

involving the use of myocardial contrast agents, may allow this method to form the new cornerstone of noninvasive assessment of chest pain in women.

We propose that, when accessible, dobutamine stress echocardiography be considered as the initial diagnostic test in preference to exercise electrocardiography in women with uninterpretable ST segments and as a second-line screen in all those with intermediate to high postexercise test risk of coronary artery disease. Myocardial perfusion scintigraphy should be reserved for women with poor echocardiographic windows or those who are unable to tolerate the dobutamine.

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REPLY: Recent data indicate that there is no gender-based difference in diagnostic accuracy of dobutamine echocardiography (1) and stress perfusion scintigraphy (2) in detecting coronary artery disease, mainly if the silent majority is considered (3). Therefore, both tests are an adequate alternative to a nondiagnostic exercise electrocardiography test.

It is generally accepted that stress echocardiography may be more specific than stress perfusion scintigraphy and that this test is more sensitive than stress echocardiography (4). Thus, stress perfusion scintigraphy would be indicated in patients with high prevalence of coronary artery disease, and stress echocardiography in patients with low prevalence. However, specificity values of dobutamine echocardiography in the silent majority, reported by Brull et al. and by Dionisopoulos et al. (1) in the select minority (74% and 79%, respectively), are clearly lower than our own (91%) in the silent majority of women (3). Our results should prompt us to consider stress myocardial scintigraphy also in women with low prevalence of coronary artery disease.

According to the variability of all these data, which may indicate different characteristics of patients, methods, level of operator skill and interpretation criteria, we do not think it advisable to propose, as Brull et al. do, dobutamine echocardiography as the initial diagnostic test when results of exercise electrocardiography are uninterpretable, with perfusion scintigraphy being reserved for women with poor echocardiographic windows or who are unable to tolerate dobutamine. From our point of view, both tests have similar indications, and each hospital, depending on different

factors such as feasibility and experience, should decide which test is preferable for each patient, either woman or man.

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Inverse Correlation Between ^{99m}Tc-Tetrofosmin Uptake and P-Glycoprotein in Non-Small Cell Lung Cancer

TO THE EDITOR: We read with interest the article by Kostakoglu et al. (1) in which they report an inverse correlation between the tumor-to-normal tissue uptake ratio and the expression of P-glycoprotein (Pgp) determined by immunohistochemistry in 46 patients with lung cancer (26 squamous cell carcinomas and 20 small cell carcinomas). We would like to describe our experience with ^{99m}Tc-tetrofosmin (TF), another Pgp substrate (2), in patients with non-small cell lung cancer (NSCLC) and its correlation with Pgp expression determined by immunohistochemistry.

A total of 18 patients (17 men, 1 woman; age range 52-83 y) with NSCLC (2 with undifferentiated large cell carcinoma, 5 with adenocarcinoma and 11 with squamous cell carcinoma) were studied by ^{99m}Tc-TF and thoracic SPECT. The ^{99m}Tc-TF study was performed during the week before surgery. It involved the intravenous administration of 740 MBq (20 mCi) ^{99m}Tc-TF for the acquisition, 10 and 60 min later, of anterior and posterior planar images. SPECT acquisition was performed at 70 min. Image processing included semiquantitative analysis of the uptake in certain areas of interest outlined in transverse, coronal and sagittal SPECT sections to compare the counts in tumor tissue with those registered in healthy tissue, which provided the ^{99m}Tc-TF uptake index. Paraffin-embedded samples were taken for immunohistochemical staining using JSB-1, a monoclonal antibody that binds to an internal epitope of Pgp, at a dilution of 1:20. The results were considered to be positive when >10% of the visible cells were stained.

The immunohistochemical study of the 18 tumors identified 12 Pgp-positive lesions (2 adenocarcinomas, 2 undifferentiated large cell carcinomas and 8 squamous cell carcinomas) and 6 Pgp-negative lesions (3 adenocarcinomas and 3 squamous cell carcinomas).

For the Pgp-positive tumors, size ranged between 2.0 and 6.5 cm in largest diameter (mean 3 ± 1.2 cm), between 15% and >60% of

the cells stained on immunohistochemical study and the ^{99m}Tc -TF uptake index ranged from 1 (lesions in which uptake was absent) to 1.60 (mean 1.29 ± 0.26).

For the Pgp-negative lesions, size ranged between 1.5 and 8.2 cm (mean 4.2 ± 2.6 cm), between 0% and 10% of the cells stained on immunohistochemical study and the uptake index for ^{99m}Tc -TF ranged from 1.52 to 2.29 (mean 2.02 ± 0.32).

The difference between the uptake indices in Pgp-positive and Pgp-negative tumors was statistically significant ($P < 0.001$). Thus, our results, like those reported by Kostakoglu et al. (1) with ^{99m}Tc -methoxyisobutyl isonitrile (MIBI), demonstrate an inverse relationship between TF uptake index and the density of Pgp expression according to immunohistochemistry. These data indicate the value of both ^{99m}Tc -MIBI and ^{99m}Tc -TF scintigraphy in the functional evaluation of Pgp and validate the results of previous experimental studies at the clinical level (3–5).

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REPLY: We thank Dr. Tabuenca et al. for sharing their experience on the use of ^{99m}Tc -tetrofosmin (TF) imaging in the detection of P-glycoprotein (Pgp) overexpression in lung cancer. They report an inverse correlation between the tumor-to-normal tissue ratios and the expression of Pgp determined by immunohistochemistry. We would like to express some additional considerations concerning the Pgp expression pattern and communicate our experience.

In the data presented, there are overlapping numbers between Pgp-positive and Pgp-negative tumors in TF index that are sources of potential confusion. On the other hand, a multitude of factors appear to influence the detection of Pgp, including its heterogeneous expression, use of immunological reagents of variable Pgp specificity and differences in methods of analysis. Only a subpopulation of tumor cells expresses the MDR1 gene that encodes Pgp, hence heterogeneity constitutes a fundamental enigma that could cause false-negative immunohistochemistry results. By the same token, ^{99m}Tc -TF might fall short, detecting multidrug resistance (MDR) in tumors with partial overexpression of the gene.

Aside from the issue of antigenic heterogeneity, other factors

such as subsets of cells expressing varying and multiple resistance mechanisms that may well coexist could also be held accountable for any observable discrepant results between Pgp expression levels and ^{99m}Tc -TF imaging data (1). Despite the substantial role of Pgp in conferring drug resistance, MDR is a multifactorial phenomenon, and more than one mechanism can operate within the same or different cell subpopulations of the tumor. Accordingly, coexpression of 2–3 MDR-related proteins has been observed in 64% of the cell lines (2). In the same context, preliminary reports have suggested that drug-resistant cell lines displaying MDR-associated protein and lung resistance protein are also associated with reduced intracellular drug accumulation and retention (3,4).

Because the transport of any radiotracer into the tumor is also governed by biological properties of the diffusing molecules, the lack of or reduced volume of blood flow to the tumor can be responsible for poor penetration of radiopharmaceuticals in tumors with either low-level or no Pgp expression accompanied by low tumor-to-background ratios. In such patients, a tumor perfusion agent such as ^{201}Tl , whose initial tissue distribution has been well documented to correlate with regional perfusion, enables one to perform dual-isotope imaging to assess the perfusion status of the tissues. Similarly, in our previous study, the tumors with necrotic components had significantly lower tumor-to-background ratios than those with no necrosis excluding those with strong Pgp positivity probably because of poor vascularization (5).

An additional concern is the fact that Pgp might be expressed in the tissue but might not be optimally functional, in which case functional studies such as ^{123}Rh efflux studies should be performed to determine the functional capacity of the Pgp pump (6).

Lung tumors might not be conducive to the evaluation of Pgp distribution, because most specimens are obtained by bronchoscopic biopsy, which might not represent the entire tumor characteristics. Therefore, extreme caution should be exercised when evaluating lung biopsy specimens using immunohistochemistry to avoid erroneous results for the presence of Pgp.

More importantly, to determine clinically significant levels of MDR1 expression, quantitative analysis of MDR1 expression should be performed, because a modest increase in the levels of drug resistance may be sufficient to enable refractory tumor but may not be sufficient for ^{99m}Tc -TF imaging to detect the MDR1 gene. Briefly, using the previous data related to methoxyisobutyl isonitrile imaging and these data on ^{99m}Tc -TF imaging, one could identify only a subset of patients with high probability of developing MDR. Yet, their role in predicting clinical outcome will be determined only after imaging data have been correlated with response-to-therapy data.

Conclusions derived from this interesting study should be considered provisional until they are confirmed by studies with increased numbers of patients and more sensitive and quantitative methods performed at the molecular level.

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