



Each month the editor of *Newsline* selects article on diagnostic, therapeutic, research, and practice issues from a range of international publications. Many selections come from outside the standard canon of nuclear medicine and radiology journals. Note that although we have divided the articles into diagnostic and therapeutic categories, these lines are increasingly blurred as nuclear medicine capabilities rapidly expand. Many diagnostic capabilities are now enlisted in direct support of and, often, in real-time conjunction with therapies. These briefs are offered as a monthly window on the broad arena of medical and scientific endeavor in which nuclear medicine now plays an essential role.

DIAGNOSIS

Prognostic Value of Normal MPI in CAD

In an article published in the January 1 issue of the *American Journal of Cardiology* (2006;97:1–6), Schinkel et al. from the Erasmus Medical Center (Rotterdam, The Netherlands) reported on the long-term prognostic and predictive capabilities of stress ^{99m}Tc -tetrofosmin SPECT in patients with coronary artery disease (CAD). The study involved identification and follow-up of 147 consecutive patients with previous myocardial infarction and/or myocardial revascularization, who underwent exercise bicycle or high-dose dobutamine-atropine stress ^{99m}Tc -tetrofosmin myocardial perfusion imaging and had normal results both during stress and at rest. In the follow-up period of 4–8 years, 20 patients (14%) died, 10 (7%) of whom died as a result of cardiac causes. Twelve patients (8%) experienced nonfatal myocardial infarction. Annual cardiac death rates were 0.5% during the years 1–3 and 1.3% in years

4–6. Rate-pressure products at rest and rate-pressure products at peak stress were independent predictors. The authors concluded that patients with a history of CAD have “a very low cardiac death rate during the 3 years after a normal finding” on stress ^{99m}Tc -tetrofosmin SPECT but suggested that repeat testing should be considered 3 years after the initial evaluation.

American Journal of Cardiology

PET and Myocardial Viability Testing

Tarakji et al. from the Cleveland Clinic Foundation (OH) reported in the January 17 issue of *Circulation* (2006;113:230–237) on the use of ^{18}F -FDG PET to identify patients with advanced left ventricular systolic dysfunction for whom revascularization might lead to improved survival. The retrospective analysis included survival data on “early intervention” in 765 patients with advanced left ventricular systolic dysfunction (ejection fraction $\leq 35\%$) and with no significant valvular heart disease who underwent ^{18}F -FDG PET imaging. Early intervention was defined as any cardiac intervention (surgical or percutaneous) within the first 6 months after the imaging study. Almost one-third of patients (230 patients, 30%) underwent early intervention. Of these, 25% underwent open heart surgery, 5% underwent percutaneous revascularization, and 70% were treated medically. The authors used 39 demographic, clinical, and imaging variables to propensity-match 153 of the 230 patients undergoing early intervention with 153 of the patients who were treated medically. The early intervention group experienced a markedly lower 3-year mortality rate than the group that did not undergo early intervention (15% and 35%, respectively). The authors concluded that regardless

of the degree of viability on PET imaging, early intervention may be associated with improved survival in patients with heart failure.

Circulation

Caffeine and Myocardial Flow Reserve

In an article that received international media attention as individuals headed back to the gym in early January, Namdar et al. from University Hospital (Zurich, Switzerland) reported in the January 17 issue of the *Journal of the American College of Cardiology* (2006;47:405–410) on a PET study indicating that caffeine intake decreases exercise-induced myocardial flow reserve. The study included 10 healthy volunteers in whom ^{15}O - H_2O PET was used to quantify regional myocardial blood flow (MBF) at rest and immediately after supine bicycle exercise in both normoxia and inhalation-simulated hypoxia conditions. Imaging was repeated 50 minutes after oral ingestion of caffeine (200 mg). The authors found that although resting MBF was not affected by caffeine at normoxia, it was significantly increased at hypoxia. Exercise-induced hyperemic MBF, however, decreased significantly after caffeine at both normoxia (by 22%) and hypoxia (by 39%). The surprising conclusion was that in healthy individuals, “a caffeine dose corresponding to 2 cups of coffee significantly decreased exercise-induced MFR at normoxia and was even more pronounced during [simulated] exposure to altitude.”

Journal of the American College of Cardiology

Exercise or Pharmacologic Challenge for ^{13}N -Ammonia PET?

Chow et al. from the University of Ottawa Heart Institute (Ontario, Canada) reported in the January 17 issue

of the *Journal of the American College of Cardiology* (2006;47:411–416) on a study comparing uptake and retention of ^{13}N -ammonia after treadmill exercise and dipyridamole stress. The study included 26 patients who underwent treadmill exercise and dipyridamole stress ^{13}N -ammonia PET imaging. After analysis of results, treadmill exercise was found to yield larger summed stress scores, larger summed difference scores, and larger left ventricular defect sizes. The authors concluded that in patients able to achieve adequate exercise, treadmill ^{13}N -ammonia PET might more accurately reflect the true myocardial ischemic burden and so “might be the preferred method of stress for routine ^{13}N -ammonia PET myocardial perfusion imaging.”

Journal of the American College of Cardiology

PET Validation of Microdialysis Efficacy

In the December issue of the *Journal of Neuroradiology* (2005;32:348–351), Sarrafzadeh et al. from the Humboldt University (Berlin, Germany) reported on the use of ^{15}O - H_2O and ^{18}F -FDG PET to assess the efficacy of microdialysis in the detection of ischemia in patients who had experienced subarachnoid aneurysmal hemorrhage. The study included 15 such patients in whom a microdialysis catheter was inserted immediately after aneurysm clipping into the brain parenchyma most likely to be affected by vasospasm. Dialysates were collected hourly and analyzed. ^{15}O - H_2O and ^{18}F -FDG PET scans were performed between 2 and 17 days after hemorrhage. ^{15}O - H_2O PET data were coregistered with data from CT scans to provide quantification of regional cerebral blood flow within the microdialysis regions of interest. ^{18}F -FDG PET data were evaluated by visual analysis, and regions of glucose hypometabolism were observed in 10 patients with symptoms of ischemia, who also had lower regional cerebral blood flow measures than asymptomatic patients. The measured dialysates were significantly higher in symptomatic than asymptomatic patients, with glutamate

showing the closest correlation with regional cerebral blood flow. The microdialysis parameters were well correlated with glucose hypometabolism as measured by PET and with symptoms of ischemia. The authors concluded that “microdialysis is a useful tool to monitor ischemia, especially in patients with high-grade subarachnoid aneurysmal hemorrhage” and that PET provides both validation of the technique and a useful adjunct.

Journal of Neuroradiology

PET in Aging and Parkinson's Disease

In an article e-published ahead of print on January 18 in the *Journal of Cerebral Blood Flow and Metabolism*, Bohnen et al. from the University of Michigan School of Medicine (Ann Arbor) reported on PET imaging of a promising biomarker to assess monoaminergic vesicular binding in older individuals and individuals with Parkinson's disease (PD). The study included 31 individuals with early-stage PD and 75 healthy individuals, all of whom underwent continuous intravenous infusion of ^{11}C -dihydro-tetrabenazine (DTBZ) and PET imaging to estimate striatal binding of type-2 vesicular monoamine transporter. Patients with PD were also evaluated in the clinically defined “off” state using 3 assessment scales. Imaging results indicated an age-related decline in striatal DTBZ binding in normal participants of approximately 0.5% per year. In individuals with PD, specific DTBZ binding was reduced in the caudate nucleus (by 44%), anterior putamen (by 68%), and posterior putamen (by 77%). DTBZ binding was also reduced by 50% in the substantia nigra of patients with PD, and striatal and midbrain DTBZ binding was asymmetric in these patients, with greatest reductions contralateral to the most affected limbs. The authors concluded that “ ^{11}C -DTBZ PET imaging displays many properties necessary for a PD biomarker.”

Journal of Cerebral Blood Flow and Metabolism

PET and Congenital Hyperinsulinism

The utility of ^{18}F -DOPA PET imaging in congenital hyperinsulinism (CHI) was reported by 2 groups in January. Both reports noted that until quite recently, preoperative differentiation between the focal and diffuse forms of the disease (which require different treatment approaches) have relied on technically demanding and invasive catheterization techniques. Otonkoski et al. from the University of Helsinki (Finland) reported in the January issue of *Diabetes* (2006;55:13–18) on a study designed to evaluate the ability of ^{18}F -DOPA PET to provide noninvasive diagnoses. The study included 14 patients with CHI (ages, 1–42 months). In 5 patients, focal uptake of the tracer was easily visualized, and the standard uptake value (SUV) in the focal areas was more than 50% higher than that in the rest of the pancreas. Subsequent successful resections of the areas of focus were performed, and these matched the focal areas indicated on PET. Diffuse uptake of ^{18}F -DOPA was seen throughout the pancreas in the remaining 9 patients, consistent with diffuse pathology. The authors concluded that “ ^{18}F -DOPA PET is a promising noninvasive method for the identification and localization of the focal form of CHI.”

In a study e-published ahead of print on January 10 in the *Journal of Clinical Endocrinology and Metabolism*, researchers from France, Belgium, and the United States reported on an immunohistochemical validation study of this technique for preoperative differentiation between focal and diffuse CHI. de Lonlay et al. studied 4 focal and 3 diffuse CHI pancreatic surgical specimens using anti-DOPA decarboxylase and proinsulin antibodies. Immunohistochemical detection of DOPA decarboxylase showed diffuse staining of Langerhans islets in the entire pancreas in all diffuse cases but showed dense focal staining in all focal cases. Additional immunohistochemical comparisons confirmed this differentiation of results. The

authors also noted that diffuse ^{18}F -DOPA uptake observed clinically on PET in 1 child with diffuse CHI before treatment disappeared completely after carbidopa administration, suggesting that pancreatic cells can take up amine precursors and contain DOPA decarboxylase. They concluded that these results validated ^{18}F -DOPA PET as a consistent test to differentiate between diffuse and focal CHI.

Diabetes

Journal of Clinical Endocrinology and Metabolism

Cerebral Oxygen Metabolism in Stroke

In an article e-published ahead of print on December 29 in *Stroke*, Kuroda et al. from the Hokkaido University Graduate School of Medicine and the Sapporo Medical University (Japan) reported on the use of SPECT to clarify whether oxygen extraction fraction (OEF) is elevated in all patients with reduced cerebral blood flow (CBF) and impaired cerebrovascular reactivity (CVR; type 3) on SPECT and, if not, to characterize the underlying pathology when OEF is normal but CVR is impaired. The study included 46 patients with decreased CBF and CVR on *N*-isopropyl-p- ^{123}I -iodoamphetamine SPECT in the ipsilateral middle cerebral artery area attributable to occlusive carotid diseases. Additional functional parameters were assessed in all patients by ^{15}O -gas PET, and neuronal integrity was evaluated in 19 patients with ^{11}C -flumazenil (^{11}C -FMZ) PET. The authors found that OEF was significantly elevated in 20 (43.5%) of 46 patients classified as CVR type 3. The remaining 26 CVR type 3 patients had normal OEF. OEF was significantly correlated with cerebral metabolic rate for oxygen and ^{11}C -FMZ binding potential but not with other parameters. These results suggest that type 3 patients with reduced CBF and CVR “may be divided into 2 pathophysiologically different subgroups: misery perfusion attributable to hemodynamic compromise and matched hypometabolism attributable

to incomplete infarction.” Thus, the authors concluded, patients who are “type 3 but normal OEF may represent a transition stage from misery perfusion to matched hypometabolism.”

Stroke

SPECT Analysis of Recovery from Aphasia

Jodzio et al. from the University of Gdansk (Poland) reported in the December issue of *Neuropsychological Rehabilitation* (2005;15:588–604) on a study of the relationship between poststroke recovery from aphasia and changes in cerebral blood flow (CBF) and used SPECT to assess right hemisphere (RH) involvement in restitution of language. The study included 24 right-handed patients with acute aphasia after left hemisphere (LH) ischemic stroke who were examined 2 times with a 6-month interval. $^{99\text{m}}\text{Tc}$ -ECD SPECT imaging and language assessment tasks were performed at each examination. The authors found that overall initial CBF was not a predictor for future language recovery. Increased perfusion of the RH during the 6-month interval paralleled recovery from aphasia, with a correlation between changes in the right parietal CBF (but not the left) and changes in several language abilities. However, only CBF values in the LH predicted performance on the language tests at both initial and follow-up examinations. The authors concluded that “the cerebral mechanism associated with early recovery from aphasia is a dynamic and complex process that may involve both hemispheres” and suggested that this mechanism involves functional reorganization in the speech-dominant (damaged) hemisphere and regression of hemodynamic disturbances in the non-dominant (structurally intact) hemisphere.

Neuropsychological Rehabilitation

PET Imaging of Pulmonary Endotoxin Inflammation

In an article e-published ahead of print on January 19 in the *Journal of Applied Physiology*, Chen et al. from the Washington University School of Medicine (St. Louis, MO) reported on

a study of ^{18}F -FDG PET imaging of pulmonary endotoxin-caused inflammation. The study included 18 healthy volunteers divided into 3 groups of 6 for a dose escalation study of endotoxin instillation (at 1, 2, and 4 ng/kg). Each volunteer received a baseline PET scan. Endotoxin was delivered by bronchoscopy into a segment of the right middle lobe, and each volunteer underwent PET imaging approximately 24 hours later, followed by bronchoalveolar lavage (BAL). BAL neutrophil counts were significantly higher in the highest dose group. Autoradiography performed on cells harvested by BAL showed specific deoxyglucose uptake limited to neutrophils. The rate of ^{18}F -FDG uptake was greatest in the highest dose group, with a consistent increase in the rate of uptake after endotoxin instillation compared with baseline. The authors concluded that “the inflammatory response to low-dose endotoxin in a single lung segment can be visualized and quantified by imaging with ^{18}F -FDG PET.”

Journal of Applied Physiology

PET/CT and NSCLC in High TB Areas

Low et al. from the Singapore General Hospital reported in the January issue of *Respirology* (2006;11: 84–89) on a study of the utility of PET/CT in the evaluation of non-small cell lung cancer (NSCLC) in Singapore, where tuberculosis (TB) rates are moderately high compared with those in Europe and North America. This retrospective study included a large group of patients who underwent PET/CT imaging for suspected NSCLC. Seven patients were found to have a solitary pulmonary nodule, for which PET/CT yielded a sensitivity of 100% and specificity of 75%. One patient's PET/CT was false-positive as a result of active tuberculosis. The authors identified 41 patients from the larger group who underwent PET/CT for staging of NSCLC, with 1 false-positive (active tuberculous lymphadenitis) and 1 false-negative. This yielded a sensitivity of 92.3% and a specificity

of 95%. The authors concluded from these and histologic confirmation data that PET/CT for the evaluation and follow-up of solitary pulmonary nodules and NSCLC can provide “additional useful information to conventional radiology for treatment planning and a non-invasive determination of prognosis” but cautioned that “physicians need to be aware of the limitations of this imaging modality, particularly when tuberculosis has a high prevalence in the population.”

Respirology

¹¹C-mHED and ¹⁸F-FDG PET in Pheochromocytoma

In an article e-published ahead of print on January 19 in the *Annals of Surgical Oncology*, Mann et al. from the University of Washington (Seattle, WA) reported on the utility of a combination of ¹⁸F-FDG and norepinephrine analogue ¹¹C-metahydroxyephedrine (¹¹C-mHED) PET in the diagnosis and localization of pheochromocytomas. The study included 14 patients with suspected pheochromocytoma who underwent either CT or MR imaging and ¹³¹I-metaiodobenzylguanidine (¹²³I-MIBG) planar imaging. PET imaging was performed using ¹¹C-mHED as a tracer for dynamic adrenal imaging and a torso survey and ¹⁸F-FDG for a torso survey. Pheochromocytoma was confirmed by pathology in 8 patients. ¹³¹I-MIBG planar imaging failed to detect 1 or more confirmed sites of disease in 4 of these patients. ¹¹C-mHED PET correctly identified all sites of confirmed disease. ¹⁸F-FDG-PET detected all sites of adrenal and abdominal disease in all 8 patients but did not identify bone metastases in 1 patient. ¹²³I-MIBG and ¹⁸F-FDG PET were each negative in the 6 patients without pheochromocytoma, but 1 such patient with adrenal medullary hyperplasia had a positive ¹¹C-mHED PET scan. The authors noted that PET scanning for pheochromocytoma offered both improved quality and resolution over current diagnostic approaches and concluded that “PET may significantly influence the clinical management of patients with a suspicion of

these tumors and warrants further investigation.”

Annals of Surgical Oncology

¹¹C-MTO PET in Adrenocortical Tumors

Hennings et al. from the Uppsala University Hospital and Uppsala Imanet AB (Sweden) reported on January 10 ahead of print in the *Journal of Clinical Endocrinology and Metabolism* on a study correlating ¹¹C-metomidate (¹¹C-MTO) PET in adrenocortical tumors with histopathologic findings. The retrospective study included a large pool of ¹¹C-MTO PET studies that were matched to 75 histopathologic examinations from 73 individuals. These patients had been operated on or biopsied for adrenal tumors, with the following histopathologic diagnoses: adrenocortical adenoma (26), adrenocortical cancer (ACC; 13), adrenocortical hyperplasia (8), pheochromocytoma (6), metastasis (3), and tumors of nonadrenal origin (19). ¹¹C-MTO PET showed a sensitivity of 89% and specificity of 96% in identifying adrenocortical origin of the lesions. Pheochromocytomas, metastases to the adrenal gland, and nonadrenal masses were tracer negative. PET was able to differentiate lesions >1–1.5 cm in diameter from normal adrenocortical tissue. Standard uptake values (SUVs) were higher in aldosterone hypersecreting adenomas, and the SUV ratio between tumor and the contralateral gland was significantly higher in all hormonally hypersecreting adenomas and in ACC. The authors concluded that ¹¹C-MTO PET is a specific and sensitive method for diagnosing adrenocortical tumors, with special promise in the imaging work-up of adrenal incidentalomas, primary aldosteronism, or ACC.

Journal of Clinical Endocrinology and Metabolism

PET and the “Wearing Off” Phenomenon in PD

Nimura et al. from the Miyagi National Hospital (Japan) reported in the December issue of the *Journal of Neurosurgery* (2005;103:968–973) on the use of PET to elucidate the mechanisms behind the often observed

“wearing-off” phenomenon that accompanies levodopa treatment for Parkinson’s disease (PD). The study included 3 patients who were experiencing the phenomenon. Each patient underwent ¹¹C-raclopride PET imaging (once before and once 1 hour after levodopa administration) both before and after deep brain stimulation of the subthalamic nucleus (STN). Clinical features at all study periods were analyzed by 2 scales, and all scores on these scales were improved “dramatically” after deep brain stimulation. Before surgery, the administration of levodopa significantly reduced tracer uptake in the putamen. After surgery, the change in tracer uptake was almost unaffected by administration of levodopa. The authors concluded that “deep brain stimulation of the STN induces the stabilization of synaptic dopamine concentrations in the striatum and may attribute to the alleviation of levodopa-related motor fluctuations.”

Journal of Neurosurgery

PET/CT in Head and Neck Carcinoma

In an article published in the January issue of the *Archives of Otolaryngology—Head and Neck Surgery* (2006;132:12–16), Ha et al. from the Johns Hopkins University School of Medicine (Baltimore, MD) reported on the role of PET/CT in the management of early- and advanced-stage primary head and neck squamous cell cancer. The study included 36 patients with previously untreated disease who underwent staging CT or MR imaging of the neck before undergoing PET/CT as part of initial diagnostic evaluations. PET/CT was found to provide additional information that confirmed existing treatment plans in 25 patients (69%) and altered management in 11 patients (31%). In the latter group, 6 patients’ tumors were upstaged. Treatment plans were altered in 4 of 8 patients with early-stage disease and 7 of 28 patients with advanced-stage disease. Eighteen of the patients progressed to surgery, and PET/CT correctly identified the primary tumor in

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each of these patients. The technique also correctly staged regional nodal disease in 9 of 16 patients. The authors concluded that, "the use of PET/CT is important in the initial treatment planning of early-stage and advanced-stage head and neck squamous cell carcinoma."

*Archives of Otolaryngology—
Head and Neck Surgery*

THERAPY

Radiolabeled Lym-1 with RIT in NHL

In an article published in the December issue of *Cancer Biotherapy and Radiopharmaceuticals* (2005;20:662–670), Shen, from the University of Alabama (Birmingham), and collaborators from other institutions reported on splenic volume change and nodal tumor response in non-Hodgkin's lymphoma (NHL) after radioimmunotherapy (RIT) using a radiolabeled Lym-1 antibody. The study included 29 patients with NHL who were treated with radiolabeled-Lym-1 and 9 breast cancer patients treated with radiolabeled ChL6, BrE-3, or m170. Each patient underwent CT splenic imaging before and after RIT. The authors found that in 13 of the 29 NHL patients, little or no change in splenic volume was noted after RIT, despite

splenic radiation doses as high as 23.1 Gy. In the reference group of breast cancer patients, little or no change was noted in splenic volume after RIT, despite doses as high as 14.4 Gy. Splenic volumes decreased in 13 of the NHL patients and increased in the remaining 3 patients after RIT. The results also suggested that therapeutic remission was more likely when splenic volume decreased after RIT. Of the 10 NHL patients with a >15% decrease in splenic volumes after RIT, 5 had complete and 5 had partial nodal responses. Of the 19 NHL patients with a <15% decrease in splenic volume after RIT, there were 5 complete responses and 7 partial responses. The authors concluded that RIT with radiolabeled-Lym-1 may benefit NHL patients with splenomegaly, "with reduction in splenic volume likely owing to a therapeutic effect on malignant lymphocytes."

*Cancer Biotherapy and
Radiopharmaceuticals*

Salvage ¹³¹I-Labeled mAb Therapy in Recurrent Brain Tumors

Reardon et al. from Duke University Medical Center (Durham, NC) reported in the January 1 issue of the *Journal of Clinical Oncology* (2006;24:115–122) on the results of a study

designed to assess the efficacy and toxicity of intraresection cavity ¹³¹I-labeled murine antitenascin monoclonal antibody 81C6 (¹³¹I-m81C6) in patients with recurrent malignant brain tumors. The study included 43 such patients with recurrent glioblastoma multiforme (33), anaplastic astrocytoma (6), anaplastic oligodendroglioma (2), gliosarcoma (1), and metastatic adenocarcinoma (1). Each patient was injected with 100 mCi of ¹³¹I-m81C6 directly into the surgically created resection cavity, followed by chemotherapy. Patients were followed for a median of 172 weeks. At the end of 1 year, 63% of the group of patients with glioblastoma multiforme or anaplastic astrocytoma were alive, and 59% of the patients with anaplastic astrocytoma or anaplastic oligodendroglioma were alive. Median overall survival for these 2 groups was 64 and 99 weeks, respectively. These survival rates are greater than those identified in retrospective studies of patients treated with surgery and ¹²⁵I brachytherapy. Toxicity was termed "acceptable." Administration of a fixed millicurie dose resulted in a wide range of absorbed radiation doses to the resection cavity. The authors noted that they are now conducting a phase II trial using patient-specific ¹³¹I-m81C6 dosing to deliver 44 Gy to the resection cavity followed by standardized chemotherapy.

Journal of Clinical Oncology