The incorporation of time-of-flight information into PET imaging improves quality by reducing image noise.

**Background:** Additional location information is available from the differential arrival times of annihilation photons in coincidence detectors that result in the improvement in PET image quality. Does this time-of-flight (TOF) information improve image quality, leading to better detectability?

**Objective:** To compare PET detection of hot lesions using TOF information and resolution recovery with conventional PET.

**Methods:** A localization receiver operating characteristic (LROC) analysis was performed comparing standard PET, standard PET with resolution recovery, TOF PET, and TOF PET with resolution recovery for the task of lesion detection. Twenty-six Ge-68 spherical lesions ranging in size from 6 to 16 mm were placed in an anthropomorphic body phantom with an F-18 background solution. The phantom was scanned 12 times over 3 days on a prototype TOF PET scanner, and image sets were generated from each of the 4 reconstruction algorithms listed above. LROC results for lesion detection were compiled for both an automated numeric observer and for 5 human observers. The performance of the different reconstruction algorithms was determined from the area under the LROC curves.

**Results:** The results from the numeric observer show that resolution recovery provides a benefit over standard PET, whereas the incorporation of TOF information outperforms resolution recovery. The inclusion of both TOF information and resolution recovery yielded the best results. This trend was also followed for the human observer study. While there was no statistical significance between TOF and resolution recovery applied separately (LROC area, 0.66 vs 0.69; \( P =0.88 \)), the LROC area improved to 0.87 (\( P =0.002 \)) when both were employed.

**Conclusions:** The inclusion of TOF information does improve observer performance in the detection of small lesions in the phantom study. The authors speculate that these results will be replicated in clinical studies, and they are in the process of participating in an evaluation using clinical data.

**Reviewer’s Comments:** The authors conclusively show that detection of small lesions is significantly improved in phantom studies when TOF information is included, and even more so when it is combined with resolution recovery. Similar results are expected in human studies in terms of more clearly defining small abnormalities. However, for many pathologies, the likelihood that an abnormality is malignant is size dependent. Improving image quality will certainly allow the better detection of all small abnormalities, but the specificity for some of these lesions may be substantially lower than the 80+% usually associated with PET imaging. (Reviewer-Mark T. Madsen, PhD).

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Keywords: PET, Time-of-Flight PET, Observer Study, LROC

Print Tag: Refer to original journal article
LV Perfusion Defects--Regadenoson vs Adenosine

Regadenoson Induces Comparable Left Ventricular Perfusion Defects as Adenosine: A Quantitative Analysis From the ADVANCE MPI 2 Trial.
Mahmarijan JJ, Cerqueira MD, et al:

J Am Coll Cardiol Img 2009; 2 (August): 959-968

There is no significant scintigraphic difference between pharmacologic stress with regadenoson compared to adenosine.

Background: Total and ischemic left ventricular (LV) perfusion defect sizes are important prognostic indicators. It has not yet been clearly shown that regadenoson is comparable to adenosine in terms of the severity and extent of perfusion defects seen on myocardial perfusion scintigraphy.

Objective: To determine whether regadenoson induces LV perfusion defects of similar size and severity as seen with adenosine stress.

Methods: The ADVANCE MPI 2 (Adenosine versus Regadenoson Comparative Evaluation for Myocardial Perfusion Imaging) study was a prospective, double-blind, randomized trial. It compared the results from MPI for patients undergoing adenosine versus regadenoson. All patients underwent 2 separate imaging procedures. The first scan utilized adenosine stress in all patients. The second scan used either regadenoson (n=495) or adenosine (n=260). Quantitative analysis was performed to determine total LV perfusion defect size and extent.

Results: The baseline adenosine gated MPI SPECT scan was similar in patients randomized to a second scan with adenosine versus regadenoson. No significant differences in total or ischemic perfusion defect sizes were observed between the regadenoson and adenosine groups. There was an excellent correlation between adenosine and regadenoson in terms of total ($r=0.97$) and ischemic ($r=0.95$) LV perfusion defects. The difference in LV ejection fraction, perfusion defect severity, and perfusion defect extent from study 1 (adenosine stress in all patients) to study 2 (adenosine or regadenoson) was similar in both patient groups, indicating no significant difference between agents.

Conclusions: Regadenoson and adenosine produce virtually identical scintigraphic results on rest-stress MPI.

Reviewer's Comments: This is the latest of several research studies showing similar results when comparing adenosine to regadenoson. Of note, regadenoson is easier to administer since it does not require an infusion pump and may have an improved side-effect profile. Although the price is not nearly as low as with dipyridamole, the shorter administration time of regadenoson may have important cost savings. (Reviewer-Thomas F. Heston, MD).

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Keywords: Adenosine, Regadenoson, Myocardial Perfusion Scintigraphy

Print Tag: Refer to original journal article
Neuroblastoma—Which Imaging Method Is Best?

123I-MIBG Scintigraphy and 18F-FDG PET in Neuroblastoma.
Sharp SE, Shulkin BL, et al:


18F-FDG PET and 123I-MIBG SPECT are important imaging modalities for children with neuroblastoma.

**Background:** 18F-FDG PET and 123I-metaiodobenzylguanidine (123I-MIBG) SPECT have both been used successfully to image neuroblastomas in children. Studies comparing the relative value of these procedures to each other in this patient population are limited.

**Objective:** To compare the accuracy of these 2 imaging modalities in children with neuroblastoma.

**Design:** 18F-FDG PET and 123I-MIBG with SPECT were performed in all individuals. Accordingly, 113 paired studies were reviewed from 60 patients with a median age of 3.1 years. The authors made the comparisons for 3 separate groups: stage 1 to 2 disease, stage 3 disease, and stage 4 disease.

**Results:** In the 13 patients with stage 1 to 2 disease, 18F-FDG PET depicted more primary tumor or locoregional disease than did 123I-MIBG in 9 of 13 paired studies from 6 patients. In the remaining 4 patients with stage 1 to 2 disease, the 2 imaging studies were equivalent. However, in the 10 stage-3 subjects (15 paired scans), 123I-MIBG demonstrated more tumor sites than did 18F-FDG PET in 5 scans from 4 subjects, whereas 18F-FDG PET was superior in 4 other individuals. Finally, in stage 4 disease (85 paired imaging studies in 40 subjects), 123I-MIBG demonstrated more disease in 24 patients, whereas FDG was superior in 8 individuals; the remaining patients showed equivalent disease for both. The authors note that most of the 123I-MIBG-positive PET-negative cases involved skeletal/marrow metastases.

**Conclusions:** 18F-FDG PET was superior for stage 1 to 2 disease, but 123I-MIBG was the superior agent in stage 4 disease.

**Reviewer’s Comments:** Although it was not directly assessed by the authors, there is little doubt that specificity would be better for 123I-MIBG versus 18F-FDG PET in this clinical setting. Based on the authors’ data, it seems that both 18F-FDG PET and 123I-MIBG are required for effective evaluation of stage 3 and 4 patients. I suspect PET with 124I-MIBG will likely be the next major imaging advance for neuroblastoma.

(Reviewer-David Bushnell, MD)

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Keywords: Neuroblastoma, 18F-FDG PET, 123I-MIBG

Print Tag: Refer to original journal article
Exercise Workload Predicts Risk of Ischemia

Achieving an Exercise Workload of ≥10 Metabolic Equivalents Predicts a Very Low Risk of Inducible Ischemia: Does Myocardial Perfusion Imaging Have a Role?

Bourque JM, Holland BH, et al:

J Am Coll Cardiol 2009; 54 (August 4): 538-545

In patients with an intermediate to high risk of coronary artery disease, achieving >10 METs on exercise stress testing is associated with a very low prevalence of significant ischemia on myocardial perfusion imaging.

**Objective:** To identify the prevalence of significant ischemia (defined as a reversible defect affecting ≥10% of the left ventricle [LV]) on rest-stress SPECT imaging relative to workload achieved on exercise ECG testing in intermediate- to high-risk patients referred for myocardial perfusion imaging (MPI).

**Background:** High exercise capacity is a strong predictor of an excellent prognosis. The role of MPI in these patients is questionable.

**Design:** Prospective cohort study.

**Participants:** All patients referred for SPECT MPI during a 1-year period were initially evaluated (n=2794). Those undergoing pharmacologic stress (n=1398), and those who exercised to <10 metabolic equivalents (METs) and did not achieve 85% of their maximum predicted heart rate (n=340) were excluded. The final cohort size was 1056.

**Methods:** A prospective analysis was performed on the results of 1056 consecutive patients who underwent quantitative exercise gated MPI. These patients were categorized on the basis of exercise capacity (<7, 7 to 9, or ≥10 METs). Workload was compared with imaging outcomes, primarily the prevalence of ≥10% LV ischemia. Individuals who reached ≥10 METs but <85% of maximum age-predicted heart rate were included.

**Results:** 974 patients attained ≥85% of their maximum age-predicted heart rate. Of these, 473 (approximately 50%) achieved ≥10 METs, and 2 had significant ischemia (a prevalence of 0.4%, roughly 1 of 250). Those who were unable to attain at least 7 METs had an 18-fold higher prevalence (7.1%; P <0.001) of significant ischemia on MPI. There were 430 patients who reached ≥10 METs but without exercise ST-segment depression, and none of these had ≥10% LV ischemia. This compared to a prevalence of significant ischemia of nearly 20% (14 of 70) in patients achieving <10 METs with ST-segment depression.

**Conclusions:** In patients with an intermediate to high clinical risk of coronary artery disease, achieving ≥10 METs with no ischemic ST-segment depression was associated with a 0% prevalence of significant ischemia. At the University of Virginia, a large percentage of patients (31%, or 430 of 1396 patients undergoing exercise stress MPI) fall into this category.

**Reviewer’s Comments:** This study confirms previous research showing an excellent prognosis for those with an excellent exercise capacity. However, note that the researchers did not look at clinical outcomes directly, but rather used myocardial perfusion imaging results as a surrogate end point. (Reviewer-Thomas F. Heston, MD).

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Keywords: CAD, Exercise Capacity, ECG Stress Testing

Print Tag: Refer to original journal article
PET/CT is superior to stand-alone CT for evaluation of recurrent colorectal cancer.

**Background:** There is ongoing debate as to whether PET/CT should be performed with or without IV contrast. On one hand, it is important to be certain that IV contrast will not introduce artifacts into the PET images; on the other hand, it must be determined whether IV contrast truly enhances the accuracy of the imaging procedure. In some clinical settings, IV contrast may be necessary for optimal accuracy, while in other settings, it may not be worthy of the associated risk of contrast reaction or renal damage.

**Objective:** To focus on the value of contrast-enhanced CT (ceCT) when PET/CT is performed in patients with colorectal cancer.

**Design:** Retrospective study.

**Methods:** PET/CT was evaluated in 170 individuals with suspected recurrence from colorectal cancer. CT was obtained both with and without contrast enhancement in each case. Truth data were obtained through histology or clinical/imaging follow-up.

**Results:** Recurrent or metastatic disease was ultimately established in 74 subjects. On a per-patient basis, the sensitivity for PET/ceCT, PET/noncontrast-enhanced CT (nceCT) and stand-alone ceCT was 93%, 89%, and 79%, respectively. These differences were statistically significant for PET/ceCT versus ceCT and PET/nceCT versus ceCT, but not for PET/ceCT versus PET/nceCT. On a per-patient basis, the specificity for PET/ceCT, PET/nceCT, and stand-alone ceCT was 96%, 95%, and 94%, respectively. Overall, PET/ceCT affected patient management in 64 individuals (38%). Moreover, PET/ceCT had a further impact on patient management beyond ceCT in 12 subjects (7%) and PET/nceCT 4 (2%).

**Conclusions:** "Integrated PET/contrast-enhanced CT is an accurate modality for assessing colorectal cancer recurrence and led to changes in the subsequent appropriate therapy."

**Reviewer's Comments:** Once again, it is clear that PET/CT, either with or without IV contrast, should be preferred over stand-alone ceCT for assessment of patients with suspected recurrent colorectal cancer. However, the data from this study does not resolve the issue of whether or not IV contrast is a necessary component of PET/CT. (Reviewer-David Bushnell, MD).

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Keywords: PET, CT, Colorectal Cancer

Print Tag: Refer to original journal article
The International Society for Clinical Densitometry (ISCD), which certifies physicians and technologists, revises Official Positions (OPs) on skeletal health assessment in children and adults every 2 years. The most recent (2007) ISCD OPs have been accepted by the American Association of Clinical Endocrinologists, the American Society for Bone and Mineral Research (ASBMR), The Endocrine Society, the North American Menopause Society, and the National Osteoporosis Foundation (NOF). The World Health Organization (WHO), however, published a report on the diagnosis of osteoporosis in early 2008 that differed somewhat from the ISCD. The WHO prefers reference databases and for osteoporosis diagnosis adopted a T-score ≤ -2.5 at the femoral neck. The reference standard from which the T-score is calculated is a female, white, aged 20 to 29. The ISCD supports the use of a female reference database for women and a male reference database for men, whereas the WHO supports using the female reference for both men and women. The ISCD OP uses the term "osteopenia," but prefers the terms "low bone mass" or "low bone density." The ISCD recommends the use of Z-scores for premenopausal women and men <50 years old. The rationale is that T-scores in premenopausal women and men <50 years of age might overestimate fracture risk and lead to unnecessary treatment with pharmacologic agents. The use of vertebral fracture assessment by dual energy x-ray absorptiometry (DEXA) is currently encouraged. Prevalent vertebral fracture is predictive of future fracture. Vertebral fracture assessment by DEXA detects vertebral fractures at less cost and lower radiation exposure than conventional x-ray.

**Reviewer's Comments:** In 2004, the WHO convened a "scientific group on assessment of skeletal health at the primary care level." This conference led to recent publication of the FRAX algorithms based on age and clinical risk factors, which classify patients into requiring (1) treatment, (2) bone mineral density evaluation, or (3) no treatment. If widely followed, that could seriously reduce the DEXA utilization, but I doubt that will happen. DEXA provides the unique data vital for treatment monitoring. Bone mineral density measurement (the best measure of fracture risk) has become more user friendly thanks in no small part to the OPs of the ISCD. (Reviewer-C. Richard Goldfarb, MD).

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**Keywords:** Osteoporosis, Bone Density Measurement
Reversing the Trend of DWBS

The Case for Obtaining a Diagnostic Whole-Body Scan Prior to Iodine 131 Treatment of Differentiated Thyroid Cancer.
McDougall IR:

Thyroid 2009; 19 (August): 811-813

This editorial recommends routine diagnostic radioiodine whole-body imaging prior to ablation of thyroids remnants.

There is current controversy regarding the value of diagnostic whole-body scan (DWBS) to stage differentiated thyroid cancer prior to ablation with iodine 131 (131I). Some choose not to perform a DWBS with either low-dose 131I or 123I. They argue that most patients with differentiated thyroid cancer have an excellent prognosis. Further, given the generally good outcome of a diagnostic scan, reliance can be put on the image performed following a larger ablative dose, which in any case is thought to be more sensitive than the diagnostic scan. Some cite concerns with so called stunning in which the diagnostic doses of 131I may reduce the uptake of therapeutic radioiodine. Finally, fixed ablative doses of 131I have been reported to be generally successful in eliminating a thyroid remnant, even without a pre-treatment diagnostic study. In the August 2009 issue of Thyroid, Dr Van Nostrand and colleagues report the diagnostic whole-body radioiodine scan to alter patient management in >50% of 355 cases. Specifically, there were cases in which no uptake occurred on the diagnostic scan in the expected thyroid remnant, several more foci in the neck than originally expected, unexpected nodal uptake, distant metastasis, 24-hour uptake of >15% in the remnant, and extensive physiologic uptake in the breast or other radiosensitive regions. The patient with no uptake in the thyroid remnant could have been spared unnecessary ablation, while patients with extensive breast uptake probably should have received a lower dose. Those with more foci in the neck than originally expected, those with unexpected lymph node uptake, and those with distant metastases should have been treated with higher doses of 131I than the standard ablation dose. Finally, those with substantial thyroid remnant would probably have benefited from completion thyroidectomy rather than ablation. The American Thyroid Association official guidelines stated in 2006 that the pretherapy scans are useful if the results would alter the decision to treat or the activity of radioiodine is to be administered. Those guidelines, however, stated that they were based on opinion, but that no objective evidence had been published to support or refute the recommendation. The paper by Dr Van Nostrand now provides that data. It is suggested that the DWBS be established as a routine.

Reviewer's Comments: The current trend both here and in Europe is to dispense with the DWBS and rely exclusively on postablation imaging. Time expenditure (ie, extra imaging visits and cost concerns especially when Thyrogen is used) have fuelled the trend away from diagnostic pretherapy whole-body imaging. I find the arguments in this editorial quite compelling and will try to reverse the trend on my home turf. (Reviewer-C. Richard Goldfarb, MD).

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Keywords: 131I, Differentiated Thyroid Cancer

Print Tag: Refer to original journal article
In patients on low-iodine diets, furosemide causes a significant decrease in urinary excretion of radioiodine and higher blood concentration.

Background: Following therapeutic 131I for ablation of postsurgery thyroid remnants or for the treatment of metastases, rapid elimination of unbound 131I is imperative. A popular method to accelerate renal elimination of 131I is fluid loading and diuretic administration. But there are no well-designed studies of diuretic therapy effects on radioiodine excretion.

Objective: To assess the effect of diuretic therapy on urinary excretion of 131I in radioiodine ablation after thyroidectomy and to gauge whether diuretics might be useful in daily practice in patients with differentiated thyroid cancer (DTC).

Design/Participants: This prospective study involved 43 patients (35 females) after total thyroidectomy with no history of kidney diseases. Before 131I therapy, sonography confirmed the presence of both kidneys without evidence of hydronephrosis. Serum BUN and creatinine were normal. Patients received no suppressive or substitution therapy with thyroid hormone after total thyroidectomy until thyroid-stimulating hormones (TSH) reached 35 μIU/mL. A low-iodine diet began 2 weeks before the 131I treatment. The 24-hour 131I uptake in the thyroid remnant and the diagnostic 131I whole-body scan were performed with 3 millicuries of 131I before the radioiodine ablation. Remnant uptake was 3.55% ± 3.45%. Twenty patients received doses of 150 millicuries 131I while 23 were given 100 millicuries for postoperative ablation. Postablative whole-body scan was performed 3 days after dosing. Twenty-three randomly selected patients took furosemide (20 mg) and potassium chloride (250 mg) orally 3 hours after the 131I administration, and then every 8 hours for 3 days.

Results: Blood radioactivity was significantly higher in patients given furosemide and potassium chloride than in the control group. Urinary excretion of 131I in patients treated with furosemide and potassium chloride was significantly lower than in the control group in all time periods after 131I. During the first 3 days, the patients with furosemide had 50% more micturitions ($P < 0.001$), and 70% larger volume of urine ($P < 0.001$). The exposure dose after 72 hours was 1.6 times higher in patients treated with furosemide than in the control group ($P < 0.01$) due to decreased urinary excretion.

Conclusions: Furosemide causes a significant decrease in urinary excretion of radioiodine and higher blood concentration in patients on a low-iodine diet. Consequently, furosemide should not be used in radioiodine ablation of patients previously iodine depleted by low-iodine diets.

Reviewer's Comments: This is a clinically pertinent paper that is certain to influence practice patterns, particularly my own. It was almost intuitive that fluid loading and diuretic administration would increase urinary excretion of 131I and reduce blood radioactivity. The best explanation for the paradoxical results is that the patients were on low iodine diets, which in turn, reduced their iodine pool. It is noteworthy that the landmark paper by Seobold and colleagues that found diuretics able to reduce 131I body concentration studied patients on a normal iodine-containing diet. (Reviewer-C. Richard Goldfarb, MD).

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Keywords: Radioiodine Urinary Excretion, Furosemide

Print Tag: Refer to original journal article
Limited Sensitivity for Detection of HCC Associated With 18F-FLT

Imaging of Proliferation in Hepatocellular Carcinoma With the In Vivo Marker 18F-Fluorothymidine.

Eckel F, Herrmann K, et al:

J Nucl Med 2009; 50 (September): 1441-1447

18F-FLT PET has limited sensitivity in the diagnosis of hepatocellular carcinoma.

**Background:** 3'-deoxy-3'-18F-fluorothymidine (18F-FLT) is an investigational PET radiopharmaceutical (not approved by the Food and Drug Administration) that has been developed for imaging of cellular proliferation. Retention of 18F-FLT inside the cell is a function of thymidine kinase 1. Thymidine kinase, which phosphorylates 18F-FLT, is also a key enzyme in DNA synthesis. Therefore, 18F-FLT uptake is also considered a marker of active cell proliferation.

**Objective:** To determine the detection rate of hepatocellular carcinoma (HCC) with 18F-FLT PET.

**Methods:** 18 patients with suspected HCC were imaged with 18F-FLT PET. The images were obtained on a dedicated PET scanner 45 minutes after the injection of approximately 300 MBq of 18F-FLT. Thirteen patients also underwent contrast-enhanced MRI and 5 patients underwent contrast-enhanced CT scans. Ki-67 immunohistochemical staining, which is an in vitro marker of cell proliferation, was obtained in 12 tumors for correlation with 18F-FLT uptake.

**Results:** 16 patients were diagnosed with HCC and 2 patients were diagnosed with cholangiocarcinoma. Eleven of 16 HCC tumors showed 18F-FLT uptake higher than surrounding normal liver resulting in a sensitivity of 69%. 18F-FLT uptake was above normal liver background in both cholangiocarcinomas. The mean standardized uptake value (SUV) in HCC tumors was 7.6 compared to 6.3 in normal liver. The average maximum SUV in HCC tumors was 9.0. The mean SUV in 2 cholangiocarcinoma tumors was 11.1 and 16.8. There was a significant correlation between Ki-67 immunohistochemistry labelling index and 18F-FLT uptake in the tumors. Tumors with a labelling index >5% showed 18F-FLT uptake greater than normal liver, whereas 4 of the 5 tumors with a labelling index <5% showed 18F-FLT uptake less than normal liver. After an average follow-up of 12.5 months, 5 patients have died and 13 are alive. The hazard ratio for mean tumor SUV was 1.20, suggesting a trend for reduced survival with high 18F-FLT uptake; however, this did not reach statistical significance likely due to the small number of patients.

**Conclusions:** 18F-FLT PET has limited sensitivity in detection of HCC; however high 18F-FLT uptake in HCC tumors may represent an adverse prognostic factor.

**Reviewer’s Comments:** Routine FDG PET studies also have limited sensitivity for diagnosis of HCC. C-11 Acetate appears to perform better for diagnosis of primary HCC; however, this radiopharmaceutical is limited to institutions with an on-site cyclotron. Imaging hepatic lesions with 18F-FLT is also challenging due to its intense liver uptake secondary to hepatic glucuronidation of 18F-FLT. On the other hand, if the presented data are confirmed in larger studies, the prognostic information obtained from 18F-FLT PET may help with treatment decisions of patients with HCC. (Reviewer-Yusuf Menda, MD).

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Keywords: FLT, Hepatocellular Carcinoma

Print Tag: Refer to original journal article
Technique to Improve PET Image Quality

A Practical Way to Improve Contrast-to-Noise Ratio and Quantitation for Statistical-Based Iterative Reconstruction in Whole-Body PET Imaging.

Fin L, Bailly P, et al:

Med Phys 2009; 36 (July):3072-3079

PET spatial resolution varies across the field of view and requires location-based mapping of the point spread function to compensate for spatial resolution losses.

Background: PET spatial resolution is best at the center of the field of view and degrades as the source moves toward the detectors. Resolution recovery methods can improve PET image quality, but this dependence on the source location has to be measured and included.

Objective: To describe and test a method for improving PET image quality by compensating for spatial resolution across the scanner field of view.

Methods: The spatial resolution of a commercial PET scanner was measured with a point source every 2 cm from the center to the edge of the scanner field of view. Cylindrical symmetry was assumed and a lookup table was created that generated the spatial resolution point spread functions for each point by interpolating between the measured points. A reconstruction algorithm was developed that incorporated the point spread information into the forward projection portion of the reconstruction. The resolution recovery method was tested with the IEC phantom, with the 6 fillable spheres loaded with 18F-fluorine (18F) solution. The contrast between the spheres and the phantom background activity was 4 to 1. The phantom data were reconstructed with the standard clinical reconstruction algorithm and with the resolution recovery algorithm. Parameters were adjusted to equalize the image variance and the contrast-to-noise ratio was used as a figure of merit.

Results: The parameters that equalized the image variance between the reconstruction algorithms were reported. When resolution recovery was applied, the contrast-to-noise ratio improved by 37% and 20% for the 10-mm and 13-mm spheres, respectively, while smaller changes were found for the larger spheres. The recovery coefficients for the 4 smallest spheres were at least 20% higher for the reconstructions with resolution recovery than for the standard clinical algorithm.

Conclusions: The authors conclude that their resolution recovery method based on point spread measurements provides a substantial improvement in contrast for objects that are close in size to the system spatial resolution. They expect that this improvement will lead to better detection and clinical outcomes.

Reviewer’s Comments: The approach described by the authors provides the framework for accomplishing PET resolution recovery. The implementation of this technique is beyond the means of most clinics, but those with sufficient physics or engineering support would be able to replicate this work. Because of the improvement in image quality associated with resolution recovery, it seems likely that such techniques will become the industry standard over the next several years. (Reviewer-Mark T. Madsen, PhD).

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Keywords: PET/CT, OSEM, System Matrix, Noise, Contrast-to-Noise Ratio, Quantitation

Print Tag: Refer to original journal article
18F-DOPA PET is superior to 123I-MIBG and CT/MRI in detecting neuroendocrine disease in patients presenting with catecholamine excess.

**Background:** Neuroendocrine tumors (NETs) are rare, but when symptomatic, can cause significant morbidity associated with excessive levels of catecholamines. Identifying disease is a key component in the management of these patients, as surgical resection often provides a cure. Also, identifying disease extent allows adequate treatment planning.

**Objective:** To compare the efficacy of 6-[F-18]fluoro-L-dihydroxyphenylalanine positron emission tomography (18F-DOPA PET) to 123I-metaiodobenzylguanidine (123I-MIBG) and CT/MRI in detecting neuroendocrine disease in patients with catecholamine excess.

**Participants:** As opposed to other studies that have included patients with suspected neuroendocrine disease, this study included patients with documented catecholamine excess, comparing the various modalities in detecting the causative lesions. A total of 48 patients with documented catecholamine excess were included in the study.

**Methods:** All patients underwent 18F-DOPA PET, 123I-MIBG, and CT/MRI imaging. Patient- and lesion-based analyses were performed. Whole-body metabolic burden was derived from the 18F-DOPA PET to reflect overall tumor activity. Also evaluated was whether the catecholamine levels correlated with image positivity and the benign or malignant nature of disease. Histopathology served as a limited gold standard in 45 of the 48 patients, as 45 patients went to surgery.

**Results:** On both a per lesion and per patient basis, 18F-DOPA PET was better in detecting lesions than 123I-MIBG and CT/MRI, with no significance difference between the latter 2. A higher sensitivity was found when 18F-DOPA PET and CT/MRI were used in combination. There was a correlation between biochemical marker levels and the pathological nature of disease (benign vs malignant). However, there was a correlation between overall tumor burden as detected by 18F-DOPA PET and catecholamine levels. **Conclusion:** 18F-DOPA PET is superior to 123I-MIBG and CT/MRI in detecting disease in patients with catecholamine excess, with the combination of 18F-DOPA PET and CT/MRI likely providing the most information.

**Reviewer's Comments:** Interesting study that explores the utility of 18F-DOPA PET in detecting neuroendocrine tumors (NETs) in patients with catecholamine excess. Patients with neuroendocrine disease commonly present with symptoms prompting evaluation of catecholamine biomarkers. As such, this study is quite clinically relevant because, although rare, NETs are high on the differential among symptomatic patients with elevated catecholamines. This study also echoes that of others that have shown the synergistic nature of functional and anatomical imaging, as the sensitivity of disease detection is enhanced when both modalities are used. However, as 123I-MIBG still provides adequate lesion detection sensitivity, may likely be more available than the cyclotron produced 18F-DOPA PET and is less expensive, it will likely remain a mainstay in NET imaging. (Reviewer-Damita Thomas, MD).

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Keywords: Catecholamine Excess, 18F-DOPA PET, Catecholamine Producing Tumors

Print Tag: Refer to original journal article
Bone scan is probably unnecessary in initial staging of prostate cancer in patients with a Gleason sum <5.

**Objective:** To determine the relationship between prostate-specific antigen (PSA) level, Gleason sum, or clinical T level, as well as the probability of detecting bone metastasis in patients with newly diagnosed prostate cancer.

**Participants/Methods:** Transition zone core biopsies and ultrasound-guided peripheral biopsies were performed on 709 Japanese patients with suspected prostate cancer. Prostate cancer was detected in 339 patients (47.8%) of whom 297 underwent radionuclide bone scanning regardless of PSA level, Gleason sum, or clinical T stage. Bone scans were performed using Tc-99m methylene diphosphonate (MDP) as a radiotracer soon after the pathological diagnosis of prostate cancer was made. In cases where the bone scan was indeterminate, additional studies were performed using bone CT, MRI, and/or plain film evaluation.

**Results:** The presence of metastasis remained indeterminate in 1 patient despite additional bone CT and MRI following radionuclide scanning. In the remaining 296 patients in whom bone metastases were detected, there was good correlation between log (PSA) and probability of bone metastasis (correlation coefficient, 0.949; \( P < 0.05 \)). By extrapolation, the probability of bone metastasis for PSA <10 ng/mL was 5%. In this study, of the 69 patients with PSA values <10 ng/mL who underwent radionuclide bone scanning, none were found to have metastasis. Of the 96 patients with PSA values from 10 to 29.9 ng/mL, 3.1% were found to have bone metastasis. There were no metastases detected in patients with Gleason sums <5 or in patients with Gleason sums >5 and PSA <15 ng/mL. Clinical T level of I or II was not found to be a significant independent predictor of bone metastasis in this study.

**Conclusions:** The authors conclude that bone scan may be unnecessary in patients with newly diagnosed prostate cancer with PSA level <15 ng/mL or Gleason sum <5.

**Reviewer’s Comments:** This study replicates earlier results dating back to at least 1991, which suggest that bone scans may be unnecessary in patients with newly diagnosed prostate cancer with PSA level <10 ng/mL. The Society of Surgical Oncology’s surgical practice guidelines for prostate cancer recommend preoperative bone scan only for patients with PSA >8 ng/mL. (Reviewer-Shayne Squires, MD).

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Keywords: Prostate Cancer, Bone Scan, PSA

Print Tag: Refer to original journal article
FDG PET and MRI each have good sensitivity for detecting cardiac sarcoidosis, but MRI probably has better specificity.

**Objective:** To evaluate the sensitivity and specificity of 18F-FDG PET and MRI for cardiac sarcoidosis.

**Participants/Methods:** 21 consecutive patients with sarcoidosis and suspected cardiac involvement were enrolled in this study. Inclusion criteria were any of the following electrocardiographic or echocardiographic findings: right bundle branch block; intraventricular conduction defect; left axis deviation; atrioventricular block; ventricular tachycardia; premature ventricular contraction; abnormal Q or ST-T changes; abnormal wall motion; regional wall thickening or thinning; or left ventricular dilatation. Exclusion criteria included any of the following: history indicative of ischemic heart disease; uncontrolled diabetes mellitus; or any type of myocardial disease. Each patient underwent 99mTc-sestamibi scintigraphy, 18F-FDG PET, and cardiac MRI within 4 weeks. Prior to PET imaging, free fatty acid levels were measured. Unfractionated heparin was administered to 19 patients in order to increase free fatty acid levels and suppress uptake of 18F-FDG by normal cardiomyocytes. Cardiac MR images were acquired before and after the IV administration of gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA). PET and MR images were each interpreted by 2 readers blinded to the clinical characteristics. The heart was divided into 16 segments, and each patient's images were classified according to 1 of 4 patterns of myocardial tracer uptake: none; focal; diffuse; or focal on diffuse. The patterns "none" and "diffuse" were regarded as normal. Cardiac sarcoidosis was diagnosed according to the criteria of the Japanese Ministry of Health and Welfare Guidelines for Diagnosing Cardiac Sarcoidosis.

**Results:** 8 of 21 patients were diagnosed with cardiac sarcoidosis using the standard criteria. Sensitivity and specificity for PET was 87.5% and 38.5%, respectively; while MRI had a sensitivity of 75% and a specificity of 76.9%.

**Conclusions:** Both 18F-FDG PET and cardiac MRI have high sensitivity for detecting cardiac sarcoidosis, but the specificity of PET is lower than previously reported.

**Reviewer's Comments:** Correlation between the 2 modalities was low/fair in this study (Cohen's kappa index, 0.28). Both PET and MRI may be detecting different abnormalities associated with the same disease—sarcoidosis. (Reviewer-Shayne Squires, MD).

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Keywords: Cardiac Sarcoidosis, FDG-PET, Cardiac MRI

Print Tag: Refer to original journal article
A negative whole-body leukocyte scintigraphy study carries a favorable prognosis in patients with fever of unknown origin.

**Objective:** To re-evaluate the sensitivity and specificity of 111In-labelled leukocytes imaging for the diagnosis of fever of unknown origin (FUO) in light of recent changes in the spectrum of diseases causing it and advances in diagnostic technology.

**Participants/Methods:** Study subjects consisted of all patients referred for 111In-labelled leukocyte imaging over a 2-year period to investigate the cause of FUO. Anterior and posterior whole-body planar images of each patient were acquired at 3 and 24 hours following IV administration of 111In-labelled leukocytes (16 MBq). Case records for each patient were retrospectively reviewed to determine the ultimate cause of FUO. Follow-up data were available for 54 patients who underwent imaging and fulfilled criteria for FUO. Follow-up duration was 6 months. True positives were identified as images that showed an abnormal focus that was later confirmed to be the cause of fever. True negatives were images that showed no abnormality and no cause of fever was identified on follow-up. False positives were images that showed an abnormal focus that was subsequently confirmed not to be the cause of fever or not verified by further investigation. False negatives were images that showed no abnormality, but a cause of fever was identified by other investigation.

**Results:** Overall sensitivity and specificity was 60% and 71%, respectively. The positive predictive value was 55%, and the negative predictive value was 75%. In patients who had undergone surgery within 2 months prior to scanning, the specificity and positive predictive value were higher (82% and 83%, respectively), while the negative predictive value was lower (56%). A cause for FUO was identified in 31 of 54 patients. Eleven patients had noninfectious causes for FUO (7 autoimmune, 4 cancer); of these, 2 were false positives (metastatic breast cancer and renal cell cancer) and 9 were true negatives.

**Conclusions:** 111In-labelled leukocyte scintigraphy remains a useful modality for identifying the cause of FUO, particularly in postoperative patients.

**Reviewer's Comments:** Typically, patients are referred for leukocyte scintigraphy for FUO investigation after most other diagnostic options have been exhausted. The proportion of FUO due to malignancy appears lower than historically reported, perhaps due to overall improvement in cancer detection. This study shows that despite a changing spectrum of disease and improvement in other diagnostic modalities, leukocyte scintigraphy retains its usefulness in identifying the cause of FUO. Although 42% of patients in this study had no cause for FUO identified, all had spontaneous resolution or resolution after antibiotic treatment, suggesting that a negative leukocyte scintigraphy scan implies a good prognosis even if no cause for FUO is found.

(Reviewer-Shayne Squires, MD).

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Keywords: Fever of Unknown Origin, Leukocyte Scintigraphy

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18F-FDOPA PET May Aid Early Identification and Management of PD Patients

Simple Ratio Analysis of 18F-Fluorodopa Uptake in Striatal Subregions Separates Patients With Early Parkinson Disease From Healthy Controls.

Jokinen P, Helenius H, et al:

J Nucl Med 2009; 50 (June): 893-899

18F-FDOPA PET may be useful in the early identification and management of patients with PD; PET can discriminate elderly persons who have early PD from healthy individuals.

**Background:** The use of 6-18F-fluoro-L-dopa (18F-FDOPA) PET reflects the pathology of Parkinson disease (PD), which includes the diminished dopamine content in the striatum of those affected. As such, uptake on 18F-FDOPA PET in PD patients is diminished. Although previous studies have shown that 18F-FDOPA PET can distinguish PD patients with more advanced disease from their healthy cohorts, this study is the first to attempt to show that 18F-FDOPA PET can also separate patients in the earliest stages of the disease from healthy controls.

**Objective:** To determine if 18F-FDOPA PET can distinguish elderly patients with PD from healthy matched controls.

**Participants/Methods:** 89 patients in the early stages of PD (defined as nonmedicated patients with 2 of the characteristic symptoms) underwent 18F-FDOPA PET scans that were compared to the scans of 21 healthy age-matched controls. 18F-FDOPA uptake was quantified using 2 approaches: bilateral striatal to occipital ratios (SORs) and calculation of an influx constant $K_{\text{ref}}$ using 90-minute dynamic imaging. Receiver operator curves (ROCs) were calculated to determine how well each uptake quantification method stratified PD subjects from healthy subjects.

**Results:** The SOR and $K_{\text{ref}}$ values of the PD patients were significantly lower than those of the controls, with ROCs showing that both methods discriminate PD subjects from healthy subjects. The investigators found that the less cumbersome method of using SORs was just as good at adequately reflecting uptake. They also found that the decrease in uptake was more pronounced on the side contralateral to physical symptoms, and that the specific region of this decreased uptake was also significant, being more pronounced in the posterior putamen than in the caudate nucleus or ventral striatum.

**Conclusions:** 18F-FDOPA PET can reliably distinguish early-stage PD patients from age-matched healthy controls.

**Reviewer's Comments:** Clinically applicable, this research study not only yields promising results, it can also be easily transitioned into a busy clinical practice by using a simpler quantification scheme (SORs as opposed to the cumbersome dynamic imaging to obtain the $K_{\text{ref}}$). The major drawback of this study is the lack of clinical follow-up to determine if patients progressed to a stage requiring medication to (at the very least) determine if 18F-FDOPA PET did accurately identify patients with PD. The authors point out, however, that most PD studies suffer from this limitation as the gold standard is definitive diagnosis at autopsy. Nonetheless, this is a promising study suggesting that 18F-FDOPA PET may be useful in the early identification and management of those with PD. (Reviewer-Damita Thomas, MD).

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Keywords:18F-FDOPA, Parkinson Disease, PET Imaging

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PET/CT More Specific Than BS for Detection of Skeletal Metastases

The Role of Whole-Body FDG PET/CT, Tc 99m MDP Bone Scintigraphy, and Serum Alkaline Phosphatase in Detecting Bone Metastasis in Patients With Newly Diagnosed Lung Cancer.

Min J-W, Um S-W, et al:


PET/CT is as sensitive as bone scan for the detection of skeletal metastases in patients with newly diagnosed lung cancer.

Objective: To compare the sensitivity, specificity, and agreement between bone scans (BSs) and whole-body fluoro-D-glucose positron emission tomography (FDG PET) for the detection of bone metastases in patients with newly diagnosed lung cancer.

Participants/Methods: This retrospective study included all patients with newly diagnosed lung cancer who were referred for evaluation for bone metastases. All patients underwent both whole-body imaging with 2-deoxy-2-[18F]fluoro-D-glucose (18F-FDG) PET/CT and bone scan. Each patient underwent imaging with both modalities prior to the initiation of therapy and again ≥6 months later. Serum alkaline phosphatase (ALP) was measured in each patient within 5 days of PET/CT scanning. The presence of bone metastases were confirmed 1 of 4 ways: (1) progression of skeletal lesion on follow-up imaging (PET/CT or BS); (2) confirmation by plain films, CT, or MRI; (3) positive initial findings on both PET/CT and BS in the same lesion with symptoms; and, (4) histological confirmation. Absent 1 of these 4 criteria, patients were considered to have no bone metastases. The average patient follow-up time was 333 days.

Results: The study enrolled 182 patients, including 136 men. The average interval between PET/CT and BS was 8.5 ± 14 days. Small cell lung cancer accounted for 7.7% of cases, half of which were extensive. The distribution of stage in cases of non-small cell lung cancer was as follows: 19% stage I; 7.1% stage II; 44.6% stage III; and 29.2% stage IV. The sensitivity and specificity of PET/CT for skeletal metastases was 93.3% and 94.1%, respectively. BS was 93.5% sensitive and 44.1% specific. Serum ALP was 26.7% sensitive and 94.1% specific. There was poor agreement between PET/CT and BS (Cohen's kappa index, 0.19).

Conclusions: PET/CT and BS have similar sensitivity for the detection of skeletal metastases in patients with newly diagnosed lung cancer, but PET/CT is much more specific.

Reviewer's Comments: In the initial staging of newly diagnosed lung cancer, BSs are probably unnecessary in patients who undergo Kifet PET/CT scanning. It is worth noting, however, that in this study, there were 2 false negatives by PET/CT, and each of these were positive on BS. (Reviewer-Shayne Squires, MD).

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Keywords: Lung Cancer, PET/CT, Bone Scan, Bone Metastases

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Pharmacologic stress with dipyridamole can cause transient left ventricular contractile dysfunction as well as exercise stress.

**Objective:** To determine whether transient left ventricular contractile dysfunction (TLVD) occurs following pharmacological stress (dipyridamole).

**Participants/Methods:** This retrospective study included 439 patients who underwent treadmill exercise stress (n=220) or dipyridamole stress (n=219). Gated SPECT (GSPECT) images of the heart were acquired using a 2-day protocol with Tc-99m methoxy-isobutyl-isonitrile (MIBI) as the tracer. Left ventricular ejection fraction (LVEF), LV volume, and the transient ischemic dilatation ratio (TID) were automatically calculated using commercially available software developed at Cedars-Sinai Medical Center (Auto SPECT, Autoquant). Difference LVEF (DLVEF) was calculated as stress LVEF minus rest LVEF. TLVD was considered to be present if DLVEF was < -5%. Nongated images were used to generate semiquantitative perfusion scores using the standard 20-segment model and 5-point scoring system. Summed stress scores, summed rest scores, and summed difference scores (SDS) were generated. Ischemia was considered present if the SDS was > 3. Coronary angiography was performed in 74 patients (33.2%) with ischemia.

**Results:** There was no significant difference in the rate of stress-induced ischemia between the exercised and pharmacologically stressed groups (50.8% overall). In patients with ischemia, the stress LVEF was significantly lower than the rest LVEF ($P < 0.0001$). In patients without ischemia, there was no significant difference between the stress and rest LVEF. Additionally, the DLVEF was significantly lower for patients with ischemia than for patients without ($P < 0.0001$). No significant difference in LVEF was seen between exercise and dipyridamole stress groups. Overall, TLVD was observed in 9% of patients without ischemia and 36% of patients with ischemia ($P < 0.0001$). The incidence of TLVD was not different between the exercise group and the pharmacological stress group. In patients with ischemia who underwent coronary angiography, 81.1% had stenosis > 50%. There was significant negative correlation between TID ratio and DLVEF for all groups of patients.

**Conclusions:** Pharmacologic stress with dipyridamole can result in TLVD in patients with coronary artery disease (CAD).

**Reviewer’s Comments:** The mechanism whereby pharmacologic stress induces LV dysfunction in patients with CAD needs further investigation. It cannot be attributed only to "steal" from epicardial arteries, because in this study, it occurred equivalently in patients with mild, moderate, and severe ischemia. (Reviewer-Shayne Squires, MD).

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Keywords: DLVEF, Myocardial Perfusion Imaging, Pharmacologic Stress

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Myocardial-suppressed 18F-FDG PET/CT imaging may be potentially useful in imaging vulnerable plaques.

**Background:** It is well known that acute myocardial infarctions (MIs) are commonly due to the acute rupture of plaques that are rich in inflammatory cells. As 18F-FDG PET/CT images any process with a hypermetabolic glucose utility, it will detect cells of inflammation as well, raising the possibility of its use as a noninvasive modality to identify these plaques before rupture.

**Objective:** To evaluate 18F-FDG PET/CT as a noninvasive tool to identify vulnerable coronary artery plaques.

**Participants/Methods:** 32 patients who underwent 18F-FDG PET/CT imaging for oncologic purposes and preoperative cardiac angiography were evaluated. Criteria for positive angiography included the presence of 50% lesion severity to ensure vulnerable plaques were not missed. Patients were instructed to follow a special low-carbohydrate, high-fat content diet prior to imaging to suppress myocardial FDG uptake. The PET/CT images were then compared to angiographic findings to determine if a correlation between the 2 was evident. A separate cohort of patients who underwent conventional fasting in preparation for imaging was compared to patients who followed the special diet prior to imaging, to specifically look at how the diet impacted myocardial FDG uptake.

**Results:** It was discovered that most patients (20 of the 32) using the modified preparation protocol had adequate myocardial FDG suppression, maximum myocardial standard uptake value (SUV_{max}) ≤ 5, enabling adequate evaluation of coronary arteries, where the mean SUV_{max} of FDG-positive vessels was 2.6 compared to 1.9 for negative vessels. In the separate cohort of conventional fasting versus special dietary preparation, it was shown that myocardial uptake was significantly lower in the latter group compared to the former (mean SUV_{max} of 2.5 vs 8.8). It was also found that in adequately suppressed myocardium, a correlation between FDG activity and disease detected at angiography trended toward significance (0.07).

**Conclusions:** Myocardial-suppressed 18F-FDG PET/CT imaging may be potentially useful in imaging vulnerable plaques.

**Reviewer’s Comments:** This study explores the potential of 18F-FDG PET/CT in detecting vulnerable plaque in coronary arteries. Although interesting that a trend toward significance (0.07) was seen between FDG activity and lesions detected on angiography, there is still extensive work to be done. Despite the use of the special dietary preparation, 37% of patients still had significant myocardial FDG uptake, precluding evaluation of coronary arteries. Another major concern with the technique is the spatial resolution afforded by PET, as it may not provide the degree of resolution needed to adequately detect disease in the epicardial vessels, particularly smaller ones. These are just 2 of many issues that need further evaluation, but raise an interesting possibility of this modality in detecting cardiovascular disease. (Reviewer-Damita Thomas, MD).

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Keywords: 18F-FDG PET/CT, Coronary Artery, Vulnerable Plaque

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Most deaths due to coronary artery disease occur in low- to middle-income countries. Implementation of appropriateness guidelines may help improve access in developing countries and decrease excess utilization in developed countries.

**Background:** In 2005, 4 out of 5 deaths from cardiovascular disease (CVD) occurred in low- to middle-income countries. Early detection of disease through the appropriate utilization of nuclear myocardial perfusion imaging is thought to be helpful in preventing and increasing survival from an adverse cardiovascular event.

**Objective:** To review the use and availability of nuclear cardiology procedures around the world and to offer strategies to develop regional centers to achieve quality imaging worldwide.

**Participants/Methods:** The International Atomic Energy Agency member and nonmember states were surveyed regarding the annual utilization of nuclear cardiology procedures. Imaging statistics were also collected from the American Society of Nuclear Cardiology, the European Society of Cardiology, and the European Association of Nuclear Medicine. In addition, myocardial perfusion imaging use was assessed by obtaining statistics from nuclear cardiology working groups within several nations. Utilization was categorized as high (>1,000 procedures/100,000 population per year), moderate-high (250 to 999/100,000), moderate (100 to 249/100,000), low-moderate (50 to 99/100,000), and low (<50/100,000).

**Results:** The U.S., Canada, and Israel had high utilization rates. Most Western European countries, Australia, and Japan had moderate-high utilization rates. South America had low utilization, except for the countries of Argentina, Brazil, Colombia, and Uruguay. Low utilization was also present across Eastern Europe, Russia, and Asia. Utilization generally mirrored a country’s gross domestic product. Nuclear cardiology utilization was higher in developing countries that neighbored moderate-high utilization countries (eg, Algeria and Egypt).

**Conclusions:** Global utilization of nuclear cardiology varies substantially. This is possibly influenced by physician access to training and education programs. Developing regional training centers may help guide the appropriate utilization of nuclear cardiology and aid developing nations in addressing the impact of CVD.

**Reviewer’s Comments:** There is a nice figure included in this article showing that the highest utilization rate is in the U.S., Canada, and Israel. Western Europe (with the notable exception of Great Britain), Australia, and Japan have moderate-high utilization. These authors propose that a greater application of appropriateness criteria may decrease utilization in the U.S. and Canada. The establishment of regional physician training centers may help increase the availability of nuclear cardiac imaging in developing countries. (Reviewer-Thomas F. Heston, MD).

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**Keywords:** Nuclear Cardiology, Population, Utilization, Training, Education, Appropriateness

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