

Selective Amobarbital Test for the Determination of Language Function in Patients with Epilepsy with Frontal and Posterior Temporal Brain Lesions

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Summary: *Purpose:* Selective amobarbital tests with selective temporary inactivation of the left frontal operculum and/or the left parietotemporal cortex were performed in 5 patients with left-hemispheric epileptogenic lesions in or adjacent to classical Broca's and/or Wernicke's area. The aim was to assess language functions in these brain regions before surgery, to tailor the surgery according to the individual functional importance of these brain regions, and to predict postoperative outcome.

Methods: Amobarbital was injected by transfemoral selective catheterization of the arteries supplying the target areas. Along with neuropsychological and neurological testing during the amobarbital procedure, EEG recordings were performed in all patients, and [^{99m}Tc]HMPAO-single photon emission computed tomography (SPECT) in 2 patients.

Results: After the amobarbital injection into the left frontal opercular region, there was no recognizable language dysfunction in 3 patients. In these 3 patients, the lesions in or adjacent to the frontal operculum were completely resected without

postoperative language impairment. In the remaining 2 patients, temporary language impairment after the amobarbital injection into the left frontoopercular and Wernicke's region, respectively, suggested language functions in these areas. Surgery was restricted to the left mesiotemporal lobe in 1 patient. In the other patient, the tumor infiltrating the frontal operculum was restrictively resected. Postoperatively, the first patient had no language impairment, but the latter had transient global aphasia, from which she recovered.

Conclusions: Selective temporary amobarbital inactivation of brain regions that may be associated with language has clearly indicated the presence or absence of language functions in these regions. The test contributed substantially to planning of the surgical approach in each patient. The predictive value of the amobarbital test was demonstrated by the postoperative outcome. **Key Words:** Language representation—Selective amobarbital memory test—Selective amobarbital language test—Presurgical epilepsy evaluation—[^{99m}Tc]HMPAO single photon emission computed tomography.

The intracarotid amobarbital procedure (IAP, Wada test) with anesthesia of one hemisphere is traditionally used to determine the laterality of language dominance (1) and to assess memory functions in candidates for epilepsy surgery (2). In Zurich, the inauguration of the selective amygdalohippocampectomy (AHE) (3) led to the search for new strategies to predict postoperative memory deficits. The aim was to modify the Wada test in such a way that (a) the amobarbital was delivered exclusively but thoroughly to the mesiobasal temporal lobe (TL) structures considered for surgery, and that (b) the extratemporal ipsilateral brain areas remained unaffected by the drug. The selective TL amobarbital

memory (sTLAM) test, used in Zurich since 1986, consists either of the anterior procedure with injection of amobarbital into (a) the anterior choroidal artery (acha); or (b) into the acha, the posterior communicating artery, and the ophthalmic artery after temporary balloon occlusion of the internal carotid artery distal to the origin of the acha (4-6); or of the posterior approach with injection of amobarbital into the P2 segment of the posterior cerebral artery (5-8). To date, 64 patients have received a sTLAM test. In 41 patients, the amobarbital was injected directly into the acha; in 18 patients the test was performed using the balloon occlusion technique, and in 5 patients (in 3 of them in addition to the anterior sTLAM) the posterior approach was chosen. In all these patients, the amobarbital procedure was performed ipsilaterally to the epileptogenic focus, and only 2 patients underwent bilateral sTLAM test. There were no compli-

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cations, and the predictive value for postoperative memory functions in patients with mesiobasal TLE was good (6). The long-standing experience with the selective memory Wada test encouraged us to apply selective amobarbital strategies in patients with neocortical epileptogenic lesions affecting the classical language areas, i.e., Broca's and Wernicke's language area of the left hemisphere. Noninvasive neuropsychological methods (tachistoscopic lexical decision task) demonstrated unclear or left hemispheric language dominance in these patients. The rationale for the selective strategy instead of a global hemispheric strategy was that in presence of an epileptogenic lesion the language function might have shifted in the same hemisphere from the classic language areas to other remote ones. Because hemispheric inactivation would not be able to show this, a spatially restricted and topographically precise delivery of the amobarbital to the target structures was intended. The frontoopercular region was temporarily inactivated by an amobarbital injection into the left frontoopercular branch of the middle cerebral artery; the temporal parietal region was inactivated by application of the barbiturate into the ramus temporalis superior of the left middle cerebral artery. To date, we have performed the selective extra-temporal amobarbital test in 4 patients with left hemispheric epileptogenic foci involving the frontal operculum and in 1 patient with a presumably epileptogenic lesion in the left temporoposterior neocortex. We report our first results of this newly developed amobarbital language test. The clinical course of the patients, the role and procedures of selective amobarbital testing, the surgery performed, and the postoperative outcome are described.

PATIENTS AND METHODS

Patient 1

Since age 6 months, patient 1, a 15-year-old left-handed girl had had epilepsy with complex partial seizures (CPS) and tonic seizures with tonic-clonic convulsions. Magnetic resonance imaging (MRI) showed cortical dysplasia of the left superior frontal gyrus. [¹⁸F]Fluorodesoxyglucose-positron emission tomography ([¹⁸F]FDG-PET) showed focal left frontobasal hypometabolism. As shown with invasive EEG monitoring using nine subdural strips and two bilateral four-contact-foramen ovale (FO) electrodes, the CPS originated in the left frontopolar cortex. The generalized tonic-clonic seizures (GTCS) had onset with bilateral synchronous spike waves. The left frontal resection was tailored by intraoperative electrocorticography (ECoG) with recording of one seizure, which yielded, in addition to confirmation of the frontoorbital onset zone, a second epileptogenic region in the inferofrontal gyrus situated near the frontal operculum. The epileptogenic and the lesional zones

could be resected, since in this patient selective amobarbital inactivation of the left frontal opercular area had no detectable effect on language function. The histopathological findings showed abnormal migration with nodular cortical heterotopias, focal cortical dysplasia, and gyral synecy. The surgery caused no additional neurological or neuropsychological deficits and the girl was completely seizure-free for the entire 23-month follow-up period.

Patient 2

Patient 2, a 28-year-old right-handed female had had CPS since age 6 years. MRI showed multiple cortical and subcortical parenchymal ischemic lesions in the left anterior middle temporal gyrus and in the temporoposterior cortex. [¹⁸F]FDG-PET disclosed no signs of focal hypometabolism. Proton magnetic resonance spectroscopy (¹H]MRS) with volume of interest (VOI) in the left hippocampus indicated disturbed glial metabolism with slightly increased inositol and increased glutamate and its derivatives (Glx). The seizures recorded with FO electrodes showed seizure onset in the mesiobasal TL structures with strong involvement of the temporolateral neocortex. Due to transient aphasia immediately after the amobarbital inactivation of the sensory language area (Table 1), surgery was restricted to the mesiobasal TL structures, leaving the lesion untouched. The histopathological findings showed gliosis. Postoperatively, the patient was completely seizure-free for the 43-month follow-up period and had no language deficits but did have moderate impairment of verbal memory.

Patient 3

At age 27 years, the patient, a 29-year-old right-handed woman, had presented with CPS with epigastric aura, subjective weakness of the right arm associated with stiffness of the right hand, and vegetative signs. MRI showed a lesion in the left frontal operculum (Fig. 1). Selective amobarbital inactivation of the frontal opercular area had no detectable effect on language functions. Therefore, the tumor was completely resected. There was no postoperative language impairment. The histopathological findings showed a ganglioglioma of World Health Organization category 1 (WHO I). The patient has been completely seizure-free without neurological deficits for the 55-month follow-up period.

Patient 4

Patient 4, a 30-year-old left-handed man, had had an unremarkable history until age 30 years. Occurrence of secondarily generalized seizures led to a neurological evaluation with MRI findings of a tumor in the left inferoposterior frontal gyrus (Fig. 1). The EEG was normal. Tachistoscopically treated language dominance was unclear. Fortunately, in this patient, selective amobarbital inactivation of both the motor and the sensory lan-

TABLE 1. Assessment of memory, frontal functions, and language

Parameter	Patient/Age(yr)/sex									
	1/15/F		2/28/F		3/29/F		4/30/M		5/30/F	
Tachistoscopically tested language dominance	Unclear		Unclear		Left hemispheric		Right (?) hemispheric		Left hemispheric	
Neuropsychological tests	Preoperative	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative	
RAVLT	2/0	15/0	8/0	11/0	15/0	13/0	10/0	15/0	15/0	
Recall	3/3	12/0	3/0	10/0	13/0	10/0	11/0	13/0	14/0	
RVDLT	ND	13/0	10/0	8/0	12/0	11/0	10/0	ND	14/0	
Recall	ND	13/0	10/0	6/0	11/0	10/0	9/0	ND	13/0	
Rey CF Test	ND	11/0	9/0	16/0	15/0	10/0	10/0	10/0	—	
Verbal Fluency Test ^a	1/5/2	19/0/4	41/1/6	19/0/2	19/0/0	28/0/0	23/0/0	20/0/0	29/0/0	
Figural Fluency Test ^b	3/1/7	30/0/0	66/0/1	18/0/2	24/0/0	30/0/0	24/0/2	23/0/0	40/0/0	
Weigl-type sorting test, two-group test	ND	5/0	4/0	ND	3/0	5/0	5/0	4/0	ND	
Stroop Color-Word Test ^c	ND	30/1	24/0	21/0	27/1	17/1	36/1	29/1	26/0	
AAT	No deficits	No deficits	No deficits	No deficits	No deficits	No deficits	No deficits	Naming difficulties	Naming, 89; comprehension, 91; Token Test, 94	
Results	Oligophrenia, frontal dysfunction	Slight impairment of frontal functions	Impaired verbal memory	Slight impairment of right frontal functions	Slight impairment of left frontal functions	Normal	Normal	Discrete naming difficulties	Naming difficulties apparent in spontaneous speech	
Social status	Special schooling for mentally retarded	Housewife	No change	Auxiliary worker	Training for office work	Fully employed as technician	No change	Fully employed as nurse	Disability pension	

RAVLT, Rey Auditory Verbal Learning Test (11); RVDLT, Rey Visual Design Learning Test (12); CF, Complex Figure (12); AAT, Aachen Aphasia Test (16). The numbers separated by a slash designate correct/incorrect answers, numbers separated by two slashes designate correct/rule break/repetition, Patient 1 did not undergo any neuropsychological testing. This mentally retarded girl was carefully examined postoperatively by 2 neurologists (H.G.W. and M.H.), who noted overall improvement in her mental and cognitive abilities.

^a From Rey (12).

^b From Perret (13).

^c From Regard et al. (14).

guage areas did not cause any language deficit; therefore, the tumor (astrocytoma WHO II) was removed radically. The patient was seizure-free during the 20-month follow-up period with no language or neurological deficits.

Patient 5

At age 24 years, a 30-year-old right-handed woman had presented with simple partial seizures (SPS) with an olfactory aura and short lasting CPS. The diagnostic procedures showed a tumor (astrocytoma WHO II) in the left insular region, which was radically removed. Postoperatively, the patient was seizure-free with no postoperative deficit for 30 months. Recurrence of tumor infiltrating the left frontal operculum, the frontal pole, the frontobasal regions, as well as the insula and the mesio-basal temporal lobe structures, required reoperation. Selective amobarbital inactivation of the opercular region caused transient aphasia. Therefore, tumor resection was limited to the temporal lobe, with preservation of the frontal lobe to avoid postoperative language deficits. Despite the limited resection, the patient had transient global aphasia postoperatively. The aphasia diminished in the 12-month follow-up period, with persistence of some

anomic disturbance. During the 12 months, the patient experienced two focal sensory Jacksonian seizures.

Results of the pre- and the postoperative neuropsychological testing and the social status of all patients are shown in Table 1.

Amobarbital test procedure

Amobarbital application was performed according to our sTLAM procedure (4–6). In the first step, the arteries supplying the target brain areas were identified by a diagnostic angiogram of the internal carotid arteries (percutaneous transfemoral catheterization technique). The arteries into which the amobarbital was to be injected were then selectively catheterized and visualized by contrast medium (Fig. 2). Finally, with the catheter tip remaining in the same position as during the selective angiogram, the amobarbital was injected. Immediately after the injection, the patient was tested for focal motor deficits, visual field defect, and sensory neurological deficits. Language abilities were assessed by testing for naming, comprehension, reading, and word repetition. The test procedure was monitored by video; EEG was performed simultaneously with scalp electrode recordings accord-

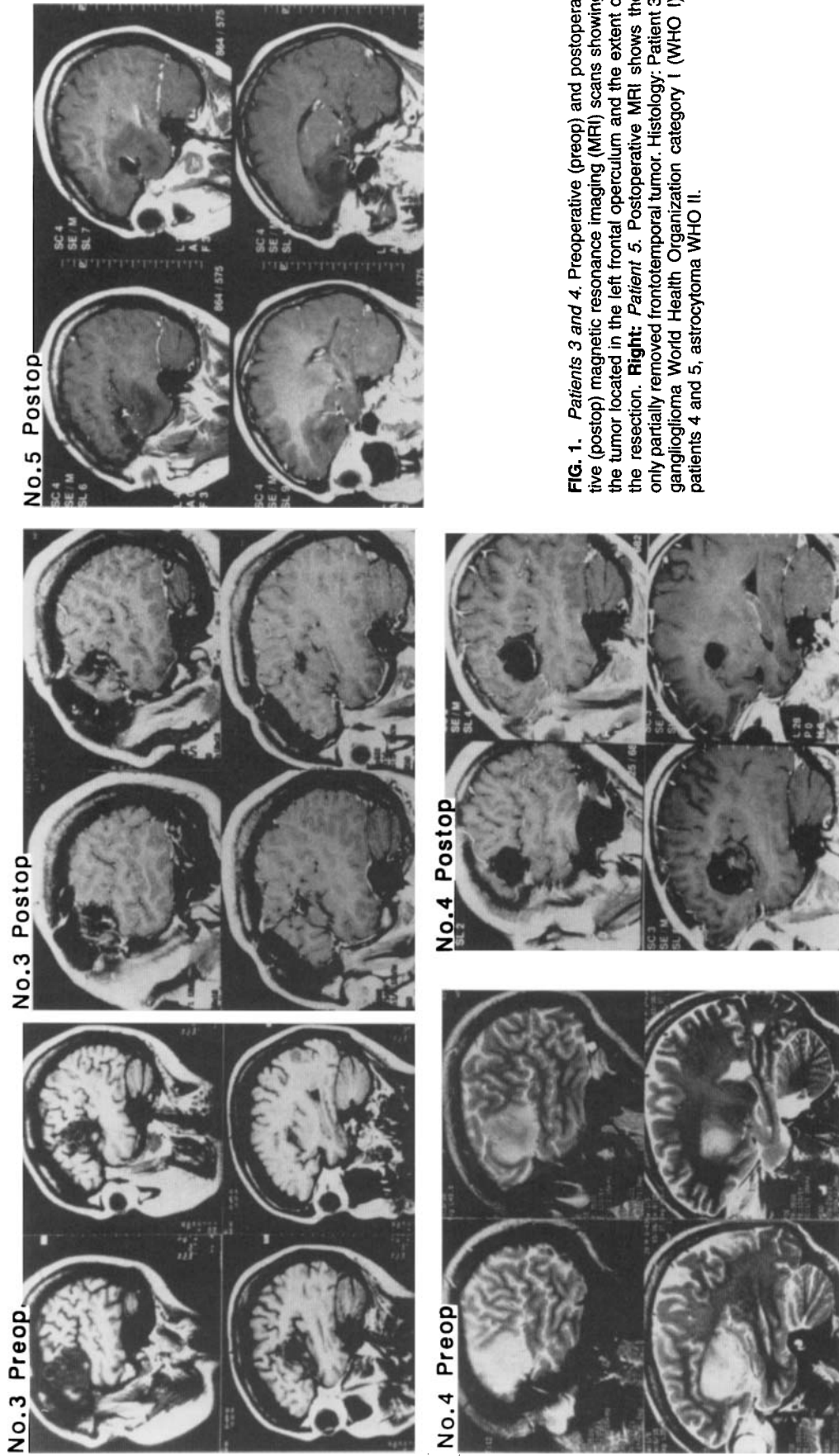
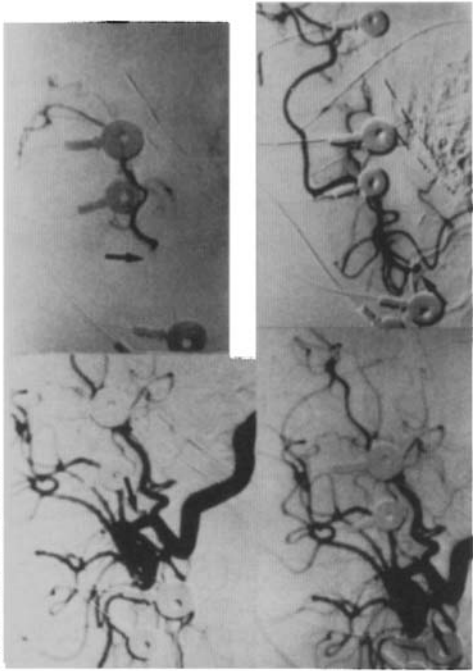
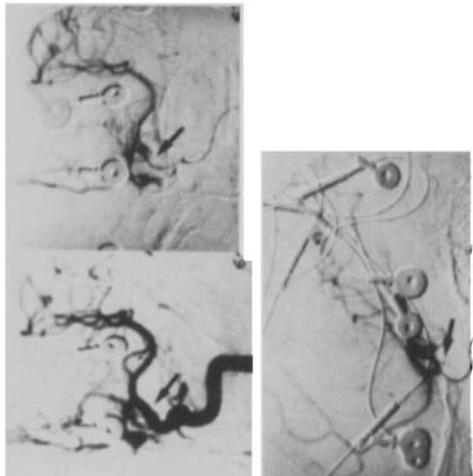


FIG. 1. Patients 3 and 4. Preoperative (preop) and postoperative (postop) magnetic resonance imaging (MRI) scans showing the tumor located in the left frontal operculum and the extent of the resection. **Right: Patient 5.** Postoperative MRI shows the only partially removed frontotemporal tumor. **Histology: Patient 3,** ganglioglioma World Health Organization category I (WHO I); patients 4 and 5, astrocytoma WHO II.

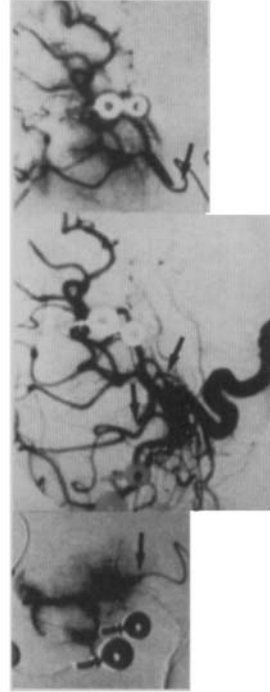
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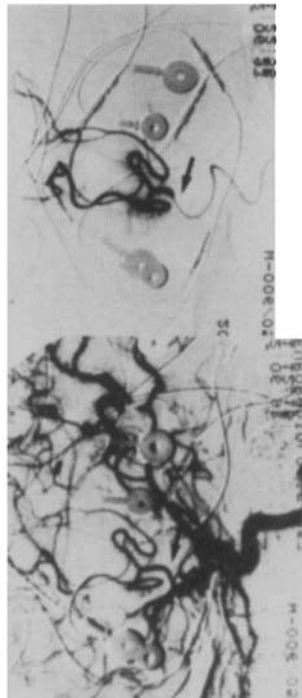
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No.3(V.M.)



No.5(L.M.)



FIG. 2. Angiograms of our 5 patients showing the left internal carotid artery and/or its selectively filled branches. Position of the catheter tip is indicated by an arrow. *Patient 1.* Anteroposterior (AP) view (**top left**) of internal carotid artery and AP (**right**) and lateral (**bottom**) views of the selectively filled anterior and middle cerebral arteries. *Patient 2.* Lateral view of the internal carotid artery with its branches (**top right**). Selectively filled anterior chorooidal artery and ramus temporalis superior of the middle cerebral artery (**bottom right**); *Patients 3 and 5.* Lateral view of the internal carotid artery angiogram (**left**) and the frontoopercular branch (**right**). *Patient 4.* Lateral view of the internal carotid artery (**middle**), the frontoopercular artery (**left**), and the ramus temporalis superior of the middle cerebral artery (**right**).

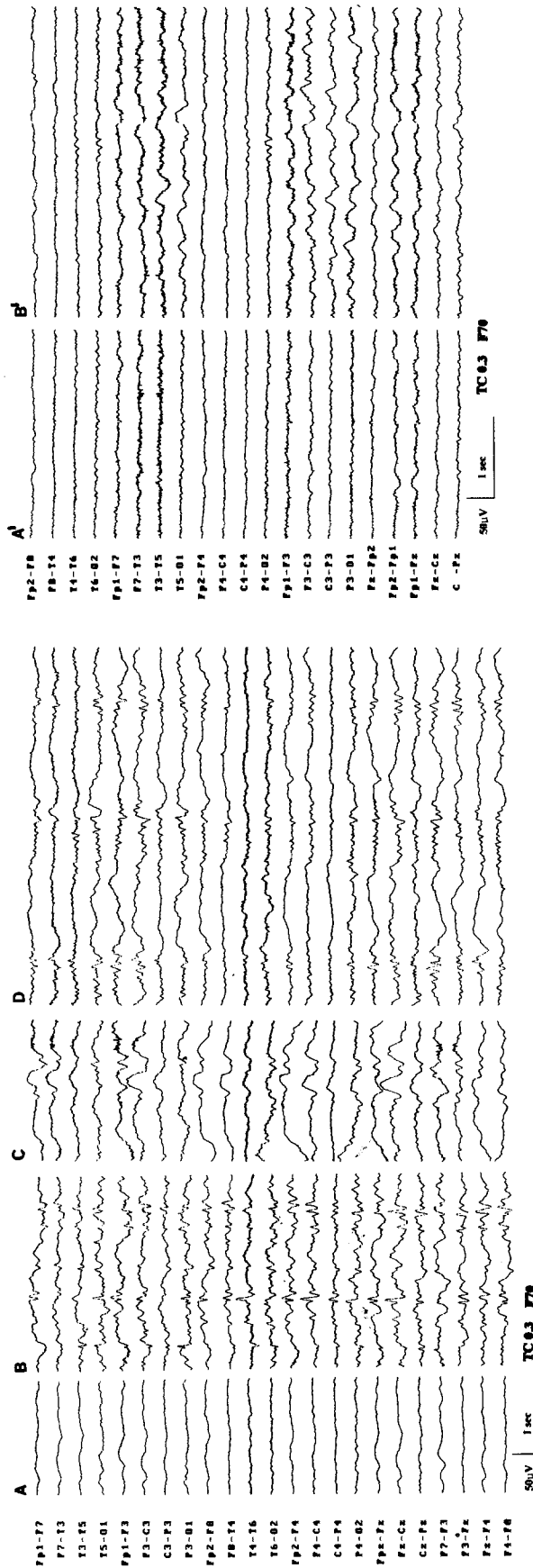


FIG. 3. Surface EEG recorded during the selective language Wada test in patients 1 (left) and 4 (right) showing the changes after the amobarbital injection. Baseline (A), sharp-waves with left frontal accentuation (B), bifrontal delta-waves (C), suppression-burst pattern (D), baseline (A'), left-hemispheric delta-waves (B').

ing to the International 10/20 System (Fig. 3). In patient 2, in addition to the scalp EEG, the EEG of the mesio-basal TL structures was recorded with bilateral four-contact FO electrodes. In patients 1, 3, and 5 the left-hemispheric opercular region was temporarily inactivated by injection of the amobarbital into the left frontoopercular branch of the middle cerebral artery. In patients 2 and 4, two different selective amobarbital tests were performed. In patient 2, in addition to selective inactivation of the presumed posterior sensory language region with injection of amobarbital into the ramus temporalis superior of the left middle cerebral artery, memory functions were evaluated by sTLAM with injection of amobarbital into the left acha (4–6). In patient 4, the first selective amobarbital test was aimed at inactivation of the presumed frontal motor language area. The second test was aimed at inactivation of the posterior temporoparietal language region. Because the effect of amobarbital lasts ~6–8 min (17), an interval of 30 min between the two injections ensured no interference between performance of the two procedures. The second amobarbital procedure was started after the patient recovered completely and after return of the patient's EEG to baseline.

In patients 1 and 2, [99m Tc]technetium-hexamethylpropylene-aminoxime single photon emission tomography ([99m Tc]HMPAO-SPECT) was performed 1 h after completion of the neuropsychological test with a rotating gamma camera (Picker Prism 3000, Bedford Heights, OH, U.S.A.; 120 projections, high-sensitivity, parallel-beam collimator, 64 × 64 matrix) (Table 2). The [99m Tc]HMPAO was coinjected with the amobarbital (intraarterially); therefore, the HMPAO distribution corresponded to the brain regions irrigated by the amobarbital (Fig. 4). In patient 2, who underwent two amobarbital procedures, the [99m Tc]HMPAO injection was combined with the amobarbital application into the left acha to visualize amobarbital distribution in the mesio-basal TL regions.

Selective extratemporal Wada test results

The IAP with selective inactivation of the frontoopercular and the parietotemporal brain regions proved effective in all our patients. Selective amobarbital inactivation of the left-hemispheric frontoopercular region produced no language deficits in patients 1, 3, and 4. Surgical resection of the left frontooperculum or adjacent brain regions left these patients with unimpaired lan-

TABLE 2. Details of amobarbital procedure in 5 patients

Patient	injected artery (amobarbital)	Dosage of amobarbital (mg)	Motor deficits	Neuropsychology	EEG changes after amobarbital injection	HMPAO-SPECT
1	Left anterior and middle cerebral arteries	100	Right hemiparesis	No language impairment	7 s postinjection—pseudorhythmic sharp waves for 13 s with left frontal accentuation, then bifrontal delta waves for 13 s, followed by suppression burst pattern lasting 160 s	Regional tracer distribution left frontal
2	Left anterior choroidal artery	65	Slight paresis of the right arm	No memory decline	Questionable slowing in left FO electrode for ~20 s after the injection; 64 s postinject—occurrence of 1–1.5/s sharp waves in the left FO electrode without changes in EEG activity in right FO or in surface electrodes	Regional tracer distribution of the left mesio-basal TL structures
	Ramus temporalis superior of the left middle cerebral artery	65	Right hemianopsia	Language impairment	100 s postinjection—1.5–3/s sharp waves in the left FO electrode with no other EEG changes	
3	Left frontoopercular branch	110	Paresis of the right arm	No language impairment	No changes	ND
4	Left frontoopercular branch	40	No deficits	No language impairment	No changes	ND
	Ramus temporalis superior of the left middle cerebral artery	40	Right hemiparesis	No language impairment	7 s postinjection—left hemispheric delta waves with a duration of 56 s	ND
5	Left frontoopercular branch	80	No deficits	Global aphasia	No changes	ND

SPECT, single photon emission computed tomography; FO, foramen ovale (10).

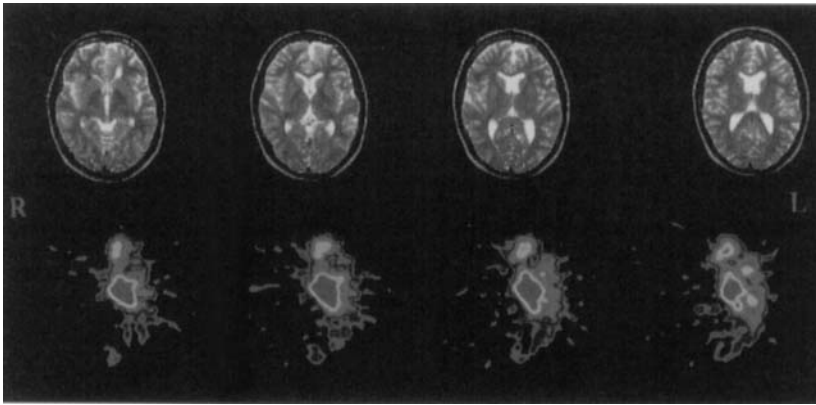


FIG. 4. Transverse sections of [^{99m}Tc]HMPAO-single photon emission computed tomography of patient 1 (with corresponding magnetic resonance imaging slices) showing HMPAO distribution in the left frontal lobe after simultaneous intraarterial co-injection of amobarbital and of 5 MBq [^{99m}Tc]HMPAO into the left anterior and middle cerebral arteries.

guage functions, demonstrating the reliability of the amobarbital procedure. Inactivation of the posterotemporo-parietal region in patient 2 caused naming, comprehension, and word-repetition deficits. Therefore, in this patient, the epileptogenic area in the mesiobasal TL structures was removed, since the risk of postoperative language deficits that might have resulted from a temporolateral cortical resection was considered too high. Postoperatively, patient 2 did not develop language deficit and was seizure-free. Temporary amobarbital inactivation of the left frontooperculum in patient 5 resulted in transient global aphasia. Therefore, the frontoopercular tumor was partially resected. Despite the limited tumor resection, patient 5 developed global aphasia immediately after surgery. Except for naming difficulties, the aphasia in patient 5 resolved in the postoperative course. The amobarbital procedure is described in further detail in Table 2.

DISCUSSION

In the traditional IAP, the effect of the temporary anesthesia is routinely validated by confirmatory tests such as testing for the presence of neurological deficits, monitoring of EEG changes (18–20), and more recently, by SPECT (21–23). Despite the rather small target brain areas perfused by the amobarbital in our patients, the proper temporary inactivation could be demonstrated by at least one concomitant test performed during the procedure. Of seven tests performed in our 5 patients, the drug caused temporary neurological deficits in five, and induced EEG changes in four procedures (Table 2 and Fig. 3). The sharp wave activation in patient 2, which occurred >1 min after injection of the drug into the left acha, must be interpreted with caution, however. Amobarbital-induced EEG responses usually occur 6–12 s after drug application, substantially earlier than the sharp wave activation observed in patient 2 in the course of sTLAM (Table 2) (18,20,24). Therefore, proper inactivation of mesial TL structures in patient 2 and the predictive value of the memory test is questionable. Indeed,

patient 2 displayed a decline in verbal memory functions after AHE, which contradicts the preoperative finding of intact memory during the IAP. The results of subsequently performed test with amobarbital injection into Wernicke's area were valid.

The HMPAO distribution overlapped exactly the brain region perfused by the amobarbital (Fig. 4) in patients 1 and 2. Since 1994, [^{99m}Tc]HMPAO- or [^{99m}Tc]ethylcysteinate-dimer (ECD)-SPECT has been routinely included in our sTLAM test protocol and proved to be worthwhile for validation of amobarbital delivery to the mesiobasal TL structures (6). The confirmatory SPECT evidence is of particular importance, because former [^{99m}Tc]HMPAO studies performed after conventional IAP indicated incomplete hemispherical barbiturate perfusion with considerable intraindividual variation (21,22). In particular, the mesiobasal TL structures showed inconsistent barbiturate perfusion, varying between 72 and 18% after the IAP. Therefore, Coubes et al. (21) and Jeffery et al. (22) emphasized the need for caution in the use of the IAP to predict neuropsychological outcome after removal of mesiobasal TL structures.

An alternative approach to study language representation is preoperative (25) or intraoperative (26) electrical cortical stimulation. However, despite their high reliability, these methods have several limitations. Whereas the presurgical Wada test contributes to the decision to recommend epilepsy surgery, intraoperative cortical mapping can be applied only in patients for whom a decision for surgical intervention has already been made. Moreover, the latter method is limited to highly cooperative patients who can tolerate brain surgery without general anesthesia.

Our results indicate that selective temporary inactivation of brain regions, which may be associated with language functions, can be safely and effectively performed. In our 5 patients, the functions of the irrigated target areas could be clearly determined and the effect of the amobarbital was confirmed in 4 of the 5 patients (80%) by at least one concomitant test performed during the

procedure. In 3 patients, the selective amobarbital test with inactivation of the frontal operculum suggested no language function of this classic motor language area and thus allowed radical surgery without risk of postoperative language impairment. In patient 5, the fibrillary astrocytoma invading Broca's region was not removed completely because of the amobarbital-verified language functions present in that brain region. Despite the limited resection, patient 5 had a transient complete aphasia postoperatively. Because language function improved postoperatively, the global aphasia in patient 5 might have been caused at least to some degree by postoperative edema. Without the preoperatively acquired knowledge of the left frontal language representation in patient 5, a more radical tumor resection would probably have caused permanent and severe language deficits. The Wernicke's language region remained surgically untouched in patient 2, whose lesion was in the temporo-posterior neocortex. Fortunately, removal of the epileptogenic zone located in the mesiobasal TL structures led to complete relief of seizures.

Because of the small number of patients in our study, our results with regard to selective amobarbital inactivation of presumed language areas are preliminary. Despite the favorable results in our patients, caution must be used in administering the selective amobarbital tests because they carry all potential risks of an invasive procedure. Therefore, use of these procedures should be restricted to a highly selected group of patients. The complication rate in the conventional IAP is ~0–5% (27). The selective posterior TL amobarbital procedure has been associated with such serious complications (8) that it has been discontinued at some epilepsy centers (28). Although no complications resulted from the posterior TL amobarbital procedure in our center, indication for its use is restricted in our institution as well. The dangers associated with the amobarbital tests warrant a search for safer and noninvasive tests of brain function. Both positron emission tomography (PET) (29) and functional MRI (fMRI) (30,31) have proven effective in mapping language functions to certain brain areas. Two recent fMRI studies confirmed the conventionally (by IAP) assessed language dominance in patients with TLE (32,33). These new noninvasive functional techniques might soon replace the traditional invasive methods not only for assessment of language but also for assessment of other cognitive functions. However, whether their predictive value with regard to postoperative outcome is equal to that of the IAP remains to be shown. Functional imaging studies indicate only what structures support a cognitive function, not what structures are indispensable to normal cognitive functioning.

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