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# Multi Center Clinical Trial Confirms FMTVDM©℗ MPI in Seven Modern Clinical Laboratories in the USA and Asia. Artificial Intelligence (AI) with True Quantification

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## Abstract

**Background:** The foundational work for nuclear cardiology began with Blumgart's 1925 study of "circulation time." The method was quantitative, yielding measurements of isotope change over time. The development of Myocardial Perfusion Imaging (MPI) resulted in qualitative images with clinician interpretation, yielding a 35% error rate when sensitivity and specificity were taken into account. The initial use of Tl-201 was largely replaced by Tc-99m isotopes, which as others and we have now shown, like Tl-201, redistribute albeit what was once thought to be slower than Tl-201 is actually faster than Tl-201 .

Our initial work demonstrated that FMTVDM provides the first truly quantitative method removing human qualitative error, providing for the first truly quantitative Artificial Intelligence (AI) method for Nuclear Cardiology. This study looked at a multicenter study to determine FMTVDM©℗ use in clinical laboratories.

**Methods:** Four hundred and one men and women between the ages of 21 and 85 years were studied in seven centers in the US. and Asia, using FMTVDM©℗. Results were compared to coronary angiography.

Using FMTVDM©℗ redistribution measurements, percent diameter stenosis (%DS) was calculated and using proprietary equations an Artificial Intelligence (AI) determination of the coronary flow reserve ["quantified/Fleming coronary flow reserve©" (QCFR/FCFR)] was determined and compared with the QCA derived measurements using best fit regression analysis.

**Results:** Each of the seven centers underwent training to familiarize them with FMTVDM©℗ and implement its clinical use. Determination of the accuracy of the centers FMTVDM©℗ measurements and implementation of the AI program was determined by comparing the final AI derived QCFR/FCFR with that obtained using QCA measured CFR. The resulting coefficient of determination 0.87582 (p<0.0001) demonstrated a "strong" relationship between the AI FMTVDM©℗ method and QCA measured results.

**Conclusion:** FMTVDM©℗ AI provides the first ever "quantified," "enhanced" AI method for measuring coronary artery disease (CAD) beginning with the measurement of isotope redistribution and ending with the calculation of QCFR/FCFR© using the patented proprietary equations. This patented method is applicable to any device capable of measuring isotope activity over time including but not limited to hand-held probes, planar, SPECT and PET. This provides confirmation that clinical centers can be trained to implement the First AI "Truly Quantitative" Nuclear Cardiology method since its inception in 1925.

## Background

The foundational work of nuclear cardiology began with Blumgart's 1925 study of circulation time. Blumgart focused on quantitatively measuring isotope change over time. Since then Nuclear Cardiology has focused on qualitative image interpretation resulting in sensitivity and specificity issues. A demand for reducing patient radiation exposure has additionally resulted in a call for "stress-first/stress-only/stress-stress" imaging.

A preliminary VA study demonstrated FMTVDM©℗ "stress-stress" imaging statistically out performed conventional two-injection MPI "stress-rest" approach, while lowering patient mSv radiation exposure [1-15] with FMTVDM©℗ resulting in statistically improved clinical outcomes, providing the only True quantitative AI method [16-18] removing the qualitative errors made using "stress-rest" MPI methods [19,20], and reducing the amount of patient exposure during MPI as seen in Figure 1. This study examined the ability to implement FMTVDM©℗ in seven different centers in the USA and Asia.
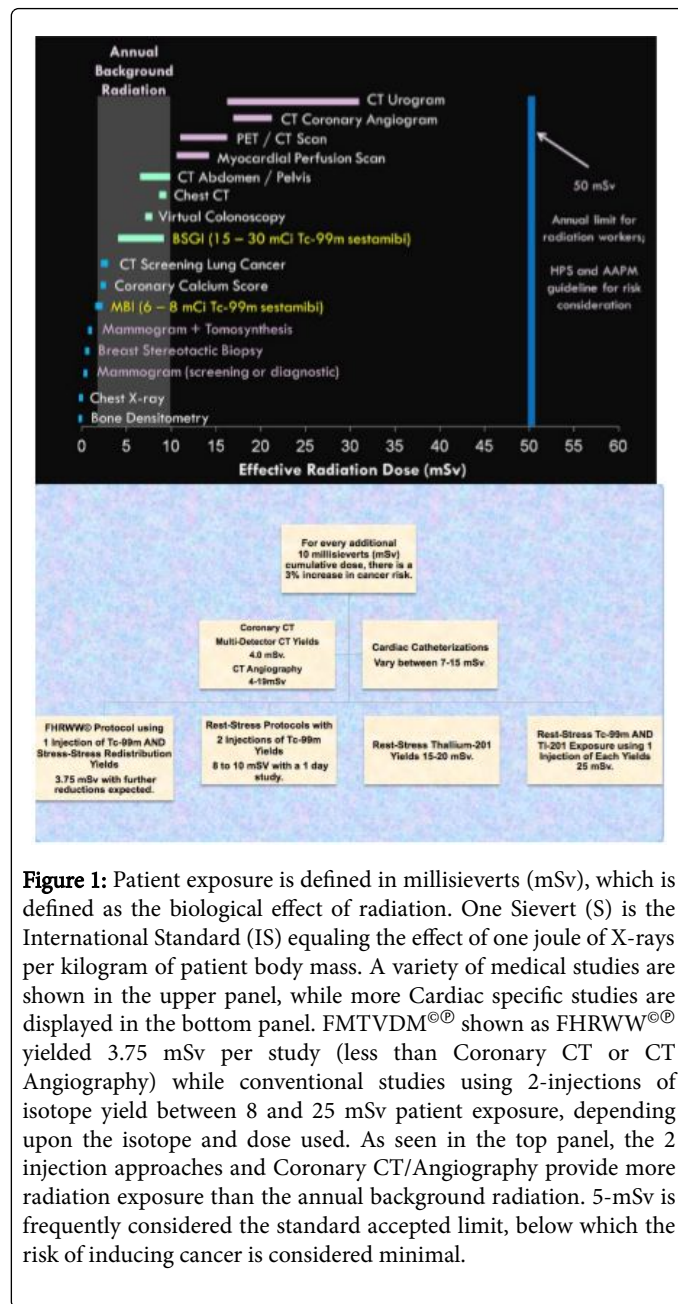
**Figure 1:** Patient exposure is defined in millisieverts (mSv), which is defined as the biological effect of radiation. One Sievert (S) is the International Standard (IS) equaling the effect of one joule of X-rays per kilogram of patient body mass. A variety of medical studies are shown in the upper panel, while more Cardiac specific studies are displayed in the bottom panel. FMTVDM©℗ shown as FHRWW©℗ yielded 3.75 mSv per study (less than Coronary CT or CT Angiography) while conventional studies using 2-injections of isotope yield between 8 and 25 mSv patient exposure, depending upon the isotope and dose used. As seen in the top panel, the 2 injection approaches and Coronary CT/Angiography provide more radiation exposure than the annual background radiation. 5-mSv is frequently considered the standard accepted limit, below which the risk of inducing cancer is considered minimal.

## Materials and Methods

### FMTVDM©℗

Following the protocol detailed in FMTVDM©℗ 401 men and women were studied as detailed previously [15] at seven different Centers-of-Excellence (COE).

### Coronary arteriograms

Following standard procedures previously detailed [10-14] coronary angiography was performed, %DS and QCA results were obtained. Initial visual reporting of percent diameter stenosis (%DS) was

determined only after clinicians had undergone extensive training necessary to reduce the qualitative errors [21].

### Calculation of %DS from isotope redistribution

The derived isotope redistribution was then calculated using pixel-by-pixel isotope measurement to determine redistribution wash-in (initial delay in isotope uptake) as described previously [4-7] and redistribution washout (failure to retain isotope) or expected (normal) redistribution as shown in Figure 2.
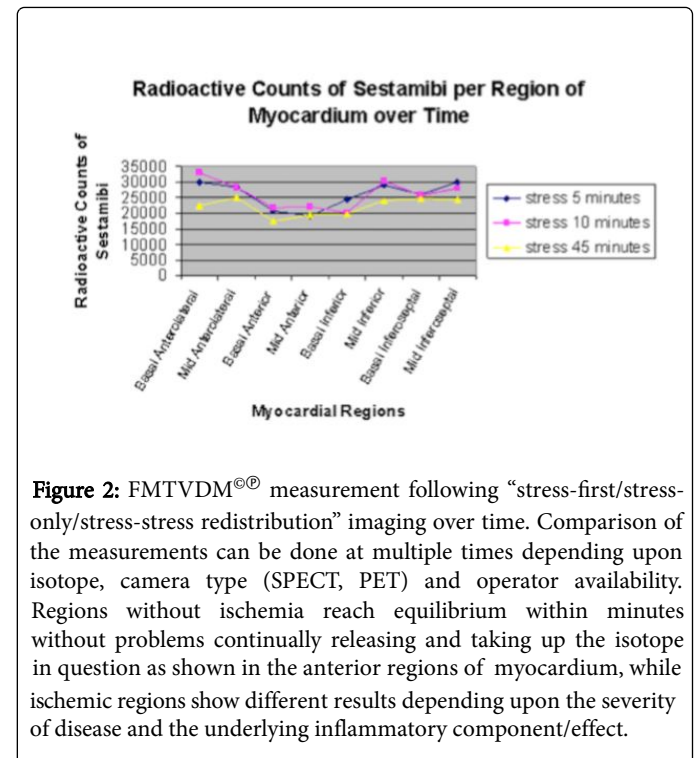


**Figure 2:** FMTVDM©℗ measurement following "stress-first/stress-only/stress-stress redistribution" imaging over time. Comparison of the measurements can be done at multiple times depending upon isotope, camera type (SPECT, PET) and operator availability. Regions without ischemia reach equilibrium within minutes without problems continually releasing and taking up the isotope in question as shown in the anterior regions of myocardium, while ischemic regions show different results depending upon the severity of disease and the underlying inflammatory component/effect.

Calculation of Quadratic/Fleming Coronary Flow Reserve (QCFR©, FCFR©) from Isotope Redistribution determined %DS: The AI proprietary equations and process derived from measured human coronary artery analysis [10-14] followed the FMTVDM©℗ protocol (p=3.8 x $10^{-8}$) directly introducing those measurements into proprietary equations protected by patent #9566037 automatically deriving CFR. The measurements and subsequent derivation of CFR (QCFR/FCFR) were done at multiple times and are NOT dependent on isotope, camera type (SPECT, PET), camera company or operator availability.

### Statistical analysis

Comparison of FMTVDM©℗ measured/quantified isotope redistribution and subsequent AI calculated Quadratic/Fleming Coronary Flow Reserve (QCFR©, aka. FCFR©) Using the FMTVDM©℗ and proprietary equations (QCFR©, aka. FCFR©), 401 individuals were studied and the AI quantified results from the FMTVDM©℗ Proprietary equations derived (QCFR©/FCFR©) were compared with QCA derived outcomes. Residual plots were analyzed for data bias. The comparison of QCFR© (aka FCFR©) derived from the FMTVDM©℗ with QCA measured CFR was performed using regression analysis and best fit linear regression modeling.

## Results

Following assessment of each clinical facility to determine adequately trained personnel, operators at 7-Centers of Excellence (COE) were recruited to conduct "stress-first/stress only/stress-stress" FMTVDM Imaging. Outcomes were independent of isotope, camera type, Camera Company or "stressor" employed. Outcome analysis was obtained using AI measured and quantitatively derived CFR (QCFR©/FCFR©) results using FMTVDM©℗ measurements and proprietary equations, compared with that obtained from direct QCA. The results from the 7COE yielded regression analysis of y=(0.8758•x)+0.4291, where y=the QCFR and x=the QCA measured CFR. The R2 value 0.87582 demonstrated the 7-COE accurately, consistently and reproducibly clinically implemented FMTVDM©℗ to derive by AI, QCFR©/FCFR© in all 401 patients.

## Discussion

The first step in the demonstration of a new method for diagnostically studying a health problem is to compare the new test with the currently accepted approach [4-7]. If the results are promising investigators conduct a single center clinical trial [15]. If the newer method provides better clinical and diagnostic outcomes than the currently accepted method [4-7,15] and provides a significant advancement for the field [16-20], a multicenter trial is initiated to demonstrate that clinicians with various backgrounds, in various clinical settings are able to accurately, consistently and reproducibly utilize the new diagnostic test and obtain the expected outcomes.

In this study, seven COE from the USA and Asia independently conducted clinical MPI studies using FMTVDM©℗ using the first true quantification method for nuclear imaging studies and AI. The outcomes demonstrated the ability of each COE to accurately, consistently and reproducibly use FMTVDM©℗ to diagnose the level of clinical disease without error, while saving time, reducing healthcare costs and markedly decreasing patient radiation exposure with potential associated risks.

## Conclusions

FMTVDM©℗ utilizing AI accurately, consistently and reproducibly provided true quantification of CAD in 7-COE in the USA and Asia. The utilization of AI FMTVDM©℗ provided accurate, consistent and reproducible quantitative CFR beginning with the true quantification of isotope redistribution using the patented proprietary equations independent of isotope, camera type (SPECT, PET), camera company, operator variables or site location. FMTVDM©℗ provides the first truly quantitative, truly AI Nuclear Imaging of CAD and CFR introducing a new era of nuclear cardiology. The use of FMTVDM©℗ provides the first ever "Quantitative" AI method able to differentiate tissue vascularity and metabolism and as such provides an evolutionary quantum leap forward for the fields of nuclear cardiology and nuclear medicine.

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