Delineation of Impaired Regional Myocardial Perfusion by Positron Emission Tomography With H$_2^{15}$O

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Positron emission tomography with $^{15}$O-labeled water (H$_2^{15}$O) can be used to delineate abnormal regional myocardial blood flow in experimental animals. To determine the feasibility of this method in humans, we studied 33 subjects (9 normal volunteers and 24 patients with angiographically documented coronary artery disease) at rest and after myocardial hyperemia induced with intravenous infusion of dipyridamole. At rest, the myocardial region demonstrating the lowest relative H$_2^{15}$O activity exhibited 71±8% of activity in the region with peak activity in control subjects and 62±17% in patients (p = NS). After the dipyridamole infusion, differences between the two groups were accentuated. In control subjects, activity in the region with lowest relative radioactivity averaged 77±5% of that in the region with peak activity. In patients, it averaged 55±22% of activity in the region with peak activity (p<0.01). Results in patients with ischemia with or without a history of remote myocardial infarction were not significantly different. In 22 of the 24 patients, the region with lowest relative perfusion corresponded anatomic to the region of myocardium distal to a stenosis. Thus, delineation of regional myocardial perfusion in patients with coronary artery disease is possible with positron emission tomography and H$_2^{15}$O. Further studies will be necessary to prospectively determine sensitivity and specificity. (Circulation 1988;78:612–620)

Noninvasive delineation of regional myocardial perfusion in patients has been difficult. Conventional scintigraphy is limited by spatial resolution and by incomplete correction for attenuation and spillover of radioactivity from sources overlying or underlying the myocardium. Positron emission tomography (PET) has been developed in part to overcome these limitations. It permits accurate estimation of the distribution of compounds of physiological interest labeled with positron-emitting isotopes within the limits of spatial and temporal resolution of the particular instrument used and in keeping with the path lengths of positrons in tissue.

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$^{13}$N-labeled ammonia$^{2-4}$ and $^{82}$Rb$^{5-7}$ have been successfully used to estimate regional myocardial blood flow in experimental animals and in patients. $^{82}$Rb is particularly attractive in the clinical setting because it is generator produced, which obviates the need for an on-site cyclotron. However, the use of these tracers for quantification of flow entails some limitations. Single-pass extraction and myocardial retention of $^{13}$N-labeled ammonia are influenced by flow$^{2,3,8}$ as well as by cell membrane integrity$^9$ and the metabolic state of the myocardium$^{8,9}$. Extraction of $^{82}$Rb also varies with flow and metabolism.$^{5,6,10}$

An ideal perfusion tracer should be either freely diffusible or completely extractable and retainable by myocardium on a single pass through the coronary circulation without having its kinetics altered throughout the range of flow studied or by the metabolic status of the myocardium. $^{15}$O-labeled water (H$_2^{15}$O) is essentially a freely diffusible tracer in the heart with uptake that does not vary despite wide variations in flow rate$^{11}$ or changes in the metabolic state of myocardium associated with prolonged ischemia or reperfusion.$^{11-14}$ $^{15}$O is a useful
tracer for the assessment of myocardial perfusion because its short half-life (2.1 minutes) allows rapid, sequential measurement of perfusion in myocardium of patients during resting conditions or during pharmacologically induced vasodilator stress.

We and others have shown that PET with $^{15}$O-labeled water can be used to quantify myocardial blood flow throughout wide ranges of flow in experimental animals. We recently demonstrated that blood flow thus detected distal to a subcritical coronary stenosis was normal at rest but that the hyperemic response to dipyridamole was attenuated in regions distal to stenoses of 50–70% diameter. The present study was designed to determine whether this approach is possible in patients and to assess its usefulness in delineating impaired nutritive flow in patients with angiographically documented coronary artery disease.

**Subjects and Methods**

**Preliminary Studies: Training Set**

Before beginning the studies described below, we tried vigorously to define the optimal protocols for appropriate positioning of patients, administration of tracer, data acquisition, and data processing. These protocols involved preliminary studies of 64 subjects (47 men and 17 women), who were 26–83 years of age (mean, 53.7 years). Coronary artery disease was documented in 46 subjects either by history and electrocardiographic changes or by angiography. Studies were performed during resting conditions exclusively in 24 subjects and before and after infusion of dipyridamole in 40 subjects. The administered dose of $^{15}$O varied from 20–170 mCi (mean, 77.8 mCi), that is, 0.29–1.98 mCi/kg. $^{15}$O was administered as a bolus, by a constant infusion, or as a bolus followed by infusion. Data collection and processing intervals varied from 40 seconds to 5 minutes. The initial studies, which were performed after a bolus administration of 50–120 mCi H$_2^{15}$O, resulted in a loss of data because of saturation of detectors and data transfer rates. Conversely, lower doses administered by constant infusion resulted in counting data that were too low for suitable analysis of images. The protocol that was finally chosen was optimized to balance instrument performance characteristics (avoiding saturation of detectors and data transfer rates), dosimetry, counting statistics, and brevity of data collection.

**Subjects: Test Set**

Thirty-three subjects of whom 24 were patients with angiographically documented coronary artery disease and nine who were normal volunteers (controls) were studied with the optimal protocol. The mean age of control subjects was 30 years (range, 23–68 years). Five were men, and four were women. Eight were younger than 30 years of age. All had normal electrocardiograms, no history of cardiac disease, and no evident cardiac risk factors. One was a 68-year-old man who underwent coronary angiography for diagnosis of atypical chest pain and was found to have angiographically normal coronary arteries.

The mean age of patients was 55 years (range, 37–72 years). Eighteen were men, and six were women. Eight had suffered remote myocardial infarction. Each had undergone coronary angiography within the 12 months preceding the PET studies (mean, 51 days; range, 0–341 days). None had left ventricular hypertrophy, and all had normal left ventricular ejection fractions at rest (mean, 0.68 ± 0.09).

**Quantitative Angiography**

All narrowings of coronary arteries other than minor luminal irregularities were analyzed with computer-assisted image reconstruction. Briefly, films obtained in orthogonal biplane views were projected at fivefold magnification, and cineframes were selected for lesion clarity at comparable points in the cardiac cycle in each view of a perpendicular projection pair. The arteriographically defined lumen was traced by an experienced angiographer from the proximal to the distal portion of the stenosis. A segment of the catheter of known dimensions was traced to provide a scaling factor. The border information was digitized by a MacTablet (Summagraphics, Fairfield, Connecticut) interfaced with a Macintosh SE computer and transmitted by telephone to the Cardiovascular Research and Training Laboratory at the University of Washington, Seattle, Washington, for analysis.

The computer program that was used reduces the lesion image to scale by compensating for pincushion distortion, out-of-plane magnification, and optical magnification with calibrations obtained from each x-ray system used in each catheterization laboratory. The program calculates and prints luminal diameter of the "normal" proximal and distal segments and of the point of greatest narrowing. Percent diameter and area reduction in the stenosis are computed, as well as lesion length, estimated atheroma mass, stenosis Reynolds number, flow resistance, and peak intimal shear stress. The variability of results with this method averages ±3% for percent stenosis estimates and ±0.10 mm for minimum diameter estimates.

**Protocol**

The experimental protocol was approved by the Human Studies Committee of the Washington University Institutional Review Board, and the nature of the study was explained to each subject before obtaining written, informed consent. Patients and control subjects were studied in a random sequence. Each subject was positioned in Super PETT I, a whole-body positron tomograph that permits simultaneous acquisition of data sufficient for reconstruction of seven transaxial slices with a center-to-center slice separation of 1.5 cm and a slice thickness of 1.14 cm. A tomographic transmission scan of the
chest was obtained with a $^{68}$Ge/$^{51}$Ga ring source to correct for photon attenuation of the emitted radiation. This scan was viewed before the collection of emission data to ensure proper positioning of the patient so that four to six of the seven cross-sectional imaging planes were through the heart. Correct positioning was maintained throughout the study with the use of a light beam and indelible marks on the subject's torso. Polyurethane molds were made individually for each subject before each study and were used to stabilize the head, neck, and upper torso of the subject so that movement between data acquisitions was minimized. Emission data were collected in high-resolution mode.

To assess relative myocardial blood flow with PET, we used $H_2^{15}$O and a method previously developed and validated in experimental animals in our laboratory.\textsuperscript{11,13} After collection of attenuation data, 0.5 mCi/kg $H_2^{15}$O was injected as a bolus through a large-bore catheter inserted into an antecubital vein. Data collection began at the start of the infusion for 150 seconds, in list mode, and with time-of-flight correction.\textsuperscript{16} Filtered reconstructions provided resolution within the plane of reconstruction of 13.5 mm. After a 5-minute interval to allow decay activity of the tracer to baseline levels, we administered by inhalation 40–50 mCi $^{15}$O-labeled carbon monoxide ($C^{15}$O) to label the blood-pool. After a subsequent interval of 30–60 seconds to allow clearance of carbon monoxide from the lungs, data were collected for 5 minutes. After completion of data collection during baseline conditions, an intravenous infusion of 0.56 mg/kg dipyridamole was administered over 4 minutes (Persantine, supplied by Boehringer-Ingelheim, Ridgefield, Connecticut). After 4.8±2.3 minutes to permit development of peak responses of flow, the tomographic imaging sequence was repeated. $C^{15}$O was administered again after the dipyridamole and $H_2^{15}$O data acquisition to minimize any inaccuracy in subtraction (see below) that may result from a change in cardiac dimensions with dipyridamole.

**Determination of Regional Myocardial Blood Flow**

To correct for the contribution of radioactivity emanating from intravascular tracer to apparent tissue radioactivity, blood-pool images were obtained after administration by inhalation of 40–50 mCi $^{15}$O. This tracer binds avidly to red blood cells. In each pixel, the $H_2^{15}$O activity attributable to tracer in the vascular pool was determined from the product of $C^{15}$O counts in that pixel and the ratio of $H_2^{15}$O to $C^{15}$O counts in the left ventricular blood-pool. The calculated value was subtracted on a pixel-by-pixel basis from total $H_2^{15}$O activity to yield tissue $H_2^{15}$O activity.\textsuperscript{11}

Data were reconstructed into cumulative 120-second frames corrected for isotope decay. Images of the distribution of myocardial $H_2^{15}$O were analyzed by interactively defining transmural regions of interest. Three regions of interest (septal, anterior, and lateral) were defined for midventricular reconstructions, and four regions of interest (septal, anterior, lateral, and posterior) were defined for the more apical reconstructions. To determine the reproducibility of the analysis, both interobserver and intraobserver variability were characterized. With observers blinded to all clinical and angiographic information, as well as to previous tomographic analysis where applicable, the range of variability between analyses was within 10% for both interobserver and intraobserver comparisons.

Each defined myocardial region of interest was compared with the region in the same tomographic reconstruction that contained peak radioactivity. Relative radioactivity was expressed as percent peak activity for each reconstruction. The single region with the lowest relative activity was identified and used as reference for purposes of comparisons between studies.

**Statistics**

Student's $t$ test (paired or unpaired as appropriate) was used to compare groups by normally distributed variables such as hemodynamics. Nonparametric statistics were used when appropriate, and comparisons were made with the Mann-Whitney $U$ test and the Wilcoxon signed rank test. Data are presented as mean ± SD.

**Hemodynamics**

Heart rate, blood pressure, and the electrocardiogram were recorded before and after baseline imaging and at least every 2 minutes after the initiation of the infusion of dipyridamole until tomography was complete. In control subjects, heart rate increased from a baseline of $61±7$ beats/min to $87±11$ beats/min at an average of 8.7 minutes after beginning the infusion of dipyridamole ($p<0.001$). Mean blood pressure changed from $86±8$ mm Hg to $91±10$ mm Hg ($p=NS$). In patients, heart rate increased from $66±12$ beats/min ($p=NS$ compared with control subjects) to $84±12$ ($p=NS$ compared with control subjects) at an average of 6.4 minutes after onset of infusion of dipyridamole ($p<0.001$ compared with baseline). Mean blood pressure at baseline was $99±15$ mm Hg ($p<0.05$ compared with control subjects) and did not change significantly after dipyridamole infusion, $101±16$ mm Hg ($p=NS$ compared with control subjects).

Dipyridamole induced occasional flushing or headache. In five patients, attenuating the effects of dipyridamole was necessary because of prolonged angina. In these patients, aminophylline was administered after imaging.

**Tomographic Estimates of Blood Flow**

Three tomographic reconstructions that were obtained in a representative study of a normal
control subject are shown in Figure 1. The upper-left panel shows a midventricular PET reconstruction obtained after the intravenous infusion of H\textsubscript{2}\textsuperscript{15}O. The upper-right panel shows a reconstruction at the same level obtained after the inhalation of C\textsuperscript{15}O. The lower-left panel shows the myocardial distribution of H\textsubscript{2}\textsuperscript{15}O imaged as the subtraction of radioactivity due to H\textsubscript{2}\textsuperscript{15}O in blood on a pixel-by-pixel basis after normalization for blood-pool activity in a left ventricular region of interest. Myocardial images obtained with positron tomography are shown with a transaxial orientation. The most cephalad reconstructions show only the basal aspect of the anterior wall. The midventricular sections show the septum and lateral walls as well. The discontinuity that is posterior in midventricular sections is attributable to the mitral valve apparatus and atria that are below the spatial resolution of positron tomography. The most apical sections show the posterior and inferior walls of the heart. In all reconstructions shown, the septum is on the left, the anterior wall is on the top, and the lateral wall is on the right.

Results in all normal control subjects showed homogeneous H\textsubscript{2}\textsuperscript{15}O activity in each left ventricular reconstruction, which is indicative of homogeneous perfusion. There were no regional disparities in activity of H\textsubscript{2}\textsuperscript{15}O at rest, and dipyridamole stress did not induce regional disparities. After dipyridamole infusion, all myocardial regions in reconstructions from control subjects exhibited at least 70% of peak myocardial H\textsubscript{2}\textsuperscript{15}O activity. An example of results from a normal control subject is shown in Figure 2. Results in patients with coronary artery disease showed significantly greater heterogeneity of H\textsubscript{2}\textsuperscript{15}O activity. An example of results from a patient is shown in Figure 3. Angiography 1 month before study had demonstrated a high-grade occlusion of the proximal left anterior descending artery and no other significant lesions. Tomographic reconstructions for this patient showed homogeneous H\textsubscript{2}\textsuperscript{15}O activity in the most cephalad section (top of figure) during resting conditions and vasodilator stress. The midventricular sections showed decreased accumulation of H\textsubscript{2}\textsuperscript{15}O in anterior and anteroseptal regions. The regional decreases of activity were marked in the rest study and became even more prominent after vasodilator stress.

To compare results from patients with coronary artery disease with those from normal control subjects, a "defect slice" was identified for each subject, that is, the single tomographic reconstruction that contained the region demonstrating the lowest H\textsubscript{2}\textsuperscript{15}O activity for the entire individual study. The resting and stress studies were analyzed separately so that a resting slice and a stress defect slice were identified. Normal control subjects would not be expected to exhibit perfusion defects during physiological conditions. Likewise, even a patient with diffuse, severe three-vessel coronary artery disease would be expected to have some regions of myocardium proximal to stenoses that nevertheless were perfused normally. Therefore, a very basal tomographic reconstruction that delineates only a small region of the heart may demonstrate no regional...
perfusion abnormalities. To avoid simply comparing normally perfused regions from patients with those from normal control subjects, the single tomographic reconstruction that contained the region with the lowest H$_2$O$_xy$ activity was identified for each subject and used as a reference. In normal control subjects, the diminished regional radioactivity that was identified most likely reflected reduction of count recovery because of partial volume effects.

In control subjects at rest, the region exhibiting the lowest H$_2$O$_xy$ activity yielded counts averaging 71 ± 8% of those in the region with peak activity (Figure 4). In patients, the region exhibiting the lowest activity yielded counts averaging 62 ± 17% of those in the region with peak activity (p = NS). In contrast, a distinction between the two groups became apparent when results after dipyridamole stress were considered. In the control subjects, activity in the region with the lowest activity averaged 77 ± 5% of that in the region with peak activity.

In patients, it averaged only 55 ± 22% of that in the region with peak activity (p < 0.01).

To further clarify how responses to dipyridamole differed in patients and control subjects, the relative homogeneity of activity in the tomographic reconstruction acquired after infusion of dipyridamole was compared with the relative homogeneity of activity in the reconstruction from the same anatomic level in the study at rest. Because the single region with lowest activity in the resting study of a given individual was not always the single region of lowest activity in the study after dipyridamole (especially in normal subjects in whom homogeneity of activity was the rule), we selected the region of lowest activity from the study after infusion of dipyridamole (i.e., the defect slice) and compared it with the same tomographic level of the ventricle from the resting study. This approach was designed to focus on the response of the myocardial region with minimal coronary flow reserve. As shown in Figure 5, normal subjects exhibited no difference.
between the mean percent peak activity in the study after infusion of dipyridamole compared with the resting study (77% both before and after dipyridamole). In contrast, patients exhibited a decrease of the mean percent peak activity in the study after infusion of dipyridamole compared with the rest study [55 ± 22% compared with 70 ± 18% (p<0.01)].

In studies involving a freely diffusible tracer, the tracer should measure perfusion alone. The metabolic state of the tissue (including infarction) should have no effect on the measurement. To determine whether the inclusion of patients with remote myocardial infarction introduced a bias in the patient group, data from the eight patients with previous myocardial infarction were analyzed separately as shown in Figure 6. During resting conditions in the patients with previous infarction, the region exhibiting the lowest relative activity yielded counts averaging 65 ± 19% of those in the region with peak activity. These are values not significantly different from those in patients without previous infarction in whom the region demonstrating the lowest relative

activity exhibited counts that averaged 60 ± 16% of those in the region with peak activity (p=NS). Likewise, in the studies performed after infusion of dipyridamole, there was no difference in the mean percent peak activity in patients with previous infarction compared with values in patients with no previous infarction (54 ± 24% vs. 55 ± 22%, p = NS) although these values were distinctly different from those in normal subjects.

The coronary lesions, defined angiographically, in the 24 patients were compared with the locations of the region of lowest activity after dipyridamole infusion, defined by PET as shown in Table 1. Because our analysis delineated relative myocardial perfusion (i.e., one region of myocardium was defined as having maximal activity for comparison with others) only one “defect” region was identified for each subject. Thus, in patients with stenoses in more than one vessel, only the region with the lowest relative perfusion was selected. All but two patients exhibited a tomographic perfusion defect in a locus corresponding to the distribution of tissue supplied by one of the stenosed vessels. In these two patients (patients 5 and 7), the stenosis involved a small, nondominant circumflex vessel, and the region of lowest activity was in the anterior wall. Although there were no discrete stenoses in the left anterior descending artery in either patient, diffuse luminal narrowing was present throughout the left anterior descending coronary artery in both. This may account for the relative decrease in counts in the anterior wall in these two patients.

**Discussion**

Nutritive myocardial blood flow distal to coronary stenoses is dependent upon the presence or absence of multiple lesions in a series, the geometry
of individual lesions, the lengths of the narrowed segments, and collateral flow among other factors. In our study, angiographic data were used as a "gold standard" to compare H215O PET data. However, conventional interpretation of angiograms underestimates severity of lesions in as many as 95% of vessels with greater than 60% diameter stenoses. Even when angiograms are analyzed quantitatively, the hemodynamic significance of stenoses is not always clear. In our study, angiographic data were used as a "gold standard" to compare H215O PET data. However, conventional interpretation of angiograms underestimates severity of lesions in as many as 95% of vessels with greater than 60% diameter stenoses. Even when angiograms are analyzed quantitatively, the hemodynamic significance of stenoses is not always clear. Assessment of myocardial perfusion with H215O and PET is designed to characterize noninvasively the functional significance of coronary stenoses at rest and in limiting coronary flow reserve.

Dipyridamole increases coronary blood flow without producing a concomitant increase in myocardial oxygen demands. Accordingly, coronary flow reserve can be assessed after administration with minimal risk of myocardial tissue damage. Results of many studies document the usefulness of dipyridamole-induced vasodilation for detection of limitation of coronary flow reserve. Many investigators have used single photon-emitting radionuclides such as 201Tl for this purpose. Single photon emission computed tomography (SPECT) has been useful, but quantification is limited because extraction and retention of 201Tl vary with flow and with changes in the metabolic activity of myocardium. The positron-emitting tracers 13NH3 and 82Rb have been used successfully to characterize alterations of myocardial perfusion in patients with coronary artery disease. Images obtained with both are of high quality. Because extraction and retention of both tracers are influenced by the metabolic states of myocardium, as well as by perfusion, these tracers can be used to evaluate myocardial meta-

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RCA, right coronary artery; LAD, left anterior descending coronary artery; Cx, circumflex coronary artery.

†Determined by positron emission tomography.
‡Collateral vessels angiographically visible.
bolic activity, as well as flow, if enough tracer can be delivered to the myocardial segment in question.

Water labeled with $^{18}$O is almost freely diffusible even with hyperemic flow. Its uptake is essentially unaltered by changes in the myocardial metabolic state. Accordingly, its use is compatible with several assumptions inherent in application of a one-compartment mathematical model for quantification of perfusion. Because of its short half-life, sequential measurements of perfusion can be made with a low radiation burden. The whole-body dose for combined rest and dipyridamole studies [two H$_2^{15}$O (25–30 mCi) studies and two C$_2^{15}$O (40–50 mCi) studies] is 0.25 REM/70 kg.

Nevertheless, several limitations must be considered. Low counting statistics after blood-pool subtraction (a range of 100–400 counts/voxel/min in normal myocardium in studies during resting conditions and after infusion of dipyridamole) result in images that are “noisier” than those with $^{13}$NH$_3$ or $^{82}$Rb. Results of rest studies, with their intrinsically lower counting statistics, are affected. As noted previously, the region of lowest activity in the study of a subject at rest was not always identical in the same subject after dipyridamole infusion primarily because of the low signal-to-noise ratios in resting images. In patients, no significant difference in the average percent peak activity in the region of lowest activity in the studies during resting conditions compared with after dipyridamole infusion (62 ± 17% vs. 55 ± 22%) was evident. The physiological response to dipyridamole became evident, however, when results in the defect slice in the study after dipyridamole infusion were compared with those results in the same tomographic sections from the resting study. There was a decrease in the mean percent peak activity in patients (70 ± 18% to 55 ± 22%), and there was no change in control subjects. An additional limitation is the need to label the blood pool with C$_2^{15}$O after each H$_2^{15}$O study (i.e., both at rest and after infusion of dipyridamole) to minimize inaccuracies in subtraction that may result from a change in cardiac dimensions.

In this study, we have demonstrated the feasibility of noninvasive characterization of myocardial perfusion with H$_2^{15}$O and PET in human subjects. Although differences in response to dipyridamole were assessed qualitatively with the method of regional analysis, patients with coronary artery disease were distinguished from control subjects. The presence of a remote myocardial infarction does not appear to bias results. In addition, regions of lowest relative perfusion correlate well with regions of supply distal to angiographically defined coronary stenoses. Further studies involving a larger control group and patients with a wide spectrum of coronary artery disease will be necessary to prospectively determine the sensitivity and specificity of this imaging technique.

Some present instrumentation limitations preclude quantification of flow in absolute terms by PET. As we have shown previously, cardiac and respiratory motion impair absolute quantification of radiation emitted from the myocardium. In addition, whenever the dimensions of the object being imaged are less than twice those of the resolution of the instrument, apparent radioactivity in the reconstruction is less than actual radioactivity because of decreased count recovery (partial volume effect). We have observed previously that myocardial radioactivity determined in the anterior region with PET is somewhat low compared with radioactivity assayed by direct counting of tissue samples because of the lower recovery of counts from the anterior wall compared with recovery in the lateral, septal, and posterior walls. A transverse section through the chest of a dog provides a slightly oblique section through the posterior left ventricular wall, which results in a thicker cross section than that of the anterior wall and an apparent decrease of radioactivity in the anterior wall because of partial volume effects. Corresponding tomographic anatomy pertains in human subjects as well although midventricular reconstructions are much less affected than more apical reconstructions. Thus, systematic underestimation of counts may occur in anterior regions in normal control subjects and in patients. In addition, the data transfer rate of our current tomograph limits the administered dose of H$_2^{15}$O to 0.5 mCi/kg injected as a bolus. With future modifications, this limitation should be overcome.

Quantification of myocardial perfusion with H$_2^{15}$O and PET is likely to overcome many limitations of alternative approaches. Recently, determination of the arterial input function obtained from a region of interest in the left ventricular blood-pool has been validated in dogs, obviating the need for invasive arterial blood sampling. With a method of correction for spillover and partial volume effects originally proposed by Henze et al and validated in our laboratory with phantoms, we have recently demonstrated the feasibility of quantification of flow in dogs and in healthy, human volunteers in absolute terms. Thus, objective evaluation of effects of interventions designed to improve nutritional myocardial flow should be obtainable in patients.

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References


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