PET Imaging of Pulmonary Fibrosis

TO THE EDITOR: We read with interest the article by Wallace et al. (*1*) describing PET imaging of pulmonary fibrosis in a rabbit model. We were pleased to find that, in general, their data confirmed our own results, obtained in a pilot study and reported in abstract form (*2*). In their article, Wallace et al. raise several important questions, which we believe our pilot study might help resolve. In addition to PET scanning, we have performed cellular resolution autoradiography and some biodistribution studies of both the *cis*- and the *trans*-isomer of fluoroproline (FP) and believe that this additional information will help in the interpretation of the PET signal in this potentially important application.

Our basic methodology was similar to that of Wallace et al. (*1*). A lower dose of microcrystalline silica particles, 50 mg of 5-μm particles in 0.5 mL of normal saline, was instilled into the right upper lobe of anesthetized rabbits' lungs under direct vision through the biopsy channel of a neonatal pediatric bronchoscope. At intervals after instillation, the rabbits were anesthetized again, and 1 ear vein was cannulated for injection of radioactive marker. The artery in the contralateral ear was cannulated for withdrawal of blood samples. Each rabbit was positioned with its thorax within the field of view of a PET scanner. Several animals were scanned simultaneously.

Cis- or *trans*-^{18}F-FP was prepared as previously described (*3*), dissolved in normal saline, and injected into the ear vein of each rabbit. Emitted radioactivity was measured by PET scanning for 6 successive frames of 15 min. Unlike Wallace et al. (*1*), we had few problems in localizing the ^{18}F signal to the challenged area. ^{18}F-FP data were corrected for attenuation using the transmission scan data, and the ratio of the uptake rate of radioactivity in the challenged (right lobe) regions of interest to that in the unchallenged (left lobe) regions of interest was calculated. Individual animals were scanned up to 6 times over the 13-wk course of the experiment (measured from instillation of silica).

Silica challenge of the lung increased the uptake of *trans*-^{18}F-FP, first detectable at 13 d. The PET signal peaked at 6–8 wk and by 13 wk, in contrast to the findings of Wallace et al. (*1*), had declined significantly. However, at that time the signal was still above baseline. ANOVA with least significant difference testing ($P < 0.05$) showed that ^{18}F-FP uptake at 41 and 54 d was significantly different from that at day 0; that ^{18}F-FP uptake at 54 d was significantly different from that at 0, 5, and 7 d; and that ^{18}FP uptake at 41 d was significantly different from that at 0, 5, 7, and 13 d. In a single study with the *cis*-isomer, uptake at 6 wk differed little from that observed after the *trans*-isomer. The difference in time course of the signal between our study and that of Wallace et al. might have been due to the scanning interval (90 min, compared with 180 min). The signal acquired over the shorter interval will reflect primarily uptake, whereas that over the longer interval will reflect protein synthesis (*4*) (but only with the *cis*-isomer). However, an alternative explanation is that the maintenance of the signal perceived by Wallace et al. reflects the increased density of scar tissue rather than active collagen synthesis, as no dynamic analysis of their data was presented and the data do not appear to have been corrected for density.

In our pilot study, tissue samples were taken and counted in a γ-well counter after *cis*- and *trans*-^{18}F-FP at 6–8 wk after challenge—a single rabbit in each case. In 2 other rabbits, high-performance liquid chromatography analysis was performed on samples of plasma and urine after injection of *trans*-^{18}F-FP.

After both isomers of ^{18}F-FP, uptake was clearly greater in the challenged lung than in the nonchallenged lung, confirming the results obtained by PET scanning. Little or no uptake occurred in heart or muscle. Nor was there any uptake into bone, as would have occurred should the ^{18}F-label have dissociated from the ^{18}F-FP during the scanning period. In liver and kidney, uptake was markedly greater for the *cis*-isomer than for the *trans*-isomer. However, this difference would not have affected the pulmonary signal.

As indicated above, counting of tissue samples showed that there was no appreciable uptake into bone with either isomer, suggesting that defluorination during the study was minimal. This finding was confirmed by high-performance liquid chromatography after *trans*-^{18}F-FP injection. Only the parent compound could be detected in blood and urine. No free fluoride could be detected.

In a single rabbit 13 wk after instillation of microcrystalline silica, ^{3}H-proline was coinjected with the *trans*-^{18}F-FP. After the PET scan, the animal was killed and the lungs were immediately removed and inflated to a pressure of 15 cm with formol saline and processed for microautoradiography.

In sections from the control lung, the architecture was normal and the grains developed by autoradiography were distributed randomly, with no evidence of localized uptake. The challenged lung showed disruption of the architecture and massive interstitial thickening. Autoradiographic grains were associated with the cellular component of the lesion, principally fibroblasts (probably myofibroblasts). The acellular fibrotic area in the center of the lesion showed no increase in radiolabeling.

In conclusion, our pilot studies agree with the findings of Wallace et al. (*1*) that, in response to a fibrotic stimulus to the lung, it is possible to monitor increased uptake of ^{18}F-FP into the challenged region by external imaging using PET. Our preliminary studies show that this signal likely reflects upregulation of proline transport into fibroblasts, rather than collagen synthesis. This possibility needs to be confirmed in further studies. *Cis*-proline and *trans*-proline appear to give similar signals up to 90 min. This finding is consistent with the signal's reflecting proline transport rather than collagen synthesis, as there is evidence that although the isomers behave similarly in the former, they differ appreciably in the latter (*4*,*5*). PET imaging of ^{18}F-FP clearly has considerable potential in monitoring the fundamental processes involved in the development of scarring of the lung and other tissues in living animals and perhaps in patients. We look forward to further development of this technique.

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REPLY: The pilot study of ^{18}F-fluoroproline (FP) imaging of silica instillation–induced pulmonary fibrosis in rabbits (*1*), supplemented with information in the above letter to the editor and our investigations (*2*), suggest that PET imaging using ^{18}F-FP has the sensitivity to detect metabolic events involved in pulmonary response to some respirable quartz dust exposures. The studies used different isomers of FP, *cis* in ours (*2*) and mostly *trans* in the other, as reported in the letter, and images were read for different scanning intervals. These factors may be involved in the differences seen in response versus time after dust challenge. All emission data in our study were corrected for tissue attenuation, as reported (*2*), and planned analyses of shorter scanning-time data acquired in our study may clarify the question, but the much stronger dust doses administered in our study (in which instillation was purposefully not directed to a particular lung or lobe as an added experimental blindfold) might be a significant factor.

The range of conditions of exposure and response under which early or progressive stages of disease such as silicosis or asbestosis could be so detected or evaluated as metabolic events (e.g., exacerbated uptake or incorporation in collagen synthesis of the labeled proline analog) is to be determined. Questions of specificity persist: tritiated-proline autoradiography has been used for some time to study fibroblast synthesis of collagen (*3*), but little quantitative information exists on the fractional distribution of the label between alveolar cells involved in the inflammatory response (e.g., neutrophils) versus interstitial fibroblast incorporation of the labeled proline. ^{18}F-FDG has been shown to be taken up specifically by inflammation-related neutrophil influx in response to microcrystalline silica challenge (*4*). Further, it might be important to use tritiated FP itself in addition to tritiated proline in such studies. A report on diastereomeric effects on 4-^{18}F-FP metabolism and uptake in tumors in mice (*5*) indicated differences between uptake and incorporation for different FP isomers.

The questions of the adequacy of the sensitivity and specificity of the method (e.g., for application in studies of occupational exposure and disease) appear to be amenable to investigation. If found to be accurate, the technique potentially would be highly useful diagnostically. However, as a cautionary note to clinical trials: We have seen evidence of eosinophilic endarteritis in some lung histopathology sections of our rabbits. We are investigating this finding to determine whether the vascular inflammation was endemic to the animals or was caused by FP or by nonradiolabeled contaminants in our test article, such as residue from protective groups on the precursor used in ^{18}F-FP synthesis.

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Motionlike Artifacts in Myocardial SPECT

TO THE EDITOR: We read with interest the article by Blagosklonov et al. (*1*), which suggests a possible explanation for motionlike artifacts (MA) associated with ^{201}Tl SPECT myocardial perfusion imaging (MPI). As they and others note (their references 4–8, 11, and 12), the history of rotational SPECT MPI is checkered with artifact issues prompting a variety of protocol, hardware, and software modifications intended as corrective measures, including dual-isotope imaging, prone imaging, breast binding, motion correction, resolution recovery, and attenuation correction. Still, in the presence of all of these remedial measures, the incidence of false-positive MPI studies remains in the 20%–40% range (*2*). Some of these proposed corrective measures have been found to actually increase the potential for false-positive MPI studies.

The work of Blagosklonov et al. (*1*) is intended to show that the rapid early washout (REW) of thallium is a significant cause of MA in myocardial perfusion images that are acquired on dual-head SPECT systems when imaging commences too soon after cessation of exercise. It is true that the 2-compartment model for uptake and redistribution of a diffusible tracer predicts REW of the tracer after the peak of maximum uptake, which is then followed 10–20 min later by transition to a more gradual or steady-state washout phenomenon. The 12-min delay in initiation of MPI proposed in

the article of Blagosklonov et al. is intended to avoid initiation of image acquisition during this period of REW. Unfortunately, their work as presented does not conclusively demonstrate that this is the sole or even a plausible explanation for MA.

In particular, 2 aspects related to their own data could have been further explored to conclusively demonstrate the cause-and-effect relationship between REW and MA. First, the REW phenomenon in their data could be approximately corrected for by applying an image-by-image scale factor to their stress images based on the well-behaved difference between the pairs of stress/rest curves as shown in their Figure 6. The differences between these 2 curves could serve as a good estimate of the relative counting rate alterations in the stress images caused by the REW phase. Admittedly, this type of correction would be an approximation of what is actually going on in all regions of the image, but in normal myocardium all regions of the heart will demonstrate similar uptake and washout dynamics. Therefore, if the authors' premise is correct, the application of this approximate corrective technique should demonstrate a reduction in the MA shown in the images of their Figure 1.

A second opportunity to clearly establish the proposed causal relationship between REW and MA would use the SPECT data that the authors obtained using the Mayo cardiac phantom filled with ^{99m}Tc. Unfortunately, the only application of this phantom by the authors was to verify that imaging an object in the presence of a rapidly decaying count rate (simulating REW) would indeed result in a discontinuity between their images 16 and 17. If the authors had taken an additional step and reconstructed the 2 sets of SPECT phantom images (acquired with 25 s per frame vs. 120 s per frame), they should then have been able to demonstrate MA in the 120-s phantom images corresponding to those shown in their Figure 1. Again, we are left without conclusive proof.

The lack of definitive data to support the authors' premise leads us to suggest an alternative explanation. It is well known that cardiac creep during sequential image acquisition has the potential to cause artifacts in tomographically reconstructed images (their references 11 and 12). Furthermore, the literature contains ample evidence that cardiac volume changes of 10%–15% are routinely seen during the 15 min after exercise, when the patient reclines for supine imaging (*3*,*4*). Furthermore, these changes have been demonstrated to be a function of position (*5*).

In general, tomographic reconstruction algorithms behave somewhat poorly in the presence of inconsistencies in the sequential image dataset to which they are applied. Therefore, changes in the actual size (volume) of the left ventricle could likely be another potential cause of MA. This fact also serves to explain the improvements in SPECT myocardial perfusion image quality observed when a prone imaging sequence is added after supine imaging, thus allowing time for cardiac volumetric equilibrium to be achieved. The authors present nothing to exclude this alternative explanation, which is also consistent with their observations. In other words, introducing a 15-min delay in the commencement of imaging after the patient reclines will coincidentally delay the acquisition of the rotational SPECT data to the time when volumetric changes in the left ventricle are minimized.

The authors go on to refer to a previous report of an increase in false-positive perfusion abnormalities detected by dual-head gamma cameras in comparison with single-head systems (their reference 9). The more rapid acquisition of MPI sequences is facilitated by multiple-detector SPECT systems, which serve to compress the total image acquisition interval into an earlier time frame, when poststress volume changes are more pronounced.

We routinely perform clinical nonrotational SPECT MPI studies in our laboratory using a multipinhole tomographic technique (*6*) that allows all images in the MPI dataset to be acquired coincidentally. This methodology allows us to monitor volume changes throughout the 20- to 30-min imaging interval after graded treadmill exercise. We have computed the ungated, average changes in the size of the heart chambers during the first 3 min versus the final 3 min of our acquisitions: percent volume change = (volume$_{\text{first 3 min}}$/volume$_{\text{final 3 min}}$ −1.0) × 100%. This protocol has been applied to 300 consecutive patients undergoing graded treadmill exercise testing and has shown the average ungated volume change in these patients to be +4.0%. Changes greater than 12.0% have been demonstrated in 13.5% of our patients. These findings are consistent with the published data (*3*–*5*).

The fact that ultimately emerges from these discussions is the inherent limitation associated with a methodology that uses a moving detector system to image an object that is dynamically changing in size, location, and intensity. It should not be surprising that the artifact issues associated with rotational SPECT systems are sometimes intensified with the desire to gate these images and correct for attenuation and creep, especially if the corrective methodology is incorrectly identified or applied. The simultaneous multipinhole SPECT MPI technique that we prefer (*6*) acquires all the images in a manner that is less affected by any temporal variables because changes in size and position of the heart affect all views equivalently. This simultaneous approach to SPECT MPI also takes better advantage of the increased sensitivity of multiple-detector systems.

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REPLY: We thank the authors of the above letter for their comments.

As stated in our article, the decrease of activity in the heart region during the first 10 min after ^{201}Tl injection may induce artificial perfusion defects in some patients after the exercise stress test (*1*). Thus, we suggest that the decrease in ^{201}Tl concentrations in myocardium or blood could be one of the main causes of the artifacts described.

The results of our phantom study, performed under the conditions of a constant volume of the ventricle and no motion of the heart, confirmed that the decrease of activity alone provoked the

leap in counts. However, the reconstructed images from a phantom study cannot be used because the above-mentioned conditions are too different from in vivo conditions.

Regarding the image correction based on rest curves, our results showed that the relationship between stress and rest curves was not linear and could not be used for correction even in "healthy" patients. In addition, the artifacts appeared more often in patients with myocardial ischemia. In these patients, the rest images cannot be used to correct the poststress images because perfusion defects detected in poststress studies usually disappear at rest.

Despite the advantages of the nonrotational technique described by Kirch et al. (*2*), the approach requires the use of a triple-head gamma camera, and unfortunately, in our department, we work only with dual-head gamma cameras.

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PET Detection of Melanoma Metastases in Lymph Nodes

TO THE EDITOR: I read with great interest the research work by Crippa et al. (*1*). The report detailed clinical experience with 38 melanoma patients examined for nodal metastases by ^{18}F-FDG PET. The purpose of the study was to establish the accuracy of ^{18}F-FDG PET in the diagnosis of nodal metastases and to determine the smallest detectable volume of disease. The study population apparently comprised melanoma patients with documented (clinically known) lymph node metastases demonstrated by a variety of conventional techniques (physical examination, CT, or ultrasound). Patients underwent preoperative ^{18}F-FDG PET followed by lymphadenectomy. PET images were interpreted in a masked fashion and were compared with lymph node histology. The study found a sensitivity of 95%, a specificity of 84%, and an overall accuracy of 91% for the detection of melanoma lymph node metastases. PET detected all metastases $\geq$ 10 mm in diameter, 83% of metastases 6–10 mm in diameter, and 23% of metastases $\leq$ 5 mm in diameter. The authors concluded that PET could detect small amounts of macroscopic disease but did not have acceptable sensitivity in the detection of microscopic disease.

The report of ^{18}F-FDG PET sensitivity for detection of nodal metastases of various sizes is a useful contribution to the literature, and the data are consistent with multiple prior reports on ^{18}F-FDG PET for melanoma staging. However, the authors conclude that their findings "encourage the use of FDG PET in melanoma patients with doubtful lymph node involvement." This conclusion is not supported by the data because the population studied had clinically obvious lymph node metastases. The statement seems misleading and is probably incorrect if it is extrapolated to patients with clinically normal lymph nodes.

The performance of ^{18}F-FDG PET as a diagnostic test will vary depending on the prevalence of detectable disease in the population to which it is applied. This principle is illustrated in a study (not referenced by the authors) addressing the use of PET for the primary staging of patients with clinically localized melanoma (*2*). In a prospective controlled study of 70 melanoma patients with cutaneous melanoma $>$ 1.0 mm in Breslow depth localized to the skin, the Indiana University group found that PET had a sensitivity of 17% and sensitivity of 96%, compared with sentinel lymph node histology, in 89 nonpalpable lymph node basins. Half of all positive scans were false-positive, and false-negative scans were noted 5 times more often than true-positives. Furthermore, for no patient were the PET findings confirmed to show distant metastatic disease at the time of the scan.

The authors' conclusions cannot be extrapolated to patients with clinically doubtful (i.e., nonpalpable) lymph nodes because these patients have a lower prevalence of detectable disease. We have reported typical lymph node tumor volumes that exist in melanoma patients who are staged by sentinel lymph node biopsy (*3*). About 20% of these patients harbor occult lymph node metastases. Although the range of tumor burdens encountered in this population is broad (0.1–3,618 mm^3), the median tumor volume is only about 5 mm^3. Sixty-five percent of all nodal tumor burdens observed were less than 10 mm^3, and 73% were less than 30 mm^3. By comparison, the spatial resolution of modern PET scanning equipment in common use today is about 5.5–6 mm, which corresponds to tumor volumes in the 87- to 113-mm^3 range. This volume mismatch and the low prevalence of disease (especially disease within the range of PET detectability) largely explain the poor performance of ^{18}F-FDG PET observed in patients with early-stage melanoma. Even with avid ^{18}F-FDG uptake, most lymph node tumor nodules in this population are far too small to be visualized by today's imaging technology.

To be defined for any clinical situation, the clinical utility of ^{18}F-FDG PET must be prospectively studied in precise clinical scenarios. ^{18}F-FDG PET is a useful staging tool for selected melanoma patients with recurrent or metastatic disease (American Joint Committee on Cancer [AJCC] stages III and IV). However, critical analysis of the collective PET literature reveals little evidence that ^{18}F-FDG PET can be recommended for lymph node staging in clinically localized melanoma (AJCC stages I and II). With a sensitivity of at least 95%, sentinel node biopsy is the gold standard for nodal staging in early-stage melanoma. ^{18}F-FDG PET should not be considered an acceptable alternative.

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