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## **Reply**

Eric J. Russell

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## Dear Editor-in-Chief:

I wish to congratulate Eric Russell for his conscientious and thought-provoking commentary on the status of carotid stenting. The technique of carotid stenting is about to begin a new phase of additional rigorous scrutiny and investigation. The National Institute of Neurologic Disorders and Stroke (NINDS) recently has approved and funded a large multicenter, multinational, randomized, controlled trial comparing carotid stenting with carotid endarterectomy. The Carotid Revascularization Endarterectomy vs. Stent Trial (CREST) plans to begin training and credentialing interventionalists this summer, and recruitment is expected to begin late this year or in early 2000. The trial will address the relevant efficacy of carotid stenting and carotid endarterectomy in a North American Symptomatic Carotid Endarterectomy Trial (NASCET)-like population of patients with symptomatic high-grade stenoses. We anticipate that 2500 patients will need to be recruited to satisfy the statistical requirements of the study. It is essential that this landmark trial have the full involvement of and commitment from the neuroradiologic community.

This landmark trial is the initiative of a neuro-radiologist, Robert Ferguson, Chairman of the Department of Radiology at Queens University Hospital in Kingston, Ontario. After his pivotal work in organizing the North American Cerebral Percutaneous Transluminal Angioplasty Registry (NACPTAR), Dr. Ferguson collaborated with Robert Hobson, Director of Vascular Surgery at the New Jersey Medical School, Newark, New Jersey and the principal investigator of the VA Cooperative Trial of Endarterectomy, as well as with me and others, to form the CREST Trial group. Indeed, neuroradiologists have been instrumental in the rapid development and current success of this technique. Beginning with the pivotal and ongoing work of Jacques Theron in Caen, France and the pioneering contributions of Jiri J. Vitek at the University of Alabama at Birmingham, the technique has now gained wide acceptance. Eric Russell diminishes the rigor of the well-planned IRB-approved clinical trials that were begun at the University of Alabama at Birmingham in 1994 (1). The results of these well-conducted and critically audited prospective registries provided the clinical findings that gained the acceptance of physicians throughout the world and, more importantly, industry support, without which, further device and technique development would have been impossible. Most importantly, study participants were subjected to independent neurologic evaluation 24 hours postprocedurally, a standard to which the NASCET has never been held. The statement that no long-term outcome information is available is incorrect. Late results have been reported, and multiple groups now have confirmed the rarity of neurologic events after stent intervention (2). Similar-

ly, our experience has been analyzed carefully in terms of risk stratification on the basis of clinical symptoms and morphologic characteristics of lesions (3). Similarly, a great deal of information has been promulgated concerning the use of coronary wires and balloons to cross and predilate high-grade lesions. Furthermore, cerebral protection during stent placement is an active area of investigation, and current carotid stent symposia have focussed on a variety of new devices designed to provide cerebral protection. The political, regulatory, and reimbursement ramifications of this technique remain beyond our control. We consider the definition of carotid stenting as a significant-risk procedure to be quite arbitrary. This definition ignores the 6% incidence of death and stroke that occurs with carotid endarterectomy (4). In our most recent experience, we have completed 136 procedures with no deaths, no major strokes, and a 1.6% incidence of minor nondisabling strokes. In our institution, the neurologist would like to consider carotid stenting as the standard of care for their patients, but this technique remains incorrectly labeled as high-risk, federally unapproved, and nonreimbursable.

At least one prospective, randomized, controlled trial has been completed comparing carotid angioplasty (stenting in 1 of 3 of cases), to carotid endarterectomy. This trial compared the learning curve of the radiologists involved against the mature results of experienced vascular surgeons in major regional centers. The results from CAVATAS have been reported and will be published soon. There was no difference between the incidence of minor or major neurologic events in this randomized trial. I am confident that the CREST study will validate the results that have emerged from numerous registries throughout the world. The results of CREST, however, will not be available for at least 6 years. In the meantime, the CREST group will be conducting, with the NINDS and the FDA, industry-supported, rigorous, prospective registry studies in the very large population of patients who will never and can never be studied in prospective, randomized trials. Neuroradiologic involvement in carotid stenting has been pivotal in its development, and will continue to be essential if the procedure is to emerge as it should as a safer, more comfortable, and less invasive alternative to carotid endarterectomy.

Sincerely,

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### Reply

Dr. Roubin's comments concerning the *AJNR* commentary on carotid artery balloon angioplasty and stenting (CABAS) are welcome (1). Dr. Roubin is known as a thoughtful and innovative investigator, and he is commended for his approach to this evolving technology. He has treated a high-risk patient population, and yet has shown results competitive with surgical carotid endarterectomy (CEA). He understands the risks involved. Recently he has been quoted as saying, "It is important that a realistic and comprehensive classification of the neurologic complications be used when a newly evolving technique such as carotid stenting is evaluated." He has also asserted that "independent oversight when the incidence of neurologic complications is assessed cannot be overemphasized (2)." Unfortunately, these rules are not uniformly adhered to by all performing either CABAS or surgical endarterectomy.

His summary of events since the formulation of the previous commentary (1) provides an update of this fast-moving field. Dr. Roubin anticipates that the European CAVATAS trial, comparing angioplasty (with or without stenting) and CEA, will show no difference between either treatment approach or minor and major neurologic events. One hopes that publication of those results will include sufficient case material regarding stenting and an adequate categorization of degree of stenosis to provide guidance. There also will be a need to look carefully at patient data to consider whether this study will be applicable to practice in North America.

Dr. Roubin also suggests that the rigor of the well-planned, IRB-approved clinical trials begun at his former institution, the University of Alabama at Birmingham, was demeaned in the commentary (1). This is not what was written. In fact, the data from the referenced study were outlined in the commentary in a factual and favorable manner. That study, which included pre- and postprocedural neurologic evaluation, complete cerebral angiography, and appropriate use of neuroimaging follow-up, serves as a model for similar efforts. It is clear that Dr. Roubin's multidisciplinary group, which included an interventional neuroradiologist, deserves much credit for having the vision and drive to show that CABAS is a competitive technique.

Controversy in the initial phases of development of a new therapy is common and should not dissuade active pursuit of a potentially valuable technique. Nevertheless, the practice that prompted the commentary is the increasingly widespread promotion and performance of CABAS by those less

experienced, less thoughtful, and less competent than Dr. Roubin and his colleagues, before there is scientific proof of its safety and efficacy. It is natural that groups of physicians with appropriate individual or team expertise will continue to investigate this procedure, considering encouraging short- and intermediate-term outcome data already available. We must realize, however, that the favorable data to date comes from a few highly skilled teams. Others who also perform CABAS may not have adequate training and experience, and may not have comparable results. One recent report in the *Journal of Vascular Surgery* suggests that the learning curve for CABAS may be quite steep in some circumstances, despite internal institutional control of a carefully designed study (3). This recent European single-center study, meant to be a randomized comparison of CABAS and CEA, was halted when five of seven patients who underwent CABAS had a stroke.

Dr. Roubin also writes that the "statement that no long-term outcome information is available is incorrect," and he goes on to say that "late results have been reported and multiple groups now have confirmed the rarity of neurologic events after stent intervention." In support, he cites one reference to his own published abstract presented in 1996 (4). Despite that study's title, the abstract refers to only 22 cases maximally followed, and these were only followed for 6 months. For stroke disease prevention, this is characterized best as little more than short-term and certainly far from long-term. That this patient group was followed longer term is not indicated in the abstract; if that was done subsequently, the accurate peer-reviewed publication reference is anticipated. It is wondered, in fact, whether the patients were incorporated into a later (1997) report by the same group, discussed in the commentary (5), dealing with Palmaz stent collapse in 11 (16%) of 70 cases, requiring repeat angioplasty in five and stenting with an alternative device in three. The carotid is an artery that is apt to be subjected to a degree of mobility and torsion greater than others for which stents are approved for use, and caution about enthusiastic promotion before completion of randomized trials is appropriate.

The general call by many for long-term follow-up also relates to published data regarding the real incidence of restenosis after stenting in the carotid and elsewhere; an incidence perhaps higher than that observed with CEA (6-13). Also, we should remember that today's "best medical therapy" has advanced beyond that available in the past and that neither CEA nor CABAS have been compared with this advancing target.

It should not be forgotten that the target of CABAS therapy is the brain, not the neck, kidney, or heart. The most important risk of this procedure is atherothrombotic cerebral embolization, whether from clot formation on instruments or debris from treated plaques. Dr. Theron, a neuroradiologist whom Dr. Roubin properly credits as a CABAS in-

novator (14), has presented results showing that angioplasty and stenting shower particulate material with the potential to damage the brain (Annual meeting of the Radiological Society of North America [abstract], December 1998). From personal observation, intraprocedural and postprocedural neurologic testing is employed variably in the community during the performance of CABAS. Because avoiding, detecting, and treating any complication is a fundamental aspect of the practice of any medical procedure, direct intracranial endovascular rescue, which requires special expertise, should be an available option at any institution performing CABAS. In recognizing the essential role that the neuroradiologist plays in CABAS, Dr. Roubin also clearly appreciates the training and expertise that a neuroradiologist possesses. This is important for performing and interpreting the diagnostic neuroangiogram, and for performing intracranial vascular navigation and intra-arterial stroke rescue.

Dr. Roubin provides a welcome announcement of the recent approval of funding for the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) in North America. This landmark event, important and welcome, is in no small part because of the efforts of Dr. Roubin.

One hopes that within fewer than the 10 years required for NASCET, CREST will produce solid, randomized, clinical outcome data comparing appropriate parameters of nondisabling stroke, disabling stroke, and death for CABAS and CEA. The CREST trialists have an important responsibility to assure that their case material is at least as rigorous as the landmark CEA trials, with patient populations clearly defined.

With the CREST approval, there is the opportunity to caution that protocol methods be very precise in the definition of carotid stenosis measurement and other clinical parameters, striving to go beyond some limitations inherent in previous studies. For example, despite a well-organized and detailed method for verifying duplex sonographic assessment for carotid stenosis in centers participating in the ACAS trial, the ACAS data indicate that 8% of patients were declared ineligible for CEA after angiographic verification of the degree of stenosis (15). Most of this discrepancy was likely because of inadequate correlations between sonography and angiography, despite detailed planning.

For those patients who are excluded from conventional angiographic study in the CREST, it is hoped that an improved correlation with angiographic stenosis assessment beyond that of ACAS is being developed by CREST organizers for two reasons. First, improved correlation would enable the sufficient recruitment of CREST collaborators. Second, this improvement would help clarify the ambiguities others have highlighted in the multiple methods available for stenosis measurement. Although CREST investigators expect a "NASCET-like" patient population, how these patients will be categorized in CREST for various parameters, in-

cluding stenosis measurement, needs to be clear. Many authors during the last 5 years have referred to the so-called "NASCET method" of stenosis assessment from angiography without attention to the details of how the measurement was actually carried out in NASCET (6–20).

A commonly overlooked detail in NASCET methods is the assessment criteria of "near occlusion." Accurate assessment of "near occlusion" is important. This group of patients is at the highest risk for intervention, whether by CEA or CABAS. Skewing the patient population in either arm can alter the results of any trial. Measurement of the distal "normal" internal carotid, of course, will be misleading if the diameter has begun to decrease because of a critical proximal stenosis. When deemed appropriate to measure, the distal normal carotid was measured in NASCET "where the walls [were] parallel," another detail often not adhered to in publications claiming to use the "NASCET protocol."

Although there has been some lack of attention to detail in the literature regarding stenosis measurement, one hopes that CREST trialists will be very rigorous in detailing stenosis categorization. The collaboration of physicians from multiple disciplines, including some without the tradition of detailed evaluation of cerebral and cervical vasculature, demands a precise method of stenosis measurement. This precision should ensure that "NASCET protocol" stenosis measurement begins with a thorough assessment of the intracranial circulation from all potential routes in order to uncover subtle signs of near occlusion that are frequently encountered. Without this, the future results of CREST cannot be considered a true comparison and extrapolation from NASCET. Now that the NINDS has decided to support CREST, all those who have an interest in CABAS and CEA need to support the trial, and join to maximize its validity.

Dr. Roubin provides details concerning the preliminary registry studies for CABAS that have supported the planning and acceptance of the randomized CREST. He points out the importance of the basic data provided by the North American Cerebral Percutaneous Transluminal Angioplasty Registry (NACPTAR), but provides no references indicating where readers may review the data. Such studies are important but do not replace the need for the CREST, as Dr. Roubin is well aware.

According to the American Heart Association document, coauthored by Dr. Roubin and referred to in the initial commentary, "the technology and techniques for carotid angioplasty and stenting are available, as are a limited degree of experience and a high level of interest (21)." The relatively promising data this procedure yields at certain institutions is commendable and encouraging. Nevertheless, it must be appreciated that these results generally have been achieved by using numerous physical resources and involving investigators from many disciplines, and that there is no clear indi-



cation yet of safety and efficacy without the results of controlled trials. That CREST will perform a randomized trial is an important step forward. Experienced interventional neuroradiologic teams need to gear up to support this trial. At the same time, the patients for study need to undergo rigorous assessment and categorization within the trial so that its results will have broad-reaching application, as a natural extension of the recent, exemplary endarterectomy studies.

Sincerely yours,

Eric J. Russell  
Member, Editorial Board

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### Gradient- and Spin-Echo MR Imaging of the Brain

In their study comparing gradient- and spin-echo (GRASE) and T2-weighted fast spin-echo imaging of the brain, Rockwell et al (1) conclude that T2-weighted GRASE images are better at depicting lesions with paramagnetic susceptibility effects. Although this is likely true, as fast-spin-echo images have diminished susceptibility artifact, the authors fail to note previous reporting of hemosiderin-containing lesions from hemorrhage that were not visible on GRASE images but were seen on conventional spin-echo images (2). Therefore, neither GRASE nor fast spin-echo images should supplant gradient-echo images for the detection of hemosiderin.

Furthermore, we wish to caution readers that the contrast properties and sensitivity to detection of T2 hyperintense lesions on rapid, hybrid imaging sequences depend on the specific implementation of the pulse sequence, and particularly the k-space trajectory used for data acquisition (3-5). Two prior studies have shown that GRASE images have diminished sensitivity to T2 hyperintense lesions when compared with conventional spin-echo images (2, 6), although, admittedly, conventional spin-echo images may be more sensitive to small lesions than fast spin-echo images. Consequently, before reliance is placed on using rapid hybrid sequences in clinical practice, each site should develop its own experience and familiarity with these sequences.

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### Reply

I would like to thank Drs. Patel and Klufas for their interest and comments regarding our recent publication in the *AJNR* (1).

We agree with Drs. Patel and Klufas regarding the issue of paramagnetic brain lesion demonstration as a function of the MR imaging technique used. We have demonstrated that GRASE imaging performs better than fast spin-echo imaging in this respect. This can be explained by two factors. First, despite the implementation of multiple 180 refocusing RF pulses, the effects of static magnetic field inhomogeneity in GRASE imaging are not minimized to the same degree as in fast spin-echo imaging. This is related to the off-resonance echoes used to fill the periphery of k-space (2). The greater the number of these off-resonance echoes, the greater is their representation in the center of k-space and, hence, the greater is their contribution to the overall image signal. Second, the effects of time-varying magnetic field variability are more pronounced in GRASE compared to fast spin-echo techniques. This is related to differences between the two techniques regarding the shortest achievable time interval between the Hahn spin-echo. In GRASE imaging, this interval has to be longer in order to accommodate the multiple gradient-echo reversals (3-5).

Formal comparison between GRASE imaging and conventional spin-echo and gradient-recall echo imaging, as related to the demonstration of paramagnetic brain lesions, is lacking. We believe, however, that both conventional spin-echo and optimized gradient-recall echo readouts are superior for the demonstration of paramagnetic brain lesions to the GRASE technique currently in question. As a result of much longer echo-times (echo-spacing), selective T2 relaxation enhancement from molecular diffusion through regions of variable magnetic field is much greater in conventional spin-echo imaging than in GRASE imaging. The effects of accumulated phase and chemical shifts in the few non-Hahn echoes acquired in our GRASE technique are probably not enough to outweigh the differences in echo-times (echo-spacing). This, however, may not be true for GRASE techniques implementing a greater number of gradient echoes per 180-180 interval. Also, in gradient-echo recall imaging, with relatively long echo-times optimized for paramagnetic brain lesion detection, both static and time-varying magnetic field inhomogeneities contribute to selective T2 relaxation

enhancement, resulting in exaggeration of signal loss compared to GRASE imaging (6).

Hyperintense brain lesion demonstration on MR images depends on contrast resolution, spatial resolution, signal-to-noise, and artifacts related to human and technical factors. When contrast resolution, spatial resolution, and signal-to-noise are identical across the different MR imaging techniques, and the human factor is eliminated, conventional spin-echo techniques probably will be superior to the different fast hybrid spin echo-based techniques. This is because of the inherent technique-related artifacts. In both fast spin-echo and GRASE imaging, there is further modulation in signal along the phase-encoding direction related to T2-decay resulting from variable echo times. This modulation affects the spatial-encoding process in the phase direction and results in ghosting and blurring artifacts. These artifacts are proportional to the number of echoes per TR interval, the echo-spacing, and the scheme used to fill k-space. Shorter echo-spacing (between the echoes within a 180-180 interval) and nonsequential (interleaved) phase-encode ordering through the echo train in GRASE imaging actually may reduce signal modulation between segments of k-space compared to fast spin-echo techniques (7).

It is important to emphasize that, with fast hybrid MR imaging techniques, high temporal resolution can be exchanged for better spatial resolution, signal-to-noise, and contrast resolution (longer TR). In our study, a longer TR was used with the faster GRASE technique whereas the scan time per sequence similar remained the same. This may explain partially the better demonstration of hyperintense brain lesions on GRASE images. Also, fast imaging reduces the chance of human-related image artifacts. The effect of these artifacts commonly outweigh differences in inherent technique-specific artifacts.

We agree with Drs. Patel and Klufas that the advantages and disadvantages of fast MR imaging techniques compared to conventional spin-echo have to be tested in the clinical setting. In addition to differences in MR imaging hardware and software available at various clinical sites, practicing radiologists have to factor in the type of patients being imaged.

Continual improvements in MR hardware performance and pulse sequence design has and will continue to reduce the need for T2-weighted conventional spin-echo techniques. I also would like to point out that optimized high resolution (256 × 512 matrix), T2-weighted GRASE imaging already has replaced both conventional and fast spin-echo techniques for routine brain imaging at several clinical sites in Europe and the United States.

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### The Evolutionary and Embryologic Basis for the Development and Anatomy of the Cavum Veli Interpositi

I read with interest the recent article by Chen et al entitled, "Sonographic Characteristic of the Cavum Veli Interpositum" (1). The regional anatomy of the cavum veli interpositi is complex and difficult to understand. I would like to point out the following anatomic information that is in variance with some of the statements made in the above-mentioned publication.

The ependymal roof of the third ventricle is covered by a double layer of pia mater, the tela choroidea (2). The embryologic basis for this double-layered tela choroidea was outlined diagrammatically in 1932 By Frazer (3), modified by Brash (4), and reproduced in the neuroradiologic literature (5). It results from the overlapping of the third ventricle by the enlarging forebrain (Fig). During an early fetal stage, the prosencephalon and diencephalon are covered by a continuous layer of pia mater. With further brain development, the expanding cerebral vesicles of the forebrain, covered by its own pia mater, overlaps the pia mater of the third ventricle, resulting in the double-layered tela choroidea (velum interpositum) of the roof of the third ventricle. The anterior aspect of the tela choroidea, which is closed, is at the inter-ventricular foramen where the pia mater folds on itself. When the posterior end remains open, the potential space between the double layers of the tela choroidea forms the cavum veli interpositi that communicates with the quadrigeminal cistern. The internal cerebral veins are located between the two layers of the cavum veli interpositi (2).

Certain human embryologic changes are a "recapitulation" of evolutionary modifications. Therefore, examining the changing anatomy of various adult vertebrate brains facilitates understanding the overlapping of the third ventricle by the expanding human fetal cerebrum (5). In the shark's linear brain, the cerebrum is anterior to the diencephalon.

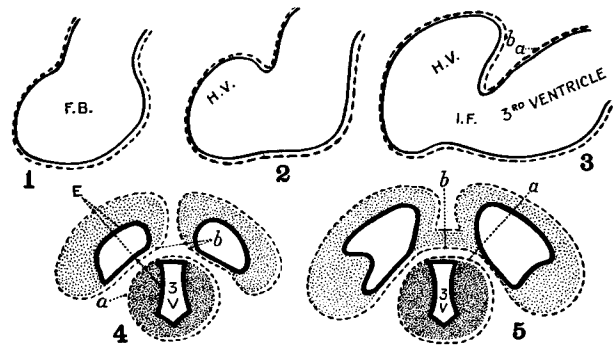


FIG. Diagram demonstrating the formation of the double-layered tela choroidea (velum interpositum) of the third ventricle in the human.

- 1) The developing neural tube includes the forebrain (FB) which is surrounded by the pia mater (broken line).
- 2) and 3) The expanding vesicle of the cerebral hemisphere (HV) carries its own pia mater (b) which overlaps the pia mater (a) of the third ventricle. IF signifies intraventricular foramen.
- 4) A double layer of pia mater (b, a) is interposed between the two cerebral vesicles and the third ventricle (3V). E signifies ependyma.
- 5) The two layers of pia mater (b, a) over the third ventricle persist after connection of the hemispheres by the commissures.

The entire roof of the diencephalon (third ventricle) is visible, and consists of a single layer of pia mater covered by a prominent venous plexus. In reptiles and primates, the expanding cerebrum overlaps the diencephalon, resulting in the double-layered tela choroidea of the third ventricle.

In summary:

- The velum interpositum is the double-layered tela choroidea of the third ventricle.
- The cavum veli interpositi is within the double-layered tela choroidea of the third ventricle, not superior to it.
- The internal cerebral veins are within the cavum veli interpositi, not inferior to it.
- The correct nomenclature is velum interpositum and cavum veli interpositi.
- Finally, a discussion of fluid-filled structures in the pineal region should include an enlarged suprapineal recess of the third ventricle. This recess may be quite large, and may extend posteriorly below the splenium (5, 6).

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### Reply

We would like to thank Dr. Kier for pointing out issues regarding the evolutionary and embryologic basis for the development and anatomy of cavum veli interpositi (CVI) in our recent article. First, we want to emphasize that we did use the term "Cavum veli interpositi" in our original submission. During the peer review process, however, a referee opined that "Cavum veli interpositi" is not an appropriate term. We agree with Dr. Kier that "Cavum veli interpositi" is probably more appropriate than "Cavum velum interpositum" (1, 2), which is rarely used in the literature. Relative to the issues of embryogenesis and formation of CVI and its related radiologic anatomy there are, to my knowledge, only a few published papers in the English-language literature (3, 4). The main point is whether the tela choroidea, by embryologic or anatomic definitions, includes the cisternal space of CVI at or near the term age of human brain development. According to Zellweger and van Epps (4), the tela choroidea of the third ventricle originates from the roof plate of the diencephalic region by a protrusion of a fold of pia mater into the primitive neural tube at about the third fetal month. With further development, the pia mater fold is pushed backward, forming the final tela choroidea of the third ventricle. It encloses a horizontal sac or fissure under the fornix, which opens behind and under the splenium of the corpus callosum where its pia mater is connected to the pia mater covering the median fissure of the cerebrum. The sac-like pia fold carries the name "transverse or choroidal fissure." In the majority of cases, the choroidal fissure closes. When it persists, the choroidal fissure is called "CVI or cisterna interventricularis." CVI is a true cisternal structure communicating with the quadrigeminal cistern, as has been shown by comparing pneumoencephalography and autopsy specimens (3). Some investigators suggest that it is a part of the anterior extension of the quadrigeminal cistern. There is no doubt that the tela choroidea forms the roof of the third ventricle; the tela choroidea itself is, by definition, the structure where the pia and ependyma approximate. It contains, however, a pair of internal cerebral veins, so it is debatable whether the CVI and its roof (the hippocampal commissure) still can be included as parts of tela choroidea or part of the third ventricle as it relates to radiologic anatomy. In the published literature, the anatomic location of this cavum has

been described frequently as above or superior to the third ventricle. The internal cerebral veins course within the tela choroidea on the roof of the third ventricle. Thus, anatomically, they are inferior or lateral to the CVI CSF space. Although our study did not aim to provide the embryologic evidence of the origin of the CVI, we reported that the color-coded internal cerebral veins on sonographic studies are anatomic landmarks to CVI. They are inferior or inferolateral to the CVI, but do not enter it. This raises a similar question as to whether the mega cisterna magna is a part of the fourth ventricle because it is now widely accepted that the mega cisterna magna is formed by the evagination of the tela choroidea of the fourth ventricle.

In summary, we believe:

- The velum interpositum originates from a fold of pia mater protrusion, which forms the final tela choroidea of the third ventricle.
- The cavum veli interpositi is a true cistern situated above (but not communicating with) the third ventricle.
- The internal cerebral veins form parts of the inferolateral or lateral boundaries of the CVI but are not anatomically within it.
- Both terms "Cavum veli interpositi" and "Cavum velum interpositum" have been used interchangeably in the English-language literature, and the former is more appropriate.
- An enlarged suprapineal recess of the third ventricle is a frequent finding in patients with obstructive hydrocephalus, but is extremely rare if ever seen as a normal variant in neonates and infants.

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