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ABSTRACT

BACKGROUND AND PURPOSE: There is mounting evidence supporting the benefit of intra-arterial administration of vasodilators in diagnosing reversible cerebral vasoconstriction syndrome. We prospectively quantified the degree of luminal diameter dilation after intra-arterial administration of verapamil and its accuracy in diagnosing reversible cerebral vasoconstriction syndrome.

MATERIALS AND METHODS: Patients suspected of having intracranial arteriopathy on noninvasive imaging and referred for digital subtraction angiography were enrolled in a prospective registry. Intra-arterial verapamil was administered in vascular territories with segmental irregularities. The caliber difference ($\text{Caliber}_{\text{post}} - \text{Caliber}_{\text{pre}}$) and the proportion of caliber change ($[(\text{Caliber}_{\text{post}} - \text{Caliber}_{\text{pre}}) / \text{Caliber}_{\text{pre}}] \times 100\%$) were used to determine the response to verapamil. The diagnosis of reversible cerebral vasoconstriction syndrome was made on the basis of clinical and imaging features at a follow-up appointment, independent of the reversibility of verapamil. Receiver operating characteristic curve analysis was performed to determine the best threshold.

RESULTS: Twenty-six patients were included, and 9 (34.6%) were diagnosed with reversible cerebral vasoconstriction syndrome. A total of 213 vascular segments were assessed on diagnostic angiography. Every patient with a final diagnosis of reversible cerebral vasoconstriction syndrome responded to intra-arterial verapamil. The maximal proportion of change ($P < .001$), mean proportion of change ($P = .002$), maximal caliber difference ($P = .004$), and mean caliber difference ($P = .001$) were statistically different between patients with reversible cerebral vasoconstriction syndrome and other vasculopathies. A maximal proportion of change $\geq 32\%$ showed a sensitivity of 100% and a specificity of 88.2% to detect reversible cerebral vasoconstriction syndrome (area under the curve = 0.951). The Reversible Cerebral Vasoconstriction Syndrome-2 score of ≥ 5 points achieved a lower area under the curve (0.908), with a sensitivity of 77.8% and a specificity of 94.1%.

CONCLUSIONS: Objective measurement of the change in the arterial calibers after intra-arterial verapamil is accurate in distinguishing reversible cerebral vasoconstriction syndrome from other vasculopathies. A proportion of change $\geq 32\%$ has the best diagnostic performance.

ABBREVIATIONS: AUC = area under the curve; CD = caliber difference; IA = intra-arterial; ICAD = intracranial atherosclerotic disease; DSA = digital subtraction angiography; PACNS = primary angiitis of the central nervous system; PC = proportion of change; RCVS = reversible cerebral vasoconstriction syndrome; ROC = receiver operating characteristic; TCH = thunderclap headache

Reversible cerebral vasoconstriction syndrome (RCVS) comprises a group of disorders characterized by prolonged-but-reversible vasoconstriction of the cerebral arteries. It is usually characterized by self-limited and reversible multifocal narrowing, which is associated with acute-onset, severe, recurrent headaches with or without additional neurologic deficits.¹ Vasoconstriction often involves distal cerebral arteries, develops in the first

4–5 days after symptom onset, and persists for >3 weeks.² Due to the lack of specific criteria, the presumptive diagnosis needs to be confirmed with reversibility of angiographic abnormalities within 12 weeks of clinical onset.^{3,4} Other intracranial stenotic arteriopathies such as primary angiitis of the central nervous system (PACNS), Moyamoya disease, or intracranial atherosclerotic disease (ICAD) present with similar findings on initial noninvasive

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imaging.^{5,6} Distinguishing these conditions early in their course is crucial because treatment options are different, have potential adverse effects, and may affect clinical outcomes.⁷ Clinical and radiologic differences between RCVS and PACNS have been described;⁸ however, a prompt and accurate diagnosis remains challenging in patients with atypical presentation.⁹

Calcium channel blockers have been used to challenge vasoconstrictive changes in patients with suspected RCVS.¹⁰⁻¹⁸ However, other arteriopathies may have reversible changes with time, and it is unclear whether calcium channel blockers can be used reliably to diagnose RCVS. We evaluated the degree of response to intra-arterial (IA) infusion of verapamil as a diagnostic tool in distinguishing RCVS from other intracranial vasculopathies.

MATERIALS AND METHODS

After institutional review board approval, patients were enrolled in a prospective registry for patients with intracranial vasculopathy between September 2017 and January 2020. As part of the clinical protocol at our institution, patients with possible underlying vasculopathy are routinely referred for digital subtraction angiography (DSA). IA verapamil challenge was performed as part of the diagnostic DSA. Demographic, clinical, laboratory, and radiologic data were collected from electronic medical charts at discharge and last follow-up.

Diagnosis of RCVS

The final diagnosis of RCVS was adjudicated after the last outpatient follow-up and was based on the criteria proposed by Calabrese et al.¹ The adjudication was independent of the reversibility of vascular changes after IA verapamil. The criteria proposed by Calabrese et al include the following: 1) severe, acute headache with or without neurologic signs or symptoms, 2) normal or near-normal CSF analysis findings (protein level <80 mg%; leukocyte count < 10 mm³; and normal glucose level), 3) angiography documenting multifocal segmental cerebral artery vasoconstriction, 4) no evidence of aneurysmal SAH, and 5) reversibility of angiographic abnormalities within 12 weeks after onset.

IA Verapamil Challenge

DSA was performed with selective catheterization of the internal carotid and vertebral arteries. Subtracted images were reviewed, and if there was evidence of irregularities suggestive of an underlying vasculopathy, 5 mg of IA verapamil was slowly administered for 10 minutes in the most affected vascular territory. Blood pressure was closely monitored to avoid a drop of >5 mm Hg in mean arterial pressure during the IA administration of verapamil. If the patient experienced any substantial drop in blood pressure, the IA infusion was stopped and resumed only once the blood pressure was back to baseline. A total of 5 mg of verapamil was diluted in saline to a final concentration of 0.5 mg/mL and manually infused at a continuous rate of 1 mL/min through the side port of a 3-way valve connected to the diagnostic catheter and to a continuous heparinized saline infusion. A repeat angiogram of the same vascular territory was obtained 10 minutes following the IA administration of verapamil.

Radiologic Assessment

Qualitative and quantitative assessment was performed using PACS software. To achieve accurate measurements before and after verapamil injections, we used the same projection angle, source-to-object distance (x-ray tube to patient), and patient-to-detector distance in both angiograms. We used 2× magnification for imaging assessment in all cases. The qualitative assessment of reversibility was performed blindly, comparing pre- and post-verapamil angiograms that were provided by the Department of Radiology without any identifiers (name, time, or order). Anterior-posterior, lateral, and oblique projections were evaluated by 2 experienced neurointerventionalists (E.A.S. and S.D.). Both reviewers were blinded to clinical data and did not know the sequence of pre- and post-verapamil angiograms. Score sheets to determine arterial involvement, vascular territory affected, and morphologic changes between both angiograms were collected (On-line Figs 1 and 2). Vascular territories were divided as follows: 1) proximal branches: A1, M1, P1, vertebral artery, and basilar artery; 2) middle branches: A2, M2, P2, superior cerebellar artery, anterior-inferior cerebellar artery, posterior-inferior cerebellar artery; and 3) distal branches: A3, M3–M4, P3, and any other more distal branch. Morphologic changes were reported as the following: 1) concentric, smooth tapering (“sausaging”); 2) eccentric narrowing, irregular/notched; and 3) segmental dilation, using the same description by Singhal et al.⁸ The response to IA verapamil was graded as a dichotomous variable (yes/no).

A quantitative assessment was performed by measuring the caliber of different arterial segments on pre- and post-verapamil angiograms.¹⁹ The diameter of proximal, middle, and distal arterial branches was measured in millimeters. For each patient, the intracranial artery located in the most affected vascular territory was identified; this artery usually showed multiple irregularities suggestive of a vasculopathy process. The area of maximal narrowing of each vascular segment was measured on pre- and post-verapamil angiograms. After visual inspection, areas that appeared more stenotic in each segment were measured; the reviewer registered only the shortest caliber in each segment and used the same area for assessing the patient’s second angiogram. Measurements were performed by the same reviewers in a different session at least 4 weeks from the initial subjective assessment. Again, reviewers were blinded to clinical data and the order of the angiograms. Two objective measurements of change (reversibility) were statistically tested as predictors of RCVS:

$$1) \text{ Caliber Difference} = \text{Caliber}_{\text{post}} - \text{Caliber}_{\text{pre}}$$

$$2) \text{ Proportion of Change} = \left[\frac{(\text{Caliber}_{\text{post}} - \text{Caliber}_{\text{pre}})}{\text{Caliber}_{\text{pre}}} \right] \times 100\%.$$

For each equation, mean and maximal values were used (a total of 4 measurements per arterial segment). Changes in diameter were analyzed with a receiver operating characteristic (ROC) curve to determine the best threshold in diagnosing RCVS.

The performance of the RCVS-2 score was compared with the objective radiologic determination of reversibility. The RCVS-2

Table 1: Baseline, clinical course, and work-up among patients with and without RCVS

Variable	RCVS (n = 9)	No RCVS (n = 17)	P ^a
Age (mean) (yr)	44.9	55.7	.06
Women (%)	8 (88.9)	10 (58.8)	.19
Race			
White (%)	8 (88.9)	12 (70.6)	.39
African American (%)	1 (11.1)	2 (11.8)	
Other (%)	0 (0)	3 (17.7)	
Medical history			
Migraine (%)	4 (44.4)	0 (0)	.008
Depression/anxiety (%)	8 (88.9)	3 (17.6)	.001
Hypertension (%)	2 (22.2)	14 (82.4)	.009
Trigger/associated condition	7 (77.8)	2 (11.8)	.002
Vasoconstrictive drugs			
SSRI (%)	6 (66.7)	1 (5.9)	.002
Illicit drugs (%)	0 (0)	1 (5.9)	.65
Postpartum (%)	2 (22.2)	0 (0)	.11
Clinical presentation			
Thunderclap headache (%)	5 (55.6)	1 (5.9)	.01
Other headaches (%)	2 (22.2)	5 (29.4)	.54
Focal neurologic signs			
Hemiparesis/aphasia (%)	5 (55.6)	10 (58.8)	.99
Visual symptoms (%)	3 (33.3)	1 (5.9)	.10
Seizures (%)	2 (22.0)	1 (5.9)	.27
Diagnostic work-up			
ESR (mean) (mm/h)	22.5	43.9	.31
CRP (mean) (mg/L)	3.0	1.9	.61
Normal CSF ^b (%)	2/5 (40.0)	4/9 (44.4)	.99
Brain biopsy (%)	1 (11.1)	1 (5.9)	.58
Abnormal neuroimaging findings (%)			
Infarct (%)	3 (33.3)	13 (76.5)	.046
Multiple (%)	2/3 (66.7)	12/13 (92.3)	.35
Borderzone territory (%)	2/3 (66.7)	1/13 (7.7)	.08
IPH (%)	0 (0)	4 (23.5)	.26
SAH in convexity (%)	5 (55.6)	2 (11.8)	.03
CTA/MRA with vasculopathy			
CTA [n = 14] ^c (%)	2/5 (40)	5/9 (55.6)	.99
MRA [n = 16] ^c (%)	2/6 (33.3)	10/10 (100)	.008
Patients with intracranial vasculopathy on DSA not detected by CTA and/or MRA (n = 26) (%)	6/9 (66.7)	3/17 (17.6)	.028
RCVS-2 score of ≥ 5	5 (55.6)	1 (5.9)	.01

Note:—CRP indicates C-reactive protein; ESR, erythrocyte sedimentation rate; IPH, intraparenchymal hemorrhage; SSRI, selective serotonin reuptake inhibitor.

^a P value calculated using a *t* test, χ^2 test, or Fisher test as appropriate.

^b Normal CSF if <5 cells and <50 mg/dL.

^c Number of examinations performed including both groups.

score is a semiquantitative scoring system developed as a bedside diagnostic algorithm. This grading system adjudicates points to different categories as follows: single or recurrent thunderclap headache (TCH) = +5 points, involvement of the intracranial carotid artery = −2 points, a vasoconstrictive trigger = +3 points, female sex = +1 point, and the presence of subarachnoid hemorrhage = +1 point. A score ≥ 5 has a high sensitivity and specificity in diagnosing RCVS.⁹

Statistical Analysis

Continuous variables are presented as mean $\pm$ SD, and categorical variables are presented as frequency and percentage. Distributions of values for mean and maximal measurements of reversibility (caliber difference [CD] and proportion of change [PC]) were tested for

normality using the Shapiro-Wilk method. For normally distributed variables, Student *t* tests were used to compare means. For nonparametric variables, Mann-Whitney *U* tests were used to compare the medians between the size groups. For categorical values, χ^2 or Fisher tests were applied as appropriate. An ROC analysis using the Youden index was performed to establish the best cutoffs for measurements of reversibility (CD and PC) to diagnose RCVS. The RCVS-2 score was also compared with our objective assessments of reversibility in pre- and post-verapamil angiograms using the DeLong test. A 2-sided *P* value $< .05$ was considered significant. All statistical analyses were performed with SPSS Statistics 25.0 (IBM).

RESULTS

Twenty-six patients with intracranial vasculopathy and suspected RCVS were included in the study. Nine patients had a confirmed clinical diagnosis of RCVS (34.6%); 8 with ICAD; 7 with undetermined intracranial vasculopathy; and 2 with PACNS (Table 1).

Qualitative Assessment

Both reviewers reported an angiographic response to IA verapamil in 88.9% (8/9) of patients in the RCVS group versus 41.2% (reviewer 1) and 47.1% (reviewer 2) in the no-RCVS group (On-line Table 1). The Cohen κ analysis demonstrated poor intraobserver agreement to subjectively detect RCVS by comparing pre- and post-verapamil DSAs (reviewer 1: $\kappa = 0.41$, *P* = .019; reviewer 2: $\kappa = 0.35$, *P* = .037). Also, the interrater reliability to detect overall vascular changes was very poor ($\kappa = 0.28$, *P* = .149).

Quantitative Assessment

Two hundred thirteen vascular segments were assessed on DSA, and 87 (40.5%) had post-IA verapamil changes. The statistical analysis showed significant differences in all measurements of reversibility for patients with RCVS, including maximal PC (*P* < .001), mean PC (*P* = .002), maximal CD (*P* = .004), and mean CD (*P* = .001) compared with patients without RCVS (Table 2 and On-line Table 2). The Cohen κ analysis demonstrated substantial interobserver agreement for objective vessel diameter measurements ($\kappa = 0.86$).

CD and PC as Predictors of RCVS

ROC curve analysis was performed to establish the best PC and CD thresholds in diagnosing RCVS (Fig 1). Maximal PC $\geq 32\%$ had a sensitivity of 100% and a specificity of 88.2% to detect RCVS, with an excellent area under the curve (AUC) of 0.951. However, an RCVS-2 score of ≥ 5 points had a sensitivity of 77.8% and a specificity of 94.1%, achieving a nonstatistically significant lower AUC in the analysis (0.908) ($P = .47$). Mean PC and mean CD performed similarly in the analysis (AUC = 0.886 and 0.882, respectively), whereas maximal CD performed the worst (AUC = 0.840) (Table 3).

DISCUSSION

Reversibility of intracranial vasoconstriction is the key to diagnosing RCVS. In this study, the objective assessment of caliber changes

in affected arteries after the IA infusion of verapamil was accurate and reliable in distinguishing RCVS from other intracranial arteriopathies. The degree of response to IA verapamil quantified as improvement in the caliber of each vascular segment had an excellent performance as a predictor of RCVS. A maximal proportion of change $\geq 32\%$ in post-verapamil angiograms showed better diagnostic performance than the RCVS-2 score. The subjective assessment of vessel caliber before and after IA administration of verapamil was poor and should not be used routinely as the only marker of reversibility on RCVS.

Patients with typical RCVS symptoms who present with TCH have a well-known trigger and a mild evolution with angiographic changes that generally resolve in 12 weeks.⁴ However, the clinical presentation of RCVS is variable, and patients may present without

TCH in up to 15% of cases.²⁰ Patients without TCH may experience severe forms of RCVS, present with coma or confusion due to stroke or posterior reversible encephalopathy syndrome, or have fulminant RCVS. The clinical spectrum of RCVS varies among different populations, and the diagnosis of atypical cases can be challenging.²¹ Moreover, the classic “string of beads” appearance of vasoconstriction has been described in only 12%–81% of patients with RCVS.⁴

Previous reports have suggested the benefit of calcium channel blockers (nifedipine, verapamil, and nimodipine) and phosphodiesterase inhibitors (milrinone) in diagnosing and treating RCVS (On-line Table 3).^{11–18,22–24} Diagnosis entails the IA infusion of these drugs to determine the improvement in the caliber of the affected vascular segment. Other vasculopathies such as ICAD and PACNS usually do not improve after these challenges or have a milder response, perhaps suggesting some degree of overlap between these conditions. Ospel et al¹⁸ used verapamil in diagnosing RCVS by documenting the reversibility of vascular changes in 11 patients. Luminal narrowing was classified as mild = $<30\%$ of normal caliber, moderate = 30% – 60% of normal caliber, and severe =

Table 2: Reversibility measurements among patients with and without RCVS

Reversibility Measurement ^a	RCVS ($n = 9$)	No RCVS ($n = 17$)	P Value ^b
Maximal PC (%)	50.6 $\pm$ 13.6	21.7 $\pm$ 12.5	<.001
Mean PC (%)	20.4 $\pm$ 9.8	6.2 $\pm$ 6.0	.002
Maximal CD (mm)	0.54 $\pm$ 0.27	0.25 $\pm$ 0.17	.004
Mean CD (mm)	0.23 $\pm$ 0.13	0.07 $\pm$ 0.08	.001

^aReversibility measurements shown as mean $\pm$ SD.

^bP value was calculated using the Mann-Whitney *U* test, given a nonparametric distribution of data.

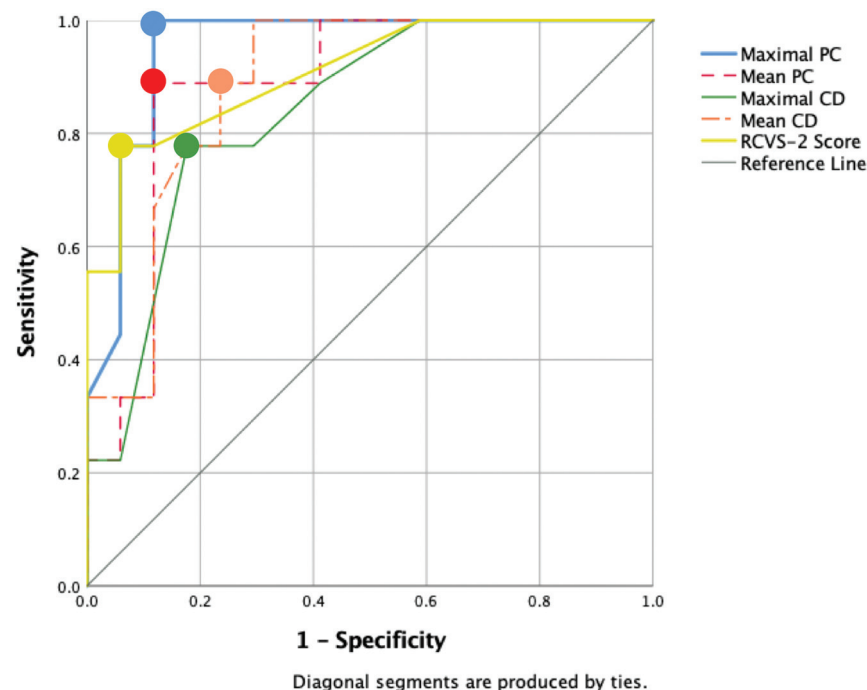


FIG 1. ROC analysis to predict RCVS using objective reversibility measurements and RCVS-2 scores. Circles identify best coordinates (cutoffs) for each curve.

Table 3: Cutoffs, AUC, sensitivity, specificity, and positive and negative predictive values of different reversibility measurements

Reversibility Measurement	Cutoff	AUC	95% CI	Sen	Spe	PPV	NPV
Maximal PC (%)	≥ 32	0.951	0.87–1.00	100	88.2	81.8	100
Mean PC (%)	≥ 14.4	0.886	0.76–1.00	88.9	88.2	80	93.8
Maximal CD (mm)	≥ 0.45	0.840	0.68–0.99	77.8	82.4	70	87.5
Mean CD (mm)	≥ 0.125	0.882	0.75–1.00	88.9	76.5	66.7	92.8
RCVS-2 score (points)	≥ 5.0	0.908	0.79–1.00	77.8	94.1	87.5	88.9

Note:—NPV indicates negative predictive value; PPV, positive predictive value; Sen, sensitivity; Spe, specificity.

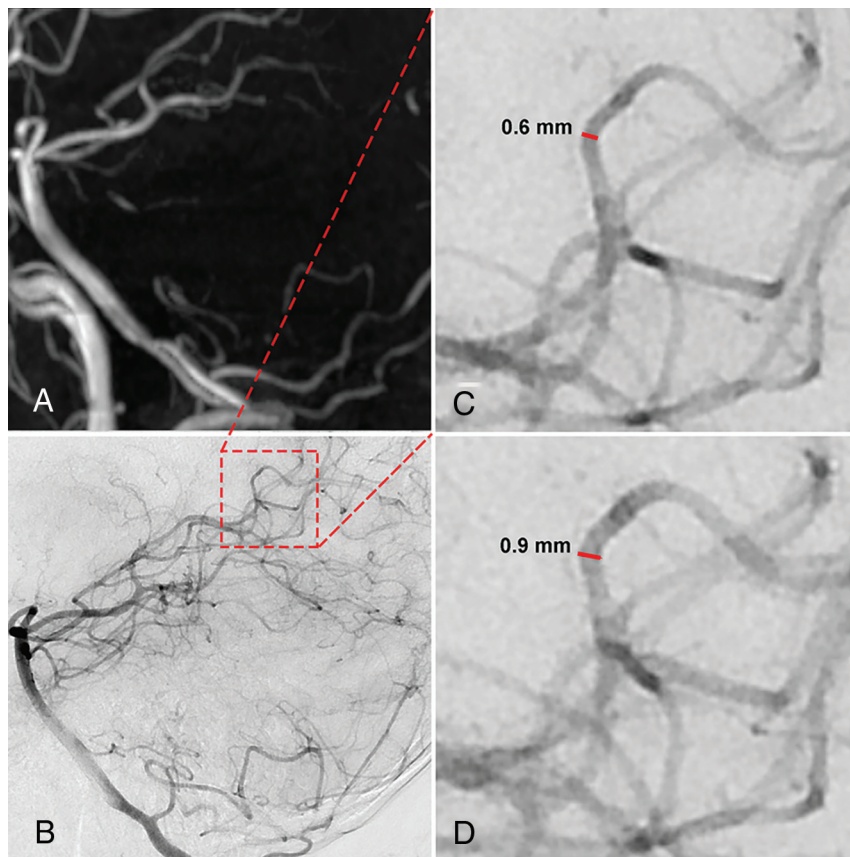


FIG 2. A, Contrast-enhanced MRA of a patient with atypical RCVS. The posterior cerebral artery branches appear unremarkable. B, Lateral angiogram with areas of segmental narrowing in the posterior circulation. C, Pre-verapamil infusion DSA shows the caliber of a P3 branch = 0.6 mm. D, Post-verapamil infusion DSA shows a 0.3-mm CD (0.9 – 0.6 mm, 50% PC) in the P3 branch at the same level. These subtle changes in distal branches were not diagnosed in subjective assessments.

>60% of normal caliber. We have objectively documented that a maximal proportion of change of 32% in the lumen diameter after the administration of IA verapamil had a sensitivity of 100% and a specificity of 82% in diagnosing RCVS. All the RCVS cases included in our series were confirmed as RCVS on follow-up using strict diagnostic criteria.

The sensitivity and specificity of DSA in diagnosing RCVS has not been assessed in blinded studies.⁴ However, the sensitivity of indirect methods of angiography such as CTA and/or MRA is about 70% compared with DSA.²⁵ Furthermore, patients may have normal findings on the first DSA if performed early. Thus, subsequent angiograms may be required 1 week after the onset of symptoms to document changes.²⁶ Our subjective assessment showed poor intra- and interobserver agreement when determining caliber changes in the middle and distal branches. In our cohort, these vascular regions are involved in approximately 89% and 72% of cases, respectively. Singhal et al¹⁸ also reported 92% and 86% of changes affecting the middle and distal branches, respectively. The accuracy of CTA/MRA in detecting mild changes in the distal branches is lower than that of DSA due to their inferior spatial resolution (Fig 2).^{2,27,28} The sensitivity of CTA and MRA in detecting small (<3-mm) aneurysms is inferior to that of DSA.²⁹ The accuracy of these

noninvasive imaging modalities in determining <1-mm caliber changes in the middle and distal branches is insufficient compared with DSA. The objective DSA quantification of changes in the diameter of vascular segments after the administration of IA verapamil demonstrated high accuracy in detecting RCVS (Fig 3). Therefore, objective rather than subjective quantification of subtle changes in pre- and post-IA verapamil angiograms should be routinely performed to ascertain the correct diagnosis.

The role of DSA in RCVS has been criticized for its invasiveness, radiation exposure, use of contrast, and lack of scope for intervention.³⁰ Moreover, the IA administration of vasoactive drugs has been questioned due to the risk of iatrogenic hypotension, reperfusion injury, and theoretic disruption of the blood-brain barrier.³¹ While most patients with RCVS have a good outcome, a considerable number of patients will experience a more fulminant course that results in permanent disability or death. This occurs most prominently in patients with atypical clinical presentations whose diagnosis and subsequent treatment are delayed.³¹ There is growing evidence that IA administration of vasoactive drugs can be done safely and that DSA may be therapeutic in addition to

its valuable diagnostic capabilities.^{10,13} It is also possible that the verapamil-induced vasodilation shortens the course of the illness and lowers the chances of subsequent ischemic complications. We recommend DSA with IA verapamil challenge for patients with atypical RCVS presentations (without TCH or classical triggers), slow disease evolution, or an alternative diagnosis being entertained. DSA is particularly helpful if there is an intracranial lesion (ischemic or hemorrhagic) and normal indirect angiographic findings (CTA/MRA) in the setting of a suspected intracranial vasculopathy like RCVS.

This study is limited by the small number of patients. RCVS is a rare condition, and a more thorough assessment would require a prospective multicenter study. Another limitation is the intrinsic selection bias favoring recruitment of sicker patients. Every patient had abnormal imaging findings with evidence of an ischemic stroke and/or hemorrhage at presentation, but almost half did not have the typical TCH. Milder cases of RCVS with typical presentation were not referred for DSA. Therefore, the reversibility of vasoconstriction and the diagnostic accuracy of the IA verapamil challenge are yet to be proved in most cases of RCVS. An ideal statistical comparison between the 2 diagnostic tools became difficult due to few patients with atypical

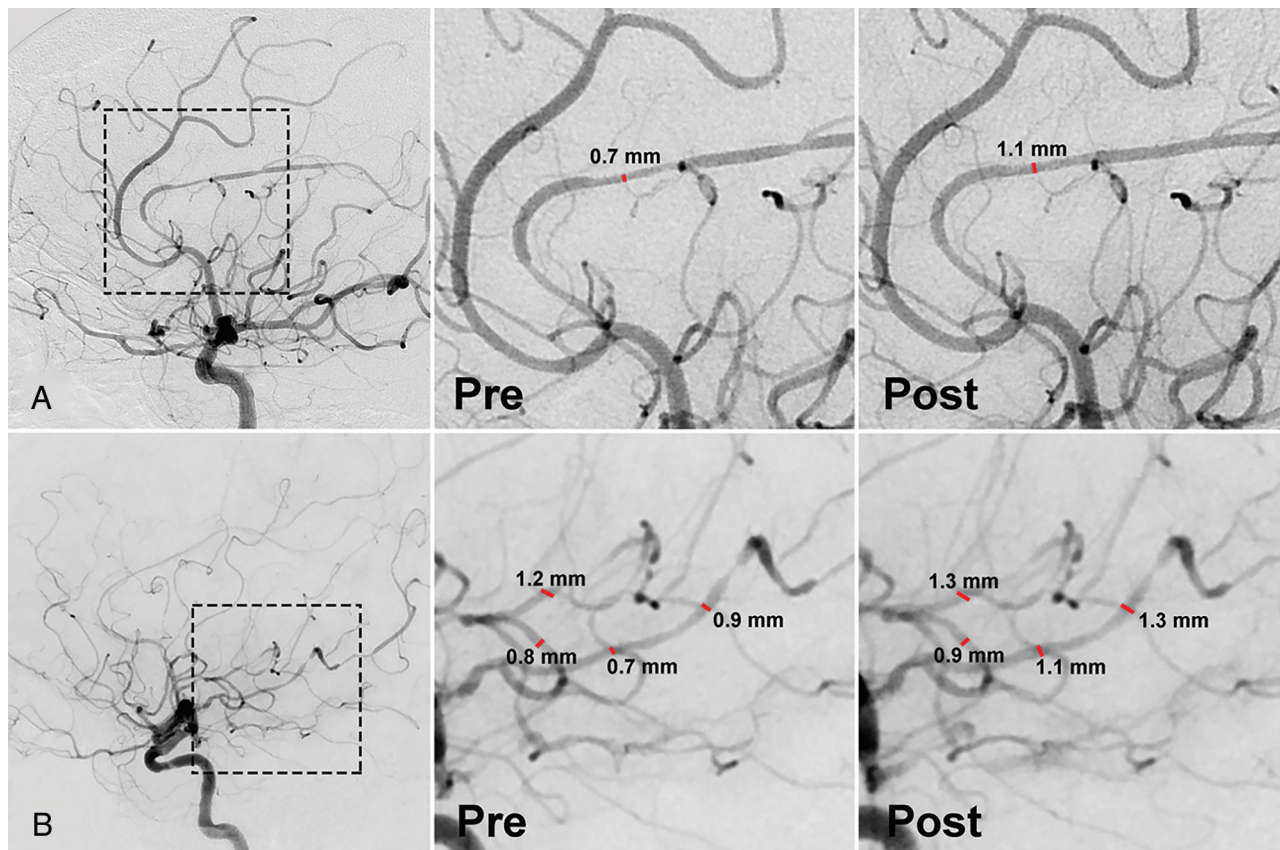


FIG 3. A, Patient with RCVS in the right anterior cerebral artery territory. B, Patient with RCVS in the right posterior cerebral artery territory. Note the classic string of beads pattern of the affected branches. The square delineates zoomed-in areas of the angiogram that were blindly analyzed by 2 readers. These measurements were later labeled as pre- and post-IA verapamil.

presentations of RCVS, even at a high-volume stroke center. The method used for objective vessel-caliber assessment in this study might seem laborious, but for a vascular neuroimaging-trained physician, it would take only a few additional minutes at the workstation. With the recent overwhelming advances in neuroradiology using artificial intelligence,³² an automated assessment tool might be feasible in the near future.

CONCLUSIONS

Objective quantification of the caliber of affected arterial segments on pre- and post- IA verapamil angiograms has a high diagnostic yield in patients with atypical RCVS. A maximal proportion of change $\geq 32\%$ had the best performance as a diagnostic tool and was superior to both subjective assessment of reversibility and the clinical RCVS-2 score.

Data are available on reasonable request. Additional unpublished data will be made available by the corresponding author with an appropriate request.

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