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Internal carotid balloon test occlusion does require quantitative CBF.

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FORUM

Editor's note: From time to time a particularly provocative Letter-to-the-Editor is received. Rather than include such letters as part of the "Letters to the Editor" feature, occasionally we will elect to have a "Neuroradiology Forum," in which the original comment, responses, and additional remarks solicited by the Editor are published. The following forum was stimulated by a comment contributed by Dr Howard Yonas et al.

Internal Carotid Balloon Test Occlusion Does Require Quantitative CBF

We would like to respond to the three articles in the Nov/Dec issue of *AJNR* (1–3) concerning the use of cerebral blood flow (CBF) studies with Tc-99m HMPAO SPECT as an aid for reducing the associated risk of stroke following acute internal carotid artery (ICA) occlusion. Risk assessment for acute ICA occlusion has been an area of great interest at the University of Pittsburgh. Over 400 balloon test occlusions (BTO) have been performed in conjunction with xenon-enhanced tomographic (Xe/CT) CBF measurement as an aid to guide decision making in patients who may require carotid occlusion. Although not consistently stated in all previous articles, our criterion for identification of patients with high risk for developing cerebral infarction has been asymmetrically reduced blood flow on the side of occlusion with the development of CBF values below 30 mL/100 g/min (4). We believe that using only the development of hemispheric asymmetry due to BTO is too sensitive and lacks adequate specificity for distinguishing a group of patients at elevated risk of hemodynamic infarction.

Based on the quantitative analysis of CBF response to BTO in a randomly selected group of patients ($n = 156$), we would like to support, but also advise caution, regarding some of the conclusions of the *AJNR* articles. Our concerns are based on our observation, which is similar to the results of Monsein et al (3), that, immediately following BTO, CBF may rise differentially either on the side of occlusion or on the contralateral side. Without absolute flow values, asymmetries at normal or even elevated CBF levels may be given unwarranted significance.

We agree with Peterman et al (1) and Moody et al (2) that, regardless of the technique utilized, having an ICA-occluded CBF study increases the sensitivity for detecting patients at higher risk for hemodynamically induced stroke after permanent internal carotid artery occlusion, compared with exclusive reliance on neurologic examinations during BTO. Because qualitative SPECT studies are dependent on the development of asymmetry, it is important to appreciate that 26.9% (42/156) of our patients who revealed no asymmetry prior to BTO developed asymmetry (contralateral-ipsilateral/average $>10\%$) during BTO. We identified three different types of CBF responses leading to asym-

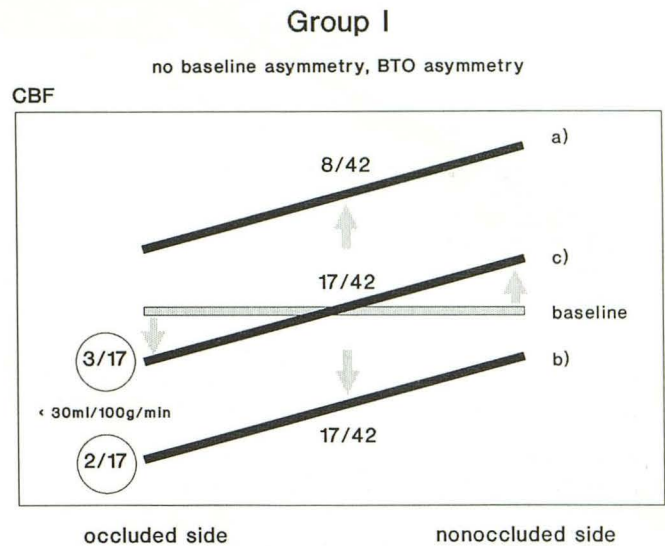


Fig. 1. Schematic illustration of CBF response in 42 patients, who presented with symmetric baseline CBF values, but developed hemispheric asymmetries due to BTO. Bilateral (a) increase, (b) decrease, and (c) increase on nonoccluded side with simultaneous decrease on occluded side have been observed.

metry (Fig. 1): 1) In 5.1% (eight/156) of patients, asymmetry developed due to an asymmetrical *increase* in CBF on both sides during BTO. Considering that this group presented with average CBF values of 64 (45–119) mL/100 g/min and 76 (52–137) mL/100 g/min on the occluded and the nonoccluded side, respectively, these patients cannot be considered to be at increased risk of developing ischemia. 2) In 10.9% (17/156) of patients, asymmetry developed during BTO by decreasing CBF more on the occluded and the nonoccluded side. Only 11.8% (two/17) of this group dropped CBF values below 30 mL/100 g/min due to BTO. 3) In 10.9% (17/156) of patients, CBF dropped on the occluded side and increased on the nonoccluded side, resulting in asymmetry. Only 17.6% (three/17) of patients in this group exhibited flow values below 30 mL/100 g/min. Thus, while asymmetry alone would identify 26.9% (42/156) of patients to be at risk, our criteria (4) would identify only 3.2% (five/156).

Like Moody et al (3) we are concerned about the group (9.6% of our series, 15/156) who presented with baseline (preocclusion) asymmetry and had an increased asymmetry during BTO (Fig. 2): 1) In 7.1% (11/156) of patients, CBF fell 19% on the occluded side, but CBF fell below 30 mL/100 g/min only in two of these patients. The average asymmetry of these 11 patients increased from 17% to 32%. 2) In two of these 15 patients, CBF *increased* bilaterally, resulting in increased asymmetry (12%–21%). This group of patients were not likely to have an increased hemodynamic risk from carotid occlusion because they exhibited CBF values between 53.4 and 77.0 mL/100 g/

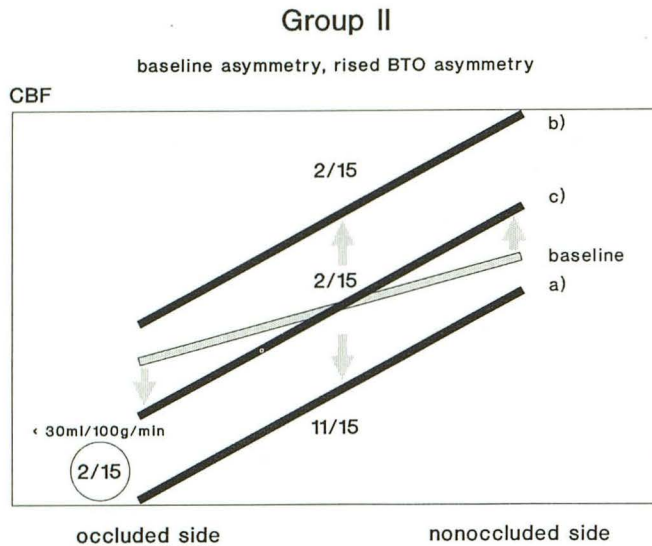


Fig. 2. Schematic illustration of CBF response in 15 patients, who showed asymmetry prior to BTO and increased asymmetry during BTO. Bilateral (a) decrease, (b) increase, and (c) increase on nonoccluded side with simultaneous decrease on occluded side have been observed.

min during BTO. 3) The remaining two from the group of 15 patients demonstrated decreased CBF on the occluded side and increased CBF on the nonoccluded side. Asymmetry in this group increased from 19% to 31% during BTO and CBF values ranged between 35.8 and 63.7 mL/100 g/min during BTO.

Between September 1982 and June 1991, 34 patients underwent acute therapeutic ICA occlusion guided by our Xe/CT CBF criteria. Fifteen (44%) of these patients would not have met the criteria of symmetry (contralateral-ipsilateral/average < 10%) considered to be the limit of normal by Risberg et al (5).

While quantitative Tc-99m HMPAO SPECT imaging in combination with clinical BTO may be sensitive enough to identify most patients at risk for hemodynamic stroke after ICA sacrifice, it lacks the specificity available from quantitative CBF studies. Excluding patients from therapy based on qualitative Tc-99m HMPAO SPECT will reduce one's stroke rate. Unfortunately a significant number of patients who could safely tolerate ICA sacrifice, and in whom ICA sacrifice might be the best therapeutic choice, will also be excluded.

Although Xe/CT is a demanding technology, it has been proven to be a safe and reliable clinical study. The technique is totally noninvasive and because studies which require 6 minutes of data acquisition can be repeated within 20 minutes, baseline and BTO studies can be both completed within an hour. Even though we and others have been concerned that xenon inhalation can alter CBF, recent studies have shown that this has no significant effect on the Xe/CT CBF-derived flow calculation (6, 7). In the near future, the availability of Xe/CT systems that are cost effective and independent of CT manufacturers should overcome earlier problems of limited distribution.

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Editor's note: This comment by Yonas et al was sent to the authors of the three articles cited within it. Their responses follow.

Reply

Assessment of Collateral Cerebral Circulation during Test Occlusion of the Carotid Artery

A number of direct and indirect techniques are available that allow assessment of cerebral perfusion. In the context of cerebral test occlusion studies, a methodology that has a high enough sensitivity to exclude those that will have inadequate collateral circulation, and thus be spared the risk of hemiplegia, is necessary. Stable xenon/CT, Xe¹³³ external probe, Xe¹³³ SPECT, H₂O¹⁵ PET, transcranial Doppler (TCD), EEG, stump pressures, and other modalities appear to meet this requirement. At the same time, the chosen methodology must not be too sensitive, or those

who might have benefited from carotid occlusion might be unnecessarily rejected and required to face the hazards of their original disease. As long as the specificity of the test is also high, however, a high sensitivity can be tolerated.

Tc-99m HMPAO SPECT test occlusion studies as described by Peterman et al (1), Moody et al (2), and Eckard and Purdy (3) have a high sensitivity but suffer from a low specificity because they are nonquantitative. This becomes a dangerous situation because the sensitivity of such tests can be easily altered by changing the acquisition, display, and interpretation of the information gathered. The importance of this principle is demonstrated by our own data. We have noted subtle changes with Tc-99m HMPAO SPECT and TCD (unpublished data) between baseline and test occlusion studies on almost every test occlusion study we have done. We could, therefore, potentially exclude all patients from having permanent occlusion of the carotid artery.

On the other hand, when tolerance of an occlusion test of the carotid artery is based upon accurate cerebral blood flow (CBF) data, the specificity of the methodology is increased, resulting in fewer people being inappropriately prevented from having permanent occlusion. For this reason, we enthusiastically agree with Yonas et al (see letter) that, at this time, decisions about the adequacy of cerebral test occlusion during occlusion tests are optimally based upon quantitative measurements of CBF.

Although Dr Yonas's group has demonstrated the safety and utility of the stable xenon/CT balloon test occlusion methodology, we have some concerns. Although Dr Yonas claims, "The technique is totally non invasive . . ." his group (4) has reported an incidence of 3.7% complications of which the predominance was dissections of the carotid artery. We have never experienced this complication and believe that transporting a patient to a CT scanner with a catheter in the carotid artery and inflating and deflating the balloon in a blind fashion can only increase the potential of these untoward events. Furthermore, compared to SPECT, the equipment continues to be expensive and less available, the spatial resolution is relatively poor, and the patient receives a higher radiation dose.

For these reasons, we believe that a methodology that provides high-resolution quantitative CBF information and is either portable or allows transport of the patient to the instrument after the balloon has been removed will be the most useful in the long run. At the present time, further improvements in attenuation and scatter correction, sensitivity and spatial resolution, tracers, and blood sampling or input function acquisition are required before SPECT will fulfill this need.

Before any particular level of CBF is universally accepted as critical for maintenance of normal cerebral function in humans, further validation is required. Furthermore, several other issues need to be addressed. For how long should the test be performed and how many CBF measurements should be obtained? Should patient activity, blood pressure, or other physiological indicators be considered during or after the test occlusion? Should the auto regulatory capac-

ity of the cerebral circulation be assessed in conjunction with test occlusion of the carotid?

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Reply

We reviewed with interest the comments by Yonas et al, stressing the need for true quantitative information when assessing asymmetries of cerebral perfusion that develop during balloon test occlusion of an internal carotid artery. Their data suggest that the evaluation of SPECT images using semi-quantitative methods may have a much higher false positive rate than those seen in truly quantitative methods such as Xe-CT. We acknowledge that quantitative methods are preferable, but do not agree that a false positive asymmetry discovered on SPECT imaging necessarily results in withholding of treatment. In many cases, patients developing perfusion asymmetries during balloon test occlusion are suitable candidates for vascular graft to augment blood flow to the ipsilateral hemisphere. The action taken following a false positive study is more likely to be a modified surgical approach rather than withholding of treatment. Given the high stroke morbidity associated with permanent internal carotid artery sacrifice, the performance of occasional "unnecessary" grafting procedures may result in lower overall surgical morbidity.

Although all of their data is not available for review, the 3.2% of patients identified to be "at risk" due to perfusion asymmetry is well below the reported incidence of stroke associated with permanent carotid sacrifice. We would be interested to hear their explanation for this. A flow threshold that is too low will increase the number of false negative studies and increase the number of postoperative strokes.

The authors have considerable experience (over 400 cases) with balloon test occlusion. At many institutions, test occlusion is an infrequently performed procedure and would not warrant the purchase of Xe-CT equipment. SPECT imaging offers the advantage of requiring no equipment beyond what is found in most Nuclear Medicine

departments, being less labor intensive, and having no need for a second balloon inflation during imaging. The cost effectiveness and availability of SPECT imaging make it an attractive alternative for institutions where balloon test occlusion is an infrequently performed procedure. The accompanying relatively high false positive rate should reduce the incidence of stroke associated with the procedure. The cost for this is that it may increase the number of vascular graft procedures performed, and, in rare cases, result in withholding of treatment. However, we think that semi-quantitative analysis of SPECT images provides a significant improvement over reliance on neurologic testing alone.

With the proliferation of PET imaging centers, the future of quantitative cerebral blood flow imaging during balloon test occlusion probably rests in this modality. The radiopharmaceuticals $^{13}\text{-NH}_3$ and $^{11}\text{-C-Nicotine}$ have suitable half lives for the identification of flow abnormalities during test occlusion and we suspect that in the future PET imaging will play an important role in the assessment of cerebral hemodynamics during interventional procedures.

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Reply

We agree with Yonas et al that quantification of regional cerebral blood flow (rCBF) probably would increase the specificity of Tc-99m HMPAO cerebral perfusion SPECT and internal carotid balloon test occlusion (BTO) in detecting clinically silent cerebral hypoperfusion, identifying patients at higher risk for infarction post-permanent occlusion. Like xenon-enhanced tomographic (Xe/CT) cerebral imaging with BTO, Tc-99m HMPAO with BTO is evolving from rCBF pattern identification to rCBF quantification (1-4). At present, there is no generally accepted technique for quantitating rCBF in mL/100 g/min using Tc-99m HMPAO SPECT imaging, although Monsein et al have reported early work in this area (5). Even without quantification, our experience does not suggest that a significant decrease in specificity occurs. We believe that Tc-99m HMPAO SPECT scanning is more suitable than Xe/CT in evaluating rCBF during BTO. However, no study to date has reported enough patients to show statistical evidence that any type of cerebral blood flow imaging with BTO is beneficial.

We would expect the rate of clinically silent hypoperfusion during BTO to match the 5%-20% reported rate of infarctions post-permanent occlusion in patients with clinically negative BTO (2, 3, 6). In our report, two of 17 patients (11%) met our criteria of clinically silent, reversible, asymmetric hypoperfusion (7). We have now studied a

total of 32 patients, five of whom met our criteria (16%). These rates are well within the expected 5%-20% rate. Thus, our method of Tc-99m HMPAO rCBF pattern identification does not seem to be overly sensitive.

Monsein et al had a higher rate of asymmetric Tc-99m HMPAO scans with BTO than would be expected, perhaps related to the increased sensitivity of their four-headed SPECT camera (5). They began to quantify rCBF using a ratio of brain SPECT scan to peripheral arterial blood counts. With further development of this technique, rCBF may be routinely quantified with Tc-99m HMPAO SPECT scans.

Yonas et al argue in favor of Xe/CT with BTO, citing their unpublished data of 156 patients. If the rCBF dropped below 30 mL/100 g/min during BTO, their patients were categorized as moderate risk for infarction post-permanent occlusion; the rCBF pattern did not matter. New hemispheric asymmetry developed in 42/156 patients; pre- and post-BTO asymmetry was present in 15/156 patients. Five of the 156 patients (3.2%) met their criteria for moderate risk for infarction post-permanent occlusion. Thirty-four patients, 15 of which had asymmetry, underwent permanent carotid occlusion.

These data raise several questions. The 3.2% moderate risk rate is lower than the expected 5%-20% rate; however the 5%-20% rate, based on small studies, has a large variance (2, 3, 6). It is unclear how many patients with asymmetry and rCBF below 30 mL/100 g/min underwent permanent carotid occlusion. Patient outcome post-permanent occlusion is not mentioned; we do not know if moderate risk patients were indeed at risk for infarction post-permanent occlusion.

Yonas et al describe Xe/CT as noninvasive and safe. Both Xe/CT and Tc-99m HMPAO SPECT scans are noninvasive; BTO, which is performed in both, is an invasive procedure. Xe/CT with BTO has a reported complication rate of 3.7%, most of which are arterial dissections (8). With an uninflated balloon catheter in the internal carotid artery, the patient is transferred to the CT department. The balloon is then inflated without fluoroscopy. We have had no complications other than a groin hematoma. The Tc-99m HMPAO is injected intravenously while the balloon catheter is inflated under fluoroscopy in the angiography suite. The pharmacokinetics then allow the balloon catheter to be deflated and removed before the patient is transported to the nuclear medicine department for the SPECT scan.

We would agree with Yonas et al that Xe/CT is a demanding technology that is still not widely available. Most nuclear medicine departments with a SPECT camera can perform a Tc-99m HMPAO SPECT scan. Thus, BTO with Tc-99m HMPAO is available in most large institutions with active neurosurgery, otolaryngology, neuroradiology, and nuclear medicine departments.

In conclusion, we agree that rCBF quantitative determination probably would increase BTO specificity in identifying patients at risk for infarction post-permanent carotid occlusion. Using Xe/CT, the University of Pittsburgh has been a forerunner in rCBF imaging. However, we believe BTO with Tc-99m HMPAO SPECT imaging is a safer and

more widely available technology. Tc-99m HMPAO rCBF quantification, currently under development, probably would increase BTO and Tc-99m HMPAO specificity. Since the risk of infarction following permanent occlusion in patients who have clinically passed BTO is relatively low (5%–20%), a large study under controlled circumstances is required to evaluate the predictive value of a positive test. It is unlikely that a single center will be able to acquire enough patients with permanent carotid occlusion, so we are pursuing a multicenter study. Finally, moderate risk patients need not be excluded from permanent carotid occlusion; arterial bypass may be performed in addition to permanent occlusion to prevent infarction postocclusion.

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Editor's note: Dr Yonas' comment was also sent to Richard Frackowiak, MA, MD, FRCP, Professor of Clinical Neurology and Assistant Director of the MRC Cyclotron Unit, Hammersmith Hospital, London. Dr Frackowiak is a recognized authority on cerebral blood flow and agreed to respond although he admits to little experience in either Tc-99m HMPAO SPECT scanning or xenon CT scanning. His commentary follows.

Reply

Since I have neither major experience in Tc-99m HMPAO SPECT scanning nor in xenon CT scanning, I can

only look at this issue from the perspective of a practicing vascular neurologist and someone with more than a passing interest in cerebrovascular hemodynamics.

The first issue is that clinical practice, before high technology investigations became available, clearly demonstrated that stroke could occur following occlusion of the internal carotid artery for therapeutic purposes, not only on the operating table, but also in a delayed fashion, up to a number of days later. The reason for this was not entirely clear at the time although various proposals were raised, including 1) hemodynamic compromise of a critical nature that required some further insult to tip the brain into ischemia and 2) the possibility that clots might form proximally or distally to the occlusion and act as the site of origin of investigations of cerebral hemodynamics have only limited value. Having said that, embolization into a region with impaired hemodynamics should, on a priori grounds, be more dangerous than that into an area where perfusion and vascular reserve mechanisms are normal.

The three recent papers are of great interest (1, 2, 3). I think it is clear that asymmetry of perfusion may occur for a number of reasons before, during, and after balloon occlusion. Before occlusion, such asymmetry may represent areas of previous ischemia and infarction that may also have been clinically silent. During occlusion, they may indicate areas of hemodynamic compromise, and following ischemia, they may represent differential reactive hyperperfusion, or ischemic damage caused by the balloon occlusion, which may itself have remained clinically silent. I think that the point, made forcefully in the commentary from Pittsburgh, that absolute levels of blood flow would be helpful to make these distinctions, is well taken. It should, however, be remembered that hypoperfusion in response to vascular occlusion is a comparatively late phenomenon suggesting critical hemodynamics. The initial response to decreased perfusion pressure is a reactive vasodilation that maintains perfusion. Indeed, it is the "disobliteration" of such occlusion with reperfusion into a dilated vasculature that may be responsible for some of the postocclusive hyperperfusion. It is not until this vasodilating reserve is exhausted that perfusion begins to fall in response to further falls in perfusion pressure and, at this stage, function and metabolism are maintained by an increasing fractional extraction of energy substrates.

This brings me back to the issue of absolute levels of blood flow. Clearly, one must perform an estimation prior to balloon occlusion given that the test itself might conceivably result in some permanent neuronal loss. Secondly, because the circle of Willis distributes the perfusion pressure from each carotid artery to both sides of the brain, occlusion on one side may have effects on both. Asymmetries may therefore be small and this suggests that absolute falls in blood flow are as important to detect as any asymmetry. This point is again made by the group from Pittsburgh. They appear to have the largest experience and certainly their results would seem to confirm conclusions that could be drawn from theory. This phenomenon of a bilateral effect on perfusion clearly makes the ratio method insensitive in relative terms. The article

by Moody et al (2) is unable to help us empirically in this respect as only six cases are described. The most powerful argument produced for Tc-99m SPECT method is that it is easy to perform and gives a snapshot measurement of cerebral blood flow which can be obtained by making the tracer injection at the time of occlusion itself. The article by Peterman and her colleagues (1) refers to 17 patients, which is also rather a small number. The results of this article are marred by the fact that the control scan was performed after the balloon inclusion. It is also unfortunate that one of 15 with symmetric perfusion subsequently developed a stroke. The fact that this stroke occurred during intraoperative hypotension and was ipsilateral to the occluded carotid strongly suggests a hemodynamic mechanism and, therefore, impaired hemodynamics on that side compared to the contralateral side. It seems that, in this case, the symmetrical SPECT scan failed to reveal a differential and compromised hemodynamic environment.

The Pittsburgh group's experience is certainly much larger than anyone else's. However, there are considerable reservations regarding the xenon CT method, largely because the sensitivity to change in xenon concentration in the brain is really rather poor using Hounsfield units. The suggestion that a CBF of 30 mL/100 g/min is a significant threshold also seems rather arbitrary. One fact missing from this commentary is the outcome of ICA occlusion in the 34 patients who underwent this treatment between September 1982 and June 1991. This would be particularly interesting in the 44% of patients who would not have met the criterion of symmetry considered to be the limit by Risberg et al (4).

In summary, it is difficult not to be left with the impression that the clinical research articles concerning this rare problem, which is usually found in the context of an aneurysm of the internal carotid that is inoperable, are determined largely by loyalty to a technique than any other considerations. This does seem to be an area where pooling of rare material and careful thought regarding the underlying pathophysiology before appropriate measurements are made would lead to a much more satisfactory answer to the question than the reporting of small groups of patients and the championing of locally available techniques.

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