

Effect of Intraarterial Papaverine on Cerebral Circulation Time

James M. Milburn, Christopher J. Moran, DeWitte T. Cross III, Michael N. Diring, Thomas K. Pilgram, and Ralph G. Dacey, Jr

PURPOSE: To measure the mean cerebral circulation time (CCT) in patients with symptomatic vasospasm stemming from subarachnoid hemorrhage and to determine any change after papaverine treatment. **METHODS:** We studied 27 patients who received intraarterial papaverine from November 1992 to August 1995 to determine the CCT in 59 carotid territories. CCT was measured from the first image in which contrast was seen above the supraclinoid internal carotid artery to the peak filling of parietal cortical veins. Angiograms at the time of presentation were examined in 19 of the 27 patients. A control population of 19 patients (30 carotid territories) was also studied. **RESULTS:** The mean CCT on presentation was 6.8 seconds \pm 1.1. The prepapaverine mean CCT was 6.1 seconds \pm 1.2. The immediate postpapaverine mean CCT was 3.8 seconds \pm 0.8. CCT decreased in 58 of 59 territories treated with papaverine; the mean change was -35.7% . In eight of these patients, CCT rose on the following day to 6.1 seconds \pm 1.1. In the control group, mean CCT was 5.9 seconds \pm 0.8. The mean CCT in patients with subarachnoid hemorrhage was slightly prolonged on presentation relative to that in control subjects. **CONCLUSION:** Intraarterial papaverine produces a consistent decrease in CCT in patients with vasospasm.

Index terms: Vasospasm; Subarachnoid space, hemorrhage; Cerebral blood flow; Brain, effects of drugs on

AJNR Am J Neuroradiol 18:1081-1085, June 1997

Ischemia resulting from vasospasm is a major source of morbidity and mortality in patients with subarachnoid hemorrhage (SAH) after rupture of a cerebral aneurysm. Vasospasm usually begins on the third day after SAH, peaks at 6 to 8 days, and resolves by about the 12th day (1). After a ruptured aneurysm is protected by clipping or coiling, most patients with symptomatic vasospasm are treated with hypertensive-hypervolemic-hemodilution (triple-H) therapy and calcium channel blockers (2, 3). Symptomatic vasospasm resistant to such medical therapy may respond to endovascular balloon angioplasty and intraarterial papaverine. The success

of endovascular therapy has been gauged by reports of increased arterial diameter on preprocedural and postprocedural angiograms and of improvement in the clinical grade of treated patients (4).

We noted somewhat prolonged angiographic cerebral circulation times (CCT) in many patients with SAH and shorter CCTs after papaverine infusion. This observation was of interest, as mean CCT is related to cerebral blood flow (CBF). If papaverine causes consistent changes in CCT, this may give further insight into blood flow dynamics and optimal treatment strategies in patients with vasospasm. The purpose of this study was to measure the mean CCT in patients with SAH on presentation and at the time of endovascular vasospasm treatment to determine whether the CCT changed significantly after papaverine infusion and, if so, the duration of response.

Materials and Methods

We conducted a retrospective study of all patients who received intraarterial papaverine therapy at our institution

Received September 3, 1996; accepted after revision December 19.

From the Section of Neuroradiology, Mallinckrodt Institute of Radiology (J.M.M., C.J.M., D.T.C.), and the Departments of Neurology (M.N.D.), Radiology (T.K.P.), and Neurosurgery (R.G.D.), Washington University School of Medicine, St Louis, Mo.

Address reprint requests to Christopher J. Moran, MD, Mallinckrodt Institute of Radiology, Washington University School of Medicine, 510 S Kingshighway, St Louis, MO 63110.

AJNR 18:1081-1085, Jun 1997 0195-6108/97/1806-1081

© American Society of Neuroradiology

for treatment of clinical vasospasm from November 1992 to August 1995. Symptomatic vasospasm was diagnosed if patients had new neurologic deficits or a decreased level of consciousness after exclusion of hydrocephalus, cerebral edema, infection, or metabolic disturbances. All patients had vasospasm resulting from SAH associated with rupture of a saccular aneurysm. All patients received triple-H therapy and calcium channel blockers before undergoing angiography, and these measures were continued after papaverine infusion. Patients who received both papaverine and angioplasty during the same procedure were excluded. Patients whose angiograms did not include proper venous phase images were also excluded. Application of both these criteria resulted in exclusion of 24 treatments in 13 patients.

CCT for this study was modified from that of Greitz (5) and was defined as the interval between the first image in which contrast was visible above the supraclinoid internal carotid artery to the venous image with the highest concentration of contrast in the parietal cortical veins. In digital subtraction angiography, numerous frames are acquired for each angiographic run, but all images are not filmed. By convention at our institution, early and peak arterial filling as well as capillary and peak venous filling are filmed. This filming sequence occasionally requires interpolation of frame numbers to measure CCT. To blind the readings, all identifying data on the films were covered so only the angiographic images were displayed. The films were selected and organized on a different day from the CCT readings. The data were collected as absolute CCT, and the percentage of change was also calculated.

CCTs were calculated for all angiograms obtained at presentation and before and after papaverine infusion. We measured CCTs for 59 cerebral hemispheres in 27 patients (17 women and 10 men) who ranged in age from 33 to 81 years (mean age, 58 years). Some of the patients had a single carotid artery infused while others had bilateral infusions. Repeat infusions were also performed in some patients. The initial angiogram obtained at the time of presentation was available in 19 of these patients. The initial angiograms in the remaining eight patients were obtained at other institutions and were unavailable for review. Eight of the patients had repeat angiograms the day after papaverine infusion, and these were also examined.

Papaverine was infused into the cervical internal carotid artery at the C1–2 junction, typically initiated at a rate of 300 mg over 15 minutes. The average total dose in each carotid territory was 304 mg, with a range of 100 to 600 mg. The rate of infusion was adjusted according to the change in intracranial pressure, which is monitored continuously in all patients receiving papaverine at our institution. The cerebral perfusion pressure (mean arterial pressure – intracranial pressure) was kept greater than 60 mm Hg by slowing the infusion if the rise in intracranial pressure compromised cerebral perfusion pressure. All angiography was performed with digital subtraction imaging acquired at two frames per second. Nonionic contrast material was used in all cases.

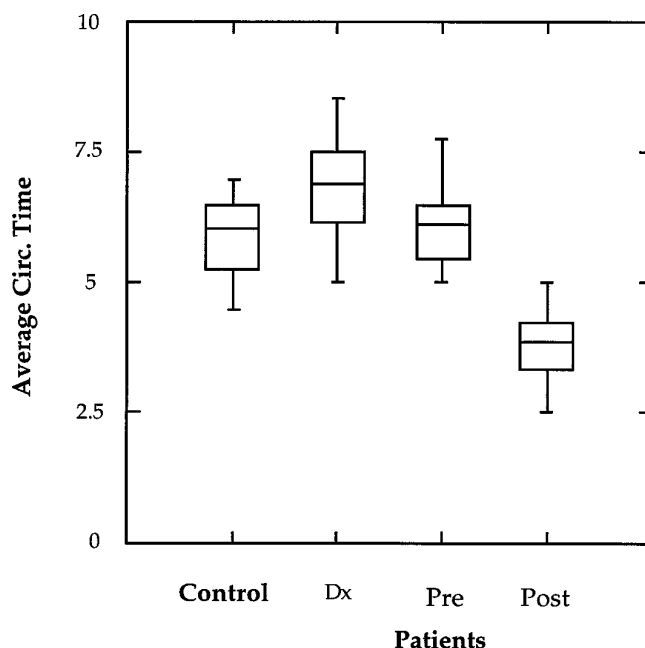


Fig 1. Average CCTs (in seconds) in the control group and in patients with SAH on presentation (*Dx*) and before (*Pre*) and after (*Post*) papaverine treatment. The middle bar represents the mean; the top and bottom of the box represent the 75th and 25th percentiles, respectively. There is a statistically significant difference between the patients on presentation and the control group, and between the prepapaverine and postpapaverine groups.

For a control population, we studied 17 consecutive patients undergoing cerebral angiography at our institution. Most patients were being examined for carotid atherosclerotic disease. Excluded were patients with evidence of ipsilateral extracranial or intracranial carotid stenosis greater than 30%, intracranial hemorrhage, tumor, aneurysm, or vascular malformation. Application of these exclusion criteria left 30 carotid territories for the control group. These patients included 11 females and six males who ranged in age from 15 to 78 years (mean age, 46 years).

Exploratory data analysis of CCTs consisted of plotting the data and constructing box plots to display the general trends (Fig 1). Differences between the groups as a whole were tested using analysis of variance (ANOVA). Means and standard deviations were calculated as a basis for comparing the CCTs of groups in a pairwise fashion.

Measurement reproducibility was evaluated using test-retest analysis by repeating the CCT measurements in 25 carotid territories. Pearson's correlation coefficient for the original and repeat measurements was $r = .95$. The average difference was 1.3% with a standard deviation of 13.8%.

Results

The control patients had a mean CCT of 5.9 seconds \pm 0.8. The patients with SAH had a

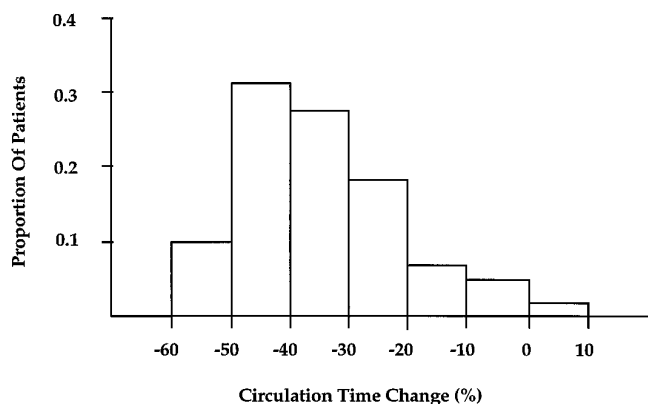


Fig 2. Proportion of patients relative to the percentage of change in CCT. Fifty-eight of 59 treatments resulted in a decrease in CCT. The greatest proportion of patients had a decrease between 40% and 50%.

mean CCT of 6.8 seconds \pm 1.1 at initial presentation. For patients in whom symptomatic vasospasm developed that was resistant to medical therapy, the prepapaverine CCT was 6.1 seconds \pm 1.2 and the postpapaverine CCT was 3.8 seconds \pm 0.8. CCT decreased after 58 of 59 papaverine infusions with a mean change of -35.7% (Fig 2).

The ANOVA model showed that the CCT in the four groups differed from one another when considered together ($P < .001$). Post hoc comparisons showed statistically significant differences in CCT between the patients at presentation and the control group, and between patients before and after papaverine treatment ($P < .05$).

We also recorded findings in the subset of patients treated with papaverine who had repeat angiography the next day to assess for recurrent vasospasm. There were eight carotid territories in this group. Papaverine infusion was repeated in five of these patients, and a similar decrease in CCT was observed. The mean CCT before papaverine on day 1 was 6.3 seconds \pm 1.2, with a decrease in CCT to 3.8 seconds \pm 0.5 after papaverine. The next day, mean CCT in these carotid territories had increased to 6.1 seconds \pm 1.1. The increase from postpapaverine CCT on day 1 and CCT the next day was statistically significant (paired *t* test, $P < .01$), while prepapaverine CCT on day 1 was statistically indistinguishable from CCT the next day.

Discussion

CCT was defined by Greitz in 1956 (5) as the interval between the maximum opacification of

the carotid siphon and the maximum opacification of the parietal veins. Using Triurol contrast agent, he found the mean CCT to be 4.13 seconds \pm 0.78. Leeds and Taveras (6) later used Hypaque and found CCT to be 4.37 seconds \pm 0.83. Greitz (7) repeated his work with Urograin and found a CCT of 3.43 seconds \pm 0.51. Normal circulation time in the vertebrobasilar system is different from CCT, so the data from these treatments was not included in this study (8).

Vasospasm is a leading cause of morbidity and mortality after SAH from aneurysmal rupture. Its presence is detected in up to 70% of angiograms obtained 4 to 12 days after the hemorrhage. Clinical vasospasm with ischemic neurologic deficits occurs in 20% to 30% of patients. Of these, half will either die or be left with serious neurologic deficits (9).

The goal of vasospasm treatment is to increase CBF to prevent infarction. Medical measures include triple-H therapy and administration of calcium channel blocking agents. Papaverine infusion and balloon angioplasty performed alone or in combination may be useful in the treatment of vasospasm resistant to these measures. Although angioplasty has gained considerable popularity as the primary interventional method at many institutions, papaverine adds the potential benefit of treating both large and small intracranial arteries. Many authors have described the use of papaverine infusion (4, 10, 11) and angioplasty (12, 13) for the treatment of symptomatic vasospasm.

Both angioplasty and papaverine therapy have associated risks of complications. Arterial rupture is a known risk of angioplasty (13, 14), and rapidly increasing intracranial pressure can occur during papaverine infusion (15) (E. E. Angtuaco, C. J. Moran, D. T. Cross, "The Role of Intracranial Pressure Monitors in Papaverine Therapy," presented at the annual meeting of the American Society of Neuroradiology, Chicago, Ill, April 1995); thus, at our institution, all procedures are accompanied by continuous monitoring of intracranial pressure. Mydriasis has been reported (16) as well as a depressive effect on respiration with vertebrobasilar infusion (17, 18). Thrombocytopenia has also been reported (19).

Several methods have been used to measure cerebral hemodynamics in patients with vasospasm. Transcranial Doppler sonography has been used after SAH to identify vasospasm at

an early stage to initiate prompt treatment (20). Positron emission tomography (21) and xenon computed tomography (CT) (22) provide a quantitative assessment of regional blood flow in patients with vasospasm, but these methods are available only at a few institutions. Single-photon emission computed tomography may reveal qualitative evidence of regional ischemia produced by vasospasm (23). This last method has the advantage of more widespread availability.

Angiographic measurement of CCT can be used to evaluate cerebral hemodynamics. Gado et al (24) showed CCT to be proportional to mean transit time using $C^{15}O$ -labeled hemoglobin. This relationship is useful, as mean transit time is equal to the ratio of cerebral blood volume/CBF. Therefore, CCT may be used to observe changes in CBF if cerebral blood volume is known.

The goal of papaverine therapy in patients with symptomatic vasospasm is to increase CBF to reverse ischemia and prevent infarction. We have shown a consistent decrease in CCT after papaverine infusion in these patients, and although we have only measured CCT for this study, the information can be useful for evaluating changes in blood flow. If one assumes the cerebral blood volume has increased as a result of papaverine infusion (papaverine is a potent vasodilator), a decrease in CCT indicates a large increase in CBF. If we assume that cerebral blood volume remains constant, a measured decrease in CCT also indicates an increase in CBF. It is highly unlikely that cerebral blood volume decreases with the infusion (25).

Other factors may have an effect on CBF and consequently CCT. Changes in $Paco_2$ and Pao_2 can have a significant effect. Most patients were intubated and ventilator settings were not changed. Pulse oximeter readings were likewise stable. Finally, prepapaverine and postpapaverine angiograms were usually obtained within 20 to 30 minutes of each other, so the $Paco_2$ and Pao_2 probably did not change significantly. Mean arterial pressure and intracranial pressure may also affect CBF. If changes in either mean arterial pressure or intracranial pressure cause cerebral perfusion pressure to fall outside the autoregulatory range of 50 to 160 mm Hg, CBF will either decrease or increase. In each of our papaverine infusions included in this study, cerebral perfusion pressure remained between 60 and 150. Changes in CCT have been described

with different arteriographic contrast media (5, 7). All arteriography in this study was done with nonionic contrast material, so contrast selection was not a factor in CCT measurement. Vasoactive metabolites, central neuronal mechanisms, and blood viscosity can also affect CBF (26).

The CCT findings in the subset of patients who underwent cerebral angiography the day after papaverine therapy add insight into the duration of the effect of papaverine. These data suggest the greatest papaverine effect may last less than 1 day. However, we must consider that this small subset of patients is biased toward those suspected of having recurrent vasospasm, and in other patients the effect may have been longer. The CCT at repeat angiography was less than that at presentation and before infusion the previous day, and it was only slightly longer than that of control subjects. However, these differences did not reach statistical significance.

The CCTs measured in our study were higher in control, prepapaverine, and postpapaverine groups than that reported in historical data (5-7). This is in part explained by our choice of an earlier arterial measurement point. Our measurements began with the first image in which contrast was seen above the supraclinoid internal carotid artery rather than from the point of maximum opacification of the carotid siphon, as this image is more routinely filmed at our institution. In addition, our patient population was older than the patients studied by Greitz. His patients had a mean age of 33 years (5) and 40 years (7), compared with a mean of 46 years in our control subjects and 58 years in our treated population. The use of nonionic contrast material may also be a factor, as previous authors have reported variations with different types of contrast media.

In conclusion, we have shown that intraarterial papaverine causes a decrease in CCT in patients with symptomatic vasospasm. From other studies, this should be an indicator of increased blood flow to the brain. While our subset of patients receiving papaverine the next day suggests that the duration of the physiological effect may be temporary, it may be sufficient to protect the patient from an infarction during the period of greatest risk. Evaluation of CCT may prove to be helpful in predicting the clinical response to papaverine, although further studies are needed to compare these data with clinical outcome.

References

1. Weir B, Grace M, Hansan J, Rothberg C. Time course of vasospasm in man. *J Neurosurg* 1978;48:173-178
2. Origitano TC, Wascher TM, Reichman OH, Anderson DE. Sustained increased cerebral blood flow with prophylactic hypertensive hypervolemic hemodilution ("triple-H" therapy) after subarachnoid hemorrhage. *Neurosurgery* 1990;27:729-740
3. Haley EC, Kassell NF, Torner JC. A randomized trial of nicardipine in subarachnoid hemorrhage: angiographic and transcranial Doppler ultrasound results: a report of the cooperative aneurysm study. *J Neurosurg* 1993;78:548-553
4. Clouston JE, Numaguchi Y, Zoarski GH, Aldrich EF, Simard JM, Zitnay KM. Intracranial papaverine infusion for cerebral vasospasm after subarachnoid hemorrhage. *AJNR Am J Neuroradiol* 1995;16:27-38
5. Greitz T. A radiologic study of the brain circulation by rapid serial angiography of the carotid artery. *Acta Radiol* 1956; Suppl 140: 1-123
6. Leeds NE, Taveras JM. Changes in local circulation time in frontal and parietal tumours studied by rapid serial angiography. *Acta Radiol (Diagn)* 1963;1:332-342
7. Greitz T. Normal cerebral circulation time as determined by carotid angiography with sodium and methylglucamine diatrizoate (Urografin). *Acta Radiol* 1968;7:331-336
8. Greitz T. Evaluation of circulation time in angiography of the vertebral artery. *Acta Radiol (Diagn)* 1969;9:300-309
9. Heros RC, Zervas NT, Varsos V. Cerebral vasospasm after subarachnoid hemorrhage: an update. *Ann Neurol* 1983;14:599-608
10. Kassell NF, Helm G, Simmons N, Phillips CD, Cail WS. Treatment of cerebral vasospasm with intra-arterial papaverine. *J Neurosurg* 1992;77:848-852
11. Marks MP, Steinberg GK, Lane B. Intraarterial papaverine for the treatment of vasospasm. *AJNR Am J Neuroradiol* 1993;14:822-826
12. Newell DW, Eskridge JM, Mayberg MR, Grady MS, Winn HR. Angioplasty for the treatment of symptomatic vasospasm following subarachnoid hemorrhage. *J Neurosurg* 1989;71:654-660
13. Higashida RT, Halbach VV, Dowd CF, Dormandy B, Bell J, Hieshima GB. Intravascular balloon dilatation therapy for intracranial arterial vasospasm: patient selection, technique, and clinical results. *Neurosurg Rev* 1992;15:89-95
14. Linskey ME, Horton JA, Rao GR, Yonas H. Fatal rupture of the intracranial carotid artery during transluminal angioplasty for vasospasm induced by subarachnoid hemorrhage. *J Neurosurg* 1991;74:985-990
15. McAuliffe W, Townsend M, Eskridge JM, Newell DW, Grady MS, Winn HR. Intracranial pressure changes induced during papaverine infusion for treatment of vasospasm. *J Neurosurg* 1995;83: 430-434
16. Hendrix LE, Dion JE, Jenson ME, Phillips CD, Newman SA. Papaverine-induced mydriasis. *AJNR Am J Neuroradiol* 1994;15: 716-718
17. Barr JD, Mathis JM, Horton JA. Transient severe brainstem depression during intraarterial papaverine infusion for cerebral vasospasm. *AJNR Am J Neuroradiol* 1994;15:719-723
18. Mathis JM, DeNardo A, Jenson ME, Scott J, Dion JE. Transient neurologic events associated with intraarterial papaverine infusion for subarachnoid hemorrhage-induced vasospasm. *AJNR Am J Neuroradiol* 1994;15:1671-1674
19. Miller JA, Cross DT, Moran CJ, Dacey RG, McFarland JG, Diringer MN. Severe thrombocytopenia following intra-arterial papaverine for the treatment of vasospasm. *J Neurosurg* 1995;83: 435-437
20. Aaslid R, Huber P, Nornes H. Evaluation of cerebrovascular spasm with transcranial Doppler ultrasound. *J Neurosurg* 1984; 60:37-41
21. Frackowiak RSJ, Lenzi G-L, Jones T, Heather JD. Quantitative measurement of regional cerebral blood flow and oxygen metabolism in man using ¹⁵O and positron emission tomography: theory, procedure and normal values. *J Comput Assist Tomogr* 1980; 6:727-736
22. Pistoia F, Horton JA, Sekhar L, Horowitz M. Imaging of blood flow changes following angioplasty for treatment of vasospasm. *AJNR Am J Neuroradiol* 1991;12:446-448
23. Lewis DH, Eskridge JM, Newell DW, et al. Brain SPECT and the effect of cerebral angioplasty in delayed ischemia due to vasospasm. *J Nucl Med* 1992;33:1789-1796
24. Gado M, Eichling J, Grubb R, Phelps M, Raichle M, Ter-Pogossian MM. Appraisal of the angiographic circulation time as an index of cerebral blood flow. *Radiology* 1975;115:107-112
25. Malkinson TJ, Cooper KE, Veale WL. Induced changes in intracranial pressure in the anesthetized rat and rabbit. *Brain Res Bull* 1985;15:321-328
26. van Dellen JR. Craniocerebral trauma. In: Bradley WG, Daroff RB, Fenichel GM, Marsden CD, eds. *Neurology in Clinical Practice*. Boston, Mass: Butterworth-Heinemann; 1996;2:941-971