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# LETTERS

## Measurement of Hippocampal T2 in Epilepsy

We were interested to read the commentary by C. R. Jack (1) that accompanied our article on new methods of measurement of hippocampal T2 relaxation time (2). We would like to address some of the points raised. The rationale for selecting a 120-millisecond second echo was that with a 30-millisecond first echo it placed the hippocampal T2 measurements approximately midway between the two echo times and optimized the reliability of the data. For studies such as these, the precision of the measured T2 value in the hippocampus is not of relevance. What is of prime importance is the establishment of a tight and consistent normal range and the differentiation of normal from abnormal tissue, with the severity of the imaging abnormality corresponding to the biological abnormality.

The dual-echo method has sufficient signal-to-noise ratio, as evidenced by our reproducibility. Further, the dual-echo method is not a "linear approximation"; it gives a value (T2) of a single exponential decay constant, which has exactly the same meaning as the results of a multiecho fit.

The multiecho fit does have two theoretical advantages. First, it can be used over a greater range of T2; this is not an issue for measuring hippocampal T2 because we have optimized the dual-echo sequence for the range of T2 values found in vivo. Second, if suitable multiexpoential curve fitting is done, multiple T2 components can be found within the same tissue. We have not found this to be useful or reliable in the assessment of hippocampal T2 using the 16-multiecho sequence; thus, this is not a practical advantage.

We have recently reported the correlation between hippocampal T2 time measured with the 16-multiecho sequence and quantitative neuropathologic measures (3). Studies to assess the severity of hippocampal pathology with hippocampal T2 time measured with the dual-echo method are in progress. We have also shown the advantages of the dual-echo method in that it readily allows construction of a profile of T2 throughout the length of the hippocampus, identifying patients with focal anterior hippocampal sclerosis (4).

Finally, we agree with Dr Jack that measures of repeatability of continuous variables have often been done in a nonrigorous fashion. Having reviewed the statistical method most carefully, we are in no doubt that calculation of the coefficient of reliability and the limits of agreement is the most stringent and appropriate method for reporting repeatability of continuous measures either between raters or for test-retest reliability. The limit of agreement (two standard deviations of the mean of the difference between two measures) is useful in that a repeat result outside of this limit has a less than 5% change of arising by virtue of measurement error. A correlation coefficient is inadequate for assessing repeatability. If a second measurement on a subject was always twice the value obtained on the first measurement, the correlation coefficient would remain extremely high. The coefficient of variation refers to the spread of a variable in a normal distribution, being represented by the standard deviation of the measure itself divided by the mean. Although a high coefficient of variation implies a very variable measure within a population, it is not in itself a measure of test repeatability. Percent variation of the mean of two measures will determine only whether there is a systematic bias between two measurements or not. Clearly, for a reliable measure in the same subject measured twice this should be zero.

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### *Reply*

The authors are entirely correct in stating that the most important attributes of any quantitative imaging approach are consistency and accurate scaling with the area of interest. The linear two-point fit approach to T2 relaxometry advocated by the authors appears to meet these criteria adequately. This approach, while functional, should not lead readers to the perception that in vivo quantitation of tissue T2 relaxation is either simple or trivial. Groups that have taken a rigorous approach to in vivo T2 relaxometry have identified a number of difficult technical issues, for example (*a*) contamination of the T2 decay curve by stimulated echoes, (*b*) the deleterious effects of imperfect section-selective and refocusing pulses, (*c*) the requirement that in order to characterize adequately the decay curve a sufficient number of echo times must be sampled, and (*d*) the multiexponential relaxation behavior of many tissue

types. Examples of rigorous treatment of these issues are found in the reference list below (1–6).

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## Dosimetry of Radiologic Techniques for Dental Implant Planning

I have read with considerable interest and concern the paper by Diederichs et al, "Must Radiation Dose for CT of the Maxilla and Mandible Be Higher than That for Conventional Panoramic Radiography?" The authors should be complimented on their development of a task-specific technique for computed tomography (CT) of the jaws at reduced patient dose. Their method shows considerable promise, and further exploration by these authors or others should follow. However, there are two basic problems with the dosimetric portion of the paper: the choice of procedures for which patient doses were compared and the method by which the comparison was made.

There are two competing techniques for obtaining images for treatment planning for endosseous dental implants: CT and conventional tomography. Thus, the meaningful comparison should be between these two, rather than between CT and panoramic radiography. Panoramic radiography complements either CT or conventional tomography; it competes with neither.

For decades, many investigators have struggled with methods for comparing patient doses from procedures whose beam spectral qualities and projection geometries were very different. The effective dose (formerly effective dose equivalent), developed by the International Commission on Radiological Protection, has been widely accepted as the best solution to date for this dilemma. However, it requires extensive measurements, computer simulation, and so forth to estimate doses to exposed organs that are sensitive to radiation-induced stochastic effects. The authors apparently tried to simplify the dosimetric problem by measuring dose to skin overlying the parotid glands, assuming that it was a reasonable estimate of dose to the subcutaneous portion of the parotids. However, this ignored doses to the other, more deeply placed organs in the head and neck that are known to be sensitive to radiation carcinogenesis. These include the deep portions of the parotids, other salivary glands, bone marrow (in the cervical vertebrae, mandible, and calvarium), and brain. Thus it is not likely that their doses represent meaningful estimates of biologically significant patient doses from these procedures.

Published estimates of effective doses from typical head CT scans have generally been about 2 mSv (2), while those for panoramic radiography have been some 5 to 10 $\mu$Sv (3)—a 200- to 400-fold difference. Thus, it is unlikely that the claimed 30-fold reduction of patient dose from the CT procedure would yield an effective dose comparable to that for panoramic radiography.

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### *Reply*

We acknowledge that conventional tomography is the main competing technique for CT in this context. To date, both techniques can be performed in addition to the panoramic radiograph. We also agree that the additional techniques should be compared instead of the additional CT and the baseline radiograph. White found the effective dose for a conventional full-mouth series to be 84 $\mu$Sv on average, compared with 5 to 10 $\mu$Sv for the panoramic radiograph (1). The effective dose of the additional conventional work-up might therefore be a multiple of the panoramic study. On the other hand, panoramic radiography and spiral CT have common technical parameters: Both are tomographic, both have a tube-detector/film system (at least partially) rotating around the head, both are performed within few seconds/minutes, both can cover a similar distance along the longitudinal axis of the patient, and both can display all teeth and most of the alveolar ridge in one image. But do both come with a similar radiation dose? According to Dr Gibbs, we tried to simplify the dosimetric problem by measuring the dose at one organ only. He also states that this measurement is not likely to represent the biologically significant effective dose. There

would indeed be some limitations with our dosimetric part if the purpose of our study had been not the estimation of the *magnitude* but a precise estimation of the effective dose:

1. The distribution of the organ doses is not equal for both techniques. In the head, CT produces isodoses that are roughly circular in the transverse plane and are smaller in the middle of the head. Panoramic radiographs make horseshoelike isodoses, with an "anterior opening" and smaller values in the middle, anteriorly, and anterolaterally. This is because rays are exiting at these locations while with CT they are exiting and entering at all locations in the field of view.

2. The dose/mAs quotients for different CT scanners can vary more than ±50% (2, 3); they can also vary for different conventional equipment.

3. In our measurement, the scanning volume of the CT (measured by the path length of table movement: 7.2 cm) is not equal to the volume exposed by panoramic radiography (estimated by dividing the height of the exposed film by the magnification factor: about 13 cm).

4. The filtering of the X rays might be different, and therefore X-ray absorption in deeper tissues might be different.

We therefore agree that our rough estimate of radiation dose would have been more precise if we had measured doses with more sensitive detectors (capable of $<10$ $\mu$Gy) at multiple sites using different conventional and CT scanners. Dr Gibbs concludes that a 200- to 400-fold difference in effective dose between a head scan and a panoramic radiograph contradicts our conclusion, considering that we have reduced dose only 30-fold. This 30-fold factor results from a comparison of our protocol with one used by Kassebaum et al (4), who examined the mandible and maxilla with 140 mAs and 50% overlap. We could show that the measured difference in surface dose is fully explained by the differences in scanning parameters, taking into account overlap, tube voltage, and mAs. The source for the 2 mSv for a head scan cited by Dr Gibbs (5) refers to a publication of the British National Radiological Protection Board (3). In this, the average effective dose for CT of the facial bones was calculated to be 0.69 mSv, compared with 2 mSv for a CT scan of the head. The corresponding scanning parameters for CT of the facial bones were 120 to 140 kV, 505 mAs, 14.5 sections per exam with an increment of 4.77 mm, and a section thickness of 4.78 mm (mean values, n = 93). This corresponds to an average table travel of 6.9 cm, which is within 5% of our study. Based on proportionality of photon flux and tube current, a reduction from 500 mAs to 20 mAs (40 mA at pitch 2 and gantry rotation frequency 1/s) results in a factor of 25. The difference in tube voltages (120 kV versus 80 kV in our study) accounts for a factor between 2 (no filtering) and 5 (extensive filtering). This is based on the fact that radiation dose increases with tube voltage by the second to fourth power, depending on filtering. In a study by Felsenberg et al (6), the factor was found to be about 3 for 125 kV versus 85 kV for a Somatom DRH CT scanner. This increases the factor to about $3 \times 25 = 75$ (50 to 125). If the 0.69 mSv quoted in the NRBP publication (3) is divided by 75, one gets 9 $\mu$Sv (6 to 14 $\mu$Sv). Incidentally, it appears not only that the surface doses at the location of the parotids are similar for both techniques, but also that this estimated value for effective dose of our CT protocol (6 to 14 $\mu$Sv) is most certainly of *similar magnitude* to the values estimated by White et al (1) for panoramic radiography (5 to 10 $\mu$Sv).

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## MR Analysis of the Corpus Callosum

We read with interest the recent article by Kier and Truwit, "The Normal and Abnormal Genu of the Corpus Callosum: An Evolutionary, Embryologic, Anatomic and MR Analysis" (1). The authors have carried out a method for the study of the genu of the corpus callosum (CC), using a line connecting the mamillary body–anterior commissure–CC (the MAC line). In 1800 patients with a normal CC studied with magnetic resonance (MR), the genu projected anteriorly to the MAC line. Retrospective analysis of 113 patients with abnormalities of the CC was also performed. The authors report no cases in which only the genu was present in its normal position, and in which the body and the splenium were absent.

On the basis of these data, on genu development in human fetuses at different gestational ages, and considering that in 18 cases the entirety of the CC lies behind or at the MAC line, the authors hypothesize that the CC does not develop in an anterior-to-posterior direction, but bidirectionally starting from the anterior body. Is the presence of

the CC behind the MAC line in the pathologic cases caused by the absence of the genu? Could a genu presenting a delayed or absent forward movement be considered instead? Why not consider that what is seen behind the MAC line in their Figure 8, defined by the authors as "genulike," as the genu of the CC, even if only rudimentary?

We have recently set up two methods for the evaluation of the morphology of the CC, both in its entirety and in single portions: the angle method (2) and the grid Talairach application (3). As far as the genu of the CC is concerned, our data show that the totality of the healthy subjects evaluated (58 cases) did not show alterations, whereas in a group of syndromic patients (62 cases), alterations of the genu were found in 8 cases with the angle method and in 3 cases with the Talairach grid method. Moreover, a reduced thickness of the genu as an isolated finding has never been reported; instead, it has been observed in global hypoplasia of the CC (3 patients). In 13 patients, a reduced thickness has been observed in the posterior portion of the CC.

On the basis of our data, we believe that only the simultaneous use of several methods in each case can demonstrate a morphologic alteration of the CC and, in particular, of the genu. In fact, the use of several methods is needed because each one is specific to point out certain characteristics (thickness, morphology of the entirety of the CC and of its single parts, position of the CC in relation to other cerebral structure). Moreover, two of our syndromic subjects exhibited CC hypogenesis. In neither one did we observe hypogenesis of the genu. Instead, in these patients we observed, as referred by the same authors, the presence of the genu and also of the anterior portion of the body.

Nevertheless, we do not believe such a finding is the proof that the embryogenic development of the CC starts from the body and proceeds in an anterior-posterior direction. It could be possible if the development of the different portions (first the body followed by the genu, splenium, and rostrum) is asynchronous, although this path of development seems unlikely. Moreover, the hypothesis that the CC develops first in the region of the anterior body and grows bidirectionally should be supported by the simultaneous finding of hypogenesis or reduced thickness of the genu and of the posterior portion of the body or of the splenium, a finding that has not to our knowledge been reported. On the contrary, we have found only an isolated hypogenesis or a reduced thickness of the posterior portion of the CC.

In conclusion, even if the bidirectional growth of the CC is an interesting and possible hypothesis, we believe that further studies on a larger number of cases, especially in the embryonal period, both neuroradiologic, anatomic, and most of all histologic (to show the origin of the different fibers), are needed for a final validation.

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*Reply*

We appreciate the interest of Drs Gabrielli, Carloni, and Coppa in our article. We agree that in some pathologic cases, a rudimentary genu is present behind the MAC line. In the legend of our Figure 8 we state that the anterior end of the corpus callosum may represent the genu remaining in its early fetal position. This is in agreement with the first two questions posed by Drs Gabrielli, Carloni, and Coppa.

As described in our article, the MAC line was selected because the mamillary body and anterior commissure can always be identified on an adequate sagittal MR image of the brain. It is easy to apply in an everyday clinical setting. We were aware that several other methods for studying the topography of the CC have been described in the literature, including the ones by Drs Gabrielli, Carloni, and Coppa. However, our article did not concern itself with the overall topography of the CC, and the MAC line was not compared with other methods. The MAC line was found to be most useful in the evolutionary and embryologic analysis of the genu. As stated in the introduction of our article, the use of the MAC line was presented in 1989.

We agree with Drs Gabrielli, Carloni, and Coppa that the use of several methods of CC analysis in pathologic cases can be of help in the analysis of the underlying abnormalities. We also agree that the theory of bidirectional growth of the CC could benefit from validation by further study.

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## CT Angiography of the Circle of Willis: Is Spiral Technology Always Necessary?

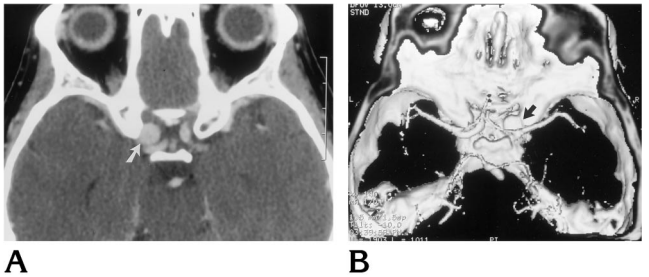
The development of spiral CT has greatly advanced the technique of CT angiography. Fast data acquisition allows coverage of a large area during the arterial or venous phase of an intravenous contrast bolus. Depending on the area to be scanned and the clinical question, the timing of the injection relative to the start of scanning can be adjusted to produce high-quality angiograms. The success of CT angiography is evidenced by its increasing acceptance as a routine exam. However, this procedure is not performed in some centers because of a lack of a spiral

scanner. Although conventional CT scanners are being rapidly replaced, many are still in heavy use. Lack of spiral technology does not necessarily negate CT angiography. In fact, a few authors report success using nonspiral CT angiography techniques (1, 2).

Ideally, CT angiograms are performed using a spiral technique. However, when a spiral scanner is not available, a CT angiography protocol designed for use on a nonspiral scanner can be implemented. Our protocol uses a total of 90 mL of nonionic contrast administered at 3 mL/s, with a 15-second scan delay. We use the dynamic serial axial acquisition mode on a nonspiral CT scanner (HiLight Advantage, General Electric Medical Systems, Milwaukee, Wis) with 140 kVp, 170 mA, 2-second scan time, 1.5-mm collimation and table speed, and 3.5-second interscan delay, which can generate 17 images and a maximum coverage area of 25.5 mm. The images can be reconstructed using the same techniques as with images acquired with a spiral technique.

Using a nonspiral technique, the circle of Willis can be well delineated with adequate visibility of bone and vascular detail. The major limitation of nonspiral CT angiography is less coverage area and decreased visibility of the more distal segments of the anterior, middle, and posterior cerebral arteries. Screening patients eligible for this technique is highly selective and is based on an understanding that nonspiral CT angiography is limited by its inherent slower image acquisition time and smaller area of coverage. As judged by our neurosurgeons, the quality of the spiral and nonspiral examinations is comparable (Figs 1 and 2). Like spiral CT, the milliamperes and peak kilovolts can be adjusted to maximize the area of coverage. Our maximum coverage area without severely reducing image quality is 46.5 mm (31 images) with 120 kV(p) and 140 mA using a 2-second scan time.

This nonspiral technique cannot be substituted in all indications where spiral CT angiography is used in neurovascular imaging. It should be limited to regions in which the exam requires only a short distance of coverage. For larger structures such as the aorta, this can be problematic; however, in neurovascular imaging there are three

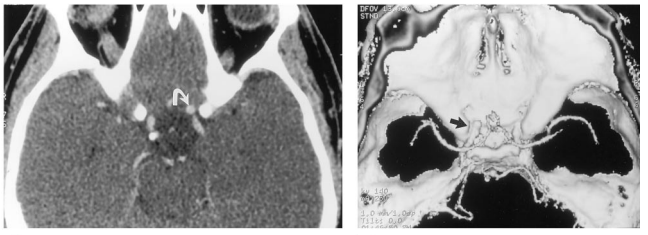


A B

Fig 1. A 44-year-old woman with a carotid ophthalmic aneurysm.

*A*, Axial source image from nonspiral CT angiogram shows aneurysm (*arrow*).

*B*, Shaded surface display projectional image from nonspiral CT angiogram shows relationship of aneurysm to anterior clinoid process (*arrow*).



A B

Fig 2. A 34-year-old man with a carotid ophthalmic aneurysm.

*A*, Axial source image from spiral CT angiogram shows aneurysm (*arrow*).

*B*, Shaded surface display projectional image from spiral CT angiogram shows relationship of aneurysm to anterior clinoid process (*arrow*).

sites where this technique may be applicable. The circle of Willis, which spans a short craniocaudal distance, is an ideal site for nonspiral CT angiography. The carotid bifurcation and vertebrobasilar system can also be studied, but the region of interest would have to be focused to the carotid bifurcation itself or a specific segment of the vertebrobasilar system. Use of this technique in these locations requires realization that a tandem stenotic lesion might be excluded from the area scanned; thus, we can recommend use of the technique for stenotic disease only when correlative studies are available to target the exam to a specific region. This type of focused exam could provide useful anatomic data for correlation with the physiologic flow data of carotid ultrasound and/or MR angiography when these exams are inconclusive.

We believe that in selected cases nonspiral CT angiography can be substituted for spiral CT angiography without a significant sacrifice in image quality. For centers without spiral scanners, this information should increase the options available for neurovascular imaging. For centers that have both spiral and nonspiral scanners, this information can increase flexibility in scheduling and possibly patient throughput.

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*Comment*

The letter from Dr Brown et al raises some interesting points but causes some concern for us. We agree wholeheartedly with their statement that the development of spiral CT has greatly advanced the technique of CT angiography. As they point out, spiral CT is gaining increasing acceptance as a routine examination. We believe that some of this growth can be attributed to the judicious evaluation of spiral CT in a blinded fashion when compared with other accepted imaging modalities. We also agree with their statement that CT angiograms should ideally be performed using a spiral technique. Spiral CT angiography has several advantages over conventional CT angiography not fully pointed out in the preceding letter.

Spiral CT angiography provides a volumetric acquisition that allows overlapping reconstructions of the data to be created (for example, a set of 2-mm collimated sections can be reconstructed at 1-mm increments). This has been shown to result in improved longitudinal spatial resolution and reduced "stair-step" artifact on multiplaner resolution or 3-D renderings when compared with nonoverlapping reconstructuring (1). Overlapping sections cannot be reconstructed with a conventional CT scanner unless overlapping sections are acquired by advancing the table less than the collimator width between scans. However, this strategy requires that more sections are acquired to cover the same distance, increasing exam time and the radiation dose. Overlapping reconstructions from spiral scan data involve no additional radiation.

A second major difference between spiral and nonspiral CT angiography is that the spiral CT technique allows for rapid coverage along the longitudinal axis at the same time that peak enhancement of the vasculature is obtained by a bolus injection. For example, we typically image the cervical carotid artery during a 30-second contrast bolus using a 3-mm/s table speed and 2-mm section thickness, giving a total of 9 cm of coverage in a 30-second scan time (2). In the circle of Willis we can reduce table speed and collimation to improve image resolution and still obtain excellent coverage with spiral scanning. Here we may typically use 1.0-mm collimation and 1.3-mm/s table speed to scan for 40 seconds over 5.2 cm (3). By imposing a bolus duration that is close to the scan duration, enhancement is maximized throughout the scan. If this strategy were used for nonspiral scans, the bolus duration would have to be substantially longer, requiring a reduced contrast flow rate and/or increased volume.

The acquisition characteristics described by Brown et al require 5.5 seconds per section (2-second scan time plus 3.5-second interscan delay) and generates 17 images over a 2.55-cm distance. This necessitates a total scan time of 93.5 seconds. They further state that with alterations in peak kilovolts and milliamperes, 31 images can be acquired (4.65 cm), but this would require 170.5 seconds. In contrast, spiral CT performed with 1-mm collimation and a pitch of 1.5 would result in superior longitudinal resolution, yet require only 31 seconds to acquire 4.65 cm. Brown et al call for the use of a 30-second-long bolus for their proposed study of the circle of Willis, which enables them to maintain a rapid bolus (3 mL/s flow rate). However a bolus duration of only 30 seconds is 18% to 32% of their total scan time (using either of the two protocols they proposed). This strategy will therefore result in lower levels of arterial enhancement on the majority of images and may even limit diagnostic accuracy. In addition, the distances covered even with the long scan time are clearly rather limited, varying between 2.55 cm and 4.65 cm using the suggested protocols. As Brown et al therefore point out, the use of this technique in locations such as the carotid bifurcation or vertebrobasilar system does not allow for evaluation of long segments of vasculature and lowers the likelihood of discovering tandem stenotic lesions.

Finally, we would be cautious about the success Brown et al describe having been reported using nonspiral CT angiography techniques. Two examples are in the area of aneurysm detection, a 1982 paper by Asari et al and the 1992 paper by Aoki et al. These were collected retrospective experiences of 15 patients each that were evaluations of aneurysms with CT angiography directly compared with conventional angiography. Neither of these papers speaks to the issue of sensitivity or specificity in the detection of these lesions and they certainly do not compare the technique with spiral CT angiography. It is in the area of aneurysm detection that the most circle of Willis studies have been done using both spiral and nonspiral techniques. We are aware of two blinded comparisons between nonspiral CT angiography and conventional angiography evaluating aneurysm detection. A study by Ogawa et al (4) evaluated detection rates for 73 aneurysms using two blinded readers and found sensitivities of 67% and 70%. They used a faster scan protocol than suggested by Brown et al with 3.5 seconds per section, to obtain 25 sections in 87.5 seconds. They also injected their bolus at a slower rate (1.0 mL/s with 100 mL total). Eighteen (25.7%) of 70 aneurysms were in the imaging volume but not seen by either observer. Three aneurysms were outside of the imaging volume and the authors concluded that this problem has been solved "by the use of helical CT, by which a large imaging volume can be covered in a shorter time." A second study by Hope et al (5) evaluated 94 aneurysms in 63 patients. This study used 2-mm sections with 1-mm overlap to obtain 30 sections. They describe a "fast-scan" protocol that gives 7 sections per minute and therefore requires 4 minutes 17 seconds. Over 2 minutes, 120 mL of contrast was administered (1 mL/s). Therefore, a low bolus rate was used over less than 50% of the scan time. Nevertheless, the authors report a sensitivity of 90.4%. However, they report a specificity of only 50%, suggesting a high number of false-positive calls. This certainly would be disconcerting if a patient were triaged to aneurysm surgery on the basis of such a result. The authors also experienced false-negative results caused by aneurysms outside the

imaging volume and, as with the previous paper cited, they suggested this would be improved with helical scanning. Similar retrospective experiences have been reported for spiral CT angiography; in addition, blinded comparisons with conventional angiography have shown rates of sensitivity and specificity rivaling another noninvasive technique, MR angiography (6–8). Sensitivities for spiral CT angiography appear to be similar or higher than those reported by Ogawa et al (4) and Hope et al (5) for nonspiral CT angiography, with rates of 87% to 96% (7–9). However, comparison of these results can be misleading and could well relate to the number of small aneurysms (<5 mm) in an individual series.

It is not our aim to say that the nonspiral technique is not as good as spiral CT angiography for aneurysm detection based on the results obtained in one blinded study as compared with another study. Indeed, these limited studies cannot be directly compared. Instead we would point out that there are inherent advantages of spiral CT angiography over nonspiral angiography. Rather than suggest, as Brown et al have, that centers with both spiral and nonspiral scanners implement their nonspiral scanners for angiographic evaluation, we would recommend that centers instead use their nonspiral scanners for conventional anatomic studies, reserving more time on their spiral units for CT angiography when it is needed. This begs the question about what should be done in the institution without spiral scanning capability. Unfortunately we do not feel that there are adequate data to make a concrete recommendation. We can only advise caution in the face of what at best could be described as limited data regarding the efficacy of nonspiral CT angiography.

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## Does Papaverine Cause Endothelial Injury in Clinically Relevant Doses?

We read with interest the recent article by Yoshimura et al, "Intraarterial Infusion of High-Concentration Papaverine Damages Cerebral Arteries in Rats" (1). Intraarterial papaverine has been used in the treatment of vasospasm in a variety of settings such as subarachnoid hemorrhage, catheter-induced vasospasm, and vasospasm after resection of arteriovenous malformation or after trauma (2). Several dose regimens have been suggested for injection in the internal carotid artery (ICA) or by superselective injection into the proximal branches of the intracranial vessels (2). As early as 1974, Johansson (3) showed that intravenous papaverine increased blood-brain barrier vulnerability during induced hypertension in cats. We therefore share the authors' concern regarding vascular injury with intraarterial papaverine. We have some reservations, however, regarding the clinical applicability of their findings.

The average brain weight of adult rats weighing 250 to 300 g is approximately 1.9 g (D. S. DeWitt, D. S. Warner, personal communications). Under pentobarbital anesthesia (50 mg/kg intraperitoneal injection) the cerebral blood flow (CBF) decreases by approximately 40% and in rats is about 60 mL/100 g per minute (4, 5). Assuming these values for brain weight and CBF, the total CBF in rats under pentobarbital anesthesia is approximately 1.14 mL/min. Let us further assume that under these conditions approximately two thirds of the cerebral blood flow is through the carotid arteries and one third through vertebral arteries. Hence, blood flow through each carotid artery of a rat under pentobarbital anesthesia is 0.38 mL/min.

In their study, the authors varied the drug concentration as well as the rate of infusion. The total volume of drug solution infused was kept constant at 0.2 mL. The total infusion time was set at 0.1 (6 seconds), 1, and 10 minutes. We can therefore calculate the concentrations of papaverine in blood irrigating the distribution of the ICA territory by dividing total dose of drug by total flow through the ICA during the infusion. From the calculations shown in the Table, it is evident that when papaverine is infused at a rate of 2 mL/min into the rat ICA, the volume of drug solution delivered in 6 seconds (0.2 mL) exceeds the volume of blood irrigating the ICA territory (0.04 mL) by an order of magnitude. If we assume no reflux or leakage of

**Equivalent human doses likely to cause endothelial injury**

| Infusion Time, min* | Concentration (w/v), %/Total Drug, mg* | Rat ICA Territory Blood Flow Volume, mL (ICA Territory Blood Flow × Infusion Time) | Total Rat ICA Territory Flow Volume, mL (Rat ICA Territory Blood Volume + Drug Volume) | ICA Concentration, mg/mL (Total Dose/Total Rat ICA Territory Blood Volume) | Human ICA Territory Blood Volume, mL (96 mL/min × Infusion Time) | Equivalent Human ICA Injection Dose, mg (see text) | Injury%* (Area of Endothelial Injury/Area of Normal Endothelium) |
|---|---|---|---|---|---|---|---|
| 0.1 | 4/8 | 0.038 | 0.238 | 33.6 | 10 | 2021 | 31.9 |
| 0.1 | 2/4 | 0.38 | 0.238 | 16.8 | 10 | 1011 | 23.6 |
| 1 | 4/8 | 0.38 | 0.58 | 13.8 | 96 | 2021 | 7.2 |
| 0.1 | 1.4/2.8 | 0.38 | 0.238 | 11.8 | 10 | 707 | 15 |
| 10 | 4/8 | 3.8 | 4 | 2 | 960 | 2021 | 0 |

* Data from Yoshimura et al (1).

the drug solution, such a rapid injection results in a very high drug concentration in the blood perfusing the ICA territory. For example, infusion of 4% solution at 2 mL/min results in a blood concentration of 33.4 mg/mL of papaverine in the ICA distribution.

Based on our calculations, it seems that the vascular injury described by Yashimura et al occurred with an ICA territory blood concentration of ≥11.8 mg/mL. To calculate the dose of papaverine required to produce a similar concentration in the human ICA distribution, we need to estimate the human carotid blood flow in conditions in which intraarterial papaverine is likely to be used, for example, after subarachnoid hemorrhage. In patients with grade III or IV subarachnoid hemorrhage, the CBF is approximately 30 mL/100 g per minute (6). If we consider the worst-case scenario and assume a CBF of 20 mL/100 g per minute, the net blood flow to the human brain weighing 1200 g is 240 mL/min. Approximately 40% of the total CBF in humans is provided by each carotid artery (7). Thus, during severe vasospasm each ICA will provide 96 mL/min of flow to the brain. We can then calculate the dose of drug required to produce a desired blood concentration of papaverine in ICA territory of a patient by using the formula: dose of papaverine required (mg) = $V_{ICA} \times C_d \times C_f/(C_d - C_f)$, where $C_d$ is the concentration of the drug solution (mg/mL), $C_f$ is the final concentration in the ICA (mg/mL), and $V_{ICA}$ is the volume of blood irrigating the ICA territory (mL) (infusion time [min] × blood flow in ICA [mL/min]). By applying this formula we can deduce that in order to achieve a blood concentration of 11.8 mg/mL of papaverine in the human ICA distribution, we would need to inject 707 mg of the drug or 51 mL of a 1.4% drug solution in 6 seconds.

Intracarotid papaverine for clinical use has been infused more slowly: a 100 mL of 0.3% solution is usually infused over 20 to 60 minutes (8–13). Rarely, slightly higher doses of the drug have been used clinically (14). By applying our assumptions to a patient with vasospasm with an ICA flow of 96 mL/min and receiving 100 mL of 0.3% solution of papaverine over 20 and 60 minutes (8–13), we obtain a blood concentration of papaverine in the ICA territory of 0.05 and 0.16 mg/mL, respectively. In our own study, using more distal infusion sites, 7 mg/min papaverine at a flow rate of 1 mL/min was infused into a second- or third-division branch of the middle cerebral artery. The calculated blood flow to the pedicles was approximately 20 mL/min, yielding a blood concentration of 0.35 mg/mL (2).

In conclusion, the delivered concentrations of papaverine for clinical use are two orders of magnitude less than the concentration found by Yoshimura et al to be toxic to the cerebral vasculature. We would caution against extrapolating their results to the clinical use of intraarterial papaverine and making any conclusions about the therapeutic index of the drug for human use.

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*Reply*

Favorable results have been reported in patients receiving intraarterial infusions of papaverine in the treatment of cerebral vasospasm after subarachnoid hemorrhage (1–5). Others encountered complications during the infusion of papaverine (6, 7) and papaverine-resistant vasospasm has been reported (8). Because inappropriate doses and/or concentrations may result in unfavorable clinical outcomes, we undertook our experimental study to call attention to the toxic effects of papaverine on the cerebral artery. We realize that the delivered concentrations of papaverine in the clinical setting are orders of magnitude smaller than the concentrations used in our experimental study and in our discussion we warned against extrapolating our results to the clinical use of intraarterial papaverine.

We posit that "selective" infusion at the cervical ICA is less effective than "superselective" infusion because the former method does not allow the targeting of a particular branch with severe vasospasm for dilatation. As shown in Figure 3A, infusion of 50 mL of 0.4% papaverine at the ICA did not produce dilatation of the right anterior cerebral artery (ACA), which was the site of severe vasospasm. However, as shown in Figure 3B, the superselective infusion of 10 mL of 0.2% papaverine at the origin of the ACA resulted in dilatation. When papaverine is infused superselectively at the severely spastic artery, the microcatheter almost completely occludes the vessel, especially when the site of infusion is the ACA, the distal middle cerebral artery, basilar artery, or their branches. Under these conditions, the concentration of the papaverine solution is not diluted by the cerebral blood flow and the delivered concentration is in direct contact with the vascular endothelium. In addition, even when papaverine is infused at a more proximal site at a slower infusion rate, the solution is not always adequately diluted and some of the infused papaverine reaches the important arterial branches in laminar flow mode near the infusion site (eg, the lateral striate arteries, the anterior choroidal artery, the perforating branches of the basilar artery).

We have reported that 0.2% papaverine completely dilated the spastic artery after subarachnoid hemorrhage in the clinical setting and that this concentration effectively dilated the normal artery in our in vitro experiments (4). In 1992 we presented favorable clinical results when 0.2% papaverine was infused at a flow rate of 1 mL/min at distal spastic arteries that could not be treated with balloon angioplasty (1). Since then, we have infused papaverine at the top of the ICA and have found this method to be effective, especially in patients with diffuse vasospasm (5).

On the other hand, infusion at the top of the ICA required higher doses or higher concentrations of papaverine to obtain dilatation of proximal portions of intracranial arteries (5). In our experience, transient neurologic deficits, including hemiparesis and consciousness disturbance, occurred more often at higher concentrations of the drug (0.8% to 1.4%) than at higher doses of 0.2% or 0.4% papaverine. Transient severe neurologic events in patients treated with intraarterial papaverine have also been reported by others (6, 7). Conversely, in our experience, the infusion of low concentrations of papaverine tended to be less effective, required longer infusion times, and resulted in irreversible neurologic deficits. As our literature search did not discover earlier studies of the toxicity of intraarterial papaverine on the cerebral vasculature, we designed a study in which we examined the effects of papaverine on the cerebral vasculature of rats.

According to Joshi et al, they infuse papaverine at 7 mg/mL per minute at a second and third division branch of

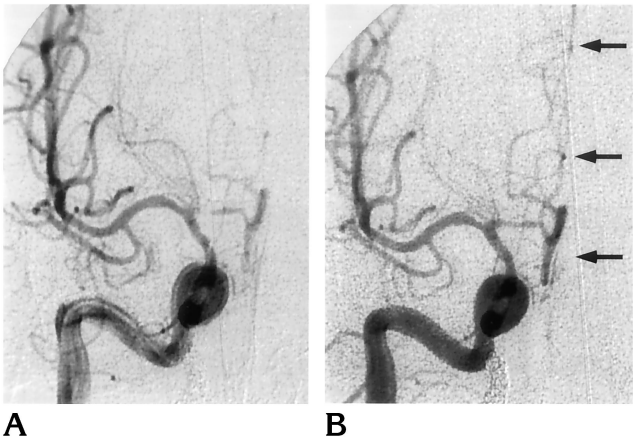


Fig 3. *A*, Right carotid angiogram shows a residual severe vasospasm at the anterior cerebral artery after intraarterial infusion of 50 mL of 0.4% papaverine at the internal carotid artery (*arrows*).

*B*, Right carotid angiogram shows complete dilatation of the anterior cerebral artery after superselective infusion of 10 mL of 0.2% papaverine at the origin of the anterior cerebral artery.

the middle cerebral artery, and calculate the infused concentration as 0.35 mg/mL taking into account cerebral blood flow. We counter that the microcatheter used for the infusion almost certainly occludes the narrow, severely spastic vessel, resulting in its exposure to 7 mg/mL papaverine. To date, there is no published evidence whether even at doses as high as 7 mg/mL papaverine induces microinjury to the endothelium of the artery.

It is necessary to determine the upper concentration limit of papaverine for superselective infusion in the clinical setting. In the rat model, it is almost impossible to achieve topical infusion to a cerebral artery. Therefore, we attempted to mimic this situation to determine whether high concentrations of papaverine result in damage to the cerebral artery. To gain a better understanding of the toxic effects of superselective papaverine infusion, models using larger animals, for example dogs or monkeys, should be examined.

We suggest that it is necessary next to examine the safety and efficiency of papaverine infusion combined with one or more other drug(s) in the treatment of cerebral vasospasm and to develop safer and more effective drugs for the clinical setting.

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Erratum

The August article “Thrombogenicity of Hydrophilic and Nonhydrophilic Microcatheters and Guiding Catheters” by Kallmes et al (*AJNR* 1997;18:1243–1251) failed to mention that the project was funded by Target Therapeutics Inc, Fremont, Calif.

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