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ORIGINAL RESEARCH

Cerebral Venous Thrombosis: Diagnostic Accuracy of Combined, Dynamic and Static, Contrast-Enhanced 4D MR Venography

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BACKGROUND AND PURPOSE: MR including MRV is an established method to diagnose CVT. However, it remains unsettled which MR imaging modalities offer the highest diagnostic accuracy. We evaluated the accuracy of a combined, dynamic (1.5 seconds per dataset) and static (voxel size, 1.1 × 0.9 × 1.5 mm), contrast-enhanced MRV method (combo-4D MRV) relative to other established MR/MRV modalities.

MATERIALS AND METHODS: A total of 39 patients with CVT (n = 20) and control subjects (n = 19) underwent combo-4D MRV, 2D TOF MRV, GRE imaging, and T2W imaging. For these modalities, diagnostic accuracy (ROCs) for CVT affecting 53 out of 234 predefined venous segments was determined. Sensitivity and specificity were separately calculated for different stages of CVT (acute/subacute/chronic).

RESULTS: Combo-4D MRV showed the highest accuracy (AUC, 0.99 [95% CI, 0.97–1.0]; sensitivity, 97% [84%–100%]) for thrombosed dural sinuses. For all thrombosed segments including cortical veins, its sensitivity was best (76% [64%–84%]; AUC, 0.92 [0.88–0.96]), followed by TOF MRV (72% [59%–81%]; AUC, 0.93 [0.88–0.97]). Even for chronic CVT, it showed a relatively high sensitivity of 67% (30%–90%). For thrombosed cortical veins alone, GRE images achieved the highest sensitivity (66% [46%–81%]; AUC, 0.88 [0.78–0.97]). Specificities of all modalities ranged from 96% to 99%.

CONCLUSIONS: Combo-4D MRV showed an excellent accuracy for the diagnosis of dural sinus thrombosis. The analysis of dynamic patterns of contrast enhancement in dural sinuses appeared useful to identify chronic thrombosis. To diagnose thrombosed cortical veins, GRE images should primarily be analyzed.

ABBREVIATIONS: AF = acceleration factor; AUC = area under the respective reader-specific ROC curve; CI = confidence interval; CVT = cerebral venous thrombosis; DSA = digital subtraction angiography; FA = flip angle; GRE = gradient recalled-echo; MRV = MR venography; NA = number of averages; MIP = maximum intensity projection; MPRAGE = magnetization-prepared rapid acquisition of gradient echo; ROC = receiver operating characteristic; T2W = T2-weighted; TA = acquisition time; TOF = time-of-flight; VIBE = volumetric interpolated brain examination; TSE = turbo spin-echo

Cerebral venous thrombosis accounts for 0.5% of all strokes.[1-3] Accurate and prompt diagnosis of CVT is crucial, because timely and appropriate therapy can reverse the disease process and significantly reduce the risk of acute complications and long-term sequelae.

MR-based neuroimaging plays a primary role to allow for early diagnosis. However, the sensitivity of nonenhanced MR images is reduced due to a considerable variation of the signal intensity of venous thrombi on T1-weighted, T2W, and GRE images according to the thrombus age.[2,4-6] Thus, MRV is still regarded as necessary for confirmation of CVT.[2,3,5]

Static contrast-enhanced 3D MRV techniques, which enable a superior visualization of intracranial veins relative to TOF MRV,[4,7-10] have only been tested in smaller series for diagnostic yield in CVT.[4,8] Moreover, chronic dural sinus thrombosis is still considered a diagnostic challenge of static contrast-enhanced MR and 3D MRV with long acquisition times, as the organized thrombus may contrast enhance.[4,11,12]

Alternatively to those static methods, a dynamic analysis of cerebral venous flow by using time-resolved contrast-enhanced 3D MR angiographic techniques may be applied. Such sequences generate subtracted images of the arteriovenous bolus transit similar to the principle of DSA.[13-15] Pilot data suggested such images as promising tools to diagnose dural sinus thrombosis.[14,16] However, these dynamic sequences require careful adjustment of spatial and temporal resolutions as well as signal intensity-to-noise ratio, which is often at the cost of a lower spatial resolution.[13,14,16] Thus, a combination of a dynamic sequence and a static, spatially highly resolved, 3D MRV may be an advantageous approach.[17]

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The goal of this study was to determine the accuracy of a combined application of dynamic (1.5 second/3D dataset) and static (voxel size, 1.1 × 0.9 × 1.5 mm) 3D MRV by using a single injection of contrast media, hence termed combo-4D MRV. We hypothesized that this method is overall superior to TOF MRV, GRE, and T2W MR images for the diagnosis of CVT, including patients with chronic CVT.

Materials and Methods

Patients

At our institution (large cerebrovascular tertiary care center), all patients with clinical suspicion of CVT, intracranial vascular malformation, and/or with intracranial hemorrhage of unclear etiology undergo a standardized MR imaging protocol, including the study protocol sequences. These cases were prospectively entered in an in-house data base. In a retrospective analysis of this data base between June 1, 2005 and September 30, 2007, the study population was selected (22 women and 17 men; mean age ± SD, 49.1 ± 15.4 years; range, 21–79). Waiver of informed consent for retrospective analysis of medical charts and patients' images was given by the institutional review board.

For the diagnosis of CVT, the following standard of reference was applied: 1) history and clinical manifestations compatible with CVT; 2) 2 experienced neuroradiologists (S.M. and S.G.W) evaluated all study protocol MR/MRV modalities for signs of CVT by side-by-side consensus reading; and 3) both neuroradiologists additionally reviewed images of DSA ($n = 9/39$), contrast-enhanced CT/CT angiography/venography ($n = 24/39$), or both ($n = 5/39$). CVT was diagnosed in 19 consecutive patients by this standard of reference. In addition, 1 patient with extensive dural sinus and cortical vein thrombosis was included who had solely undergone noncontrast-enhanced CT scan that disclosed numerous hyperattenuated cord signs.

For the control group, 19 consecutive patients were selected by the following criteria: they were proved negative for CVT by the above-mentioned standard of reference; they were not included if a confirmatory DSA/CVT/CT was either not available or the time interval between these examinations and the study MRV was too long (average interval, 6.2 days: range, 0–56; SD, 12.5), or if MR imaging demonstrated abnormalities other than ischemia or hemorrhage (eg, tumor, patent arteriovenous malformation). Intracranial hemorrhage was present on MR images in 9 and 10 patients of the CVT group and the control group, respectively.

Proved CVTs were classified according to the interval between initiation of symptoms and MR examination as previously reported.[18,19] Five out of 20 (25%) CVTs were imaged at the acute stage (mean interval, 1.2 days; range, 1–2), 10 out of 20 (50%) at the subacute stage (mean interval, 7.0 days; range, 3–11), and 5 out of 20 (25%) CVTs were imaged at the chronic stage (mean interval, 833.8 days; range, 44 days–7 years).

MR and MRV Protocols

MR examinations were performed on a 1.5T MR scanner (Avanto; Siemens, Erlangen, Germany) by using a 12-channel head coil. Patients underwent the following sequences in the stated order: T2W images, GRE images, 2D TOF MRV, followed by a single intravenous dose (0.1 mmol/kg) of gadobutrolum (Gadovist 1.0; Schering, Basel, Switzerland) administered with a power injector at a rate of 3 mL/s, simultaneous with the start of the acquisition of the dynamic 3D MRV sequence. In immediate succession, the static 3D VIBE MRV was obtained. MR parameters were: axial T2-TSE (TR/TE, 4620/98 ms; FA, 150°; 24 sections; section thickness, 5 mm; matrix size, 512 × 384; FOV, 230 × 201 mm; TA, 2.15 minutes; NA, 2; AF, 2), coronal T2-TSE (TR/TE, 6970/101 ms; FA, 150°; 24 sections; section thickness, 5 mm; matrix size, 448 × 381; FOV, 230 × 201 mm; TA, 3.24 minutes; NA, 2; AF, 2), axial GRE images (TR/TE, 730/19.6 ms; FA, 20°; 24 sections; section thickness, 5 mm; matrix size, 256 × 205; FOV, 230 × 173 mm; TA, 1.54 minutes; NA, 1), and 2D TOF MRV (TR/TE, 26/7.2 ms; FA, 60°; 45 coronal sections; section thickness, 4 mm; FOV, 200 × 188 mm; matrix, 256 × 256; TA, 3.51 minutes). For combo-4D MRV, the dynamic contrast-enhanced MRV sequence is a commercially available time-resolved MR angiographic technique based on a 3D radio frequency-spoiled fast low-angle shot sequence (TR/TE, 1.74/0.64 ms; FA, 15°; FOV, 255 × 255 mm; matrix, 128 × 128; slab thickness, 123.2 mm; 64 sagittal sections [entire head coverage] with zero-filling of *k*-space data in the partition direction [section resolution 64%]; in-plane resolution, 2.0 × 2.0 mm; TA, 37.5 seconds; AF along phase-encoding direction, 3; AF along partition-encoding direction, 2; number of volumes, 25; temporal resolution, 1.5 seconds per 3D dataset).[14-16] The first dataset was discarded, and magnitude subtraction of subsequent volumes from the second dataset was performed to remove background signal intensity. The static contrast-enhanced 3D VIBE MRV is a 3D radio frequency-spoiled fast low-angle shot sequence (TR/TE, 9/3.38 ms; FA, 10°; slab thickness, 168 mm; section thickness, 1.5 mm; FOV, 220 × 220 mm; matrix, 256 × 192; 112 sagittal sections with zero-filling of *k*-space data in the partition direction [section resolution 75%]; TA, 2.46 minutes; AF, 2; voxel size, 1.1 × 0.9 × 1.5 mm).[7,10]

Image Analysis

Images of all patients were reviewed independently by 2 experienced radiologists (C.R. and J.B.) blinded to the patients' names and clinical or other imaging findings. Each observer viewed 4 MR/MRV modalities per patient separately (T2W images, GRE images, TOF MRV, combo-4D MRV). In this manner, image analysis was divided into separate sessions for each MR/MRV technique that grouped the studies in a random patient order. These sessions were performed over a period of 5 months, with a minimum time gap of 1 month, to suppress any recall bias from studies originating from the same patient. In 1 patient with chronic CVT, GRE images were technically inadequate. Six predefined venous segments were evaluated: the superior sagittal sinus, the straight sinus, both lateral sinuses including the region from transverse sinus to the jugular bulb, and right and left cortical venous segments defined as any cortical vein of the right and left hemispheres, respectively. These segments were independently classified into 5 categories according to the presence or absence of CVT: 1 = definitely or almost definitely absent, 2 = probably absent, 3 = uncertain, 4 = probably present, 5 = definitely or almost definitely present.[4] All sequences including static MRV source images were analyzed on a 3D workstation allowing for multiplanar reformations and targeted MIPs. For the dynamic MRV part, automatically generated sagittal and coronal whole-brain MIP images were analyzed first. Second, if the patency of a vein was unclear, the observers had the additional opportunity to assess any individual venous phase in freewheeling 3D mode.

The diagnostic criteria for CVT were as follows: on T2W images, isointense or hyperintense signal intensity inside a cerebral vein lacking a normal flow signal intensity void; on GRE images, a typical magnetic susceptibility effect was only regarded as a positive sign if the lumen of an affected venous segment was encompassed by a strong

Table 1: Reader agreement rates for CVT at venous segment level

	Imaging Technique			
	T2W	GRE	TOF MRV	Combo-4D MRV
Polychoric correlation test	0.83	0.64	0.88	0.95
Binary test	0.89	0.87	0.89	0.94

hypointense signal intensity that was enlarged compared with adjacent normal veins[5,6]; on TOF MRV images, a lack of normal venous flow signal intensity was considered positive. To rule out the possibility of an anaplastic or hypoplastic sinus, source images were analyzed. On the static part of combo-4D MRV, an intraluminal hypointense or isointense filling defect was considered positive. Along with these images, the dynamic part was assessed to exclude the possibility of enhancing chronic thrombosis imitating a patent vein. Here, the following discrepant findings between dynamic and static MRV were considered indicative of chronic CVT: a venous segment shows lacking or irregular contrast enhancement at predominantly early venous phases of dynamic MRV, either with or without further increase of the enhancement at later venous phases, but it reveals a normal appearing contrast enhancement on static VIBE MRV images.

Statistical Analysis

The ratings of the 2 readers were assessed at the venous segment level; that is, the ratings of all 6 predefined venous segments per patient were compared with the respective standards of reference. For each of the 4 sequences, ROC analysis was performed overall, and for dural sinuses and cortical veins separately. The diagnostic accuracy was determined by calculating the AUC. CIs for the average AUC over both readers were calculated, and pair-wise comparisons between all modalities were performed. To obtain average sensitivity and specificity for each sequence, thrombosed venous segments correctly located as probably present or definitely present (score $\geq$4) were regarded as correctly diagnosed sites of CVT. Sensitivities and specificities were calculated for dural venous sinuses and cortical venous segments, for the CVT subgroups and at the patient level, separately. For the latter, each patient was categorized as correctly diagnosed if at least 1 venous segment was correctly judged as positive of CVT.

Reader agreement for each technique was summarized by polychoric correlations. Polychoric correlations estimate what the correlation between readers would be if ratings were made on a continuous scale; they are, theoretically, invariant over changes in the number or "width" of rating categories. We prefer polychoric correlations to the more frequently used (weighted) κ measures, as they are easier to interpret and because the latter require the somewhat arbitrary selection of weights, because κ coefficients depend strongly on the rating frequency of each reader (and not only on their association), and because κ can only be interpreted as a chance-corrected measure of agreement under the unrealistic assumption of statistical independence of readers.[20] In addition to polychoric correlations, we summarized raw reader agreement for the binary test where test scores of 4 or 5 were categorized as a positive test.

All CIs and tests were based on bootstrap standard errors. To account for potential correlation of results for venous segments within patients, we used a cluster bootstrap (ie, patients and not segments were resampled). We sought to improve the coverage probabilities of CIs for sensitivities and specificities by adding 2 correctly classified and 2 falsely classified patients with only 1 venous segment before performing the boostrap, in analogy to the Agresti and Coull CIs.[21] *P* values were not adjusted for multiple comparisons. All reported tests were performed at a 2-sided 5% significance level. Analyses were performed with the statistical software R version 2.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

CVT was diagnosed in the 20 patients in a total of 53 out of 234 sites. Thirty-four of these were thrombosed dural venous si-

Table 2: Average sensitivity and specificity for 2 readers and 53 sites of CVT in 39 patients assessed on venous segment level and on patient level

	Imaging Technique, % (95% CI)				Pair-wise Difference, *P* Value[a]
	T2W	GRE	TOF MRV	Combo-4D MRV	
Venous segment level[b]					
All segments, all stages					
Sensitivity (n = 53)	62 (48–74)	49 (34–64)	72 (59–81)	76 (64–84)	[2](.002), [5](.006)
Specificity (n = 181)	98 (94–99)	98 (94–99)	96 (92–97)	99 (96–100)	[3](.02)
Dural venous sinuses, all stages					
Sensitivity (n = 34)	72 (55–84)	39 (24–57)	82 (66–92)	97 (84–100)	[1](.003), [2](<.001), [3](.03), [4](.03), [5](<.001), [6](.005)
Specificity (n = 122)	99 (95–100)	98 (94–99)	95 (90–97)	99 (95–100)	[3](.02), [4](.007)
Cortical veins, all stages					
Sensitivity (n = 19)	45 (27–64)	66 (46–81)	53 (35–69)	37 (20–58)	[2](.01)
Specificity (n = 59)	95 (86–99)	97 (87–100)	98 (89–100)	99 (91–100)	
All segments					
Sensitivity, acute stage (n = 16)	56 (25–85)	56 (36–74)	75 (44–96)	63 (44–76)	N/A
Sensitivity, subacute stage (n = 31)	63 (48–75)	50 (29–71)	71 (57–80)	84 (67–94)	N/A
Sensitivity, chronic stage (n = 6)	75 (36–94)	20 (6–61)	67 (32–88)	67 (30–90)	N/A
Patient level, all stages[c]					
Sensitivity (m = 20)	75 (56–85)	55 (38–71)	83 (63–91)	90 (69–97)	[2](<.001), [5](.002)
Specificity (m = 19)	97 (77–100)	95 (74–100)	79 (58–90)	100 (80–100)	[3](.009), [4](.04)

Note:—n refers to the number of venous segments included in the calculation; m refers to the number of patients included in the calculation.
[a] Superscripts 1, 2, 3, 4, 5, and 6 indicate significant difference between combo-4D MRV and T2W, combo-4D MRV and GRE, combo-4D MRV and TOF MRV, TOF MRV and T2W, TOF MRV and GRE, and between GRE and T2W, respectively.
[b] Binary test on venous segment level, ie, test is positive if score is >3.
[c] Binary test on patient level, ie, test is positive for patient if score >3 for any of the patient's venous segments.

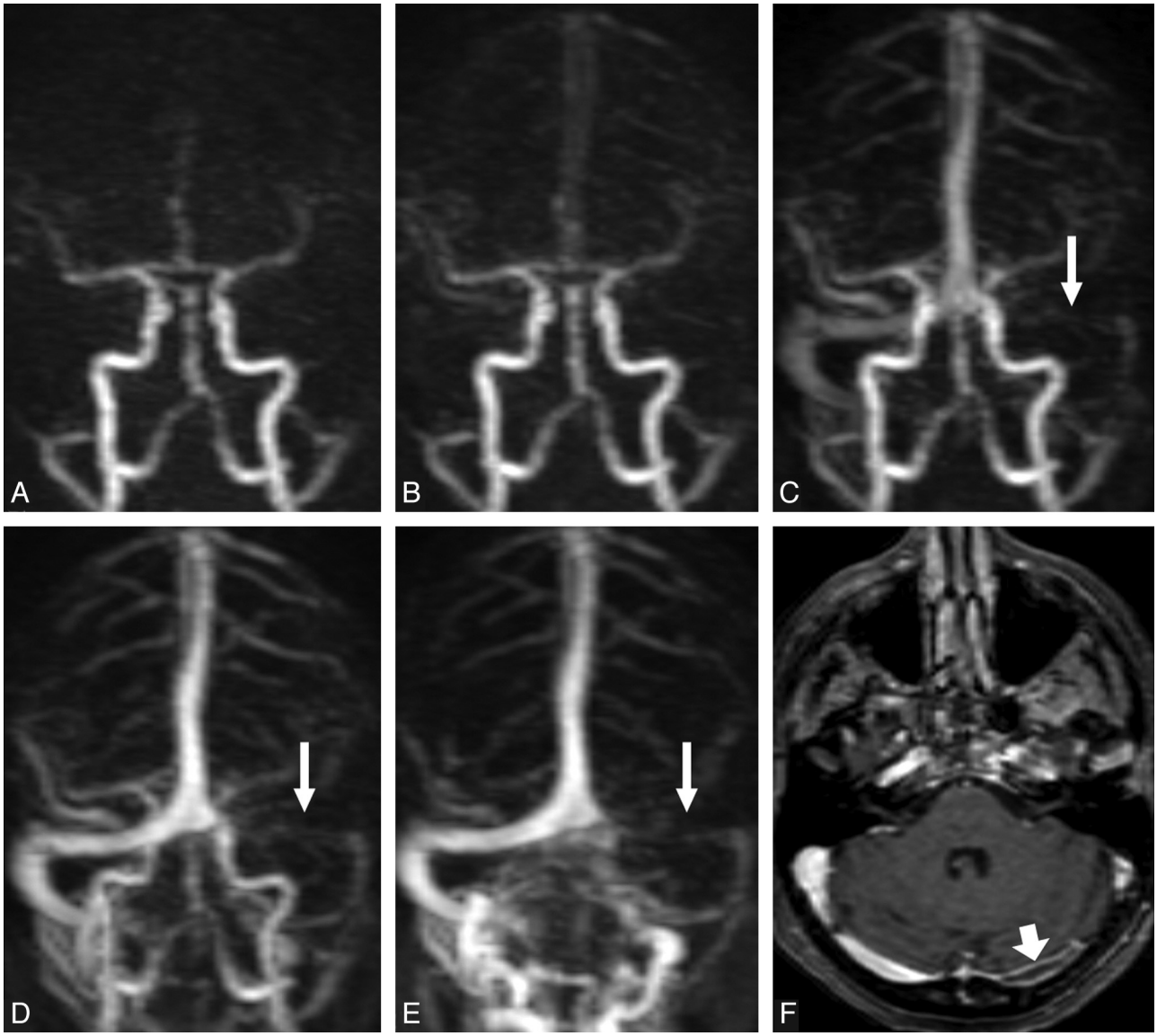

Fig 1. Fifty-six-year-old woman with subacute left proximal lateral sinus thrombosis (duration of symptoms, 5 days). The arteriovenous transit of a contrast bolus is depicted on the dynamic series of combo-4D MRV (*A–E*; coronal MIP reformations of time-resolved contrast-enhanced MRV; temporal interval between images, 1.5 seconds). At early venous phase, faint filling of cortical veins and the superior sagittal sinus is noted (*B*). At subsequent later venous phase, the left proximal transverse sinus does not show increased contrast filling other than very faint peripheral enhancement of its dural wall (*long arrow* in *C*). At following later venous phases, no increase in contrast filling of this sinus portion is observed (*long arrow* in *D* and *E*). On axial static image of combo-4D MRV (contrast-enhanced 3D VIBE sequence), a hypointense filling defect within the proximal left transverse sinus is depicted (*small arrow* in *F*).

nuses, and 19 were thrombosed cortical veins. Ten individuals had both thrombosed sinuses and cortical veins, 9 had only thrombosed sinuses, and 1 had a singular thrombosed cortical vein. The mean number of thrombosed sites depended on the stage of CVT; it was 3.2 (range, 2–5), 3.1 (range, 1–6), and 1.2 (range, 1–2) in cases of acute, subacute, and chronic CVT, respectively. Reader agreement was generally good (Table 1); it was best for combo-4D MRV (0.95) and worst for GRE imaging (0.64).

Sensitivities depended on the type of affected cerebral veins (summarized in Table 2). For all venous segments, significant differences in sensitivity were only found for combo-4D MRV (76%) versus GRE imaging (49%) and for TOF MRV (72%) versus GRE imaging ($P = .002$ and $P = .006$, respectively). For dural venous sinuses, combo-4D MRV (Fig 1) had the highest sensitivity of 97%, whereas GRE imaging was worst, with a sensitivity of only 39%. In this subgroup, sensitivities of both MRV modalities were significantly higher when compared with GRE and T2W imaging. Combo-4D MRV also showed a significantly higher sensitivity compared with TOF MRV ($P = .03$, Fig 2). For cortical veins, none of the methods exceeded a sensitivity of 66%, with GRE imaging (Fig 3) providing the best and significantly higher sensitivity compared with combo-4D MRV ($P = .01$).

Sensitivities for the different MR modalities showed variations according to the stage of CVT when assessed on venous segment level. In acute CVT, TOF MRV and combo-4D MRV had the best sensitivity with 75% and 63%, respectively. In subacute CVT, the latter was markedly better than the remaining 3 sequences, with a sensitivity of 84% (On-line Video). In chronic CVT, sensitivities of all modalities ranged between 67% and 75% except for GRE imaging, which was least sensitive with 20% (Fig 4).

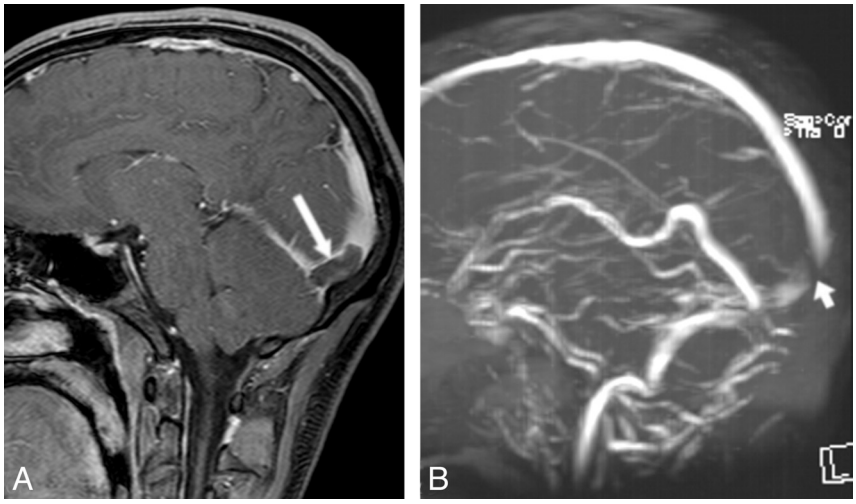

Fig 2. Twenty-five-year-old man with subacute thrombosis (thrombus age, 4 days) of posterior portion of superior sagittal sinus, torcular region, and right lateral sinus. Sagittal source image of static VIBE part of combo-4D MRV reveals large isointense filling defect within posterior portion of superior sagittal sinus extending into torcular area (*long white arrow* in *A*). On sagittal whole-brain MIP reconstructed image of 2D TOF MRV, most of this thrombus shows hyperintense signal intensity mimicking flow. The small vertical signal intensity gap (*short white arrow* in *B*) was misinterpreted as artifact on a single section derived from in-plane signal intensity loss (coronal acquisition). No flow signal intensity is depicted in thrombosed right lateral sinus.

Specificities for all MR imaging sequences on the venous segment level were excellent, with values ranging between 96% and 99%. However, the specificity of combo-4D MRV was significantly higher compared TOF MRV for all venous segments as well as for dural venous sinuses alone (99% versus 96%, $P = .02$; and 99% versus 95%, $P = .02$; Fig 5).

In the assessment of sensitivities on the patient level, combo-4D MRV was best with 90%, followed by TOF MRV, T2W, and then GRE images. Thereby, combo-4D MRV and TOF MRV performed significantly better than GRE imaging ($P < .001$ and $P = .002$, respectively). Specificity of all sequences ranged between 95% and 100%, except for TOF-MRV with 79%, which was significantly lower compared with combo-4D MRV ($P = .009$) as well as with T2W images ($P = .04$).

In the analysis of diagnostic accuracies, combo-4D MRV and TOF MRV performed best for overall assessment of all venous segments. Pair-wise comparisons of the AUCs (Table 3) show that these methods were significantly better than both T2W and GRE imaging ($P < .05$). Between both MRV methods, no statistically significant difference was found ($P = .76$). At the assessment of dural venous sinuses only, again both MRV techniques were significantly better than T2W ($P \leq .01$) and GRE imaging ($P < .001$), and there was a trend that combo-4D MRV was superior to TOF MRV (AUCs of 0.99 and 0.96, respectively; $P = .15$). For cortical venous thrombosis, TOF MRV and GRE performed best and showed quite similar accuracies. Despite the low sensitivity of TOF MRV for cortical vein thrombosis (53%), this sequence demonstrated a significantly better accuracy in comparison to combo-4D MRV ($P = .02$) and versus T2W imaging ($P = .01$).

The apparent discrepancies between diagnostic accuracies obtained from the ROC analysis and sensitivities/specificities calculated by the binary method, particularly for combo-4D MRV and TOF MRV, were related to the use of relative (ROC analysis) versus absolute cutoffs (binary test) in the readers' ratings required for the diagnosis of CVT. A high sensitivity required readers to be confident in their diagnosis of CVT (ie, assign a score of >3), whereas for a high AUC it is only required that readers rate CVT cases higher than controls, regardless of the absolute value of the score. Indeed, 29.2%, 53.8%, and 17.0% of both readers' ratings were lower, equal, and higher on TOF MRV compared with combo-4D MRV for all thrombosed venous segments, respectively. At the assessment of thrombosed dural venous sinuses only, 35.3%, 58.8%, and 5.9% of both readers' ratings were lower, equal, and higher on TOF MRV compared with combo-4D MRV, respectively. In contrast, 18.4%, 44.8%, and 36.8% of both readers' ratings were lower, equal, and higher, respectively, in the analysis of thrombosed cortical veins.

Discussion

In this study, the diagnostic accuracy of a combined, dynamic and static, contrast-enhanced MRV in CVT was compared with established MR and MRV sequences. Combo-4D MRV demonstrated the highest overall sensitivity (binary test) among the 4 assessed techniques for all thrombosed venous segments, with its overall accuracy (ROC analysis) being superior to T2W and GRE imaging, and equivalent to TOF MRV. Its overall specificity (binary test) was again superior to TOF MRV. Its incomplete overall sensitivity of 76% is most likely related to the inclusion of thrombosed cortical veins that are notoriously difficult to assess on MRV due to their high variability in number, size, and location.[6,22] In dural venous sinus thrombosis alone, it showed the highest sensitivity (97%) and specificity (99%) among the 4 assessed techniques. Although only a trend toward superior accuracy was found on ROC analysis between combo-4D MRV (AUC of 0.99) and TOF MRV (AUC of 0.96), a significantly higher sensitivity and specificity was demonstrated with the binary test (97% versus 82%) in cases of dural venous sinus thrombosis. For both techniques, readers thus graded almost all thrombosed venous sinuses relatively higher compared with nonthrombosed ones, explaining the similar AUCs. However, they were more reluctant to assign a confidence score of >3 (probable or definite thrombosis) for the TOF MRV method, thus explaining the higher sensitivity of combo-4D MRV. Indeed, the readers assigned lower scores on TOF MRV compared with combo-4D MRV for 35.3% of all thrombosed dural venous sinus seg-

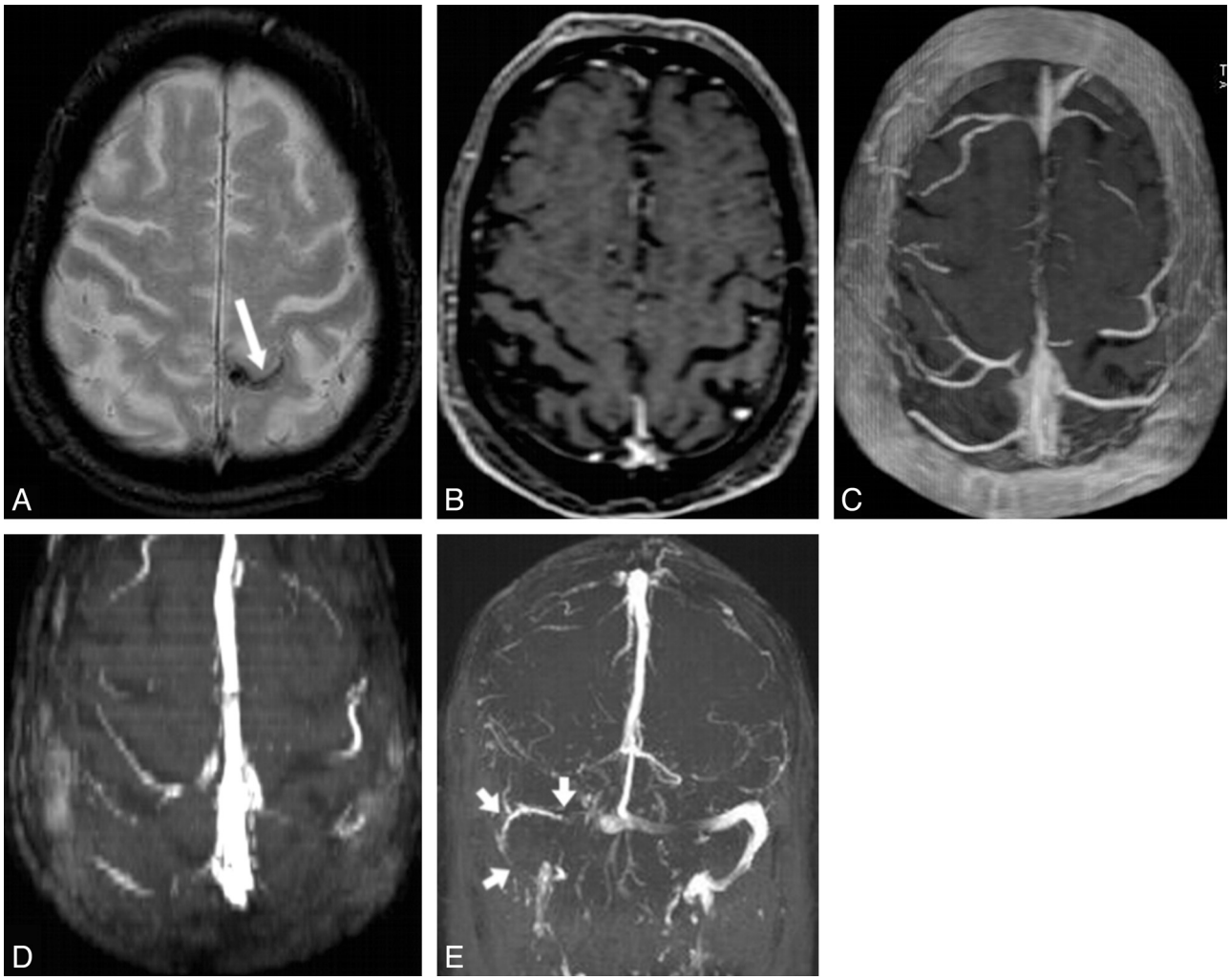

Fig 3. Seventy-six-year-old man with acute venous thrombosis involving left parietal cortical vein (thrombus age approximately 1 day). GRE image shows typical magnetic susceptibility effect with hypointense signal intensity and blooming in left parasagittal parietal cortical vein (*long white arrow* in *A*). Static 3D contrast-enhanced VIBE MR venographic images from combo-4D MRV are centered on region of interest (*B* and *C*). No evidence of cortical venous filling defect can be seen on axial image (*B*) and targeted axial thick-slab MIP reformation (thickness, 20 mm; *C*) of VIBE sequence in corresponding area. Likewise, this thrombosed cortical vein is not evident on 2D TOF MR venogram, as demonstrated by targeted axial thick-slab (thickness, 20 mm; *D*) and standard coronal whole-head (*E*) MIP reformations. On the latter image, additional thrombosis of right lateral sinus is depicted (*short white arrows* in *E*).

ments and higher scores only for 5.9%. These discrepancies indicate an overall higher reader confidence in diagnosing dural venous sinus thrombosis with combo-4D MRV.

Despite proved superiority for the depiction of normal cerebral veins, the diagnostic performance of static contrast-enhanced MRV methods in CVT was only tested for a subset of methods in smaller series.[4,7-10] Conventional contrast-enhanced MR images and MPRAGE MRV images with relatively long acquisition time (6–8 minutes) showed incomplete sensitivities for CVT related to contrast-enhancement of chronic sinus thrombosis mimicking sinus patency.[4,11,12] In our series, the combined analysis of dynamic contrast-enhancement patterns enabled the identification of chronic sinus obliteration by its delayed enhancement characteristics on the dynamic part of combo-4D MRV. In this manner, contrast media uptake into chronic thrombus that is composed of vascularized connective tissue components was clearly visualized on the static contrast-enhanced MRV part despite its relatively fast acquisition (2.46 minutes). Moreover, this relatively specific appearance of dynamic contrast enhancement may also enable a differentiation between cases of acute/subacute and chronic thrombosis. However, the temporal differences in contrast enhancement may be subtle: for this reason, 1 case of chronic sinus obliteration in our series was missed by 1 of the 2 observers. A precise differentiation between very early enhancing thrombus and slow flow within partially recanalized channels was not possible, as the exact time interval for chronic thrombus to exhibit enhancement is still unknown. An estimation of this interval appears difficult, as it may also significantly vary with thrombus age as well as sequence parameters (temporal resolution, asymmetric *k*-space sampling). A pattern of contrast-enhancing channels in partially recanalized chronic dural sinus thrombosis was recently described in a small selected series.[12] Likewise, these investigators could not accurately discriminate early enhancing thrombus from recanalized channels on images of a fast static contrast-enhanced MRV sequence triggered at peak venous enhancement (TA, 3.24 minutes). Instead, a better description of partially recanalized chronic thrombosis was obtained from a combined analysis of TOF MRV (flow analysis) *and static* contrast-enhanced MRV (vascular morphology analysis) in their study. Similarly, a combination of delayed dynamic enhancement within a dural

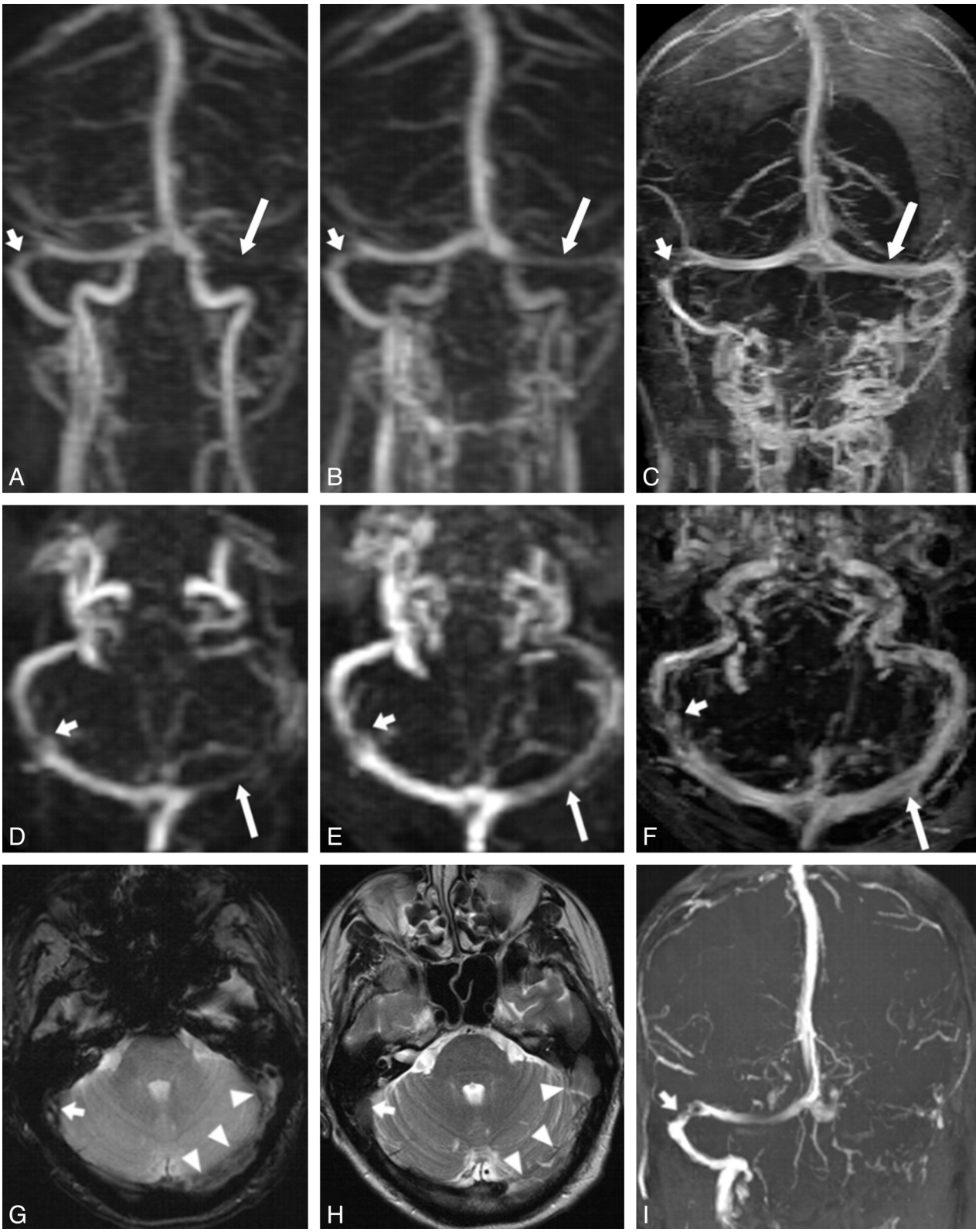

Fig 4. Fifty-three-year-old man with chronic left lateral sinus thrombosis (thrombus age approximately 7 years). Combo-4D MRV consisting of dynamic 3D contrast-enhanced MR venographic images and static 3D contrast-enhanced VIBE MR venographic images. *Upper panel*, Coronal MIP reformations of combo-4D MRV demonstrate chronic thrombosis of the left lateral sinus. On early venous phase image of the dynamic MRV series (*A*), a thin channel of contrast enhancement is depicted within a large gap inside the left transverse/sigmoid sinus (*long arrow*). An increase in this contrast enhancement is noted at the subsequent later venous phase (time delay of 1.5 seconds between dynamic images) on the corresponding image (*long arrow*, *B*). On the static MRV image (*C*), intense contrast-enhancement mimicking patency of these sinuses is disclosed (*long arrow*). Note also focal postthrombotic changes inside the right lateral sinus (*short arrows*) without dynamic contrast enhancement. *Middle panel*, Targeted axial oblique MIP reformations (parallel to the course of the lateral sinuses) of combo-4D MRV show more clearly the dynamic enhancement patterns of chronic left lateral sinus thrombosis (*D–F*). *Lower panel*: On corresponding axial GRE image, no relevant magnetic susceptibility effect is observed in the affected venous sinuses (*G*; *short arrow* and *arrowheads*). On T2W image, chronic thrombus reveals an isointense signal intensity (*H*; *short arrow* and *arrowheads*). Complete loss of normal flow signal intensity in left lateral sinus and jugular bulb, as well as irregular signal intensity void at the right transverse/sigmoid sinus junction are depicted on coronal MIP reformation of 2D-TOF MRV (*I*).

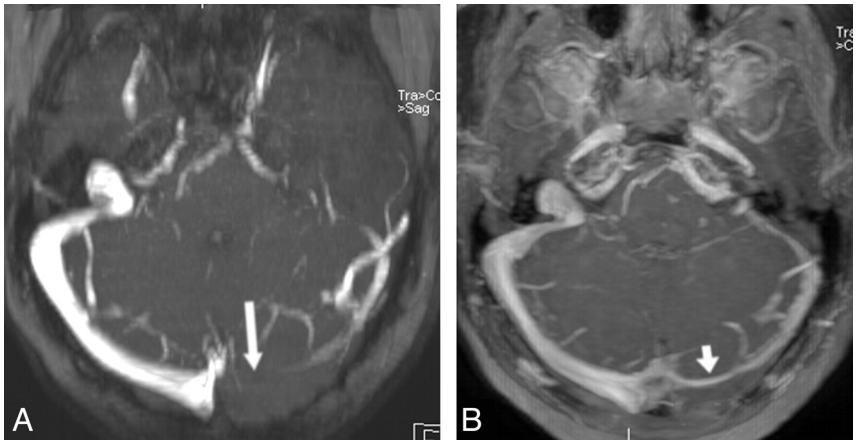

Fig 5. Forty-three-year-old man who underwent MR and MRV investigation for posterior fossa hemorrhage. Axial thick-slab MIP reformations of 2D TOF (*A*) and static part of combo-4D MRV (contrast-enhanced 3D VIBE, *B*) are targeted on lateral sinuses (slab thickness, 20 mm). On TOF MRV image, large flow gap in proximal transverse sinus is demonstrated (*long white arrow* in *A*). Combo-4D MRV image shows hypoplastic transverse sinus without evidence of thrombosis (*short white arrow* in *B*).

Table 3: AUC and comparisons between imaging techniques for 2 readers and 53 sites of cerebral venous thrombosis in 39 patients

	AUC Estimate			
	Reader 1	Reader 2	Average (95% CI)	Pair-wise Difference, *P* Value
All veins				
Combo-4D MRV	0.94	0.90	0.92 (0.88–0.96)	[a](.03), [b](.03)
TOF MRV	0.92	0.93	0.93 (0.88–0.97)	[c](.005), [d](.02)
GRE	0.83	0.89	0.86 (0.81–0.91)	
T2W	0.85	0.83	0.84 (0.78–0.91)	
Dural venous sinuses				
Combo-4D MRV	0.98	1.00	0.99 (0.97–1.00)	[a](.005), [b](<.001)
TOF MRV	0.95	0.96	0.96 (0.92–1.00)	[c](.01), [d](<.001)
GRE	0.81	0.87	0.84 (0.79–0.89)	
T2W	0.89	0.91	0.90 (0.84–0.96)	
Cortical veins				
Combo-4D MRV	0.87	0.73	0.80 (0.70–0.90)	
TOF MRV	0.87	0.90	0.89 (0.78–0.99)	[c](.01), [e](.02)
GRE	0.85	0.91	0.88 (0.78–0.97)	
T2W	0.77	0.70	0.74 (0.60–0.87)	

Note:—Superscripts a, b, c, d, and e indicate significant differences between combo-4D MRV and T2W, combo-4D MRV and GRE, TOF MRV and T2W, TOF MRV and GRE, and between TOF MRV and combo-4D MRV, respectively.

sinus segment on combo-4D MRV, missing flow signal intensity on TOF MRV, and absent flow signal intensity void on T2W images may indicate chronically occluded sinus rather than partial recanalization in our patients (Fig 2). However, such side-by-side analysis of MR modalities was not performed as part of this study. Therefore, further research including a defined-interval follow-up study of acute sinus thrombosis to better define the time to enhancement of chronic thrombus with the combo-4D MRV method is necessary.

A major drawback of static MRV approaches is that the imaging appearance of dural sinus thrombosis, in particular chronic thrombosis, can overlap with that of dural arteriovenous fistulas.[12,23] This may lead to false diagnosis, as the latter entity frequently occurs as a sequela of chronic CVT and is clinically initially often undiagnosed.[24] Therefore, the adjunct of a dynamic MR angiographic sequence, as in combo-4D MRV, may be of added value, as it also enables the diagnosis of arteriovenous shunts with high confidence.[13-15,17] However, the clinically very important differentiation between both entities requires further research, as this was not the focus of our present study.[12,25]

The overall reduced sensitivity of combo-4D MRV for chronic CVT (67%) was mainly related to missed cortical vein thrombosis. This included a single case of chronic isolated cortical vein thrombosis that was missed on all 4 modalities individually. It was solely identified at evaluation of the standard of reference (side-by-side analysis of all modalities). Isolated cortical venous thrombosis is a relative rare entity, and GRE images were found helpful for its diagnosis.[2,26] However, a decline of typical magnetic susceptibility artifacts in chronically occluded cortical veins can make them indistinguishable from normal cortical veins that exhibit a uniform hypointense signal intensity in contrast to the dural sinuses on GRE images.[5] Although derived from findings of a single case, our results suggest that the diagnosis of isolated cortical venous thrombosis, particularly if at chronic stage, may still be challenging when using a single MR technique. Overall, GRE images offered the best, but only incomplete, sensitivity for thrombosed cortical veins. The low sensitivity was most evident at chronic stage (20%) and may therefore be partly related to the time course of magnetic-susceptibility artifacts. Moreover, we also disclosed a low sensitivity of GRE images for dural sinus thrombosis. This result was presumably caused by a false interpretation of signal intensities at boundaries between tissues of differing magnetic susceptibility, eg, between the bony skull creating a low signal intensity and the transverse sinuses. Similar limitations were recently reported for other regions at the skull base with affection of the sigmoid sinuses and jugular bulbs.[5,27]

The overall lower sensitivity of T2W images in our study may be attributed to the poor delineation of thrombosed cortical veins, as well as to the hypointense appearance of acute staged thrombus simulating a normal flow signal intensity void.[2,5,11] On TOF MRV, many typical flow-related artifacts (eg, in-plane flow, slow flow, intravoxel dephasing), which are partly related to the orientation of the imaging plane, may contribute to an overall reduced sensitivity.[2,7,16,28] These artifacts may be overcome by the application of sequential oblique sections or by dual-plane acquisitions of 2D TOF MRV.[29,30] Furthermore, improved spatial resolutions by using parallel

imaging methods may also help to decrease flow-related artifacts in 2D TOF MRV.

Limitations of our study relate to the small number of patients included in the subgroup analysis (eg, acute, subacute, chronic CVT). Moreover, the separate analysis of singular MR or MRV sequences does not reflect a real reporting practice for examinations in patients with suspicion of CVT (side-by-side analysis of different sequences). However, the present study is necessary to gain information on the impact of individual sequences for the diagnosis of CVT. Alternatively, a combination of non-contrast-enhanced MRV techniques (2D TOF and phase-contrast MRV) may also be applied to diagnose CVT. We did not include this approach in our study, as its ability to differentiate chronic sinus thrombosis remains unclear. Furthermore, there has continued to be technical progress in the 2 component parts of the combo-4D MRV method since the start date of this study, such as higher spatial and temporal resolutions, which may provide improved performance in diagnostic accuracy in the future.[9,31]

Conclusions

Combo-4D MRV provides an excellent accuracy for the diagnosis of thrombosed dural sinuses at all stages. Compared with TOF MRV, its overall accuracy was equivalent, but its sensitivity and specificity were significantly better in dural venous sinus thrombosis. Moreover, the hitherto challenging cases of chronic sinus obliteration can be detected by a dynamic appearance of contrast-enhancement on combo-4D MRV. We recommend its application to be accompanied by GRE imaging, which showed the best sensitivity for cortical vein thrombosis.

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