Evaluation in Dogs of a New Double-Dose Technique for Imaging Changes in Myocardial Perfusion

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Assessment of myocardial perfusion with thallium immediately before and after an intervention that alters blood flow has been difficult due to presence of residual activity from the first tracer dose at the time of the second imaging. In a canine model we investigated a technique using two separate thallium injections during an intervention and after its reversal. Images were obtained after each injection, and a difference image was obtained by subtracting the first from the second image to correct for tracer persisting from the first injection. Interventions on coronary blood flow included: transient occlusion, subcritical stenosis with dipyridamole infusion, and permanent occlusion. The first images showed defects corresponding to the occlusion or stenosis, while the "difference" images correlated with myocardial perfusion at the time of the second injection. This technique allows rapid evaluation of changes in perfusion in response to interventions, and may find application in several clinical procedures.

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Thallium-201 imaging is being used with increasing frequency in the assessment of regional myocardial perfusion. The greatest use has been in the diagnosis of coronary artery disease in conjunction with such procedures as exercise testing (*1–7*), dipyridamole infusion (*8–10*), and ergonovine provocation of spasm (*11*). In addition, thallium has been used to assess the effects of interventions designed to restore myocardial perfusion, such as coronary artery angioplasty (*12–13*) and thrombolysis (*14–17*). It is often the objective in such studies to determine differences in perfusion at two points in time. One approach to acquiring such data is to inject separate doses of thallium at the time of each desired assessment of perfusion, with imaging after each dose (*18*). This technique, however, is limited because one must wait a prolonged period after the initial thallium injection and imaging before the second injection in order to allow the residual activity from the first injection to decay or be cleared. The alternative is to acquire "redistribution" images (*19–20*) 3 to 4 hr after the initial injection, but this approach necessitates a long study time and may not provide an accurate assessment of perfusion at the time of the delayed images (*21–22*).

Recently initial experience has been reported with an approach using a double-dose thallium injection combined with dipyridamole infusion to detect coronary artery disease in human subjects (*23*). The method uses digital subtraction of the image obtained after the first injection from that obtained after the second, and permits rapid assessment of changes in myocardial perfusion.

This study was undertaken to assess the technique under a variety of clinically relevant situations in an experimental canine model in order (a) to compare the observed thallium distributions of the subtracted images with blood flows measured by microspheres, and (b) to explore a number of technical considerations inherent in the method.

METHODS

Canine preparation. Ten adult mongrel dogs (weight 20–30 kg) were anesthetized with i.v. chloralose (140 mg/kg) and urethane (1400 mg/kg i.v.). They were intubated and placed on a respirator, maintaining arterial pO_2 in the 100–150 mmHg range. The heart was exposed through a left thoracotomy and suspended in a pericardial cradle. A catheter was inserted into the subclavian vein for

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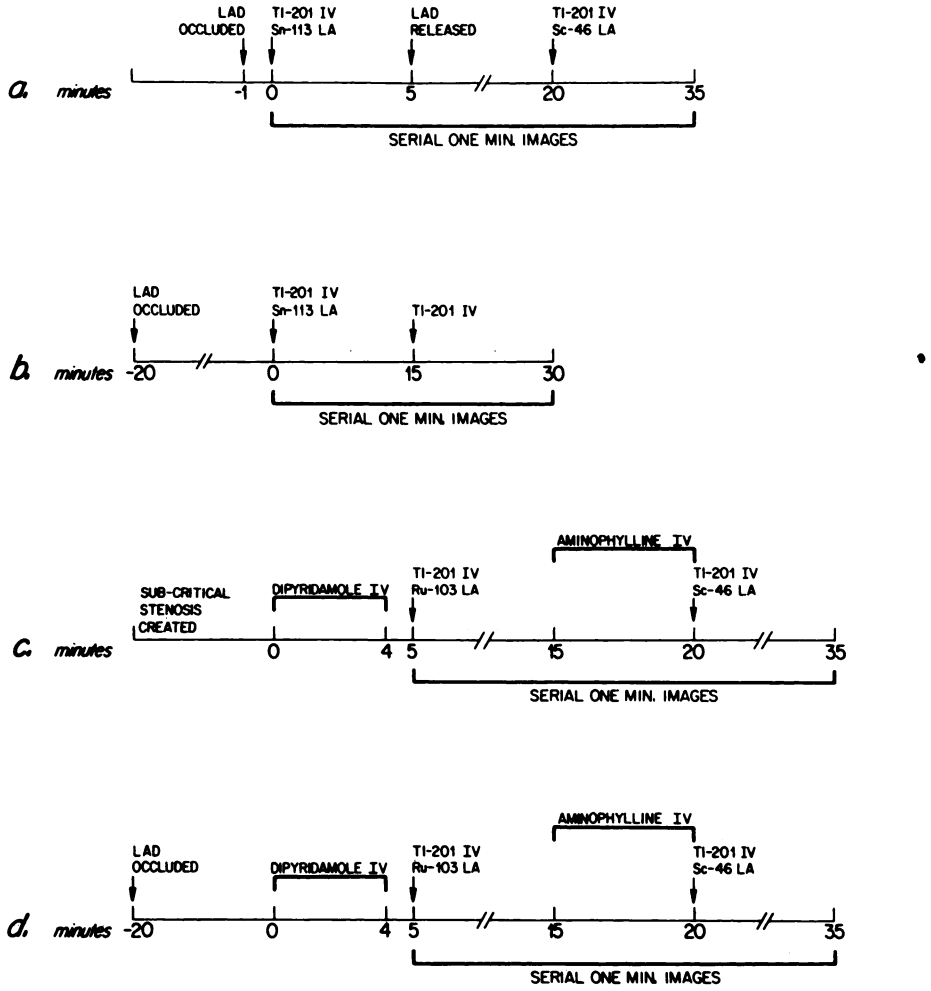

FIG. 1. Timing of interventions for individual protocols, (a) Protocol 1a: occlusion-release model, (b) Protocol 1b: permanent-occlusion model, (c) Protocol 2a: dipyridamole infusion model with subcritical stenosis, (d) Protocol 2b: dipyridamole model with permanent occlusion.

dipyridamole and thallium administration. A second catheter was inserted into the left atrium for injection of microspheres to determine regional myocardial blood flow. Through the subclavian artery a catheter was placed with its tip in the aortic arch to monitor aortic pressure and to obtain specimens of blood for microsphere reference samples and blood gases. The proximal left circumflex and left anterior descending (LAD) coronary arteries were dissected free.

Aortic and left-atrial pressures were monitored continuously throughout the experiment and recorded on paper. Arterial pH, pCO_2, and pO_2 were also monitored to ensure maintenance in the physiologic range.

Imaging techniques. Thallium imaging was performed using a standard-field-of-view gamma camera. The detector was positioned to obtain a 15° left posterior oblique view of the heart. The energy window covered 60-80 keV. The camera was interfaced to a computer and 1-min images were collected serially in 128 × 128 matrix.

Specific protocols. Interventions designed to alter blood flow in the LAD were studied in ten open-chest dogs. Either mechanical restriction of flow or a combination of mechanical restriction and an intravenous dipyridamole infusion were utilized. The protocols are described in detail below.

Protocol 1a: Occlusion-release model (Fig. 1a). A snare consisting of 2-0 silk suture material was placed around the LAD and adjusted for complete occlusion of the vessel. One minute after occlusion, thallium-201 (1.5 mCi) was injected intravenously, and simultaneously 4.5 million tin-113-labeled microspheres (8-10 μ, 30 μCi total activity) were injected into the left atrium. Arterial reference blood samples were collected beginning immediately before and continuing for 2 min after injection of the microspheres. Serial 1-min thallium images were then obtained beginning with the first injection and continuing until the end of the experiment. Five minutes after the first injection, the LAD snare was released. Twenty minutes after the first injection, a second dose of thallium-201 (1.5 mCi) was injected intravenously while scandium-46-labeled microspheres were injected simultaneously into the left atrium. The size and activity of the scandium-46 microspheres were the same as for the tin-113 microspheres. Arterial reference blood samples were again obtained for 2 min. Thallium imaging was continued for 15 min after the second thallium injection. The animal was then killed.

Protocol 1b: Permanent-occlusion model (Fig. 1b). The procedure followed was similar to that in the occlusion-release Protocol 1a with the following exceptions: (a) the LAD was occluded 20-30 min before the first thallium injection and tin-113 microsphere administration; (b) the occlusion was not subsequently released; (c) the second thallium injection was administered 15 min after the first; and (d) regional myocardial blood flow was determined only once, at the time of the initial thallium injection.

TABLE 1. COMPARISON OF MYOCARDIAL BLOOD FLOW WITH THALLIUM IMAGES

		Myocardial blood flow (ml/min-g)				Blood Flow ratio		Thallium images	
		Initial		Final		Ant/Post		First	
Animal	Protocol	Ant‡	Post¶	Ant	Post	Initial	Final	Composite	Difference
1	1a	0.38	1.78	1.60	1.70	0.21	1.05	AD*	N
2	1a	0.28	0.98	1.14	1.08	0.29	1.06	AD	N
3	1b	0.05	1.73	—	—	0.03	—	AD	AD
4	1b	0.30	0.74	—	—	0.40	—	AD	AD
5	2a	1.40	3.40	2.09	2.54	0.41	0.82	AD	N
6	2a	0.91	3.29	1.21	1.54	0.28	0.79	AD	N§
7	2a	0.40	1.29	0.92	0.64	0.31	1.44	AD	AH†
8	2a	1.49	3.90	1.87	1.31	0.38	1.43	AD	AH
9	2b	0.13	6.65	0.01	0.82	0.02	0.01	AD	AD
10	2b	0.02	1.22	0.01	0.87	0.02	0.01	AD	AD

Abbreviations:
* AD = Anterior defect.
† AH = Anterior hyperemia.
‡ ANT - Anterior.
§ N = Normal.
¶ POST = Posterior.
Key to protocols:
1a = Occlusion release.
1b = Permanent occlusion.
2a = Dipyridamole sub-critical stenosis.
2b = Dipyridamole permanent occlusion.

Protocol 2a: Dipyridamole infusion with subcritical-stenosis model (Fig. 1c). An adjustable snare was placed around the proximal LAD. Electromagnetic flow probes were positioned around the left circumflex coronary and around the LAD just proximal to the snare. Coronary blood flow was monitored by the flow probes, along with aortic and left-atrial pressures. Stenosis of the LAD was created with the adjustable snare, such that resting flow was not reduced yet the hyperemic response after occluding the vessel for 5 sec with a hemostat was nearly abolished.

An intravenous dipyridamole infusion was begun at a dose of 0.08 mg/kg-min and continued for 4 min. At 5 min after the start of this infusion, thallium-201 (0.8–1.2 mCi) was injected intravenously. Simultaneously, ruthenium-103-labeled microspheres were injected into the left atrium (size and activity the same as for tin-113). Two-minute arterial blood samples were withdrawn for calculation of regional myocardial blood flow. Serial 1-min thallium imaging then began and continued until the time of sacrifice. Ten minutes after the first thallium injection, aminophylline was infused intravenously (75 mg over 5 min) to reverse the effects of the dipyridamole. At the completion of the aminophylline infusion, a second dose of thallium-201 (1.0–1.5 mCi) was injected intravenously while scandium-46-labeled microspheres were injected into the left atrium. Arterial reference blood samples were again obtained for 2 min, and thallium imaging was continued 15 more minutes.

Protocol 2b: Dipyridamole infusion with permanent-occlusion model (Fig. 1d). The procedure followed was as in Protocol 2a with the following exception: the LAD was totally occluded 20–30 min before the beginning of the dipyridamole infusion, and it remained occluded.

Analysis of data. *1. Images.* Following collection of the serial 1-min images, 64-by 64-pixel regions containing the myocardial images were selected from the original 128 × 128 matrix for further analysis. The four 1-min images preceding the second thallium injection were added together to form a composite image hereafter designated "first composite" image. Similarly, four images, beginning with the fourth image after the second thallium injection, were added to form a "second composite" image. The three 1-min images immediately following the second injection were not used for analysis in order to allow the thallium enough time to be cleared from the blood pool. The first composite image was then subtracted from the second composite image to yield a "difference" image, thus eliminating the contribution of residual radioactivity from the first injection to the tracer distribution after the second injection. Images were interpreted by the consensus of two observers.

2. Tracer counting. Following sacrifice of the animal at the end of the experiment, the heart was removed and regions of the myocardium corresponding to the LAD and left circumflex distributions were each divided into 24 segments (0.8–1.2 g/segment). Samples were counted in a well counter for 5 min to collect at least 10,000 counts for each tracer. The energy windows for the nuclides were as follows: tin-113, 350–435 keV; ruthenium-103, 440–600 keV: and scandium-46, 800–1200 keV. A computer program was used to correct for activity spilling from one window into another. Regional myocardial blood flow was calculated by the computer from the reference blood samples and myocardial counts (*24*). Myocardial blood flows were expressed as ml/min per gram of tissue, and as a ratio of the flow for the left circumflex artery zone to that for the LAD zone.

RESULTS

For each protocol, the thallium distribution in the first composite and "difference" images were compared with regional myocardial blood flow as derived from the microsphere data. Table 1 summarizes the qualitative assessment of thallium distribution in the

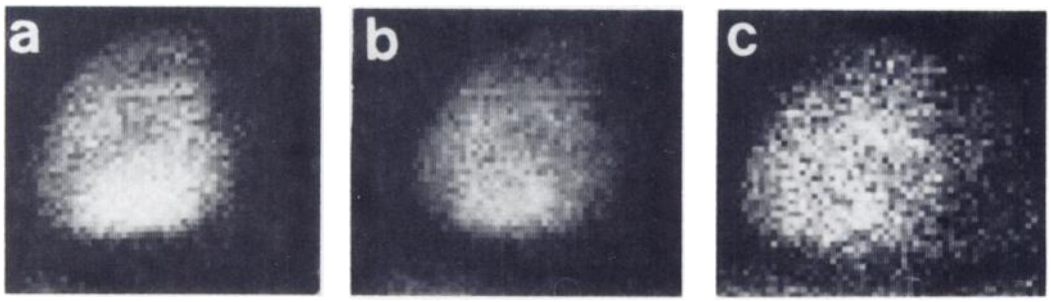

FIG. 2. Thallium-201 images, 15° left posterior oblique view, for occlusion-release model (Protocol 1a): (a) first composite image during occlusion showing anterior defect, (b) second composite image after release of occlusion, (c) "difference" image showing nearly complete filling in of anterior defect.

anterior and posterior walls for these images, along with the corresponding microsphere-determined coronary blood flows.

In Protocol 1a (occlusion-release model, N = 2), the first composite images of both animals showed defects in the anterior wall during coronary artery occlusion (Fig. 2a). These defects correlated with the coronary blood-flow data, showing greater blood flow in the posterior wall, supplied by the left circumflex, compared with the anterolateral wall, supplied by the LAD. The "difference" image showed "filling in" of the initial defect, associated with a concomitant increase in microsphere-determined blood flow after release of the coronary occlusion (Fig. 2c) at the time of the second thallium injection.

In Protocol 1b (permanent-occlusion model, N = 2), both the first composite and "difference" images showed defects in the anterior wall (Figs. 3a and 3c). This was expected, since the LAD was totally occluded at the time of both thallium injections.

In the dipyridamole subcritical-stenosis model (Protocol 2a, N = 4), the first composite images during subcritical stenosis and dipyridamole-induced hyperemia showed defects in the LAD distribution (anterior wall; Fig. 4a). The blood flows, measured immediately after the dipyridamole infusion was completed, showed flow to the posterior wall greater than that to the anterior wall. Following "reversal" of the effects of the dipyridamole by aminophylline, blood flow to the anterior wall increased whereas flow to the posterior wall decreased in all animals. The "difference" images for Animals 5 and 6 showed nearly complete filling in of the initial defect (Fig. 4c). In Animals 7 and 8, the area containing the initial defect not only filled in, but had greater thallium uptake than the posterior wall (Fig. 5a-c), consistent with the anterior-to-posterior wall-flow ratio greater than 1.0 after aminophylline. Such a reversal in the flow ratio was probably due to several factors. Upon administration of dipyridamole, the aortic pressure significantly decreased in nearly all animals. In some, this caused a significant decrease in flow in the "stenosed" vessel relative to the pre-dipyridamole level (as monitored on the electromagnetic flow probe), and may have caused some areas of the myocardium to become ischemic distal to the "stenosis." When the dipyridamole was reversed by aminophylline, the aortic pressure increased, causing a concomitant increase in flow in this vessel. The fact that some hyperemia was detected suggests that ischemia may, indeed, have been present during the dipyridamole infusion, and that the occlusion was probably not tight enough to completely abolish such a hyperemic response.

In Protocol 2b (dipyridamole permanent occlusion), both the first composite and "difference" images from Animals 9 and 10 showed anterior defects, as expected (Fig. 6).

DISCUSSION

This study was undertaken to validate a thallium-based technique by which changes in regional myocardial perfusion could be assessed immediately before and after interventions. The technique uses two separate thallium injections, the first a short time before and the second a short time after an intervention. The image obtained after the second injection is a composite of the thallium distribution due to both injections. It was therefore necessary to find a method of correcting for the persisting portion of the first injection that distorted the second image. By digitally subtracting an image obtained just before the second injection (the first composite image) from the one obtained a short time after the second injection (the second composite image), the "difference" image obtained should, in theory, reflect thallium distribution due solely to the second injection. The results presented from four different models of interventions on coronary blood flow indicate that, in experimental animal models, the "difference" images do correlate with coronary blood flow at the time of the second injection.

In the occlusion-release model (1a), the "difference" image

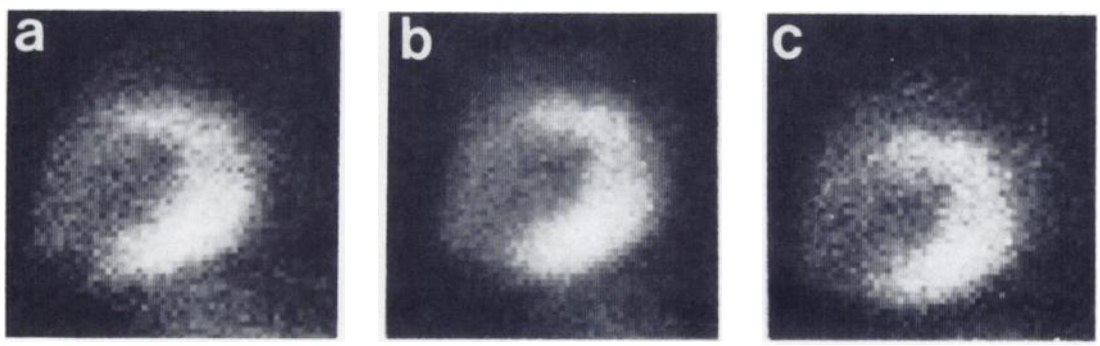

FIG. 3. Thallium-201 images, 15° left posterior oblique view, for permanent-occlusion model (Protocol 1b): (a) first composite image during occlusion, showing anterior defect, (b) second composite image with vessel still occluded, (c) "difference" image showing persistent defect.

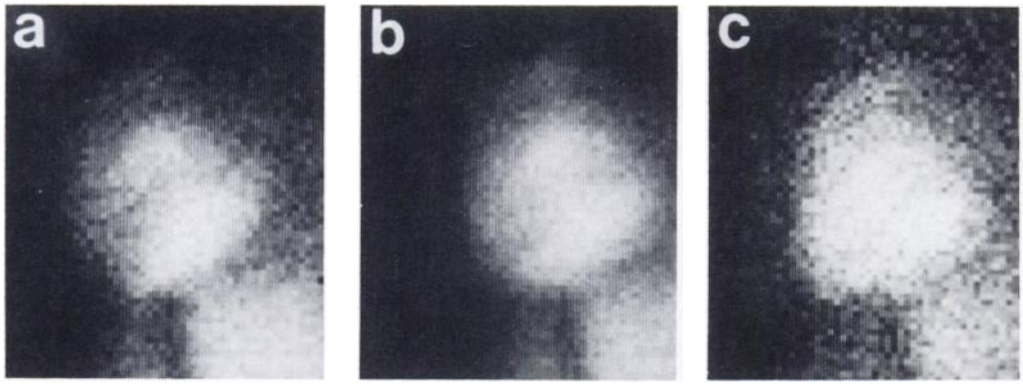

FIG. 4. Thallium-201 images, 15° left posterior oblique view, for dipyridamole subcritical-stenosis model (Protocol 2a): (a) first composite image during subcritical stenosis and dipyridamole-induced hyperemia showing anterior defect; (b) second composite image following reversal of effect of dipyridamole by aminophylline; (c) "difference" image showing nearly complete filling in of defect.

correctly showed filling in of the initially ischemic area. Such a model might correspond to clinical studies involving coronary spasm, thrombolysis with streptokinase, or transluminal angioplasty.

In the permanent-occlusion models without (1b) and with (2b) dipyridamole, there were, as expected, similar defects on both the first composite and "difference" images. This model might correspond to a clinical setting involving an area of scar from a prior infarction.

In the dipyridamole subcritical-stenosis model (2a), the difference image again correlated with blood flows at the time of the second injection. In Animals 5 and 6, there was almost complete filling in of the initial defect. In Animals 7 and 8 (in which the anterior-wall flow became slightly greater than that in the posterior wall following aminophylline administration) the difference image reflected this "relative" hyperemic response, as shown in Fig. 5c. This model might correspond to diagnostic thallium imaging with exercise or dipyridamole.

Technical considerations. Several factors and potential sources of error must be considered in this type of "difference" imaging. To correct the second composite image accurately for the effects of the first injection, the first composite image should be obtained as close as possible to the time of the second injection. If a significant interval were to exist between them, the effects of washout and redistribution subsequent to the first composite image would cause inaccuracies in estimations of the persisting background. However, if it were desired to obtain "diagnostic" images soon after the first injection, and a delay then existed before the second injection, a set of mask images could still be obtained just before the second injection. This mask image would then be subtracted from the second composite image to obtain the "difference" image.

Another important factor to consider is the amount of noise in the "difference" image relative to the first composite image. The "noise" in the former can be reduced by increasing the dose of the second injection. However, if the total thallium dose is to be limited to a specific value, this would necessitate a decrease in the dose of the first injection with a concomitant increase in noise in the first composite image. Thus, for a given dose of thallium, there is a trade-off between the noise in the first composite and "difference" images (see Appendix).

The limitation of such a trade-off may be decreased by newer Tc-99m-labeled radiopharmaceuticals that are being developed as myocardial imaging agents (*25–27*). These agents should allow a higher tracer activity to be injected because of the shorter half-life. This should enhance the utility of this subtraction technique by achieving lower noise "difference" images.

An additional technical problem presented by "difference imaging" is that the first and second composite images must be well aligned in order for the subtraction to be accurate. In our protocols, this problem was overcome by keeping the camera in the same position for acquisition of all images obtained. For more than one view, however, an alternative approach would be necessary. One method would be to use a technique, similar to the optical alignment methods used in radiation therapy, by which the camera could be accurately repositioned so that the first and second composite images would be in the same location in the field. Another solution would be to use a computer algorithm to automatically realign the thallium images after collection. Such a computer algorithm has been described (*28*). Finally, tomographic imaging, using either fixed camera position or computer-controlled rotation of the camera, would permit superposition of serial images without the need for re-alignment, while preserving the ability to assess perfusion to all regions of the myocardium.

Clinical implications. The split-dose, digital subtraction tech-

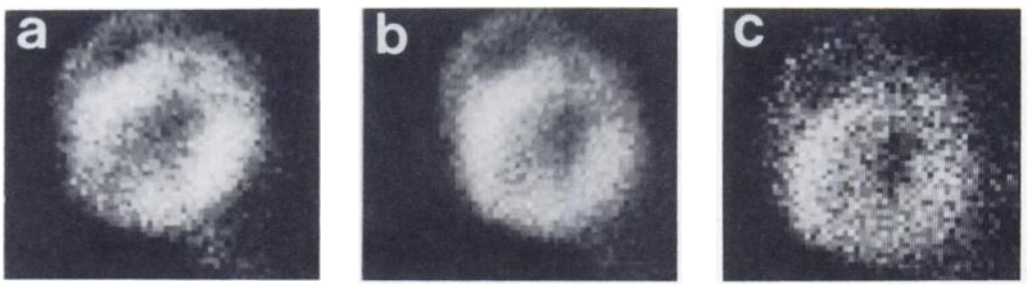

FIG. 5. Thallium-201 images, 15° left posterior oblique view, for dipyridamole permanent-occlusion model (Protocol 2a): (a) first composite image during subcritical stenosis and dipyridamole-induced hyperemia, showing anterior defect; (b) second composite image following reversal of effect of dipyridamole by aminophylline; (c) "difference" image showing greater uptake of thallium in anterior relative to posterior wall.

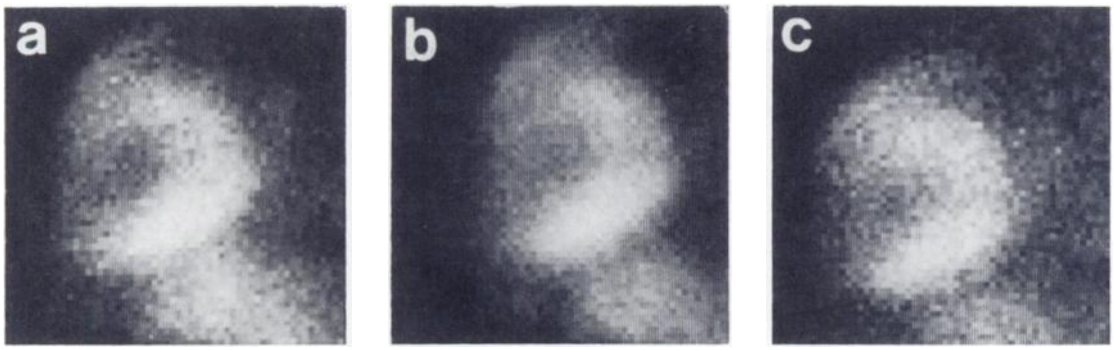

FIG. 6. Thallium-201 images, 15° left posterior oblique view, for dipyridamole permanent-occlusion model (Protocol 2b): (a) first composite image during occlusion and dipyridamole-induced hyperemia, showing anterior defect; (b) second composite image following reversal of effect of dipyridamole by aminophylline; (c) "difference" image showing persistent anterior defect.

nique may find utility in assessing the effects of acute interventions, such as angioplasty and thrombolysis, on coronary blood flow and myocardial perfusion. In addition, the technique may be applied to improve currently used exercise and dipyridamole imaging tests (*23*) for diagnosing coronary artery disease. Initial work with exercise thallium imaging used two separate injections, one during exercise and the second at rest (*18*). However, in order to prevent residual myocardial activity from the exercise image from interfering with the rest image, a 4-day interval between the two studies was usually required. To avoid this, single thallium injections with two sets of imaging (initial and delayed) were subsequently used (*19–20*). However, the process of "redistribution" depends upon a number of uncontrollable variables that determine both the time course and filling in of an initially ischemic zone (*21–22*). Further, at least several hours are required between initial and delayed images, thus markedly prolonging the study time. Digital subtraction of thallium images, as described in the present study, might permit isolation of thallium uptake due to individual injections before and after an intervention, and therefore permit rapid determination of changes in myocardial perfusion without the need for redistribution imaging.

In conclusion, we have investigated a technique that allows rapid evaluation of changes in perfusion in response to interventions and may find application in exercise or dipyridamole studies as well as procedures performed to restore myocardial blood flow.

ACKNOWLEDGMENT

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APPENDIX

A signal-to-noise ratio (SNR) can be defined for a region of pixels that represent a "uniform" radiation flux as the mean number of counts/pixel, N, divided by its standard deviation (SD).

$$SNR_N = \frac{N}{SD_N} = \frac{N}{(N)^{1/2}}$$

The mean difference, N_D, found by subtracting pixels containing a mean of N_A counts from those containing N_B counts has a variance given by:

$$VAR_D = VAR_A + VAR_B \text{ or}$$

$$SD_D = (N_A + N_B)^{1/2}$$

An index of the relative "noise" between regions containing an average of N_D and N_A counts can be obtained by defining a quotient, R, of the corresponding signal-to-noise ratios (SNR) of the individual regions:

$$R = \frac{SNR_D}{SNR_A} = \frac{N_D/SD_D}{N_A/SD_A} = \frac{(N_B - N_A)/(N_A + N_B)^{1/2}}{N_A/(N_A)^{1/2}} \quad (1)$$

If N_A represents the mean counts/pixel in a region of the first composite image following the first injection, and N_B is the mean counts/pixel in the same region of the second composite image following the second injection, then N_B can be approximated by:

$$N_B = N_A + N_A \cdot \frac{Q_2}{Q_1} \cdot \frac{D_2}{D_1} \quad (2)$$

where Q_1 and Q_2 represent the coronary blood flows relative to total cardiac output in the myocardial region in Eq. (1), and D_1 and D_2 represent the activity of thallium administered with each injection.

Combining Eqs, (1) and (2),

$$R = \frac{\frac{Q_2}{Q_1} \cdot \frac{D_2}{D_1}}{\left[\frac{Q_2}{Q_1} \cdot \frac{D_2}{D_1} + 2\right]^{1/2}} \quad (3)$$

This calculation assumes that the initial distribution of tracer to the myocardium is proportional to regional blood flow, and that there has been no significant change in myocardial radioactivity from several minutes after the first injection to the time of the first composite image acquisition just before the second injection. If it is elected to obtain a separate "diagnostic" image immediately after the first injection and a "mask" image just before the second injection, and assuming the myocardial activity has decreased between the diagnostic and mask images by a factor K, Eqs. (1) and (2) would need to be modified as follows:

$$R = \frac{(N_B - K \cdot N_A)/K \cdot N_A + N_B)^{1/2}}{N_A/(N_A)^{1/2}}$$

$$N_B = K \cdot N_A + N_A \cdot \frac{Q_2}{Q_1} \cdot \frac{D_2}{D_1},$$

so that Eq. (3) becomes:

$$R = \frac{\frac{Q_2}{Q_1} \cdot \frac{D_2}{D_1}}{\left[\frac{Q_2}{Q_1} \cdot \frac{D_2}{D_1} + 2 \cdot K\right]^{1/2}}$$

It would be desirable to have high signal-to-noise ratios for both the first composite and "difference" images, but the dose of tracer and the imaging time place constraints on these goals. An alter-

native strategy, therefore, might be to attempt to equalize the signal-to-noise ratios between the two images (i.e., R = 1) for a given total dose of tracer.

Several examples will serve to illustrate the effect of changes in the parameters in Eq. (3) on the value of R.

Example 1. $Q_2/Q_1 = 1$, $D_2/D_1 = 1$; R = 0.58. Even when coronary blood flow has not changed between injections, and the amount of thallium is identical for both injections, the "difference" image for this region will contain more random noise than the first composite image.

Example 2. $Q_2/Q_1 = 0.5$, $D_2/D_1 = 1$; R = 0.32. As expected, if coronary blood flow decreases between the first and second injections, thallium uptake in that region due to the second injection will be lower than that due to the first injection, and the "difference" image for this region will be even noisier than in Example 1. The value of R could be increased to 0.58 by making the second dose (D_2) twice the first, although this would increase the total dose administered unless D_1 is reduced. A similar increase in R could be obtained for the same initial value of $D_1 + D_2$ by cutting D_1 by a factor of 0.66 and increasing D_2 by a factor of 1.33. However, the absolute S/N ratio in the first composite image would be decreased by this maneuver.

Example 3. ($Q_2/Q_1 = 2$, $D_2/D_1 = 1$) or ($Q_2/Q_1 = 1$, $D_2/D_1 = 2$); R = 1. Thus, if flow increases by a factor of two for equal doses of thallium, the S/N ratios of these regions of the first composite and "difference" images will be equal. This equality will also hold if flow remains constant but the dose of the second injection is made twice that of the first.

Sometimes, modification of the order in which first and second injections are administered relative to an intervention may significantly influence the relative "noise" between images. For example, in Protocol 2a, flow to the posterior wall showed a significant decrease between the two injections, thereby causing the "difference" image in this region to be considerably "noisier" than the corresponding region in the first composite image. A modification to this protocol would be to administer the first thallium injection before the dipyridamole infusion, with the second injection administered at peak drug effect. In this case the "difference" image would probably contain a thallium defect, whereas the first composite image would not. Because the flow to the posterior wall had increased between the first and second injections, this modification would be expected to create a more favorable ratio of the "noise" in the "difference" image, compared with first composite image, in that region of the heart.

Thus a trade-off may be necessary not only in choosing the dose of thallium for each injection but also in the order of interventions in a study so as to optimize the signal-to-noise ratio in a particular region of the images.

REFERENCES

1. ISKANDRIAN AS, LICHTENBURG R, SEGAL BL, et al: Assessment of jeopardized myocardium in patients with one-vessel disease. *Circulation* 65:242-247, 1982
2. ROZANSKI A, BERMAN DS, GRAY R, et al: Use of thallium-201 redistribution scintigraphy in the preoperative differentiation of reversible and non-reversible myocardial asynergy. *Circulation* 64:936-944, 1981
3. MELIN JA, PIRET LJ, VANBUTSELE RJ, et al: Diagnostic value of exercise electrocardiography and thallium myocardial scintigraphy in patients without previous myocardial infarction: A Bayesian approach. *Circulation* 63:1019-1024, 1981
4. TURNER JD, SCHWARTZ KM, LOGIC JR, et al: Detection of residual jeopardized myocardium 3 weeks after myocardial infarction by exercise testing with thallium-201 myocardial scintigraphy. *Circulation* 61:729-737, 1980
5. DUNN RF, BAILEY IK, UREN R, et al: Exercise induced ST-segment elevation. Correlation of thallium-201 myocardial perfusion scanning and coronary arteriography. *Circulation* 61:989-995, 1980
6. PATTERSON RE, HOROWITZ SF, ENG C, et al: Can exercise electrocardiography and thallium-201 myocardial imaging exclude the diagnosis of coronary artery disease? Bayesian analysis of the clinical limits of exclusion and indications for coronary angiography. *Am J Cardiol* 49:1127-1135, 1982
7. ISKANDRIAN AS, SEGAL BL: Value of exercise thallium-201 imaging in patients with diagnostic and non-diagnostic exercise electrocardiograms. *Am J Cardiol* 48:233-238, 1981
8. GOULD KL, WESTCOTT RJ, ALBRO PC, et al: Non-invasive assessment of coronary stenosis by myocardial imaging during pharmacologic coronary vasodilatation. II. Clinical methodology and feasibility. *Am J Cardiol* 41:279-287, 1978
9. ALBRO PC, GOULD KL, WESTCOTT RJ, et al: Non-invasive assessment of coronary stenosis by myocardial imaging during pharmacologic coronary vasodilatation. III. Clinical trial. *Am J Cardiol* 42:751-760, 1978
10. FRANCISCO DA, COLLINS SM, GO DA, et al: Tomographic thallium-201 myocardial perfusion scintigrams after maximal coronary artery vasodilation with intravenous dipyridamole. Comparison of qualitative and quantitative approaches. *Circulation* 66:370-379, 1982
11. RICCI DR, ORLICK AE, DOHERTY PW, et al: Reduction of coronary blood flow during coronary artery spasm occurring spontaneously and after provocation by ergonovine maleate. *Circulation* 57:392-395, 1978
12. HIRZEL HO, NUESCH K, GRUENTZIG AR, et al: Short- and long-term changes in myocardial perfusion after percutaneous transluminal coronary angioplasty assessed by thallium-201 exercise scintigraphy. *Circulation* 63:1001-1007, 1981
13. SCHOLL JM, CHAITMAN BR, DAVID PR, et al: Exercise electrocardiography and myocardial scintigraphy in the serial evaluation of the results of percutaneous transluminal coronary angioplasty. *Circulation* 66:380-390, 1982
14. REDUTO LA, FREUND GC, GAETA J, et al: Thallium redistribution following intracoronary streptokinase in acute myocardial infarction: relation to changes in left ventricular performance. *Circulation* 64:IV-33, 1981 (abst)
15. MADDAHI J, GANZ W, BERMAN D, et al: Intracoronary thrombolysis in evolving myocardial infarction: assessment of myocardial salvage by intracoronary thallium scintigraphy. *Circulation* 64:IV-9, 1981 (abst)
16. SIMOONS ML, SERRUYS PW, BRAND M, et al: Myocardial salvage by intracoronary thrombolysis in acute infarcts, documentation by thallium scintigraphy. *Am J Cardiol* 49: 973, 1982 (abst)
17. MARKIS JE, MALAGOLD M, PARKER JA, et al: Myocardial salvage after intracoronary thrombolysis with streptokinase in acute myocardial infarction: Assessment by intracoronary thallium-201. *N Engl J Med* 305:777-782, 1981
18. RITCHIE JL, TROBAUGH BG, HAMILTON GW, et al: Myocardial imaging with thallium-201 at rest and during exercise. Comparison with coronary arteriography and resting and stress electrocardiography. *Circulation* 56:66-71, 1979
19. POHOST GM, ZIR LM, MOORE RH, et al: Differentiation of transiently ischemic from infarcted myocardium by serial imaging after a single dose of thallium-201. *Circulation* 55: 294-302, 1977
20. BLOOD DK, MCCARTHY DM, SCIACCA RR, et al. Com-

parison of single-dose and double-dose thallium-201 myocardial perfusion scintigraphy for the detection of coronary artery disease and prior myocardial infarction. *Circulation* 58:777-788, 1978

21. BERGMANN SR, HACK SN, SOBEL BE: 'Redistribution' of myocardial thallium-201 without reperfusion: Implications regarding absolute quantification of perfusion. *Am J Cardiol* 49:1691-1698, 1982
22. OKADA RD, LEPPO JA, STRAUSS HW, et al: Mechanisms and time course for the disappearance of thallium-201 defects at rest in dogs. Relation of time to peak activity to myocardial blood flow. *Am J Cardiol* 49:699-706, 1982
23. OKADA RD, LIM YL, ROTHENDLER J, et al: Split dose thallium-201 dipyridamate imaging: A new technique for obtaining thallium images before and immediately following an intervention. *J Am Coll Cardiol* 1(5):1302-1310, 1983
24. HEYMANN MA, PAYNE BD, HOFFMAN JIE, et al: Blood flow measurements with radionuclide-labeled particles. *Progr Cardiovasc Dis* 20(1):55-79, 1977
25. DEUTSCH E, BUSHONG W, GLAVAN KA, et al: Heart imaging with cationic complexes of technetium. *Science* 214:85-86, 1981
26. SULLIVAN PJ, WERRE J, OKADA R, et al: Comparison of Tc-99m DMPE to 201 thallium biodistribution. *Am J Cardiol* 49:980, 1982 (abst)
27. BUSHONG WC, WEINTRAUB WS, BODENHEIMER MM, et al: Assessment of myocardial perfusion using a newly developed technetium diars complex: comparison to 201 thallium and radioactive microspheres. *Am J Cardiol* 49:979, 1982 (abst)
28. LIM YL, CHESLER DA, BOUCHER CA, et al: A new computer analysis to quantitate and display regional thallium-201 uptake following coronary angioplasty. *Clin Res* 30:201A, 1982 (abst)