Are separate normal data files required for quantitative pharmacologic stress radionuclide myocardial perfusion imaging?

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Visual or Qualitative Image Analysis: Limitations

Stress radionuclide myocardial perfusion imaging has been firmly established as the noninvasive method of choice for diagnosing coronary artery disease (CAD).[1] The assessment of myocardial perfusion imaging can be either qualitative or quantitative. Qualitative assessment involves visual inspection of images and subjective comparison of radiotracer uptake of one ventricular segment to another segment. A segment with relatively reduced uptake is judged to be abnormal.

An important limitation of visual analysis is that it requires extensive experience. Nevertheless, considerable intraobserver and interobserver variability may exist even among experienced interpreters. It has been well documented that the degree of perfusion abnormalities relate to a patient's short- and long-term outcome.[1-3] Because of the subjective nature of qualitative visual analysis and the increased chance of inconsistent interpretations, potentially important prognostic information may be lost in individual patients.

Quantitative Analysis

Quantification, or quantitative analysis, of myocardial perfusion imaging is widely used to objectify and standardize the process of interpreting and analyzing images.[4-9] There are two methods of quantification: circumferential profiles and polar maps (Figures 1 through 4).

Both approaches are based on the same principle. With circumferential profiles, the relative myocardial distribution of a radiotracer is graphically represented by relative count density curves, whereas with polar maps, or bull's-eye displays, the relative myocardial distribution of radiotracers is displayed as color-coded relative–count-density concentric rings. Circumferential profile display has the distinct advantage of maintaining a direct visual relation between the graphic display and tomographic radionuclide images. However, multiple graphs are required to display count distribution in the entire left ventricle. Polar map display has the advantage of compressing the entire left ventricle into a single image. This feature, however, is also a disadvantage because this graphic display is "two steps removed" from reconstructed tomographic images. Thus it is more difficult to recognize artifacts on polar map display than on circumferential profile display.

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Why a Normal Data Base?

Marked myocardial perfusion abnormalities are easily identified both on circumferential profiles and on polar maps without a normal reference data base. However, small myocardial perfusion abnormalities are difficult to distinguish from normal variations in regional radiotracer uptake. To identify small perfusion abnormalities consistently and reproducibly, a normal reference data file is important, if not crucial.

Normal data files provide a benchmark against which the interpreter can measure the digitized image data of an individual patient quantitatively. By comparing the patient's image with normal date files, the following questions can be answered quantitatively: Is there a perfusion abnormality? How large is it? Is the abnormality reversible? How extensive is defect reversibility?

What Is Normal? Normal data files initially were generated from images acquired in patients with angiographically normal coronary arteries. It was quickly apparent, however, that this approach was flawed because a significant number of patients with normal coronary angiograms had visually abnormal radionuclide myocardial perfusion images, even when artifacts were taken into consideration. There are two possible explanations for this finding, both of which are well accepted. Patients who have angiographically normal epicardial coronary arteries may have symptoms of chest pain severe enough to justify referral for cardiac catheterization. Although the epicardial coronary arteries may appear angiographically normal, it is conceivable that these symptomatic patients have microvascular disease; in these patients impaired coronary flow reserve has been

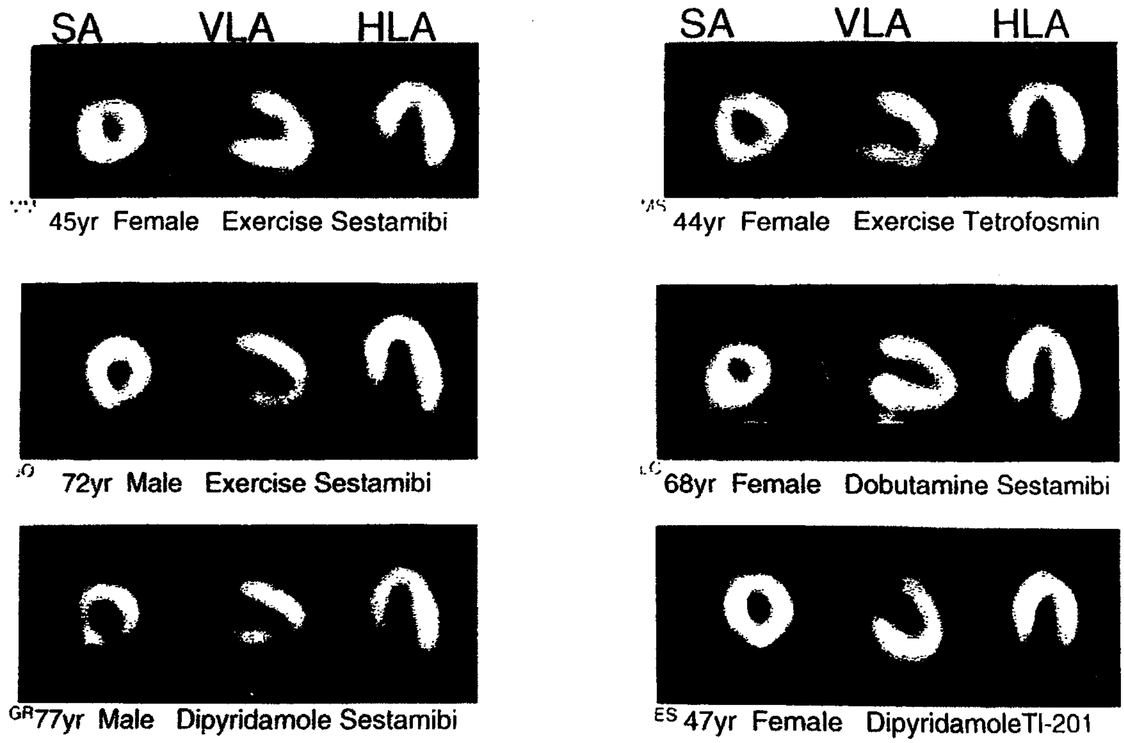

Figure 7. Normal SPECT images from men and women after exercise or after pharmacologic stress. Note similarity in images independent of sex or stress modality. (*HLA*, Horizontal long axis; *SA*, short axis; *VLA*, vertical long axis.)

ıetween normal regional variation in tracer uptake and .bnormally decreased regional uptake. This ability can ıe acquired through the experience of reviewing and nterpreting hundreds of normal and abnormal myocarlial perfusion images.[14] Nevertheless, even the most xperienced interpreter may at times be inconsistent and .se varying diagnostic criterion levels, thereby affecting he balance between sensitivity and specificity for detecion of disease. Building sufficient experience in the nterpretation of myocardial perfusion images may take onsiderable time. Even with experience, however, viual analysis is not flawless, because of its subjective ıature. Because radionuclide images are intrinsically ˌuantitative images, computerized image analysis with :ormal reference data base is a logical approach to acilitate and enhance reproducibility and accuracy of mage interpretation.

Generating the Normal Data Base. We are still aced with the issue of how to generate a normal data ıase. Computer digitization of images allows permanent torage of normal images and quantification of normal mage patterns and its variations. From such normal data iles an "average normal image" can be composed. Because it is not unreasonable to assume that normal ·ariations of myocardial images are normally distributed, he lower limit of normal radiotracer myocardial distribution traditionally has been defined as "mean valu minus two standard deviations."[4] The lower limit c normal therefore constitutes a 95% confidence limit. Fiv percent of normal images may fall outside of these limit and some abnormal images may fall within these limit Generation of a sufficiently large normal data base ca be a considerable undertaking. For instance, it is nc appropriate to generate a normal data file from norma myocardial perfusion images obtained in patients re ferred to the laboratory. These patients most likely ha symptoms suggestive of heart disease or had risk facto for CAD. In most laboratories, patients with norma myocardial perfusion images have a preimaging likel hood of CAD that is ≥10%. Normal image data files a more accurately generated from persons who were priori defined as "normal" by nonradionuclide imagin clinical variables. Currently, a thoroughly accepte method for generating normal data files is to recru persons with very low (<3%) likelihood of CA through stepwise probability analysis on the basis of th absence of symptoms, age, sex, and exercise electroca diography. In general, persons who meet criteria for lo likelihood of disease are not patients referred to th nuclear imaging laboratory but must be recruited a healthy volunteers.[4]

In addition to normal variation in radiotracer uptak

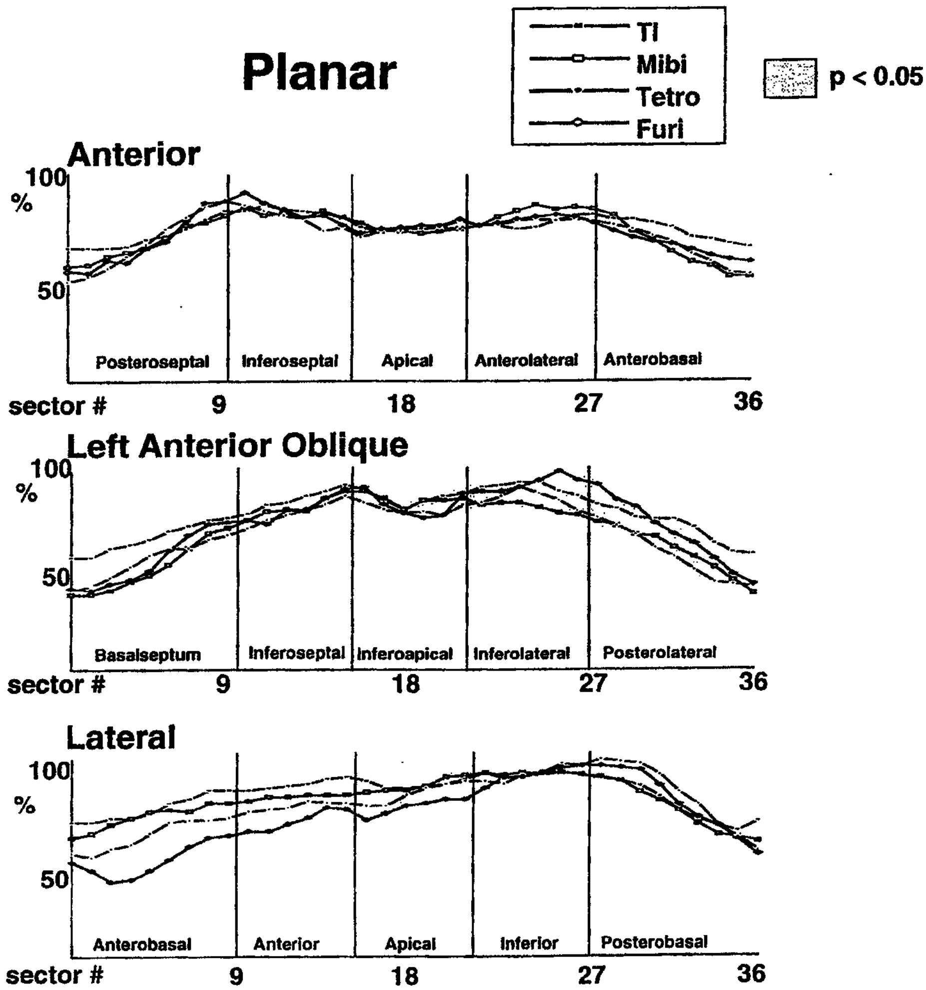

Figure 8. Quantitative comparison of lower-limit-of-normal curves of four radiopharmaceutical agents in planar anterior, left anterior oblique, and left lateral views. *Shaded segments,* Statistically significant differences among curves of various radiotracers. (*Tl,* ^{201}Tl, other abbreviations as in Figure 2.) Reprinted by permission of the Society of Nuclear Medicine from: Naruse H, et al. J Nucl Med 1996;37:1783-8. Figures 2-5.

a distinct problem with myocardial perfusion imaging is the occurrence of artifacts due to attenuation. Some commercially available software provides normal data files for men and women.[15] This distinction may be helpful, although the degree of normal attenuation by breast tissue or left hemidiaphragm may vary considerably among individual persons and is often unpredictable.

A Normal Data Base for Every Imaging Variable? The appearance of normal myocardial perfusion images is also affected substantially by the specific radiotracer used. In addition, myocardial perfusion images characteristically differ depending on the physiologic condition during radiotracer injection, namely injection at rest or during stress or injection during physical exercise or pharmacologic stress. Some investigators have suggested that it is necessary to establish normal data files for each of the various imaging acquisition protocols, for the use of single or multiheaded gamma cameras, for various types of collimators, for different imaging orbits, and for different filtering methods, in addition to data files for sex (as mentioned earlier) and age. Although such considerations are theoretically entirely valid, it may never be practical to establish normal reference data files for every conceivable imaging variable and condition.

A Simplified Approach

Unless the goal is to achieve complete computerized and automated image interpretation, it is proposed that physicians should be less ambitious and more practical and should simplify their approach to computerized quantitative image interpretation. The ultimate purpose

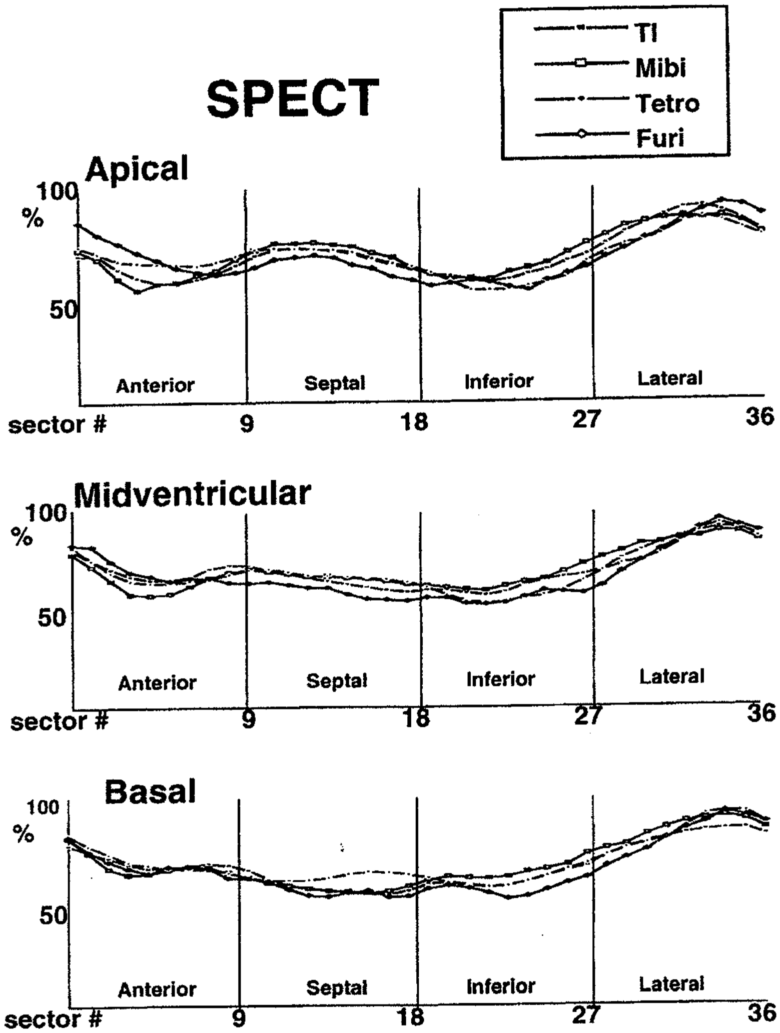

Figure 9. Quantitative comparison of lower-limit-of-normal curves of four radiopharmaceutical agents in SPECT apical, midventricular, and basal regions. There was no statistical significant difference (Kruskall-Wallis test) among normal curves of various radiotracers. (*Tl*, ^{201}Tl, other abbreviations as in Figure 2.) Reprinted by permission of the Society of Nuclear Medicine from: Naruse H, et al. J Nucl Med 1996;37:1783-8. Figures 2-5.

of quantifying myocardial perfusion images with normal reference data files is primarily to enhance the reproducibility of interpretation and to express perfusion abnormalities quantitatively.[16,17]

There does not seem to be a problem in visually identifying normal myocardial perfusion images under a multitude of conditions. Indeed, one normal myocardial perfusion image is much like another normal myocardial perfusion image (Figures 5 through 7). Most of the noticeable differences exist between images acquired with ^{201}Tl-labeled agents and those acquired with ^{99m}Tc-labeled agents. Even then, it is not the image of the myocardium but the relative distribution and accumulation of the radiotracer outside the heart that is markedly different. Differences in the appearance of images are also well explained by differences in the degrading effect of low-energy background scatter, which is less with ^{99m}Tc than with ^{201}Tl.

The purpose of quantification with normal data files is not necessarily more sophisticated than that with visual image analysis: we still inquire as to what extent the patient's image is comparable to or different from a "representative normal image."

In our laboratory, normal data files have been generated from images of healthy volunteers with low (<3%) likelihood of having CAD (Figure 2). However, before the individual images are entered in the data base, each image is visually inspected for quality (absence of motion artifacts and adequate count density) and for the absence of obvious artifacts (for instance, those caused by breast or diaphragmatic attenuation). Thus the normal data files consist of normal digitized images, similar to

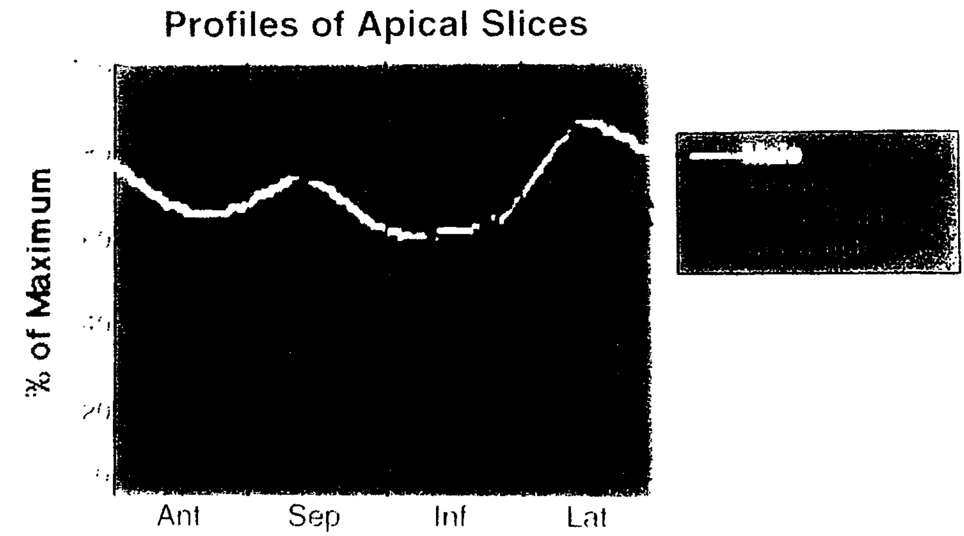

Figure 10. Exercise circumferential count distribution profiles acquired with ^{99m}Tc-labeled tetrofosmin SPECT in apical slices. *White curve*, Average profile in men; *gray curve*, average profile in women; *black curve*, composite lower-limit-of-normal profile used for SPECT imaging (including curves of both sexes). Profile in women is close to average lower-limit-of-normal profile, although not identical. Profile in men shows higher value in anterior wall compared with profile in women and average profile.

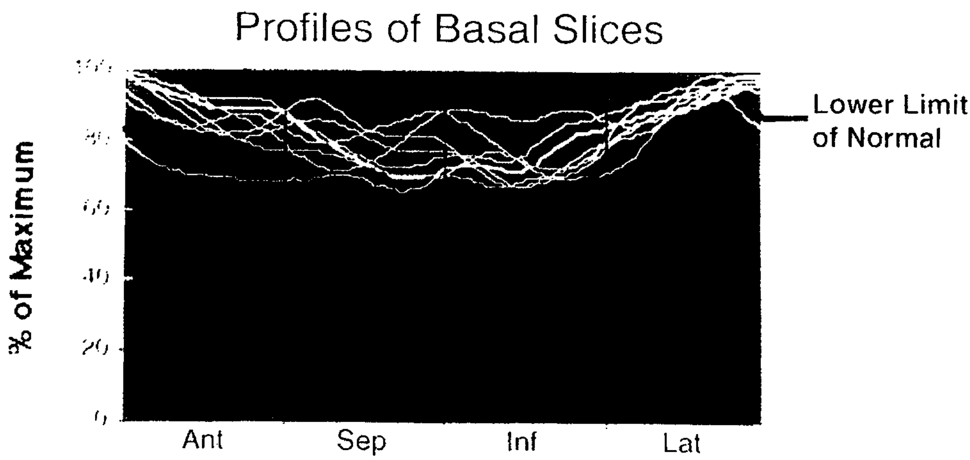

Figure 11. Circumferential count profiles in basal slices of visually normal dipyridamole ^{99m}Tc-labeled sestamibi SPECT images. *Black line*, lower-limit-of-normal count distribution of exercise ^{99m}Tc-labeled sestamibi imaging. Dipyridamole circumferential profiles are largely within normal range determined from physical exercise images.

the "ideal normal image" that physicians have in mind when performing visual image analysis.

Quantitative Comparison of Normal Data Files with Various Radiotracers. We compared quantitatively normal data files of various radiotracers in planar and single photon emission computed tomographic (SPECT) imaging.[18] With planar imaging, significant differences exist among various tracers, most likely because of the marked difference in background activity and the effect of an imperfect background sut algorithm (Figure 8). With SPECT imaging, th ences between various tracers was statistically nificant, although the lower limit of normal cur not identical (Figure 9).

How To Use a Normal Data Base. Quant with a normal reference data base is associated following limitations. First, the lower limit of distribution represents one end of a 95% co interval: images of some clinically normal persons may be just outside this "normal" range, whereas some images of clinically abnormal persons may be within this range. Second, normal data files do not incorporate artifacts. Therefore every image should be inspected for the possible presence of artifacts. For instance, sex-specific data files do not account for breast attenuation artifacts in every woman and therefore should be inspected as usual (Figure 8).

For quantitative planar imaging, radiotracer-specific normal data files are mandatory. For SPECT imaging, radiotracer-specific normal data files are preferred, though not necessary. In our laboratory we use separate normal data files for various radiopharmaceutical agents and for planar and SPECT imaging. However, we do not use separate data files for men and women (Figure 10), nor do we use separate data files for pharmacologic vasodilation, adrenergic stress, or resting images. Moreover, we use the same data files for the processing of images acquired on different gamma cameras.

When To Use a Normal Data Base. A normal data base should be viewed as a benchmark against which a patient's image can be compared. Image quantification with normal data files is of considerable clinical usefulness. First, it may serve as a measure for quality assurance. Quantitative analysis can be viewed as a highly consistent and objective "second observer." Second, image quantification enhances intraobserver and interobserver reproducibility.[16] Third, image quantification allows quantification of perfusion defect size and defect reversibility, which has been shown to have prognostic value.[2,3] Fourth, quantitative analysis is particularly useful in studies with mild or equivocal perfusion abnormalities. In these studies quantification may greatly enhance the confidence of interpretation. Thus the graphic display of image data enhances consistency of interpretation. However, computer quantification should not be accepted as the ultimate and invariable truth. Quality control and alertness for the potential presence of artifacts remain the first crucial steps in image interpretation.[5,6,13,16]

When Are Separate Normal Data Files Necessary? Another issue is whether separate normal data files are required for pharmacologic-stress myocardial perfusion imaging. Normal myocardial perfusion images after pharmacologic vasodilation with dipyridamole and adenosine or after adrenergic stress with dobutamine are very similar to normal images after exercise. In our laboratory we have used exercise normal data files to quantify perfusion images obtained after pharmacologic vasodilation or stress for >10 years. In our experience in >7000 planar and SPECT studies, visually normal myocardial perfusion images after pharmacologic vasodilation or stress are without exception quantitatively normal when compared with exercise normal data files (Figure 11).

Therefore, although it is preferable to generate normal data files for each pharmacologic stress agent, this step may not be practical and most likely is unnecessary if image quantification is used with good understanding of its value and limitations. Computerized quantification with normal data files provides a powerful modality to improve the overall diagnostic yield and, at the same time, to enhance the reliability, accuracy, confidence, and reproducibility of interpretation.[5]

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