False-Positive Findings on Myocardial Perfusion SPECT

TO THE EDITOR: Recently, there have been 3 articles (*1–3*) published in *The Journal of Nuclear Medicine* attempting to define various artifactual sources that contribute to the unacceptably high rate of myocardial perfusion SPECT (MPS) studies with false-positive findings. Each article suggests a different protocol modification intended to reduce the incidence of false-positive MPS findings. The first paper (*2*) suggests a 15-min wait before initiation of poststress thallium SPECT. The second paper (*3*) concludes that 360° SPECT acquisition is superior to 180° acquisition, thereby doubling the acquisition time. The most recent paper (*1*) proposes that additional poststress prone images, commenced 20–40 min after reclining the patient for supine imaging, result in MPS interpretations that correlate more accurately with the clinical outcome.

We suggest an alternative and consistent explanation for the diagnostic improvements described in these studies. All 3 papers present protocol modifications that coincidentally result in an additional "equilibration" period during which the patient is supine. Thus, the diagnostic improvements demonstrated in all 3 of these papers could alternatively be concluded to be the result of the additional delay or prolongation that is inadvertently introduced by each of these protocols.

More thorough development of the methodologies described in all 3 papers could have redirected the authors to very different conclusions from those presented. We suggested alternative approaches in previous letters to the editor about the 2 earlier papers (*2,3*). In the case of the most recent paper (*1*), Hayes et al. could have conclusively demonstrated the validity of prone imaging if they had simply chosen to randomize the order in which the prone and supine imaging sequences were performed. Unfortunately, this work as presented indicates that none of their patients underwent prone imaging before supine imaging. Because the authors chose not to alternate the order of their poststress supine and prone acquisitions, we are left with the possibility that it was actually the 20-min delay before the onset of prone imaging, not the prone versus supine position of the patient, that gave rise to the benefits shown by their data. In a guest editorial that appears immediately following (*1*), Lee et al. (*4*) weakly support the work of Hayes et al. by indicating that they "might use additional prone imaging" until attenuation correction achieves "robust results." Attenuation-induced artifacts are often described to be the nemesis of rotational SPECT, but neither attenuation correction nor prone imaging is widely used in practice because prolongation of the acquisition is not a welcome encumbrance in most busy clinical imaging laboratories. Furthermore, we submit that when the patient is reproducibly positioned and ^{99m}Tc agents are used for both stress and rest images, and time is allowed after reclination for volumetric equilibration to be complete, there should be little if any artifactual stress/rest difference in MPS images due to attenuation. This leads us to wonder why additional resting prone images have not also been proposed as beneficial.

It also remains true that even the application of "robust" attenuation correction using sequential CT/SPECT transmission/emission myocardial perfusion tomography has not been shown to consistently eliminate the elusive "diaphragmatic attenuation" artifacts. All of this further supports our contention that another phenomenon is the dominant factor in generating false-positive MPS findings, namely, ventricular volume changes that occur during image acquisition when begun too soon after reclination of the patient. Positional changes (upright to supine) and poststress dynamic changes in the volume of the human left ventricle are well documented in the cardiac physiology literature.

In our previous work (*5*), we have graphically and statistically described the changes in left ventricular volume that occur during the 20 min following graded treadmill exercise and reclination of the patient for imaging. On the basis of these measurements, we propose that it is primarily these dynamic, positionally dependent ventricular volume changes that are the dominant factor generating artifacts when sequential, rotational SPECT images are reconstructed using standard, commercially available software. Until we fully comprehend the complexity of the myocardial perfusion imaging problem and design nonrotational SPECT systems (*6*) that accommodate its most demanding aspects, it will be difficult to advance the state of the art in nuclear cardiology to any higher level of clinical utility than is currently achieved by rotational SPECT systems.

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Periareolar Injections and Hot Sentinel Nodes

TO THE EDITOR: The article by Pelosi et al. (*1*) supports our previously published results (*2*) and those of others concerning the superiority of areolar type injections over subdermal/intradermal injections, as well as perilesional injections, in delivering activity to the sentinel node. A few additional points warrant mention.

Having dynamically monitored the results of 3 different injection methods performed sequentially on the same patient in a single imaging session, we noted that the efficiency of delivering activity to the sentinel node, that is, the percentage of the injected dose that appears to end up in the sentinel node, is much higher (>3–6 times higher) for areolar-cutaneous "junction" injections than for intradermal injections above the tumor (2,3). This superiority is even more dramatic when compared with perilesional injections: The activity delivered to the sentinel node is up to 50–100 times higher by areolar-cutaneous "junction" injections than by perilesional injections in select patients (2,3).

Most of the literature comparing areolar injections with dermal or perilesional injections is unclear on the exact details of areolar injection methods. Terms such as *subareolar, periareolar, circumareolar,* or just *areolar* are used. Exact location, depth of injection, and other factors are not sufficiently detailed in many articles, making comparisons or exact reproduction difficult. Questions about injecting into lactiferous ducts are not raised. Furthermore, the investigators do not generally quantify the efficiency of the various injection techniques, as we did (2). Upon review, most of these articles do not demonstrate either in figures or in numeric data an effect as dramatic as that of the areolar-cutaneous "junction" injection technique in delivering activity to the sentinel node, or the higher efficiency given the higher injection doses generally used. A similarly high efficiency is suggested in Figure 2 of Pelosi et al. (1) and probably reflects the similarity of their technique to our areolar-cutaneous "junction" injections as depicted in Figure 1.

Hybrid injection techniques, defined as combinations of perilesional and dermal or areolar injections, provide an option for centers wishing to visualize internal mammary and other extraaxillary nodes. The deep perilesional injection component of these hybrid injection techniques allows visualization of internal mammary and other extraaxillary nodes, whereas the areolar-cutaneous junction injection component provides the ability to generate extremely hot sentinel nodes, with their associated benefits (2–5).

When performing areolar injections, one should not overlook the unique image patterns that are produced. One occasionally sees patterns of lymphatic dilation that appear as focal concentrations of activity, or "pseudosentinel nodes," which can persist for some time after injection. If not properly identified as pseudosentinel nodes by lymphoscintigraphy before the start of surgery, these could potentially mislead the surgeon, unnecessarily prolonging surgery and causing fruitless searching (2,3,6).

Another pattern, the "reverse echelon node," has rarely been noted. Its presence requires that at least 2 hot nodes be removed to avoid potentially missing the true sentinel node (2,3,7). The reverse echelon node is along the lymphatic channel tributary supplied by the areolar injection—upstream of the point at which that tributary joins the main channel draining the perilesional injection site to the sentinel node. The reverse echelon node, because it is on its own tributary, is closer to and only drained to by the areolar injection. In contrast, the perilesional injection is initially on a different tributary before all tributaries merge to a common channel to the sentinel node. Nevertheless, the sentinel node visualized by the perilesional injection, downstream in a sense, was also always a node draining the areolar injection in our series (2). Theoretically, both nodes should be removed for maximal sensitivity.

Such pattern analysis is possible only if real-time monitoring of the serial imaging results of sequential, dissimilar injection methods is performed in a single imaging session (2,3). Unfortunately, this type of pattern analysis, along with attempts to quantify the results of the different injection methods, is nearly completely lacking in the literature.

Whether the injections have to be performed at the areolar-cutaneous junction site closest to the tumor or can be performed equally well at any other site around the areola is not clear. We choose to inject at the junction site closest to the tumor from a pragmatic standpoint, as probably did Pelosi et al. (1). Using deeper, higher-volume subareolar injections, Kern at times noted multiple pathways simultaneously exiting the areolar area, but most seemed to converge (8). In another, more recent, article, Maza et al. noted a 0% false-negative sentinel node rate as evidenced by follow-up axillary lymph node dissection in patients with disease proven by lumpectomy or core-needle breast biopsy who received subareolar injections at 8 or more sites around the areolar margin during lymphoscintigraphy (9). Drainage from the different areolar injection methods probably leads to the same sentinel nodes. However, their efficiency in doing so is different.

By far the main goal of sentinel lymph node biopsy, as compared with traditional axillary dissection, is to reduce morbidity while maintaining sensitivity. The hotter sentinel node provided by the areolar-cutaneous "junction" injections (and similar injections described by Pelosi et al. (1)) assists in morbidity reduction for several reasons. It allows easier detection with the handheld probe at the skin surface, which should assist with the targeted approach by allowing a more direct path to the sentinel node target. This should reduce morbidity through a reduction in the extent of dissection. With a hot node, triangulated skin marking is facilitated, which can also guide the surgeon in determining where to make the initial incision, especially important in obese patients. In obese patients, a hot node offsets the negative effects of attenuation. In patients scheduled for surgery the day after lymphoscintigraphy, the negative effects of decay can be offset with a hotter node from the start.

Nevertheless, given the prominent lymphatic tracks that can arise with the areolar injection techniques we have noted here, we suggest dynamic monitoring and multiple views, including the standing/sitting position, to best map out what is really happening in the patient. In our opinion, not striving for a hotter node and not performing lymphoscintigraphy with triangulated skin markings, but simply depending on intraoperative probe detection alone, as practiced by some centers, goes against the very goal of morbidity reduction that sentinel lymph node biopsy promises.

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REPLY: Our study (*1*) validated the periareolar (PA) injection technique and underlined some of its reported advantages over the subdermal/peritumoral technique. In particular, we found the following: the sentinel lymph node (SLN) identification rate was significantly higher for PA injection of tracers (labeled nanocolloid or blue dye) than for subdermal/peritumoral injection; at lymphoscintigraphy, the number of late images necessary to visualize the SLN was significantly reduced (20% for PA injections vs. 39.5% for subdermal/peritumoral injections); and with the PA injection technique, the need for image-guided injection was bypassed for patients with nonpalpable tumors.

The PA injection technique is easy to perform and simpler than the other mentioned techniques. In a volume of 0.5 mL, we inject, as a single aliquot, 20–40 MBq of ^{99m}Tc-labeled Nanocoll (Nycomed Amersham Sorin S.r.l.). As shown in Figure 1 of our paper (*1*), the nanocolloid is injected subdermally at the PA site (1–2 mm from the areolar-cutaneous "junction" (*2*)), at the level corresponding to the tumor. Then, to aid clearance of radiocolloids, a gentle massage is performed.

The injection of such a low volume (0.5 mL) of labeled nanocolloid (instead of sulfur colloid) allows the procedure to be completed in a few minutes, without using anesthetic or causing discomfort to the patient.

In their letter, Kim et al. suggest, first, a new injection technique at the areolar-cutaneous junction to increase the efficiency of delivering activity to the sentinel node (*2,3*) and, second, lymphoscintigraphic "dynamic monitoring and multiple views . . . to best map out what is really happening in the patient" after tracer injection. Their goal is to minimize morbidity from SLN biopsy in patients with early breast cancer.

We thank Kim et al. for their letter and agree with them that, theoretically, their suggested solutions would improve the accuracy of SLN biopsy. However, as reported for different studies in which axillary lymph node dissection was performed after SLN biopsy, the false-negative rate of SLN biopsy in patients with early breast cancer is rather low, ranging from 5% to 10% (*4–6*). Kim et al. did not report an improved false-negative rate from using the multiple-injection technique and dynamic monitoring of radiotracer distribution. In addition, the increased number and volume of injections, and the use of a multiple-view dynamic acquisition for lymphatic mapping, increases patient discomfort and lengthens the procedure. Therefore, we believe that further studies on larger patient populations are mandatory to quantify the real improvement achievable with the technique suggested by Kim et al.

To visualize the axillary SLN in patients with early breast cancer, PA injection of 20–40 MBq of labeled nanocolloid in a low, 0.5-mL, volume, is suggested.

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