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# USVAH Study Demonstrates Statistically Significant Improvement in Diagnosis and Care of U.S Veterans Using FMTVDM-FHRWW©℗ "Quantitative" Nuclear Imaging. The Era of Truly Quantitative Stress-First, Stress-Only Imaging has begun!

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## Abstract

**Background:** Myocardial perfusion imaging (MPI) has evolved over the last several decades with improvements in equipment and isotopes. Despite these limitations sensitivity and specificity of this study remains 65%-85% principally due to "qualitative" interpretation of the results. Numerous investigators have recommended changes in protocols and quantification of data to increase the diagnostic accuracy of this non-invasive physiologic test. Initial investigations have demonstrated the ability to "quantitatively" measure isotope redistribution with planar, SPECT and PET using FMTVDM©℗. This study was designed to compare the diagnostic and treatment outcomes of U.S. Veterans undergoing conventional "stress-rest" "qualitative" imaging using Technetium 99m isotopes (Sestamibi and Myoview) compared with FMTVDM©℗ "quantification" isotope redistribution using a single dose of the isotope.

**Methods:** Forty-one U.S. Veterans were studied using pharmacologic and exercise stress approaches with either Sestamibi or Myoview following routine MPI Imaging protocols compared with FMTVDM©℗. The results were compared with coronary angiography.

**Result:** Angiographic coronary artery disease (CAD) was defined using both 50% and 70% diameter narrowing/stenosis (%DS). Accuracy of a "qualitative" (yes/no) test in the determination of the presence or absence of CAD is measured by the ability of the test to find CAD when present (sensitivity) and to show that CAD is not present (specificity) when absent, based upon the arbitrarily assigned value for %DS. The sensitivity, specificity and accuracy of "qualitative" MPI assessment of 50% DS CAD was 50.0%, 88.2% and 70.7% for the left coronary artery system and 29.2%, 64.7% and 43.9% respectively for the right coronary artery system. These values improved to 59.1%, 89.5% and 73.2% for the left coronary artery system and 64.3%, 85.2% and 78.0% respectively for the right coronary artery system when 70%DS was used as the cutoff for CAD. No differences noted between either of the technetium 99m isotopes or cameras used for either the "qualitative" or "quantitative" (FMTVDM©℗) methods. FMTVDM©℗ provides the First Ever "quantitative" Nuclear Cardiology MPI test, which consequently defines CAD not on a yes/no basis, but "quantitatively." As such, the accuracy of FMTVDM©℗ must be compared first to a "quantitative" measure which is known; viz. isotope decay using TFM. Results of FMTVDM©℗ is then not simply a yes/no result, but rather a "quantitative" value which places the "extent" of CAD on a measured continuum much as a coronary angiogram would, specifically a quantitative coronary angiogram (QCA). FMTVDM©℗ demonstrated a statistically significant relationship between CAD and %DS ($r=0.75$, $p<0.001$).

**Conclusion:** Modern Nuclear Cameras have relied completely upon "quality" control methods, which do exactly that; they provide for "qualitative" control but not "quantitative" control. The accuracy of the cameras ability to correctly count the resulting scintillations from which "quantitative" analysis and even "qualitative" images are displayed for clinician interpretation are dependent, has never been established or used in either the experimental or clinical areas of Medicine. This study demonstrated the importance of first using TFM from the FMTVDM©℗ for "quantitative" camera calibration and correction prior to conducting MPI. Even with the correction of the "quantitative" errors in the Nuclear Cameras, errors in "qualitative" MPI resulted in a conservative estimate of misdiagnosis of CAD 35% of the time. These errors result in potential life threatening CAD being missed as demonstrated here. This same CAD is accurately measured using the new "quantitative" MPI test (FMTVDM©℗ ), which accurately "quantify" the exact extent of CAD. FMTVDM©℗ provides the first "quantitative" Nuclear Cardiology and Medicine test, ushering in the era of "machine learning" and "quantitative" Nuclear Cardiology and Medicine providing accurate, reproducible measurement of CAD in less time and with less radiation than the prior "qualitatively" applied method of "physician interpretation" of CAD, reducing healthcare costs and improving patient throughput and clinical management.

**Keywords:** FMTVDM©℗ ; TFM; Quantitative nuclear cardiology; Quantitative nuclear medicine; Veterans; Myocardial perfusion imaging

## Introduction

While diagnostic testing and decision making in the treatment of atherosclerotic coronary artery disease (ASCAD/CAD) tends to revolve around evidence of anatomic (cardiac catheterization [1], coronary computed tomography, intravascular ultrasound [2,3] etc., disease, it has been well established that this inflammatory [4-6] process may smolder for years and that up to 85% of all myocardial infarctions occur with <30% diameter narrowing. It is therefore, important for us to look for new ways to uncover this smoldering inflammatory disease process

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when intervention may be more beneficial to the patient and potentially less costly to the patient and society at a time when health care costs are a major issue.

When teenagers learn to buy their first automobile, they learn an important lesson. Not every car that looks good runs well. This same lesson applies to the diagnosis and treatment of ASCAD; "qualitative" imaging can be deceptive and miss what can only be accurately measured using "quantitative" methods.

The lesson is to accurately determine how well the car runs, or in this case, how well the heart runs. Hence, the importance of physiologic testing; i.e. testing to see how well the heart runs. Prior to nuclear imaging of the heart, now called myocardial perfusion [7,8] imaging (MPI), patients ran on a treadmill (exercise stress testing/EST) under the belief that this would precipitate chest pain (angina) and perhaps electrocardiographic and hemodynamic changes which would indicate problems with coronary blood flow.

Until recently, it was believed that this was purely the result of narrowing within the lumen of the artery. It has since been demonstrated that angina is the result of regional blood flow [9,10] differences; hence, the importance of quantifying such areas of the heart by analyzing regions of interest (ROI).

These differences in regional blood flow work through mechanisms as of yet not completely understood, although as clearly demonstrated [4-6,9,10] is the result of chemical mediators responding to the regional blood flow differences.

The ability to precipitate these differences in regional blood flow can be accomplished *via* the utilization of MPI and pharmacologic or exercise stress testing. While nuclear tracers (isotopes) have improved over the years, many misconceptions [11-17] have plagued the field limiting the accuracy of MPI with sensitivities and specificities of 65%-90% in most published investigations [11-18]. The era of Nuclear Cardiology and Nuclear Medicine to date has been limited by this "qualitative" method of image interpretation.

During our initial [4,5,20] efforts to better understand the underlying inflammatory component of CAD *via* MPI, static and dynamic imaging revealed differences in the qualitative appearances and "quantitative" redistribution measurements of acquired MPI images [21-31], seen following pharmacologic stressing of individuals. "Quantitative" measurements of 5 minute and 60 minute acquired images of both Sestamibi and Myoview clearly revealing that these technetium isotopes redistribute and this redistribution began at 5 minutes post isotope injection [32-42] and not later as previously thought.

Other investigators have noted similar differences between initial static and subsequent dynamic imaging of the heart [32-36] allowing for enhanced detection of congestive heart failure [33,37-40], cardiomyopathies [41,42,], Prinzmetal's angina [43,44] and underlying coronary artery disease [33,39,45-56] including evidence of wash in [53,54] indicative of critical lesions not detected by conventional MPI.

In the same way that quantitative coronary arteriography (QCA) is used to "quantify" changes (sometimes subtle, sometimes not) in coronary anatomy and blood flow in the cath lab, so too does FMTVDM©℗ imaging "quantify" measurements following pharmacologic or EST allow us a more advanced look at the physiologic (imaging) function of the heart in the same way that modern computers built into today's cars allow the detection of functional problems within the car before the trained (certified, experienced) mechanic can detect it.

Given these recent investigations into improving the detection of ischemia by quantifying isotope counts on multiple (sequential) images following pharmacologic and exercise stress, we set out to compare the "quantitative" FMTVDM©℗ method with the "qualitative" validity of MPI readings at a US government Veterans Healthcare facility based upon diagnostic interpretations provided by board certified nuclear cardiology and medicine physicians and coronary arteriography results obtained by Board Certified General Invasive Cardiologists in the cardiac catheterization laboratory.

FMTVDM©℗ "quantified" changes in isotope redistribution at 5 and 60 minutes post "stress" (enhancement). Assessment of the effect of both isotope decay for technetium 99m compounds and the actual changes in isotope redistribution were measured and compared with percent diameter stenosis (%DS) obtained by cardiac catheterization and the "qualitative" MPI interpretations.

## Methods

Forty-one subjects were studied at a Veterans Hospital following informed consent procedures for diagnostic studies. Patients were all referred by primary care providers to determine the extent of coronary artery disease. Participants signed informed consent (IC) for the stressor component of the study.

IC is not required at the institution for injection or imaging of a nuclear isotope. All subjects were de-identified in accordance with Veterans Administration (VA) Manual 3, Part I, Chapter 9, Section 9A (4). Results of studies were obtained under the Freedom of Information Act (FOIA).

### Myocardial perfusion imaging (MPI) protocols

Patients were brought to the nuclear cardiology department in the fasting state with an intravenous catheter inserted into either the right or left antebrachium. Patients underwent pharmacologic stress (adenosine or dobutamine) or EST per standard VA protocols.

**Adenosine stress**: Those receiving adenosine were given 140 mcg/kg/min for a total of 4 minutes with 25-30 mCi of isotope (Sestamibi or Myoview) given at the completion of the second minute of adenosine infusion followed by a saline flush to assure delivery of the isotope into the venous system. Hemodynamic and electrocardiographic data were collected at baseline, 2 and 4-minutes infusion, in addition to 1, 3 and 5-minutes post adenosine infusion. Patients then underwent image acquisition 5-minutes after peak pharmacologic "enhancement" (stress) per hospital protocol with the patient placed in a supine position for imaging. Image acquisition was repeated at 60 minutes post isotope infusion per hospital protocol. Resting images were obtained using hospital protocol as laid out in Figure 1. The 5 minute and 60 minute acquisitions were used for FMTVDM©℗ and the 1 hour and resting image results were used for "qualitative" conventional MPI image interpretation.

**Dobutamine stress**: Those receiving dobutamine [57-61] pharmacologic enhancement (stress) did so as already described in the literature. Hemodynamic and blood pressure monitoring occurred at 1 minute 30 seconds into each phase of the pharmacologic stress and during recovery until hemodynamically and clinically stable. The injection of the isotope was given at peak dobutamine infusion followed by 2 minutes of continued infusion of dobutamine at the peak rate. Patients then underwent the same imaging sequence described above under adenosine stress.

**Exercise stress (EST):** Those following exercise stress imaging [17,60] were injected with the isotope after obtaining 85% maximum predicted heart rate (MPHR) and exercised for an additional two minutes per protocol as previously described in the literature. Hemodynamic and blood pressure monitoring occurred at 1 minute 30 seconds into each phase of the exercise enhancement (stress) of coronary blood flow and during recovery until hemodynamically and

clinically stable. Patients then underwent the same imaging sequence described above under adenosine stress.

### Single photon emission computed tomography (SPECT) cameras

Thirty-seven of the 41 studies were completed using a Philips Forte Dual Head SPECT camera using general all (GAP) purpose collimators with the heads positioned at 90 degrees per manufacturers specifications. A 15% window was used with a 64 by 64 matrix. Image acquisition [19,20] was obtained using standard step and shoot approach with 25 seconds per view beginning in right anterior oblique (RAO) and terminating in the left posterior oblique (LPO) position. Jet stream software was used per manufacturer's instructions to quantitatively measure regions of interest (ROIs). Acquired images were reconstructed using a Butterworth filter and standard back projection with reconstruction of short, horizontal and long axis views as previously described [17]. Four of the 41 studies were completed using a Picker Axis Dual Head SPECT camera using a low energy general all (LEGAR-PAR) purpose collimator with parallel hole positioning. The heads were positioned at 102 degrees per manufacturer specifications. Acquired images were reconstructed using a Butterworth filter and standard back projection with reconstruction of short, horizontal and long axis views as described above. A 15% window was used with a 64 by 64 matrix with 34 views obtained over 30 seconds per view. Image acquisition began in the RAO position and terminated in the LPO position. Picker camera software was used for ROI measurements.

### FMTVDM©℗ method (The Fleming method for tissue and vascular differentiation and metabolism using same state single or sequential quantification comparisons) [21-31]

The specific details of FMTVDM Imaging have already been discussed in great detail elsewhere [21-31] as has conventional MPI imaging. The sequence of actual "enhancement" ("stress") and imaging are shown in Figure 1. However, the initial component of the patented method is the "quantitative" measurement set-up of the Nuclear Cameras; "quantitative control". Each camera must be calibrated to assure that it is accurately measuring the decay of isotopes, ensuring that it is capable of accurately measuring changes in isotope distribution and scintillation over time. To do this, the primary author developed a method, which is included as part of the patent FMTVDM©℗. This first part is called "The Fleming Method" (TFM) and it measures the capability of each nuclear camera to correctly measure isotope decay and consequently redistribution. As shown in Figure 2, a camera initially calibrated using TFM was shown to be losing 34% of its data, making it initially incapable of correctly "quantifying" results and impairing resulting "qualitative" images.

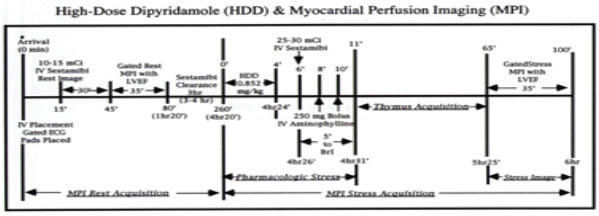


**Figure 1:** FMTVDM©℗ protocol for evaluation of Sestamibi Redistribution.

Determination of tissue viability can be made from Regions-of-Interest (pixel-to-pixel) redistribution measurements using 5-minute and 60-minute post isotope injection during MPI Rest Acquisition (discussed elsewhere but included in the FMTVDM ©℗ complete protocol). Determination of ischemia (CAD) and %DS calculation is made by quantitatively comparing Regions-of-Interest (pixel-to-pixel) isotope redistribution measurement at 5- and 60-minutes post isotope injection, with calculation of redistribution wash-in and redistribution washout pursuant to patent # 9566037 license

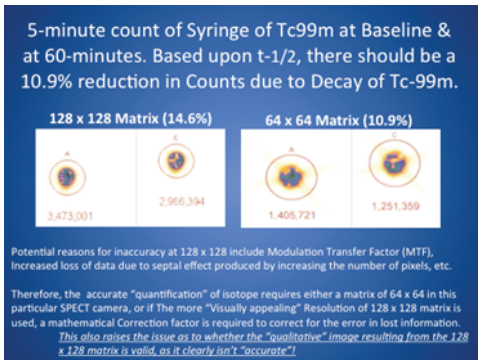


**Figure 2:** "Quantitative" Calibration of Nuclear Camera using TFM©℗. The use of a 128 x 128 matrix resulted in 33.9% loss of data, which did not occur with the 64 x 64 matrix. TFM detects, calibrates and corrects for this error in measurement. The error also clearly results in incorrect images for "qualitative" analysis by physicians/clinicians, which is corrected by TFM; however, the limitations of "qualitative" MPI interpretation remain.

TFM calibrates and corrects for these "quantitative" and consequential "qualitative" errors.

Figure 3 shows the comparison of one veteran who had critical LAD, first diagonal and first obtuse marginal disease, which was missed by the standard "qualitative" MPI (Figure 3a) but "quantitatively" measured using FMTVDM©℗ (Figure 3b). The before and after angiographic result of stenting the lesions is shown in Figure 3c.

### Visual interpretation of myocardial perfusion imaging (MPI)

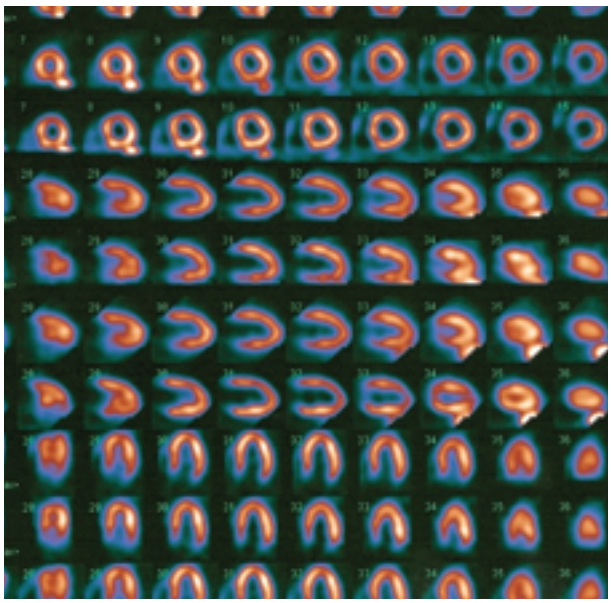

**Figure 3:** Comparison of "qualitative" MPI with "quantitative" FMTVDM and coronary angiography.
**Figure 3a:** Dynamic resting image to assess myocardial damage and dynamic stress image to assess ischemia with and without attenuation (AC) correction. Components a, b and c are the same Veteran with the coronary arteriogram performed immediately after FMTVDM©℗ was completed. **3a:** The format displayed shows coronal short axis (top 4 rows), vertical long axis (rows 5-8) and the horizontal (rows 9-12) long axis rows. Rows 1-2, 5-6, and 9-10 show images using non-attenuation corrected images. Rows 3-4, 7-8, and 11-12 show the same regions using AC. Rows 2,4,6,8,10 and 12 show "resting" images while rows 1,3,5,7,9 and 11 reveal the same regions of myocardium following pharmacologic "enhancement" (stress); in this case adenosine. These images were "qualitatively" interpreted as "normal" showing no evidence of ischemia.

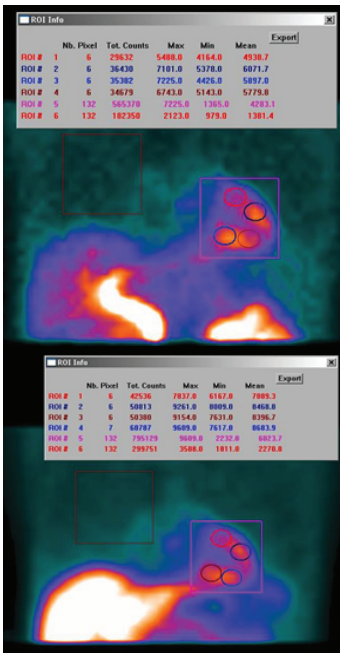


**Figure 3b:** Sestamibi "Wash-in" Redistribution showing critically diseased LAD system requiring Emergent STENT Intervention. The upper panel represents the FMTVDM©℗ results acquired 5-minutes post isotope infusion, while the lower panel represents the FMTVDM©℗ acquired at 60-minutes. The basal anterior wall demonstrated "wash-in" with a value of 4938.7 at 5-minutes and 7089.3 at 60-minutes. The results of other FMTVDM©℗ are included but not discussed due to space limitations and the ability of the reader to continue the process given the orientation provided. The use of the standard "qualitative" MPI "stress-rest" 60-minutes and rest (Figure 3a) images completely failed to find this critical three vessel disease, which required Emergent Stent Intervention.

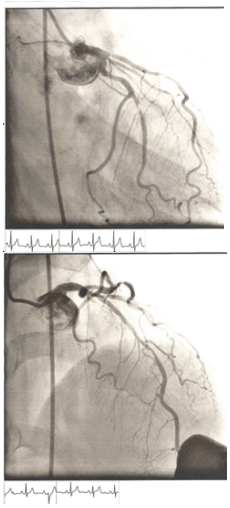

**Figure 3c:** Pre and post coronary arteriography and PCI stent intervention of three critically stenosed coronary arteries in a Veteran with angina and early ST elevation.

**3c:** Following FMTVDM©℗, the patient was immediately taken to the Coronary Arteriography Laboratory where stents were emergently placed in his critically diseased LAD, first diagonal and first obtuse marginal. At the time the patient was taken for PCI, he was experiencing angina and beginning to display ST elevations. The upper panel shows the pre-stent arteries and the lower panel shows the results post-intervention following insertion of a cypher RX drug eluting 3.5 x 8 mm stent for the 80% DS ostial lesion of the LAD, a cypher RX drug eluting 3.0 x 33 mm stent for the 75% DS proximal LAD lesion and a Cypher RX drug eluting 3.0 x 13 mm stent for the 80% DS ostial lesion of OM1.

Two Board Certified Nuclear Cardiology and/or Medicine physicians independently interpreted MPI results using standard and attenuation correction (AC) images (Figure 3a) in all but four of the participants. These four studies were performed on the Picker camera, which did not have AC capability but were interpreted by the physicians in the same manner. These four studies were done while the Philips camera was undergoing scheduled maintenance. The AC images obtained using the Philips camera used Gadolinium as a source with accompanying camera software. The reporting of ischemia by the physicians became the final reporting of patient results in accordance with hospital policy.

**Coronary angiography [57,58]:** Veterans were brought to the cardiac catheterization laboratory for diagnostic evaluation of coronary lumen disease (percent diameter stenosis, %DS) in the fasting state. Patients were prepped in the usual manner after signing IC per hospital protocol. Coronary angiography was performed using Seldinger and Judkins techniques with arterial access obtained from either the right or left femoral artery. Subjects were subsequently injected with contrast using either Ultravist 370 for non-renally impaired individuals or Visipaque 320 for those with questions regarding renal function. A single head Philips Flat Detector (FD) 20 was used at 15 frames per second (fps) and an 8 inch field. Images were recorded digitally and reviewed by two Board Certified Invasive Cardiologists with %DS assigned based upon consensus of the two Cardiologists and the use of calipers to "quantify" angiographic results.

**Statistical analysis:** Regions-of-interest (ROIs) for "quantitative" measurement of isotope measurement and redistribution were drawn by the Nuclear Technologists with "quantification" of isotope made using the computer software provided by the specific camera companies. Chi-square analysis of comparison of disease present by cath and "qualitative" MPI were determined and sensitivity, specificity and accuracy calculated from the results. Correlation coefficients of linear regression and p-value (significance levels) were calculated using the "quantitative" %DS and FMTVDM©℗ values, using Pearson's product-moment correlation.

## Results

### Camera calibration and correction

Using TFM from the FMTVDM©℗ , both SPECT Nuclear Cameras underwent "quantitative" control in contrast to "quality" control currently implemented in Nuclear Cardiology and Medicine departments. Analysis as shown in Figure 2 demonstrated a 34% loss of data using the 128 x 128 matrix which was corrected for using TFM by calibrating the camera to a 64 × 64 matrix resulting in "accurate" "quantification" and subsequent "qualification" imaging.

### Differences in isotopes and camera systems

There were no statistically significant differences in outcomes between either of the two technetium 99m isotopes used or the nuclear cameras once TFM was applied. As such the results of both camera systems and nuclear isotopes are combined here for both "qualitative" and "quantitative" (FMTVDM©℗) analysis.

### MPI "qualitative" analysis of CAD

Angiographic coronary artery disease (CAD) was defined using both 50% and 70% diameter narrowing/stenosis (% DS) [1]. Assessment of the accuracy of a "qualitative" (yes/no) test in the determination of the presence or absence of CAD is measured by the ability of the test to find CAD when present (sensitivity) and to show that CAD is not present (specificity) when absent based upon the arbitrary number

(e.g. % DS narrowing or stenosis) chosen to define CAD. The overall accuracy for a "qualitative" test can then be defined. When considering 50%DS as the cutoff for CAD, "qualitative" interpretation of CAD for the left coronary system (left main, left anterior descending and the circumflex arteries with their respective branches) found CAD in 14 of the 24 veterans, correctly identifying the absence of CAD in 15 of 17 veterans. The sensitivity, specificity and accuracy was 50.0%, 88.2% and 70.7% respectively. When interpreting results for the right coronary artery system 7 of 24 with disease were correctly identified with CAD while 11 of 17 were correctly identified as not having CAD, yielding a sensitivity, specificity and accuracy of 29.2%, 64.7% and 43.9% respectively. The results are shown in Table 1.

When the arbitrary definition of CAD was changed to a cutoff of 70% DS, 13 of the 22 Veterans with left coronary artery system disease were "qualitatively" identified by MPI, while 17 of the 19 Veterans without CAD were correctly identified, yielding a sensitivity, specificity and accuracy of 59.1%, 89.5% and 73.2% respectively. "Qualitative" image interpretation of the right coronary artery system yielded a sensitivity, specificity and accuracy of 64.3%, 85.2% and 78.0% respectively, with clinician interpretation correctly identifying disease in 9 of 14 Veterans and correctly excluding disease in 23 of 27 Veterans. The results are shown in Table 2.

## FMTVMD©℗ "quantification" of CAD

Since FMTVDM©℗ is a "quantitative" measure of isotope scintillation [21-31] it does not provide a yes/no answer, just as coronary, particularly "quantitative" coronary arteriography (QCA) [1,6,17,59-60] does not. Rather both QCA and FMTVDM©℗ provide absolute "quantitative" measurements of CAD, with FMTVDM©℗ using the TFM component to "quantitatively" calibrate and provide for the accurate, reproducible "quantitative" measurement of isotope redistribution to define FMTVDM©℗, just as QCA measurement is dependent upon certain known standards to calibrate and adjust its measurements to 100% accuracy [1,17,57-60]. The regression analysis and correlation coefficient between %DS as measured by calipers with the FMTVDM©℗ "quantitative" measurement of isotope redistribution measured using the 5 and 60-image measurements, resulted in a parabolic relationship between "quantitative" %DS measurements and the redistribution of the isotope measured by FMTVDM©℗ with %DS equaling FMTVDM©℗ squared multiplied by 0.011; yielding an R-value of 0.75, $p<0.001$. A partial representation of the FMTVDM data is provided in Table 3.

| | Cath ≥ 50% DS | Cath<50%DS | | Cath ≥ 50% DS | Cath<50%DS |
|---|---|---|---|---|---|
| MPI Read+ | 14 | 2 | MPI Read+ | 7 | 6 |
| MPI Read- | 10 | 15 | MPI Read- | 17 | 11 |
| MPI Sensitivity | 0.5 | | MPI Sensitivity | 0.292 | |
| MPI Specificity | 0.882 | | MPI Specificity | 0.647 | |
| MPI Accuracy | 0.707 | | MPI Accuracy | 0.439 | |
| *Using 50%DS as the cutoff for CAD, 24 of the 41 Veteran had CAD (58.5%). +equals interpretation that CAD is present, -equals interpretation that CAD is absent. | | | | | |

**Table 1**: Qualitative assessment of MPI study interpretation Defining CAD as lumen narrowing (%DS) as Fifty (50) Percent*.

| | Cath ≥ 70% DS | Cath<70%DS | | Cath ≥ 70% DS | Cath<70%DS |
|---|---|---|---|---|---|
| MPI Read+ | 13 | 2 | MPI Read+ | 9 | 4 |
| MPI Read- | 9 | 17 | MPI Read- | 5 | 23 |
| MPI Sensitivity | 0.591 | | MPI Sensitivity | 0.643 | |
| MPI Specificity | 0.895 | | MPI Specificity | 0.852 | |
| MPI Accuracy | 0.732 | | MPI Accuracy | 0.78 | |
| **Using 70% as the cutoff for CAD, 22 of the 41 Veterans had CAD in their left coronary artery system and 14 of the 41 had CAD in their right coronary artery system. +equals interpretation that CAD is present, -equals interpretation that CAD is absent. | | | | | |

**Table 2**: Qualitative assessment of MPI study interpretation Defining CAD as lumen narrowing (%DS) as Seventy (70) Percent**

An example of the resulting "quantification" of FMTVDM©℗ is seen in Figure 3b, showing both the "qualitative" MPI results Figure 3a interpreted as free of CAD and the FMTVDM©℗ measurement of CAD together with the coronary angiogram (Figure 3c) obtained of that same Veteran pre and post-stent placements.

## Discussion

With the advent of Nuclear Cardiology and Nuclear Medicine by Blumgart [60], physiologic investigation of disease was underway. One would have expected a continuation of what appeared to be efforts to "quantify" disease using Nuclear Cameras and isotopes. Unfortunately, this was not the case and Nuclear Cardiology and Medicine elected to focus on "qualitative" "interpretation" of images displayed after acquisition without the development of a "quantitative" method to determine if even the "qualitative" images were correct. Augmented to this limitation, is human inattentional blindness, which despite best intentions, is simply the result of being human. As Drew [61] et al. have clearly demonstrated, even the most "trained" observer faces limitations based upon our expectation of what we believe we will see. Such has been the development of Nuclear Cardiology and Nuclear Medicine to date.

Similarly, while initially discovered by accident when Frank Mason Sones accidentally injected the right coronary artery of a man at the Cleveland Clinic on 30 October 1958, the field of coronary arteriography has primarily been left to human qualitative interpretation and in many cases still is [1]. However, the use of Quantitative Coronary Arteriography (QCA) [1,6,17,59-60] has done much to reduce these human errors.

FMTVDM©℗ is a multi-step patented method for "quantifying" Nuclear Imaging including but not limited to Nuclear Cardiology. Like QCA, the first component of the patent, TFM, utilizes "a known" standard against which to measure, viz. isotope half-life decay to "measure" changes in isotope decay and distribution over time. This initial measurement, assessment and calibration of Nuclear Cameras and Computers provide the first step in FMTVDM©℗ "quantification" of CAD. Coupled with the remaining components of the patent, FMTVDM©℗ provides the first ever "quantitative" Nuclear measurement of CAD that goes far beyond the simple "qualitative" limitations of "experienced" clinicians. This process of Artificial Intelligence (AI)/ Machine Learning (ML) allows the diagnostician "quantitative" measurement of the exact extent of CAD, from which treatment decisions can subsequently be made and monitored, through reimaging the patient using FMTVDM©℗ to determine "actual patient oriented, patient focused" treatment response". FMTVDM©℗ was compared with the standard "stress-rest" "qualitative MPI approach which has been the mainstay of Nuclear Cardiology for decades. By comparison, standard "qualitative" MPI imaging was accurate in the determination of left coronary disease only 70.7% of the time when CAD was defined as 50%DS and 73.2% of the time when CAD was defined as a 70%

| ID | Isotope | Total FMTVDM© | Left Coronary System FMTVDM© | Right Coronary System FMTVDM© | H: L | EF | Left Coronary System %DS | Right Coronary System %DS |
|---|---|---|---|---|---|---|---|---|
| A | Mibi | 42 | 19 | 54 | 2.2 | 60 | 30 | 98 |
| E | Mibi | 34 | 33 | 54 | 2.3 | 44 | 25 | 94 |
| G | Mibi | 50 | 32 | 55 | 2.9 | 64 | 80 | 60 |
| H | Mibi | 42 | 21 | 45 | 2.6 | 67 | 20 | 30 |
| I | Mibi | 51 | 39 | 28 | 2.3 | 51 | 0 | 0 |
| J | Mibi | 71 | 77 | 79 | 1.9 | 61 | 90 | 50 |
| K | Mibi | 32 | -39 | -4 | 2 | 52 | 80 | 0 |
| M | Mibi | 52 | 48 | 53 | 2.2 | 33 | 50 | 30 |
| N | Mibi | 19 | 3 | 23 | 2.1 | 64 | 30 | 0 |
| O | Mibi | 52 | 52 | 55 | 1.9 | 42 | 80 | 95 |
| P | Mibi | 31 | 3 | 24 | 1.8 | 59 | 0 | 70 |
| Q | Mibi | 49 | -11 | 57 | 1.6 | 18 | 90 | 100 |
| R | Mibi | -46 | 16 | 19 | 2.1 | 67 | 50 | 30 |
| T | Mibi | -58 | -100 | -65 | 1.6 | 29 | 85 | 20 |
| U | Mibi | -3 | -1 | 4 | 2 | 48 | 0 | 0 |
| A2 | Mibi | 47 | 42 | 47 | 2 | 50 | 100 | 70 |
| B2 | Mibi | 42 | 21 | 42 | 2.3 | 48 | 60 | 80 |
| C2 | Mibi | 52 | 32 | 66 | 2.0 | 59 | 25 | 70 |
| a | Myo | 48 | 22 | 42 | 2.1 | 55 | 40 | 50 |
| b | Myo | 63 | 40 | 61 | 2 | 59 | 85 | 98 |
| g | Myo | 11 | 26 | 12 | 2.6 | 66 | 90 | 0 |
| k | Myo | 50 | 39 | 46 | 2.1 | 52 | 60 | 70 |

Iso=isotope used, Mibi=Sestamibi, Myo=Myoview, H: L=Heart to Lung ratio, EF=Percent left ventricular ejection fraction. The H: L and EF data are shown to demonstrate they were collected. They are not discussed within the scope of this publication.

**Table 3:** Representive FMTVDM© data collected.

or greater DS. For right coronary artery (RCA) disease, "qualitative" MPI results in these Veterans only accurately identified RCA disease in 43.9% of those with 50% DS or 78.0% of the time when CAD was defined as being 70% DS or greater. The clinical example presented of "wash-in" measured by FMTVDM© provides a clear example of the clinical importance of diagnostic and treatment monitoring using the "quantitative" method provided by FMTVDM© and its superiority over "qualitative" MPI.

As demonstrated by clinical example in this study, there were Veterans with critical CAD requiring percutaneous intervention (PCI) to save their lives, which were simply missed by "qualitative" MPI. The limitations of the currently used "qualitative" MPI method are clear and the medical and lay literature is replete with examples and studies showing these limitations, yet until now there was not a "quantitative" method available to correct this problem. Until now it was not even clear why these limitations existed or what could be done to "quantify" Nuclear Cardiology and Medicine. FMTVDM© provides the first and much needed answer to that and other questions, including diagnostic and "patient focused" treatment decision making capabilities. FMTVDM© reduces imaging time, radiation exposure of patients and clinical personnel and healthcare costs by eliminating errors made in a conservative 35% of "qualitative" MPI cases.

## Conclusion

The era of "qualitative" interpretation of MPI studies has produced a conservative error rate of 35% resulting in missed opportunities to treat CAD and minimal but still present risks of MACEs from unnecessary invasive procedures. Human limitation in diagnosing from "qualitative" "imaging [efforts hampered" by the demonstrated failure to have and implement "quantitative" controls (TFM) to correct the loss of 34% (camera dependent) of the information coming from the patient during "Nuclear Cardiac and Medical Imaging"] the true presence or absence of CAD which needs to be treated, as well as the inability of the current "qualitative" MPI method to effectively determine the risks and benefits of treatment decisions, mandates a change to "quantitative" imaging. This "quantitative" imaging method for both Nuclear Cardiology and Medicine has now been established *via* FMTVDM© . The era of "qualitative" Nuclear Cardiology and Medicine is over. The era of "quantitative" FMTVDM© Imaging has just begun.

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### Clinical Trial

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FMTVDM© has been issued to the Primary Author.

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