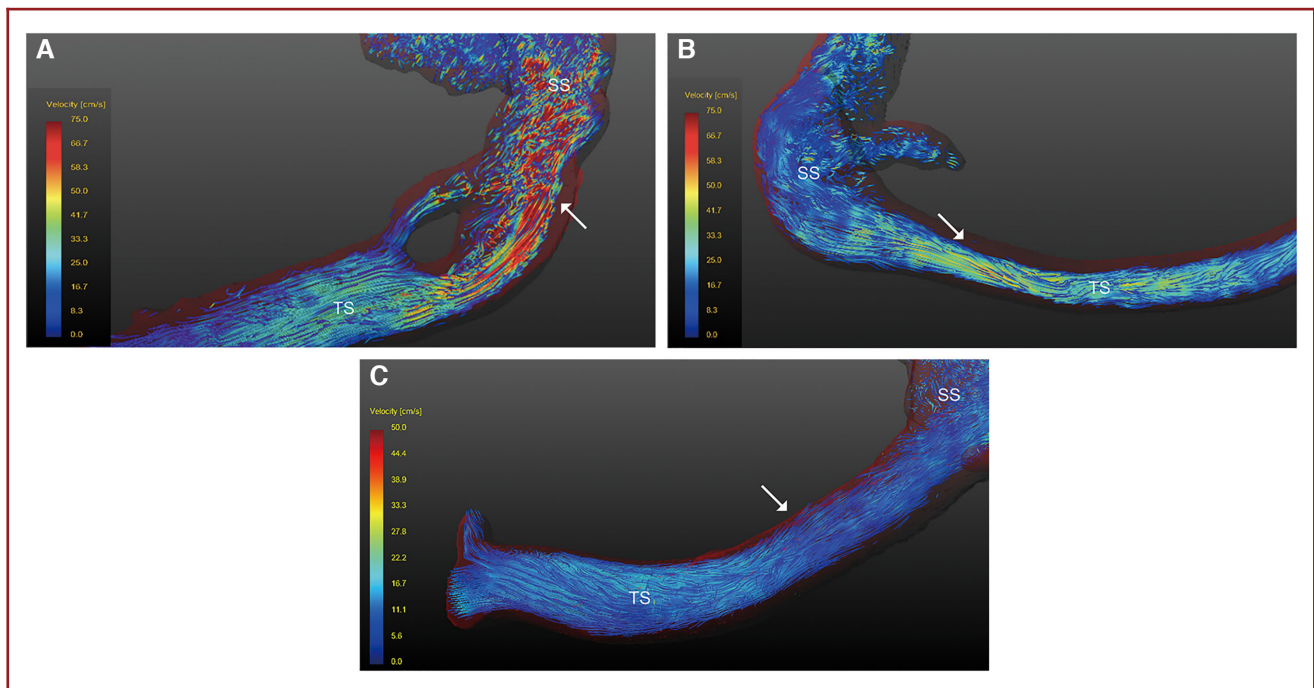
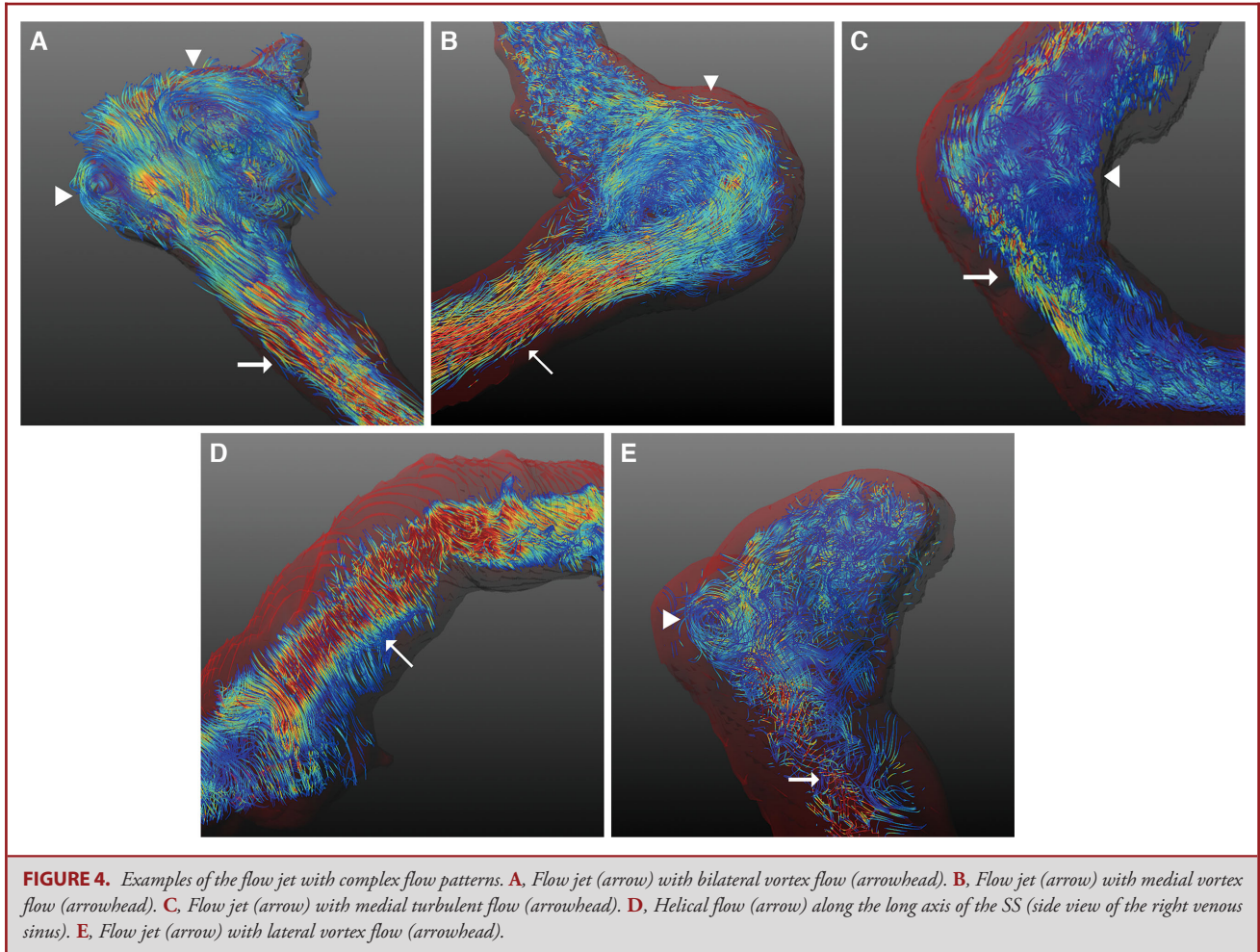


FIGURE 3. A and B, Two cases with flow jet in the TS/SS. **A,** A 29-yr-old man with proximal TS stenosis. The intracranial pressure is 320 mmH₂O, and the CVPG is 16.9 mmHg. The flow jet is oriented along the long axis of the SS and has a high velocity (toward the red end of the scale). **B,** A 22-yr-old woman with right PT for 1 yr and mid-TS stenosis. The CVPG is 1.98 mmHg. The flow jet is oriented along the long axis of the TS with a slow blood flow velocity (toward the blue end of the scale) in the TS. **C,** A normal volunteer with no TSS and symptoms. This case showed a stable and low blood flow velocity with no flow jet in the TS.



have shared characteristics in terms of physiopathological mechanisms and venous sinus fluid dynamics; it is reasonable to study PT and IIH patients together as a cohort of the patient group. Third, although we used the mean velocity of 3 contours in statistical analysis, regression toward the mean could not be avoided. Fourth, because lumbar puncture is an invasive examination, it was not performed in all patients; therefore, the relationship among cranial pressure, the CVPG, and blood flow velocity was not included in this study.

CONCLUSION

This study demonstrates that the trans-stenotic blood flow velocity difference correlates significantly with the CVPG in TSS, representing a novel application of 4D flow MRI. As a noninvasive imaging technique, 4D flow MRI can be used as a screening or complementary tool to decide which TSS may benefit from invasive venous manometry.

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Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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