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AJNR Am J Neuroradiol 2000, 21 (2) 386-390
http://www.ajnr.org/content/21/2/386

AJNR Am J Neuroradiol 21:386–390, February 2000

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BACKGROUND AND PURPOSE: **Several recent studies have shown that sonographic contrast agents may affect transcranial Doppler evaluation of the arterial peak systolic velocity (PSV). Some investigators reported an increase in PSV, and others reported no change in PSV compared with baseline values. This study was conducted to determine the effect of sonographic contrast agent on PSV measured in normal middle cerebral arteries.**

METHODS: **Continuous spectral Doppler sonography was performed on the right middle cerebral artery of 20 participants with angiographically proven normal intracranial vasculature. Videotaping was performed in each case from the initiation of the administration of contrast medium until the effect of the contrast agent on the PSV subsided. The PSV values were normalized for each participant, were pooled, and were plotted as a function of time.**

RESULTS: **PSV increased in all participants after the administration of contrast material; the mean maximum increase was 24 ± 7.4% (mean ± standard deviation) (range, 15−36%). The mean duration of PSV increase was 320 ± 97 s (range, 165−465 s).**

CONCLUSION: **The middle cerebral artery PSV increased substantially after the administration of contrast material. This effect needs to be considered if velocity thresholds developed for disease detection without the use of contrast materials are used when contrast agents are administered.**

Transcranial Doppler sonography is a noninvasive, portable method for evaluating intracranial hemodynamics. It is most often used to detect acute vasospasm after subarachnoid hemorrhage (1) by identifying abnormally elevated peak systolic velocities in intracranial arteries. Serial measurements may be used to monitor the response to therapy for vasospasm. Similarly, transcranial Doppler sonography may also be used to evaluate other entities such as brain edema (2), stroke (3, 4), and neoplasm (5) by detecting alterations in flow velocities. Additionally, detection of changes in Doppler flow velocity in the middle cerebral artery of children with ventriculoperitoneal shunt failure has shown promise as a noninvasive method of assessing shunt function (6). Unfortunately, the vessel under investigation is generally not directly visible, the angle of insonation is frequently only estimated, and, because of sound attenuation by the bony calvarium, the signal-to-noise ratio is often suboptimal. These limitations affect the reproducibility and reliability of the procedure.

Several promising preliminary studies have recently investigated the use of sonographic contrast agents with transcranial Doppler sonography (5, 7−10) for potentially reducing the number of technically inadequate examinations. Studies in other organs, however, have shown these agents to cause an increase in measured arterial velocities (4, 11). It is unknown whether this occurs intracranially. If it does, the effect may be significant; transcranial Doppler sonography relies on arterial velocity measurement and comparison of the values obtained with threshold levels developed for detection of pathologic abnormalities. This study was performed to determine whether bolus administration of a galactose-based contrast agent during transcranial Doppler sonography in adults with normal cerebral arteries causes an alteration in measured arterial peak systolic velocity (PSV), and if it does, to determine its magnitude and duration.

Received April 22, 1999; accepted after revision October 8.

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Methods

Patient Population

Approval for this study was obtained from the institutional review board of our institution, and informed consent was obtained in all instances after the nature of the procedure was fully explained. The study sample included 20 patients (12 male and eight female patients; mean age, 55 ± 15 years; age range, 17−77 years). The patients were originally admitted for evaluation of suspected arteriovenous malformation (n = 4), intracranial arterial stenosis (n = 4), subarachnoid hemorrhage (n = 3), extracranial arterial stenosis (n = 3), epistaxis (n = 2), vasculitis (n = 1), cystic lymphangioma (n = 1), venous angioma (n = 1), and meningioma (n = 1). In all patients, the intracranial arteries were proven to be normal by cerebral digital subtraction angiography before contrast-enhanced transcranial Doppler sonography was performed.

Transcranial Doppler Sonography Protocol

All cases were studied by an experienced radiologist (H.G.K.) using a 2-MHz probe (Acuson XP128; Mountainview, CA) through a unilateral right transtemporal window. Power Doppler sonography was performed with the gain optimized by imaging at the noise floor (12) and was used to facilitate vessel localization and angle-correction of spectral Doppler waveforms in all cases. Doppler energy output had a maximal in situ intensity of 226 mW/cm^2 spatial peak time average intensity corresponding to 99 W/cm^2 spatial peak pulse average intensity. The examinations were recorded with continuous video home system videotaping. The videotapes were later jointly reviewed by three of the authors (H.G.K., P.G., K.J.M.), with results determined by consensus. Only the right middle cerebral artery was studied. The Doppler gain was standardized; it was adjusted until noise first became apparent in the background of the spectral tracing. A baseline examination was performed for 5 min before the administration of contrast material. A galactose-based contrast agent (Levovist; Schering AG, Berlin, Germany) was then IV-administered to all patients via an 18-gauge needle in an antecubital vein during a 20-s interval. Contrast medium was injected at a dose of 2.5 g diluted in 7 mL of 0.9% saline resulting in a concentration of 300 mg/mL (total volume, 11 mL). A 5-mL bolus flush of 0.9% saline was then administered. No complications or adverse reactions occurred. Uninterrupted angle-corrected spectral Doppler sonography was obtained of the right middle cerebral artery from the initiation of the administration of contrast material until the effect of the contrast agent on the PSV subsided. The mean PSV of the middle cerebral artery was determined from the videotapes at 15-s intervals by averaging the PSV values of three consecutive waveforms.

Data Analysis

To determine whether the alterations in contrast-enhanced middle cerebral artery PSV compared with baseline PSV were statistically significant, a one-sample *t* test for differences between means was performed on the initial and maximum PSV values for all patients with statistical significance at the $P < .01$ level. Because we wanted to analyze the data of all patients as a whole and because the baseline PSV values varied from patient to patient, it was necessary to normalize the data for each patient before consolidating all data. This was done for each patient by dividing the post-injection PSV values for each 15-s time increment by the pre-injection PSV values. The data from all patients for each 15-s interval after the administration of contrast material were then pooled, and means and standard deviations of the pooled normalized PSV values for each time increment were calculated. These data, with standard error bars, were then displayed as a single composite plot (Fig 1).

Results

The results for each patient are displayed in the Table. A plot of mean normalized PSV data for all patients as a function of time is also shown (Fig 1). Representative spectral Doppler waveforms are illustrated (Fig 2). The middle cerebral artery PSV increased after the administration of contrast material in all patients, with the mean maximum percent increase compared with baseline for all patients being 24 ± 7.4% (range, 15−36%). This increase in PSV for all patients considered together was highly statistically significant ($P < .005$). The mean duration of contrast-induced PSV increase was 320 ± 97 s (range, 165−465 s). The mean normalized PSV for all patients returned to values within 5% of baseline after 240 s (Fig 3).

Discussion

Sonographic contrast agents markedly increase the reflectivity of blood, thereby allowing for better visualization of vessels. Before they can be fully utilized for Doppler sonography, however, it must be determined whether Doppler sonography–detected velocities change after the administration of the contrast agents. Initial studies in this regard have shown differing results. Forsberg et al (13) reported that contrast agents produce up to a 45% increase in the PSV of the rabbit aorta and up to a 17% increase in PSV in vitro. They suggest that this velocity increase is artifactual and is caused by the limited dynamic range available in the scanner display. Abildgaard et al (14) showed the PSV to increase by 5% and the end-diastolic velocity to increase by 6% in the common carotid arteries of six piglets after the administration of contrast material. Based on an in vitro study, Petrick et al (11) concluded that a galactose-based contrast agent had no direct effect on Doppler frequencies. They suggest that any increase in PSV obtained in vivo after the administration of contrast material is artifactual and owing to enhancement of signals that were already adequate before the administration of the contrast material, with the resulting sonographic echoes exceeding the dynamic range of the scanner. They further suggest that reducing the Doppler gain easily compensates for this effect. Gutberlet et al (15) noted a mean maximum Doppler frequency shift increase of 38% in hepatic transplant arteries after the administration of contrast material but did not detect any increase in Doppler shift in the common carotid arteries of healthy human volunteers after the administration of contrast material (16). They proposed that the hepatic transplant arteries were less than optimally seen before the administration of contrast material and that the contrast agent caused higher frequency signals to be detected. They concluded that in the superficially located common carotid artery, where the signal is presumably already of sufficient intensity, these higher shifts were detected without the use of a contrast agent.

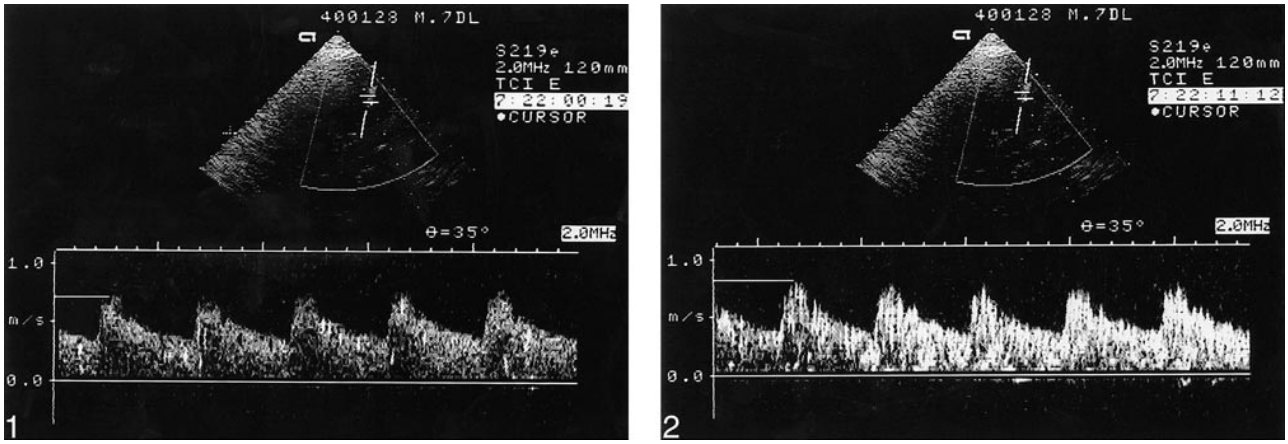

FIG 1. Plot of mean normalized PSV for the aggregate patient data as a function of time. Time ''zero'' on the horizontal axis denotes baseline PSV before the administration of contrast material. *Vertical lines* at data points are error bars denoting ± 1 SD. Note that the mean PSV increases fairly rapidly, reaching a maximum within approximately 1 min of injection. Mean PSV remains elevated to approximately 5% above baseline until approximately 4 min after injection.

FIG 2. Representative waveforms at the onset of contrast effect and at peak enhancement. Note the marked enhancement of the Doppler spectrum after the administration of contrast material and the apparent increase in PSV after the administration of contrast material compared with before.

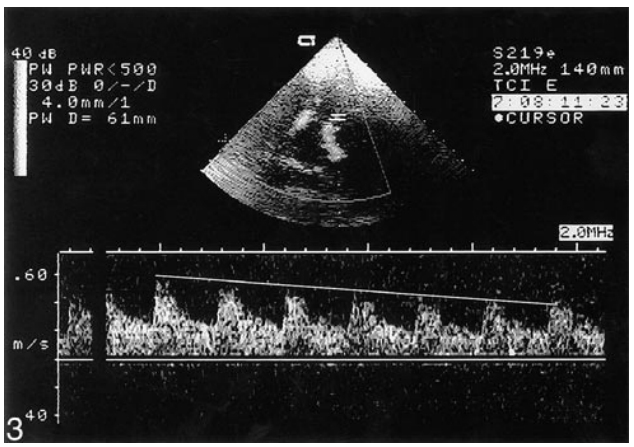

FIG 3. Representative waveforms showing tapering velocities corresponding to a decrease of contrast effect are shown.

If contrast agents are to be optimally used clinically, it must be known whether measured velocity increases after the administration of contrast material and whether the cause is artifactual. If velocities increase, one cannot simply administer a contrast agent and measure velocities. Some sort of correction will be needed to counteract this measured velocity increase, whether it be the development of new velocity standards for use with contrast agents or a reduction of the Doppler gain, as Petrick et al have suggested (11).

Our study was designed to determine the amplitude and time course of the effect of a bolus-administered galactose-based contrast agent on the PSV during transcranial Doppler sonography. We therefore sequentially measured PSV in the right middle cerebral arteries of patients in whom adequate waveforms could be obtained before the administration of contrast material. Our attention focused on the right middle cerebral artery only so that it could be continuously insonated. It is assumed that our results can be extrapolated to other branches of the circle of Willis.

Our results show that when Doppler waveforms are adequate for measurement before the administration of contrast material at a standardized Doppler gain and the Doppler gain remains unaltered when the contrast agent is administered as a bolus, the measured PSV increases fairly prominently, up to 36% compared with baseline in our study. A substantial degree of velocity elevation lasts for at least several minutes (Fig 1), with the mean PSV increase still approximately 5% above baseline at 4 minutes after the administration of the bolus. Thus, one cannot administer a contrast agent during transcranial Doppler sonography, leave the Doppler gain unaltered, obtain PSV values in arteries that had adequate Doppler spectra before the administration of the contrast material, and necessarily expect to detect pathologic abnormalities by applying velocity criteria developed for use without a contrast agent. Doing so may cause a post-injection

Effect of sonographic contrast material on measured peak systolic velocity in normal middle cerebral arteries

Patient (No.)	Age (yrs)	Baseline MCA Velocity (cm/s)	Postcontrast Maximum MCA Velocity (cm/s)	Increase of Maximum MCA velocity (%)	Duration of PSV Increase (s)
1	17	100	135	35	345
2	24	114	155	36	240
3	45	75	92	23	360
4	48	82	95	16	465
5	50	60	73	22	285*
6	52	76	88	16	285
7	53	61	76	25	405
8	53	76	89	17	240
9	54	64	76	19	240
10	57	66	83	26	465
11	58	79	91	15	270
12	61	70	85	21	225
13	61	80	93	16	345
14	64	52	70	35	165
15	65	45	57	27	360
16	65	61	79	30	240
17	65	75	102	36	440
18	68	58	69	19	425
19	72	58	76	31	180
20	77	84	100	19	410
Mean value	55	72	89	24	320
SD	15	16	22	7.4	97

* In this patient, data was only collected to 285 seconds post-injection due to a technical problem with the videotape, the recording was interrupted prematurely, and the PSV was still 13.4% above baseline at that time.

PSV that was normal before the administration of contrast material to exceed a velocity threshold, falsely suggesting abnormality when none is actually present. To compensate for the measured PSV increase, Petrick et al (11) suggest that ''. . . it is easy to compensate for the over-enhancement responsible for the artifact by reducing the gain.'' Gain reduction may be the correct mechanism to use because it does reduce the measured PSV (11), but we do not share the view presented by Petrick et al that it is easy to do. Gain reduction is subjective, and what is adequate gain for one observer may be too little or too much for another. It may therefore be necessary to standardize gain reduction after the administration of contrast material in this setting, but to do this, further study is required. Alternatively, if gain reduction cannot be standardized for a bolus injection, it may still be necessary to revise current velocity thresholds. Further investigation into this topic is required as well.

A recent in vivo study has investigated continuous infusion, rather than bolus administration, of a microbubble contrast agent for enhancement of the Doppler signal in the human femoral artery (17). It may be that the infusion technique, which results in lower maximum enhancement than does the bolus technique, causes a low enough PSV increase that it does not significantly interfere with the use of current PSV thresholds developed for disease detection without the use of a contrast material. Nonetheless, further study would also be required to evaluate this issue.

There are limitations to our study. First, it does not explain why we observed an increase in middle cerebral arterial PSV. It only shows that if contrast agent is administered in the settings of this experiment, an increase in PSV is measured. Second, our study does not address the effect of a contrast agent on the PSV of an artery that cannot be adequately insonated before the administration of contrast material, because we could not measure pre-injection velocities in such instances. Our study, however, clearly shows that bolus administration of a microbubble contrast agent during a transcranial Doppler sonography examination causes a substantial, time-dependent increase in the measured PSV of an artery of which the waveforms were already technically adequate before the administration of contrast material. This effect lasts for a substantial amount of time and needs to be taken into account if PSV thresholds that were developed for disease detection without the use of contrast material are used after contrast material is administered.

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