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Attenuation Correction Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging

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Clinicians now rely heavily on the results of single-photon emission computed tomography (SPECT) myocardial perfusion imaging for diagnosing coronary disease and for planning therapy. However, the technique is imperfect for these purposes, mainly because of technical limitations, the most prominent of which is the effect of soft-tissue attenuation on apparent tracer distribution. Providers have attempted to compensate for this by a number of indirect approaches. Recently, validated hardware and software solutions for directly correcting image data for soft-tissue attenuation have become widely available commercially. Optimal application requires an understanding of the technical details that differ somewhat from system to system, the quality control prerequisites, knowledge of the importance of the transmission map quality, and how dedicated SPECT and SPECT–computed tomography systems present different challenges. In addition, the clinical literature is expanding rapidly, including studies on diagnostic accuracy, image appearances, quantitative analysis, appropriate patients for attenuation correction, clinical utility, incremental value in relation to ECG-gating, and risk stratification.
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Single-photon emission computed tomography (SPECT) myocardial perfusion imaging is now relied on daily around the world for diagnosing coronary artery disease (CAD), risk-stratifying patients for likelihood of myocardial infarction or cardiac death, and guiding management decisions for people with known or suspected CAD. By many standards, it has become a "mature" technique, with only limited new developmental research. Specifically, the lack of new radionuclides and minimal changes in acquisition equipment have relegated much of the current research to its clinical applications. A notable exception is attenuation correction. Through equipment modifications and new software, these methods address the major shortcomings of SPECT imaging: inaccuracies in diagnoses and inefficiencies in patient management resulting from mistaking soft-tissue attenuation artifacts for true perfusion defects.

This subject has been of intense interest to practitioners, industrial competitors and has involved professional societies, as meta-analyses have demonstrated that attenuation artifacts limit SPECT's diagnostic accuracy and impact cost-effectiveness.[1,2] The necessity of a solution has led to new FDA-approved hardware and software products from all major vendors, statements from professional societies,[3,4] attempts to realize new Current Procedural Terminology codes to recognize the additional costs associated with attenuation correction, and a plethora of scientific and clinical research concerning methods of acquiring attenuation corrected studies and its impact on accuracy.

Indirect Approaches to Addressing Soft-Tissue Attenuation

Solutions to the impact of attenuation fall largely into the categories of historically indirect approaches and direct approaches involving measurement of patient-specific attenuation. Four indirect approaches are commonly used in daily nuclear cardiology practice to address the frequent problem of soft-tissue attenuation: adjunctive planar acquisitions, prone imaging, ECG-gating, and image quantitation.

Planar Imaging

Inspection of a steep lateral planar image can be helpful in separating the inferior wall of the heart from the effects of an

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overlapping hemidiaphragm.[5] Additionally, in women, the left breast can be lifted up and out of the field of view, taped, and the lower border can be delineated with a lead marker. If it proves impossible to remove the breast from the field of view, at a minimum the marker serves as a quality control tool to ensure that the breast is positioned identically at stress and at rest imaging. With thallium-201 (^{201}Tl) imaging, the early poststress images can also be useful for visualizing and quantifying lung-uptake of ^{201}Tl. Limitations of this approach to recognizing and overcoming the problems of soft-tissue attenuation are several: it requires additional image acquisitions; a declining number of technologists and physicians are comfortable with planar images; the technique is not helpful unless done with careful attention to patient and breast positioning; and there is no published data on its effect on SPECT's diagnostic accuracy or patient outcomes.

Supine Plus Prone Imaging

Acquisition of an additional SPECT image with the patient lying prone, performed after supine imaging, has been shown in some patients to overcome inferior wall attenuation artifacts. This technique rarely will be helpful with attenuation from breast tissue or underarm fat-pads. Its impact on diagnostic accuracy has only limited validation,[6] but a recent publication has shown that the event rate after supine only, or supine plus prone imaging if the supine image shows an inferior wall abnormality was similar.[7] The limitations are the negative effects on laboratory through-put and efficiency, scant supportive literature, uncertainty about the limits of normality for inferior wall appearances when images are acquired prone, and frequent creation of an anterior wall defect.[8]

ECG Gating

Inspection of functional images from ECG-gated SPECT can be useful in distinguishing attenuation artifact from coronary disease: if there is a corresponding regional perfusion and wall motion abnormality, the diagnosis of CAD can be made with certainty.[9] However, normal wall motion in the presence of a reversible or partially reversible perfusion defect neither confirms nor refutes an attenuating source. Furthermore, some patients with normal wall motion and fixed perfusion defects at stress and rest may have CAD with nontransmural injury and, therefore, this pattern cannot be ascribed to artifact with any degree of certainty.

Quantitation

Quantitative analysis of myocardial perfusion compares a patient's relative distribution of tracer against a database of patients with known coronary anatomy. It was not designed to overcome attenuation, and in fact these programs all incorporate significant compromises in recognition of the frequent occurrence of attenuation artifacts: different criteria for abnormality in women versus men, and wider limits of acceptance of normality for the anterior wall in women and the inferior wall in men.[10] Quantitation has been shown to not improve declining interpretive accuracy by visual assessment in obese patients.[11]

Direct Approaches to Attenuation Correction

The lack of widespread adaptation and standardization of all of the aforementioned "indirect" approaches to overcoming attenuation artifacts has led to a multifaceted effort to devise algorithms that directly address the problem. After "first-generation" attenuation correction solutions failed to achieve desired results, the Society of Nuclear Medicine and the American Society of Nuclear Cardiology published a blueprint for providers and industry describing what was perceived as the ideal: methods that did not interfere with workflow efficiencies, that did not create new interpretive artifacts, that would result in gender independent distributions of tracer, and that optimally would provide quality assurance tools.[3] The importance of the transmission map used for attenuation correction was emphasized, along with the need to ensure adequate count density. As of this writing, most single-photon camera vendors have commercially available hardware and software attenuation correction capability.

Technical Issues

Physics of Attenuation

Attenuation of photons within the patient is generally accepted as the physical factor most affecting quantitative accuracy and interpretation of myocardial perfusion SPECT images.[9,12,13] Physical models of attenuation describe a complex set of energy and tissue-dependent interactions as photons traverse the body.[14] The energies of single photon-emitting radioisotopes (70-360 keV) and physical properties of tissues show the predominant effects are photoelectric absorption and Compton scattering interactions.[14,15]

Attenuation is an exponential process described by the linear attenuation coefficient (μ), commonly expressed in units of cm^{-1}, and represents the probability per unit path length that interactions will occur.[14] When μ is measured, the value obtained depends on the proportion of scatter included in the measurement.[14] In computed tomography (CT), μ is expressed in Hounsfield units relating all μ values to the value for water.[15] Attenuation interactions also can be characterized by the half-value layer, which represents the path length required to reduce the beam intensity by 50%.[14,15] For the relevant energy range, these values are approximately 4 to 6 cm in soft tissue and illustrate the dramatic impact of attenuation. For SPECT, the spatial distribution of μ and its impact on the projection images is unknown and therefore additional information is needed to correct for these effects. As will be described, independent measurement of the attenuation distribution is utilized with new reconstruction algorithms to perform attenuation correction.

Figure 1 illustrates the impact of photoelectric and Compton scattering and the widely variable values of μ in the thorax. In contrast to PET imaging where the integral attenuation is always calculated along the total path through the body along a line of response,[16] SPECT attenuation correction requires the integral attenuation from the point of emission in the direction of the

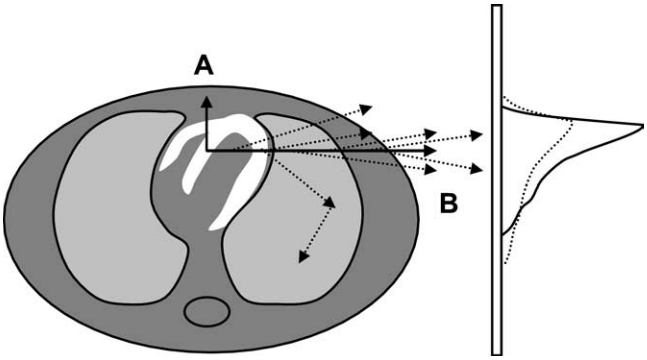

Figure 1 Attenuation of photons and impact on measured projections. (A) photoelectric absorption. (B) Compton scattering illustrating multiple possible paths. Attenuation causes quantitative errors as well as distortions in the projection profiles that are propagated into the reconstructed images. Knowledge of the attenuating distribution is required for attenuation correction. Solid lines depict true profile; dotted lines depict attenuated profile.

detector along the line of response only. Therefore, reconstruction of the attenuation distribution is required.[17,18] Early studies showed that attenuation correction methods applied to homogeneous distributions of μ such as with abdominal SPECT were insufficient.[19-21] It also was recognized that precise emission and transmission alignment was required to account for such factors as patient movement or changes in anatomical position between scans in response to stress. The trend was therefore toward patient-specific rest and stress measurements acquired simultaneously with the emission data when possible. These key requirements largely shaped the current approach to SPECT attenuation correction systems.

Equipment for SPECT Attenuation Correction

Commercialized SPECT attenuation correction systems measure the nonhomogeneous attenuation distribution utilizing external collimated radionuclide sources[17,18] or x-ray CT with hybrid systems.[22,23] The latter use conventional diagnostic x-ray sources and detector arrays in serial alignment with the SPECT scanner. Both approaches have unique technical requirements and implications for laboratory efficiency.

External Radionuclide Source Systems

Figure 2 illustrates the basic configurations currently used for myocardial perfusion SPECT attenuation correction. Figure 2A shows the most widely implemented approach on dual 90° detector systems in which 2 collimated line sources scan uniformly across the field of view of the opposing detector. Gadolinium-153 (^{153}Gd; $t_{1/2}$ = 242 days, 97 keV and 103 keV) is most widely implemented as the source on these systems.[20] A collimated planar beam of photons traverses the patient forming a complete projection profile as the source moves across the full field of view parallel to the system axis. Within the detector, an electronic mask defines a narrow spatial "window" opposite the source and moving in unison. Photons detected in this spatial window are subject to the energy window settings for the transmission source. This approach allows maximal separation of the transmission and emission images. Transmission sensitivity is limited by the restricted field of view, limited source strength, and effect of source and detector collimation. In practice, crossover of photons between the emission and transmission sources requires compensation and may result in technical artifacts[24] with diagnostic implications if improperly implemented.[25] This effect may restrict the imaging protocol sequence or utilize hardware and software techniques for compensation.[26]

Figure 2B illustrates an external radionuclide source approach whereby a series of 14 collimated and shuttered line sources are positioned in an "array" opposite each detector such that the full detector field of view is irradiated simultaneously.[27] The sources are also ^{153}Gd and are designed with increasing activity toward the central field of view to maximize counts through the more attenuating regions of the patient. This approach provides significantly greater transmission sensitivity compared with a scanning line source approach as the full field of view is irradiated. A limitation is that crossover of photons is increased proportionally to the transmission field of view and limits acquisition to sequential protocols for ^{201}Tl studies.

Figure 2C illustrates a third approach to transmission imaging that uses 2 scanning point sources collimated to be incident at oblique angles on the opposing detectors.[28] ^{133}Ba point sources ($t_{1/2}$ = 10.5 years, 356 keV gamma emissions) translate along the system axis simultaneously or sequentially with the emission acquisition. The transmission source is positioned such that the beam is incident on the detectors at an angle to the hole axes. Transmission photons penetrate the collimator septa for detection. ^{133}Ba has significantly higher emission energy and places it well above the emissions of ^{99m}Tc and ^{201}Tl but may have significantly increased downscatter into the emission window. For all radionuclide source configurations, the result is a set of transmission projections for reconstruction of attenuation coefficient distributions on transverse planes and subsequent reconstruction of attenuation corrected images.

Computed Tomography-Based Systems

Recently, hybrid SPECT/CT systems consisting of multidetector SPECT coupled with conventional CT systems have been introduced.[22,23] Developed primarily for anatomical and metabolic image fusion in the oncology community, these systems use the CT image for attenuation correction of myocardial perfusion SPECT images. Early systems included low-energy CT capabilities but have recently been expanded to include high-quality multislice imaging systems. Figure 3A illustrates the basic configuration for a hybrid SPECT/CT system and representative CT images (Fig. 3B). All studies are acquired sequentially on these systems as a result of positioning of the SPECT and CT components. Because of the very high photon flux from the x-ray source, the attenuation map may be acquired using fast (few seconds) or slow (few minutes) protocols with spiral and indexed modes. The very high degree of resolution allows visualization of artifacts not seen in lower resolution radionuclide source images. However, CT systems may have unique artifacts

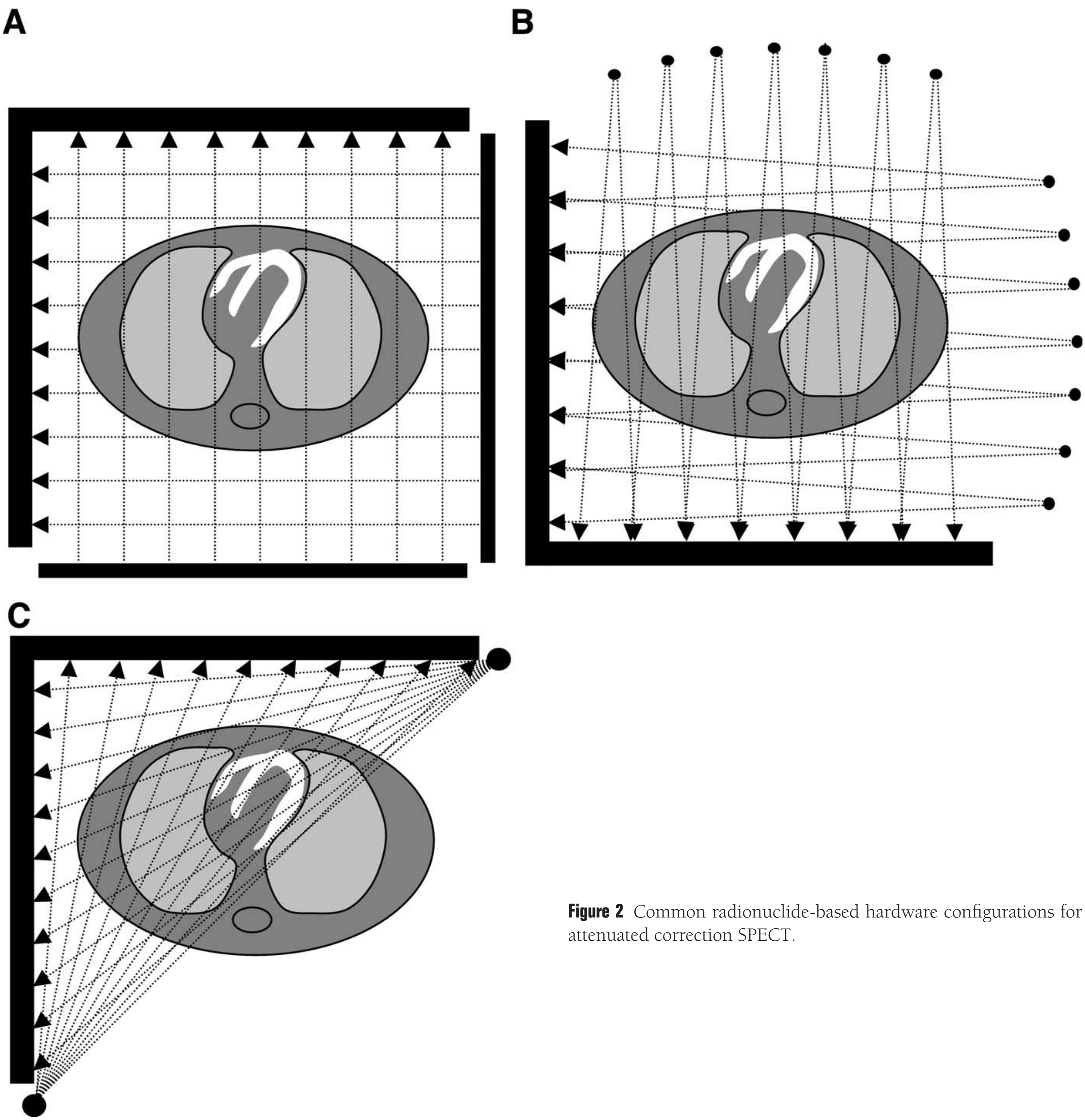

Figure 2 Common radionuclide-based hardware configurations for attenuated correction SPECT.

resulting from the impact of oral and intravenous contrast and beam-hardening artifacts from metallic objects such as with coronary stenting[29,30] that are not readily observable with the scintillation-based images. The impact and management of these effects is still under study.

Quality Control for SPECT Attenuation Correction

It is well accepted that a high quality attenuation map applied appropriately is essential for accurate attenuation correction.[4,31,32] Early publications of clinical attenuation correction studies commented little or not at all on quality control methods or criteria for acceptance of quality.[33] High-quality attenuation maps provide a valuable indicator of the overall quality of the transmission study. Attenuation maps of high quality are characterized by high count density, minimal or no truncation of the transmission projections, high quality reference scans, precise alignment of emission and transmission data and minimal noise.[31]

Transmission Count Density Requirements

Several factors within the radionuclide source system can negatively impact count density. These include mechanical

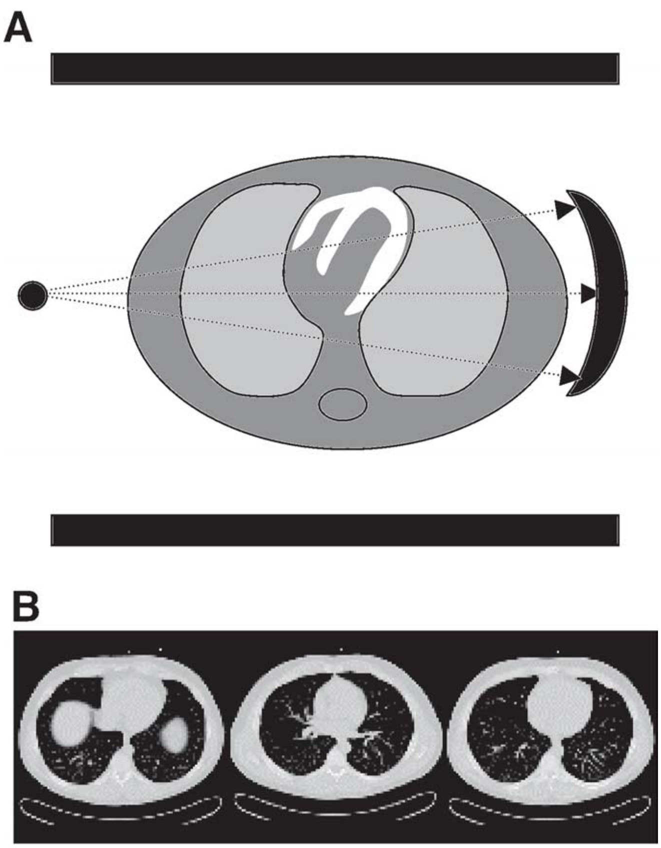

Figure 3 Representative attenuation maps from x-ray SPECT/CT (left to right, inferior to superior).

misalignment or malfunction of the source housing, decay of transmission sources, or insufficient imaging acquisition time; the latter becoming more significant in patients with large body habitus or excessive attenuation. Some systems provide software to estimate optimal acquisition time requirements directed at assuring sufficient counts using a short prescan with the transmission sources.[34] With x-ray CT transmission, the abundant photon flux from these systems provides adequate counts, provided proper calibration is maintained.[23]

Image Truncation and Truncation Compensation

Truncation of the transmission scan occurs when a portion of the patient's body moves outside of the field of view for a number of angles and must be minimized or prevented.[35-37] Figure 4 illustrates a truncation artifact in an attenuation map obtained on a radionuclide based system. The measured attenuation distribution is incorrect, as indicated by the very bright regions and may produce attenuation correction artifacts as the errors are propagated into the corrected emission images.[38] The location of the artifact is critical and has different implications depending on the orbital range affected.[39,40] Gregoriou and coworkers[36] have shown that the detection of perfusion defects can be significantly decreased in the presence of severe truncation. This has led to the development of robust reconstruction algorithms that are less sensitive to the missing information[26,37,41-44] and special consideration to the orbital set up of the study. Interestingly, in early studies using divergent beam geometry for transmission imaging on a triple detector system, essentially all patients were truncated to some degree[41,42] This was accomplished by use of reconstruction algorithms that compensated intrinsically for truncation but these systems were not commercialized.[41,42]

The likelihood of truncation increases with increasing body size and decreasing detector field of view. A current trend in gamma camera design is toward dedicated cardiac systems with small field of view detectors. These systems will have increased truncation based their dimensions. Attenuation correction methods currently being implemented on these systems use new algorithms for compensation and will require new criteria for artifact recognition. Chen and coworkers recently demonstrated the impact of truncation artifacts on attenuation corrected images for small field of view studies based on simulated truncation from nontruncated large field of view patient studies.[40] Additionally, Case and coworkers have performed preliminary validation of a conjugate symmetry reconstruction method to compensate for transmission truncation on small field of view systems.[45] Figure 5 illustrates patient attenuation maps reconstructed without truncation and with significant truncation simulated on a small field of view system. X-ray SPECT/CT systems generally have a large field of view and truncation is less likely, but can occur, particularly with subjects who have a large body mass index (BMI). The system field of view may be smaller than the gantry opening and therefore large patients may experience truncation.

Reference ("Blank") Scans

Transmission reconstruction requires independent measure of the response of the detector to the incident flux in the absence of attenuating media (table, gantry components etc.). "Reference scans" for radionuclide and x-ray CT systems measure this quantity along each line of response. They are required to remain stable over time as a single reference scan is typically applied to all projections in a patient study. The profile of the reference scan is determined by the geometry of the source-detector combination and the shape of the incident photon beam. Evans and coworkers recently described artifacts in the reference scan and the impact on attenuation corrected images for a scanning line source geometry using ^{153}Gd.[46] Some systems require multiple measures

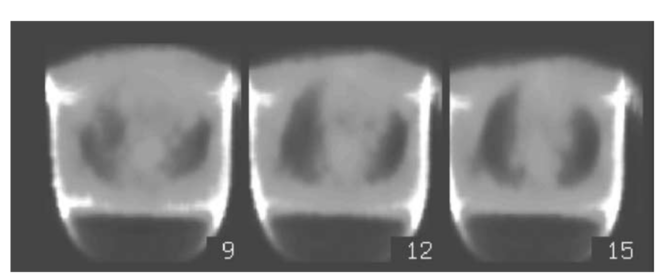

Figure 4 Illustration of severe truncation artifacts in a very large patient on the left and right sides.

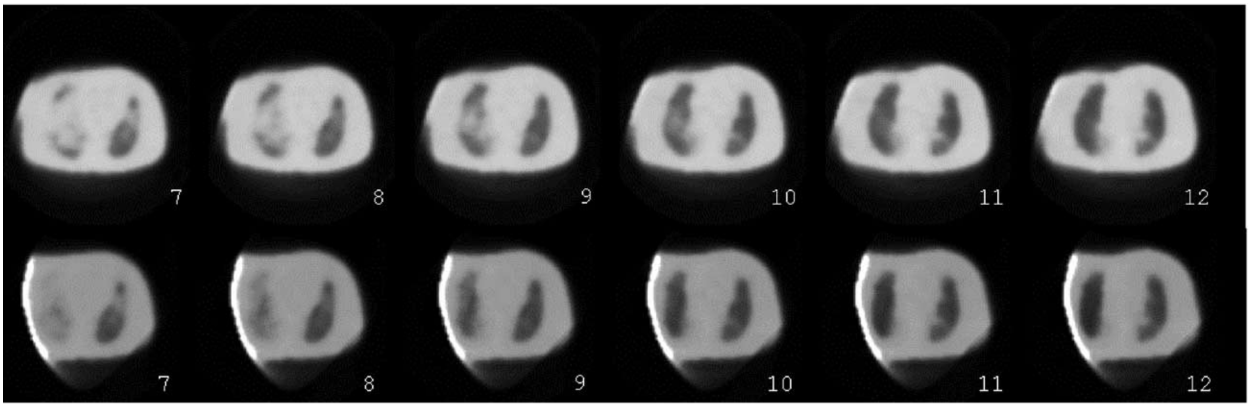

Figure 5 (Top row) Attenuation maps reconstructed without truncation on a large field of view SPECT system. (Bottom row) Illustration of truncation artifact when imaged on a small field of view SPECT system. Artifact is shown as bright "arc" on right side of patient.

of the reference scans at various angles to compute an average response to minimize any potential variation with angle. SPECT/CT systems use a similar approach to reference scan measurement or they may use an indirect approach whereby the attenuation coefficients are calibrated against a phantom.[22,23]

Downscatter Artifacts

Attenuation correction studies are inherently multi-energy studies and require separation of photopeaks. Figure 6 illustrates the impact of ^{99m}Tc tracer photons detected in the ^{153}Gd transmission energy window and the characteristic underestimation of attenuation coefficients in the attenuation map. This artifact may be avoided by timing of acquisitions based on the emission and transmission photopeak energies and software or hardware methods. The appearance of these artifacts in the attenuation map indicates a compromised attenuation correction study and should be carefully reviewed before clinical interpretation. ^{201}Tl SPECT studies require special consideration for downscatter because of the relatively low energy of the major photopeaks relative to most transmission source energies. With ^{133}Ba transmission sources, there is considerable downscatter to the common emission energies and the preferred approach would be sequential (separate) acquisition of the emission and transmission scans. However, with this scheme, movement between scans becomes a source of error. CT-based studies are performed sequentially and the very high flux dominates the count rates from ^{99m}Tc and ^{201}Tl in the x-ray window and, therefore, crossover is negligible.

Misregistration of Emission and Transmission Scans

As a result of the exponential nature of the attenuation process and the large differences in attenuation coefficients of adjacent soft and lung tissues in the thorax, alignment of the transmission and emission data is critical for all methods of

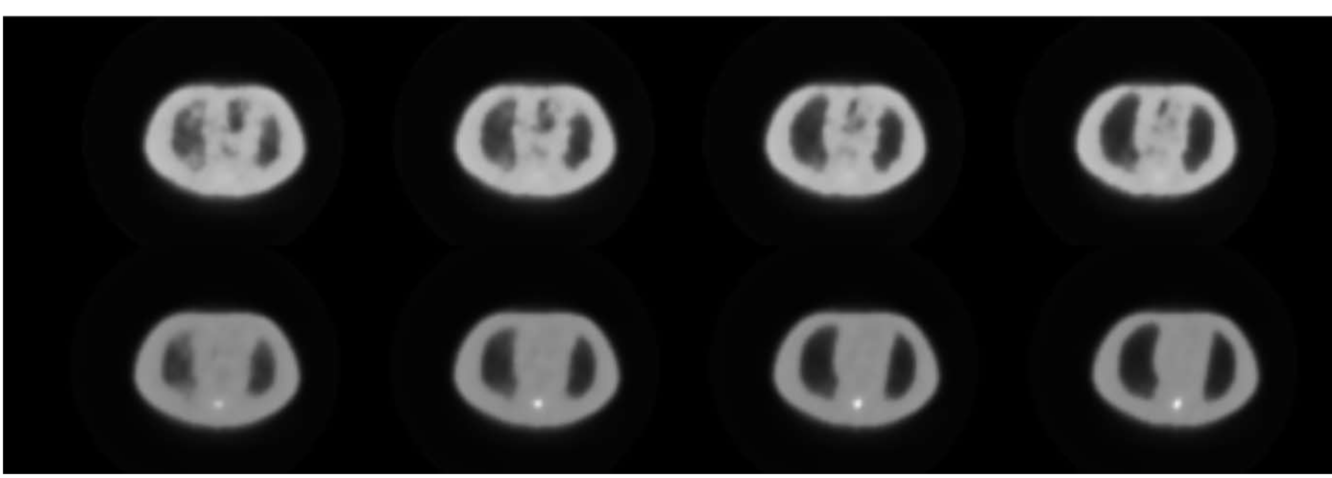

Figure 6 Illustration of errors in the attenuation map on successive transverse planes from ^{99m}Tc downscatter into the 100-keV photopeak of the ^{153}Gd transmission source. Top row represents the effect of downscatter into transmission image and the bottom row the corresponding transverse images after correction. Note image scaling differences are caused by the "spine," which has greater attenuating density as indicated by its "brighter" appearance.

attenuation correction. Stone and coworkers[47] showed that, for transverse and axial shifts of 2.9 cm, the normalized myocardial SPECT activity was decreased in certain regions of the heart by 20% to 35%. For a 12-degree rotational shift, the error was on the order of 10% to 20%, compared with a normalized variation of 20% to 25% in the image with no attenuation correction. The results indicate that registration errors of 2 to 3 cm can seriously affect image quality in both phantom and human images. McCord and coworkers[48] found regional count losses of 30% from a 2-cm shift with ^{18}F-2-deoxyglucose (FDG)-PET studies, a similar result using external ^{68}Ge road sources for transmission imaging. Loghin and coworkers recently reported that of 1177 rest-dipyridamole PET perfusion studies, 252 (21.4%) had artifactual defects due to attenuation-emission misregistration,[49] highlighting the significant frequency of occurrence and the importance of correction methods.

A more subtle source of misregistration is the mismatch between the very high spatial resolution of CT images and the lower spatial resolution of SPECT images. Nanette and coworkers showed with FDG-PET that mismatches as a result of smoothing the transmission images to minimize noise artifacts, can result in errors in absolute and relative quantitation of regional perfusion.[49] Misregistration at tissue boundaries, such as the lateral wall and lung interface can result in artifacts and interpretive errors. Although this work investigated these effects for PET, the principle applies to SPECT/CT.

The relative merits of using a "fast" or "slow" CT image acquisition protocol is under debate for myocardial perfusion SPECT/CT applications.[51] Acquisitions times ranging from a few seconds to one minute for a total volume CT are possible on modern systems.[52] Fast acquisitions minimize blurring from cardiac and respiratory motion but sample the heart and anatomy at a specific instance in the cardiac cycle, thereby potentially leading to mismatch artifacts and attenuation correction weighted toward a single point in the cycle. Slower protocols integrate the information, sampling over multiple cardiac cycles, but provided lower resolution images from cardiac and respiratory motion. Breatholding techniques are also under investigation to minimize the impact of blurring and mismatch as a result of respiratory motion.[52,53] Because of the very rapid ($<$1 s/slice) capabilities of current x-ray systems, respiratory motion becomes significant during the time of acquisition. In contrast, radionuclide-based systems have a slower acquisition rate and the data are integrated over multiple respiratory cycles resulting in a "blurring" of the transmission images. In effect, AC is performed with an averaged attenuation map. The current trend is toward the development of faster methods to maximize laboratory efficiency and the development of methods to recognize and correct misregistration when it occurs.

Impact of Attenuation Correction in the Presence of Extracardiac Activity

In the conventional (nonattenuation corrected) SPECT scan, attenuation by subdiaphragmatic structures greatly suppresses the detection of activity from this region.[54] When attenuation correction is applied in the presence of excessive subdiaphragmatic activity, the relative magnitude of this activity is enhanced and may be superimposed on the myocardium, particularly toward the inferior region of the heart.[54] Visualization and quantitation of cardiac perfusion may be compromised and 'hot-spots' may result that can lead to improper image scaling of other regions of the myocardium. This effect has been proposed as a source of artifact with the appearance of decreased perfusion in the critical anterior region of the heart and can occur with both radionuclide- and x-ray CT-based systems.

Scatter Compensation in Attenuation Correction

The detection of scattered photons in the emission photopeak causes loss of contrast resolution and quantitative accuracy in the measurement of attenuation coefficient values. Scattered photons are detected in both radionuclide-based and CT transmission images. Scatter content is significantly a less in CT because of the detection process. Optimal attenuation correction requires a quantitative matching between the energy content of the emission images and the attenuation coefficient values. Ideally, there is complete scatter rejection in both and only photopeak photons at a single energy are represented. In this case, simple scaling procedures can be used to relate the energy differences between tissues. Current scintillation detector systems do not permit scatter-free measurements and, therefore, attenuation correction methods use approximate methods for scatter compensation.[55] Insufficient accommodation of scatter has been shown to affect the accuracy of attenuation corrected images.[13,44] Based on physical principles and comparison with PET studies, where contrast resolution is significantly greater than SPECT, the sensitivity of attenuation correction for the detection and localization of perfusion defects is expected to improve as more accurate scatter correction evolves. The trend is toward the use of broader regions of the spectrum permitted by more generalized energy window capabilities[56-58] and list mode application to improve scatter estimation. Scatter correction is more complicated for ^{201}Tl SPECT than for ^{99m}Tc agents because of the greater complexity of the emission spectrum. However, recent advances suggest that emerging methods of attenuation correction will include scatter correction and will be applied to ^{99}Tc and ^{201}Tl images, allowing application to single and dual isotope protocols.

Dosimetry of Transmission Scans for Attenuation Correction

Several published reports have examined the radiation dose to the patient as a result of performing external radionuclide-based transmission scanning for attenuation correction. Almeida and coworkers used anthropomorphic phantom studies and thermoluminescent dosimeters to demonstrate that for myocardial perfusion SPECT studies with acquisition time of 15 to 30 min, and 2 ^{153}Gd scanning line sources of 108.1 mCi each, the effective dose was approximately 1.1

mrem.[59] Bellemann and coworkers[60] recently confirmed these results in an independent study calculating an effective dose of 0.73 mrem for a 20-min san also using ^{153}Gd scanning line sources. Although effective dose will increase with increased imaging time or higher transmission sensitivity systems, these studies suggest that effective dose from radionuclide source transmission scans is very low compared with the dose from the imaging tracer.

Estimates of effective dose from x-ray SPECT/CT systems are determined largely by the same factors determining dose in conventional radiological chest CT. SPECT/CT provides a significantly higher quality of attenuation measurement as a result of the greater photon flux and corresponding higher spatial resolution. Chenen and coworkers, using Li-F based thermoluminescent dosimetry and the Alderson phantom assessed the radiation exposure of patients in several standard protocols in multislice CT They found for different chest protocols, an effective dose of 750 to 1290 mrem,[61] considerably higher than for radionuclide based protocols. However, use of lower resolution CT scanners and advanced pulsing methods for attenuation correction application may reduce the effective dose considerably from these values.[23]

Iterative Reconstruction

Attenuation correction advanced to clinical implementation as a result of new reconstruction algorithms referred to collectively as iterative algorithms.[19,62-64] Iterative algorithms provide a broad mathematical framework that permits the modeling of physical processes and noise characteristics from the emission and detection processes.[19] These algorithms are applied to reconstruct attenuation maps and for reconstruction of the attenuation corrected images. Algorithms closely related to the maximum-likelihood expectation-maximization (MLEM) algorithm,[19] or the ordered subset expectation maximization,[65] are most commonly used in commercial systems. The ordered subset expectation maximization (OSEM) algorithm accelerates reconstruction speed by utilizing subsets of the projection data in a specified order. All iterative algorithms use a model of the image acquisition process (forward projection) and are derived to converge to an optimally accurate image. Starting with an estimate of the image on each transverse plane, projection is calculated based on the forward projection of the estimate through the attenuation map. Differences between these calculated projections and the measured data are used to "update" the transverse plane estimate to a more accurate image. Successive application of this process increases the likelihood that the estimated transverse image is the source of the measured projection data given the model of the imaging process. Although theoretical criteria are well described for stopping the reconstruction process,[66] most practical applications are based largely on empirical study of the various implementations. The model of the imaging process also may include scatter processes and effects of distance-dependent spatial resolution of the collimated detector.[67] The distance-dependent change in spatial resolution contributes to the inconsistency between measured projections and has been approximated through filtering techniques[68,69] and through incorporating the spatial resolution information in the reconstruction model.[70] Figure 6 illustrates the iterative reconstruction process using a Bayesian approach applied to the transmission projection data acquired from ^{153}Gd scanning line sources (Fig. 6A) generating the attenuation map, and the reconstruction of the transverse emission images corrected using the previously calculated attenuation map (Fig. 6B). SPECT/CT systems also may incorporate iterative methods for attenuation map reconstruction. However, given the abundant x-ray flux from these systems, conventional reconstruction methods such as filtered backprojection are quantitative and accurate for estimating the attenuation map and therefore are most frequently used. Iteratively reconstructed images appear different than filtered backprojection images, as illustrated in a later section, as some contrast may be lost because of the absence of a ramp filter with filtered back projection reconstruction. Hutton and coworkers and Miller and coworkers[71,72] have discussed some of the differences relevant to clinical interpretation.

Clinical Issues

The literature contains considerable documentation of the role of attenuation correction in daily nuclear medicine practice. Its impact on diagnostic accuracy, performance in the obese, and incremental value to ECG-gating have been demonstrated. Gender-independent quantitation programs are increasingly available commercially, and patient outcome studies are beginning to appear in the literature.

The Attenuation-Corrected Scan

When implemented optimally, the distribution of radionuclide to all myocardial regions should be nearly uniform in the absence of significant coronary artery disease. Male and female distributions should be similar. The right ventricle should be more visible. The basal septum and lateral walls often appear longer in the long-axis images.

Links and coworkers[73] have reported that with one of the hardware/software approaches there may be fewer counts at the apex even in the absence of significant CAD. Their data indicate that apical thinning is seen as frequently with as without attenuation correction and that coronary disease is inferred only when it is severe. Because others have not reported this, this may not be common to all attenuation correction methods. In fact, although gradually becoming more similar in their technical approach, attenuation correction methods remain largely nonstandardized compared with conventional imaging.

For the most part, it is best to interpret attenuation corrected studies in conventional fashion—inspecting first the rotating projection images for quality control, appearance of the left and right heart, potential sources of artifact, and for possible regions of abnormal uptake or absence of uptake of tracer; then the static images; and finally the ECG-gated images. Only then would the interpreter also inspect the attenuation corrected images, to assist in resolution of whether

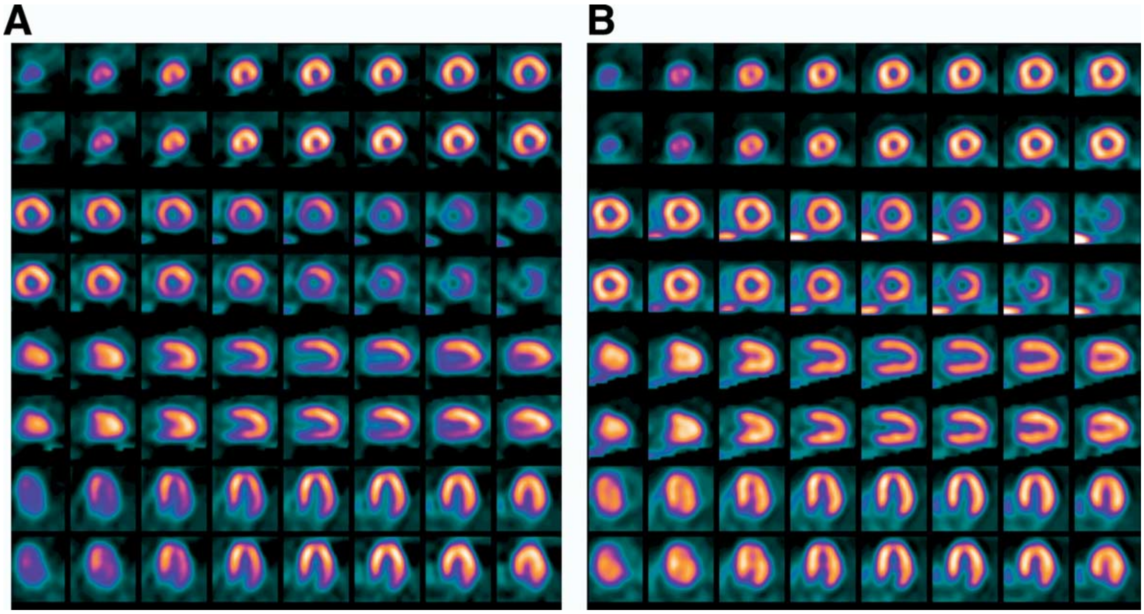

Figure 7 Large male patient with an apparent perfusion defect of the inferior wall in the nonattenuation-corrected images (A) and uniform count distribution after attenuation correction (B). He exercised for 7 min on the Bruce treadmill with no chest pain and no ST segment changes.

findings on the nonattenuation corrected images may be artifactual. Most often, the attenuation corrected images will appear more uniform in tracer distribution, and there will be a tendency to read fewer studies as probably normal or probably abnormal or equivocal.[74] When a new perfusion defect becomes apparent, it is indicative of hypoperfusion that would have been missed on nonattenuation-corrected images. The usual etiology of this is "matched" attenuation artifacts so that a truly hypoperfused region appears to have similar counts to an opposing region that in fact is attenuated.

As indicated previously, the attenuation corrected images will be affected by liver and loops of bowel if these contain a significant amount of radionuclide. The inferior wall may not be interpretable in some cases, and the anterior wall may appear relatively photopenic. Especially with ^{99m}Tc sestamibi and pharmacologic stress, there needs to be fastidious attention to detail to avoid this as much as possible. Patients should present after 4 to 8 h of fasting, and imaging needs to be delayed up to 45 minutes after resting or posthyperemic pharmacologic stress.

If attenuation correction is performed with dual-isotope protocols, in which the technetium but not the ^{201}Tl images are attenuation corrected, it can be helpful to inspect the 2 image sets separately and then with the 2 stress image sets together, one attenuation corrected and one not.

Because the individual frames of the gated images are not attenuation-corrected, attenuation correction will have no effect on either visual or quantitative functional assessments. However, if quantitative programs that were developed for nonattenuation corrected studies are employed for objective evaluation of perfusion, they will often spuriously identify abnormalities at the base of the heart. This is because with attenuation correction, basal portions of the heart and surrounding structures such as the atria tend to be more prominent and get incorporated into the search parameters of the software. Software developed specifically for attenuation-corrected images should be employed; in this case, the maps will be independent of gender.

Effects on Diagnostic Accuracy

Specificity

One of the major goals of attenuation correction is improved specificity through a homogeneous distribution of tracer in normal patients. Several investigators have studied low-likelihood patients and demonstrated significant advantages to attenuation correction. Ficaro and coworkers[41] showed lateral-to-posterior and basal-to apical wall ratios of near unity in 10 healthy volunteers studied with ^{201}Tl. In later studies, Ficaro and coworkers[42] and then Prvulovich and coworkers[75] demonstrated not only improved normalcy in patients with $<5\%$ likelihood of CAD but also a gender-independent quantitative distribution of tracer. Other investigators[75-77] have reported improvements in specificity in patients with follow-up angiography, in comparison with nonattenuation-corrected images. Figure 7A shows an example of a male patient with what appears to be a partially reversible perfusion defect inferiorly on the nonattenuation-corrected images, whereas Figure 7B shows after attenuation correction normal inferior wall uptake. Figure 8A shows an anterior wall partially reversible defect in a female patient, that normalizes after attenuation correction.

Sensitivity

The impact of attenuation correction on sensitivity has been more difficult to determine, partly because in many of the investigations the readers have been blinded to whether the

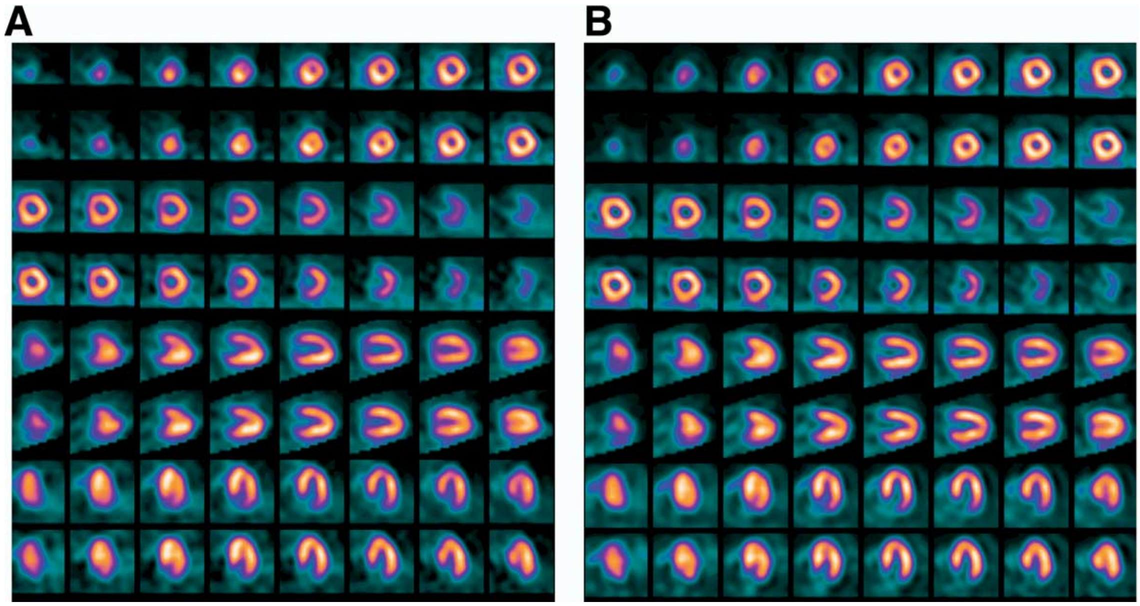

Figure 8 Female patient with a reversible apical perfusion defect suggesting left anterior descending ischemia (uncorrected images in A), that is normal after attenuation correction (B).

images were or were not attenuation corrected. This has the effect of forcing the readers to assume that abnormalities might be artifactual, with resulting sensitivities of corrected and uncorrected images being similar. However, a number of studies have shown a consistent small increase in sensitivity, [58,75-78] and there are numerous anecdotes to suggest that in some circumstances attenuation correction can both detect CAD that would otherwise be missed and better characterize the full extent and severity of disease. There are several potential explanations for this. One is that with uncorrected data, the reader may recognize the presence of an attenuation artifact, and mistakenly attribute the entire abnormality to artifact when in fact there is a combination of hypoperfusion and artifact. Second is that by making the distribution of tracer more uniform, milder degrees of hypoperfusion may become evident. Consider a male patient with significant inferior wall attenuation; if the anterior wall is hypoperfused, this may be overlooked because it appears more normal than the inferior wall. A third cause was referred to earlier, and might best be appreciated by considering a male with both a protuberant abdomen and a thick upper torso. Because the anterior and inferior walls will have reduced "apparent" counts, it will be easy to miss lateral wall hypoperfusion because the image may now seem close to homogeneous. The technical incorporation of accurate scatter correction methods that provide spatially dependent compensation, may potentially provide improved defect contrast without the introduction of additional artifact, especially for mild and moderate disease not adequately detected with current methods. Figure 9 is an example of a patient in whom attenuation correction has resulted in recognition of an ischemic region missed by nonattenuation-corrected SPECT.

Duvernoy and coworkers[79] hypothesized that because attenuation correction eliminates regional perfusion biases, it could increase sensitivity for recognizing left main CAD. They studied 28 patients with left main disease and 34 "controls" with 2-vessel CAD. A left main defect pattern was present on 64% of attenuation corrected versus only 7% of uncorrected images. Specificity was equal. More disease was recognized in a greater number of territories with corrected versus uncorrected SPECT: 2.14 versus 1.43.

ECG Gating, Attenuation Correction, or Both?

Because ECG-gating is performed routinely today with SPECT perfusion imaging and because it can be helpful in differentiating artifact from coronary disease, it is important to know whether attenuation correction adds accuracy not just to static SPECT perfusion images, but after the information provided by gating also has been factored in. Links and coworkers[80] recently examined this matter in a study that included 66 subjects; 32 had coronary angiography (27 with significant CAD) and 34 had a statistical low-likelihood for CAD. Studies were read by consensus of 2 readers who were blinded to all clinical information, for presence of CAD and for coronary territory of abnormality. The readers interpreted static images and then added the information from gating. Both sensitivity and normalcy improved progressively through static (85%/54%), gated but noncorrected (78%/62%), static attenuation corrected (93%/77%), to gated attenuation-corrected (96%/85%) image sets. Sensitivity was the highest for all 3 coronary territories for the combination of gating and attenuation correction, while normalcy was highest with gating and attenuation correction for the right and left anterior descending coronary arteries.

A larger study has more recently been completed and reported in abstract form. Bateman and coworkers[81] performed a consensus blinded read of images from 247 patients, of

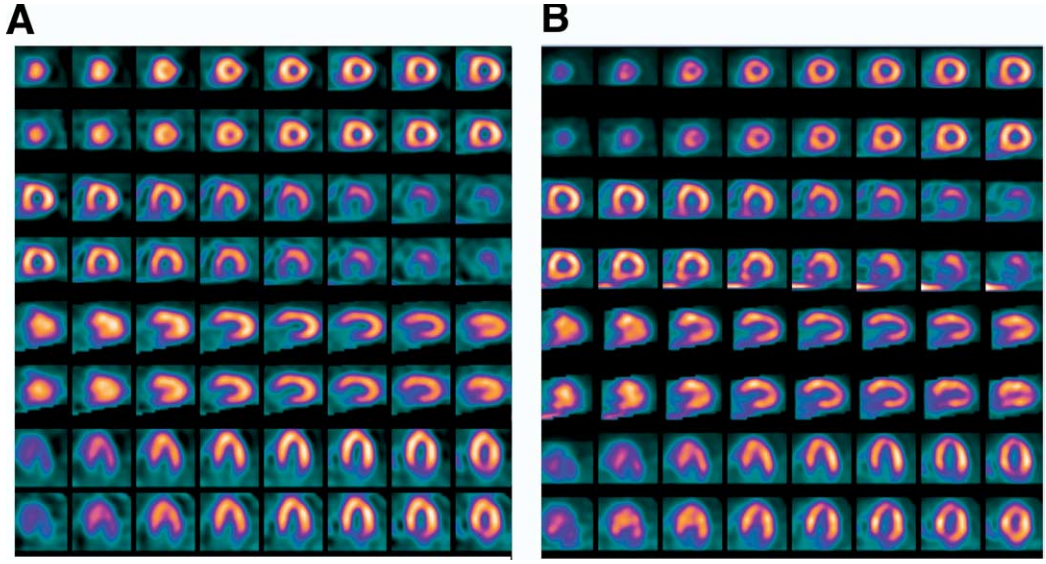

Figure 9 Obese male patient (BMI = 35) with a large perfusion defect inferiorly in a region of previous myocardial infarction (uncorrected images; A). After attenuation correction (B), the inferior wall fixed defect is unchanged, but there is now evident a reversible perfusion defect of the anterior wall and apex. At coronary angiography, the right coronary artery was occluded and the left anterior descending had an 80% stenosis.

whom 118 had angiography within 90 days (90 of whom had significant CAD and 28 did not) and 129 had a low-likelihood of disease. The interpreters scored gated attenuation corrected and gated nonattenuation-corrected images independently and without knowledge of whether the images were or were not attenuation-corrected. The results showed that the attenuation-corrected studies were associated with a significant improvement in both specificity (64% to 86%) and normalcy (93% to 98%), with no change in sensitivity. Taken together, these 2 studies confirm that gating and attenuation correction provide synergistic and complementary information and should be used together for optimal diagnostic accuracy.

Performance in the Obese

Although it can be difficult to predict who will have images compromised by attenuation artifacts, obese men and women present 2 important issues for attenuation correction: will the current algorithms work as well in the obese as in the nonobese and will the value of attenuation correction be greater in this patient population? Previous work by Hansen[11] has shown that diagnostic accuracy of nonattenuation corrected SPECT is lower in the obese, and quantitative analysis does not improve this.

Three studies have addressed the performance of attenuation correction in the obese. Heller and coworkers[74] compared interpretive certainty, diagnostic accuracy, and perceived need for a rest study in 90 patients studied with stress-only imaging, with the patients subdivided into those who were or were not obese (BMI >30 kg/m^2). The percent of studies that could be interpreted as definitely normal or abnormal was similar for obese (79%) and nonobese (87%) people, with the corresponding percentages for nonattenuation corrected images being 28% and 43%. The perceived need for a rest image after a stress-only attenuation-corrected image was also the same for obese (45%) as for nonobese (42%) people. Diagnostic accuracy was unaffected by BMI.

Bateman and coworkers[82] also examined this through a blinded consensus read of 116 patients. Body mass index was normal (<30) in 60 patients and 30 or greater in 56. All patients underwent coronary angiography within 60 days. Gated noncorrected and corrected images were presented randomly and independent of one another. For the obese and nonobese population, sensitivity was the same for attenuation corrected and noncorrected images (Table 1). Specificity was higher overall for attenuation-corrected images. In addition, specificity fell dramatically as BMI increased without attenuation correction, but remained high with attenuation correction.

Finally, Grossman and coworkers[83] recently applied quantitative analysis to compare the performance of attenuation-corrected and uncorrected SPECT in 95 overweight persons, having mean BMI of 32 kg/m^2. Normalcy improved from 52% to 90%, and specificity improved from 29% to 57% with attenuation correction.

Table 1 Sensitivity and Specificity of Corrected and Noncorrected ^{99m}Tc Sestamibi SPECT in Nonobese (BMI <30) and Obese (BMI >30) Patients (Adapted from Bateman et al[82])

	Sensitivity (%)		Specificity (%)	
	Non-AC	AC	Non-AC	AC
All patients	88	86	50*	79
BMI <30	90	90	64	82
BMI >30	87	82	41*	76

*P < 0.05.

These 3 studies suggest that attenuation correction performs well in the obese, and unlike nonattenuation-corrected studies, does not appear to have accuracy erode with increasing body habitus. They do not imply that attenuation correction should only be used in the obese, as there is a large accumulated data to indicate that attenuation correction also enhances specificity and normalcy in the nonobese. Perhaps an appropriate conclusion is that attenuation correction is preferred if available, and is especially useful in the obese.

Gender-Independent Quantitative Programs

The commercially available software programs for quantitatively assessing SPECT myocardial perfusion assume regional variations in the perceived distribution of tracer to account for anticipated attenuation differences between individuals. Obviously all variations in body habitus cannot be accounted for, but data indicate that at least using gender-specific analyses has helped to enhance diagnostic specificity. Because attenuation correction eliminates these apparent differences in tracer distribution, a single quantitative database can be used independent of gender. As discussed above, Ficaro and coworkers[41] first showed this in a series of patients in whom quantitative specificity improved from 46% to 82%, and normalcy improved from 76% to 95%, comparing noncorrected with attenuation corrected data. The same study also demonstrated a statistical improvement in detection of individual coronary stenoses.

Grossman and coworkers[83] recently reported the derivation and then the clinical validation of a new gender-independent quantitative program for normal distribution of tracer and criteria for abnormality. The control database, developed by evaluation of 112 patients, showed no significant segmental differences in mean and standard deviation of counts for male and female populations for attenuation corrected data, with 7 of 20 segments showing significant differences between the same men and women using nonattenuation corrected data. In the validation group, the single database for men and women improved specificity and normalcy, with no loss in sensitivity, compared with noncorrected quantitative analyses.

Stress-Only Imaging

It is recognized that a normal stress image connotes a low-risk for subsequent events, just as has been demonstrated for stress/rest image sets. However, stress-only imaging has not been commonly performed, largely because there is enough nonhomogeneity of tracer in the stress images for most readers to require the rest study for comparison to arrive at a more confident interpretation. As a result, the technique is less efficient and more costly than it might be if a significant proportion of studies could be completed with one image set. With attenuation correction, it is presumed that more "equivocal" images would appear definitely normal; in addition, if there is a perfusion defect that can be confidently ascribed to coronary disease and associated wall motion and thickening is normal, then ischemia can be diagnosed without the necessity for a rest image. Only in the presence of both a perfusion defect and regional contraction abnormality would a rest image be needed, to differentiate scar from hibernating or stunned myocardium.

A recently published study by Heller and coworkers[74] addresses the potential of stress-only imaging when combined with attenuation correction. Ten experienced nuclear cardiologists independently interpreted 90 stress-only gated ^{99m}Tc sestamibi SPECT images; among 41 patients with follow-up angiography, 30 had significant CAD. Another 49 patients had less than 5% likelihood of CAD. Images were interpreted for diagnostic certainty (definitely normal, probably normal, equivocal, probably abnormal, definitely abnormal) and perceived need for a rest image. After "averaging" the readers' scores, only 37% of nonattenuation corrected studies could be interpreted as definitely normal or abnormal, and the readers perceived the need for a rest image in 77% of studies. Interestingly, gating did not impact on either diagnostic certainty, as has been shown with combined stress and rest imaging, or on the perceived need for a rest study. However, attenuation-corrected data increased significantly the number of studies that could be interpreted as definitely normal or abnormal to 84% and decreased the need for a rest image to 43%. The diagnostic accuracy for attenuation-corrected stress-only imaging was 84%, with sensitivity 97% and specificity 84%.

Gal and Ahmad[84] were the first to examine the prognostic meaning of a normal stress-only image. More recently, Gibson and coworkers[85] investigated the safety of stress-only imaging in 729 patients with chest pain and with an intermediate (37%) likelihood for CAD but with a normal attenuation-corrected scan. After a mean follow-up of 22 months, the overall cardiac event rate was only 0.6% (one myocardial infarction and 3 patients with progressive angina who were subsequently referred to angiography). Without attenuation correction, 37% of the images were not normal and were normalized after attenuation correction. This affirms both the clinical usefulness and the safety of patient reclassification based on image appearance changes after attenuation correction.

Patient-Outcomes Studies

There currently is a dearth of outcomes studies based on attenuation-corrected data. The single investigation has been discussed previously in relation to stress-only imaging. It might be hypothesized that attenuation corrected data could lead to substantively different patient classifications and thus different management decisions. For example, a good percent of current images interpreted as mildly or moderately abnormal, or probably abnormal or equivocal, might be reflective of attenuation artifacts, and with attenuation correction be interpreted as definitely normal studies. Furthermore, current beliefs that mild ischemia is "benign" may be derived from pooled data that includes a significant percent of true control patients such that when the population only includes those with ischemia, event rates may be higher. These realities underscore the importance of outcomes studies based on either combined data or attenuation-corrected data alone.

It would appear that several conclusions could be reached concerning contemporary SPECT attenuation correction. There are clearly a number of technical issues that need to be well understood by both technologist and physician. Equipment needs to be appropriately quality-controlled and patients need optimal preparation. Both technologist and physician need to be particularly attentive to the quality of the transmission map. There will be more technical and professional work, but the result should be superior quality images, less over-diagnosis as a result of mistaking artifact for CAD, less unnecessary referral to coronary angiography, and in some cases better delineation of the full extent of CAD.

One remaining issue is the need for more investigation of the various approaches to attenuation correction because validation of one hardware/software solution does not ensure that others will perform the same. Even more important is re-examination of the prognostic meaning of scan results in the era of attenuation correction. Current decisions are driven by population-based studies derived from nonattenuation corrected data that may or may not be extrapolatable from attenuation-corrected images.

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