Clinical Investigative Studies

Phase-Contrast Magnetic Resonance Angiography for the Determination of Cerebrovascular Reserve

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ABSTRACT

Cerebrovascular reserve (CVR) is the potential for cerebral arteriolar dilatation to occur, in response to decreased cerebral perfusion pressure, in order to maintain constant cerebral blood flow. Diminution or absence of CVR is considered a risk factor for stroke. Current methods for determining CVR include single-photon emission computed tomography, positron emission tomography and transcranial Doppler (TCD) ultrasonography. However, significant advantages could derive from the utilization of magnetic resonance angiography (MRA) based on the concurrent acquisition of hemodynamic information (CVR and collateral flow) with phase-contrast (PC) techniques and vascular morphology with three-dimensional, time-of-flight methods. With a 1.5-T scanner and acetazolamide (AZM), an arteriolar dilator, CVR was determined in 7 normal subjects. Mean flow velocity in the middle cerebral arteries was determined by PC MRA before and after AZM administration. For comparative purposes, mean flow velocities in the same middle cerebral arteries were determined by TCD before and after AZM administration. The mean flow velocities were as follows (mean ± standard deviation, n = 7): 40 ± 8 (PC MRA) versus 61 ± 10 cm/sec (TCD) before AZM treatment and 58 ± 11 (PC MRA) versus 85 ± 15 cm/sec (TCD) after AZM administration. The increase in mean flow velocity (before vs after AZM), that is, the CVR, was 45 ± 11% as shown by PC MRA and 39 ± 14% as shown by TCD. Although significant differences were present between the mean flow velocities measured before and those after AZM administration, as determined by PC MRA and TCD, the CVR was not significantly different (45 vs 39%, respectively). These preliminary results suggest that PC MRA may be a method for determining CVR.

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Stroke is the third leading cause of death in the United States and it is attended by significant medical complications and long-term disability [1, 2]. The most common causes of stroke (i.e., ischemic cerebral infarction) are emboli or thrombi deriving from atherosclerotic disease of the extracranial or intracranial anterior and posterior circulations. Distal to an embolus or thrombus, hemodynamic insufficiency can occur. Two compensatory mechanisms for the presence of acute or chronic hemodynamic insufficiency are collateral flow and cerebrovascular reserve (CVR). CVR is the capacity for cerebral arteriolar dilatation to occur, in response to decreased cerebral perfusion pressure, in order to maintain constant cerebral blood flow (CBF). Diminution or absence of CVR is considered a risk factor for stroke [3–5]. Hence, the identification of an abnormal CVR will facilitate the implementation of prophylactic stroke treatment.

Recently, the technique of transcranial Doppler (TCD) ultrasonography has evolved to a state of clinical utility for the noninvasive determination of intracranial CBF velocity [6, 7]. Based on comparative studies, CBF velocity (cm/sec) as determined by TCD ultrasonography appears to be a useful indicator of CBF volume (ml/min) and CBF perfusion (ml/100 gm of tissue/min) as determined by xenon-133 (^{133}Xe) computed tomography and positron emission tomography [8–14]. TCD ultrasonography, in conjunction with acetazolamide (AZM) or carbon dioxide, has been employed to evaluate CVR in stroke patients [15, 16].

Magnetic resonance angiography (MRA) is evolving as a technique to evaluate the morphological aspects (e.g., stenosis, occlusion, and dilatation) of the extracranial and intra-

cranial arterial and venous circulations, including the determination of luminal diameter and thus cross-sectional area [17–19]. In addition, measurement of CBF velocity is currently being investigated [20, 21]. Thus, MRA has the potential for evaluating CBF volume (ml/min), based on measurements of velocity (cm/sec) and luminal area (cm^2), whereas TCD ultrasonography is limited to the determination of CBF velocity.

Significant advantages could derive from the utilization of MRA based on the concurrent acquisition of morphological and hemodynamic information. To the authors' knowledge, this is the first report of phase contrast (PC) MRA determination of CVR.

Hypothesis, Subjects, and Methods

The hypothesis (null hypothesis, H0) tested was as follows: There is no difference in CVR as determined by TCD ultrasonography versus MRA.

Seven subjects (3 women, 4 men; mean age, 37 yr; range, 30–52 yr) without neurological, cardiac, or vascular disease were studied. The protocol (No. 1082) for this study was approved by the Human Research Committee of Millard Fillmore Hospital and informed consent was obtained from each subject.

Transcranial Doppler Ultrasonography: A Trans-Scan ultrasound Doppler instrument (Nicolet Instrument, Madison, WI) was employed to determine CBF direction and velocity and location of the M1 segment of the right middle cerebral artery (RMCA) at a depth of 50 to 58 mm. The instrument operated at a frequency of 2 MHz pulse-wave. Blood flow direction in the RMCA was determined by detecting a change in the Doppler frequency; an increase or decrease in the frequency indicated flow toward or away from the probe, respectively. CBF velocity in the RMCA was determined by converting, via fast Fourier transformation, the measured Doppler frequency (kHz) to velocity (cm/sec). The spatial peak mean velocity (i.e., the mean velocity during a cardiac cycle) was averaged by instrument software over three to five consecutive cardiac cycles to yield the spatial peak mean velocity. The location of the segment of the RMCA that was insonated for CBF velocity determination was based on gating the received ultrasound pulse such that it emanated from a depth of 50 to 58 mm relative to the transducer face, which was in apposition to the temporal window. Prior to AZM administration (pre-AZM), RMCA blood flow velocity (baseline) was measured one to three times; the highest velocity was utilized in the calculation of CVR. Following AZM administration (post-AZM), RMCA blood flow velocity was measured every 3 to 5 minutes (over a 30-min period); the highest velocity was utilized in the calculation of CVR.

Magnetic Resonance Angiography: A Picker HPQ 1.5-T magnetic resonance scanner (Picker, Cleveland Heights, OH) was employed to determine CBF direction and velocity and location of the RMCA. Phase-contrast (PC) MRA, without cardiac gating, was utilized to determine CBF velocity; the method was similar to that reported by Enzmann and coauthors [19, 20].

Pilot MRI and MRA images were initially obtained to identify the M1 segment of the RMCA at a depth of 50 to 58 mm (Figs 1A–C). The PC MRA was then obtained in a plane orthogonal to the segment of the RMCA corresponding to that evaluated by TCD ultrasonography (Fig 1C). The PC MRA method consisted of interleaved reference and velocity-encoded sequences, each with first-order motion compensation. A bipolar velocity-sensitizing gradient (Venc = $\pm$ 100 cm/sec) was applied in the slice select direction for the velocity-encoded acquisition. Alternate echoes were employed for the reference and flow-sensitized acquisitions to minimize misregistration, due to motion, and total acquisition time.

With Picker HPQ software, the flow map was created by deinterleaving the data, reconstructing magnitude (Fig 1D) and phase images for each acquisition, subtracting phase images, performing bicubic phase correction, and then converting phase to velocity (multiply by 100 cm/sec/π) (Fig 1F). A velocity of 0 was assigned to pixels with a corresponding magnitude less than the background white matter intensity, thus excluding artifactual velocities in the vicinity of the RMCA. Bicubic phase correction was performed based on a least-squares fit to five stationary reference points adjacent to the RMCA (Fig 1E). CBF direction was indicated by the vessel luminal intensity in the flow map—hyperintensity to the right and hypointensity to the left.

Region of interest (ROI) analysis was performed with a Macintosh FX computer (Apple Computer, Cupertino, CA) and DIP Station software (Hayden Imaging Processing Group, Boulder, CO). ROI analysis was confined to voxels that occupied the lumen of the RMCA and five stationary reference points adjacent to the RMCA (see Fig 1E). The through-plane voxel size (thickness) was 5.0 mm and the in-plane voxel size was 1.2 $\times$ 2.0 mm. Based on an RMCA luminal diameter of 4 to 5 mm, components of approximately three to six voxels occupied the central aspect of the lumen. The velocity for each voxel was determined. The highest velocity, which represented the spatial peak velocity, was utilized in the calculation of CVR. Antialiasing was performed by adding or subtracting 200 cm/sec to obvious velocity outliers. Spatial peak velocities from ungated acquisitions were obtained before AZM administration (baseline) (one to three measurements) and every 3 to 5 minutes for 30 minutes (six to ten measurements) after AZM administration. The highest pre-AZM and post-AZM velocities were utilized in the calculation of CVR. To determine the feasibility of evaluating multiple vessels during a single PC MRA study, velocities in seven vessels from 1 subject who did not receive AZM were measured.

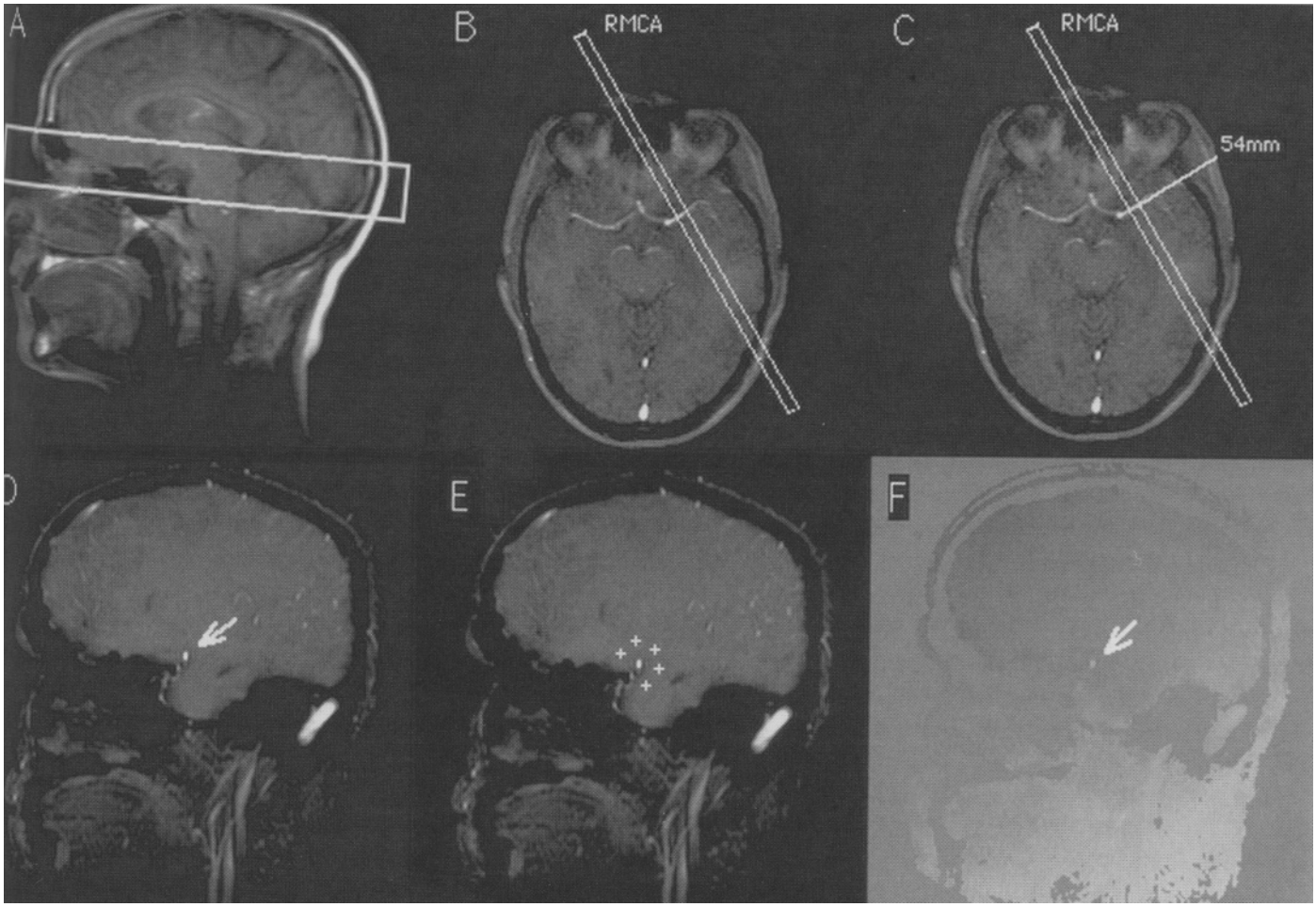

Fig 1. Representative images of PC MRA. (A) Sagittal gradient recall echo pilot image (TR 100/TE 30/90-degree flip angle/field of view [FOV] 30 cm thickness [THK] 2 cm/196 × 256 matrix/NSA 1) indicating the axial volume that contains the right middle cerebral artery (RMCA). (B) Axial two-dimensional, time-of-flight (2D TOF) MRA image (TR 15/TE 5/35-degree flip angle/FOV 30 cm/THK 2.5 mm/192 × 256 matrix/NSA 1) indicating the location of the oblique sagittal image plane through the RMCA for the PC image velocity measurement. (C) Axial 2D TOF MRA image (same as B) indicating the depth (54 mm) of the RMCA from the temporal surface. (D) Oblique sagittal magnitude image (magnitude reconstruction of velocity-encoded data [TR 40/TE 9/40-degree flip angle/FOV 25 cm/THK 5 mm/215 × 128 matrix/NSA 4]) indicating the RMCA (ovoid hyperintensity, *arrow*). (E) Oblique sagittal magnitude image (same as D) indicating five reference points (*crosses*) employed for computing the bicubic phase correction. (F) Oblique sagittal flow map (phase reconstruction of velocity-encoded data) (same as D) indicating the RMCA (ovoid hyperintensity, *arrow*). The window settings were 0 (level) and ± 100 cm/sec (width).

Cerebrovascular Reserve: CVR was defined as the maximum difference in middle cerebral artery blood flow velocity (cm/sec) before versus after AZM administration [15, 16]. From the same segment of the RMCA for each subject, the blood flow velocity was determined by TCD ultrasonography and MRA before and after AZM administration. For each subject, the two studies (TCD and MRA) were separated in time by 3 to 6 days, with random assignment of the order of the study; thus, each subject received AZM twice. Based on prior TCD studies, presence of a normal CVR was indicated by a post-AZM increase in velocity of more than 25% [15, 16].

Acetazolamide: One gram of AZM (Diamox), an arteriolar dilator, was administered by intravenous push (1 gm/10 ml of sterile water over 60 sec). Its reported onset of action occurs within 2 minutes; maximum effect, at approximately 5 to 15 minutes; and duration of action is 20 to 40 minutes [15, 16, 22, 23]. The most frequent side effects, although rare, include facial or extremity paresthesia, tinnitus, and nausea. A transient mild diuresis is common.

Statistical Analysis: A two-tailed Student's *t* test was employed to compare the mean TCD- and MRA-derived RMCA blood flow velocities before and after AZM administration. Also, the null hypothesis (H0) was tested with the two-tailed Student's *t* test at a significance level of 0.05.

Results

TCD- and MRA-derived velocities and CVR are presented in Figure 2 and Table 1. The pre- and post-AZM mean TCD-derived velocities were 61 and 85 cm/sec, respectively, with a mean CVR of 39%. The pre- and post-AZM mean MRA-

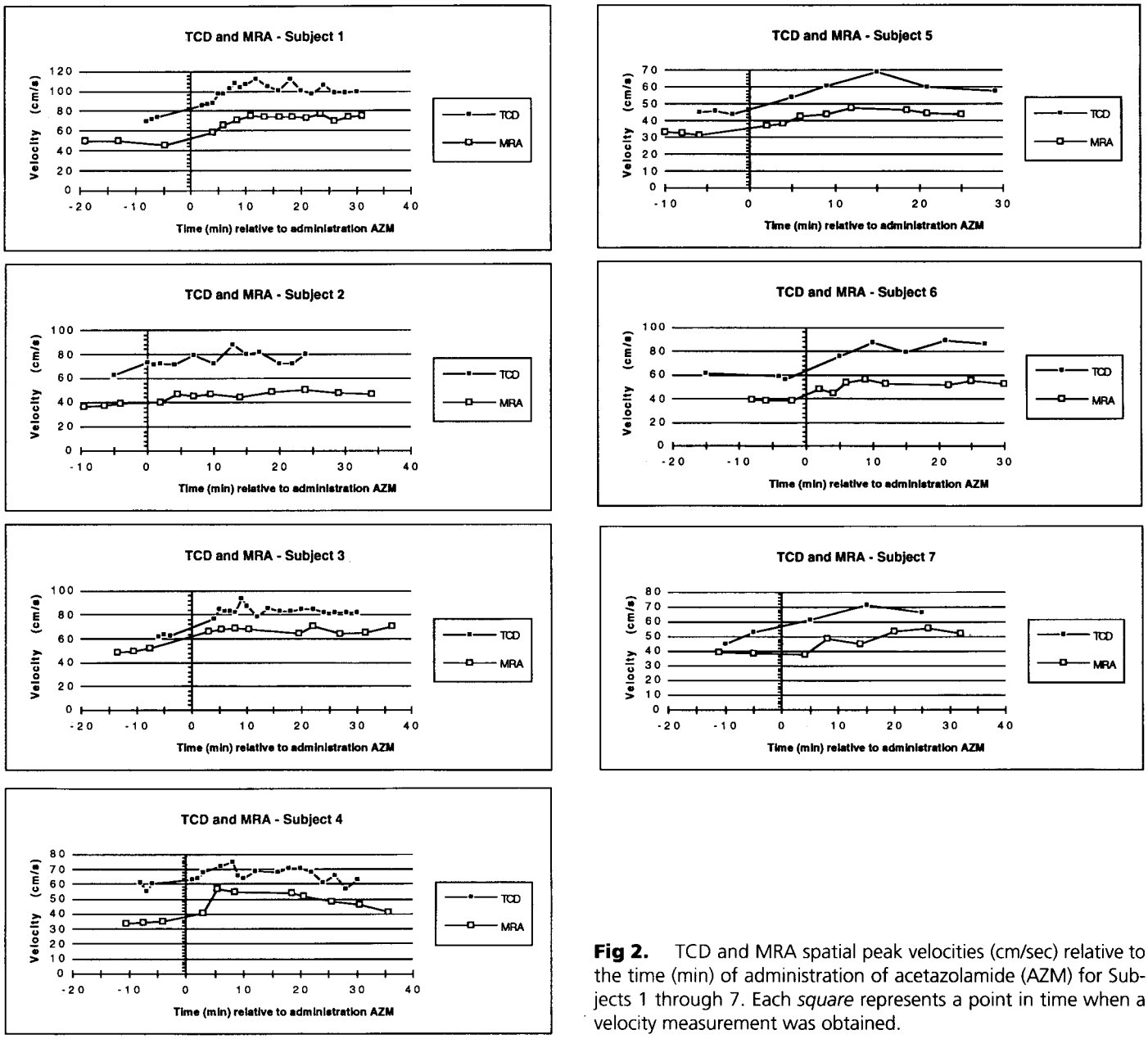

Fig 2. TCD and MRA spatial peak velocities (cm/sec) relative to the time (min) of administration of acetazolamide (AZM) for Subjects 1 through 7. Each *square* represents a point in time when a velocity measurement was obtained.

determined velocities were 40 and 58 cm/sec, respectively, with a mean CVR of 45%. The pre-AZM mean TCD-determined velocity (61 cm/sec) was significantly higher than the pre-AZM mean MRA-determined velocity (40 cm/sec) and the post-AZM mean TCD-determined velocity (85 cm/sec) was significantly higher than the post-AZM mean MRA-determined velocity (58 cm/sec). However, there was no significant difference in mean CVR as determined by TCD (39%) versus MRA (45%); therefore, the null hypothesis (H0) was accepted at a significance level of 0.05.

For all subjects, the CBF direction in the RMCA was orthograde as indicated by a hyperintense vessel lumen in the PC MRA flow map and an increase in the TCD frequency.

For 1 subject, velocities were measured with TCD and PC MRA, but without AZM administration, in seven vessels (proximal segments of the anterior, middle, and posterior cerebral arteries and distal segment of the basilar artery) (Fig 3, Table 2). With PC MRA, the velocity in each vessel was determined in less than 1 minute. Thus, the entire study for obtaining velocities in seven vessels required approximately 15 minutes (8 min for the sagittal gradient recall echo pilot and two-dimensional, time-of-flight MRA images and 7 min for the PC MRA velocity images).

The preferred technique of employing a headband to maintain the TCD transducer in position was satisfactory in 3 subjects; however, for the other 4 subjects, variability in the shape of the temporal surface relative to the location of

Table 1. TCD and MRA Velocities and Cerebrovascular Reserve (CVR)

Subject No.	TCD[a] Depth (mm)	TCD[a] Velocity (cm/sec) Before	TCD[a] Velocity (cm/sec) After	TCD[a] CVR (% Change)	MRA[a] Depth (mm)	MRA[a] Velocity (cm/sec) Before	MRA[a] Velocity (cm/sec) After	MRA[a] CVR (% Change)
1	50	72	112	56	50	50	77	54
2	56	73	88	21	49	39	51	31
3	50	64	94	47	48	52	71	37
4	54	61	75	23	58	35	57	63
5	56	46	69	50	50	33	47	42
6	56	61	89	46	56	39	56	44
7	58	53	71	34	55	35	50	43
n = 7[b]	54 ± 3[c]	61 ± 10[d,e]	85 ± 15[d,f]	39 ± 14[g]	52 ± 4[c]	40 ± 8[e,h]	58 ± 11[f,h]	45 ± 11[g]

[a]"Depth" refers to location of the segment of the right middle cerebral artery from which velocities were obtained relative to the temporal surface. TCD and MRA velocities were measured before and after acetazolamide administration with the corresponding CVR (% change in velocity).
[b]Mean ± standard deviation. Significance is based on the two-tailed Student's *t* test.
[c]Difference not significant.
[d]Difference significant at 0.05.
[e]Difference significant at 0.05.
[f]Difference significant at 0.05.
[g]Difference not significant.
[h]Difference significant at 0.05.

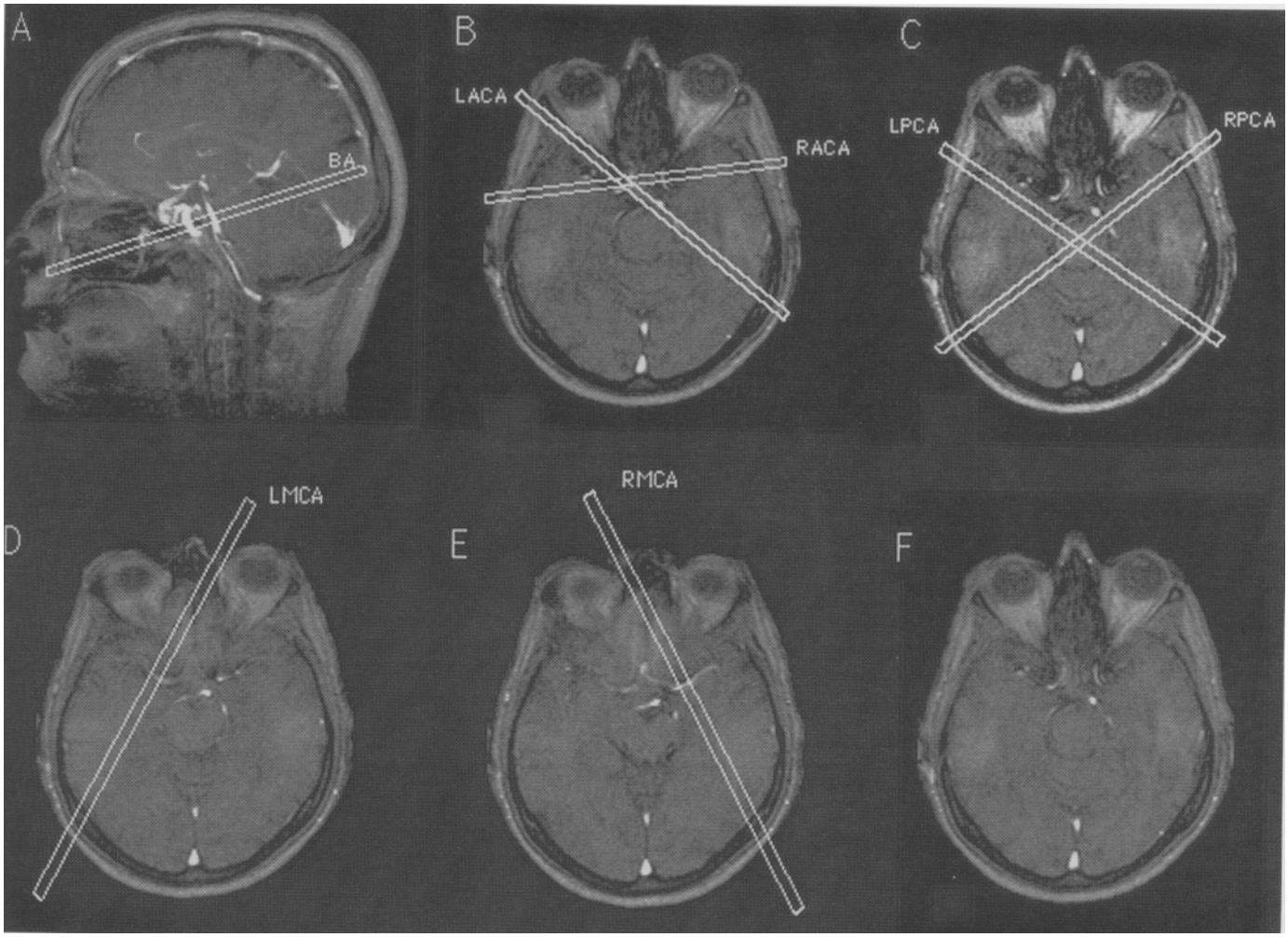

Fig 3. Two-dimensional, time-of-flight MRA images (TR 15/TE 5/35-degree flip angle/FOV 30 cm/THK 2 cm/196 × 256 matrix/NSA 1) indicating the location of the oblique image plane for the PC velocity measurement. (A) Basilar artery (BA). (B) Left (LACA) and right anterior cerebral arteries (RACA). (C) Left (LPCA) and right posterior cerebral arteries (RPCA). (D) Left middle cerebral artery (LMCA). (E) Right middle cerebral artery (RMCA). (F) Image plane for anterior and posterior cerebral arteries without markers (same as B and E); note that this one image plane demonstrated four different vessels, which reduced data acquisition time.

Table 2. TCD and PC MRA Velocities

Vessel	Velocity (cm/sec)		Depth (mm)	
	TCD	PC MRA	TCD	PC MRA
RMCA	72	32	58	61
LMCA	73	26	58	58
RACA	64	26	76	75
LACA	53	35	72	76
RPCA	54	11	68	70
LPCA	NI	12	NI	72
BA	35	24	NA	NA

RMCA and LMCA = right and left middle cerebral artery; RACA and LACA = right and left anterior cerebral artery; RPCA and LPCA = right and left posterior cerebral artery; BA = basilar artery; NI = not identified; NA = not applicable.

the RMCA precluded maintenance of a satisfactory angle of insonation and thus, the transducer was held by hand.

Three subjects experienced tingling of the face of approximately 4 hours' duration, with total resolution. Two subjects experienced headaches of approximately 3 hours' duration; they were treated with acetaminophen and the headaches resolved. All 7 subjects experienced mild transient diuresis with onset and resolution occurring within 4 hours after receiving acetazolamide.

Discussion

The pre-AZM mean TCD-determined velocity (61 cm/sec) and the mean TCD-determined CVR (39%) were within normal limits relative to established values [15, 16, 24, 25]. The mean MRA-derived CVR (45%) was not significantly different from the mean TCD-derived CVR (39%). However, due to the absence of other MRA CVR studies, a comparison with reported values was precluded. The pre-AZM (40 cm/sec) and post-AZM (58 cm/sec) mean MRA-derived velocities were significantly less than the pre-AZM (61 cm/sec) and post-AZM (85 cm/sec) mean TCD-determined velocities, respectively. Although these were spatial peak mean velocities (averaged over the cardiac cycle), the disparities were attributable to the greater temporal resolution of TCD ultrasonography; that is, the sampling frequency of velocities during the cardiac cycle was greater for TCD than for MRA. Owing to the prolonged length of diastole versus systole, the randomly obtained velocities with the ungated PC MRA method were more likely to have occurred during diastole and thus were less than the maximum spatial peak mean velocities. Also, because of the absence of angle correction, the TCD-determined velocities were most likely less than the maximum spatial peak velocities. Insonation angle correction can be accomplished with transcranial color flow duplex imaging; however, this method was unavailable for the study. Although there are current limitations to the determination of absolute velocities with MRA, utilization of relative changes in velocity seems accurate; for example, it is the relative velocity change (i.e., the difference between pre- and post-AZM velocities) that indicates the CVR. As demonstrated in this study, there was no significant difference in the relative velocity change (i.e., the CVR determined by MRA versus that determined by TCD).

Owing to the paucity of MRA studies reporting intracranial blood flow velocities, the present authors were limited in making comparisons with these results. Enzmann and coworkers [20] employed PC MRA and measured the spatial average velocity (cm/sec) across the lumen of the vessel; in association with the luminal cross-sectional area (cm^2), the flow volume (ml/min) was determined. However, the current study measured the spatial peak velocity across the lumen with PC MRA because this was the velocity determined by TCD—the gold standard for this study. Assuming a parabolic flow pattern, the spatial average velocity (V_a) is one-half the spatial peak velocity (V_p); based on a V_p of 40 $\pm$ 8 cm/sec (see Table 1, pre-AZM MRA velocity), the V_a was 20 $\pm$ 4 cm/sec, which approximates the V_a of 14 cm/sec from Enzmann and colleagues [20] (see Table 1; RMCA flow volume of 127 ml/min with a cross-sectional area of 0.15 cm^2 yields a V_a of 14 cm/sec, and left middle cerebral artery flow volume of 108 ml/min with a cross-sectional area of 0.13 cm^2 yields a V_a of 14 cm/sec).

Of potential utility is the application of PC MRA to obtain the velocity from multiple vessels during a single study. For example, in 1 subject PC MRA was applied to obtain the velocity in seven vessels (anterior, middle, and posterior cerebral arteries bilaterally and basilar artery) (see Fig 3, Table 2). Based on one velocity measurement per vessel per minute, the seven vessels were evaluated over 35 minutes, yielding five velocity measurements, one every 7 minutes, for each vessel. Thus, the CVR of seven vascular territories was determined in 35 minutes, exclusive of the initial sagittal gradient recall echo pilot and two-dimensional time-of-flight MRA images, which required 15 minutes. This temporal resolution (one velocity measurement/same vessel/7 min) appears satisfactory for evaluating CVR as evidenced by the velocity profiles reported herein (see Fig 2) and in the literature [15, 16, 23].

In conclusion, although the CBF velocities determined by MRA and TCD were significantly different, the relative changes in velocities (i.e., the CVRs) did not differ. The apparent feasibility and value of simultaneously determining the CVR of multiple vascular territories (e.g., anterior, middle, and posterior cerebral arteries) with PC MRA warrant additional study. The hemodynamic information (CVR and collateral flow) provided by the PC MRA/AZM test, in conjunction with the corresponding vascular morphology obtained by three-dimensional, time-of-flight MRA, may be very informative relative to the diagnosis and treatment of cerebrovascular disease.

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