

# Transcranial Doppler Ultrasonography As a Non-Invasive Tool for Diagnosis and Monitoring of Reversible Cerebral Vasoconstriction Syndrome

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## ABSTRACT

**BACKGROUND AND PURPOSE:** Reversible cerebral vasoconstriction syndrome (RCVS) is a vascular headache disorder characterized by severe headaches with vasospasm of cerebral arteries. Transcranial Doppler ultrasonography (TCD) has been widely applied and validated in studying vasospasm of intracranial vessels, but the role of TCD in the diagnosis and monitoring of RCVS is less well established. We sought to determine the reliability of TCD for diagnosis and monitoring of RCVS.

**METHODS:** Patients admitted to an inpatient neurology service between 2011 and 2014 with a discharge diagnosis of RCVS were retrospectively analyzed for demographics, neuroimaging, and functional outcomes. Baseline and follow-up TCD flow velocities in the middle cerebral artery ( $V_{mca}$ ) were compared relative to the final diagnosis.

**RESULTS:** The cohort consisted of fifteen patients (93% females; mean age 46.7 +/- 12.4 years); initial TCD evaluation was performed 10.9 +/- 6.6 (range 1–24) days after headache onset. Fourteen patients (93.3%) had increased flow velocities by initial TCD in at least one major cerebral blood vessel (MCA, ACA, PCA, vertebral, basilar). TCD flow velocities in the middle cerebral artery ( $V_{mca}$ ) reached a mean peak of 163 cm/s three to four weeks after the onset of thunderclap headache.

**CONCLUSION:** TCD is a non-invasive neuroimaging modality that may have potential for the initial diagnosis and subsequent monitoring of patients with suspected RCVS. Larger studies will be needed to establish its utility.

**KEYWORDS:** Reversible Cerebral Vasoconstriction Syndrome, stroke, intracerebral hemorrhage, transcranial ultrasound, imaging, RCVS, TCD

## INTRODUCTION

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by thunderclap headaches with vasospasm of cerebral arteries that may lead to other neurological complications such as stroke and subarachnoid hemorrhage.<sup>1-4</sup> Currently, conventional catheter-based cerebral angiography is the gold standard for diagnosis of RCVS.<sup>1,2</sup> Although it is an invasive procedure, diagnostic conventional angiography is

typically safe with complication rates ranging from 0.3% to 4.2%.<sup>5,6</sup> However, when performed in patients with RCVS, conventional angiography carries up to a 9% rate of neurological complications.<sup>7,8</sup> Magnetic resonance angiography (MRA) has also been shown to be a valid tool in the evaluation of RCVS.<sup>7</sup> However, MRA has limitations with regard to widespread access and availability. Transcranial Doppler ultrasonography (TCD) is a safe imaging modality that has shown great utility in following vasospasm in patients with subarachnoid hemorrhage.<sup>9-14</sup> The role of TCD in the diagnosis and monitoring of RCVS, however, is less well established. Therefore, we sought to determine the role of TCD in the diagnosis and monitoring of RCVS.

## METHODS

The study was approved by the local institutional review board. We retrospectively analyzed charts of patients who were admitted to a single, large academic medical center between 2011 and 2014 with a discharge diagnosis of RCVS who had also undergone testing with TCD. RCVS was defined as any new, abrupt onset headache with or without focal deficits and with a “string of beads” appearance on angiography.<sup>1</sup> When conventional angiography was not available, MRA was used for the diagnosis of RCVS.<sup>7</sup>

Baseline data abstracted from qualifying charts included age, gender, past medical history (diabetes mellitus, hypertension, smoking status, prior disability, medications use, illicit drug abuse history), highest and lowest blood pressure values in the emergency department, and toxicology screen. Functional disability was determined using the modified Rankin scale (mRS) score pre-admission and at discharge.

TCD was performed by experienced sonographers who were instructed to evaluate patients for vasospasm. The sonographers were blinded to the results of angiography. The middle cerebral artery (MCA), anterior cerebral artery (ACA), and posterior cerebral artery (PCA) arterial signals were obtained by insonating through the temporal windows at depths of 45mm–60mm for the MCA and 55–70mm for the ACA and PCA. For the posterior circulation, the vertebral and basilar arteries were detected through the foramen magnum at depths of 60mm–80mm and 80mm–120mm, respectively. All vessels were identified by depth and direction of arterial signal. If elevated blood flow velocities were present, additional waveforms were captured and calculated to

determine the highest mean velocity.<sup>16-18</sup> We defined 80 cm/s as the normal upper limit in the anterior circulation and 60 cm/s as the normal upper limit in the posterior circulation.<sup>9, 12, 13, 16, 19</sup> Vasoconstriction of the MCA was defined as a velocity greater than 120cm/sec and severe vasoconstriction was defined as velocity greater than 200cm/sec.

Patients were followed in outpatient clinics. Information on recurrent symptoms was recorded, and TCDs were repeated for follow-up.

Descriptive statistics were presented as means +/- standard deviations. TCD velocities as a function of time were tabulated and averaged from the cohort of patients with positive initial TCD ultrasounds in the middle cerebral artery over different time periods.

## RESULTS

During a three-year period from 2011–2014, we identified 15 patients (93% females; mean age 46.7 +/- 12.4 years) with a discharge diagnosis of RCVS who underwent testing with TCD. Twelve of fifteen patients were diagnosed with conventional angiography and three were diagnosed with MRA. Clinical characteristics of the patients are summarized in **Table 1**. Eleven of fifteen patients (73.3%) were active smokers. Two-thirds of patients had potential secondary causes of RCVS including consumption of vasoactive medications such as selective serotonin/norepinephrine reuptake inhibitors (n = 6), pseudoephedrine products (n = 1), triptans (n = 2), and use of illicit drugs such as marijuana (n = 5), cocaine (n = 1), and 3,4-methylenedioxy-methamphetamine (n = 1).

Fourteen of the fifteen patients developed neurological complications from their RCVS, including subarachnoid hemorrhage (n = 8), ischemic stroke (n = 6), and intracerebral hemorrhage (n = 4). Sixty percent of patients were discharged with some degree of disability, defined as a modified Rankin scale (mRS) score of 2 or higher.

There were 48 TCD studies in the 15 patients (average, 3.2 studies/patient). Overall, initial TCD evaluation was 10.9 +/- 6.6 (range 1–24) days after headache onset, and angiogram was performed 8.6 +/- 5.2 (range 1–15) days after headache onset. Fourteen patients (93.3%) had increased flow velocities by initial TCD in at least one major cerebral blood vessel (MCA, ACA, PCA, vertebral, basilar). Four patients (36.4%) had some degree of vasoconstriction ( $V_{mca} > 120\text{cm/s}$ ) and one patient (9.1%) had severe vasoconstriction ( $V_{mca} > 200\text{cm/s}$ ). In patients with positive TCDs, the mean flow velocity in the MCA peaked three to four weeks after headache onset. The temporal trend of TCD velocity data in the MCA is demonstrated in the figure. (**Figure 1**)

## DISCUSSION

In this retrospective case series of 15 patients with RCVS, we found the initial sensitivity of TCD to be 93.3% compared with conventional angiography or MRA, thereby

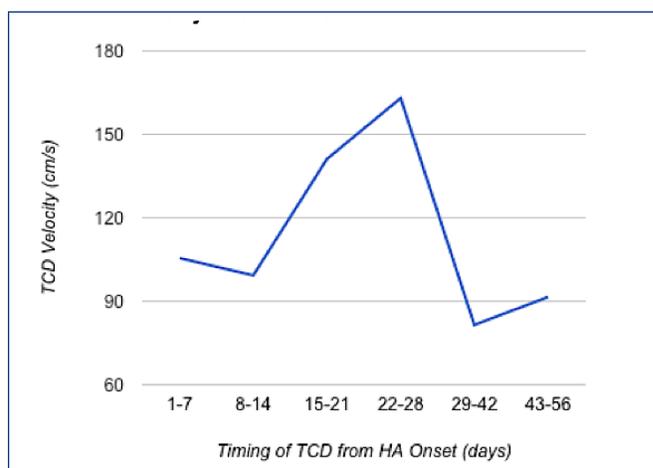
**Table 1.** Demographics of Patients with RCVS

Demographics	RCVS Cohort (N=15)
Mean Age +/- SD, yr	46.7 +/- 12.4
Female Sex, n (%)	14 (93%)
Hypertension, n (%)	6 (40%)
Diabetes, n (%)	1 (6.7%)
Migraine, n (%)	6 (40%)
Smoking, n (%)	11 (73.3%)
Vasoconstrictive medications <sup>a</sup> , n (%)	7 (47%)
Illicit Drug Exposure <sup>b</sup> , n (%)	6 (40%)
Initial SBP, mmHg +/- SD	166 +/- 24
Initial DBP, mmHg +/- SD	92 +/- 12
Cerebral Manifestations of RCVS, n (%):	
Ischemic Stroke	6 (40%)
SAH	8 (53.3%)
ICH	4 (26.7%)
SDH	1 (6.7%)
PRES	3 (20%)
Timing of angiogram, days +/- SD	8.6 +/- 5.2
Timing of initial TCD, days +/- SD	10.9 +/- 6.6
mRS > 1 prior to admission	2 (13.3%)
mRS > 1 at discharge	9 (60%)

SD = standard deviation; SBP = systolic blood pressure; DBP = diastolic blood pressure; mRS = modified Rankin scale score; SAH = subarachnoid hemorrhage; ICH = intracerebral hemorrhage; SDH = subdural hemorrhage; PRES = posterior reversible encephalopathy syndrome.

<sup>a</sup>Vasoconstrictive medications included selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, triptans, and prescribed amphetamines or over-the-counter pseudoephedrine-containing products. Illicit drugs include marijuana, cocaine, or 3,4-methylenedioxy-methamphetamine.

**Figure 1.** Mean flow velocities in the middle cerebral artery as a function of time.



highlighting the importance of TCD as a diagnostic tool for RCVS. Two prior studies, however, reported lower rates of 69-81% with serial TCD monitoring.<sup>8,16</sup> In addition, the temporal trend of flow velocities in patients undergoing serial TCD suggest that it may also be useful in the monitoring of RCVS.

This cohort was similar in age and gender to that of prior studies, although we observed higher rates of comorbid migraine relative to prior reports, 40% vs. 16-25%.<sup>2,16</sup> Unlike two large studies with idiopathic and purely cephalalgic RCVS<sup>15,16,20</sup>, we noted a high rate of secondary RCVS associated with exposure to potential vasoactive triggers for RCVS including SSRI/SNRI antidepressants, triptans, and recreational drugs like marijuana, cocaine, and MDMA.<sup>4</sup> We also observed a particularly high rate of severe cerebral manifestations in our cohort in that over 90% of our patients developed non-aneurysmal subarachnoid hemorrhage, ischemic stroke, intracerebral hemorrhage, PRES or a combination thereof. The rate of brain lesions seen in our cohort was similar to one other case series<sup>3</sup> but higher than three others.<sup>15,16,21</sup>

We observed that mean flow velocities remain elevated up to four weeks after headache onset, similar to what was described in a prior study.<sup>16</sup> Although the severity of vasoconstriction seen on TCD during the first episode of RCVS does not appear to predict the risk of recurrence, greater maximum mean flow velocity may portend a higher risk of PRES and ischemic stroke.<sup>15,16</sup> Ducros and colleagues suggest that vasoconstriction of major cerebral arteries may be the cause of infarcts during the later stages of RCVS.<sup>21</sup> Serial monitoring of vasoconstriction via TCD may therefore help to identify patients at higher risk of developing neurological complications related to RCVS. To date, there are no specific guidelines for treatment of RCVS; however, patients might benefit from early, aggressive therapy tailored towards normalizing flow velocities.<sup>4</sup>

The timing of vasoconstriction hemodynamics relative to headache onset and resolution are not well understood in RCVS. Ducros and colleagues have proposed a hypothesis of a "centripetal progression" whereby there is underlying disturbance in the control of vascular tone in small distal arteries responsible for thunderclap headaches, hemorrhages, and PRES, followed in turn by a progression towards medium- and large-sized arteries responsible for ischemic events.<sup>8</sup> This theory could explain why thunderclap headaches often precede any detectable vasoconstriction (up to 33% rate of normal early angiograms), and why detectable vasoconstriction may paradoxically persist weeks after headache onset and remission.<sup>8,16,21</sup> As such, serial TCD monitoring could help non-invasively to identify patients with suspected RCVS in whom vasoconstriction is not yet apparent on initial neuroimaging. TCD could also help identify patients in whom vasoconstriction persists after resolution of thunderclap headaches.

We acknowledge several limitations in this study. First, due to the small retrospective nature of our chart review, we

were unable to standardize the timing with which patients received their neuroimaging relative to headache onset. Second, although we tried to blind the sonographers to clinical data, some unintentional disclosure of vascular imaging is possible. Third, TCD may be limited by TCD technique and operator dependency. Fourth, the generalizability of our results may be limited by selection bias in that we only included patients with known RCVS who had also undergone assessment with TCD; we did not have data about patients with RCVS who did not undergo TCD. Therefore, we could not determine the specificity of TCD for RCVS. Finally, we did not have a control group to account for potential TCD abnormalities in asymptomatic individuals. A prior cohort revealed normal TCD velocities in healthy control subjects, so it would be unlikely to see transient TCD abnormalities in asymptomatic patients.<sup>16</sup>

## CONCLUSION

In this series, TCD was a sensitive, non-invasive tool that may prove helpful in the diagnosis of RCVS. Further studies of larger numbers of patients are needed to evaluate the utility of TCD in diagnosing and monitoring patients with RCVS.

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