Editorial: Sestamibi and the Issue of Tissue Crosstalk

In this issue, a quantitative planar method for Sestamibi imaging is described by Koster, Wackers, Mattera, and Fetterman (*1*) from Yale University. The method relies on an interpolative background subtraction algorithm recently modified by Watson and Smith (*2,3*) for Sestamibi imaging. This background subtraction algorithm, developed by Goris (*4*) and modified by us (*5*) has been widely adopted for quantitative thallium-201 (^{201}Tl) imaging. Standardizing quantitative analyses of myocardial perfusion imaging requires adopting a common background correction method. Since we are suggesting a change in the old standard for a new imaging agent, it is appropriate to raise old questions such as what is background in myocardial imaging, how is it determined in planar imaging and how can we design a valid experiment to test the background correction.

As pointed out by Goris (*6*), "background" in gamma ray imaging is not the same thing as "background" for a bench measurement of activity from a confined gamma ray source. For the latter, background can be defined as the activity remaining after the source is removed. For imaging, "tissue crosstalk" should be used instead and defined as activity in a sample region of interest within the image which originated outside the sample region. Tissue crosstalk must include activity from tissues outside the sample which Compton scatters into the collimator solid angle, and thus will be counted as being from the sample region. For a void defect in the heart, much of the tissue crosstalk comes from activity within the heart which scatters into the void. Thus, for the purpose of measuring activity distribution within an organ, tissue crosstalk cannot be determined simply by removing the organ and counting the residual activity.

There is no simple way to theoretically calculate tissue crosstalk. It is widely assumed that SPECT reconstruction does this automatically, but in the absence of corrections for attenuation and Compton scatter, even SPECT reconstruction offers only an approximation which can only be tested empirically. The interpolative method creates a "background reference plane," which is subtracted from a planar image to compensate for tissue crosstalk. As in the case of SPECT, it is an approximation which can only be tested empirically since there is no gold standard reference for tissue crosstalk. How does one arrive at a suitable approximation? How can the approximation be properly tested?

A background reference plane must be created inductively. In essence, it is a guess which may be considered a hypothesis to be tested. There is no systematic method of inductive logic as there is for deductive reasoning. In our case, we started with a well-tested method used for thallium imaging and found that it clearly caused oversubtraction near regions of high visceral uptake encountered with resting Sestamibi images (*3*). This appeared to be the result of improper shape of the background reference plane near boundary edges of high activity. The shape was modified, first by making it Gaussian and then by adjusting the rolloff so that on a few test studies the activity after background correction was the same for the rest or exercise images. Sample studies from both normal subjects and patients with persistent defects, corresponding to infarct segments in which no ^{201}Tl redistribution could be quantitatively demonstrated were tested. This produced a trial function which now must be tested in a scientifically acceptable way.

Tissue crosstalk estimation methods are not easily tested because there is no gold standard for comparison. We must first define what is to be accomplished by subtracting tissue crosstalk from a myocardial image. The background reference for ^{201}Tl was based on pragmatic criteria. Net uptake after background subtraction for a large infarct should approach zero but not go negative. After background subtraction, normal myocardium should have homogeneous uptake (allowing for attenuation by overlying tissue) and homogeneous washout. (The shape of the reference plane affects both quantitative net myocardial activity and the apparent washout.) The result should be independent of a computer matrix or gamma camera and should be reproducible in other laboratories. A key test of the reference plane is that if myocardial perfusion is unchanged, the net myocardial distribution should be the same for a rest injection as for injection during exercise (in other words, independent of tissue crosstalk). This criterion is particularly appropriate for Sestamibi because the shape and amount of tissue crosstalk differ markedly between rest and exercise images. Changes in myocardial distribution comparing rest and exercise images differentiate scar from ischemia and it is essential that changes due to crosstalk are correctly separated from changes in the actual myocardial activity. Testing this last criterion in humans is complicated by the paucity of alternative standards to indicate myocardial viability and ischemia.

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Testing the background subtraction in animal models is of dubious value since the shape of the background correction reference is certainly different in animals. Showing validity in an animal model would not infer validity in humans. Another problem in animal testing has been in differentiating "background" from "tissue crosstalk." Studies in a dog model show the activity remaining after the heart is removed and replaced with a water-filled balloon (*7*) or replaced with another heart having no tracer (*8*). This defines what could more appropriately be called "background" (activity remaining after the source is removed). Both of these studies eliminate activity within the heart which may be the most important source of "crosstalk" via Compton scatter. Our early experience with ^{201}Tl indicated that the sharp self-attenuation structure indicated by these studies did not work well for human myocardial images. The less structured reference plane as developed by Goris was substituted and proved to be more robust and also to fill the pragmatic criteria sought for the reference plane.

Extensive experience with quantitative ^{201}Tl methods used by the Cedars-Sinai program developed by Garcia (*9*) and the UVA program (*5*), as well as others which used the same reference plane, has resulted in a wide acceptance of its validity. It is natural then to compare defect magnitudes obtained by Sestamibi using quantitative ^{201}Tl as a comparative reference. Laboratory data (*10–12*) do show a linear relationship for normal and subnormal myocardial perfusion with both ^{201}Tl and Sestamibi along with similar sub-proportional uptake at higher blood flow. These data directly imply that the ratio of myocardial uptake in a defect to normal observed with ^{201}Tl should be equal to the ratio obtained with Sestamibi. The equality of defect ratios is then mandated by experimental data and may be considered a necessary condition for a valid reference plane.

We reported the development of the modified background plane (*3*) and showed that it produced defect ratios equal to ^{201}Tl defect ratios in our hands. Moreover, we showed that defect ratios from ^{201}Tl were not significantly changed by substituting the modified background plane. The modifications are actually subtle and insignificant except in situations such as rest Sestamibi images with intense visceral uptake in close proximity to the heart. We also showed that with normal subjects, ratios of Sestamibi uptake comparing contralateral left ventricle segments were unity — thus, fulfilling the homogeneity criterion for normal hearts. The paper in this issue by Koster uses the same background reference in a different quantitative program and in a new environment. It shows the equivalence of ^{201}Tl and Sestamibi defects after background subtraction in a different and somewhat larger patient group. This paper also develops a "normal profile" of integrated activity for Sestamibi using the new reference plane and demonstrates differences in resolution of valve planes but similar distribution within myocardium for a normal population of patients using ^{201}Tl. Of equal importance, the Yale study indicates that the reference plane gives similar reproducible results in another laboratory using a different quantitative program and different equipment.

It cannot be said from the Yale paper in this issue or from ours (*3*) that the reference plane has been "validated" in the sense of experimentally proving that it represents true tissue crosstalk. It can be said to be internally consistent, a fundamental requirement of any postulate or theory. These papers show consistency in comparison to quantitative ^{201}Tl results, which are based on more extensive experience. It appears from the Yale work that the reference plane provides reproducible results, and this has the potential to be of practical use for the standardization of quantitative processing. We consider this to be more important than absolute accuracy. Quantitative planar results based on this method should also be compared with SPECT results, although SPECT, as indicated, should not be uncritically assumed to be a new gold standard. Finally, as with ^{201}Tl, this technique needs to be tested in much larger populations and compared to coronary angiography and ultimately compared to clinical outcome. But first we must develop and adopt a uniform method before tests on a large clinical population can be meaningfully completed and compared.

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