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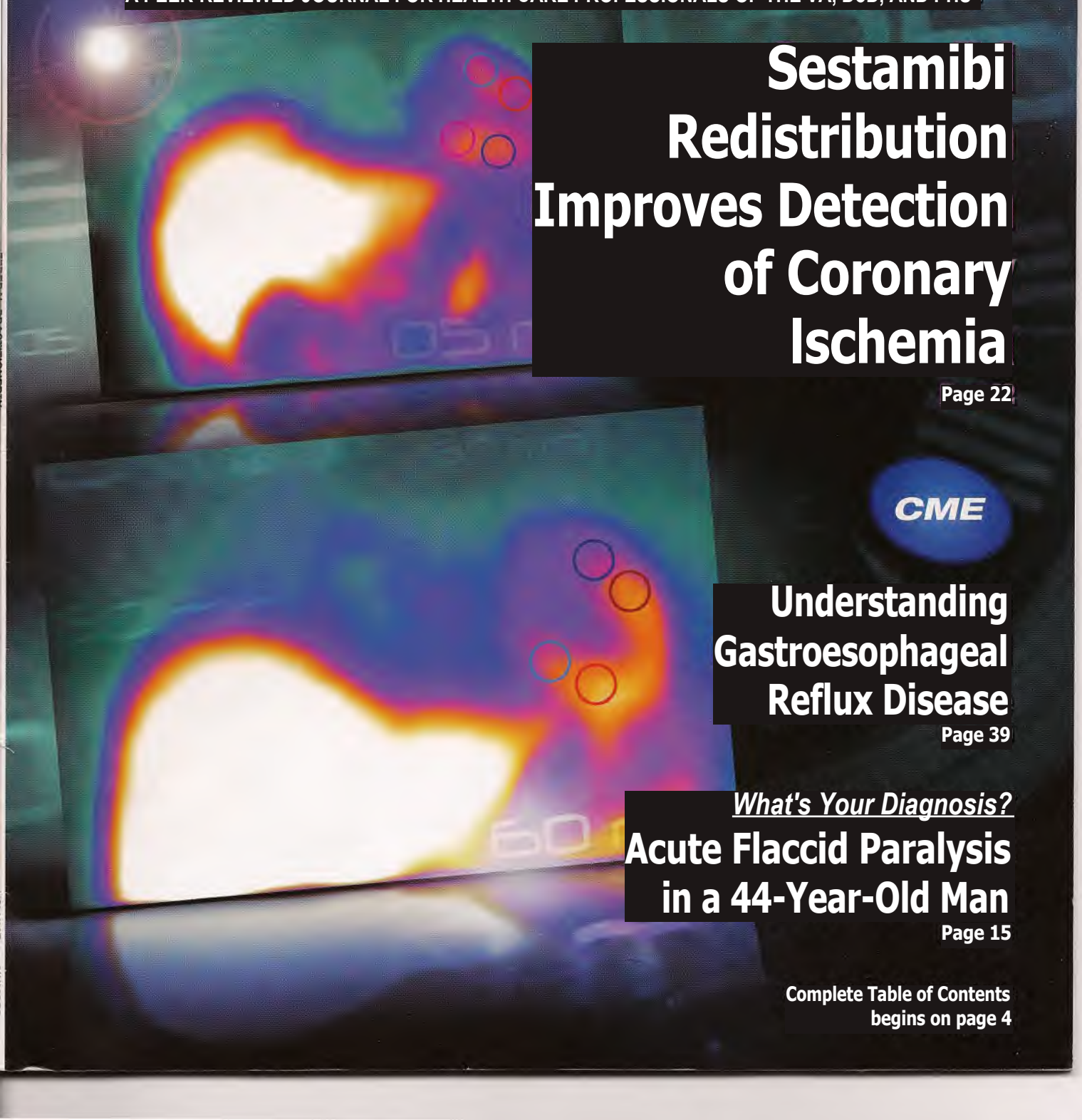

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Renewed Application of an Old Method Improves Detection of Coronary Ischemia: A Higher Standard of Care

Richard M. Fleming, MD, Gordon M. Harrington, PhD, Riaz Baqir, MD, Scott Jay, MD, Sridevi Challapalli, MD, Kayla Avery, CNMT, and Jim Green, CNMT

The diagnostic utility of traditional nuclear cardiac imaging is enhanced by using modern technology to compare absolute regional radioactive counts at two points in time during stress/stress testing.

Nuclear cardiac imaging began in 1927 with the first in a series of studies by Blumgart and Yens, which found that measuring the rate and magnitude of nuclide transfer from right arm to left arm could diagnose the presence or absence of heart disease.[1] This work was not only the first nuclear study of the heart, but the first description of quantification of disease by using a Geiger counter. The radioactive tracer thallium-201 was introduced in 1975, followed by contemporary tracers, such as technetium-99m sestamibi.

Many studies have shown that knowledge of sestamibi redistribution, as revealed by sequential stress imaging, improves detection of heart disease.[2] While these studies quantified sestamibi differences in heart to lung ratios, they did not quantify absolute radioactive counts—although the computer software to accomplish this is available. The extra step of quantifying absolute counts allows the clinician to better interpret disease by seeing information the computer uses to assign various shades of grey or color to the image.

When applied to multiple images under the same state (namely, five-minutes and 60-minutes poststress), quantifiable absolute counts can then be compared using today's single photon emission computed tomography (SPECT) cameras. Using these cameras, the clinician can look for the actual change in isotope concentration that results from various levels of ischemia—caused by differences in a coronary artery's ability to vasodilate to meet coronary blood flow demands and coronary artery blockage (Figure 1)[7]. This clinical information is diagnostically important and allows the primary care physician to determine whether medical management or an invasive cardiac procedure is the next best step in caring for the patient.

To demonstrate the advantages of obtaining absolute radioactive counts in sequential stress imaging, we designed a study to assess the clinical diagnostic utility of time-course myocardial perfusion measurements following a single injection of sestamibi to determine ischemia. We compared the results of coronary angiography—used to determine the extent of coronary lumen disease—with (1) myocardial perfusion imaging (MPI) findings using a redistribution equation we developed (the Fleming-Harrington equation) to quantify absolute radioactive counts, and (2) results of rest/stress imaging.

BACKGROUND

In 1959, Gorlin demonstrated that resting images were not diagnostically useful for ischemia and should not be used for this purpose.[8] Further discussions by Love questioned whether nuclear imaging would ever be clinically useful due to the absence of clinically useable isotopes.[9] Although the introduction of thallium-201 partially allayed those fears, the tracer was plagued with a long half-life of 72 hours. Nonetheless, thallium-201 was clinically useable for detecting ischemia by qualitatively evaluating two poststress images (at one and four hours).

The unfortunate use of the terms "stress" and "rest,"[10] however, resulted in a misunderstanding of the

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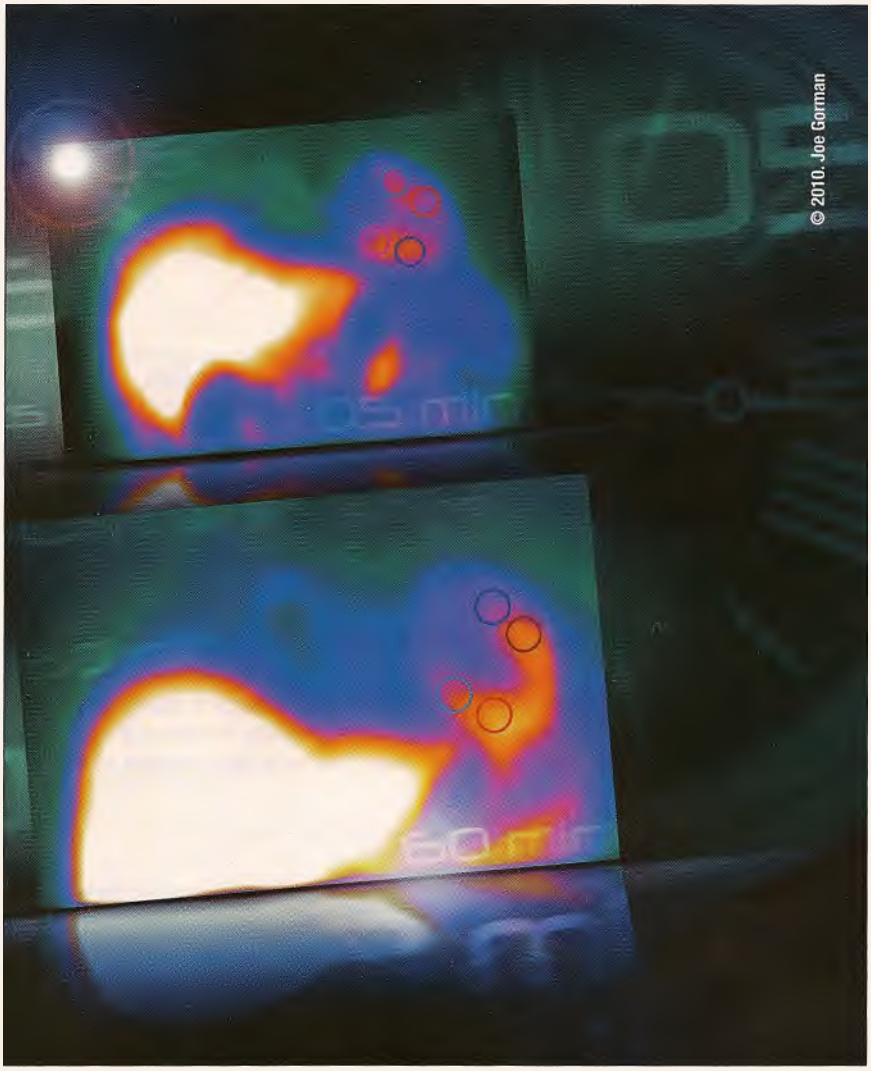
established principles laid out by Blumgart and Yens—that comparisons should be made under same-state conditions, either stress or rest. Maublant and Crane demonstrated that use of sestamibi had a washout of 28 minutes and that this washout increases under ischemic conditions because of mitochondrial calcium overload; the clinical importance of this finding had been underrecognized previously.[11,12]

Nuclear MPI using SPECT for the detection of ischemia is accomplished by comparing two images of the heart obtained at two points in time. While Blumgart emphasized comparisons under same-state conditions, clinicians since have emphasized rest/stress comparisons. The resting image more correctly can be used to determine if myocardial injury has occurred previously, but cannot be utilized to determine if ischemia is present.[1,8]

Nonetheless, most diagnosticians today compare the rest to stress images and conclude that when the images have identical findings (matching defects) no ischemia is present. However, injury/infarction noted on the resting image in the absence of ischemia (stress image) is inconsistent with the disease process as we know it, and matching defects clearly cannot mean that a region of infarction has no ischemia; rather, it merely means that the infarction is the result of ischemia. In other words, one cannot have myocardial infarction in the absence of an underlying ischemic insult to the region. Therefore, matching rest/stress images define ischemia present at the site of injury/infarction and not a simplistic absence of ischemia.[3]

Much controversy followed the institution of sequential stress imaging, which found instances of redistribution with thallium-201 after four hours but not after two hours.[4,5] The presence or absence of washin was attributed to cell viability and thus, differentiated ischemia with infarcted tissue (matched defects) from ischemia with viable tissue (nonmatched defects). Most clinicians treat contemporary tracers, such as sestamibi, as though they do not undergo redistribution (washin or washout), despite ample evidence to the contrary, including a recent investigation by Fallahi and Beiki.[2-6,10,12,16]



Recent research utilizing knowledge of sestamibi redistribution and replacing Blumgart's Geiger counter with today's SPECT camera to compare radioactive counts, both quantitatively and qualitatively, has increased the diagnostic accuracy of detecting congestive heart failure, cardiomyopathy, coronary vasospasm, and, as our initial studies established, the relationship between "inflammation" and coronary artery disease.[2-5,r1-25] In recent work, we have better defined the relationship between sestamibi redistribution and the extent of actual coronary artery disease seen in the angiography suite—yielding substantially increased diagnostic accuracy in

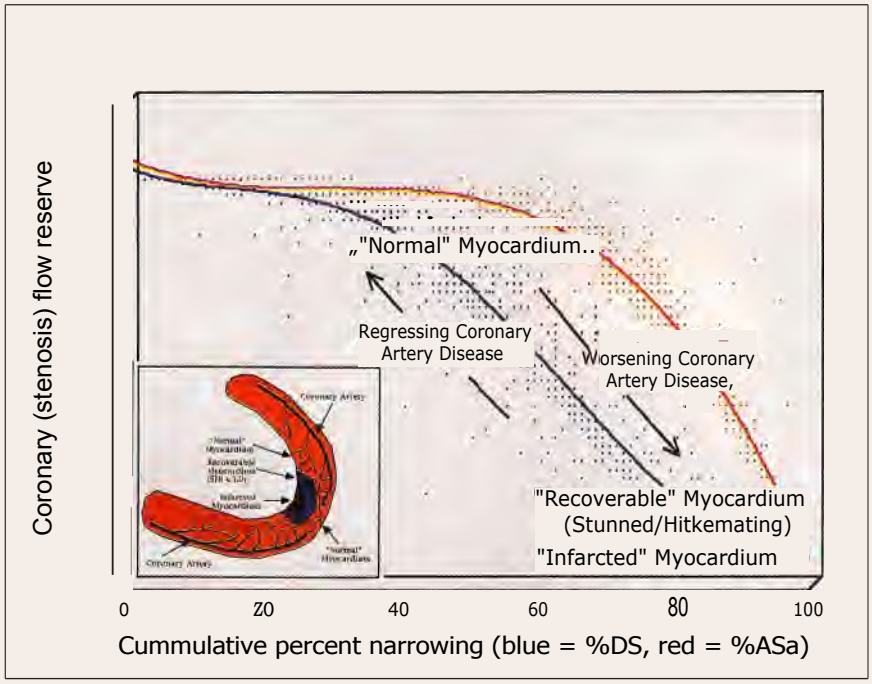


Figure 1.[7] Relationship between stenosis flow reserve and percent diameter stenosis (%DS), demonstrating that as arteries become more critically narrowed they are less able to vasodilate upon demand, requiring a longer time to achieve isotope equilibrium. a%AS = percent area stenosis.

the detection and evaluation of coronary ischemia.[26,27] The study we present here is a follow-up to our most recent work measuring sestamibi redistribution and comparing the findings with results from coronary angiography and rest/stress images.[28]

STUDY DESIGN AND PARTICIPANTS

We studied 120 men and women (aged 25 to 82 years) suspected of having ischemic heart disease, using both the rest/stress image comparisons approach and a one-day redistribution "stress/stress" approach (Figure 2). The individuals underwent exercise or pharmacologic stress with injection of technetium-99m isotope (sestamibi) per standardized MPI protocols using lexiscan (n = 61), adenosine (n = 30), dobutamine (n = 4), or treadmill (n = 25) stress.

Patients arrived at the nuclear laboratory in a fasting state according to each institution's approved protocols for MPI. Specific institutional review board (IRB) requirements were reviewed. Patients underwent additional imaging, but they did not receive further injections of radioactive materials nor were they placed under additional exercise or pharmacologic "stress"; thus, the additional acquisition of redistribution information already present (but not previously collected) did not require additional IRB approval. Therefore, use of standard patient informed consent was determined to be appropriate.

We obtained intravenous access and acquired resting images after intravenous injection of 9 to 11 mCi (333 to 407 MBq) of sestamibi per protocol. Patients returned to the lab per institution protocol to undergo the stress component of the study where they underwent either exercise (treadmill) or pharmacologic stress. Following standard protocols already described in the medical and scientific literature, we injected intravenously a bolus of sestamibi (28 to 32 mCi, 1036 to 1184 MBq) followed by a bolus of normal saline to ensure adequate delivery of the radioactive isotope into the venous system. Five minutes following delivery of sestamibi, a SPECT camera was used to obtain a five-minute image (anterior slice, single-head camera) or images (anterior and lateral slices, multiple-head camera). Fifty-five minutes later (60-minutes poststress), participants returned to the lab for final images.

DATA COLLECTION AND ANALYSIS

Image comparisons and redistribution calculations

We evaluated rest/stress images using visual, qualitative slice-to-slice comparisons. For the redistribution calculation, we drew regions of interest (ROIs) using the five-minute poststress images to quantify radioactive counts, including total heart and lung, basal and mid anterior, basal and mid anterolateral, basal and mid inferior-posterior, and basal and mid inferoseptal regions (Figure 3). We avoided the issue of cardiac creep (a form of gradual internal heart motion) by positioning the camera over the cardiac silhouette for each set of images and not leaving the camera in a fixed position over the chest wall.

We obtained dynamic images 55 minutes later and drew ROIs to match the ROIs of the five-minute images (Figure 4). Although we compared regional wall motion and ejection fraction information, we do not report th-s: 12-7 z": here as they are not relevant to thk. investigation.

We calculated redistribution results for total heart and lung and each of the eight vascular regions from the ROIs using the following equation (the Fleming-Harrington redistribution washin-washout [FHRWW] rate)[2,26,27]:

R (%) = (ROI counts [region] at 5 minutes – ROI counts [region] at 60 minutes) / (ROI counts [region] at 5 minutes) x 100 – 10

The calculation of washout is a reflection of changes in radioactive counts in each ROI measured at five minutes and again at 60 minutes. To obtain percent change, the result is multiplied by 100. Finally, if sestamibi were to be retained and not washout, a decay of 10% would be expected during the 55 minutes between the five-minute and 60-minute images; for that reason, 10% is subtracted from the result to reflect the true change in the amount of sestamibi over the course of time between the two images. This equation may be simplified mathematically as follows:

If the 5-minute counts = x, the 60-minute counts = y, and the percent washout = w multiplied by 100, then:

$w = (x - y)/x - 0.1 = x/x - y/x - 0.1 = 1.0 - y/x - 0.1 = 0.9 - y/x$ = .9 – 60-minute counts / 5-minute counts.

Comparison with coronary angiography

We then compared results of FHRWW for each vascular territory with both the rest/stress imaging results and the coronary angiography results. Angiography was performed using institutional standard practice guidelines to determine the extent of coronary artery narrowings (percent diameter stenosis [%DS]) for each of the three epicardial coronary arteries (left anterior, circumflex, and right coronary artery) and their branches in individuals who had findings of ischemia

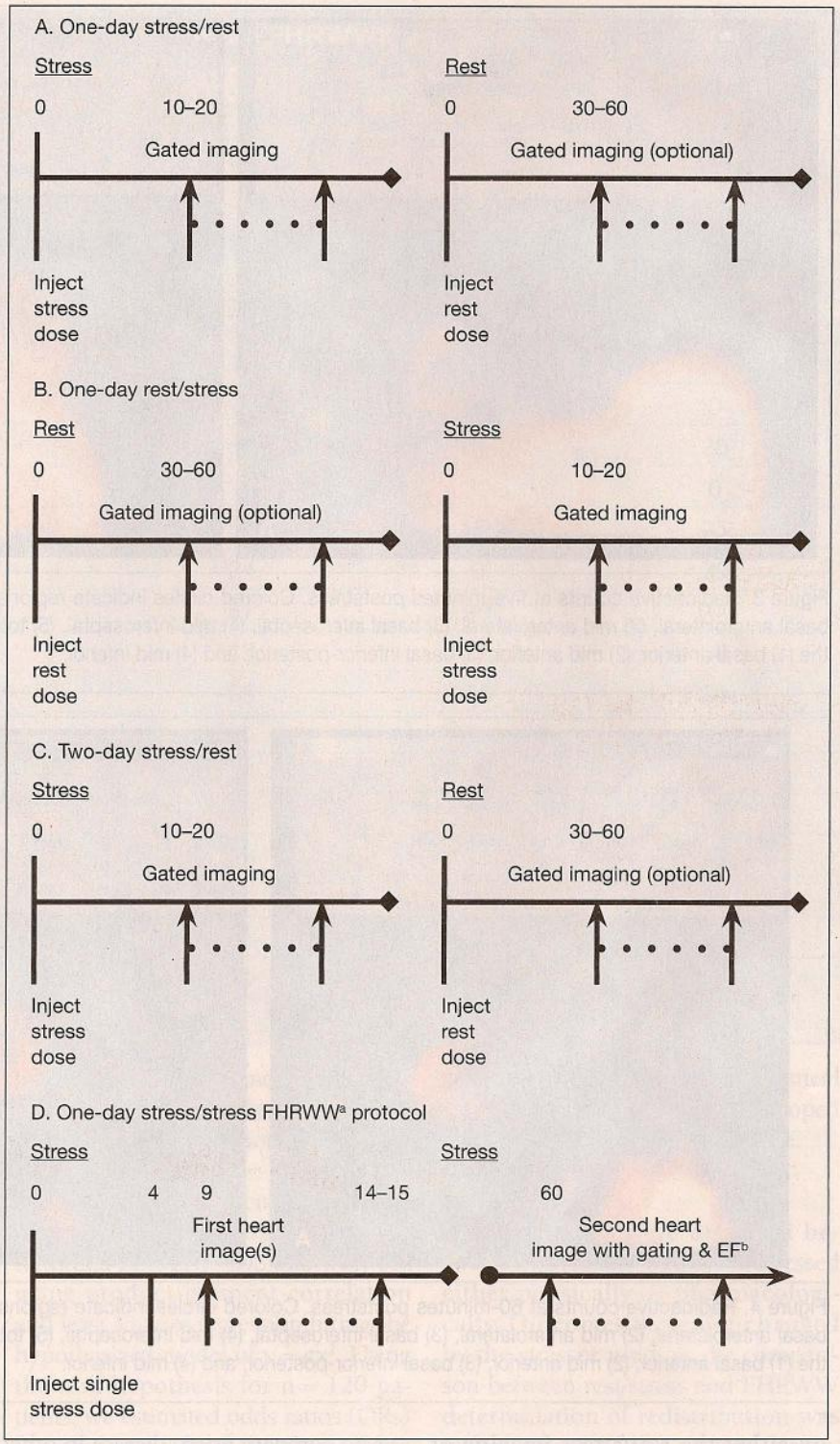


Figure 2. Multiple imaging protocols indicating time (in minutes) when doses should be administered and when imaging should be conducted. [a]FHRWW = Fleming-Harrington redistribution washin-washout. [b]EF = ejection fraction.

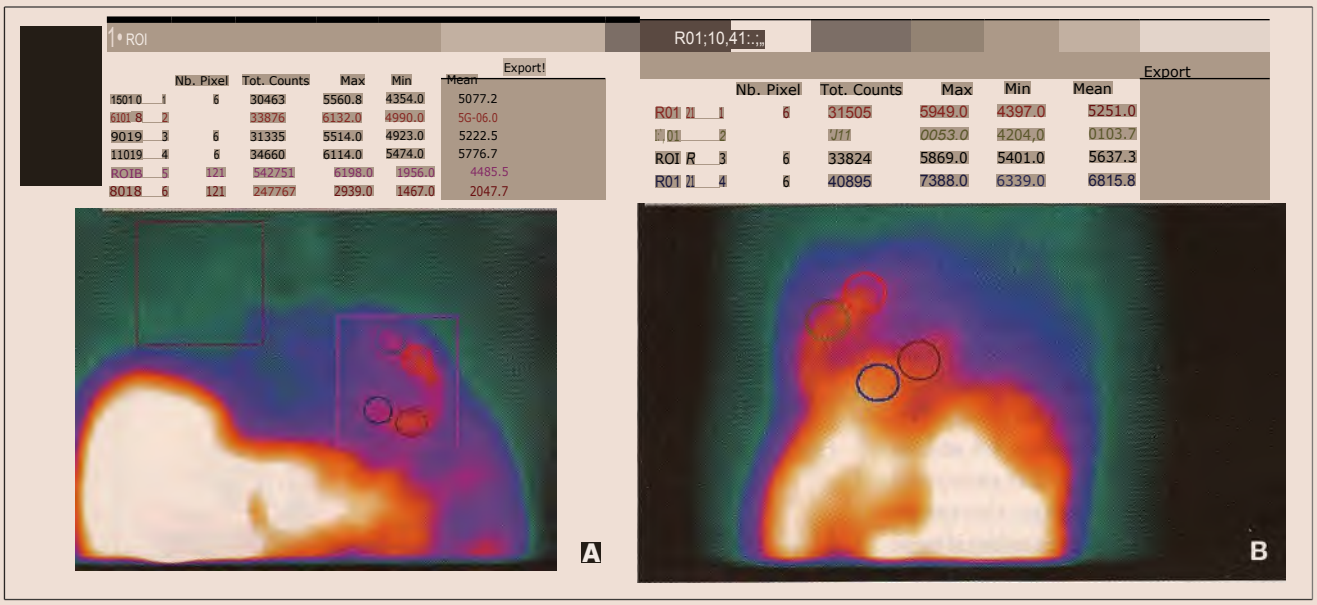


Figure 3. Radioactive counts at five-minutes poststress. Colored circles indicate regions of interest (ROIs). (A) shows ROIs for the (1) basal anterolateral, (2) mid anterolateral, (3) basal inferoseptal, (4) mid inferoseptal, (5) total heart, and (6) total lung. (B) shows ROIs for the (1) basal anterior, (2) mid anterior, (3) basal inferior-posterior, and (4) mid inferior.

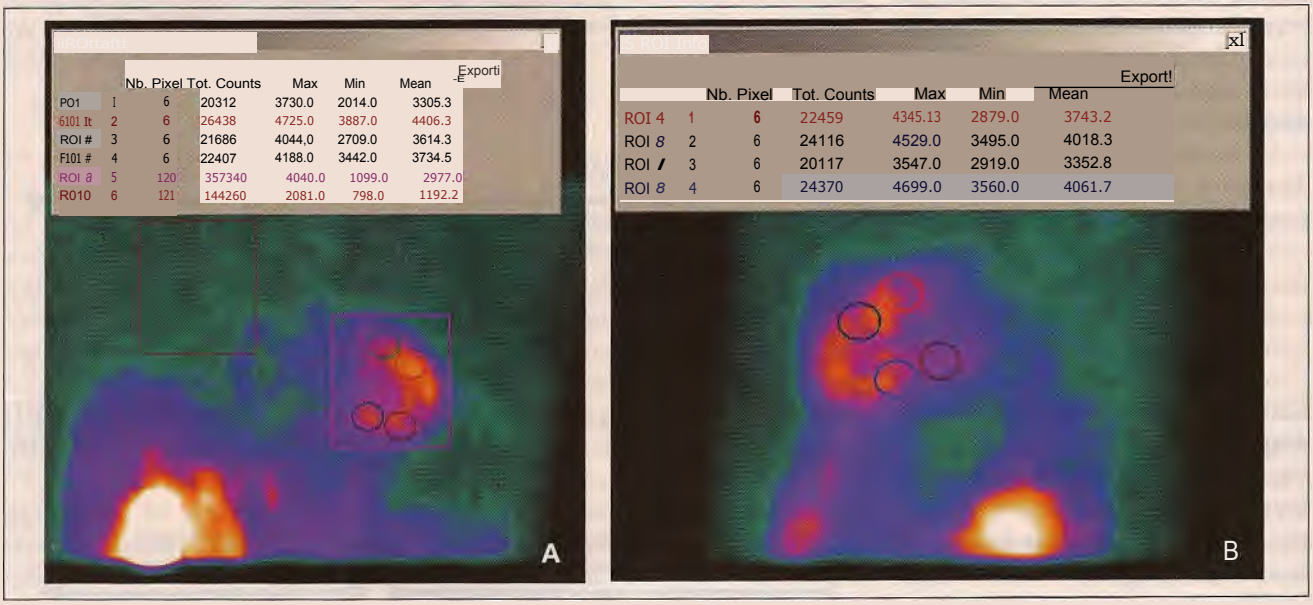


Figure 4. Radioactive counts at 60-minutes poststress. Colored circles indicate regions of interest (ROIs). (A) shows ROIs for the (1 basal anterolateral, (2) mid anterolateral, (3) basal inferoseptal, (4) mid inferoseptal, (5) total heart, and (6) total lung. **(B)** shows ROIs for the (1) basal anterior, (2) mid anterior, (3) basal inferior-posterior, and (4) mid inferior.

on either the rest/stress imaging or FHRWW redistribution measurement (Table 1). Participants with significant %DS in a particular artery with little or no coronary artery disease in other vascular territories provided comparisons of redistribution in regions with little coronary artery disease.

Of total study participants, 55% underwent coronary angiography based on clinician preference as well as findings of ischemia on either re-

Table 1.a Comparison of sestarnibi redistribution (FHRVVW and coronary angiography data

ID°	Total FHRWW	Anterior FHRWW	Inferior FHRWW	Artery matched anterior %DSd	Artery matched inferior %DSe
1	42	19	54	30	98
2	34	33	54	25	94
3	50	32	55	80	60
4	42	21	45	20	30
5	51	39	28	0	0
6	71	77	79	90	50
7	32	–39	–4	80	0
8	52	48	53	50	30
9	19	3	23	30	0
10	52	52	55	80	95
11	31	3	24	0	70
12	49	–11	57	90	100
13	–46	16	19	50	30
14	–58	–100	–65	85	20
15	0	0	4	0	0
16	47	42	47	100	70
17	42	21	42	60	80
18	52	32	66	25	70
19	48	22	42	40	50
20	63	40	61	85	98

'Table includes data for only a partial list of study participants. bFHRWW = Fleming-Harrington redistribution washin-washout. 'ID = identifying number of individual. 'Artery matched anterior %DS = percent diameter stenosis anteriorly for artery in region of FHRWW. 'Artery matched inferior %DS = percent diameter stenosis inferiorly for artery in region of FHRWW.

distribution or rest/stress imaging, obtained from a variety of commonly used protocols (Table 2). The variation in the radiopharmaceutical dose injections in these protocols illustrates the absence of a single accepted approach to MPI.

Statistical analysis

We quantified absolute isotope counts using the specific nuclear computer software provided by each of the nuclear camera companies; doing so allowed us to avoid the errors that occur when images are interpreted by making pixel-to-pixel qualitative comparisons—a common procedure. These absolute quantified counts were recorded with calculations of washout as noted above.

Correlation coefficients, confidence intervals (CIs), and P values were determined between %DS and washout using product-moment correlation and least squares regression fitting the hypothesized model of $y = cx^2$. Using the null hypothesis for n = 120 patients, we estimated odds ratios (ORs) for predicting final diagnosis from nuclear procedures. ORs were determined against coronary angiography results for both the rest/stress images and FHRWW images. Statistical analysis and graphics were developed using R-2.6.0 and GGobi software.

RESULTS

No differences were observed between individuals who were stressed either physically or pharmacologically. Outcomes were not changed by the stressor used, as the comparison between rest/stress and FHRWW determination of redistribution was independent of the type of stress. The use of regional wall motion information was used with both the rest/stress protocol and the FHRWW

Table 2. Radiopharmaceutical doses for MPIa protocols

Technetium-99m protocol	Range of technetium-99m doses, MBq (mean Res	Stress ute static)	Stress (60-minute dynamic)	Total
One-day stress/rest[26]	888-1332 (1110)		296-444 (370)	1184-1776 (1480)
One-day rest/stress[26]	296-444 (370)		888-1332 (1110)	1184-1776 (1480)
Two-day stress/rest[26]	888-1332 (1110)		888-1332 (1110)	1776-2664 (2220)
One-day stress/stress[24,26]		1110		1110

'MPI = myocardial perfusion imaging.

Table 3. ORsa for predicting final diagnosis from nuclear procedures

Diagnostic test	Diagnosis	Patients, no. Ischemic	Normal	Total	OR	Petob ORs Clc (95%)	logd (OR)	SEe
		52[9]	68[9]	120				
Rest/stress	Ischemic	30	14	44	4.88	2.3-10.3	1.57	0.37
	Normal	22	54	76				
FHRWW[1]	Ischemic	52	0	52	56.7	27.5-117.2	4.04	0.36
	Normal	0	68	68				

aORs = odds ratios. 'Pet° = alternative to the classic odds rafo. 'CI = confidence interval. 'log = logarithm. 'SE = standard error. 'FHRWW = Fleming-Harrington redistribution washin-washout. [9]number of patients determined by coronary angiography.

approach, which made it possible to look for wall motion abnormalities and ejection fraction using either approach. Since these observations are identical, regardless of which method was used to report ischemia, we do not report them here.

We analyzed the results of rest/stress image comparisons and FHRWW redistribution images and compared them with findings obtained from coronary angiography. For the rest/stress images, the OR for detecting ischemia was 4.88 with a CI (95%) of 2.3 to 10.3. For FHRWW, the OR was 56.7 with a CI (95%) of 27.5 to 117.2 (Table 3). When the results of these ORs were compared, the *t* value was greater than 6.6 ($P < .0001$).

We obtained results of %DS for each of the epicardial arteries and their branches, and plotted these results against the redistribution results for each of the eight ROIs. (We could do this only with the redistribution data, which provide quantitative results to compare with quantitative results obtained angiographically.)

Comparison of the rest/stress image results with the angiographic results showed a sestamibi rest/stress imaging sensitivity of 67%. Of the false negative results (n = 22), 18% (n = 4) had critically narrowed arteries or arteries with vulnerable plaques whose 60-minute images appeared completely norma1.[26,27] However, evaluation of the 5-minute images for redistribution (using FHRWW), revealed both qualitative and quantitative decreased uptake, demonstrating a washin effect. The 60-minute poststress images miss these washin phenomena when looked at independent of the five-minute images, yielding incorrect results.

The standard rest/stress images also yielded a specificity of 88%; of which, only one participant (0.8%) who underwent a coronary angiogram had an adverse outcome requiring cardiopulmonary resuscitation.[29] This patient had a normal sestamibi redistribution using FHRWW (Figure 5).

DISCUSSION

Many of the limitations of comparing rest/stress images of the heart result from tissue attenuation problems seen with breast artifact and diaphragmatic attenuation, flow anomalies arising from left bundle branch block, hypertrophic obstructive cardiomyopathy, and other well known and similar problems. The FHRWW redistribution approach is not associated with these difficulties because, it compares regions of the heart under same-state (poststress)

conditions, allowing us to look for absolute changes (redistribution) in isotope concentrations.

In this study, results of rest/stress image comparisons and FHRWW redistribution image comparisons were not affected by the method used to administer stress. Therefore, institutions with a preference for exercise or pharmacologic stress (regardless of which agent is used) can continue to utilize their preferred approach with the FHRWW method for detecting ischemia. They also will be able to save additional camera time by avoiding rest imaging unless they are looking for evidence of injury/infarction.[8,30]

The ORs in this study provide further confirmation that determination of sestamibi redistribution improves the detection of ischemia compared with the rest/stress method—most pronouncedly in individuals with more severe disease. The ability to obtain these images of the heart and to measure ROIs requires the use of today's SPECT cameras with their imaging and software capabilities (built into the camera systems) for comparing five-minute and 60-minute images of the heart.

Previous research has shown a parabolic relationship in humans between stenosis flow reserve (as determined by positron emission tomography) and %DS (as measured by quantitative coronary angiography).[7] The current study demonstrates a parabolic relationship (one variable depends on the square of the other) between the findings of sestamibi redistribution (as measured from images of the heart obtained by SPECT imaging) and %DS found in the cardiac catheterization laboratory (Figure 6). This parabolic relationship reveals that during sestamibi washin, a critical reduction in isotope activity initially occurs in the presence of severe ischemia, but improves with time. The consequence of such is that a significant amount of myocardium is at risk of injury/infarction.

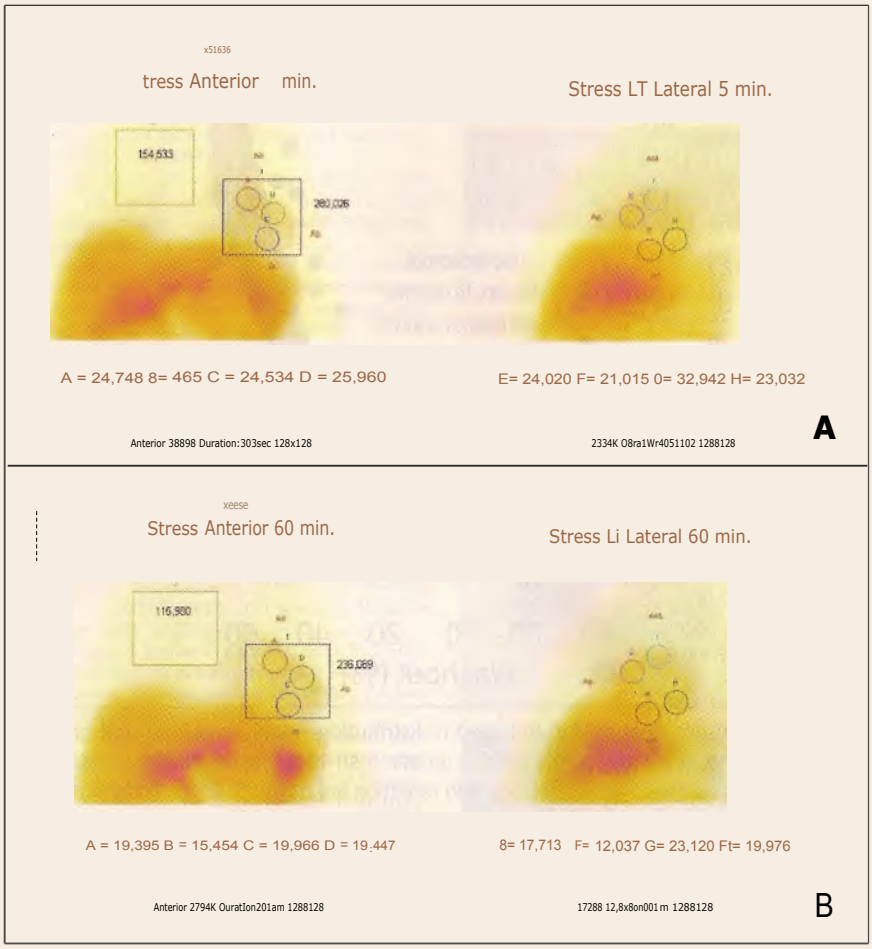


Figure 5. Normal redistribution/washout in a patient with no evidence of ischemia on coronary angiography. (A) shows results of absolute radioactive counts in each of eight myocardial regions at five-minutes poststress. The absolute total heart count was 280,026. **(B)** shows results of absolute radioactive counts in each of eight myocardial regions at 60-minutes poststress. The absolute total heart count was 236,089, representing a 5.7% washout and indicating no significant ischemia.

A washout rate of < 10% to 15%—consistent with the expected 10% radioactive decay of technetium-99m compounds—is evidence of minimal or no ischemia because the amount of tracer that myocardial tissue takes up and the amount it releases reaches equilibrium early (within five minutes) only when blood flow and cellular function are not compromised. Individuals with less critical, but still present, ischemia can be detected by washout of sestamibi and, using the parabolic relationship, practitioners can make decisions about needed medical or interventional treatment.

Also worth noting is that the rest/stress protocol requires a greater amount of radioactive isotope (1480 MBq) compared with the redistribution stress/stress protocol (1110 MBq). Not only does the patient

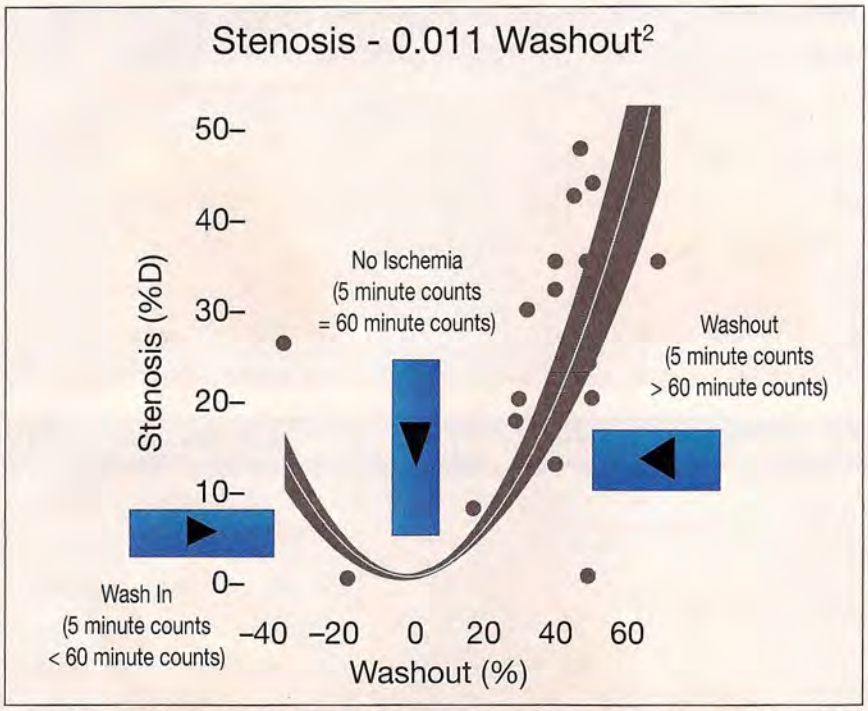


Figure 6. Parabolic relationship between redistribution washin-washout and coronary artery narrowing as seen on angiogram. A greater than 10% washout indicates ischemia. When ischemia is critical, isotope entry and retention are delayed, which is demonstrated by washin. If blood flow and myocyte function are normal, a 10% reduction in measurable isotope will be detected due to the decay curve of technetium-99m. [a]%D = percent diameter.

receive less radiation in the redistribution protocol—along with a reduction in exposure by hospital staff and the general public—but this approach optimizes use of our radioisotope resources during a time of national and international shortage.

Limitations of the current study include a failure to submit patients to coronary angiography and its associated risks if both rest/stress and FHRWW indicated no reason to subject the patient to an invasive procedure. Study participants also included individuals who were thought to have angina that would support further diagnostic evaluation.

Additional centers are currently studying FHRWW as the new standard of care to be implemented based on patient outcomes. These studies are being conducted at independent hospitals, clinics, and in university settings. Our initial reports in the literature have demonstrated that assessment of sestamibi and other technetium-99m isotopes acquired at rest will provide additional insight into tissue viability[30] in addition to ischemia. Further studies are needed.

CONCLUSION

Blumgart's original work demonstrated that sequential measurement of radioactivity obtained in same-state conditions could detect heart disease. Today's SPECT cameras allow us to replace Blumgart's Geiger counter method with our own modern measuring device to measure radioactivity under same-state (stress/stress) conditions after taking multiple images of the heart. The parabolic relationship between redistribution and ischemia shows not only the relevance of washin and washout, but also that relatively small differences in percent redistribution reflect much larger differences in ischemia. Using our redistribution washin-washout equation, we can accurately detect the presence of ischemia and compare these redistribution results with results obtained in the cardiac catheterization laboratory to improve detection of heart disease.

In addition to our work over the last decade, Sheikine and colleagues have discovered the importance of sestamibi redistribution in the detection of ischemic heart disease missed by imaging 60-minutes poststress. The authors confirm our work stating, "...where Tc-99m-sestamibi exhibited marked redistribution between early (6–8 min) and late (60–70 min) poststress imaging [led] to an underestimation of the extent and severity of ischemia on late images."[31] This paradigm shift, which we introduce today, will improve the detection of ischemic heart disease, unmasking those missed by rest/stress imaging.

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