

Potential Iatrogenic Alteration to ^{18}F -Fluoride Biodistribution

TO THE EDITOR: ^{18}F -fluoride PET has reemerged as a genuine clinical alternative to $^{99\text{m}}\text{Tc}$ -diphosphonate scintigraphy. In vivo, NaF dissociates into its salts Na^+ and F^- (fluoride). Fluoride is exchanged with OH^- (hydroxyl) ion in the hydroxyapatite matrix of the bone before migrating into the crystalline matrix (1). Approximately 50% of the injected dose localizes in bone, and bone retention of fluoride continues until bone remodeling (1). Fluoride has minimal protein binding affinity, allowing more rapid excretion of the fraction not localized in bone and favoring earlier postadministration imaging and low background activity (1). Elevation in plasma concentrations of unlabeled fluoride may reduce ^{18}F -fluoride uptake because of competition. In vivo competition is likely to increase the ratio of ^{18}F -fluoride excreted to ^{18}F -fluoride bound in bone, decreasing the percentage of the injected dose localizing in the bone. The effects on image quality may include a decrease in target organ count density and an increase in renal and bladder activity. The implications might be even more crucial for quantitation of fluoride bone uptake.

There are several fluoridated hydrocarbon-based general anesthetics that are metabolized to produce fluoride ion, which should be considered a potential confounder of ^{18}F -fluoride bone uptake. Of the fluoridated ethers, the most frequently used inhaled anesthetic agents in developed countries are enflurane, isoflurane, desflurane, and sevoflurane (2). Enflurane (Ethrane; Abbot Laboratories) has 2%–8% oxidative metabolism in the liver to produce fluoride ions to plasma levels as high as 20–40 μM (3). Sevoflurane (Ultane; Abbott Laboratories) has about 1%–5% liver metabolism, with one of the by-products being fluoride ions (3,4). Plasma fluoride concentrations in excess of 50 μM are produced; more than 50 μM is associated with renal impairment (4). Both enflurane and sevoflurane show serum fluoride ion levels peaking soon after completion of surgery (cessation of anesthetic delivery) (2,3). Nonetheless, elevated serum fluoride ion levels are high beyond 24 h. The retention of high serum levels after cessation of anesthesia is likely to represent saturation of fluoride on bone and reverse exchange from the bone surface to blood once blood concentration falls below that of bone. The implication for ^{18}F -fluoride PET is that significantly less than the usual 50% of the injected dose may localize to bone if enflurane or sevoflurane anesthesia has been used in the previous 24–36 h—perhaps longer for prolonged general anesthesia or in those with renal impairment.

Although potential competitive interaction between ^{18}F -fluoride and the by-products of inhalation anesthetics may decrease image quality, of greater importance is the potential impact of this competition on bone uptake quantitation. Further qualitative and quantitative research should be undertaken to determine the relationship and time course of interaction between fluoride ion-producing inhalation anesthetics and ^{18}F -fluoride PET image quality.

REFERENCES

1. Grant FD, Fahey FH, Packard AB, Davis RT, Alavi A, Treves ST. Skeletal PET with ^{18}F -fluoride: applying new technology to an old tracer. *J Nucl Med.* 2008;49:68–78.
2. Rang HP, Dale MM, Ritter JM, Flower RJ. *Pharmacology.* 6th ed. Philadelphia, PA: Churchill Livingstone; 2008:526–531.
3. Brunton LL, Lazo JS, Parker KL. *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* 11th ed. Philadelphia, PA: McGraw-Hill; 2006:353–360.
4. Duffy CM, Matta BF. Sevoflurane and anesthesia for neurosurgery: a review. *J Neurosurg Anesthesiol.* 2000;12:128–140.

Geoffrey M. Currie*

Hosen Kiat

Janelle M. Wheat

*The Australian School of Advanced Medicine

2 Technology Place

Macquarie University, NSW, 2109, Australia

E-mail: gcurrie@csu.edu.au

DOI: 10.2967/jnumed.109.071092

Detection of Pulmonary Embolism: Comparison of Methods

TO THE EDITOR: We read with great interest a recent article by Gutte et al. (1) in which the authors compared the diagnostic accuracy of combined ventilation–perfusion (V/Q) SPECT plus low-dose CT with multidetector CT angiography. In that prospective study, a total of 81 simultaneous studies were available for analysis, with a prevalence of 38% for pulmonary embolism (PE).

Perfusion SPECT plus low-dose CT had a sensitivity of 93%, specificity of 51%, and accuracy of 68%. This low specificity is surprising and at variance with recent data using perfusion SPECT without low-dose CT, which showed high specificity and accuracy of greater than 90% (2,3). Moreover, the general impression is that the CT information would significantly increase the diagnostic accuracy, particularly the specificity. In this context, the authors had already showed that the specificity of V/Q SPECT was 88% and increased to 100% when low-dose CT was added. We wonder what the specificity would be had the perfusion SPECT been interpreted without the low-dose CT; could the specificity of perfusion SPECT be even less than 50%? Unfortunately, because the authors did not report on the diagnostic performance of perfusion SPECT, there was no comparison between perfusion SPECT with and without low-dose CT. It would be great if the authors could comment on the results of perfusion SPECT.

There is a growing impression that SPECT is more accurate than planar imaging in the diagnosis of PE (2–4). However, V/Q SPECT is underutilized because of technical issues and the high economic cost associated with the ventilation agent. Most facilities therefore will be able to perform the perfusion SPECT but not the ventilation SPECT. The perfusion SPECT can be easily performed in a single session with the planar V/Q scan and is not associated with additional radiation exposure. However, interpretation criteria for perfusion SPECT are not yet clearly defined. Gutte et al. (1) did mention that “PE was diagnosed if one or more mismatched perfusion defects with normal ventilation were present,” but it was not clear to the readers whether only large subsegmental perfusion defects and larger defects were categorized as suggestive of PE or whether small and moderate

subsegmental perfusion defects were considered suggestive as well. We would appreciate a statement from the authors on this matter.

The discrepancy between the relatively low accuracy of perfusion SPECT plus low-dose CT and the high accuracy of V/Q SPECT plus CT in the study is considerable. It would be important to reanalyze the data to define the scintigraphic pattern responsible for the low specificity, 51%, when perfusion SPECT plus CT was used instead of V/Q SPECT plus CT. The information gained from this reanalysis would help us better understand the strengths and pitfalls of perfusion SPECT and help improve diagnostic confidence and accuracy.

REFERENCES

1. Gutte H, Mortensen J, Jensen CV, et al. Detection of pulmonary embolism with combined ventilation-perfusion SPECT and low-dose CT: head-to-head comparison with multidetector CT angiography. *J Nucl Med.* 2009;50:1987–1992.
2. Collart JP, Roelants V, Vanpee D, et al. Is a lung perfusion scan obtained by using single photon emission computed tomography able to improve the radionuclide diagnosis of pulmonary embolism? *Nucl Med Commun.* 2002;23:1107–1113.
3. Reinartz P, Wildberger JE, Schaefer W, et al. Tomographic imaging in the diagnosis of pulmonary embolism: a comparison between V/Q lung scintigraphy in SPECT technique and multislice spiral CT. *J Nucl Med.* 2004;45:1501–1508.
4. Gutte H, Mortensen J, Jensen CV, et al. Comparison of V/Q SPECT and planar V/Q lung scintigraphy in diagnosing acute pulmonary embolism. *Nucl Med Commun.* 2010;31:82–86.

Nghi Co Nguyen*

Amir Abdelmalik

Asif Moinuddin

Medhat M. Osman

*St. Louis University

3635 Vista Ave. (at Grand Blvd.)

St. Louis, MO 63110

E-mail: nguyen@slu.edu

DOI: 10.2967/jnumed.109.074237

REPLY: We greatly appreciate the interest of Dr. Nguyen and colleagues in our study (1), in which we concluded that ventilation–perfusion (V/Q) SPECT in combination with low-dose CT without contrast enhancement has an excellent diagnostic performance in patients suspected of having pulmonary embolism (PE).

Dr. Nguyen and colleagues raise an interesting point about the interpretation of perfusion SPECT alone, without low-dose or ventilation SPECT. However, as we concluded in our paper, a ventilation scan is mandatory because of the high number of false-positive test results and a specificity of only 51%. Perfusion can be used in combination with low-dose CT only if the scan results are negative (e.g., a high negative predictive value of 91%, as in our study) and, therefore, only as a rule-out test. From a subgroup analysis of our study, we concluded that planar V/Q lung scintigraphy had a specificity of 72%, which is still higher than the specificity of perfusion SPECT in combination with low-dose CT (2). Therefore, omitting the low-dose CT and using only perfusion SPECT would probably result in a low specificity and too many false-positive diagnoses.

In our study, we classified all scintigraphic mismatch defects as PE. Using PLOPED and PISAPED criteria is inappropriate because they were derived from single-view ¹³³Xe ventilation and planar perfusion imaging, which is very different from V/Q SPECT (3). Reinartz et al. used a simplified reporting scheme that regarded all mismatch defects as PE, resulting in high sensitivity (97%) and specificity (91%) on V/Q SPECT (4). The best way to report V/Q SPECT has not been clarified. There seems to be

a consensus about the need for a more simplified reporting scheme in V/Q SPECT reading, and therefore we chose to use Gestalt interpretation criteria (5).

We agree that V/Q SPECT is underutilized but could easily be applied as a routine method in most centers.

REFERENCES

1. Gutte H, Mortensen J, Jensen C, et al. Detection of pulmonary embolism with combined ventilation-perfusion SPECT and low-dose CT: head-to-head comparison with CT angiography. *J Nucl Med.* 2009;50:1987–1992.
2. Gutte H, Mortensen J, Jensen C, et al. Comparison of V/Q SPECT and planar V/Q lung scintigraphy in diagnosing acute pulmonary embolism. *Nucl Med Commun.* 2010;31:82–86.
3. Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). The PIOPED Investigators. *JAMA.* 1990;263:2753–2759.
4. Reinartz P, Wildberger JE, Schaefer W, Nowak B, Mahnken AH, Buell U. Tomographic imaging in the diagnosis of pulmonary embolism: a comparison between V/Q lung scintigraphy in SPECT technique and multislice spiral CT. *J Nucl Med.* 2004;45:1501–1508.
5. Bajc M, Neilly J, Miniati M, Schuemichen C, Meignan M, Jonson B. EANM guidelines for ventilation/perfusion scintigraphy. *Eur J Nucl Med Mol Imaging.* 2009;36:1356–1370.

Henrik Gutte*

Jann Mortensen

Andreas Kjær

*Copenhagen University Hospital

Blegdamsvej 9

Copenhagen 2100, Denmark

DOI: 10.2967/jnumed.110.074757

PET/CT with ¹⁸F-FLT Is Unlikely to Cause Significant Hepatorenal or Hematologic Toxicity

TO THE EDITOR: Therapeutic doses of cold fluorothymidine (FLT) used as antiviral therapy have been shown to cause renal, hepatic, and hematologic toxicity within 4 wk of treatment (1). This observed toxicity was of concern when investigational studies using ¹⁸F-FLT were initiated in the United States, prompting some investigators applying for a U.S. Food and Drug Administration investigational new drug application to institute eligibility criteria for hematologic (marrow), renal, and hepatic function to avoid any potential “toxicity” from even tracer doses of ¹⁸F-FLT. In fact, the current ¹⁸F-FLT investigational new drug application held by the Society of Nuclear Medicine contains such criteria. It is noteworthy that restrictive criteria on hepatorenal and hematologic parameters were implemented, although the ¹⁸F-FLT nucleoside dose (in µg) given for imaging purposes is at least 10,000 times lower than truly pharmacologic doses given for therapy with cold FLT (i.e., ~1 µg vs. >20,000 µg given as a single dose, with multiple doses typically given) (1).

Hundreds of doses of ¹⁸F-FLT have been administered worldwide (2–12). Although it seems logical that the tracer dose associated with an ¹⁸F-FLT imaging study is unlikely to cause hepatorenal or hematologic toxicity, no data pertaining to the presence or lack thereof have been reported to date. On the other hand, the current eligibility criteria requiring normal or near-normal hematologic, renal, and hepatic parameters before ¹⁸F-FLT tracer injection done for the sole purpose of avoiding presumed ¹⁸F-FLT toxicity is, in our experience, an impediment to accruing