In Vivo Quantitation of Regional Myocardial Blood Flow by Positron-emission Computed Tomography

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SUMMARY The potential of positron-emission computed tomography (PCT) for external quantitation of myocardial indicator concentrations and regional myocardial blood flow (RMBF) and the effect of left ventricular wall thickness on tracer concentration recovery by PCT was examined in seven open-chest dogs. RMBF was determined by the arterial reference technique in vivo and in vitro. Together with gamma-emitting Ce-141 microspheres, positron-emitting Ga-68-labeled microspheres were injected into the left atrium and their myocardial concentrations determined in vivo from gated and ungated cross-sectional PCT images. The loss in count recovery related to object size was corrected using postmortem and in vivo echocardiographic left ventricular wall thickness measurements. In vivo measurements of RMBF by PCT correlated linearly with in-vitro-derived RMBF (r = 0.98; n = 84), but they underestimated in vitro RMBF by an average of 40%. After correcting for wall thickness effect, in vivo measured RMBF agreed with the in vitro measurements in a one-to-one relationship (r = 0.99). The accuracy of the in vivo PCT measured RMBF was maintained when corrections for wall thickness were made from in vivo echocardiographic instead of from postmortem measurements. Gating of the PCT images improved the accuracy of the in vivo RMBF determinations. Moreover, the increase in regional count recovery during systole provided an estimate of systolic wall thickening. Changes in left ventricular wall thickness from end-diastole to end-systole measured by PCT closely correlates with the changes in wall thickness observed by echocardiography. We conclude that (1) myocardial indicator tissue concentrations, and thus, RMBF, can be accurately measured by PCT provided corrections are made for the effect of wall thickness on count recovery; (2) these corrections can be made using in vivo echocardiography; and (3) gated PCT imaging can be used to evaluate regional myocardial systolic wall thickening as an index of regional function and combined with measurements of RMBF or regional metabolism. The results represent a framework for the noninvasive measurement of RMBF and metabolism by PCT in the experimental animal and in man.

REGIONAL myocardial blood flow (RMBF) can be evaluated in man by invasive and noninvasive techniques. Invasive techniques, such as administration of xenon-133 directly into the coronary artery, permit measurement of RMBF in terms of ml/min/100 g myocardium, but this approach is highly invasive and not without risk to the patient. Noninvasive techniques, such as myocardial perfusion imaging with thallium-201, are associated with minimal patient risk, but provide only qualitative information on the distribution of myocardial blood flow. This is because the arterial input function is not determined and, even more important, absolute indicator concentrations in myocardium cannot be measured by conventional gamma camera imaging because of (1) an inability to correct for photon attenuation; (2) superimposition of radioactivity from myocardial and nonmyocardial structures; (3) the depth-dependent resolution; and (4) effects of scattered radiation.

Positron-emission computed tomography (PCT) overcomes many of the limitations inherent to conventional two-dimensional imaging and is of potential value for the accurate and noninvasive measurement of indicator tissue concentrations in vivo as established for the brain by Phelps et al. However, this quantitative capability of PCT is limited. Hoffman and co-workers demonstrated that as the size of the imaged object diminishes, apparent tissue indicator concentrations measured by PCT decrease relative to true values. For example, in one set of phantom studies, the recovery coefficient (i.e., the ratio of concentrations recovered by PCT to the true concentration) obtained with a bar phantom 10 mm thick was only 0.5. Accordingly, imaging of the 8–12-mm-thick left ventricular myocardium by PCT under the same conditions would underestimate regional indicator tissue concentrations about 50%.

The purposes of this study were to determine whether myocardial indicator concentrations and RMBF could be quantified in vivo by PCT, and to evaluate the effect of left ventricular wall thickness or concentration recovery by PCT. An open-chest dog model and albumin microspheres labeled with a positron emitter were chosen to optimize the conditions for measurements of myocardial flow, as the 100% extraction and retention of microspheres in myocardium would simplify data analysis.
Materials and Methods

Animal Instrumentation

Seven mongrel dogs, 20–30 kg (mean 26.2 kg), were studied. Each dog was anesthetized with pentobarbital sodium (25 mg/kg) and ventilated with room air. For withdrawal of arterial blood and monitoring systemic blood pressure, catheters were advanced through both femoral arteries into the abdominal aorta. After a left thoracotomy, the pericardium was incised widely and sutured to the chest wall to form a cradle in which the heart was suspended. The dogs were instrumented in the following manner (fig. 1): An electromagnetic flow probe (Series 500, Biotronix) was placed around the proximal left circumflex coronary artery. Mechanical zero flow was established during 10-second coronary occlusions with a snare placed distally to the flow probe. The snare was also used to produce hypoperfusion or reactive hyperemia of the myocardium supplied by the circumflex coronary artery. A fine polyethylene cannula was advanced through a puncture wound into the left atrium and used for injection of radioactive microspheres. Each dog's ECG was continuously monitored using standard lead II, and systemic blood pressure was recorded using a Statham P23Db pressure transducer.

Study Protocol

After instrumentation, the dogs were transported to the UCLA positron-emission computed tomograph (ECAT, Ortec Inc.). Each dog was carefully positioned so that the long axis of the left ventricle was perpendicular to the imaging plane. After recording transmission images for subsequent correction of photon attenuation, positron-emitting Ga-68-labeled albumin microspheres and gamma-photon-emitting, Ce-141-labeled, carbonized microspheres were simultaneously injected into the left atrium, either at control (two dogs), during circumflex coronary artery occlusion (two dogs), or during peak reactive hyperemia after release of the occlusion (three dogs). Only one imaging study was performed in each dog because the 68-minute physical half-life of Ga-68 would have necessitated a 5–6-hour delay until the activity would have decayed to near-undetectable levels to allow repeat studies.

After PCT imaging was completed, left ventricular wall thickness was determined in vivo by echocardiography. The levels of the cross-sectional images and wall thickness measurements were carefully marked on the surface of the left ventricle using the light beam of a laser unit incorporated into the tomograph, which shines on the ventricular surface in the image plane. Along this demarcation line, needles were placed through the myocardium to permit identification of the tissue slices that corresponded to the imaging planes after the heart was removed from the chest cavity. Each dog was then sacrificed with potassium chloride solution, the heart was removed and the left ventricle was sliced into 1-cm cross sections. The wall thickness of the two slices corresponding to the imaging planes — usually in the mid left ventricle — was then measured with a caliper at six sites, including those measured echocardiographically. The left ventricular cross sections were then divided into 1-g segments. For each of the six sites where wall thickness had been determined postmortem, two adjacent tissue samples were placed into preweighed disposable counting tubes and the activity per gram of tissue was determined by well counting. Subsequently calculated values for RMBF for each site were averaged for the two tissue samples.

PCT Imaging

Before microsphere injection, the data collection sequence of the tomograph was synchronized to the dog's cardiac cycle using a Brattle model 202 physiologic synchronizer (Brattle Instrument Corp.) that had been modified to provide gating pulses 70–1330 msec wide at 70-msec increments. In this approach, the gating signal directs the image data to one-half of a buffer memory, while alternately, the image data during the remainder of the cardiac cycle are accumulated in the other half of the buffer memory. An end-systolic window of 140 msec was selected. During this time, image data were routed into the first memory for subsequent reconstruction of an image of the myocardium in systole. As Hoffman and co-workers showed, images of all phases minus systole closely resemble end-diastolic images. More important, comparison of tracer concentration in identical regions of interest for end-diastolic vs all phases minus end-systolic images (210-msec window) gave a mean ratio of 1.01 ± 0.03 for midventricular planes. Thus, image data placed into the second half of buffer memory could be defined as end-diastolic data. The 140-msec...
end-systolic window in this study was chosen to obtain statistically adequate images for this portion of the cardiac cycle. As this window would have encompassed a large portion of the cardiac cycle at the rapid heart rates normally seen in anesthetized, open-chest dogs (approximately 150 beats/min), xylazine, a parasympathomimetic general anesthetic agent, was administered intravenously in increments of 0.5-mg doses until heart rates fell to 75–100 beats/min.

Thirty seconds after microsphere injection, cross-sectional imaging of the left ventricle was initiated. All image data were collected in the medium resolution mode with an intrinsic resolution of 1.3 cm full-width-half-maximum and a slice thickness of 18 mm. Two contiguous cross sections through the mid-left ventricle at 1-cm increments were obtained. In each plane, diastolic and systolic images were acquired simultaneously (as above) for 20 minutes, followed by ungated imaging of the same plane for another 20 minutes. This sequence was then repeated for the second plane. Thus, the total imaging time for gated and ungated images of both planes was 80 minutes. The total counts in the gated images (systole and diastole) averaged 1,250,000 for the first plane and 850,000 for the second plane, and for the ungated images 1,000,000 and 650,000 counts, respectively.

Measurement of Left Ventricular Wall Thickness

Left ventricular wall thickness was measured in vivo by echocardiography. In four dogs, only M-mode studies were obtained, and in the remaining three, two-dimensional studies were obtained as well (Eko-sector I, Smith-Kline Instruments). All M-mode studies were recorded on precalibrated, light-sensitive paper and the two-dimensional studies were photographed on Polaroid film. In each case, the transducer was applied directly to the anterolateral myocardial surface1 and the laser beam of the tomograph used for accurate placement in the imaging plane. Left ventricular wall thickness was measured by echocardiography in 20 sites in the basal of the two imaged planes. Fourteen measurements of the anterolateral and posteromedial wall were obtained by M-mode echocardiography, performed in all seven dogs. In each two-dimensional study, because of a 2-cm blind spot adjacent to the transducer, only the posterior septum and the posterior and posterolateral wall were visualized (fig. 2). The thickness of the posteromedial wall had already been measured in the M-mode, so only the posterolateral and posterior wall thicknesses were determined from Polaroid photographs of end-diastolic and end-systolic calibrated stop-action frames of the three two-dimensional studies.

Postmortem measurements were obtained in 84 sites, i.e., six sites for each of the two planes in the seven dogs. Wall thickness was determined with a caliper from the cross sections of the sliced left ventricles. Because the hearts were arrested with concentrated potassium chloride solution these measurements represented wall thickness at end-diastole.

Preparation of Microspheres

For in vitro measurements of RMBF, gamma-emitting microspheres were used. Carbonized microspheres (9 ± 1 μ) (3M Co.) were suspended in 10% dextran with one drop of Tween-80 to prevent clumping. Approximately 1.5 × 10⁸ microspheres labeled with Ce-141 were injected into the left atrium. Before injection, the microspheres were thoroughly mixed with a Vortex shaker and suspended by ultrasonification.

For in vivo measurements of RMBF by PCT, human serum albumin microspheres were labeled with Ga-68 as described previously.10-12 In brief, Ga-68 EDTA chelate was obtained from a Ge-68 → Ga-68 generator (New England Nuclear). The Ga-68 EDTA chelate was destroyed with concentrated HCl and the EDTA extracted with isopropyl ether. The resultant free Ga-68 was labeled to human serum albumin microspheres (9 ± 1 μ) pretreated with stannous chloride.12 Repeated washing of the labeled microspheres was used to remove unbound Ga-68 and

Figure 2. In vivo determination of myocardial wall thickness. (top left) Schematic representation of M-mode transducer applied directly to anterolateral myocardial surface with the echo beam reflecting off the epicardial and endocardial surfaces of anterior and posteromedial wall. (bottom left) M-mode study from a dog. Calibration markers allow accurate measurement of wall thickness. (top right) Schematic representation of two-dimensional study. The transducer is applied to the anterior surface of the left ventricle. Because of a 2-cm blind spot immediately adjacent to the transducer (bottom right), only the posterior interventricular septum, posterior wall and posterolateral wall are visualized well. LV = interventricular; LV = left ventricular; RV = right ventricular.
showed the labeling to be 95% efficient. For each injection, 2–3 mCi of Ga-68 (approximately 10⁴ particles) were used. After preparation, Ce-141- and Ga-68-labeled microspheres were placed into separate syringes, which were connected by stopcocks in series to the left atrial cannula. The Ce-141-labeled microspheres were injected first, followed immediately by the Ga-68 microspheres and a saline flush. The interval between the injections of the two sets of microspheres was never longer than 2 seconds.

Measurement of RMBF

For calculating RMBF, the arterial reference technique was used. Beginning with the microsphere administration, arterial blood was withdrawn at a rate of 4.29 ml/min with a dual-syringe Harvard infusion pump for 2.6 minutes. The content of one syringe was used as the arterial reference sample for both sets of microspheres. From the blood of the second syringe, the fraction of Ga-68 that became unbound after administration was determined. This was accomplished by measuring whole blood activity first, then separating the labeled microspheres from plasma by centrifugation and counting the activity in plasma and precipitate individually. The fraction of activity contained in plasma compared with whole blood was considered the amount of Ga-68 that became unbound from the microspheres after injection.

RMBF was calculated by the equation

\[ \text{RMBF (ml/min/100 g)} = \frac{F_a \cdot C_m}{C_b} \]

where \( F_a \) = the withdrawal rate of arterial blood (4.29 ml/min), \( C_m \) = the activity in the myocardial tissue sample (counts/min/g) and \( C_b \) = the total activity in the arterial reference sample (counts/min). For the in vitro determination of RMBF, \( C_m \) (counts/min/g) was measured by well counting of the myocardial tissue samples, while for the in vivo determination of RMBF by PCT, the myocardial concentrations of Ga-68 microspheres were determined as follows: Before imaging, a calibration factor (K) for converting counts per picture element of the PCT images to counts per milliliter was derived by measuring the counts per minute from a 1-ml sample of Ga-68 solution in a well counter. A cylinder (21 cm in diameter) containing the same solution was then imaged by PCT, a region of interest was assigned to the center of the image and the counts per picture element per minute were derived.

\[ K = \frac{\text{counts/ml/min}}{\text{counts/picture element/min}} \]

Counts per gram myocardium derived by PCT (\( C_m' \)) were calculated by

\[ C_m' = \frac{\text{counts/picture element} \cdot K \cdot W (\text{cts/g/min})}{\sigma} \]

where W is the correction factor for the effect of wall thickness on count recovery and \( \sigma \) is the specific gravity of myocardial tissue (1.05). The correction factor W was derived for a given wall thickness from the relationship between object size and count recovery previously determined in our laboratory by Hoffman et al. in measurements of bar phantoms. Computer simulations show that the count recovery of an annular object with a given wall thickness is equivalent (+ 3%) to a bar phantom of the same wall thickness, down to an inner diameter of 3 cm. Of course, care must be taken to avoid slices near the apex or valve plane of the heart, or the off-plane activity may interfere with the measurement. Counts per picture element were derived from 0.64-cm² regions of interest assigned to the left ventricular myocardium on the cross-sectional images and normalized to 60 minutes (i.e., for a 20 minute image recording time, the counts per picture element were divided by 20). Counts per gram (\( C_m' \)) myocardium were then entered into equation 1. Gallium-68 arterial reference counts (\( C_b' \)) were corrected for free Ga-68 by multiplying the total activity by the ratio of bound to total Ga-68 activity.

To compare in vivo to in vitro measurements of RMBF, the regions of interest were assigned to the left ventricular myocardium so that they corresponded to the sites of wall thickness measurements and the tissue samples. Before removing the heart from the chest, the center of the anterolateral wall, a readily defined point on the images, was identified on the left ventricular cross section. Beginning with this reference point, myocardial tissue samples and regions of interest were chosen at 60° intervals along the left ventricular circumference.

The data were analyzed with linear correlation equations using a least-squares fitting technique.

Results

Measurements of RMBF

Three representative diastolic images recorded in three individual animals are shown in figure 3. In all images, the anterior myocardium is to the left, posterior myocardium is to the right, lateral wall at the top, and interventricular septum at the bottom. Image 1 was obtained after microsphere injection during circumflex coronary artery occlusion and demonstrates a marked reduction in tracer concentration in the posterior septum and posterior wall. Image 2 was obtained after administration of microspheres at control and shows uniform tracer distribution. Image 3 was recorded after microspheres were administered during reactive hyperemia of the circumflex coronary artery. The tracer concentration is markedly increased in the posterior wall and the entire interventricular septum. Perfusion of the anterior and lateral walls was of similar magnitude in all three dogs. Although activity in the anterior wall in example 3 appears lower than that in the posterior wall, this is artifactual because of the limited gray scale of the image display, and hence, inadequate visualization of both regions simultaneously.

RMBF derived in vivo from the diastolic PCT images closely agreed in a linear fashion with RMBF determined in vitro (fig. 4). The in vivo data are not
corrected for the effect of wall thickness on count recovery. Despite the close agreement between in vitro and in vivo measurements, the in vivo values are consistently lower than the in vitro values, as evidenced by the slope of the regression line (0.60). Correction for wall thickness effect on count recovery using postmortem measurements resulted in an even better agreement (fig. 5). The in vitro and in vivo data now correlated in a one-to-one fashion. This is described by the equation

\[ \text{RMBF in vivo} = 0.7 + 0.99 \times \text{RMBF in vitro} \]

Moreover, correction for wall thickness effect reduced the mean deviation of the data about the regression line \((\text{SEE})\) from 14 ml/min/100 g to 12 ml/min/100 g.

In the intact animal, however, wall thickness can be determined only by echocardiography. Therefore, wall thickness was measured by this approach in 20 myocardial sites. When myocardial tissue concentrations measured in vivo by PCT were corrected for wall thickness effect from end-diastolic echocardiographic measurements, the resulting values of RMBF again were in close agreement with the in vitro measurements (fig. 6):

\[ \text{RMBF in vivo} = 1.0 + 0.98 \times \text{RMBF in vitro}; r = 0.98 \]

To determine whether gated acquisition of the cross-sectional PCT images did improve the accuracy of the in vivo measurements, RMBF was also calculated from the ungated PCT images. Corrections for the wall thickness effect were made from the postmortem measurements of wall thickness. The resulting lesser degree of correlation between the in vivo and in vitro data (fig. 7) may be related to some extent to the fact that the count recovery on the ungated PCT images was corrected for by end-diastolic wall thickness. The correlation improved slightly when the counts in the region of interest on the PCT images were corrected for the effect of wall thickness on count recovery.

**Figure 3.** Gated diastolic cross-sectional positron-emission computed tomographic images of the left ventricular myocardium in three dogs. A and P refer to anterior and posterior wall. Image 1 was obtained after circumflex occlusion and shows a marked reduction in tracer concentration in the posterior septum and posterior wall. Image 2 was obtained at control and demonstrates uniform tracer distribution. Image 3 was recorded after microspheres were administered during hyperemia of the left circumflex coronary artery. A marked increase in tracer concentration in the posterior wall and entire interventricular septum relative to the anterior and lateral wall is noted.

**Figure 4.** Comparison of myocardial blood flow (MBF) derived by the in vitro method vs in vivo by positron-emission computed tomography (PCT). MBF calculated in vivo by PCT was not corrected for wall thickness.
images were corrected for mean wall thickness obtained echocardiographically (fig. 8). Although the integral of wall thickness for an entire cardiac cycle on the echocardiographic recordings divided by the cycle length would have provided a more accurate mean value, it could be applied only to the M-mode measurements. The method chosen, therefore, was simply to average the end-diastolic and end-systolic wall thicknesses.

In Vivo Measurement of Systolic Wall Thickening by PCT

Eaton et al. and Garrison et al. examined the accuracy of wall thickness measurements by echo-
cardioangiography. We compared the values obtained in our postmortem study with those determined in vivo by echocardiography during end-diastole. There was an excellent linear correlation for the 20 measurements (fig. 9). Furthermore, the validity of using the relationship of object size to count recovery derived from phantom studies to the beating heart was examined by establishing an in vivo recovery coefficient which related wall thickness (in mm) to the recovery coefficient derived in vitro measured RMBF. From this, an in vivo recovery coefficient was derived for all 84 myocardial sites with wall thickness measurements. The data were fitted best by a straight line (fig. 10). For the range of wall thickness from 8–20 mm, the data fit is compared in figure 11 to the curve derived in phantom experiments by Hoffman et al.* Within this limited range, the two curves are virtually identical and support the use of the recovery coefficients derived in

**Figure 8.** Myocardial blood flow (MBF) determined in vivo from ungated image data and corrected for mean diastolic and systolic wall thickness compared with in vitro measurements.

**Figure 9.** Comparison of postmortem wall thickness measurements and echocardiographically derived diastolic wall thickness measurements.

**Figure 10.** In vivo derived relationship between myocardial wall thickness and recovery coefficient.

**Figure 11.** Comparison of the relationship between recovery coefficient and object size or wall thickness determined in vivo and derived in phantoms for the range of myocardial thicknesses seen in this study.
phantom studies for correcting in vivo measured myocardial indicator concentrations.

Systolic wall thickening would be expected to be associated with an increase in regional count recovery. As described above, the relationship between wall thickness and recovery coefficient is linear for wall thicknesses of 8–20 mm and could be used to estimate the increase in wall thickness during systole from changes in regional count recovery. The equation given in figure 10 and describing the relationship between the recovery coefficient RC and wall thickness (WT, mm),

\[ RC = 0.09 + 0.04 \cdot WT, \]

can be rearranged to

\[ WT = \frac{RC - 0.09}{0.04}. \]

Thus, systolic wall thickening can be calculated by

\[ \frac{WT_{\text{systole}}}{WT_{\text{diastole}}} = \frac{RC_{\text{systole}} - 0.09}{RC_{\text{diastole}} - 0.09} \]

If RC is substantially greater than 0.09, equation 6 may be simplified to

\[ \frac{WT_{\text{systole}}}{WT_{\text{diastole}}} = \frac{RC_{\text{systole}}}{RC_{\text{systole}}} \]

and the change in wall thickness from diastole to systole can be determined by

\[ \frac{WT_{\text{systole}}}{WT_{\text{diastole}}} = \frac{C_{\text{pct systole}}}{C_{\text{pct systole}}} \]

where \( C_{\text{pct}} \) = the tissue concentrations measured by PCT during diastole and systole and \( C \) = the true tissue concentrations during diastole and systole. \( C_{\text{diastole}} \) and \( C_{\text{systole}} \) are assumed to be equal.

Consequently, systolic wall thickening can be determined from equation 8 independent of the absolute values for wall thickness. To examine this possibility, wall thickening was calculated from PCT data by two methods: (1) using equation 6, which requires the absolute value of diastolic wall thickness to determine the \( RC_{\text{diastole}} \); and (2) using equation 8, which requires only the recovered image concentrations. The calculations were performed for both end points of the in vivo wall thickness–recovery coefficient curve, i.e., for myocardial sites with an end-diastolic thickness of 8 and 20 mm, respectively. For the 8-mm site, where the greatest error would be expected, equation 6 predicted a 20% and equation 8 an 18% increase in wall thickness during systole. For the 20-mm site, both equations predicted increases of 20%. Systolic wall thickening was subsequently computed with equation 8 for all 20 myocardial sites with echocardiographic measurements. The correlation between percent in-

crease in wall thickness predicted by gated PCT and that observed by echocardiography was excellent (\( r = 0.95 \)) (fig. 12). Thus, gated PCT permits assessment of systolic wall thickening as an index of regional myocardial function\(^7\) that can be obtained simultaneously with measurements of RMBF.

Discussion

The results indicate a consistent, high degree of correlation between RMBF determined by the in vivo PCT method compared with the in vitro method. The optimum agreement between the two measurements was accomplished when the PCT images were gated.

Technical Considerations

Alignment of Images and Tissue Slices

In correlating in vivo and in vitro measurements of RMBF in this study, we assumed that flow values were compared for the same myocardial site. Therefore, great care was taken to align the tissue slices with the image planes. Also, regions of interest were assigned to the PCT images to correlate as closely as possible with the sites of tissue sampling. Nevertheless, malalignment may still have occurred, and as a result, comparisons of flow values may have been made between two slightly different myocardial regions. However, the excellent correlation of the data for heterogenous flow conditions indicates that this error was probably small.

Regional Distribution of Microspheres

The regional distribution of microspheres may not always reflect accurately the regional distribution of
myocardial blood flow. Utley et al. have shown that spheres 9 μ in diameter are optimal for assessing RMBF in dogs. The distribution of microspheres of this size was felt to represent the red blood cell distribution. If the size was larger (25 μ or greater), the spheres preferentially distributed in the subendocardial half of the myocardial wall. When smaller spheres were used, significant nonentrapment in the microcirculation occurred — especially at high flow rates — and resulted in an underestimation of RMBF. With spheres 8–10 μ in diameter, Utley and co-workers and Buckberg and co-workers have shown that nonentrapment in the coronary circulation of dogs and sheep is less than 1%. Thus, use of 9-μ microspheres in this study should have provided accurate values for RMBF. Moreover, comparisons were made in this study between measurements obtained with two sets of microspheres. Both microspheres were of equal diameter, so a size-related effect on the microsphere distribution should cancel out. Unlike the carbonized microspheres used for the in vitro measurements, the albumin microspheres for the PCT determinations are biodegradable, which could limit the validity of comparing both measurements. However, myocardial concentrations of Ga-68-labeled microspheres changed only little over time (−3.5 ± 2.1% over 20 minutes), indicating that significant biodegradation did not occur during the period of study. Thus, any error produced by nonrepresentative distribution of microspheres should be minimal and absolute flow values derived should accurately mirror true flow.

Unbound Gallium-68

In vivo measured RMBF by PCT was corrected for the error due to Ga-68, which leached from the spheres after injection. The fraction of unbound Ga-68 was determined from the arterial reference blood sample as the fraction of total blood activity that remained in plasma after centrifugation. This value varied from 0.10–0.15 and was subtracted from the reference blood sample. To examine whether Ga-68 continued to leach off the albumin microspheres after being trapped in myocardium, we compared the decay-corrected total counts per plane of the gated and ungated images. If Ga-68 continued to come off the spheres, there would have been a significant decline in activity from the gated to the ungated images, as the time for the beginning of acquisition between planes was separated by 20 minutes. The average decline in activity was only 3.5 ± 2.1%, suggesting that leaching of Ga-68 off the microspheres was only minimal. The decline in activity may also have been caused by biodegradation of the albumin microspheres and loss of microsphere fragments through capillaries.

In Vivo Measurement of RMBF

PCT has been used previously for external assessment of RMBF. Beller et al. demonstrated in dogs the ability of PCT to visualize RMBF quantitatively. Karunaratne et al., using a double-headed positron-imaging device, compared the myocardial N-13 activity to RMBF measured with Ga-68 microspheres. Although in three sets of experiments, flow values derived from N-13 ammonia images correlated well with myocardial blood flow calculated from Ga-68 microspheres, it is not clear from their data whether a one-to-one relationship between the two sets of values existed or whether the regional distribution of activity only was measured.

Nichols et al. used PCT to quantitate RMBF by direct comparison of regional myocardial activity in the PCT images to activity in an arterial reference syringe. However, it is difficult to assess the accuracy of their PCT measurements because only mean values for normal and ischemic myocardium are provided. Two factors may have influenced the accuracy of the results: (1) The diameter of the syringe containing the arterial reference sample and myocardial wall thickness may not have been equal. If not, the recovery coefficient for the two would have been different and comparison of activity would have produced a consistent error in flow calculations. (2) Sedimentation of the labeled microspheres in the reference syringe at the time of imaging may have caused an underestimation of the true activity by PCT, unless the region of interest included the entire syringe.

The results of this study underscore the need for correcting for object size-related effects on count recovery when absolute tissue concentrations in myocardium are measured. Without such correction, the PCT-derived values underestimated RMBF by an average of 40% for end-diastolic images and, to a lesser extent, for end-systolic images, while the corrected values correlated with the in vitro measurements in a one-to-one relationship. For correction of the wall thickness effect on count recovery, the relationship between object size and count recovery determined in bar phantom studies was used. Of the phantoms used by Hoffman et al., the bar phantom would seem to correspond best to the ventricular myocardium. A bar most closely approximates the myocardium in a PCT measurement, because both have a narrow dimension (the bar or wall thickness) and a much larger second dimension (bar length or annular ring of myocardium). In both cases, the loss in count recovery is dominated by the narrow dimension with the recovery coefficient of the larger dimension nearly equal to 1. The similarity of the in vivo recovery coefficient curve and the phantom curve supports the application of the phantom curve for in vivo use.

The results indicate further that corrections for left ventricular wall thickness can be made adequately from in vivo echocardiographic measurements. The end-diastolic echocardiographic measurements compared well with the postmortem values and, when entered into the flow calculations, the high correlation between in vitro and in vivo PCT-measured RMBF was maintained.

Our results indicate that gated image acquisition is essential for accurate measurements of myocardial indicator concentrations and, in this study, of RMBF. When RMBF was calculated from ungated PCT im-
ages and corrected for the average left ventricular wall thickness obtained by echocardiography, the standard deviation of the data about the line of regression was 22 ml/min/100 g. However, gating in end-diastole and wall thickness corrections for post-mortem or echocardiographic end-diastolic measurements considerably reduced the data scatter, to a mean standard deviation about the regression line of 12 and 15 ml/min/100 g, respectively.

Determination of Regional Systolic Wall Thickening by Gated PCT Imaging

Gated PCT imaging also provided measurements of regional myocardial wall thickening as an indicator of regional myocardial function, which can be obtained simultaneously with measurements of RMBF. However, the linear relationship between wall thickness and recovery coefficient existed only in the range of wall thicknesses from 8–20 mm. Beyond this range, the response is nonlinear and the use of the regression equation between wall thickness and count recovery is no longer valid.

Gating of the PCT images thus increased accuracy of tracer concentration measurements, improved visualization of anatomical detail, and permitted simultaneous evaluation of regional function in addition to RMBF. However, as the cardiac cycle is divided into gating windows, the counts collected per time window necessarily decreased. To compensate for this count loss, longer imaging periods are required. Use of higher activities of short-lived positron-emitting radionuclides should permit use of gating windows comparable to those used for equilibrium blood pool imaging with Tc-99m (< 50 msec), while still accumulating statistically adequate counts.

Clinical Implications

The findings of this study demonstrate that PCT permits accurate measurements of RMBF. The limitation for external measurements of indicator tissue concentrations in relatively small objects imposed on PCT by the object size–related loss in count recovery can be overcome by corrections for wall thickness. Such corrections can be made from echocardiographic determinations of left ventricular wall thickness and the relationship between object size and count recovery. As Hoffman et al. pointed out, this relationship is dependent on the spatial resolution of the PCT imaging device, and hence, cannot be directly applied to studies using other PCT imaging devices. Nevertheless, the close agreement between the recovery coefficients established in vivo and those using the bar phantom suggests that this relationship can be readily determined by phantom experiments. In addition, gated acquisition of the image data not only improved visualization of anatomic detail, but also enhanced the accuracy of myocardial blood flow measurements.

To simplify data analysis, positron-emitting microspheres were used in this study because of their nearly 100% extraction fraction and entrapment in myocardium. While this technique could be used in man by administering the microspheres into the left ventricle, this approach would be invasive. More important, the effects of capillary blockade on cerebral circulation and function are unknown. The use of diffusible indicators that can be administered intravenously is therefore preferable in man. N-13 ammonia and Rb-82 have been described as potentially useful positron-emitting indicators of myocardial blood flow. Although Rb-82 can be obtained from a readily available generator system, its use as an indicator of myocardial blood flow and its response to changes in myocardial perfusion must be more precisely defined. N-13 ammonia requires on-site production, and thus, an on-site cyclotron. However, it has properties that are not unlike those of microspheres. It rapidly and almost completely clears from blood into myocardium, is extracted in myocardium in proportion to blood flow and remains metabolically trapped. Both indicators may become useful for the noninvasive assessment and quantification of RMBF by PCT in man. Our results not only indicate the possibility of measuring RMBF, but also, in a broader sense, provide the framework for measurements of regional myocardial indicator tissue concentrations and metabolism. Combined with gated data acquisition, it may permit correlations between myocardial mechanical function and flow and/or metabolism.

Acknowledgment

The authors thank Joanne Miller, Francine Aguilar and Ronald Sumida for their technical support, Tony Ricci, M.S., for his help in ECG-gated PCT data acquisition, Mary L. Griswold for preparing the illustrations and Anita Signorelli for her secretarial assistance.

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Circulation. 1981;63:1248-1258
doi: 10.1161/01.CIR.63.6.1248

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/63/6/1248.citation

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