Normalization of Stress and Delayed Thallium-201 Myocardial SPECT: Where Is the Normal Reference Area?

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We describe an unusual uptake pattern in a thallium SPECT study performed after dipyridamole infusion in a patient with a documented history of prior inferior infarction and recent typical chest pain. The stress study exhibited maximum uptake in the inferior wall. The delayed study showed an inferior defect more consistent with the notion of inferior necrosis, with a maximum uptake in the anterior wall. The authors propose a pathophysiologic interpretation consistent with coronary angiography findings, based on the assumption of coronary steal suggested by the occurrence of chest pain at the end of the dipyridamole infusion. The problem of selecting myocardial normal reference area(s) necessary to normalization prior to quantitative comparison stress and delayed studies is discussed.

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Using ^{201}Tl SPECT, the diagnosis of myocardial ischemia relies on the finding of stress-induced perfusion defects reversible on delayed studies. In many cases, visual interpretation is an acceptable diagnosis. However, interobserver as well as patient variability may cause problems of interpretation, especially in borderline studies. To solve this problem, we have developed a computer method to quantify reversible defects. The logic is similar to the one proposed by Klein et al. (*2*). Our program compares:

1. The stress patient bull's-eye to the mean stress bull's eye from 16 normals.
2. The delayed patient bull's-eye to the mean delayed bull's-eye from the same normal file.
3. The patient reversibility bull's-eye to the mean reversibility bull's-eye from the normal file.
4. The patient "reverse reversibility" bull's-eye to the mean reverse reversibility bull's-eye from the normal file.

Two different normal data bases are used, one for women and the other for men.

It appears that the only difference between our approach and that of Klein et al. lies in the fact that we use the method proposed by Goris et al. (*2*) to generate the polar maps.

Such an approach requires the normalization of stress and redistribution studies before subtraction. The aim of this case report is to emphasize the problems possibly raised by the selection of the area(s) of normalization. In other words, is the presumably most normal area (because it is the hottest one under stress) always a normal area?

CASE REPORT

A 72-yr-old patient with a documented history of inferior myocardial infarction 15 yr ago was referred to the nuclear medicine department for CAD thallium evaluation because of chest pain. Thallium-dipyridamole imaging was performed due to the patient's inability to exercise. At the end of dypyridamole infusion, the patient experienced severe chest pain, relieved by two sublingual nitroglycerin sprays.

Stress thallium SPECT (Figs. 1 and 2) exhibited maximum uptake in the inferior wall with clearly decreased uptake in anterior and septal wall and a small apical defect. Lateral uptake was intermediate but close to normality.

Redistribution SPECT exhibited maximum uptake in the anterior wall with clearly decreased uptake in the septal and inferior walls, more pronounced at the apex. Lateral uptake was within normal limits. Gated blood pool showed apical akinesis associated with an inferior hypokinesis. Septal wall motion appeared to be normal.

Contrast ventriculography and coronary angiography were performed the next day and exhibited a 90% stenosis of the left main coronary artery. The right coronary artery was patent with a stenosis of the 1st segment and widely dominant with a large collateral network towards the lateral wall. Regional wall motion analysis was consistent with that of gated blood pool.

DISCUSSION

This observation is interesting from both the potential pathophysiology of the process and the implications for image processing.

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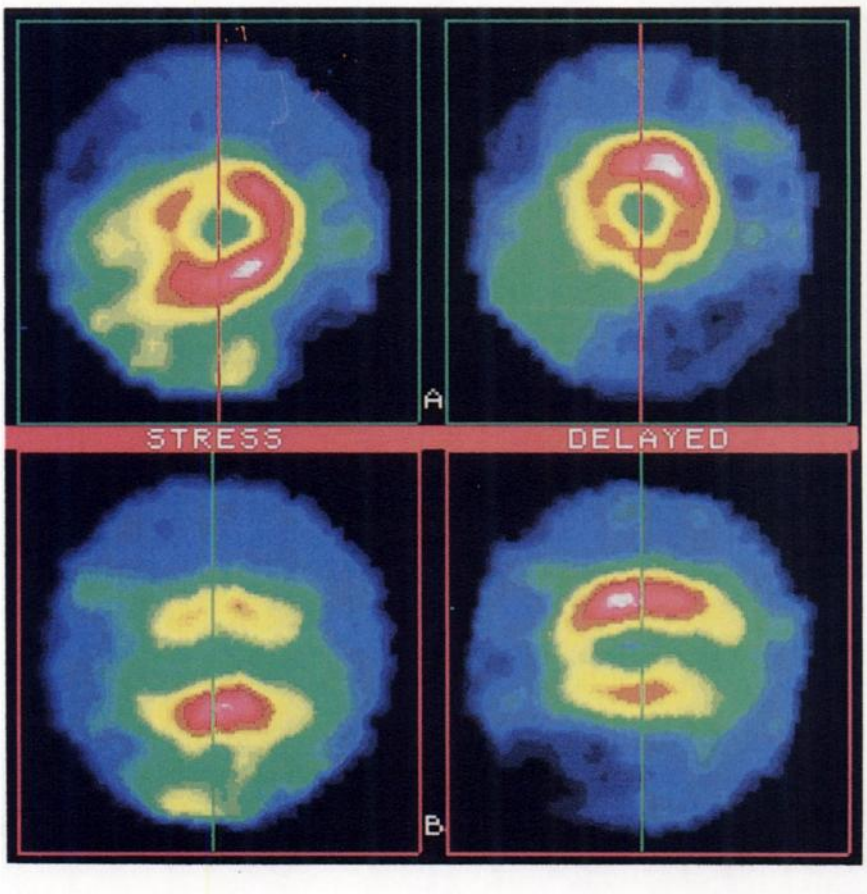

FIGURE 1. Selected slices: the display procedure systematically uses a maximum count rate normalization. (A) Short-axis slices and (B) sagittal long-axis slices. (See Fig. 2 for bull's-eye representation.)

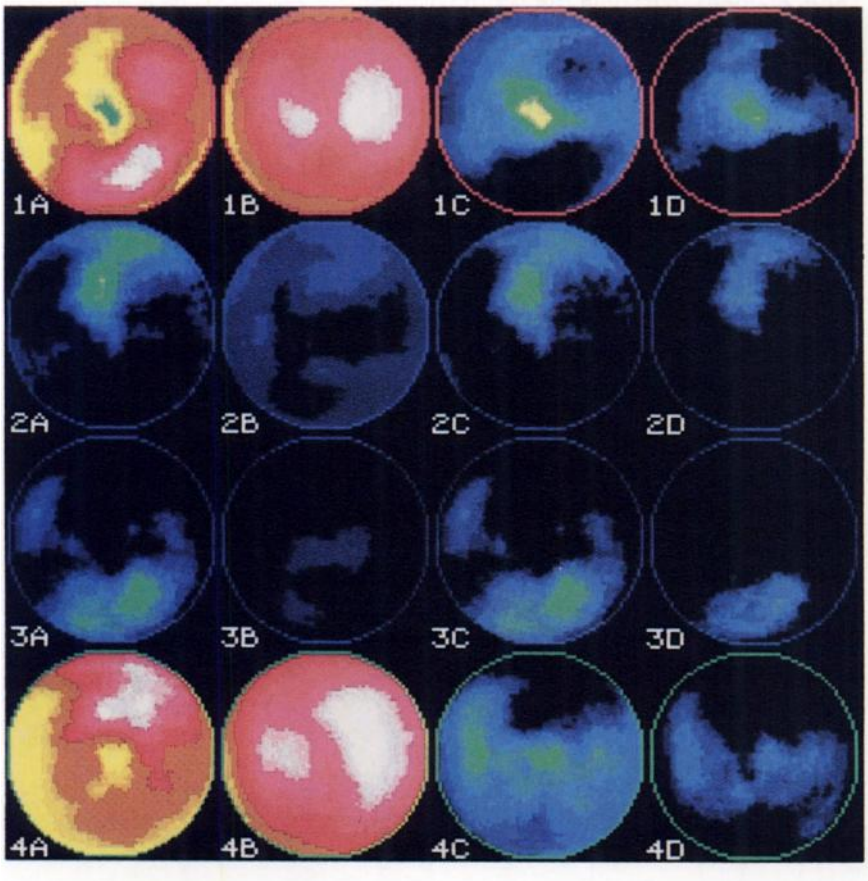

FIGURE 2. Bull's-eye quantitative analyses based on the maximum count rate density normalization. Row 1. Stress polar maps. (1A) patient; (1B) data base mean; (1C) raw difference: data base mean minus patient; (1D) difference with a 2.5 s.d. threshold: positive pixels show areas of significant decreased uptake. Row 4. Delayed polar maps: i.d. Row 2. Reversibility polar maps. (2A) patient; (2B) data base mean reversibility bull's-eye; (2C) raw difference: patient minus data base mean; (2D) difference with a 2 s.d. threshold: positive pixels show areas of significant redistribution. Row 3. Reverse reversibility polar maps. Positive pixels of three-dimensional map show areas of significant reverse redistribution.

Pathophysiologic Hypothesis

First, how was the inferior wall the area of greatest activity on the stress study? This is probably due to a coronary steal as suggested by clinical symptoms of ischemia during dipyridamole infusion. Generally, coronary steal results in diverting blood to nonischemic areas from zones of myocardial ischemia. In this case, one may reasonably assume that the coronary steal occurred from the ischemic area related to the critical stenosis of the main left coronary artery towards the inferior wall. Indeed, this area is infarcted as shown by ECG and inferior wall motion abnormality, but the obvious presence of viable myocardium and the reopening of the infarct-related artery result in better coronary hemodynamics than in the ischemic left territory, allowing blood diversion towards the less resistant zone.

Second, how could the lateral wall have good uptake despite the main left coronary stenosis? This finding is likely due to the large right coronary artery collateral network seen on coronary angiography that prevents, at least in part, circumflex territory ischemia.

Finally, the third point is the persistent decreased uptake in the septal wall that might suggest a septal necrosis which is not consistent with ECG, coronary angiography nor ventriculography findings. We assume that the severe ischemia induced by coronary steal was responsible for delayed redistribution. We did not perform 24-hr delayed SPECT which might have answered the question.

Normalization: Where is the Normal Reference Area?

Whatever the method used, circumferential profiles or bull's-eye analysis, a quantitative approach of stress and delayed studies comparison requires a normalization. This normalization has to be performed with respect to normal myocardial areas. In the ideal situation (but alas utopian when speaking of myocardial SPECT) where the SPECT data would be free of any kind of artifact, the only problem would then be to select the normal areas.

Some authors consider the area of maximum uptake in the stress study as presumably the most normal; normalization is then performed with respect to this area and the homologous one on the delayed study (*1*). We are inclined to think that this is a reasonable attitude. In this case however, the stress maximum count area is obviously not the most normal. However, bull's-eye analysis resulting from this normalization shows a redistribution in the anterior wall at least partly consistent with the patient's coronary status with no reverse redistribution anywhere.

Some authors propose maximum count rate density normalization (*3*), which consists in normalizing with respect to the maximum value of each study. In this case, both areas are presumed normal and set to the maximum, even if they do not have the same location. Despite this fact, this method is also reasonable if one may assume that the possible topographic discrepancy only results from statistical fluctuations due to anatomic and/or physiologic variability in correctly perfused areas and change in physical parameters of data acquisition and processing. Clearly, it is completely wrong in the present case since both maximum count areas are obviously abnormal. Nevertheless, the quantitative polar map analysis using this normalization (Fig. 2) shows significant redistribution in the anterior wall which is consistent with this patient myocardial perfusion status and a reverse redistribution in the inferior wall which is also likely since non-transmural infarction with patency of the infarct related coronary artery may be one of the conditions of a reverse redistribution (*4*). Therefore in this particular case, maximum count rate density normalization would better reflect the presumable pathophysiologic status.

Finally, this case does not raise any problem for diagnosis, since the results are abnormal. However, it outlines the difficulty of selecting the true area(s) of normal perfusion that might be encountered in less clear situations. In most cases, the relative inaccuracy in defining the reference area(s) will not be a serious drawback to consistently identify ischemic zones and this kind of quantitative approach is useful especially for unskilled observers. However, a more skilled observer might expect these procedures to aid in the decision about the significance of subtle redistribution. In this situation, borderline reversibility is classified as significant according to the selected normalization procedure. It implies that we have to design better normalization methods that probably require more sophisticated considerations.

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