A Novel Flow Dynamics Study of the Intracranial Veins Using Whole Brain Four-Dimensional Computed Tomography Angiography

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■ BACKGROUND: **The flow dynamics of the intracranial venous channels are fundamentally important for understanding intracranial physiology and pathophysiology. However, the method clinically applicable to the evaluation of the flow dynamics of the intracranial venous system has not been well described in the reported data. We have developed a new method to evaluate intracranial venous flow direction and velocity using 4-dimensional (4D) computed tomography angiography (CTA). The aim of the present study was to verify the accuracy and validity of 4D-CTA in a clinical setting.**

■ METHODS: **We retrospectively analyzed 97 veins from 26 patients (16 cases of arteriovenous shunt disease, 9 intracranial tumor cases, and 1 cerebral aneurysm case) who had undergone both 4D-CTA and conventional digital subtraction angiography (DSA). Using 4D-CTA, we analyzed the time-density curve with gamma distribution extrapolation and obtained the direction of the flow and flow velocity of each vein. The direction of the flow in 4D-CTA was also collated with that obtained using conventional DSA to verify the experimental method.**

■ RESULTS: **The direction of the flow determined by 4D-CTA was consistent with that of conventional DSA in 94.8% of cases. The average venous flow velocity was 64.3 mm/second and 81.8 mm/second, respectively, in the antegrade and retrograde channels affected by arteriovenous shunts.**

■ CONCLUSIONS: **The present flow analysis using 4D-CTA enabled us to evaluate the direction and velocity of intracranial venous flow. Other than some limitations, the presented method is reliable and its potential for application in clinical settings is promising.**

INTRODUCTION

The cerebral veins and dural sinuses are valveless, and the blood within them can move freely from vessels with greater resistance to vessels with lower resistance.[1,2] Accordingly, the venous return route from the brain to the heart will vary from case to case. Knowledge of the intracranial venous flow dynamics is fundamentally important to understanding the physiology of the brain and the pathophysiology of the diseases affecting the cerebral veins or dural venous sinuses, such as venous thromboses and dural arteriovenous fistulas (DAVFs). Classically, digital subtraction angiography (DSA) has been considered the reference standard for the evaluation of flow dynamics of the cerebral venous system. However, conventional DSA is invasive and does not allow for the obtainment of quantitative flow parameters such as flow volume or velocity.[3] Although some studies have reported the usefulness of 4-dimensional computed tomography angiography (4D-CTA) in analyzing the venous flow analysis in intracranial lesions,[4-6] its application has been limited owing to the lack of sufficient temporal resolution. In the present

Key words
- 4D-CTA
- Flow direction
- Flow dynamics
- Flow velocity
- Intracranial vein

Abbreviations and Acronyms
4D-CTA: Four-dimensional computed tomography angiography
AVS: Arteriovenous shunt
CTA: Computed tomography angiography
DAVF: Dural arteriovenous fistula
DSA: Digital subtraction angiography
HU: Hounsfield unit
ROI: Region of interest
SMCV: Superficial middle cerebral vein
TTP: Time to peak
TDC: Time density curve

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study, we used the novel 4D-CTA method to enhance the temporal resolution of 4D-CTA by analyzing the temporal profile extracted from the time-density curve (TDC) of the cerebral veins. This enabled us to obtain the direction and velocity of the intracranial venous flow. To validate our method, we also compared the venous flow direction obtained from 4D-CTA with that obtained from DSA in the same clinical cases.

METHODS

Patients

We retrospectively included in our study, those patients who had undergone both preoperative 4D-CTA and catheterized DSA before undergoing neurosurgery or neuroendovascular treatment from April 2016 to June 2018 at our institution. We did not exclude any patients who met the eligibility criteria. A total of 26 patients were included.

Of the 26 patients, 15 had DAVFs. For 9 patients the DAVF was located at the transverse-sigmoid sinus, for 3 at the cavernous sinus, for 2 at the anterior condylar, and for 1 at the tentorium. Nine patients had intracranial meningioma. The intracranial meningioma was located at the sphenoid wing in 5 patients, and at the cavernous sinus wall, convexity, spheno-orbital region, and the falx in 1 patient each. One patient had a pial arteriovenous fistula and one had a cerebral aneurysm. All the images used in the analyses were obtained from the patients for clinical purposes. All the participants had provided informed consent for the present study using opt-out form on the institute website before the study. The institutional ethics committee approved the present study, which was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Investigation of Flow Direction on 2-Dimensional DSA Images

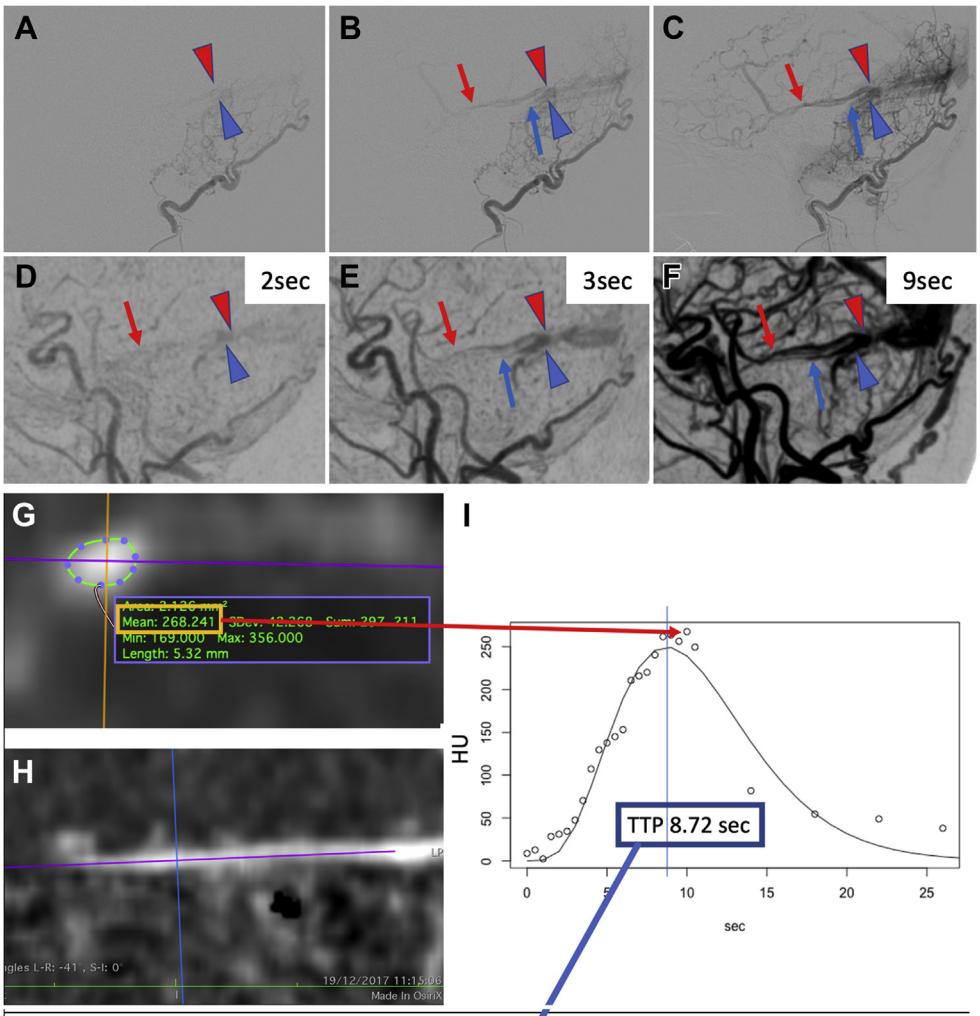
In all cases, the flow dynamics of the venous structures were investigated on conventional DSA using a C-arm angiography system (Innova 3100 [GE Healthcare, Waukesha, Wisconsin, USA]). The flow direction of the venous channels was determined by the observation of the 2-dimensional (2D) anteroposterior and lateral image sequences obtained at 4 frames/second. In each case, the superficial middle cerebral veins (SMCVs) and vein of Labbé were included in the investigation given that the venous channels were present. We targeted these 2 venous channels for the evaluation, because they were usually stable anatomical and well-developed venous structures, and it was eaxsy to recognize the flow direction on 2D-DSA. Additionally, in the patients with DAVFs, we investigated the flow direction in the venous channels with retrograde flow that were recognized on 2D-DSA, in addition to the SMCV and vein of Labbé. The typical flow examination conducted using DSA is shown in Figure 1A–C.

Dynamic CTA Protocol

In all cases, 4D-CTA was performed with a CT scanner (Aquilion One [Toshiba Medical Systems, Otawara, Japan]) equipped with 320 detector rows. Initially, a test bolus scan was performed at the level of the carotid bulb to determine the optimal timing of the dynamic scans using an intravenous injection of 10 mL of nonionic contrast material (Iopamiron; 370 mg/mL) at a rate of 5 mL/second, followed by 20 mL of saline. 4D-CTA was performed after a 50-mL bolus injection of contrast material at a rate of 5 mL/second, followed by 20 mL of saline. The unenhanced mask data set for bone subtraction was obtained before administration of contrast material. Imaging data were obtained intermittently at 2, 4, 6, 8, 10, 13, 16, 19, 22, and 60 seconds in the patients with meningiomas and aneurysm and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, and 10.5 seconds continuously and 14, 18, 22, and 26 seconds intermittently in the patients with arteriovenous shunt (AVS) disease after administration of contrast material. These times were determined from the test bolus scan. The other scan parameters were as follows: field of view, 24 cm; slice thickness, 0.5 mm; tube voltage, 80 kV; current-time products, 210 mA and 150 mA for those with tumor or aneurysm and those with AVS disease, respectively; rotation time, 1 second and 0.5 second for those with tumor or aneurysm and those with AVS disease, respectively. Representative 4D-CTA images are shown in Figures 1D–F and 2.

Investigation of Flow Direction Using 4D-CTA

In 4D-CTA, the flow dynamics were analyzed in the same venous channels as those investigated using DSA. These were the SMCV and vein of Labbé, if present, in all patients and the cortical veins with cortical reflux in those with DAVF. Analysis software OsiriX (Pixmeo Sárl, Bernex, Switzerland) enabled us to obtain the average Hounsfield units (HUs) from arbitrary regions of interest (ROIs) on the subtracted images. The HU measurements in each vein were performed for ≥2 ROIs in a straight portion of the vessel without any divergence of the tributaries. The 2 ROIs were initially set 10 mm away from each another; 1 at the most proximal part of the vein and 1 at the distal part. Owing to the tortuosity and divergence of the tributaries, in some cases, we were unable to set the distal ROI 10 mm from the proximal ROI. In such cases, we set the distal ROI at a point just distal to the tortuosity and divergence of the tributaries and >10 mm from the proximal point. The HU measurements were taken at right angles to the longitudinal direction of the observed vein at each time point (Figure 1G–I). The gamma distribution function $f(x) = \frac{x^{\alpha-1}e^{-x/\beta}}{T(\alpha)\beta^{\alpha}}$ was fitted using the least squares method to the HUs obtained from each vein to remove the recirculation effect. The TDC of each vein was estimated. The primary differentiation of the TDC was taken, and an inclination of 0 for the second time point was defined as the time to peak (TTP) of each measured point (Figure 1J). The TTP can be considered the time at which the concentration of the contrast agent reaches its maximum level in each vein. When the difference in the TTP between 2 points was >0.15 second, we determined its flow direction (Figure 1J) and compared the flow direction using 4D-CTA with that obtained using catheterized DSA. If the TTP difference was <0.15 second, we reset the distal point further distally from the initial position and again tried to determine the direction of flow. The procedure was repeated until the difference in the TTP became >0.15 second or the distance between the proximal point and distal point became 30 mm. If the difference in the TTP remained <0.15 second when the distance between the measured points had reached 30 mm, we defined the flow direction of the venous channel as "undetermined." We



J	Proximal TTP (sec)	Distal TTP(sec)	Interval (sec)	Length (mm)	Velocity (mm/sec)
Superior petrosal sinus	8.49	8.72	0.23	26	113.0
Vein of the Labbé	8.14	8.30	0.16	30	187.5

Figure 1. Typical flow analyses obtained in the present study. The images were from a 52-year-old woman with the left transverse-sigmoid sinus dural arteriovenous fistula. (**A**–**C**) Lateral views of catheterized digital subtraction angiography via the left occipital artery. (**D**–**F**) Lateral views of 4-dimensional computed tomography angiography (4D-CTA). Within each image, the time after the contrast agent arrived at the carotid bulb is shown. (**G**, **H**) Setting of the region of interest in the distal part of the superior petrosal sinus (*blue arrow* in **B**, **C**, **E**, and **F**) using 4D-CTA. The plane (**G**) parallel and (**H**) vertical to the superior petrosal sinus. (**I**) Gamma distribution fitting to the obtained Hounsfield units (HUs) and the time density curve of the distal part of the superior petrosal sinus. (**J**) Time to peak values and flow velocity of the venous channels. *Red arrowhead* indicates the proximal portion of the left vein of Labbé; *red arrow*, distal portion of the left vein of Labbé; *blue arrowhead*, proximal portion of the left superior petrosal sinus; *blue arrow*, distal portion of the left superior petrosal sinus. The distance between the distal and proximal portion of the vein of Labbé and superior petrosal sinus was 26 and 30 mm, respectively. The left lateral view of the catheterized digital subtraction angiography via the left occipital artery (**A**–**C**) revealed retrograde venous flow toward the vein of Labbé (proximal, *red arrowhead*; distal, *red arrow*) and the superior petrosal sinus (proximal, *blue arrowhead*; distal, *blue arrow*). (**D**–**F**) The lateral view of the 4D-CTA also demonstrated the same morphological features. We set the region of interest in the distal part of the superior petrosal sinus at the right plane (**G**) to the longitudinal direction of the vasculature (**H**). The average HUs were continuously obtained at each time point, and the gamma distribution function was fitted to obtain the time density curve (TDC). The primary differentiation of the TDC was taken, and we obtained the time to peak (TTP; 8.72 seconds) from the time at which the TDC inclination had become 0 (**I**).

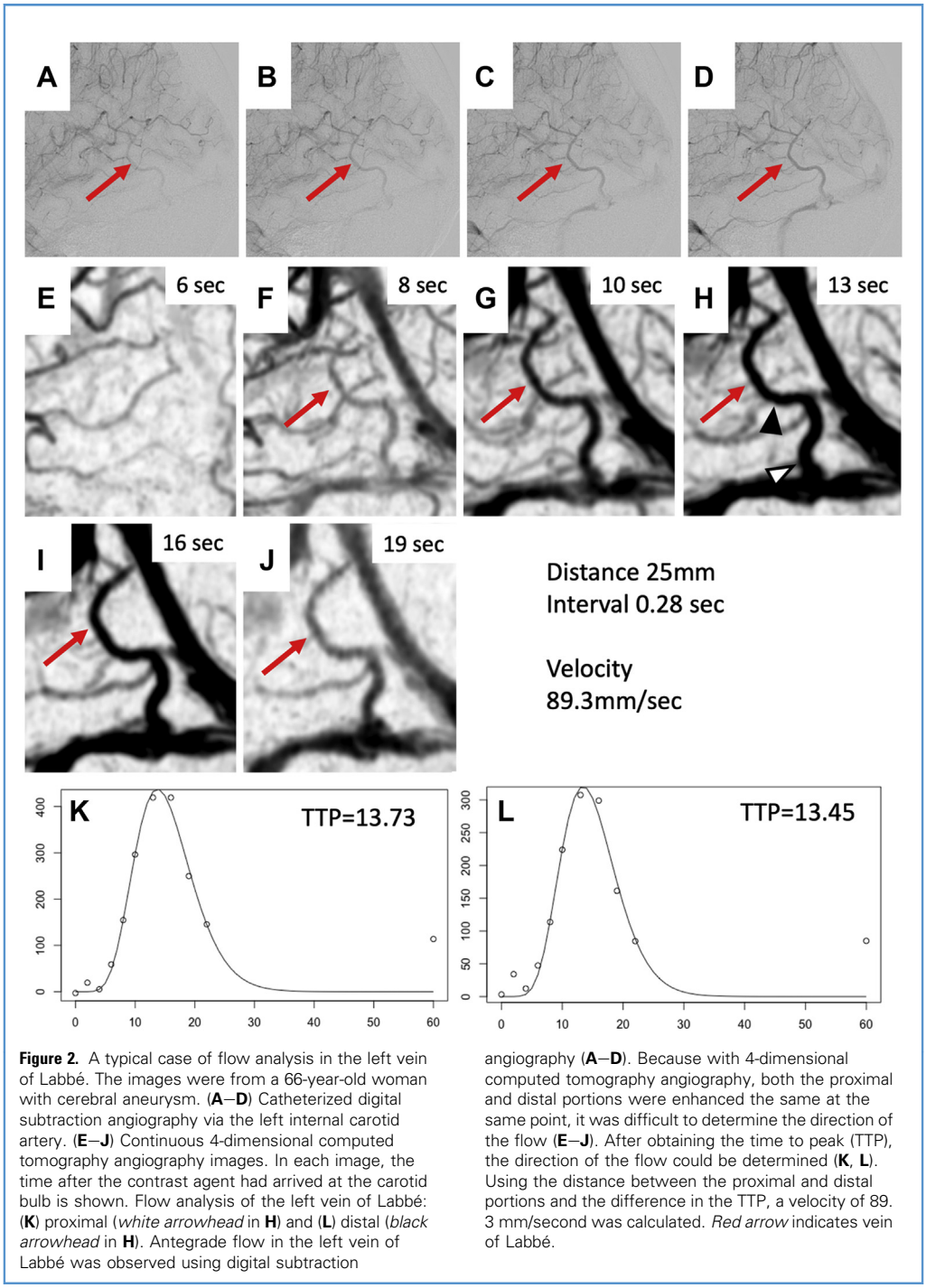


Figure 2. A typical case of flow analysis in the left vein of Labbé. The images were from a 66-year-old woman with cerebral aneurysm. (**A**–**D**) Catheterized digital subtraction angiography via the left internal carotid artery. (**E**–**J**) Continuous 4-dimensional computed tomography angiography images. In each image, the time after the contrast agent had arrived at the carotid bulb is shown. Flow analysis of the left vein of Labbé: (**K**) proximal (*white arrowhead* in **H**) and (**L**) distal (*black arrowhead* in **H**). Antegrade flow in the left vein of Labbé was observed using digital subtraction angiography (**A**–**D**). Because with 4-dimensional computed tomography angiography, both the proximal and distal portions were enhanced the same at the same point, it was difficult to determine the direction of the flow (**E**–**J**). After obtaining the time to peak (TTP), the direction of the flow could be determined (**K**, **L**). Using the distance between the proximal and distal portions and the difference in the TTP, a velocity of 89.3 mm/second was calculated. *Red arrow* indicates vein of Labbé.

further calculated the flow velocity of each venous channel by dividing the distance by the TTP difference between the 2 points. Thus, the velocity of each channel was analyzed in all venous channels, except for the veins in which we had failed to correctly detect the flow direction of the venous channel. We also investigated the influence of the character of each vein (i.e., location and antegrade or retrograde) on the flow velocity inside the venous channels.

The gamma distribution fitting and methods for obtaining the TDC have been previously reported in detail.[7] All the analyses were conducted using R, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria; available at: http://www.R-project.org/).

Table 1. Characteristics of Venous Channels Included in the Present Study

	Antegrade Flow (n = 81 Veins)			Retrograde Flow (n = 16 Veins)					
Variable	SMCV	Vein of Labbé	Total	SMCV	Vein of Labbé	SPS	Pial Vein	SOV	Total
DAVF	29	23	52	4	2	4	4	1	15
Meningioma	9	12	21	1	0	0	0	0	1
Pial AVF	3	2	5	0	0	0	0	0	0
Cerebral aneurysm	2	1	3	0	0	0	0	0	0

SMCV, superficial middle cerebral vein; SPS, superior petrosal sinus; SOV, superior orbital vein; DAVF, dural arteriovenous fistula; AVF, arteriovenous fistula.

The flow dynamic analyses in the present study were performed independently by 2 of us, and the average value was usually considered as the final value. Large discrepancies between the observers were resolved by discussion and repeating the measurements to reach a consensus.

For the statistical analysis, the Student t test as used for the continuous variables. P values < 0.05 were considered to indicate statistical significance.

RESULTS

Flow Analyses with Catheterized DSA

In the 26 patients included in the present study, we found 97 veins (81 antegrade flow veins and 16 retrograde flow veins) using catheterized DSA that met the inclusion criteria (Table 1). In the patients with DAVF, retrograde flow was observed in 15 venous channels (4 SMCVs, 2 veins of Labbé, 4 superior petrosal sinuses, 4 other cortical veins, and 1 superior orbital vein). Antegrade flow was observed in 52 venous channels (29 SMCVs and 23 veins of Labbé). In the patients with meningioma, 21 venous channels met our inclusion criteria (9 SMCVs and 12 veins of Labbé). Of these, 1 SMCV (Figure 3) showed retrograde flow owing to occlusion of its proximal end. In the patient with a pial arteriovenous fistula, the fistula was connected to the pial vein adjacent to the quadrigeminal cistern. It had a very short pial segment before joining the straight sinus. Because we could not obtain enough length of the pial venous segment for analyses, we only included the 3 SMCVs and the 2 veins of Labbé found in this patient in the analysis. In the patient with an intracranial aneurysm, 2 SMCVs and 1 vein of Labbé were found in the 2D-DSA investigation.

Flow Dynamic Analyses Using 4D-CTA

In 92 of the 97 veins (94.8%), the flow direction obtained using 4D-CTA was consistent with that using 2D-DSA. The flow velocity was also obtained in these 92 veins. The average velocity of all venous channels was 67.2 ± 4.4 (standard error) mm/second. In the antegrade veins, the velocity was 64.3 ± 4.4 mm/second, and the velocity was 81.6 ± 15.0 mm/second in the retrograde venous channels affected by DAVFs. The velocity of the retrograde venous channels was much more rapid than that of the antegrade veins. However, the difference was statistically insignificant ($P = 0.28$). The location of the vein did not have any significant influence on the velocity of the channel. The summary of the flow velocity analyses is presented in Table 2.

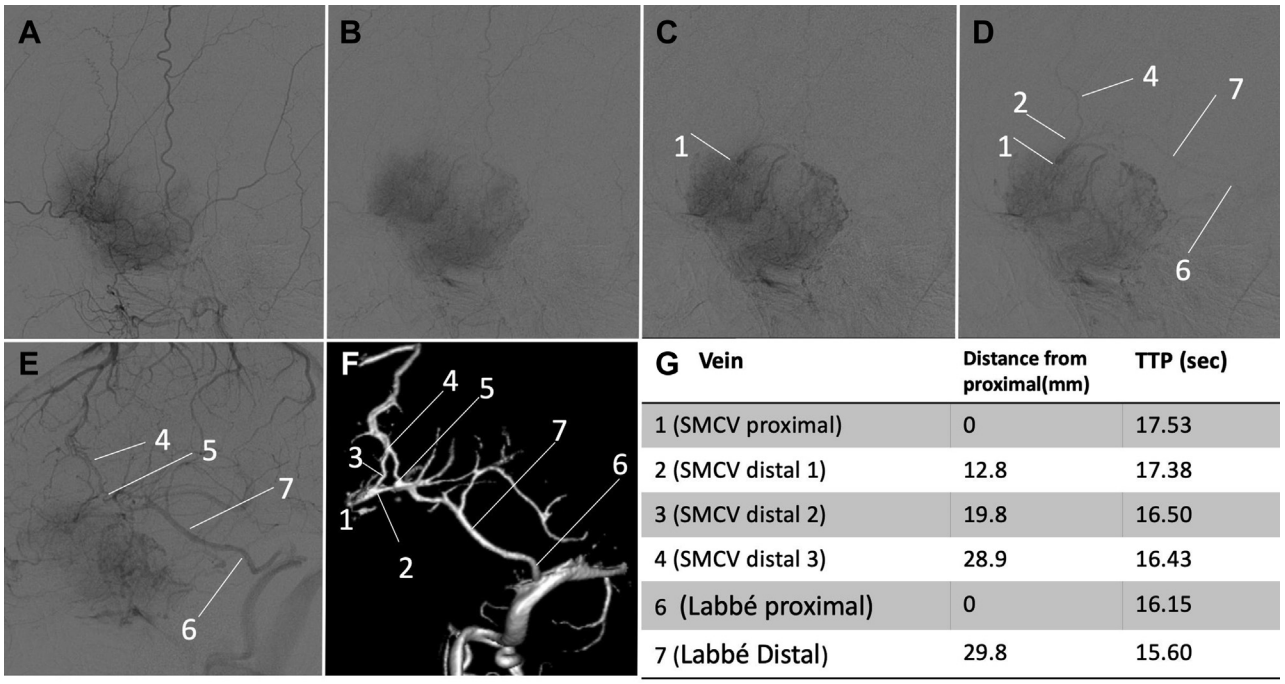
In 5 of the 97 veins (3 antegrade and 2 retrograde; 5.2%), we failed to analyze the direction of the venous flow using 4D-CTA (Table 3). In 1 vein, the direction of the venous flow was completely opposite when using DSA or 4D-CTA (Figure 3). In the remaining 4 venous channels, we could not determine the flow direction owing to insufficient differences in the TTP between the 2 ROIs, which were <0.15 second in these venous channels. In 1 of the 4 patients, an abnormal transition of the contrast concentration, which was unfitted to the gamma distribution, was observed (Figure 4).

DISCUSSION

Although the flow dynamics of the intracranial vein are fundamentally important for the understanding of intracranial physiology and pathophysiology, cerebral venous flow dynamics have seldom been described. In the present study, we developed a method to evaluate the flow direction and velocity using 4D-CTA. In the present analyses, we did not directly measure the direction and velocity of the flow. Instead, we calculated the velocity from an estimated formula. Because no method has been established by which to evaluate the intracranial venous flow dynamics, we could not fully verify the results of the present method using other methods. Accordingly, it is fundamentally important to understand the current method and limitations before its clinical application.

Method

Our current method began by obtaining the TDC at each venous channel. Gamma function extrapolation is key for the calculation of the TDC and elimination of the recirculation effect. This technique is not new and was originally developed to estimate the blood volume such as cardiac output.[8-10] However, gamma function extrapolation has seldom been applied to the cerebral venous system, except in 1 previous study.[7] The prerequisite to applying gamma function extrapolation is to assume that the whole venous system is 1 compartment and that the analyzed venous channel is an outlet of that compartment.[7,8] Accordingly, to compare the TTP in 2 locations within the venous channels, the 2 locations should belong to the same compartment. To obtain enough time difference in the TTP of each point and determine



G Vein	Distance from proximal(mm)	TTP (sec)
1 (SMCV proximal)	0	17.53
2 (SMCV distal 1)	12.8	17.38
3 (SMCV distal 2)	19.8	16.50
4 (SMCV distal 3)	28.9	16.43
6 (Labbé proximal)	0	16.15
7 (Labbé Distal)	29.8	15.60

Figure 3. Discordance in the flow analyses between 4-dimensional computed tomography angiography (4D-CTA) and conventional catheterized digital subtraction angiography (DSA). The images were from a 48-year-old woman with sphenoid ridge meningioma. (**A**–**D**) Lateral view of catheterized DSA via the external carotid artery. (**E**) Lateral view of catheterized DSA via the internal carotid artery. (**F**) Lateral view of the volume-rendering 4D-CTA image. (**G**) Results of flow analyses in the present study using 4D-CTA. The location number in each image and tabular data is consistent throughout. In this patient, the proximal portion of the left superficial middle cerebral vein (SMCV) was occluded by compression or invasion by the tumor, and the meningioma drained the retrograde SMCV and vein of Trolard to the superior sagittal sinus or via the vein of Labbé to the transverse sinus. The venous blood from the tumor ran through 1 and 2 to 4 or 1, 2, and 7 to 6 (**A**–**D**). On the internal carotid artery angiogram, the normal brain venous circulation used the same channels as the tumor, but only a part of the channel (1–3) appeared to be used (**E**). In flow analyses using 4D-CTA, the difference in the TTP shows antegrade flow (distal to proximal) in the vein of Labbé and the SMCV (**G**). In this case, the direction of flow in the SMCV differed between DSA and 4D-CTA.

the direction of flow, a longer distance would be better. However, to avoid mixing of the different venous compartments from other branches, a shorter segment would be better. To maintain a balance between these 2 factors, we set the initial distance between the 2 measured points at 10 mm. When we failed to obtain a sufficient TTP difference, we increased the distance incrementally until the TTP difference had reached 0.15 second to minimize the mixture from the different flow compartments.

Limitations of the Presented Method

Fundamentally, the presented method cannot directly measure the flow of the venous channels but can allow us to mathematically estimate the flow direction and velocity from the transition of the concentration of the contrast agent at a limited number of observation points. Accordingly, the possibility exists of a discrepancy in the flow direction and velocity between the real human body and that obtained in the present analyses. We did not correctly obtain the direction of the flow in 5 venous channels (Table 2), which might have resulted from the reasons described in the next paragraphs.

First, the involvement of several venous flow components with the examined venous channels could explain some of the failure. As stated, a prerequisite of the present method is that the 2 measurement points in each vein will belong to the same compartment. However, in the human body, small venous vasculatures can join the observed channels; thus, the involvement of several drainage components with different temporal profiles could impair the analysis results. We showed an extreme example of the influence of the involvement of the different venous components on the analysis in Figure 3. In this case, the left SMCV demonstrated retrograde flow using DSA, but the flow direction obtained using 4D-CTA was antegrade. In this case, the proximal SMCV had mostly collected delayed venous drainage from the meningioma. In the distal part, the relatively faster normal brain drainage had also joined the channel, which might have reversed the TTP pattern from proximal to distal.

The second issue concerns venous channels with a high flow profile. In 4 of the 5 cases, we failed to obtain a TTP difference adequate for analysis. One reason for this failure might have been the high venous flow velocity. Because the results from the present study contained some range of error and fluctuation in the

Table 2. Velocity of Intracranial Venous Channels Included in Present Study

Variable	Channels (*n*)	Velocity ± SE (mm/second)
All venous channels	92	67.2 ± 4.4
Antegrade venous channels	77	64.3 ± 4.4*
SMCV	41	66.1 ± 6.0
Vein of Labbé	36	62.4 ± 6.5
Retrograde venous channels	15	81.6 ± 15.0*
SMCV	4	93.4 ± 43.1
Vein of Labbé	2	87.3 ± 34.2
Superior petrosal sinus	4	82.5 ± 19.4
Pial vein	4	70.2 ± 37.3
Superior orbital vein	1	64.9 ± NA

SE, standard error; SMCV, superficial middle cerebral vein; NA, not applicable.
*Average velocity of the retrograde channels was greater than that of the antegrade channels, although the difference was not statistically significant ($P = 0.28$).

estimation values, we required adequate TTP differences between the 2 observation points to determine the direction and velocity of the flow. For example, given a velocity of >100 mm/second, venous blood will only require 0.1 second to travel 10 cm. To analyze such high-flow channels, we initially considered using a TTP difference of <0.15 second as a reference. However, this resulted in increasing failure to obtain the correct flow direction, possibly owing to the influence of the error and fluctuation in the estimated value (data not shown), and did not resolve the issue. To resolve the issue, we might need to increase the number of observational time points to minimize the error and fluctuation in the estimation, which would enable the estimation of the flow direction and velocity in high-flow channels using a smaller TTP difference.

Third, the venous drainage unfitted to the gamma distribution could also have influenced the results. As shown in Figure 4, in some cases, we observed an abnormal persistence or additional increase in the contrast concentration after the peak of the TDC. In such cases, catheterized DSA demonstrated considerable venous congestion in the hemisphere in which the vein was located. It is possible that the prolonged persistence of the contrast agent reflected congested blood flow. Thus, because in a condition of such severe venous congestion, the TDC might not be subject to the gamma distribution, the direction and velocity of the flow would not be correctly obtained from this type of TDC.

Finally, the current method was based only on imaging findings and might not always be consistent with a patient's anatomy. Additionally, images obtained with a contrast material will always be influenced by the protocol and background characteristics of the patient, such as weight, height, and cardiac function. In the present study, the ROIs were obtained by manual delineation, which could result in measurement errors. In the near future, automated selection of the ROIs might lead to more accurate and reliable analyses. Furthermore, calculation errors, unequal distribution of contrast material, pulsation, ongoing contrast material diffusion, and turbulent flow could also have influenced the results. These factors and limitations should be considered carefully when interpreting the results of the present study.

Clinical Application

Despite its importance, intracranial venous flow dynamics have not been well described in the reported data. We have assumed that this shortcoming was due to the following 2 reasons. First, given the lack of a method for quantitative evaluation, most studies concerning the influence of cerebral veins on normal brain physiology and pathological conditions have drawn their conclusions from the viewpoint of the morphological anatomy, such as the regions in which the veins drain or the diameter of veins and not from true flow dynamics analyses using flow parameters such as the flow velocity or volume. Second, the cerebral veins consist of a complicated network with large individual variations in which the venous blood can freely travel and the direction of flow in a certain vein will not always be determined. Additionally, the function of the venous channel is situated in the upstream drained tissues. The venous flow properties we obtained could have been the consequence of brain perfusion rather than the cause, and, accordingly, even if we obtained the precise downstream venous

Table 3. Reasons for Failure to Obtain Flow Direction Using 4-Dimensional Computed Tomography Angiography

		Flow Analysis Results		
Disease	Channel	DSA	4D-CTA	Reason for Analysis Failure
DAVF	SMCV	Antegrade	Unable to determine	Insufficient difference in TTP <0.15
DAVF	Vein of Labbé	Antegrade	Unable to determine	Insufficient difference in TTP <0.15
DAVF	Vein of Labbé	Antegrade	Unable to determine	Insufficient difference in TTP <0.15
DAVF	SMCV	Retrograde	Unable to determine	Insufficient difference in TTP <0.15 and atypical TDC
Meningioma	SMCV	Retrograde	Antegrade	Failure to assume "1 compartment theory"

DSA, digital subtraction angiography; 4D-CTA, 4-dimensional computed tomography angiography; DAVF, dural arteriovenous fistula; SMCV, superficial middle cerebral vein; TTP, time to peak; TDC, time density curve.

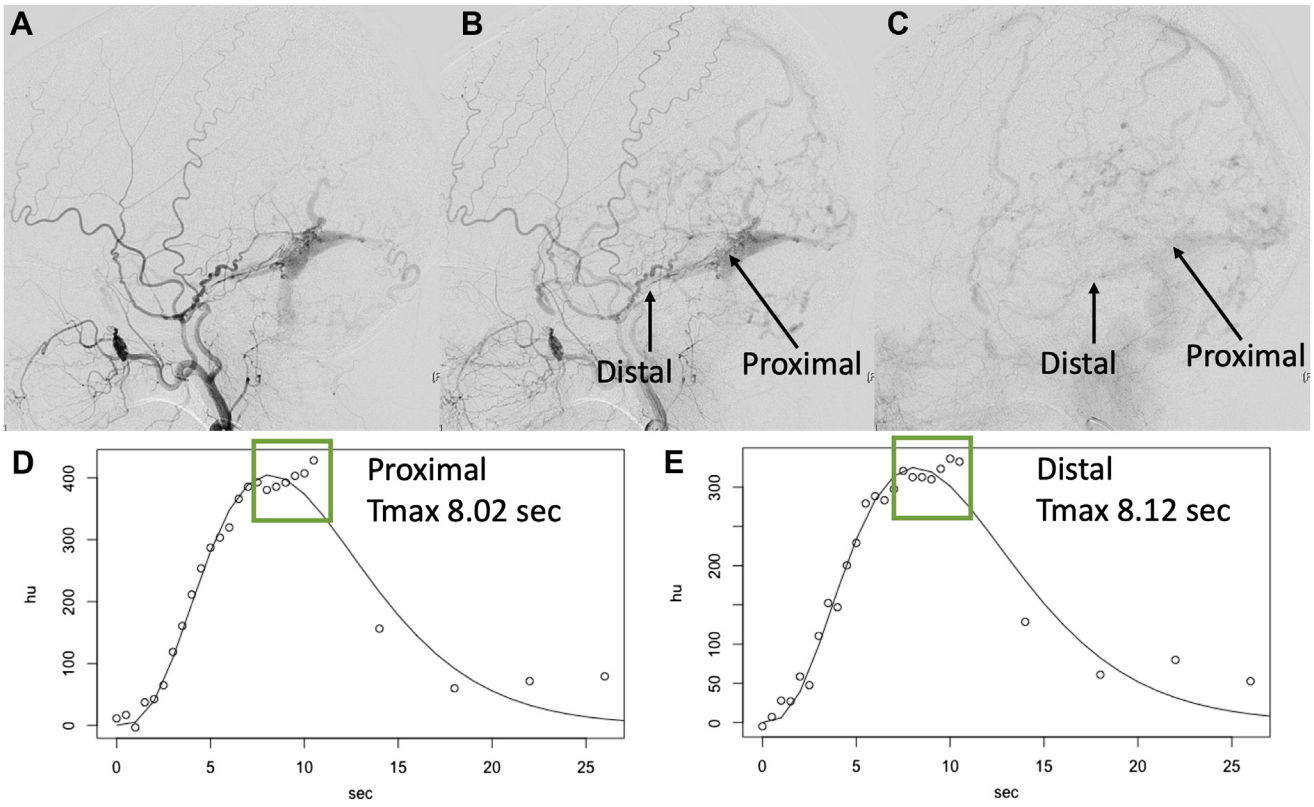


Figure 4. The cases in which we failed to analyze the flow direction owing to insufficient differences in the time to peak between the 2 observed points (30 mm from each other). The images were from a 53-year-old woman with a transverse-sigmoid sinus dural arteriovenous fistula. (**A**–**C**) Digital subtraction angiography via the external carotid artery. Fitting to the gamma distribution and time density curve in the (**D**) proximal and (**E**) distal sphenopetrosal vein. In the sphenopetrosal vein of this patient, we failed to determine the direction of the flow owing to a difference of <0.15 second in the time to peak. In this case, abnormal prolongation or a further increase in the contrast concentration was seen after the peak of the time density curve (highlighted by the *red box* in **D** and **E**). We also observed considerable venous congestion in this hemisphere.

flow properties, the function of certain venous channels would not have been fully elucidated. However, quantitative analysis of the venous channel is essential and, without it, the objective and precise evaluation of the influence of intracranial venous channels on brain physiological and pathological perfusion cannot be fully understood.

The greatest advantage of the presented method is that it enables us to estimate one of the quantitative flow properties, flow velocity, from which we can determine the degree of contribution of each vein to the brain circulation. In the present study, the average velocity in the antegrade channels was 64.3 mm/second. According to previous data, the time-averaged mean velocity in the intracranial venous channels on transcranial Doppler has been reported to be 4–17 cm/second (mean, 10.1 cm/second).[11] Other investigators have also shown a velocity of approximately 8 cm/second in the cortical vein in a healthy volunteer using 4D-flow magnetic resonance imaging.[12] These values from reported studies are slightly greater than ours. However, as stated, because the possibility exists that we failed to analyze the high-velocity venous channel, the true average velocity in the present study might have been greater than the average value. Accordingly, although we could not verify the current flow velocity obtained using 4D-CTA directly using other modalities, the average velocity from our results was mostly consistent with the data from previous studies. Therefore, our method might be clinically applicable for the evaluation of intracranial flow velocity. In addition to the flow velocity and direction, the presented method might be useful for the analysis of venous flow dynamics in a different way. Although we might not have correctly obtained the flow velocity in veins with multiple venous compartments or those with severe congestion, from another perspective, the flow profiles obtained using our method successfully reflected and detected these abnormal venous flow properties and might be useful in detecting these types of pathological entities.

We believe our method can be applied to the following clinical situations. First, neurosurgeons will sometimes consider sacrificing the cortical vein during resection of brain tumors involving the cortical vein. The method used in the present study can estimate the degree of contribution of each vein to the brain drainage using the flow velocity, which could assist neurosurgeons in their

decision-making. Second, the present current method can be used to detect the cortical venous reflux in the DAVF, which is a risk factor for aggressive behavior of DAVFs.[13] Our method can detect the retrograde directional flow and, even by analyzing only the TTP value, can easily detect the venous channel that has an abnormal early peak of the contrast agent. Because the artifacts of embolic material will impair the 4D-CTA qualities after treatment, the presented method could be useful as a pretherapeutic or follow-up evaluation for untreated patients. The results from the present study could also enhance the knowledge of pathophysiology of intracranial AVS diseases. In these lesions, the rapid high-pressure arterial flow empties into the cortical veins or dural venous sinuses and causes local and global venous hypertension, for which the knowledge of the venous flow dynamics is fundamentally important. However, a few studies have reported that the velocity in the venous channel concerning AVS flow was much faster than the normal circulation in the case of arteriovenous malformation[12] and DAVFs.[14] In addition, as described in the present study, the detailed analyses of the venous flow dynamics in AVS diseases have not been thoroughly investigated. Further quantitative flow dynamics analyses using the presented method might further elucidate this issue.

Comparison with Other Modalities

The conventional catheterized DSA technique has sufficient temporal and spatial resolution and has been classically considered to be the standard for the analysis of intracranial venous flow. "Conventional" 4D-CTA can be also used to evaluate intracranial venous flow, and several investigators have used 4D-CTA to evaluate the flow dynamics of intracranial AVS diseases.[4-6] However, owing to the lack of time resolution, it can sometimes be difficult to determine the venous flow direction from "conventional" 4D-CTA images, as demonstrated in **Figure 2E–J**. In contrast, our 4D-CTA method successfully obtained the direction of flow in ~95% of venous channels and also obtained quantitative information (i.e., the velocity of the flow), which cannot be determined using conventional DSA. Additionally, DSA is time- and cost-prohibitive and, in particular, is associated with risks of neurological complications[3] and invasiveness. Because our results were determined from estimation values obtained from the approximated TDC, conventional DSA will remain the first-line analytic method. However, we believe that if the limitations of the presented novel method are carefully considered, the presented 4D-CTA technique might be a more reliable and useful method by which to evaluate intracranial venous flow dynamics.

Some investigators have described the utility of intraoperative indocyanine green video angiography to analyze the venous flow dynamics in patients with DAVFs.[15,16] This technique enables operators to directly visualize the direction of flow, which is useful information during surgery. However, it can only evaluate venous channels within the operative view and cannot be widely applied for preoperative or postoperative general imaging examinations.

Several studies have reported the use of transcranial duplex ultrasonography for assessing intracranial venous flow dynamics.[11,14,17-20] Transcranial duplex ultrasonography is less invasive, less costly, and easy to apply in daily clinical settings. However, because the operator requires skills and experience to perform transcranial duplex ultrasonography, interobserver variability often occurs.[21] Additionally, the operator cannot evaluate arbitrary vasculature because the method measures the blood flow only through a limited narrow bone window. Accordingly, it cannot be generally applied to all clinical situations.

4D-flow magnetic resonance imaging is another technique that can be used to obtain venous flow dynamics.[12,22] It does not require radiation exposure and can directly evaluate the blood flow. However, compared with 4D-CTA, it requires a special sequence, which is not available at every hospital, and obtaining the images is a lengthy process. The advantage of the presented 4D-CTA method is that it can be applied to the general 4D-CTA protocol already in wide use. Additionally, the method enables us to retrospectively evaluate the venous flow dynamics after the examination without any additional costs or inspection time.

CONCLUSIONS

The presented method enabled us to obtain the intracranial venous flow dynamics, the direction of the flow, and the flow velocity. When the limitations of the presented method are carefully considered, it can be concluded that it is reliable and promising for clinical applications.

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