Technetium-99m-HMPAO SPECT Imaging of Cerebral Blood Flow during REM Sleep in Narcoleptics

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This study was performed to demonstrate global and regional cerebral blood flow (rCBF) changes during rapid eye movement (REM) sleep in six patients with narcolepsy using SPECT and ^{99m}Tc-HMPAO. **Methods:** Global and hemispheric HMPAO uptake as well as regional (RI) and asymmetry indices were estimated and compared between polysomnographically verified sleep onset (SO)REM and wakefulness. **Results:** The estimated global HMPAO uptake did not differ between the two conditions indicating a similar overall cortical activity. During (SO)REM sleep, hemispheric HMPAO uptake as well as calculated RI, especially in the supratemporal plane, were significantly higher on the right side than contralateral. This indicates an initially right-sided cerebral activation and a special involvement of the right, nondominant hemisphere during dreaming which is responsible for visual-spatial perceptions. Furthermore, increased RI in superior parietal regions during sleep were evident and were explained by an activation of associative areas. In thalamic regions, decreased RI were found during sleep, which may reflect thalamic dysfunction. **Conclusion:** A definite assignment of these CBF alterations to (SO)REM sleep might be problematic because of unstable boundaries between sleep stages in narcolepsy. On the other hand, specificity of such CBF changes for narcolepsy requires further study.

Key Words: rapid-eye-movement sleep; narcolepsy; regional cerebral blood flow; technetium-99m-HMPAO; single-photon emission computerized tomography

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Changes in cerebral metabolism (CM) and cerebral blood flow (CBF) during sleep have been investigated for many years (*1*) to delineate CBF changes according to different sleep stages (*2–6*). Thus, CBF reductions during nonrapid-eye-movement (NREM) sleep could be repeatedly confirmed (*4–6*). On the other hand, during rapid-eye-movement (REM) sleep, which is regarded as a special form of consciousness related to dreams and accompanied by muscle atonia, large CBF increases were initially reported (*5,7*). Recent investigations, however, indicate only small (*6*) or relative CBF increases during REM sleep in comparison to NREM sleep (*4*). The determination of cerebral metabolic rate of oxygen ($CMRO_2$) or glucose (CMRglc) during REM sleep has also demonstrated virtually no differences from values obtained while patients are awake (*4,6,8*).

Few investigations in sleep research have dealt with regional CBF (rCBF) changes during REM sleep in humans (*8–10*) or in sleep disorders (*11*). Many studies have utilized SPECT and ^{99m}Tc-dl-hexamethyl-propyleneamineoxime (HMPAO) as a blood flow tracer (*12*). With this method, absolute CBF measurements are impossible, only semiquantitative evaluation can be performed. Madsen et al. (*10*) used HMPAO and SPECT to demonstrate rCBF changes during REM sleep in healthy subjects. Relative CBF increase in the associative visual cortex and relative decrease in the inferior frontal were described. The few existing studies in humans dealing with regional CM or CBF variations during REM sleep, however, have not demonstrated concordant results (*8,9,13*).

Meyer et al. (*11*) described CBF increases in NREM as well as REM sleep in patients with narcolepsy and indicated abnormal CBF regulation during sleep. The question arises whether an abnormal regional activation could be attributed to this disease or not. The aim of the study was to: (a) analyze rCBF changes during REM sleep in patients with narcolepsy using HMPAO and SPECT; (b) investigate the perfusion pattern in this sleeping disorder; (c) study cerebral activation during sleep onset (SO)REM; and (d) evaluate the application of SPECT and HMPAO for sleep research in daily practice. Regional indices (RI) were calculated, and individual cerebral HMPAO uptake related to injected dose and calculated brain volume was estimated and regarded as another measure of semiquantification for this purpose.

MATERIALS AND METHODS

Six right-handed patients (3 women, 3 men; aged 17 to 52 yr; mean, 40.5 ± 12.5 yr) were investigated twice with ^{99m}Tc-HMPAO SPECT. All suffered from idiopathic narcolepsy for years

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with typical clinical symptoms such as: sleep attacks, hypnagogic hallucinations, sleep paralysis and cataplexy. Polysomnography and multiple sleep latency tests demonstrated an abnormal occurrence of REM sleep and excluded other sleep disorders. HLA antigen determination revealed a HLA-DR2 antigen in all patients. Transmission CT and MRI showed no abnormalities. Only one patient was permanently treated with a psychostimulant, whereas the others did not receive any therapy. All patients gave informed consent.

The first SPECT investigation was performed at noon. In a light and sound-shielded room, polysomnography was performed including EEG, submental electromyography and electrooculography. EEG was recorded unipolarly with surface electrodes placed according to the 10–20 system with a common average reference. A peripheral vein catheter was placed on the forearm of each patient initially. Polysomnographic data were analyzed online. Sleep stages were scored according to the criteria of Rechtschaffen and Kales (*2*). Two minutes after onset of the first REM phase (SOREM), 0.27 mCi/kg body weight ^{99m}Tc-HMPAO was administered. Four minutes later, after uninterrupted REM sleep, the patients were awakened as HMPAO brain concentration reached its peak 2–3 min after administration (*14*). Four patients described the occurrence of dreams, mostly associated with fear or discomfort.

Data acquisition was started after 10 min. Patients were placed in a supine position in a dentist chair, their head fixed in an appropriate head holder. SPECT studies were performed with a dual-head rotating scintillation camera, equipped with high-resolution collimators (FWHM 12 mm). The rotations lasted for 30 min and 2 × 30 projections were achieved. After prereconstruction filtering and filtered back-projection using a soft Shepp-Logan filter, 3.125-mm thick transversal cross sections were reconstructed. A correction for tissue absorption was applied using Bellini's analytical method (*15*). Finally, seven reconstructed slices were summed consecutively (*16*).

The control investigation was also performed at noon 1 wk later. Before tracer administration, patients were advised to close their eyes and relax to avoid visual activation. Wakefulness was obtained by repeatedly tapping the patients. For optimal repositioning of the patients' heads, the lateral views of the first SPECT image (90° angle) were used as references to compare the slope of the orbito-meatal line. Data aquisition was started 15 min after tracer administration.

Evaluation of SPECT Studies

SPECT studies were evaluated visually by two experienced physicians (A.S., P.I.) who compared the two studies blinded to the state (wakefulness versus (SO)REM sleep). Cerebral HMPAO uptake was estimated for semiquantification of the SPECT images. For this purpose, voxel volumes, which contain at least 36% or more of the maximal voxel counts, were summed first to obtain brain volume. This threshold was an empirically found value, which guaranteed the best correspondence between cerebral borders in SPECT studies and CT scans. The system was calibrated using a phantom with known radioactivity (near the assumed cerebral uptake) and applying the same acquisition protocol as previously described. This method enabled conversion of counts into millicuries. The brain midline was defined individually so it was possible to calculate hemispheric HMPAO uptake without the values of the midline. Global and hemispheric HMPAO uptake were expressed in percent of injected dose per 100 ml brain volume. Intraindividual reproducibility of this method has been previously described (*17*).

Additionally, 17 supratentorially located regions of interest (ROIs) were drawn manually by one investigator (A.S.) on four representative slices (Fig. 1) over one hemisphere according to Podreka et al. (*18*) with exception of region 11. This set of ROIs was mirrored across the midline with necessary minor adjustments, and was used for the second study as well. A RI (*16*) and an asymmetry index (AI) were calculated: RI = (mean counts/voxel of one ROI/mean counts/voxel of all ROI), AI = [(mean counts/voxel of right ROI minus mean counts/voxel of left ROI)/(mean counts/voxel of right ROI plus mean counts/voxel of left ROI)/2)] × 100.

Global and hemispheric HMPAO uptake values were compared intraindividually between the two investigations using the Student's t-test for paired data. An analysis of variance (ANOVA) was performed for each RI with factors side (left versus right), state (wakefulness versus (SO)REM), side × state, region × state and region × side × state and for each AI with factor state. Regional indicies values with no hemispheric differences in either state were pooled together.

RESULTS

The SPECT studies during wakefulness were normal in all instances. During (SO)REM sleep, the visual evaluation revealed a relatively increased HMPAO uptake in the right insula/right supratemporal region in 4 of 6 patients. (Fig. 2).

The calculated global HMPAO uptake did not differ between the two investigations (Student's t-test for paired data, $t = 1.28$, $p < 0.268$). During (SO)REM sleep, hemispheric HMPAO uptake was significantly higher on the right side than on the left side ($t = 3.32$, $p < 0.021$) (Table 1).

The mean values (± s.d.) of RI and AI of every ROI are listed in Tables 2 and 3. Significant right/left differences of RI with higher values on the right side were evident supratemporally during (SO)REM sleep ($F = 7.66$, $p < 0.02$), in the insula (wakefulness: $F = 7.13$, $p < 0.02$; (SO)REM sleep: $F = 11.0$, $p < 0.006$), in the inferior parietal (wakefulness: $F = 6.14$, $p < 0.03$; (SO)REM sleep: $F = 19.7$, $p < 0.001$) and superior central region (wakefulness: $F = 5.11$, $p < 0.04$; (SO)REM sleep: $F = 9.2$, $p < 0.013$). A significantly higher RI during (SO)REM sleep in comparison to wakefulness was found in the superior parietal ($F = 6.6$, $p < 0.017$) and superior frontal regions ($F = 4.28$, $p < 0.05$). In the sleep condition, the RI was significantly lower in the superior and inferior occipital ROIs ($F = 4.79$, $p < 0.04$; $F = 4.48$, $p < 0.04$, respectively) as well as in the thalamus ($F = 4.3$, $p < 0.05$) than during wakefulness. The AI of the supratemporal ROI was significantly higher during (SO)REM sleep compared to the control condition ($F = 12.4$, $p < 0.006$).

Two-way ANOVA (side × state) of the RI of the supratemporal ROI showed a tendency towards enhanced asymmetry in favor of the right side during (SO)REM sleep ($F = 3.47$, $p < 0.07$). Superior and inferior occipital regions as well as the thalami responded to (SO)REM sleep differently than the laterofrontal cortex with relatively decreased values (two-way ANOVA (region × state): $F = 4.8$, $p <$

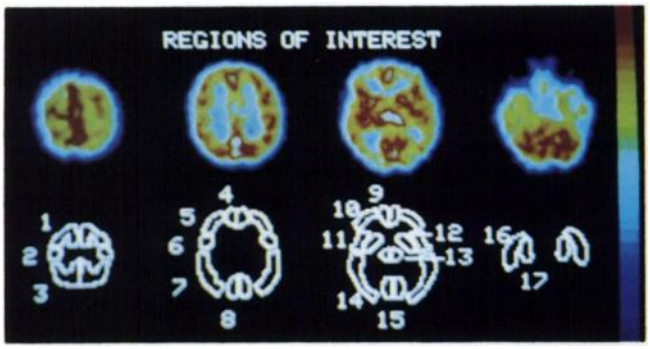

FIGURE 1. Seventeen manually drawn ROIs over representative slices. 1 = superior frontal, 2 = superior central, 3 = superior parietal, 4 = superior mesiofrontal, 5 = laterofrontal, 6 = central, 7 = inferior parietal, 8 = superior occipital, 9 = inferior mesiofrontal, 10 = frontobasal, 11 = insula, 12 = basal ganglia, 13 = thalamus, 14 = supratemporal, 15 = inferior occipital, 16 = laterotemporal, 17 = mesiotemporal.

0.03; F = 4.2, $p < 0.04$, respectively); the opposite was evident for superior parietal regions with relatively increased RI (F = 5.3, $p < 0.027$). A direct comparison between the thalami and the superior parietal cortex demonstrated an opposite behavior with relatively decreased thalamic and increased cortical values in the sleep condition (F = 8.8, $p < 0.005$). Three-way ANOVA (region ×, side × state) was useful in comparing the supratemporal and the laterofrontal region (F = 3.9, $p < 0.05$) in that it revealed a different reaction to sleep with a relatively reduced supratemporal RI on the left side together with an increased supratemporal RI on the right side.

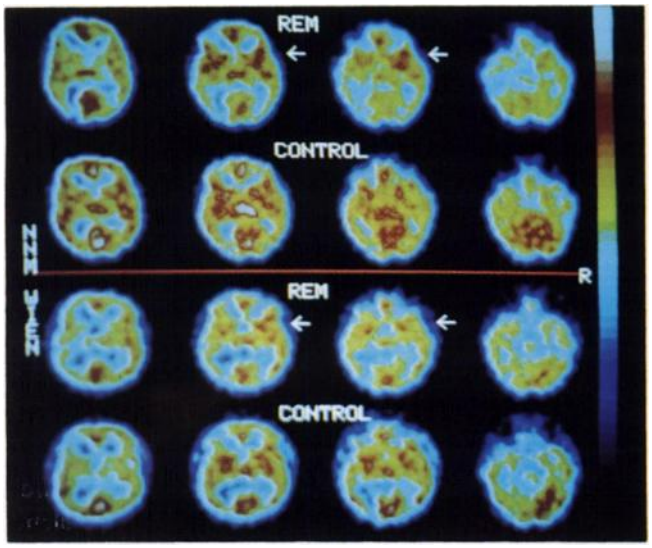

FIGURE 2. First and second row: ^{99m}Tc-HMPAO SPECT images of a 27-yr-old woman. Third and fourth row: ^{99m}Tc-HMPAO SPECT images of a 41-yr-old woman. Both patients have known untreated narcolepsy. First and third row: SPECT during wakefulness. Second and fourth row: SPECT during REM sleep, scaled on the maximum of SPECT during wakefulness. Arrows indicate enhanced asymmetric tracer deposition in the supratemporal plane/insula during (SO)REM sleep in comparison to wakefulness.

TABLE 1
Calculated Cerebral HMPAO Uptake in Percent of Injected Dose/100 Milliliters Brain Volume

	Global	Left Hem	Right Hem
(SO)REM	0.365 ± 0.044	0.327 ± 0.092	0.332 ± 0.095*
Awake	0.319 ± 0.065	0.317 ± 0.064	0.317 ± 0.068

*Left versus right hem during (SO)REM, $p < 0.021$. (SO)REM = (sleep onset) rapid-eye movement sleep; HEM = hemisphere.
Data were analyzed by Student's t-test for paired data.

DISCUSSION

CBF, CMRglc or $CMRO_2$ measurements during sleep are based on the idea that these parameters are not simply correlated to changes in cortical activity (*19*), but are additionally related indirectly to EEG alterations (*20*). Various investigations could demonstrate a correlation between slowing of EEG during NREM sleep and CBF (*5,6*) and CMRglc reductions (*9,13*). Slightly divergent results have been obtained in analyzing global or regional CBF changes during REM sleep applying SPECT, PET or the Kety Schmidt technique (*21*).

In the present investigation, cerebral HMPAO uptake was estimated and regarded as a marker of CBF. This method of evaluating cerebral HMPAO uptake did not indicate global CBF changes during (SO)REM sleep when compared to wakefulness, which could be interpreted as a similar overall neuronal activity in both stages. A lack of significant CBF alterations during REM sleep in normal subjects has been discussed by Madsen et al. (*4*) using the Kety-Schmidt technique. Discreet, but significant, CBF increases of 3%–12% have been described by Townsend et al. (*6*) during REM sleep. Data in our investigation (Table 1) indicate a slightly higher HMPAO uptake during (SO)REM sleep in patients with narcolepsy as well. The relatively early tracer administration during REM sleep, however, has to be taken into account, because significant changes may occur later.

Meyer et al. (*22*) and Sakai et al. (*5*) have indicated a right hemispheric accentuation of CBF changes during NREM sleep. The evaluation of hemispheric HMPAO uptake data in the present study revealed significantly higher uptake values on the right side during (SO)REM sleep in the patients with narcolepsy as well as relatively elevated or at least enhanced RI values (i.e., right sided) in the supratemporal plane and insula or inferior parietal cortex. Data gained could therefore be an expression of a particular, or at least earlier, involvement of the right hemisphere during REM sleep. Furthermore, the relative right hemispheric CBF increase can be interpreted as a special activation during dreaming due to right sided (or nondominant-sided) representation of visual-spatial perceptions.

Former studies dealing with rCBF or regional CMRglc changes during REM sleep have demonstrated overall CBF increases in cats (*7*) and humans (*5*). More recently,

TABLE 2
Regional Index (RI) of Different ROIs (± s.d.): Comparison between (SO)REM Sleep and Wakefulness

Region	Left Hem		Right Hem	
	(SO)REM	AWAKE	(SO)REM	AWAKE
Sup frontal	0.962 ± 0.036	0.934 ± 0.023	0.957 ± 016	0.948 ± 0.027†
Sup central	0.918 ± 0.032	0.909 ± 0.035	0.969 ± 0.024	0.950 ± 0.030*
Sup parietal	0.994 ± 0.038	0.956 ± 0.038	0.998 ± 0.044	0.963 ± 0.029†
Sup mesiofrontal	1.006 ± 0.035	0.992 ± 0.029	0.990 ± 0.033	0.994 ± 0.025
Laterofrontal	0.906 ± 0.018	0.904 ± 0.035	0.952 ± 0.015	0.925 ± 0.047
Central	0.941 ± 0.007	0.936 ± 0.052	0.961 ± 0.034	0.932 ± 0.041
Inf parietal	0.933 ± 0.025	0.950 ± 0.043	0.997 ± 0.025	0.997 ± 0.033*
Sup occipital	1.144 ± 0.016	1.179 ± 0.047	1.165 ± 0.026	1.185 ± 0.041†
Inf mesiofrontal	1.052 ± 0.044	1.047 ± 0.056	1.065 ± 0.053	1.068 ± 0.045
Frontobasal	0.930 ± 0.049	0.898 ± 0.072	0.961 ± 0.061	0.941 ± 0.076
Insula	1.019 ± 0.041	1.010 ± 0.032	1.104 ± 0.044	1.067 ± 0.042*
Basal ganglia	1.090 ± 0.067	1.097 ± 0.101	1.091 ± 0.048	1.070 ± 0.046
Thalamus	1.086 ± 0.056	1.155 ± 0.116	1.086 ± 0.052	1.149 ± 0.070†
Supratemporal	0.943 ± 0.028	0.977 ± 0.048	1.000 ± 0.053	0.979 ± 0.042*‡
Inf occipital	1.061 ± 0.068	1.117 ± 0.062	1.081 ± 0.058	1.138 ± 0.077†
Laterotemporal	0.939 ± 0.052	0.932 ± 0.059	0.941 ± 0.030	0.934 ± 0.075
Mesiotemporal	0.936 ± 0.063	0.924 ± 0.048	0.945 ± 0.039	0.918 ± 0.019

*Left versus right hem during (SO)REM.
†(SO)REM versus AWAKE (left plus right hem), at least $p < 0.05$.
‡(left/right × (SO)REM/AWAKE), $p < 0.07$.
Data were analyzed by one- and two-way ANOVA. (SO)REM = (sleep onset) rapid-eye-movement sleep, AWAKE = wakefulness, Hem = hemisphere, sup = superior, inf = inferior.

an elevated CMRglc in the gyrus cinguli (*8*) or left temporally and occipitally in humans (*9*) has been found. In a detailed autoradiographic investigation in cats, Lydic et al. (*23*) delineated CMRglc increases during REM sleep mainly in the limbic system and the thalamus. Heiss et al. (*13*) demonstrated an extraordinarily high CMRglc increase in one dreaming person in the inferior parietal and visual cortex as well as in the insula and suggested that these regions are actively involved in dreaming. A comparable result was obtained in this study. Increased asymmetry supratemporally for the right hemisphere and enhanced HMPAO uptake in the right insula and the right inferior parietal cortex during (SO)REM sleep indicate special activation of these regions in this early stage of REM sleep. Different (SO)REM-specific perfusion patterns in the supratemporal plane in comparison to the laterofrontal cortex could be demonstrated. Additionally, a parietal activation on both sides was evident during (SO)REM sleep in comparison to the laterofrontal cortex, which might be an expression of an involvement of associative areas during dreaming.

TABLE 3
Asymmetry Index (AI) of Different ROIs (± s.d.): Comparison between (SO)REM Sleep and Wakefulness

Region	(SO)REM	AWAKE
Sup frontal	0.56 ± 3.32	−1.492 ± 2.45
Sup central	−4.75 ± 3.21	−4.62 ± 4.72
Sup parietal	−0.03 ± 1.59	−0.713 ± 3.10
Sup mesiofrontal	1.61 ± 5.19	−0.237 ± 4.20
Laterofrontal	−4.64 ± 1.40	−2.175 ± 4.93
Central	−0.77 ± 3.54	0.46 ± 7.86
Inf parietal	−6.80 ± 3.89	−4.088 ± 6.64
Sup occipital	−1.80 ± 1.48	−0.533 ± 2.44
Inf mesiofrontal	0.85 ± 4.70	1.692 ± 2.98
Frontobasal	3.93 ± 7.80	5.41 ± 4.69
Insula	7.81 ± 3.99	5.263 ± 2.12
Basal ganglia	0.22 ± 3.91	−2.567 ± 5.30
Thalamus	0.04 ± 3.79	−0.192 ± 8.60
Supratemporal	6.44 ± 2.51	0.098 ± 3.62*
Inf occipital	−2.07 ± 3.73	−1.84 ± 2.38
Laterotemporal	0.17 ± 6.29	−0.128 ± 3.37
Mesiotemporal	1.17 ± 7.18	−0.668 ± 4.39

*(SO)REM versus AWAKE, $p < 0.006$.
Data were analyzed by one-way ANOVA. (SO)REM = (sleep onset) rapid-eye movement sleep; AWAKE = wakefulness; Sup = superior; inf = inferior.

Madsen et al. (*10*) used HMPAO-SPECT to delineate rCBF increases in the associative visual cortex and decreases in the inferior frontal cortex during REM sleep. Despite the fact that the results of Madsen et al. (*10*) were obtained in healthy subjects, our results from narcoleptic patients may at least be partially explained by the comparatively early HMPAO injection during (SO)REM phase because frontal deactivation may develop later. Due to different ROI size and location, the activation of the associative visual cortex in the study of Madsen et al. (*10*) might correspond to the described relative rCBF increase in the inferior parietal cortex. The RI of the primary visual

cortex was relatively diminished in sleeping patients. Lydic et al. has previously reported no CMRglc changes in the occipital cortex in cats (*23*). It also has to be considered that HMPAO is not retained linearly in high flow areas (*24*), so that modest increases in the occipital high flow areas may be underestimated at that early time of REM phase and might be detectable at more pronounced CBF increases.

Evaluation of the RI values in the thalamic region demonstrated relatively decreased rCBF values during (SO)REM sleep. Lydic et al. (*23*) found increased CMRglc in thalamic areas, whereas in the geniculate bodies a reduction in glucose metabolism was evident. Because the thalamic ROI contains the geniculate bodies, this might be an explanation for this result. But an altered function of the thalamus and its projections to the limbic system due to narcolepsy has to be discussed as well, because no perfusion changes in the limbic system during (SO)REM sleep have been observed. The missing rCBF variation in the limbic system on the other side might depend on the chosen ROIs. Lydic et al. (*23*) likewise described increased values during REM sleep in the limbic system except the hippocampus/amygdala region, which is part of the used mesiotemporal ROI. Additionally, the spatial resolution of the SPECT device has to be taken into account.

In the present study, it was possible to delineate (at least initially) a right-sided cortical activation during (SO)REM sleep, which seems to occur mainly because of enhanced uptake asymmetry in the supratemporal plane/insula. It is difficult to decide whether these changes are specific for narcoleptic patients and (SO)REM phases or not. Meyer et al. (*11*) described CBF increases during sleep in narcoleptics, irrespective of REM or NREM sleep. Maximal CBF increases during REM phase were observed right parietally, occipitally and posterior temporally. No clear differences regarding cortical perfusion during REM sleep were delineated in comparing these and the present results with the aforementioned data from former investigations with healthy subjects. As narcolepsy is characterized by impaired sleep-wake regulation due to abnormal functioning of neural generators and modulators in the brain stem, the cortical perfusion pattern during REM phase need not differ between patients and normal subjects.

On the other hand, ambiguous sleep with elements of REM or NREM sleep as well as elements of wakefulness during SOREM periods have been described in narcolepsy (*25*), indicating unstable boundaries between the sleep stages. We studied one patient with narcolepsy (unpublished data) and found that the CBF pattern during NREM sleep demonstrated relatively increased HMPAO uptake in the supratemporal plane/insula on the right side as well. Thus, further investigations have to be performed with healthy persons and during NREM sleep to decide whether CBF changes during the (SO)REM phase reflect peculiarities of cortical activation in narcolepsy at sleep onset or can be regarded as REM sleep-specific alterations.

CONCLUSION

Technetium-99m-HMPAO SPECT studies cannot provide absolute CBF measurements or absolute CBF changes. Application of this methodology to estimate cerebral HMPAO uptake made intraindividual comparisons between two investigations possible. In conjunction with the calculation of regional or asymmetry indices, a relatively comprehensive insight in cerebral perfusion could be obtained. Because ^{99m}Tc-HMPAO SPECT is easily available, it seems to be a valuable tool for investigating the physiology and pathology of sleep.

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FIRST IMPRESSIONS

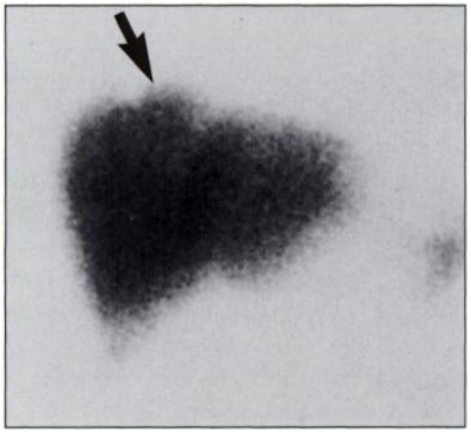

FIGURE 1.

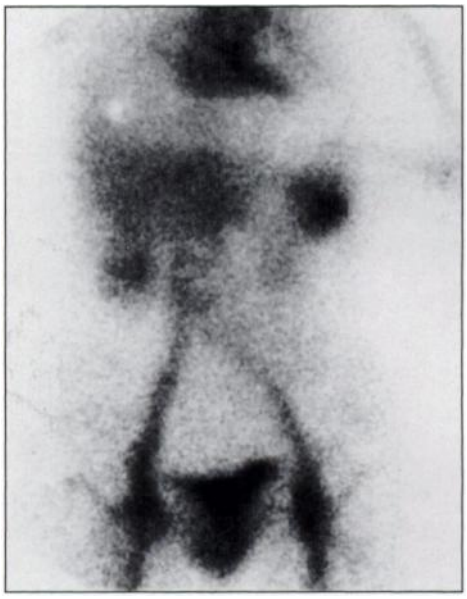

FIGURE 2.

PURPOSE
A 49-yr-old woman was examined for abdominal pain. Ultrasound revealed a hyperechoic lesion, 1.2 cm in diameter, in the right lobe of the liver. She was referred for liver-spleen imaging to assess for hepatic hemangioma. Technetium-99m-phytate imaging showed a round photopenic area in the superior part of the right lobe (Fig. 1). Hepatic red blood cell imaging performed 2 wk later detected an avascular area in the same region as the defect on the colloid image (Fig. 2). The patient wore a large ring on the fourth finger of her left hand which she used to lift her right breast during imaging.

TRACERS
Technetium-99m-phytate and Technetium-99m-RBCs

ROUTE OF ADMINISTRATION
Intravenous

TIME AFTER INJECTION
Fifteen minutes (Tc-phytate); 2 hr, Tc-RBC dynamic study, delayed imaging

INSTRUMENTATION
Apex-415 ECT camera

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