Calculation of Viable and Infarcted Myocardial Mass from Thallium-201 Tomograms

John W. Keyes, Jr., Thomas J. Brady, Patrick F. Leonard, Donald B. Svetkoff, Stephen M. Winter, W. Leslie Rogers, and Edward A. Rose

University of Michigan Medical School, Ann Arbor, Michigan

The feasibility of determining the mass of both viable and infarcted myocardium from tomographic images of thallium-201 distribution in the heart was studied in two normal dogs and ten dogs with acute infarction. Twenty-four hours after occlusion, thallium-201 was injected and 10 min later the hearts were removed and transaxial emission computed tomograms were obtained. Using the computer, an operator defined the epi- and endocardial surfaces of the left ventricle and the area of infarction in each tomogram. The computer then calculated values for total left-ventricular mass (TLVM) infarcted mass (IM) and the percentage of the left ventricle infarcted (% LVI). The calculated values were compared with measured weights, and good correlation was found between them: for TLVM, r = 0.87; for IM, r = 0.90; and for %LVI, r = 0.87. Good interobserver and intra-observer correlations were also found. Thallium-201 emission computed tomography offers a potential means to measure both myocardial mass and acute myocardial injury.

J Nucl Med 22: 339–343, 1981

Evaluation of methods designed to limit acute myocardial infarction has been hampered by the lack of an accurate, noninvasive method to distinguish and separately quantify irreversibly damaged myocardium; viable but hypoperfused, i.e., at-risk myocardium; and viable, perfused myocardium. A number of nuclear medicine techniques have shown promise of helping to overcome this problem. Using conventional imaging techniques and infarct-avid agents, such as technetium-99m pyrophosphate (PPi), several investigators have demonstrated acceptable quantification of anterior infarcts (*1–5*); moreover, single-photon emission computed tomography (SPECT) of PPi distribution has been shown to define infarct size accurately in dogs regardless of the location (*6,7*).

Delay in the time to reach peak uptake of PPi and its inability to provide differential information regarding viable and at-risk myocardium without the use of a second tracer limit the value of PPi in the assessment of acute myocardial injury. The distribution of thallium-201 in myocardium, however, directly reflects the amount of viable, perfused myocardium and outlines areas of ischemia and/or infarction immediately (*8*). In addition, the use of serial redistribution images could permit the separation of ischemic areas from truly infarcted zones in a manner similar to the use of rest/redistribution images to detect the ischemic but noninfarcted zones associated with severe coronary artery disease (*9*). Thallium-201 thus offers the possibility of separating and quantifying all zones of interest in the setting of acute myocardial infarction using a single tracer, and SPECT techniques could provide a means of making such measurements.

Although SPECT studies of thallium-201 in vivo had been reported to be of poor quality (*10,11*), tomograms obtained on isolated hearts were known to be of good quality (*10*). Anticipating that the problems with in vivo imaging would soon be overcome, given the rapid advances that were taking place in SPECT technology, we

Received June 27, 1980; revision accepted Nov. 26, 1980.

For reprints contact: John W. Keyes, Jr., MD, Div. of Nuclear Medicine, Univ. of Michigan Medical Ctr., Box 21, Ann Arbor, MI 48109.

determined: (a) to develop a technique to measure viable, perfused and ischemic/infarcted myocardial mass from thallium-201 tomograms; and (b) to evaluate the limiting accuracy of this technique through a series of bench-mark experiments using an isolated-heart model.

MATERIALS AND METHODS

Experimental model and data acquisition. Studies were conducted in 12 dogs covering a spectrum of findings ranging from no ischemia to infarcts involving almost half of the left-ventricular mass. Acute posterior myocardial infarctions were produced in ten mongrel dogs (average weight 12 kg) using the technique of Lucchesi et al. (*12*). After a fixed stenosis was applied to the left circumflex artery, the artery was totally occluded for 1 hr followed by release. On two dogs no operation was performed.

The infarcted animals were studied 24 hr after the operation. Reimer et al. (*13*) have shown that by such a time the infarct is fully evolved and there is no remaining "at-risk" zone. This assured us that the infarct zone delineated by our histologic staining process (v.i.) would correspond to the hypoperfused zone seen by thallium imaging. Three mCi of Tl-201 were given intravenously. The animals were killed 10 min later and the hearts removed. The atria were trimmed away and a thin, rigid wire was passed through the septum from apex to base. This fixation wire was then attached vertically to the center of a small rotating platform, with the apex of the heart pointing downward. Small balloons were inflated within the right and left ventricles to re-expand the ventricular cavities. The mounted hearts were positioned before a portable gamma camera with the axis of rotation (i.e., the fixation wire) centered and lying ~5 cm in front of the collimator face. The camera was thus viewing the heart approximately at right angles to its long axis. Using a high-resolution, parallel-hole collimator, images were obtained every 3° of rotation to provide 120 images. Each image was digitized into a 128 × 128 matrix and stored on magnetic disk by a small computer. Data acquisition time averaged 25 min, during which time approximately 370,000 counts were acquired.

Immediately after imaging, the hearts were sliced into sections ~1 cm thick, at right angles to the base-apex axis, and stained with nitro blue tetrazolium (NBT). The outline of the top and bottom of each slice and the border of the infarcted zone were traced on transparent acetate sheets to record the exact location and extent of the infarct. The left ventricle was then isolated. Following the border delineated by the NBT staining, the infarcted and noninfarcted areas were carefully separated and weighed.

Tomograms of the heart were calculated from the digitized projection images using a convolution type of reconstruction algorithm without attenuation correction (*10*). There were an average of five contiguous, 64 × 64 pixel tomographic images for each heart, with each tomogram representing a slice of myocardium ~8 mm thick, oriented at right angles to the long axis of the heart. The resolution in the tomographic plane was determined to be ~13 mm FWHM for the experimental setup used.

Image quantification. A computer program was developed to quantify both perfused and infarcted myocardial masses from the thallium tomograms. The technique is illustrated in Fig. 1. The individual tomographic sections are displayed on a computer terminal. The sizing program allows an operator to define interactively the number of pixels occupied by viable and infarcted myocardium. Using the computer display, the operator positions an inner and an outer circle (which need not be concentric) to correspond to the inner and outer borders of the left-ventricular myocardium (Fig. 1A–1C). The assumption of circular inner and outer outlines permits the myocardial contour to be extrapolated easily over the nonperfused (and thus nonvisualized) region corresponding to the infarct. Next the operator determines the area occupied by the infarct. This is done by using a light pen (Fig. 1D) to "flag" the appropriate area on the computer display. The circle coordinates and flagged pixels are saved by the computer and the operator proceeds with the next tomographic image until all sections of the heart have been analyzed.

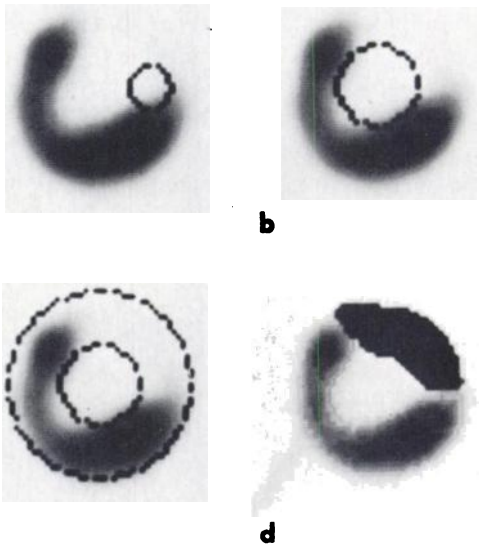

FIG. 1. (A) Thallium tomogram with inner circle as it first appears. (B) Operator-adjusted inner circle now defining inner myocardial boundary. (C) Operator-adjusted outer circle with outer myocardial boundary defined. (D) Operator-flagged posterior defect defining infarct area.

TABLE 1. SAMPLE COMPUTER PRINTOUT, WITH VALUES FOR TLVM, IM, %LVI AND RATIO OF THALLIUM UPTAKE IN INFARCTED VERSUS VIABLE MYOCARDIUM

	Total L.V.	Infarct	Viable
# Pixels	848	297	551
Ave. Cts.	414	292	480
Mass	59.6 grams	20.8 grams	38.8 grams

Infarct = 35.0% of L.V. Mass
Infarct Uptake = 60.9% of Viable Myocardial Uptake

Once all sections of a single heart have been defined, the computer calculates the masses of viable and infarcted myocardium. The total number of pixels occupied by the left ventricle is taken as the total region between the two circles. The infarcted region is the flagged area between the circles. The mass of the relevant parameter is then calculated as follows: mass = $N \cdot A_p \cdot T \cdot \rho$, where N is the total number of pixels corresponding to the desired parameter, A_p is the area of a single pixel (~0.09 cm^2), T is the slice thickness (0.8 cm) and ρ is the average myocardial density (1.05 g/cc).

The final computer printout (Table 1) includes calculations for total left-ventricular mass, infarcted mass, percentage of left ventricle infarcted, and the ratio of average thallium uptake in the infarcted zone compared with uptake in viable myocardium. This ratio was not used in the present study.

In order to determine the interobserver reproducibility of the calculations, the data for the 12 studies were analyzed separately by two observers, one a trained nuclear medicine physician who had participated in the original data acquisition and in developing the sizing program (these are the results presented in Figs. 3 and 4), and the other a medical student who had had only a short orientation to the study and the operation of the program. Intraobserver reproducibility was also evaluated by having the first observer analyze the data again after a 3-mo interval.

RESULTS

High-quality tomograms of the myocardial thallium distribution were obtained in all 12 studies. Figure 2 illustrates selected sections of a typical study. The right-hand images are the acetate tracings of the lower surfaces of four sections, with the infarct shaded for clarity. The left-hand images are the tomographic sections of approximately corresponding levels. The images do not correspond precisely due to slight differences in the levels and due to partial volume effects in the tomographic images.

The relationship between measured and calculated values for total left-ventricular mass (TLVM) and infarcted mass (IM) are represented in graphical form in Figs. 3 and 4. Using the interactive sizing program, the interobserver correlation was r = 0.91 for TLVM and r = 0.89 for IM. The intra-observer correlation for determinations made 3 mo apart was r = 0.92 for TLVM and r = 0.96 for IM.

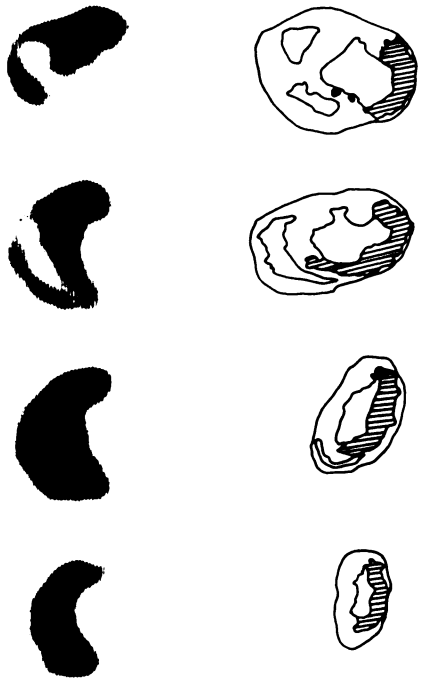

FIG. 2. Representative sections of dog's heart sliced from base (uppermost images) to near apex (lowest images). All sections are viewed in a cephalad direction. Right-hand drawings are acetate tracings of stained gross sections, with infarct shaded. Left-hand images are tomograms for approximately corresponding levels. Thallium defect corresponds closely to the posterior infarction.

DISCUSSION

The primary purpose of this study was to determine whether it was feasible—or even possible—to quantify both perfused and infarcted myocardial masses from transaxial computed tomograms of thallium-201 distribution in the heart. Given the limitations of SPECT technology at the time, it appeared unwise to attempt to answer this question using an intact animal model, as it would not have been possible to pinpoint the cause of failure had the experiments been unsuccessful. For this reason we chose an idealized model that eliminated most of the variables present in experiments on intact animals.

We feel that the feasibility of determining both perfused and infarcted myocardial masses from transaxial tomograms of thallium-201 in the heart has been established. Whether this approach can be extended to give useful, reliable results in vivo will depend upon: (a)

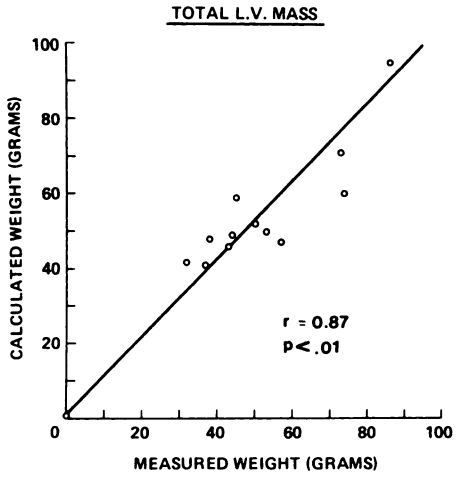

FIG. 3. Relationship between measured and calculated total left-ventricular mass in 12 dogs.

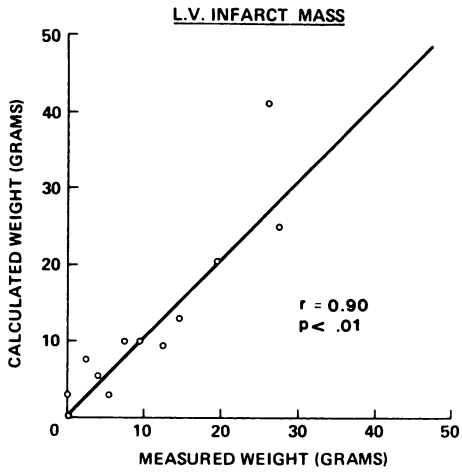

FIG. 4. Relationship between measured and calculated infarct mass in 12 dogs.

whether in the in vivo imaging situation it will be possible to produce tomograms of sufficient quality and in the proper orientation to permit the application of this sizing routine; and (b) whether the sizing program used is valid for the in vivo case.

An essential requirement for in vivo studies will be the ability to reconstruct quality tomograms using acceptable doses of thallium in an orientation that is suitable for the application of the sizing program. This means that it must be possible to reconstruct tomograms that are at right angles to the base-apex axis of the left ventricle.

Recent developments in SPECT hardware, software, and technique suggest that the answer to question (a) is definitely positive. Recently, good quality, in vivo transaxial tomograms in humans, using conventional doses of thallium, have been demonstrated by several investigators (*14,15*), and we have verified these results in our laboratory. In our own human tomographic studies, 22 min of data acquisition provide in excess of 400,000 counts from the heart with 2 mCi of Tl-201. This is quite comparable to the count levels used in the present study.

Although the tomograms obtained with rotating camera tomographs do not have the proper orientation for sizing, a set of such tomograms represents the full three-dimensional distribution of tracer within the field of view of the tomograph. Several investigators have now demonstrated that such three-dimensional data can be reorganized by computer to provide tomograms with orientations other than transaxial (*14,15*). We have verified these results in our laboratory and have been able to produce reorganized tomographic slices perpendicular to the base-apex axis of the heart from data that were originally transaxial in orientation. We thus feel that there are no technical impediments to implementing this technique in vivo.

Two possible limitations to quantitative accuracy in vivo that have not been addressed are attenuation effects and in vivo motion. We have previously demonstrated that it is possible to measure the size of acute myocardial infarcts in vivo using tomograms of Tc-99m PPi obtained without attenuation correction (*6*). We feel therefore that this is not a fundamental limitation, although attenuation could prove to be a more serious problem with thallium. A number of techniques for correcting SPECT studies for attenuation losses are known (*16,17*) and could be applied if needed. We do not feel that motion will be a serious problem. The in vivo studies described above were obtained without gating, and demonstrate excellent detail.

The sizing program that was developed in the course of this research has some potential limitations and problems. The assumption of completely circular boundaries for the myocardium is obviously artificial. Nevertheless, it is no worse than the assumptions that are used routinely in contrast angiography and ultrasound for determining chamber volume and ejection fractions. Similar assumptions were also used in the experiments of Weiss et al. (*18*), in which they demonstrated the feasibility of sizing infarcts from in vivo tomograms of C-11 palmitate. This positron-emitting radiopharmaceutical shows a pattern of uptake similar to that of Tl-201, and the success of these investigations was in part responsible for our decision to evaluate thallium for this purpose.

The assumption of relatively constant wall thickness, which is implicit in our sizing technique, would probably not hold in the setting of chronic ischemic heart disease. It should be valid in the acute infarct models that we used, and does not appear to have been a limiting factor.

We conclude that it is possible to determine the masses of both perfused myocardium and infarcted myocardium from thallium images obtained using SPECT techniques. Given recent developments in SPECT hardware and

software, there do not appear to be any technical problems blocking the application of these techniques in living subjects.

By extension from current clinical practice it should be possible to quantify both ischemic and infarcted myocardial masses and to separate these two categories by redistribution imaging. The ability to quantify the relative mass of infarcted and/or ischemic tissue in relation to total myocardial mass should have important prognostic and therapeutic implications in the management of patients with ischemic heart disease. The ability to quantify total myocardial mass may also be useful in evaluating many conditions in which total myocardial mass departs from normal.

ACKNOWLEDGMENTS

This work was supported in part by NIH Grant Nos. GM16188, GM22678 and HL21707.

Thallium-201 was supplied through the courtesy of New England Nuclear.

Stephen M. Winter and Edward A. Rose were supported in part by Medical Student Research Fellowships of the Michigan Heart Association.

The authors thank William Burmeister for technical assistance and Pamela Hendee, Vera Barton, and Diane Vecellio for secretarial and editorial assistance.

REFERENCES

1. LEWIS M, BUJA LM, SAFFER S, et al: Experimental infarct sizing using computer processing and a three-dimensional model. *Science* 197: 167-169, 1977
2. STOKELY EM, BUJA LM, LEWIS SE, et al: Measurement of acute myocardial infarcts in dogs with ^{99m}Tc-stannous pyrophosphate scintigrams. *J Nucl Med* 17: 1-5, 1976
3. BOTVINICK EH, SHAMES D, LAPPIN H, et al: Noninvasive quantitation of myocardial infarction with technetium-99m pyrophosphate. *Circulation* 52: 909-915, 1975
4. POLINER LR, BUJA LM, PARKEY RW, et al: Comparison of different noninvasive methods of infarct sizing during experimental myocardial infarction. *J Nucl Med* 18: 517-523, 1977
5. WACKERS FJT, BECKER AE, SAMSON G, et al: Location and size of acute transmural myocardial infarction estimated from thallium-201 scintiscans. A clinicopathological study. *Circulation* 56: 72-78, 1977
6. KEYES JW JR, LEONARD PF, BRODY SL, et al: Myocardial infarct quantification in the dog by single photon emission computed tomography. *Circulation* 58: 227-232, 1978
7. SINGH M, BERGGREN MJ, GUSTAFSON DE, et al: Emission computed tomography and its application to imaging of acute myocardial infarction in intact dogs using Tc-99m pyrophosphate. *J Nucl Med* 20: 50-56, 1979
8. ZARET BL: Myocardial imaging with radioactive potassium and its analogs. *Prog Cardiovasc Dis* 20: 81-94, 1977
9. GEWIRTZ H, BELLER GA, STRAUSS HW, et al: Transient defects of resting thallium scans in patients with coronary artery disease. *Circulation* 59: 707-713, 1979
10. KEYES JW JR, LEONARD PF, SVETKOFF DJ, et al: Myocardial imaging by emission computed tomography. *Radiology* 127: 809-812, 1978
11. BURDINE JA, MURPHY PH, DEPUEY EG: Radionuclide computed tomography of the body using routine radiopharmaceuticals. II. Clinical applications. *J Nucl Med* 20: 108-114, 1979
12. LUCCHESI BR, BURMEISTER WE, LOMAS TE, et al: Ischemic changes in the canine heart as affected by the dimethyl quaternary analog of propranalol, UM-272 (SC-27761). *J Pharmacol Exp Ther* 199: 310-328, 1976
13. REIMER KA, LOWE JE, RASMUSSEN MM, et al: The wave front phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation* 56: 786-794, 1977
14. LAGERGREN C: Single photon ECT of the body. In *Proceedings of a Symposium on Single Photon Emission Computed Tomography*. Bureau of Radiological Health, 1980, In press
15. RAYNAUD C: Preliminary results using a gamma-tomography system, GE 400T/Informatek SIMIS 3. In *Proceedings of Symposium on Single Emission Computed Tomography*. Bureau of Radiological Health, 1980, In press
16. CHANG LT: A method for attenuation correction in radionuclide computed tomography. *IEEE Trans Nucl Sci* NS-25(2): 638-643, 1978
17. BUDINGER TF, GULLBERG GT, HUESMAN RH: Emission computed tomography. In *Image Reconstruction from Projections: Implementation and Applications*, Herman GT, Ed. New York, Springer-Verlag, 1979, pp 147-246
18. WEISS ES, AHMED SA, WELCH MJ, et al: Quantification of infarction in cross sections of canine myocardium in vivo with positron emission transaxial tomography and ^{11}C-palmitate. *Circulation* 55: 66-73, 1977