Continuing Education Series

Thallium-201 Myocardial Imaging

New England Nuclear

North Billerica, Massachusetts

The Continuing Education Committee

Technologist Section, Society of Nuclear Medicine

This is the second article in the nuclear cardiology series. After reading and studying the article, the nuclear medicine technologist will be able to: (1) state the characteristics of thallium-201 as a myocardial imaging agent; (2) discuss instrumentation and computer methodologies used in Tl-201 imaging; (3) describe basic normal and abnormal Tl-201 myocardial imaging results; and (4) discuss Tl-201 imaging protocols including patient preparation, imaging sequences, and influencing factors.

Radioisotopes of thallium were first suggested as possible myocardial imaging agents in 1970 by researchers who noted that earlier work had shown the similarity of thallium to potassium in biologic systems. Although thallium-201 was initially selected because it is a potassium analog, it has shown other advantages for imaging and will probably remain the myocardial imaging agent of choice for some time.

Thallium is taken up and retained with greater efficiency than potassium. While the exact mechanism for this retention is not clearly understood, thallium appears to bind more firmly than potassium to certain enzymes within the cells. In addition, it appears to bind less firmly than potassium to cells in the liver; thus, there is less image interference from hepatic thallium.

Thallium-201 emits radiation with energies that are compatible with the sensitivity of a scintillation camera. Its abundant x-ray emissions (95%) in the 68–80 keV range enable high resolution imaging. Most collimators used for technetium studies may be used for imaging with Tl-201.

An important technical characteristic of this isotope is its half-life of 73.1 hr—a longer period than any comparable myocardial perfusion isotope. This half-life allows preparation and shipment of material and allows redistribution imaging.

Principles of the Thallium Study

Thallium-201 is administered as a solution of thallous chloride, adjusted to a physiologically compatible pH. Less than 40 sec after injection, approximately one half the Tl-201 has been extracted by various tissues throughout the body. Myocardial extraction efficiency of Tl-201 is extremely high—approximately 85% of the thallium that reaches myocardial cells will be taken up and concentrated intracellularly. Typically, 4 to 5% of the injected dose concentrates in the myocardium. The remainder is distributed throughout other tissues.

Thallium-201 concentration in exercised muscle is directly dependent upon the availability of blood flow to transport the injected dose to muscle cells. Any regional interruption in blood flow decreases thallium uptake in that region.

Because thallium transport depends upon perfusion, it would be easy to assume that a region with diminished thallium uptake is ischemic. In many cases, such a conclusion would be correct. However, absence of uptake in a given region may also signify a failure of the sodium-potassium pump action in those cells and this is generally associated with cell death infarction. Thus, a single thallium image with an area of decreased or absent uptake does not differentiate infarction from ischemia.

The diagnostic analysis of Tl-201 uptake patterns in myocardial cells becomes even more complicated when we realize that highly stenotic vessels may provide adequate blood flow to the myocardial regions they serve under resting conditions. It has been determined that stenotic vessels with as much as 80% occlusion may permit normal myocardial perfusion in resting patients. If such patients were imaged with Tl-201, the resulting images might show no myocardial areas suggestive of ischemic disease. Thus, the thallium image of a patient at rest cannot provide evidence that will rule out coronary artery disease.

For this reason, Strauss, Pitt, and Zaret determined that in order to visualize ischemic myocardial regions with Tl-201, the difference in perfusion between normal and ischemic areas of a patient's myocardium must be increased. They used exercise-induced stress to do this.

The exercise-redistribution study developed from observations that regions of decreased thallium uptake seen after exercise—termed "defects" in the thallium image—often tended to fill in and appear normal if the patient was imaged again several hours following exercise. Thallium imaging immediately following exercise avoids "filling in" of defects. If the thallium images made immediately after stress showed normal thallium distribution (Fig. 1) within the myocardium—no "defects" or areas of diminished uptake—the study was interpreted to mean that the patient probably did not have coronary artery disease. If, however, defects or areas of diminished uptake were detected in the postexercise studies but were not seen—or were visualized less clearly—in repeat images made several hours later, the test was interpreted to indicate that the patient probably did have coronary artery disease.

It is now generally recommended that all patients who undergo an exercise thallium study return in 3 to 4 hr for redistribution images. This recommendation is based on the reported observation that occasionally patients with severe triple-vessel disease have a normal exercise thallium perfusion study and on that basis no redistribution imaging is performed. As a result, no abnormal thallium washout pattern is observed.

The subjective interpretation of thallium studies is based on calling the area of the myocardium with the greatest concentration of tracer an area of normal perfusion, and then comparing other regions to this "normal" zone. In patients with severe disease, it is possible to have a uniformly hypoperfused ventricle, and thus a uniform distribution of thallium that could be interpreted as a normal perfusion pattern. The wise interpreter not only looks at the activity in the myocardium, but also at lung uptake. A low heart-to-lung activity ratio is a strong indicator of severe multivessel coronary disease.

It's easy to understand why an ischemic region might display less intense thallium concentration than nearby, well-perfused

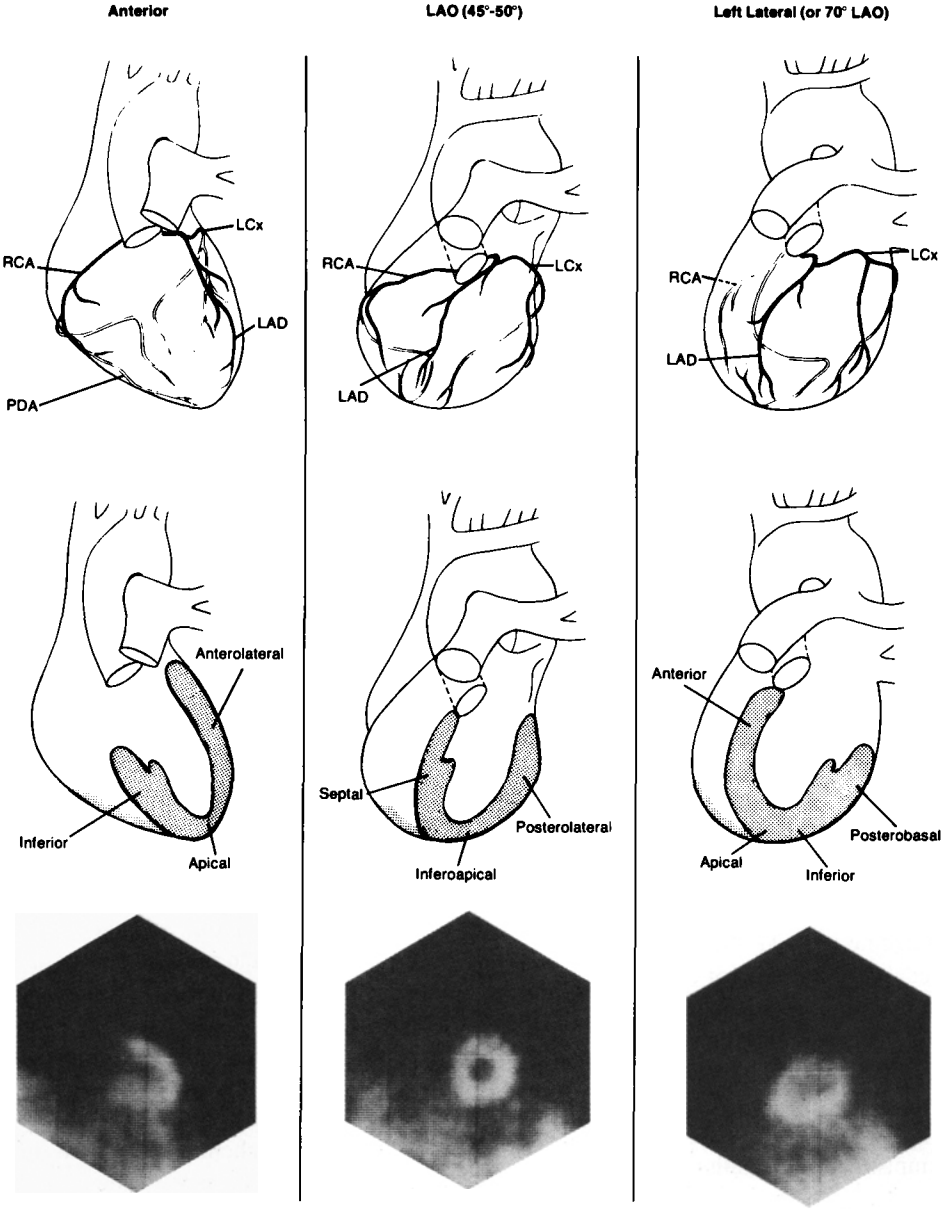


FIG. 1. Myocardial anatomy visualized on thallium-201 images.

regions. But why would such areas tend to "fill in" over time? The easy, obvious answer: as time passes, enough blood containing thallium gradually reaches these ischemic cells so that additional quantities of thallium accumulate. As a result, the difference between ischemic areas and properly perfused areas decreases.

However, this relatively simple explanation does not take into consideration the very rapid clearance of thallium from the bloodstream. The circulating half-life of Tl-201 in the bloodstream is typically less than 40 sec. If a patient is imaged an hour or more following injection, the amount of circulating thallium available from the initial dose would be expected to be quite small. In fact, thallium's circulating half-life is so short—and the affinity of properly perfused myocardial and skeletal muscles for this agent is so high—that a very small quantity of circulating thallium would be expected to be available for ischemic cells at, say, one-half hour after injection.

Thus, thallium researchers had to deal with a confirmable, repeatable phenomenon that could not be explained solely by the "prolonged uptake" concept.

As a result, the concept of "thallium redistribution" evolved. During the hours following exercise, thallium initially taken up by well-perfused myocardial and skeletal muscle slowly begins to migrate out of these cells and into the bloodstream. Therefore, the difference between intracellular concentrations of thallium in well-perfused and ischemic cells decreases over time, as the large amounts of thallium concentrated within well-perfused cells tend to be reabsorbed by the bloodstream and transported to adjacent ischemic tissue.

The redistribution concept was excellent in theory, but has only recently been supported by experimental evidence. Pohost and associates conducted dog studies that strongly support the concept of redistribution; however, more research will probably be needed to convince all medical scientists that this theory fully explains the image phenomenon observed in clinical practice.

Instrumentation for Imaging Thallium-201

The task of selecting imaging instruments for Tl-201 becomes increasingly challenging as manufacturers rush to bring more scintillation cameras and image processors to market. As the most sophisticated users of Tl-201 acquire and proselytize this new equipment, many newcomers to thallium imaging have concluded, incorrectly, that they must invest in new equipment to produce diagnostically satisfactory thallium images.

Scintillation Cameras: Older instruments pose several problems for Tl-201 imaging. First of all, such cameras have low resolution and must be used with high-sensitivity collimators, which are also typically quite poor in resolution. If a high resolution collimator is used, the time necessary to acquire enough counts to produce an image is extremely long. In addition, the inherently low resolution of older cameras reduces the minimum detectable size of an area of diminished uptake. The result is an unacceptably high incidence of false-negative studies.

Not every camera used in the nuclear medicine department may be satisfactory for imaging thallium. The resolving ability, linearity, and field uniformity of the camera used for thallium imaging should be checked daily. Camera performance should be checked at 70 to 80 keV. A daily system's check can readily and easily be accomplished with commercially available gold-195 (65–78 keV) line-grid and flood sources, or with a point source and a liquid flood source of Tl-201 and a bar phantom. The camera-computer system should at least be able to resolve 1-cm squares on a gold-195 grid source when imaged through 3.18 cm of lucite placed on the collimator face.

Collimators: While the need for a good resolution camera is almost universally accepted by experienced thallium imagers, the choice of a collimator is still subject to considerable experimentation—and disagreement.

Consider the challenge of imaging the myocardium. First, from an anterior view, the anterior wall of the heart is only about 2 in. behind the chest wall and sternum—but the posterior wall is 5 in. or more inside the chest. Under normal, optimum conditions, only about 4 to 5% of an injected thallium dose will be taken up by myocardial tissue. And while the myocardium is a relatively efficient concentrator of thallium, the myocardium-to-background ratio is—at best—less than 3:1.

If a single image alone could illustrate all myocardial pathology, or if an unlimited period of time were available for completing myocardial studies, a high resolution collimator might be used. Time and motion weigh against selection of such a collimator.

To ensure collection of all images in a postexercise study before redistribution occurs, imaging should be completed within 30 to 45 min following termination of exercise. The increased imaging time necessary using a high resolution collimator may prevent completion of studies within that period of time. Moreover, since the heart is not stationary we must question whether there will be a noticeable improvement in definition when imaging is conducted with a high resolution collimator.

The use of a high sensitivity collimator may reduce the imaging time necessary to ensure completion of postexercise studies before redistribution occurs. However, this may degrade the quality of the already limited-resolution thallium image.

Not surprisingly, the collimator most frequently recommended for clinical thallium imaging is the all-purpose parallel hole collimator. This collimator seems to offer the most satisfactory combination of resolution characteristics and imaging time.

Performing the Thallium Stress Study

Every study should begin with a detailed patient history, so that the cardiologist and the nuclear medicine physician performing and interpreting the study can take into consideration the factors influencing a patient's ability to exercise, as well as other pertinent information.

Patient Preparation: The first step is to prepare sites for attachment of the ECG electrodes. Using a drill-like device with a painless abrasive tip, the technologist removes the outer layer of dead cells from the planned electrode sites. Skin preparation ensures good conductivity of each electrode. An in-

dwelling catheter is inserted in the patient's antecubital vein, and a slow infusion of 5% dextrose in water or saline is started to prevent clot formation within the needle or the catheter before injection of the thallium dose.

A resting 12-lead electrocardiogram is recorded on the 3-channel ECG recorder. A blood pressure cuff is strapped onto the patient's arm, where it will remain throughout the test, and a resting blood pressure is taken.

The patient should be kept fasting for at least 4 hr prior to the study. Any indications that might interfere with ECG interpretation—for example, propanolol, which limits maximum heart rate—should, if clinically acceptable, be discontinued far enough in advance of the study to prevent interference.

Each thallium stress study must be directly supervised by a cardiologist or other physician trained in management of potential complications that can occur when patients with known or suspected coronary disease are subjected to stress. A defibrillator, an Ambu bag, and all necessary medications should be available for immediate use.

Stress Testing: Most physicians who use stress electrocardiography follow a standardized multistage exercise protocol termed the Bruce protocol, after its developer. The Bruce protocol consists of seven 3-min stages. At each stage, the patient runs on the treadmill, which has been set to a specific combination of speed and grade (angle).

The patient begins exercising at progressive increases of speed and grade, while the 12-lead ECG, blood pressure, and heart rate are recorded. For optimal results, the patient should attain 90% of his predicted maximal heart rate—less than this lowers the test's accuracy. If a patient has a history of angina, he may experience debilitating chest pain, an indication for termination of the test before the desired heart rate is achieved. Obviously, if potential life-threatening arrhythmias occur, the test must also be stopped immediately. Other indications for premature termination of the test include cerebrovascular insufficiency or hypotension.

When the physician determines that the patient can continue maximum exertion for approximately 1 min longer, he should order the injection of the thallium dose—typically, 1.5–2.0 mCi of Tl-201, given as thallous chloride. The patient should continue at maximum exertion for 30 to 60 sec after the injection to ensure proper thallium delivery to the myocardium—at the time when there will be a maximal differential between well-perfused and ischemic regions.

As soon as the exercise is terminated, the patient should be immediately placed upon a stretcher. After resting blood pressure and electrocardiogram recordings are made, imaging should commence immediately—preferably as soon as 3 min and no longer than 10 min after exercise has been stopped. If imaging is started any later than this, the images required will not be completed before redistribution begins.

A potential cause of nondiagnostic images is extravasation of the thallium dose. Extravasation greatly reduces the available isotope for myocardial uptake, and its occurrence may go undetected until the study is completed.

Redistribution Imaging: Repeat images of the heart should be obtained at 3–4 hr after the thallium injection. All images should be obtained at precisely the same angle as the post-stress images for accurate comparison.

The Thallium Image

Most schematic drawings of the heart incorrectly suggest that the left and right ventricles are of equal size and thickness. The total mass of the left ventricle is about three times greater than that of the right ventricle. In addition, the right ventricle receives about 10% less perfusion under normal circumstances than the left ventricle. As a result, much less Tl-201 will concentrate in the right ventricle than in the left. An understanding of this phenomenon is important to comprehension of thallium imaging.

For many years, nuclear physicians and cardiologists have attempted to determine which standardized perspectives of the myocardium consistently provide the most comprehensive information about the myocardium. Their efforts have concluded that the three most useful views are the anterior, a 40° to 50° left anterior oblique (LAO), and either a left lateral or 70° LAO view. Figure 1 compares coronary anatomy and thallium images for each of these three perspectives.

The anterior thallium image (Fig. 1, middle row) most clearly visualizes the anterolateral wall, the apex (tip) of the heart, and a region of tissue described as the inferior or inferoseptal wall—depending on the way the patient's heart lies in the chest cavity. Because the left ventricle is such a powerful pump, the anterolateral wall and septum are quite muscular, and typically appear about the same thickness in the two-dimensional "slice-through" planar view of an anterior perspective thallium study. By comparison, the apex is usually much thinner, and thus concentrates much less thallium.

Defects in thallium uptake can be seen quite easily in the septum or anterolateral wall. However, defects in the apex must be scrutinized quite carefully, comparing the thickness of the apex with the thickness of the anterolateral and septal walls. Apical ischemia does occur with reasonable frequency, but oversuppression of background counts may "create" apical defects—care must be taken to prevent false-positive readings in this region.

When the heart is viewed from the LAO perspective, the interventricular septum forms the left side of the image, and the posterolateral wall forms the right. On this view, the bottom portion of the image, which appears almost as thick as the two sides, is usually best described as the inferoapical region—the area between the apex of the heart and the inferior (lower) wall of the left ventricle. Depending upon the positioning of the patient's heart and visualization of the aortic outflow tract, the LAO image may resemble either an inverted horseshoe or a doughnut. Absence of activity in the aortic outflow region is not diagnostic of ischemic disease, because patient-to-patient variability in uptake and cardiac position is very great, even among normal patients.

The left lateral or 70° LAO view enables the physician to visualize the cross section of the anterior wall, as well as the apex, inferior wall, and posterobasal regions of the myocardium. Typically, this image is much rounder in appearance than either the anterior or LAO views.

The right ventricle is not normally visualized on rest images and only faintly on exercise images. Pronounced visualization of the right ventricle may indicate abnormal wall thickness, possibly as a result of a disease process that demands an abnormal amount of right ventricular work. The atria are also rarely visualized, because of their comparatively low tissue mass.

The rationale for using multiple views in thallium imaging is simply to provide the physician with the most informative range of views through the myocardium—within the relatively limited time period between the termination of exercise and the peak of thallium redistribution. These planar views provide the best information for determination of whether a region of apparently diminished thallium uptake is, in fact, an ischemic area, or if it is merely an artifact of position or normal cardiac anatomy.

Imaging Processing: Three techniques have emerged from these attempts to improve the diagnostic accuracy of thallium imaging: background subtraction, gated studies, and computer processing.

Background Subtraction: Because the thallium target-to-background ratio is typically within the 2.1-to-2.7-to-1 range, many clinicians routinely use a fixed ratio of background subtraction to enhance the myocardial image. This technique, variously known as background suppression, background subtraction, or contrast enhancement, does produce more esthetically pleasing images.

However, the range of normal thallium uptake varies so much between patients—and even within the myocardium of a single patient—that the application of a fixed ratio of background subtraction is not always useful. Enhancing contrast may also magnify the normal variations in thallium uptake within perfectly normal myocardial tissue. As a result, areas of slightly diminished uptake may take on the appearance of obvious defects following contrast enhancement. Conversely, areas of significantly diminished thallium uptake within high-uptake regions may "disappear" in the contrast-enhanced version of the same image.

The solution to this dilemma is not an easy one. However, many sophisticated approaches to background subtraction have been described and successfuly applied. Among these is the interpolative approach developed by Goris and coworkers, which recognizes the nonuniformity of thallium background activity. Watson and colleagues apply a modified version of this approach in their quantitative imaging technique.

Gated Studies: One innovative attempt at producing better thallium images has come from the realization that elimination of motion artifact from the images would probably enhance resolution and the ability to visualize pathology. Thus, ECG gating as in equilibrium blood pool studies can be applied to Tl-201 imaging to minimize heart motion.

Computer Processing: Most thallium imagers would agree that, under ideal circumstances, every thallium image collected should be subjected to varying degrees of computer processing. These same physicians would also say that they would not want to undertake a thallium study unless computer processing was available.

Much less agreement occurs when the question, "Can diagnostic thallium images routinely be produced without computer processing?" is asked. To appreciate the difficulty in answering this question, we must realize that different clinicians looking at the same images often do not agree in their interpretations—even under ideal curcumstances. In the multi-institutional study published by Hamilton and his associates and Wackers and his associates, these extremely experienced thallium users found that, without computer processing, they could agree on interpretation of almost 80% of the studies they examined. The degree of "interobserver variability" is similar to that reported for other nuclear medicine procedures and for coronary angiography. Whether computer processing would improve observer agreement has not been demonstrated.

Nevertheless, many physicians—experienced thallium users as well as those who may be just beginning their nuclear cardiology studies—believe that some form of image processing will make their readings more accurate and more reliable. However, the data processing systems available to nuclear medicine departments differ in their ease of use and software capabilities. For instance, because there is little agreement on the appropriate degrees and types of background subtraction and contrast enhancement, each manufacturer has tended to follow the guidance of a different consultant in nuclear medicine. One must be aware of the capabilities of the particular system in use.

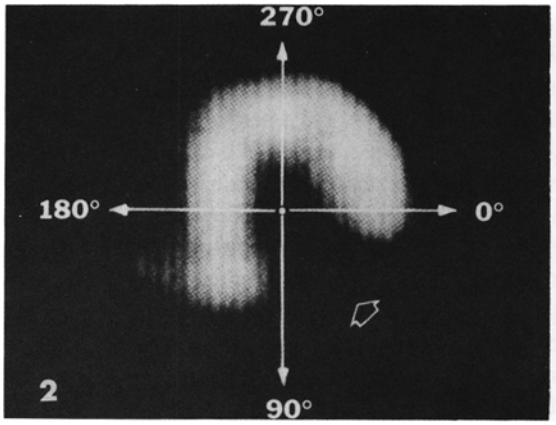
Circumferential Profiles—A Quantitative Technique: Following data acquisition, each Tl-201 myocardial image is displayed on the computer screen, where such processing as smoothing, normalization, and background subtraction may be performed. Radii are constructed from the center to points around the epicardial surface, proceeding in a clockwise fashion using standard polar coordinates (Fig. 2).

The regional myocardial distribution of Tl-201 is then determined by calculating the average—or maximum—activity per pixel along each radius, and normalizing these data to the radius with the highest activity. The normalized regional uptake of Tl-201 can then be plotted against angular position (Fig. 3), with the epicardial surface being transformed vertically downward (a radial/vertical or polar/orthogonal transformation). Since the maximal pixel values along each radius can also be defined (Fig. 4), a circumferential profile or maximal pixel count isocontour of the left-ventricular myocardium can also be displayed (Fig. 5).

A circumferential profile permits simple quantitative evaluation of thallium images—relatively free from variability in image quality and observer experience. The profile curves should facilitate comparison of exercise and redistribution data and enable a standardized interpretation of studies with evaluation of even minor degrees of redistribution.

Tomographic Imaging

One of the acknowledged limitations of scintigraphic imaging is that the typical planar radionuclide image is actually a two-dimensional representation of the three-dimensional distribution of activity within the organs.



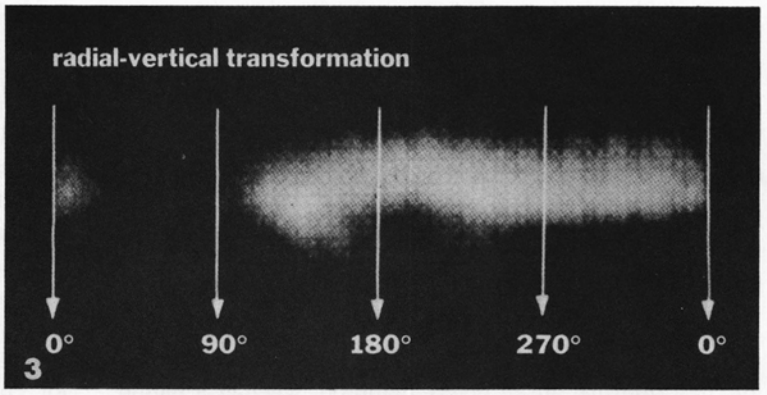


FIG. 2. Polar coordinate representation of an LAO thallium-201 image with an inferoapical perfusion defect (arrow). **FIG. 3.** Polar/orthogonal or radial/vertical transformation of data from Figure 2 with outermost radial values (representing the epicardial surface) being transformed vertically downward.

The proposed advantages of seven-pinhole imaging include simultaneous collection of all data for reconstruction with significantly shortened imaging time, a more readily quantifiable image, and improved diagnostic accuracy. The collimator is formed of a hexagonal array of pinholes with an additional hole in the center. A large field scintillation camera is recommended to provide maximum angle for viewing the heart. In addition, a computer is used to store and process 128 × 128 images for software reconstruction.

The collimator provides an LAO image from the central pinhole and peripheral views of the ventricle from the six peripheral pinholes, which "observe" the heart from various angles relative to the central aperture. The images are then computer reconstructed into tomographic planes through the ventricle (Fig. 6).

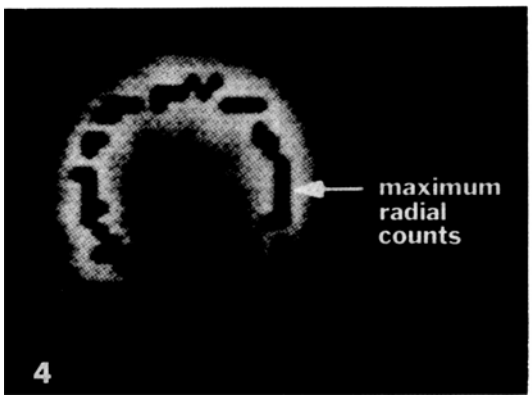
Although several investigators have reported superior diagnostic accuracy with seven-pinhole tomography, the general consensus is that diagnostic accuracy is not significantly improved over routine planar Tl-201 imaging. Seven-pinhole tomography requires extreme care on the technologist's part in order to obtain highest quality images.

Tomographic images can also be reconstructed using a parallel slant hole collimator, which obtains peripheral images of the heart for computer tomographic reconstruction. This technique as with the seven-pinhole collimator is restricted to imaging only a small area within the body. Another mechanism for tomographic imaging is with a single photon emission computed tomography (SPECT) system, which allows the scintillation camera to rotate around the patient taking images from many angles. Computer backprojection of the images allows tomographic reconstruction through any plane within the field of view.

Clinical Implications

The relatively limited resolution of currently available scintillation cameras means that thallium is most useful today in diagnosing transmural defects. This does not mean that thallium studies can detect only transmural infarctions. In fact, most small subendocardial infarctions are surrounded by a zone of ischemia similar to that surrounding a transmural infarction, so that detection of these lesions with thallium is quite possible. Therefore, to maximize the likelihood of detecting such regions, nuclear physicians interpreting thallium studies should indicate any known electrocardiographic abnormalities that suggest sites of possible ischemia or infarction. In addition, as the patient undergoes his postexercise thallium study, it may also be helpful to evaluate the stress ECG findings to determine if any additional views may be desirable for full evaluation of particular ischemic regions.

Although most thallium studies are performed in conjunction with stress electrocardiography, many physicians use thallium in rest studies as well. The primary indication for a rest



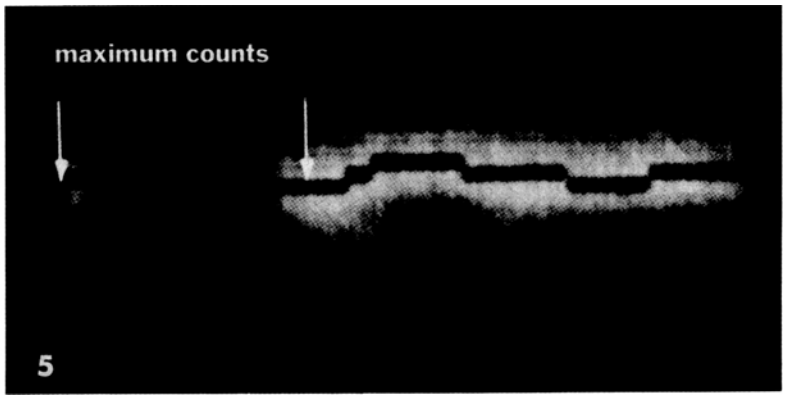


FIG. 4. Same image as in Figure 2 with assignation of maximal myocardial wall count profile. **FIG. 5.** Same data as in Figure 3 with the addition of the maximal myocardial wall count profile.

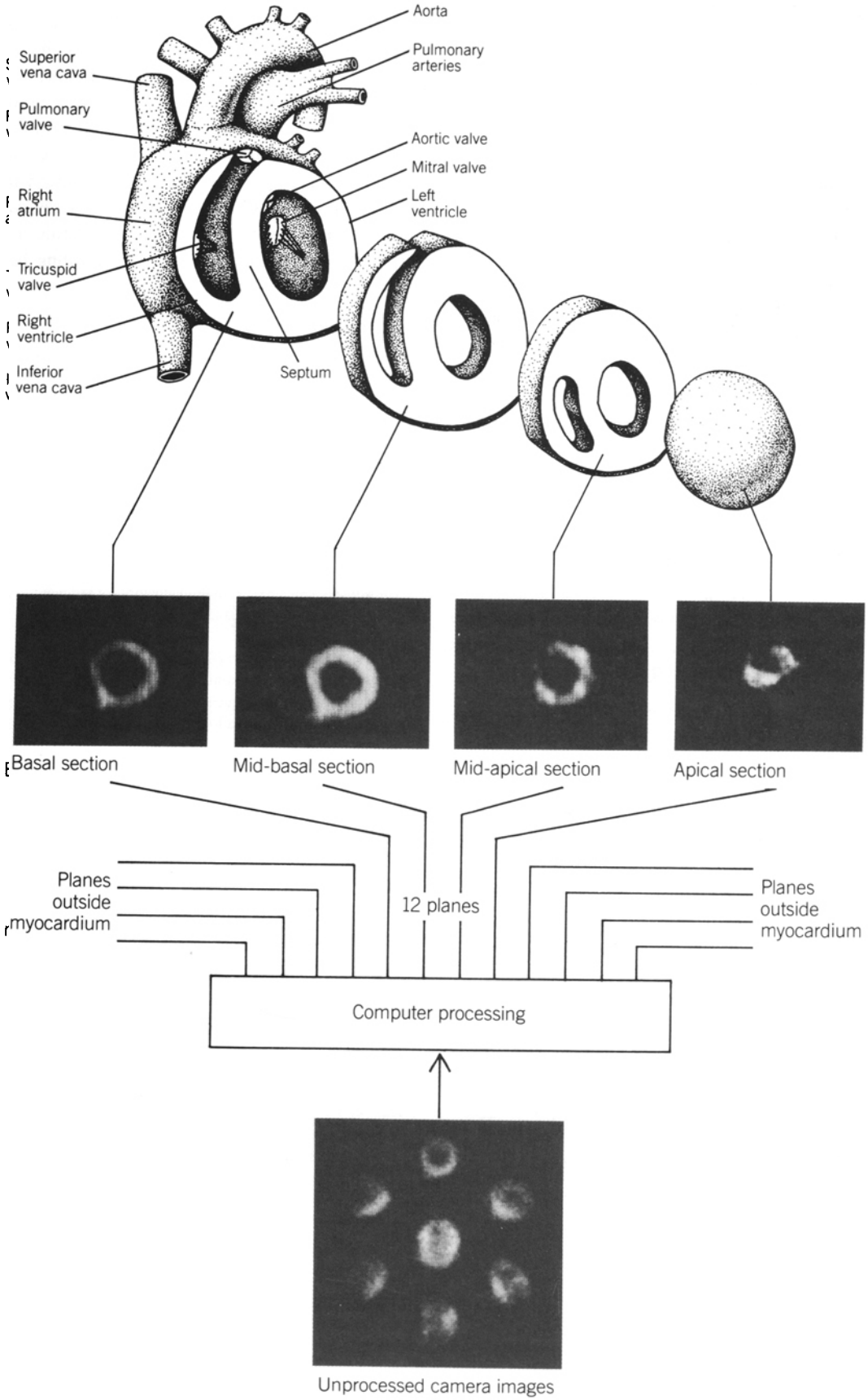


FIG. 6. Reconstruction of tomographic planes.

thallium study is "diagnosis and localization of acute myocardial infarction." Occasionally, patients may have conditions such as left bundle branch block that render ECGs nondiagnostic. In other cases, a patient may have experienced trauma that causes enzyme release from noncardiac muscle—thus masking the enzymes released by infarcted myocardial tissue. And in other circumstances, a new myocardial infarction may occur in the same region as a prior one, so that the relatively small enzyme release from the new infarction does not clearly indicate the full extent of cardiac damage—old or new.

Many institutions, particularly those equipped with mobile scintillation cameras, are exploring the use of Tl-201 as a myocardial infarction assessment agent in the CCU. Preliminary clinical experience indicates that such thallium studies can detect the presence of infarction even before diagnostic enzyme changes can be detected, and before ECGs become clearly positive.

Applications of Tl-201 imaging to CCU patients include:

- ☐ Detect infarction in patients whose ECGs remain nondiagnostic
- ☐ Localize and define the extent of infarction, thereby suggesting the magnitude of the insult and the viability of adjacent compromised ischemic myocardium
- ☐ Provide additional information about ventricular anatomy and viability, particularly in patients whose cardiac histories are not available in the acute setting.

Clinicians with extensive experience in CCU thallium imaging report that with serial imaging they can differentiate between infarction and ischemia by the same redistribution-imaging techniques used in the stress study. In Tl-201 images made of a patient with an acute infarction, areas of ischemia will fill in over time, just as they do in the stress test. Furthermore, the true degree of myocardial compromise is reflected by the combination of both ischemic myocardium and old and new infarction. From a clinical perspective, therefore, it may be equally as important to quantitate total infarction as to differentiate between old and new infarction.

The value of thallium for this clinical indication may be questioned by some physicians, because they believe that wall motion studies—either by ventriculography or by nuclear medicine procedures—can demonstrate the viability of certain areas of myocardium. While such studies provide valuable adjunctive information, they are nevertheless indirect assessments of myocardial viability.

The Future of Thallium-201 Imaging

Thallium-201 represents the best routinely available myocardial imaging agent produced to date. Technetium-labeled perfusion agents, however, would cost less and be immediately ready for use, yet these research radiopharmaceuticals have been slow in development and so far, have not provided significantly better images than those currently produced by Tl-201.

Improved myocardial perfusion images would result from improved imaging systems because resolution and sensitivity limitations are characteristics of the cameras available today. As a result, many commercial and academic researchers are exploring new intrumentation for obtaining better thallium images.

Suggested Readings

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