Increased Cerebral Blood Flow in Depressed Patients Responding to Electroconvulsive Therapy

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Considerable data support the existence of impaired regional cerebral blood flow (rCBF) in major depression. We compared rCBF in depressed patients before and after electroconvulsive therapy (ECT) to define whether the impairment is a "state"-related property or a trait phenomenon. **Methods:** Twenty patients with a major depressive disorder were studied by ^{99m}Tc-HMPAO brain SPECT, 2–4 days before and 5–8 days after a course of ECT. Three transaxial brain slices delineating anatomically defined regions of interest at approximately 4, 6 and 7 cm above the orbitomeatal line were used, with the average number of counts for each region of interest normalized to the area of maximal cerebellar uptake. **Results:** Technetium-99m-HMPAO uptake significantly increased in patients who responded to ECT but remained unchanged in patients who did not respond to the treatment (response defined as a reduction of at least 60% on the Hamilton Depression Rating Scale). An inverse correlation was observed between severity of depression and HMPAO uptake, and clinical improvement was positively correlated with the increase in tracer uptake. **Conclusions:** These findings imply that reduced rCBF in depression, as reflected in brain ^{99m}Tc-HMPAO uptake, is a "state"-related property and is reversible by successful treatment. Technetium-99m-HMPAO uptake may serve as an objective state marker for depression, as an indicator of the severity of depression and as an objective means of evaluating response to treatment.

Key Words: technetium-99m-HMPAO; brain SPECT; major depression; electroconvulsive therapy

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Functional brain imaging research in affective disorders has recently gained increased attention (*1*). Consistent with measurements derived from PET (*2–8*), decreases in global as well as regional cerebral blood flow (rCBF) in depressed patients have been reported by tomographic (*9–13*) and nontomographic (*14–16*) imaging techniques. However, several investigators (*17–19*) did not observe such differences. Furthermore, most findings (with some exceptions [*19*]) indicate that severity of depression is inversely correlated with rCBF, as measured by ^{133}Xe (*14,15*), HMPAO (*10,20*) and iodoamphetamine (IMP) (*9*), and with cerebral metabolic rate (CMR), as measured by PET (*2,3*).

Only a few studies have examined the effect of antidepressant treatments and associated remission on CMR or rCBF. Increases in CMR (*2*) and rCBF (*9*) and normalization of left–right asymmetries (*3*) have been observed in patients with remission from depression. However, no change in CMR despite remission has also been reported (*5*). Three recent studies that examined rCBF (*20,21*) and CMR (*22*) in depressed patients before and after treatment with sleep deprivation found changes (both increases and decreases) confined to responders.

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Studies examining the acute or subacute effects of electroconvulsive therapy (ECT) in depressed patients have shown reductions in rCBF (*23–26*) and CMR (*18,27,28*). Concerning the long-term effects of ECT, a significant reduction in rCBF, measured by the ^{133}Xe rCBF technique, was observed in patients with remission 0–3 mo after ECT (*23*), with a return to baseline 4–12 mo after ECT (*17,23*). Another ^{133}Xe (*29*) study found that response to ECT was associated with decreased global and rCBF, whereas nonresponse was associated with increased flow. In contrast to these ^{133}Xe studies, a recent ^{99m}Tc-HMPAO preliminary assessment (Vasile RG, Bradely FM, Bloomingdale KL, Schildkraut JJ, *unpublished observations,* 1994) revealed increased perfusion after response to a course of ECT.

Although most studies support this contention, the evanescent nature of the functional cerebral impairment in depression is still to be ascertained, along with the precise adaptations accompanying remission. To address these queries, we examined ^{99m}Tc-HMPAO uptake in a group of medication-free depressed patients before and after a course of treatment with ECT.

MATERIALS AND METHODS

Subjects

Twenty inpatients with major depression who had not responded to antidepressant medication were included in the study after having provided written informed consent (15 women, 5 men; mean age 59 ± 9.8 yr, range 41–73 yr). All patients met DSMIII-R criteria for major depressive disorder (MDD) (*30*) (11 unipolar, 9 bipolar) and had scores of at least 18 on the Hamilton Rating Scale for Depression (HAM-D) (*31*); two patients fulfilled DSMIII-R criteria for MDD with mood-congruent psychotic features. No patient had undergone ECT in the 12 mo before the study, and all had ceased taking antidepressant medication for at least 1 wk and antipsychotic medication for at least 1 mo before the ECT course. Occasional administration of short-acting benzodiazepines or chloral hydrate was permitted, but not within 12 hr of SPECT imaging. No other psychotropic medication was given for the duration of the study. All patients were right-handed, as determined by a standardized, detailed interview. Patients taking somatic medication that might affect SPECT evaluation and those with a history of neurological disorder, head trauma associated with loss of consciousness, suicide attempt, substance abuse or any current, severe medical condition were excluded from the study.

Administration of ECT

Electroconvulsive therapy was administered two or three times a week. Anesthesia and muscle relaxation were induced by intravenous administration of methohexital (0.5 mg/kg body weight [b.w.]) or pentothal (1.0–1.5 mg/kg b.w.) and succinylcholine (0.5–1.0 mg/kg b.w.). Electrode placement was bilateral frontotemporal for all patients, and a brief pulsed, bidirectional, constant stimulus was administered using MECTA-SR1 or Thymatron

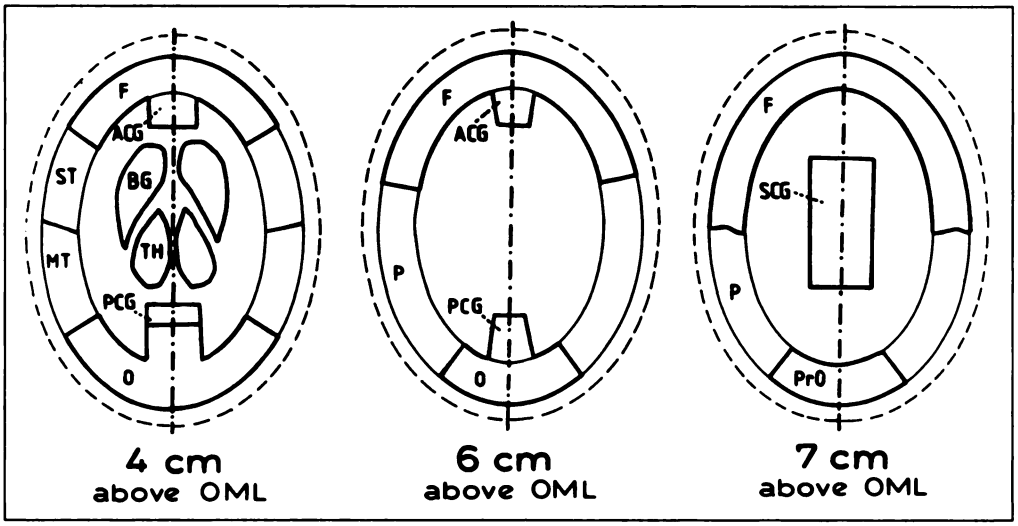

FIGURE 1. Regions of interest within the three templates. F = frontal lobe; ST = superior temporal lobe; MT = middle temporal lobe; O = occipital lobe; ACG = anterior cingulate gyrus; PCG = posterior cingulate gyrus; BG = basal ganglia; TH = thalamus; P = parietal lobe; PrO = parieto-occipital cortex; SCG = superior cingulate gyrus.

devices. Seizures were monitored with two-channel electroencephalography (EEG) and clinically in a cuffed limb. Dosage variables were adjusted during the course of treatment to elicit clinical seizures exceeding 20 sec or EEG seizures exceeding 25 sec (but less than 1 min), or both (*32*). Oxygenation through a face mask (100% oxygen) was provided throughout the procedure until resumption of spontaneous breathing. The ECT course was continued until a stable response had been achieved and (except in one case) for up to 12 treatments if the patient did not respond (mean 9.6 ± 1.7 [range 7–14] treatments per patient).

Scan Acquisition and Image Processing

SPECT imaging was performed 2–4 days (mean 2.8 ± 0.5) before the beginning of the ECT series and 5–8 days (mean 6.8 ± 1.1) after its termination.

All subjects received an intravenous injection of 740 MBq of ^{99m}Tc-HMPAO and were in a quiet, dimmed room, in a supine position with eyes open and ears unplugged. Image acquisition began after approximately 30 min. Patients were in a recumbent position, with head immobilized on a head rest and secured with Velcro straps. In addition, marks with ^{99m}Tc were made on the canthus and external auditory meatus, allowing accurate localization of the orbitomeatal line (OML).

SPECT images were obtained with a single-head rotating gamma camera equipped with a low-energy, high-resolution collimator. Data were collected in 60 projections, 25 sec per projection. Processing included normalization, backprojection, filtering, transaxial reconstruction and attenuation correction. Reconstruction was carried out with a Hanning filter on a 64 × 64 matrix and a slice thickness of 1 pixel (3.655 mm). Resolution of the system was 11 mm (full width at half maximum).

Data Analysis

Semiquantitative SPECT analysis was performed by applying preformed templates to transaxial SPECT slices, parallel to the OML. Three templates were used, based on a standardized brain atlas (*33*) delineating anatomic structures at approximately 4, 6 and 7 cm above the OML. Regions of interest (ROIs) were defined on these templates (Fig. 1). The size of the template could be visually adjusted so that its contour would generally fit any brain size (Fig. 2). The size of the ROIs within the template was relative to the dimensions of the template while the layout was constant.

The rCBF ratio was calculated for each ROI using the average number of counts divided by maximal cerebellar uptake and was subsequently used for all statistical comparisons. The data were analyzed separately for each hemisphere in the three transaxial brain slices. This method was selected after comparing rCBF measures normalized to the ipsilateral cerebral cortex; results were not different from those presented.

Because ^{99m}Tc-HMPAO uptake values were not normally distributed in our patient group, nonparametric statistics were used to compute significance levels. Pretreatment ^{99m}Tc-HMPAO uptake values were compared between responders and nonresponders and with ECT results by means of the Wilcoxon Signed Rank test, and pre-ECT versus post-ECT uptake values were compared by the same procedure in responders and nonresponders separately. The rCBF values were correlated with clinical ratings using the Spearman rank order test; p values greater than 0.05 are indicated as nonsignificant (n.s.). The Bonferroni correction for multiple testing was applied at a confidence level of 0.05, and significant values that survived correction are indicated. The Mann-Whitney *U*-test and chi-square test were used to compare background and clinical variables. Results are presented as mean value ± standard deviation (s.d.).

RESULTS

Clinical Characteristics

Eleven of the 20 patients responded to ECT with at least a 60% reduction in the pretreatment HAM-D score and maintenance of the remitted state for at least 1 wk after the treatment course. There was no significant difference in background and clinical characteristics between the responder and nonresponder groups, apart from post-treatment HAM-D scores ($p < 0.0005$).

SPECT Results

Differences between pre-ECT and post-ECT ^{99m}Tc-HMPAO uptake ratios were initially evaluated for the group of subjects as a whole (n = 20). Significant differences were observed only in the transaxial brain slice 6 cm above the OML, the anterior

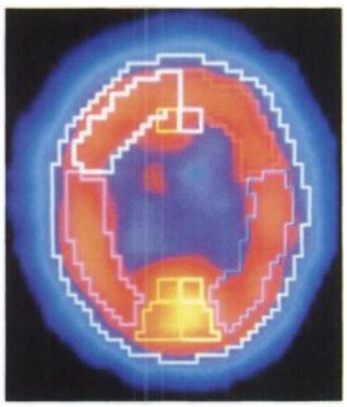

FIGURE 2. Transaxial SPECT image at 6 cm above the OML with the corresponding template as overlay.

TABLE 1
Uptake Ratios (Mean ± s.d.) in 11 Responders and 9 Nonresponders to Electroconvulsive Therapy at 4 cm above the Orbitomeatal Line

Region	Left hemisphere			Right hemisphere		
	Before ECT	After ECT	Significance	Before ECT	After ECT	Significance
			Responders (df = 10)			
Frontal	0.77 ± 0.088	0.78 ± 0.082	ns	0.78 ± 0.108	0.78 ± 0.061	ns
Sup temporal	0.75 ± 0.086	0.80 ± 0.090	0.02	0.80 ± 0.071	0.82 ± 0.084	ns
Med temporal	0.82 ± 0.059	0.88 ± 0.067	0.01	0.82 ± 0.054	0.86 ± 0.063	ns
Occipital	0.89 ± 0.046	0.91 ± 0.070	0.05	0.88 ± 0.050	0.92 ± 0.076	ns
Ant cingulate	0.71 ± 0.075	0.81 ± 0.076	0.004*	0.72 ± 0.069	0.82 ± 0.065	0.004*
Post cingulate	0.71 ± 0.036	0.82 ± 0.055	0.004*	0.71 ± 0.057	0.83 ± 0.058	0.004*
Basal ganglia	0.80 ± 0.082	0.87 ± 0.085	0.01	0.78 ± 0.103	0.86 ± 0.092	0.02
Thalamus	0.76 ± 0.083	0.80 ± 0.075	ns	0.73 ± 0.101	0.78 ± 0.063	ns
Global	0.80 ± 0.059	0.84 ± 0.062	0.02	0.80 ± 0.066	0.84 ± 0.057	ns
			Nonresponders (df = 8)			
Frontal	0.71 ± 0.090	0.69 ± 0.066	ns	0.73 ± 0.090	0.72 ± 0.037	ns
Sup temporal	0.72 ± 0.057	0.71 ± 0.042	ns	0.76 ± 0.067	0.75 ± 0.049	ns
Med temporal	0.85 ± 0.052	0.81 ± 0.058	ns	0.83 ± 0.067	0.82 ± 0.030	ns
Occipital	0.87 ± 0.052	0.85 ± 0.050	ns	0.85 ± 0.058	0.85 ± 0.056	ns
Ant cingulate	0.73 ± 0.067	0.68 ± 0.127	ns	0.76 ± 0.060	0.70 ± 0.131	ns
Post cingulate	0.81 ± 0.088	0.77 ± 0.082	ns	0.80 ± 0.071	0.78 ± 0.087	ns
Basal ganglia	0.76 ± 0.119	0.76 ± 0.058	ns	0.77 ± 0.109	0.79 ± 0.050	ns
Thalamus	0.71 ± 0.131	0.73 ± 0.025	ns	0.70 ± 0.154	0.74 ± 0.054	ns
Global	0.78 ± 0.058	0.76 ± 0.014	ns	0.78 ± 0.068	0.77 ± 0.013	ns

*Significance level survived Bonferroni correction for multiple testing.
ECT = electroconvulsive therapy; df = degrees of freedom; ns = not significant; Sup = superior; Med = medial; Ant = anterior; Post = posterior.

and posterior cingulate gyrus of the left hemisphere ($p = 0.04$ and $p = 0.03$, respectively) and the posterior cingulate gyrus of the right hemisphere ($p = 0.002$). Only the difference in the right posterior cingulate gyrus survived Bonferroni correction. We then compared rCBF values in depressed subjects with a diagnosis of unipolar disorder with those in subjects with a diagnosis of bipolar disorder, both before and after ECT. No differences were found in either assessment. Furthermore, response or nonresponse to ECT was not associated in any way with polarity ($p = 0.74$). Subsequently, data were analyzed separately for responders ($n = 11$) and nonresponders ($n = 9$) to ECT.

Responders showed a significant increase in uptake ratios 4 cm above the OML for multiple areas as well as globally in the left hemisphere, and for the anterior and posterior cingulate and basal ganglia of the right hemisphere (Table 1). The most significant change in the anterior and posterior cingulate regions of both hemispheres survived Bonferroni correction. In the brain slice 6 cm above the OML (Table 2), the responders showed significantly increased uptake in the anterior and posterior cingulate gyri bilaterally (survived Bonferroni correction) and in the parietal lobe of the right hemisphere. In the slice 7 cm above the OML (Table 3), a significant bilateral increase was observed in the frontal and parietal lobes, the parieto-occipital region and in global perfusion of the responders.

In patients who did not respond to ECT, no statistically significant change in ^{99m}Tc-HMPAO uptake ratio was observed in any of the three brain slices. In contradistinction to the responders whose ^{99m}Tc-HMPAO uptake ratios increased after ECT throughout almost all regions examined, pretreatment values in the nonresponders were higher than post-treatment values in 33 regions within the three transaxial slices (Tables 1–3).

We then compared pretreatment rCBF ratios in responders and nonresponders. No statistically significant differences were found, with the exception of the right posterior cingulate gyrus in the transaxial slice 6 cm above the OML, which survived Bonferroni correction (responders: 0.90 ± 0.07; nonresponders: 1.00 ± 0.07; $p = 0.008$).

Correlational analysis between HAM-D scores and ^{99m}Tc-HMPAO uptake ratios for all patients before and after ECT demonstrated significant inverse correlations, particularly after ECT, in many brain regions of the three slices as well as globally (Table 4). A numerical measure of the change in HAM-D scores and ^{99m}Tc-HMPAO uptake was derived by subtraction of the respective post-ECT values from the pre-ECT values. Correlations between these changes are shown in Table 4 ("Difference" columns). The degree of improvement was positively correlated with the extent of increase in ^{99m}Tc-HMPAO uptake in many brain regions and globally over the left hemisphere. For the brain slices 6 and 7 cm above the OML, brain regions exhibiting significance (after Bonferroni correction) for the "difference" variable were similar to those demonstrating increased uptake in patients who responded clinically to ECT.

DISCUSSION

The present study found that depressed patients who responded to ECT showed a significant increase in rCBF, whereas nonresponders demonstrated no change. An inverse correlation between the severity of depression and ^{99m}Tc-HMPAO uptake was detected, and clinical improvement was positively correlated with an increase in ^{99m}Tc-HMPAO uptake.

TABLE 2
Uptake Ratios (Mean ± s.d.) in 11 Responders and 9 Nonresponders to Electroconvulsive Therapy at 6 cm above the Orbitomeatal Line

Region	Left hemisphere			Right hemisphere		
	Before ECT	After ECT	p Value	Before ECT	After ECT	p Value
			Responders (df = 10)			
Frontal	0.74 ± 0.068	0.74 ± 0.101	ns	0.77 ± 0.073	0.76 ± 0.061	ns
Parietal	0.77 ± 0.061	0.79 ± 0.075	ns	0.78 ± 0.057	0.82 ± 0.046	0.02
Occipital	0.91 ± 0.090	0.89 ± 0.091	ns	0.90 ± 0.083	0.89 ± 0.074	ns
Ant cingulate	0.74 ± 0.078	0.84 ± 0.106	0.008*	0.75 ± 0.071	0.86 ± 0.104	0.004*
Post cingulate	0.93 ± 0.089	1.04 ± 0.076	0.004*	0.90 ± 0.074	1.02 ± 0.078	0.004*
Global	0.78 ± 0.058	0.79 ± 0.074	ns	0.79 ± 0.053	0.81 ± 0.048	ns
			Nonresponders (df = 8)			
Frontal	0.71 ± 0.096	0.69 ± 0.048	ns	0.72 ± 0.089	0.73 ± 0.032	ns
Parietal	0.78 ± 0.073	0.73 ± 0.028	ns	0.78 ± 0.067	0.77 ± 0.041	ns
Occipital	0.87 ± 0.059	0.82 ± 0.047	ns	0.87 ± 0.049	0.83 ± 0.063	ns
Ant cingulate	0.79 ± 0.116	0.77 ± 0.087	ns	0.77 ± 0.113	0.80 ± 0.078	ns
Post cingulate	0.98 ± 0.088	0.97 ± 0.068	ns	1.00 ± 0.071	0.97 ± 0.086	ns
Global	0.77 ± 0.073	0.73 ± 0.025	ns	0.77 ± 0.069	0.77 ± 0.028	ns

*Significance level survived Bonferroni correction for multiple testing.
ECT = electroconvulsive therapy; df = degrees of freedom; ns = not significant; Ant = anterior; Post = posterior.

The finding of an inverse correlation between the severity of depression and rCBF replicates previous reports with ^{133}Xe (*18,19*), ^{99m}Tc-HMPAO SPECT (*10,12,20,21*), ^{123}I-IMP SPECT (*9*) and PET CMR (*8*) and would appear to be a relatively robust observation. This was particularly evident for the post-ECT assessment. Before treatment, the patient sample homogeneously included depressed patients (HAM-D scores, 25.8 ± 5.6; range 18–36), whereas after ECT, more than 50% of the sample was in remission (HAM-D scores, 12.9 ± 9.3; range 1–30). This finding may explain why the correlation between rCBF and HAM-D was more accentuated after treatment. Thus, SPECT may more readily discriminate between depressed and remitted states than among depressed patients.

Our finding of increased rCBF after ECT in treatment responders is at odds with that of Silfverskiold et al. (*23*) and Nobler et al. (*29*), who reported a decrease in rCBF when assessed by ^{133}Xe. An absence of correlation between ^{133}Xe and ^{99m}Tc-HMPAO data was observed by Rubin et al. (*34*), who found no abnormality in patients with obsessive–compulsive disorder (OCD) for ^{133}Xe, whereas ^{99m}Tc-HMPAO located abnormalities. Results obtained with ^{99m}Tc-HMPAO were consistent with those previously reported in PET studies of OCD (*35*). The reason for the discrepancy between ^{133}Xe and ^{99m}Tc-HMPAO may be related to superior resolution of the latter, with its capability to identify subcortical processes or metabolic mechanisms involved in ^{99m}Tc-HMPAO uptake by

TABLE 3
Uptake Ratios (Mean ± s.d.) in 11 Responders and 9 Nonresponders to Electroconvulsive Therapy at 7 cm above the Orbitomeatal Line

Region	Left hemisphere			Right hemisphere		
	Before ECT	After ECT	p Value	Before ECT	After ECT	p Value
			Responders (df = 10)			
Frontal	0.74 ± 0.058	0.79 ± 0.070	0.05	0.75 ± 0.060	0.82 ± 0.064	0.01*
Parietal	0.77 ± 0.064	0.83 ± 0.049	0.01*	0.78 ± 0.071	0.84 ± 0.060	0.04
Parieto-occipital	0.89 ± 0.898	0.96 ± 0.49	0.03	0.87 ± 0.091	0.95 ± 0.042	0.03
Sup cingulate	0.73 ± 0.078	0.76 ± 0.089	ns	0.71 ± 0.081	0.75 ± 0.095	ns
Global	0.77 ± 0.062	0.83 ± 0.056	0.04	0.77 ± 0.066	0.83 ± 0.059	0.02*
			Nonresponders (df = 8)			
Frontal	0.73 ± 0.088	0.73 ± 0.036	ns	0.77 ± 0.101	0.75 ± 0.036	ns
Parietal	0.77 ± 0.084	0.76 ± 0.042	ns	0.80 ± 0.095	0.79 ± 0.047	ns
Parieto-occipital	0.88 ± 0.110	0.84 ± 0.074	ns	0.87 ± 0.104	0.85 ± 0.063	ns
Sup cingulate	0.70 ± 0.086	0.71 ± 0.076	ns	0.72 ± 0.077	0.71 ± 0.050	ns
Global	0.76 ± 0.084	0.75 ± 0.032	ns	0.79 ± 0.091	0.77 ± 0.034	ns

*Significance level survived Bonferroni correction for multiple testing.
ECT = electroconvulsive therapy; df = degrees of freedom; Sup = superior; ns = not significant.

TABLE 4
Spearman Correlations between Hamilton Rating Scale for Depression Scores and Cerebral Blood Flow Values

	Left hemisphere						Right hemisphere					
	Before ECT		After ECT		Difference		Before ECT		After ECT		Difference	
Region	r coeff	p value	r coeff	p value	r coeff	p value	r coeff	p value	r coeff	p value	r coeff	p value
4 cm Above OML												
Frontal	−0.03	ns	−0.61	0.004*	−0.18	ns	−0.02	ns	−0.64	0.002*	−0.49	0.02
Sup temporal	−0.07	ns	−0.65	0.002*	−0.02	ns	0.10	ns	−0.64	0.002*	0.00	ns
Med temporal	−0.54	0.01	−0.67	0.001*	−0.67	0.001*	−0.42	ns	−0.65	0.002*	−0.32	ns
Occipital	−0.44	0.05	−0.62	0.004*	−0.49	0.02	−0.32	ns	−0.52	0.02	−0.37	ns
Ant cingulate	−0.16	ns	−0.61	0.004*	−0.46	0.04	−0.12	ns	−0.64	0.002*	−0.34	ns
Post cingulate	0.03	ns	−0.26	ns	−0.62	0.004*	0.01	ns	−0.22	ns	−0.52	0.02
Basal ganglia	−0.08	ns	−0.73	0.0002*	−0.40	ns	−0.23	ns	−0.54	0.01	−0.26	ns
Thalamus	−0.24	ns	−0.48	0.03	−0.24	ns	−0.25	ns	−0.44	0.05	−0.13	ns
Global	−0.17	ns	−0.85	0.000002*	−0.49	0.02	−0.16	ns	−0.74	0.0002*	−0.38	ns
6 cm Above OML												
Frontal	−0.29	ns	−0.40	ns	−0.43	ns	−0.11	ns	−0.55	0.01*	−0.15	ns
Parietal	−0.40	ns	−0.69	0.0008*	−0.42	ns	−0.53	0.01	−0.61	0.004*	−0.46	0.04
Occipital	−0.04	ns	−0.33	ns	−0.04	ns	−0.08	ns	−0.25	ns	−0.08	ns
Ant cingulate	−0.21	ns	−0.46	0.04	−0.57	0.008*	−0.06	ns	−0.49	0.02	−0.49	0.02
Post cingulate	−0.40	ns	−0.56	0.01*	−0.62	0.004*	−0.30	ns	−0.27	ns	−0.64	0.002*
Global	−0.37	ns	−0.55	0.01*	−0.51	0.02	−0.28	ns	−0.62	0.004*	−0.40	ns
7 cm Above OML												
Frontal	−0.51	0.02	−0.46	0.04	−0.54	0.01*	−0.43	ns	−0.55	0.01*	−0.59	0.006*
Parietal	−0.41	ns	−0.79	0.00004*	−0.46	0.04	−0.48	0.03	−0.64	0.002*	−0.57	0.008*
Occipital	−0.29	ns	−0.60	0.004*	−0.48	0.03	−0.25	ns	−0.60	0.004*	−0.43	ns
Sup cingulate	−0.28	ns	−0.18	ns	−0.02	ns	−0.41	ns	−0.13	ns	−0.13	ns
Global	−0.47	0.03	−0.72	0.0004*	−0.46	0.04	−0.50	0.02	−0.70	0.0006*	−0.54	0.01*

*Denotes Bonferroni correction ($p < 0.05$) survival.

ECT = electroconvulsive therapy; coeff = coefficient; OML = orbitomeatal line; ns = not significant; Sup = superior; Med = medial; Ant = anterior; Post = posterior.

brain parenchymal cells (*36*), or to still ill-defined mechanisms. In addition, conditions of radiotracer injection or scanning or the presence of cerebrovacular disease among subjects may also contribute to a divergence in findings.

The most robust change in our study was observed in the cingulate gyrus, which is part of the paralimbic cortex. This finding is compatible with the paralimbic hypoperfusion observed in unipolar depression by Mayberg et al. (*37*). The paralimbic cortex has been proposed to have an important role in mood and emotional changes observed in depressed patients after various brain lesions (*38–42*). The findings of Mayberg et al. (*37*) suggest no apparent attenuation of regional abnormalities by concurrent antidepressant use, and they suggest comparison of medicated patients without clinical improvement with medication-responsive patients. Our study did detect attenuation of perfusion defects in the cingulate gyrus of depressed patients who responded to ECT.

CONCLUSION

If reduced rCBF, as reflected in brain ^{99m}Tc-HMPAO uptake, indeed represents a state marker for depression that is reversible by successful treatment, clinical application of SPECT imaging in the evaluation of depression and in monitoring response to treatment could be highly feasible. Another finding that could be of therapeutic relevance is the significant pretreatment difference in perfusion between responders and nonresponders in the right posterior cingulate gyrus. Although preliminary, these results offer a means of providing the proper therapeutic modality, based on individual patient characteristics rather than statistical probabilities, to patients with major depression.

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Measurement of Regional Cerebral Plasma Pool and Hematocrit with Copper-62-Labeled HSA-DTS

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We developed copper-62-labeled human serum albumin-dithiosemicarbazone (^{62}Cu-HSA-DTS) as a blood-pool imaging agent for PET. To evaluate ^{62}Cu-HSA-DTS for plasma-pool imaging and to measure the regional cerebral hematocrit, 12 normal volunteers and 7 patients with cerebrovascular disease underwent PET studies with ^{62}Cu-HSA-DTS and ^{15}O-labeled carbon monoxide (C^{15}O). **Methods:** The normal subjects were studied with both C^{15}O and ^{62}Cu-HSA-DTS. All patients were examined by ^{15}O-gas studies to measure cerebral perfusion and oxygen metabolism, followed by measurement of plasma volume with ^{62}Cu-HSA-DTS for analysis of regional cerebral hematocrit. Regional cerebral hematocrit was calculated from regional cerebral red cell volume (rCRCV) measured by C^{15}O and regional plasma volume (rCPV) measured by ^{62}Cu-HSA-DTS in each subject, and the regional cerebral/large-vessel hematocrit ratio was obtained for both cerebral hemispheres in each subject. **Results:** Mean regional cerebral hematocrit and mean cerebral/large-vessel hematocrit ratio in the 12 normal volunteers were 38.3 ± 3.45% and 0.88 ± 0.06, respectively. In the seven patients with cerebrovascular disease, regional cerebral hematocrit was significantly lower on the hypoperfused side than the normal hemisphere. The images of rCPV and rCRCV from these patients demonstrated a greater increase in rCPV than rCRCV in the hypoperfused area. **Conclusion:** These results suggest that ^{62}Cu-HSA-DTS can be used for measurement of plasma volume and that regional cerebral hematocrit may provide valuable information regarding the microcirculation in the brain.

Key Words: PET; copper-62-labeled human serum albumin-dithiosemicarbazone; plasma volume; regional hematocrit

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