Sensitivity of Computer Assisted Radionuclide Angiography in Transient Ischemic Attack and Prolonged Reversible Ischemic Neurological Deficit

Comparison with Findings in Radiographic Angiography and Transmission Computerized Axial Tomography

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SUMMARY Computer assisted radionuclide angiography (CARNA) with $^{99m}$Tc-DTPA was employed to study 143 patients with transient ischemic attacks (TIA) and 79 patients with prolonged reversible ischemic neurologic deficit (PRIND). The results of CARNA were compared with findings from radiographic angiography (RGA) in 173 patients and with findings in transmission computerized axial tomography (T-CAT) in 154 patients. In patients with TIA, CARNA showed a hemispherical perfusion deficit in 74.8%, and with PRIND 87.3%. This deficit, determined as the relative difference between the involved and the non-involved hemisphere, was significantly ($p < 0.0025$) greater in PRIND (minus 23%) than in TIA (minus 17%). Sensitivity of CARNA was independent of the interval from ictus to examination for more than 4 months. RGA in TIA revealed true positives in 82.0%, in PRIND it was 89.5%. T-CAT was positive in TIA in only 16.8% but in PRIND it was 64.4%. Combined sensitivities in TIA (92.4%) and in PRIND (94.0%) were highest with the combination of CARNA and RGA. However, in PRIND the combination of non-invasive methods (CARNA and T-CAT) revealed 93.2% positive findings. Combinations of these evaluation methods may be used to detect cerebrovascular disease in patients with such dysfunction.

Material and Methods

A total of 222 patients were studied. Of these, 143 had TIA and 79 had PRIND. The patients were further divided according to the interval of time which had elapsed between ictus and examination. Patients included in the present study were not initially examined to compare results of CARNA, T-CAT and RGA, and all 3 methods were not employed in every patient. Selection of patients for T-CAT and RGA was made by neurologists and neurosurgeons according to the patient's clinical presentation and to the scheme used in this hospital.$^6$ For 22 months, patients with TIA and PRIND who had CARNA (n = 222) were used to assemble available findings, including T-CAT (n = 154) and RGA (n = 173) results.

Radionuclide images were obtained with an Ohio Nuclear Series ON 110 gamma camera. A bolus of 370 MBq (10 mCi) of $^{99m}$Tc-DTPA was injected rapidly into an antecubital vein by accelerating the tracer with 10 ml of saline. Polaroid photographs recorded the total counts accumulated over a 3-sec period with the patient in upright position in either anterior or posterior projection. Data were transferred to an on-line computer system (CINE 200, Intertechnique) at a rate of 2.5 frames per sec for 40 sec for subsequent computer-assisted analysis. Static images were made to exclude intracranial tumor.

Time radioactivity curves were derived from 2 regions of interest, each including one hemisphere. These regions were defined by a computer program as described.$^8$ This was designed to define the contours of...
the inner calvarium and to exclude the sagittal sinus and the base of the skull (fig. 1). From the curves, a right to left hemisphere ratio was computed by dividing the areas F by F' as illustrated in figure 2. This ratio is called a relative perfusion efficiency with a normal value of 0.995 ± 0.12 (mean ± 2 SD) but 1.00 ± 0.12 is used in these calculations.* The ratio is expressed as the difference from 1.000. Thus, differences greater than 0.12 were designated "pathologic."

Reproducibility of CARNA was tested by evaluating the inter-observer variability (2 observers) in 102 patients. The paired determination for the F/F' ratio correlated well (r = 0.97). The mean value of differences was 0.004 with a standard error of 0.00332.

One hundred and fifty-four of 222 patients were examined by T-CAT. Of these, 95 had TIA and 59 had PRIND. T-CAT studies were made with an EMI CT 1010 scanner using a standard technique. In selected patients, if T-CAT was performed from the 8th to the 28th day after ictus and if the pre-contrast scan was normal, additional scans were obtained following the intravenous injection of 60% sodium diatrizoate, 1 ml/kg. Scans were evaluated according to published criteria. Tumors, abscesses, congenital and post-traumatic lesions were excluded by history, clinical status, T-CAT appearance and experience. T-CAT evaluation was used to define whether a patient had regions of altered density corresponding to intracerebral vascular disease ("true positives") in the clinically affected hemisphere.

Biplane radiographic angiography, using the Seldinger technique, was performed in 106 patients with TIA and 67 patients with PRIND. Morphology of lesions seen was evaluated only with respect to a luminal narrowing of an artery since RGA findings were used only to define whether a patient had cranial vascular disease (true positives) or not. The evaluation included determination of stenosis or occlusion of the common carotid artery, internal carotid artery and of the main cerebral arteries or their branches. If vascular lesions were found on both sides, only those sides with the higher degree of stenosis were evaluated (i.e., if stenosis and occlusion occurred, only the occlusion is listed in "results").

The clinical diagnosis of a TIA or PRIND was established as described by Schmiedek et al. Whenever the neurologic deficit lasted longer than 24 hours but then began to clear, it was designated as prolonged (PRIND). Patients with TIA complained of episodes of temporary focal cerebral dysfunction which cleared completely within 24 hours. In 10 patients with TIA and in 9 with PRIND, the clinical symptoms occurred repeatedly and they were not included in the group of patients which was designed to illustrate the sensitivity of CARNA in relation to the interval between ictus and examination.

Physicians interpreting CARNA, T-CAT and RGA studies knew the patient's clinical presentation but were not informed of the results of the other examinations.
Results

Sensitivity of CARNA in correlation with the clinical findings (TIA, PRIND) is given in table 1. In patients with TIA (fig. 1) it was 74.8%. In patients with PRIND, it was found to be 87.3%. Statistical comparison of these percentages, based on the confidence limits for the binomial distribution, revealed a significant difference on the basis of \( p < 0.01 \). If TIA and PRIND patients were taken as one group, sensitivity was 79.3%. Relative perfusion efficiency decreased for the involved hemisphere. If this parameter was expressed as the difference from 1.00, it increased from TIA to PRIND (table 1). Student's t-test for unpaired data revealed a significant difference (table 1).

Table 2 reflects sensitivities of CARNA in TIA and PRIND depending on the period of time which had elapsed from ictus to examination (1 week to more than 12 weeks). Since sub-groups are relatively small, no statistical comparison was made. In TIA and in PRIND, no considerable decrease was detected within the periods of time studied. The sensitivity of CARNA was independent of the interval from ictus to examination.

In TIA, the sensitivity of T-CAT (table 3) was significantly \((p < 0.01)\) less than that of CARNA (16.8% vs 72.6%). In PRIND, the difference was smaller (64.4% vs 83.1%). Combined sensitivity was 82.5% which was significantly higher \((p < 0.05)\) than the sensitivity of T-CAT alone (35.1%).

RGA revealed stenoses (> 50% luminal diameter) of the internal carotid arteries in 39 patients of the TIA group (fig. 3) and in 18 patients with PRIND. The artery was occluded in 40 TIA and in 30 PRIND patients. The common carotid artery was occluded in 3 patients with PRIND. Stenosis of the middle cerebral artery was found in 5 patients with TIA and in 2 patients with PRIND. Occlusion of the middle cerebral artery was found in 3 TIA and in 7 patients with PRIND. These 147 patients with angiographically confirmed lesions account for the 84.9% sensitivity of RGA in the group of patients with TIA and PRIND (table 4). If TIA and PRIND were evaluated separately, RGA was positive in 82.0% with TIA and in 89.5% with PRIND. CARNA in these groups revealed 76.4% true positives in TIA and 82.1% in PRIND. None of the differences was significant. However, combined sensitivities were higher (table 4). If TIA and PRIND patients formed one group, combined sensitivity (93.1%) was significantly higher \((p < 0.01)\) than that of either method.

To evaluate which method (T-CAT or RGA) provided more information to CARNA with combined evaluation, results from tables 3 and 4 were compared. In TIA, T-CAT added 3.2%, RGA 16.0%. The difference was significant \((p < 0.01)\). In PRIND, additive information from either method was nearly the same, resulting in a sensitivity of about 94% by either combination. Conversely, CARNA added 10.4% sensitivity to RGA in TIA \((p < 0.01)\) and 4.5% in PRIND.

Discussion

To determine the sensitivity of a non-invasive procedure in cerebrovascular disease, results of such procedure can be related to a) clinical or to b) morphological findings. Clinical findings include completed stroke (severe neurological deficits of long duration), PRIND and TIA. Morphological findings were obtained by cranial radiographic angiography (RGA) or by T-CAT.

T-CAT can show intra-cranial vascular territories damaged by cerebral infarction. Such areas are of lower density than normal. They enhance with contrast medium and 99mTc-compounds if the...
TABLE 3  Sensitivity (%) of CARNA and T-CAT in TIA and PRIND

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>CARNA +</th>
<th>T-CAT +</th>
<th>CARNA+T-CAT+ (combined)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA</td>
<td>95</td>
<td>69 (72.6%)</td>
<td>16 (16.8%)</td>
<td>72 (75.8%)</td>
</tr>
<tr>
<td>PRIND</td>
<td>59</td>
<td>49 (83.1%)</td>
<td>38 (64.4%)</td>
<td>55 (93.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>154</td>
<td>118 (76.6%)</td>
<td>54 (35.1%)</td>
<td>127 (82.5%)</td>
</tr>
</tbody>
</table>

* positive findings: n: subgroups from table 1.

TABLE 4  Sensitivity (%) of CARNA and Radiographic Angiography (RGA) in TIA and PRIND

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>CARNA +</th>
<th>RGA +</th>
<th>CARNA, RGA+ (combined)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA</td>
<td>106</td>
<td>81 (75.4%)</td>
<td>87 (82.0%)</td>
<td>98 (92.4%)</td>
</tr>
<tr>
<td>PRIND</td>
<td>67</td>
<td>55 (82.1%)</td>
<td>60 (89.5%)</td>
<td>63 (94.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>173</td>
<td>136 (78.6%)</td>
<td>147 (84.9%)</td>
<td>161 (93.1%)</td>
</tr>
</tbody>
</table>

* positive findings: n: subgroups from table 1.

blood-brain barrier is disrupted or if neovascularity develops without such a barrier.13 This occurs from about the 8th through the 28th day after ictus and is mainly correlated with severe neurologic defects. Circumscribed atrophy (fig. 3) occurs in some patients with chronic, diminished perfusion.18 Angiographically (RGA) detected stenosis or occlusion of the carotid artery are reported to be frequently associated with pathological T-CAT findings (cerebral atrophy or areas of infarction).18-19 In patients with completed stroke, T-CAT and cerebral serial scintigraphy both provide useful additional information.6,9 Thus, either non-invasive method may be used to define correctly the situation of such patients. In patients with reversible ischemic cerebral dysfunction, T-CAT was found to be less accurate.9-11 The results of the present study reveal a sensitivity of T-CAT in PRIND of 64.4% and in TIA of 16.8% (table 3, fig. 3). Therefore, especially in TIA, morphological defects in the affected hemisphere are a rare finding using T-CAT, despite the detection of stenosis or occlusion of the internal carotid artery in 75% of the TIA patients in the present study. CARNA revealed a hemispherical perfusion "deficit" in 74.8% of the TIA patients and in 79.3% of all patients (TIA and PRIND) (table 1).

To interpret correctly the "perfusion deficits" described by CARNA, it must be emphasized that CARNA — as a method using the initial tracer distribution ("wash in") within a given time to compare global hemispherical flow values — does not differentiate delay from deficit. Delayed "wash in" almost always is associated with a perfusion "deficit" or reduction (fig. 2). The results of the present study reveal that this can be observed even for 50% stenoses of the carotid artery (i.e., 75% reduction of cross section) (fig. 3), which is believed to be the level of stenosis related to marginal hemodynamic significance.4 In such patients the initial uptake in the respective hemisphere was delayed in comparison to the contralateral one (fig. 3). By employing the ratio F/F' (fig. 2), a significant difference from normal values was found between the extent of reduced (and/or delayed) hemispherical perfusion in TIA and PRIND (table 1). In PRIND, perfusion of the involved hemisphere was reduced by 23% as compared to the contralateral one. In TIA, it was diminished by 17%. CARNA reveals not only positives or negatives but provides semiquantitative data on perfusion differences, closely correlated to the patient's clinical state. CARNA cannot differentiate between hemodynamically relevant changes in only one or in those occurring in both hemispheres simultaneously. However, bilateral alterations rarely cause precisely identical changes in "wash in."6,7

Radiographic angiography (RGA) was positive in 82.0% of the patients with TIA (table 4). This sensitivity is similar to that published by others.10,11 Although sensitivity of CARNA (76.4%) was not much less, RGA additionally provides information on morphological appearance and localization of defects in the cranial vasculature and is, in contrast to CARNA, diagnostic in vertebrobasilar ischemic symptoms.9 Angiography is an invasive procedure, which is not employed as a screening method in every patient with a history of TIA and PRIND. In TIA, combined sensitivity of CARNA and RGA (92.4%) was significantly higher than the sensitivity of RGA (82.0%) (Table 4), which suggests that 10.4% of the patients with TIA were correctly identified only by the nuclear method. Similar findings have been reported by Britton et al.12 employing a special form of computer assisted measurement of regional cerebral blood flow and by Schmiedek et al.13 using invasive rCBF determination with 133Xenon.

There was no important loss in sensitivity of CARNA by an increasing interval from ictus to examination (table 2). Thus, there is no restriction on...
Figure 3. 59-year-old male with right-sided transient ischemic attack 10 days prior to the examination. A) Radionuclide angiogram shows delayed perfusion of the left hemisphere (arrow). B) Time radioactivity curves reveal delay of left-sided hemispherical perfusion (arrow). Q (right to left hemisphere) = 1.17, i.e. 17% "deficit" or 0.17 difference to 1.00 (see table 1 and fig. 2). (A and B = CARNA.) C) T-CAT (without contrast enhancement) shows borderline widening of ventricular bodies and cerebral sulci and noticeable widening of the left Sylvian fissure (arrow) the latter indicating chronically diminished perfusion. D) Cranial radiographic angiograms (sequence) show irregularities of the left internal carotid artery and a 50% stenosis of the supraclinoid portion. The origin of the internal carotid artery was normal.
employing CARNA up to 4 months after ictus. This result illustrates that a delayed and/or reduced hemispheric “wash in” (perfusion) may be found even if neurological symptoms have cleared. A TIA can occur as a focal reduction of perfusion (e.g., by emboli) within a permanently changed hemispheric perfusion. The latter was detected in 74.8% of such patients by CARNA (table 1).

CARNA may be the preferred non-invasive procedure because it detects and quantifies disorders of vascular supply in patients with TIA and PRIND. Doppler sonography can provide excellent information if an alteration in the extracranial vasculature causes cerebral dysfunction.7 When intra-cranial changes are responsible, this non-invasive method fails.3 If no computer assistance is used to evaluate cranial radionuclide angiography, results are considerably less accurate.4 Specificity of CARNA is 84.6%. If CARNA is negative (25.2% in TIA; 12.7% in PRIND), a further method must be employed to confirm the cranial vascular origin of an attack which may be RGA for TIA and T-CAT for PRIND. This diagnostic sequence leads to 92.4% detection of positives in TIA and to 93.2% positives in PRIND.

References
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