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## Why Should Neuroradiologists Study Patients with Smell Loss?

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*AJNR Am J Neuroradiol* 2003, 24 (4) 556-557

<http://www.ajnr.org/content/24/4/556.1>

This information is current as  
of June 3, 2025.

## The Promise of Computational Fluid Dynamics As a Tool for Delineating Therapeutic Options in the Treatment of Aneurysms

In this issue of the *AJNR American Journal of Neuroradiology*, Steinman et al, in their article, "Image-Based Computational Simulation of Flow Dynamics in a Giant Intracranial Aneurysm," show the *potential* usefulness of computational fluid dynamics (CFD) as a *practical* tool that can be used in the diagnosis, therapeutic planning, and postoperative monitoring of patients with intracranial aneurysms. Clearly, the computer resource requirements for the simulations performed in their study preclude such immediate applications with the use of single personal computers or workstations. However, as discussed later, this gap can actually be bridged by using currently available, state-of-the-art supercomputer systems.

One of the most important points made by Steinman et al is that the technology is now available (eg, computed rotational angiography) to generate patient-specific geometric data that can be directly integrated into a flow simulation code, which can then be used to accurately describe, in spatial and temporal detail, the hemodynamics relevant to that specific patient's aneurysm. This is a logical extension of computational modeling of aneurysms in which great progress has been made during the last decade (1–4). Armed with this information, and with the additional capability of using the code to make predictions of the hemodynamic implications of several possible therapeutic options, the physician will be in a much better position to find an optimal procedure for the patient.

Steinman et al include examples showing how the very complex 3D, unsteady velocity, pressure, and shear stress fields associated with aneurysmal flow can be visualized. It is important to note that because of the constraints imposed by publication in a paper journal, the authors have been unable to show the true power currently available in computer visualization. In practice, physicians and researchers using these tools can watch the flow evolution through the pulsatile cycle in slow motion or freeze-frame while zooming in on the relevant area of interest. Fully 3D visualization tools are now in common usage. I suspect that physicians engaged in careful study of these simulations will eventually develop powerful intuition regarding the behavior of fluid flow within the arteries, which has eluded them until now because such information has not been available in a comprehensible form.

Accurately simulating human blood flow is a daunting task. Blood is a very complex fluid, and the human vascular tree is too intricate to even consider representing in detail on any computer in the present or foreseeable future. Potentially important factors affecting hemodynamic evolution are two-phase fluid dynamics (particulates and liquids), non-Newtonian behavior, unsteadiness of pulsatile flow, and flexibility

and motion of vessel walls (5). Although present research to develop and improve models of all these elements of hemodynamics is extensive and ongoing, it is not possible to include all of them in any realistic, practical simulations. The real challenge is to establish a hierarchy of these factors and include those that are most important to the calculations at hand, considering computer resource constraints. Steinman et al chose to neglect wall motion and non-Newtonian and two-phase flow effects in their study. This is a reasonable approximation to make, considering that the emphasis in this work was on realistic vessel geometry. As the accuracy of the simulations improves or the type of blood flow being studied changes, the relative importance of the mathematical models being used must continually be reassessed. For example, the model used by Steinman et al may not be appropriate for the study of coronary artery flow, with constantly moving vessels, or the microcirculatory system, in which the erythrocyte diameter is comparable with that of vessels.

Equally important in performing hemodynamic simulations is striking a reasonable balance among the errors caused by the inadequacy of the mathematical models, the resolution limitations of the input geometry (computed rotational angiographic data), the accuracy of the numerical methods, and the spatial and temporal resolution due to the mesh generation and choice of time stepping. It is important to understand the inherent limitations of the computational simulations. It may make no sense to compute flow fields accurate to 1% if the input geometry is only accurate to 10%. Thus, code validation is an essential continuing component of CFD simulation work. In particular, any relevant fluid dynamic data that can be obtained from laboratory or clinical studies should be compared regularly with the simulations. At a minimum, this can help alert the investigator, for example, to significant errors in input geometry, which could be catastrophic in a patient-specific analysis. Improvements in laboratory and clinical fluid dynamic measurement capabilities can have a direct, positive impact on the accuracy and usefulness of the CFD simulations by helping to identify the relevant sources of error so improvements can be made. As more accurate in vivo data become available, validation comparisons such as those presented by Steinman et al can become more precise; instead of pointing out that the simulation dynamics were "broadly consistent" with the clinical data, more useful quantitative error estimates could be provided.

Future investigation in the study of the application of CFD to aneurysm treatment has two major tracks. The first is to understand as fully as possible the fluid dynamic factors leading to aneurysm formation and

rupture in general. The second, which was the main focus of Steinman et al, is to predict the hemodynamics for a specific patient and to predict the resulting flows after various possible types of intervention to assist the physician in making an optimal therapeutic choice. As the authors point out, "A number of specific hemodynamic factors—notably wall shear stress, pressure and mural stress, impingement force, flow rate, and residence time—have been implicated in aneurysm growth and rupture." However, additional research is needed to quantify the relative importance of these factors, how they might interact or correlate, and how they might relate to other factors such as mural imperfections and vessel geometry. For example, in locations common to the formation of saccular aneurysms, such as at the apex of an arterial bifurcation, it is known that maximal pressures can be two to three times greater than in the proximal artery (6). However, it is not clear whether aneurysm growth is due to a secular pattern of repeated stresses at that level or perhaps to an acute incidence in which pressures exceed those values. Once we have a better *quantitative* understanding of these hemodynamic issues, the value of the simulations in treating specific patients will significantly increase.

Although the application of the methods used by Steinman et al to real patients may seem unrealistic, considering the 72 hr per pulsatile flow cycle required for the computations on a 1-Hz Pentium III workstation, it is within the capability of present technology to reduce these numbers to a very realistic value. For example, the ASCI White System now running under the Accelerated Strategic Computing Initiative at Lawrence Livermore National Laboratory, has 8192 processors. On such a machine, the present calculations could be sped up by a factor of approximately 10,000, thereby reducing the computation time per cycle to a couple of minutes. With Moore's law (a doubling of data attenuation on computers every 18 months) appearing to be on track for the next 10 to 20 years, the sorts of simulations shown by Steinman et al will become accessible in the not-too-distant future.

If the medical community had sufficient interest in being able to avail themselves of such simulations, a national computational facility could be established (or an expansion of the 1000+ processor Beowulf cluster "Biowulf" at the National Institutes of Health Center for Information Technology could be planned), connected by the high speed Internet 2, that, with appropriate scheduling, would enable this application in the very near future at clinics around the country.

Since the late 1950s, CFD has played a major role in the development of more versatile and efficient aircraft. It has now become a "crucial enabling technology for the design and development of flight vehicles" (7). No serious aeronautical engineer today would consider advancing a new aircraft design without extensive computational testing and optimization. The potential of CFD to play a similar role in cardiovascular intervention is very high.

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## Mass Lesions of the Brain in AIDS: The Dilemmas of Distinguishing Toxoplasmosis from Primary CNS Lymphoma

In the years following the initial reports of AIDS in 1981, it was estimated that between 3% and 25% of AIDS patients in the United States would ultimately develop *Toxoplasma encephalitis* (1). Differences in the incidence of CNS toxoplasmosis reflected differences in the background rate of the parasitic infection among the population. The institution of primary prophylaxis, namely, the administration of antitoxoplasmosis therapy in the face of profound immunosuppression, has resulted in a significant decline in frequency of CNS toxoplasmosis. Following the intro-

duction of highly active antiretroviral therapy (HAART), there has been a further decline in opportunistic infections associated with HIV infection; however, the data regarding the effect of HAART on CNS toxoplasmosis remain controversial. Some investigators have noted as much as a fourfold decline in the clinical recognition of the disease and a similar decline in its presence at autopsy. Others have not found a statistically significant decline in its incidence.

Similarly, with the advent of the AIDS pandemic, the incidence of primary CNS lymphomas (PCNSL) in-

creased dramatically and, after CNS toxoplasmosis, is the second most common cause of space-occupying brain lesions in AIDS. As many as 0.6% of patients present with PCNSL concurrent with the diagnosis of AIDS, and early estimates suggested that 2% to 6% of AIDS patients would ultimately develop the disorder. Indeed, the incidence of PCNSL exceeds that of low-grade astrocytomas. Epidemiologic studies conducted since the introduction of HAART suggest a decline in the incidence of PCNSL in the AIDS population.

Usually, the patient with CNS toxoplasmosis will present with focal neurologic symptoms and signs often superimposed on a global encephalopathy. Mild hemiparesis is the most common focal finding. Headache, confusion, lethargy, brain stem and cerebellar disorders, and seizures are also observed (2, 3). These clinical features are virtually indistinguishable from those of PCNSL, which presents with confusion, lethargy, memory loss, hemiparesis, speech and language disorders, seizures, and cranial nerve palsies, in descending order of frequency. One clinical feature that is believed pathognomonic of CNS toxoplasmosis is chorea; however, it is a rare occurrence. Similarly, clinical or radiographic evidence of leptomeningeal involvement by PCNSL assists in distinguishing this disorder from toxoplasmosis.

In toxoplasmosis, neuroimaging usually reveals multiple nodular or ring-enhancing lesions with edema and mass effect. In one large study (3), only 27% of toxoplasmosis lesions were single on CT scans and only 14% on MR images. Most lesions occur in the basal ganglia (3, 4) and the frontal and parietal lobes (2, 3). The lesions of PCNSL on CT scans typically are hyperattenuated or isoattenuated, round or oval masses with homogeneous contrast enhancement and variable surrounding edema. They are often multifocal and periventricular in location. Leptomeningeal involvement may be seen. Although certain features may suggest either CNS toxoplasmosis or PCNSL, these disorders are frequently indistinguishable by neuroimaging.

Because of this diagnostic dilemma, the American Academy of Neurology published guidelines for the evaluation and management of AIDS-related intracranial mass lesions in 1998 (5). This algorithm was devised as a means to determine the need for early biopsy in the patient most likely to have PCNSL. It was predicated on the predictive values of a negative toxoplasmosis serology finding (<20% of AIDS-related CNS toxoplasmosis is associated with negative toxoplasma serology findings [3]) and of an isolated brain lesion for the absence of CNS toxoplasmosis (5).  $^{201}\text{Tl}$  single photon emission CT (SPECT) and positron emission tomography were considered optional in the algorithm.  $^{201}\text{Tl}$  SPECT has been shown to be useful in distinguishing lymphoma from non-neoplastic lesions in AIDS, but diagnostic inaccuracy persists. Similarly, metabolic studies of these lesions employing  $^{18}\text{F}$ -fluoro-2-deoxyglucose PET are also helpful in distinguishing between the infectious processes and lymphoma. The sine qua non for the di-

agnosis of CNS toxoplasmosis remained the clinical and radiographic response to antitoxoplasmosis therapy. Fortunately, the median time to neurologic response is 5 days, with a significant improvement present in more than 90% of patients by day 14 (6).

Other diagnostic measures have been suggested as means of distinguishing between the two conditions. CSF analysis by polymerase chain reaction for Epstein Barr virus and toxoplasmosis has been proposed as a means to diagnose PCNSL and CNS toxoplasmosis, respectively. Most clinicians are properly reluctant to perform lumbar punctures in the face of brain mass lesions, and these tests are not always diagnostic. MR spectroscopy has also been suggested in this context. However, many investigators question the value of MR spectroscopy and find that PET and SPECT studies may be more helpful.

The application of diffusion-weighted MR imaging with apparent diffusion coefficient (ADC) maps as a method to distinguish between these two entities is another contribution to our diagnostic armamentarium. Some caveats apply. Firstly, the number of patients in this study is small; there were only seven patients with CNS toxoplasmosis having a total of 13 lesions and only four with PCNSL having a total of eight lesions. Therefore, replication of the findings by a larger study is mandated. Most importantly, however, there was an overlap in ADC values between some of the toxoplasmosis lesions and some of those due to PCNSL. As a consequence, the technique is insufficient in itself to have diagnostic primacy. It does provide more data when determining whether to proceed to early biopsy for an AIDS-related mass lesion of the brain or to treat initially presumptively for toxoplasmosis. It will likely prove most useful, if validated, when incorporated with other parameters into an algorithm for the management of AIDS-related brain mass lesions.

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## A Radiologist with a Ruler. . .

The first day of residency, I was told that a radiologist looking for a ruler is a radiologist in trouble. During my fellowship in neuroradiology, we had a special ruler that was designed to identify shift of the pineal gland on the anteroposterior skull radiograph. The first-generation CT scanner made that ruler obsolete. We continue to train our residents and fellows in the tradition of training their eyes to identify and characterize abnormalities without the need for a ruler.

In this issue, Stafira et al found that qualitative evaluation of cervical spinal stenosis was subjective. Six neuroradiologists could not agree on the level, degree, or cause of cervical stenosis on CT or MR images in 38 patients. On the basis of these results, they recommend the implementation of semiquantitative measurement of the spinal canal on cross-sectional studies. Possible measurements discussed include a one-dimensional measurement similar to the formula used in the North American Symptomatic Carotid Endarterectomy Trial, a calculation of the ratio of the spinal canal to the vertebral body in the sagittal dimension (Torg-Pavlov ratio), or a calculation of the cross-sectional area from two measurements.

The results of this study are not particularly surprising. The difference between mild and moderate central canal stenosis and between moderate and severe central canal stenosis is blurred. Mild stenosis to one observer may be moderate to another. This is influenced by one's experience. During our careers in radiology, we fluctuate from being "overcallers" to "undercallers" based on the accuracy of our last call. With experience, the amplitude of these fluctuations decreases. The term "stenosis" itself is confusing. Our surgeons understand stenosis to mean surgical disease with significant spinal cord compression. Everything else is spondylosis.

The statistical methodology that the authors used is the standard methodology that is usually used in this type of analysis, but it is not a perfect measure of agreement. The  $\kappa$  statistic sometimes looks bad even when most observers agree. My impression from their data is that the agreement is pretty good for the degree of stenosis, particularly since the six radiologists were from various backgrounds with various training.

Stafira et al are correct that consistency in report-

ing is the most important factor in evaluating the efficacy of imaging studies and ultimately patient care. More accurately measuring the cross-sectional area or diameter of the cervical canal is likely to be more consistent, but may have limited clinical utility. The status of the spinal cord is the most important factor that influences whether a patient may benefit from decompressive surgery or whether further clinical investigations are warranted to rule out other causes of myelopathy. Houser et al (1) found a high correlation with the shape of the spinal cord and myelopathy on neurologic examination. Ninety-eight percent of patients with severe spinal cord compression, described as a "banana"-shaped cord, had myelopathy clinically, whereas the frequency of myelopathy decreased to 75% of patients with moderately severe cord compression and 71% of patients with moderate cord compression. A consistent and reproducible description of spinal cord compression may be more helpful than measuring the diameter, area, or ratio of the central spinal canal. Other contributing factors important in surgical decision making include cord signal intensity on T2-weighted images, cord caliber and shape (atrophy), involvement at multiple levels, and obstruction to the flow of contrast material in the subarachnoid space as seen at myelography. The eye can integrate multiple factors that cannot be described with a single measurement. Radiologic interpretation remains an art refined by years of experience.

Finally, the pathophysiology of myelopathy is complex. From data by Houser et al (1), 2% of patients with severe cord compression, 25% of patients with moderately severe spinal cord compression, and 29% of patients with moderate cord compression at imaging had no evidence of myelopathy clinically. Even with accurate and reproducible measurements, we must remember that our clinical colleagues are treating patients and not the images.

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## Why Should Neuroradiologists Study Patients with Smell Loss?

The practice of radiology is to understand human physiology and pathology hidden from ordinary clinical view. The accomplishments of radiology in this regard are legendary, beginning with initial observations of bone by Wilhelm K. Roentgen and continuing

to the present with developments of CT, MR imaging, PET scanning, and various functional paradigms that not only elucidate anatomic structures but also detail functions of various organs and vital physiological processes. But why study olfaction?

Loss of smell (hyposmia) is a common but hidden problem. It is common in the sense that current estimates suggest that 19 million people in the United States have some form of chronic smell loss (1, 2). It is hidden in the sense that most patients exhibit no outwardly obvious handicap associated with this loss and usually do not exhibit any nasal cavity pathologic abnormality. Yet, as a symptom, this loss reflects specific abnormalities in the biochemistry of the body. Hyposmia is a harbinger, a symptom of biochemical abnormalities in multiple organ systems that involve, among others, oncologic, nutritional, metabolic, endocrine, infectious, genetic, and hematologic processes (2). Drugs induce hyposmia (3), as does head injury (4). Patients with this symptom are not at risk so much of death as they are of eating spoiled food or becoming exposed to toxic gas. More commonly, patients are desperately unhappy because they cannot obtain gratification from eating, drinking, or appreciating odors that give the rest of us such great pleasure and social enjoyment. Another major issue related to smell loss is distortion, and patients with hyposmia may also develop phantom smell.

But why should radiologists be interested in this common but not deadly problem? The findings shown on standard radiographs, CT scans, and MR images of the brain and sinuses of these patients are usually normal except for a relatively small number of cases with sinusitis, nasal polyps, tumors of the nasal cavity, neuroepithelium, or olfactory bulbs. To investigate the underlying pathology of most of these patients, quantitative and objective methods had to be developed to evaluate smell sensation and the ability to obtain information about odors. This initial effort took the form of complex psychophysical tests involving measurements of thresholds and magnitude estimation similar to those obtained in audiology. Although useful, these tests are cumbersome, time consuming, and not always objective. What role does neuroradiology play in this problem considering that commonly used neuroradiologic studies are of little diagnostic value for evaluating this common symptom?

Multiple methods are available through which some degree of resolution of this problem can be obtained. Neuroradiologic tools such as diffusion-weighted MR imaging techniques have shown neural tracts (5) and may be used to identify underlying olfactory pathways from bulbs to the CNS, although these structures are small and difficult to identify. Labeled agents such as manganese have been placed directly into the nose of animals and can be followed by MR imaging along peripheral neural pathways directly into the brain (6, 7); these techniques have not been used in human studies but may offer a useful approach to stimulus entry and follow-through into the entire olfactory system. PET scanning offers functional evaluation of metabolically active brain regions responding to olfactory stimuli (8); however, the anatomic location of major olfactory structures at the base of the brain makes PET scanning inaccurate and difficult to quantitate. MR spectroscopy has been used to determine abnormalities in metabolite con-

centration and neurotransmitter levels (9) in specific CNS regions in which olfactory activation takes place. We (10) and others (11–15) have used functional MR imaging of olfactory function in the CNS. This technique has proved helpful to determine regional brain activation in normal study participants (10) and in patients with various forms of hyposmia (16, 17). These studies showed quantitative data that distinguished normal participants from patients with hyposmia (16–24). In addition, by using patients as their own control participants, we have developed techniques in which treatment that restored smell function to normal in previously hyposmic patients was shown to increase regional brain activation quantitatively in relevant olfactory pathways and CNS regions (18).

These functional radiologic studies deal with a complex and difficult problem. Olfaction is not a simple sensory phenomenon in which a single stimulus-response paradigm is paramount. Multiple brain subsystems impinge on this sense, such that emotion, memory, language, vision, and other sensory and cognitive phenomena influence the sensory function and thereby functional MR imaging responses to olfactory stimuli. Results of functional MR imaging studies in general, regarding variability in single participants and across participants, have been questioned (25, 26), which makes this task even more difficult. The skull can introduce multiple artifacts into functional MR images because of susceptibility effects, especially at the base of the skull near the orbitofrontal cortex. Data processing requires great care, and its analysis and noise in the system can be difficult to determine. Stimulus presentation, if not performed in a most simple manner, can introduce such profound artifacts that the olfactory signal intensity is deformed and lost among image processing artifacts.

These technical problems are compounded by clinical problems that further increase the unreliability of these results. Deformation of CNS signal intensity output can occur in the patients whom we are most interested in studying, such as those with dementia secondary to Alzheimer disease and/or vascular disease. Olfactory responses in these patients may be totally unreliable because memory, language, or emotional lack may bias results. Olfactory signals may also be deformed by these phenomena in patients with head injury if postconcussion syndrome is associated with exacerbated emotional responses but inhibition of memory and language responsiveness. Age can influence both subjective and CNS responsiveness because of changes in both peripheral (ie, olfactory epithelium) and CNS physiology, changes that may be identified by functional MR imaging (27). These problems reemphasize the need for objective, reliable, quantitative techniques by which olfaction can be measured and defective sensory pathways and responses identified.

In our experience, patients with smell loss can be identified only by objective means, using a quantitative technique to define their pathologic abnormalities. Only through the use of objective techniques can patients with hyposmia be identified, their symptoms

quantified, and their treatment followed. We think that functional techniques that are currently best understood and used by neuroradiologists are the methods that are best used to perform this task. Although currently available techniques will require further development, only through these methods can this important, common, but hidden clinical problem no longer be obscure. Just as development of blood sugar tests served to identify and characterize patients with diabetes, we think that the use of one or several of these techniques can serve to identify and characterize patients with hyposmia. Precise identification and localization of the abnormalities in the olfactory pathways will help to further define the nature of the pathologic abnormality and to evaluate the results of therapy. These tests are now available in the hands of qualified neuroradiologists and can be used to identify these patients. This effort opens a new and valuable large group of patients for neuroradiologists to study. Application of these new techniques will further the usefulness of neuroradiology in the practice of medical science.

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