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Authors
Hubbard, Logan
Malkasian, Shant
Zhao, Yixiao
et al.

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Low-radiation-dose stress myocardial perfusion measurement using first-pass analysis dynamic computed tomography: A preliminary investigation in a swine model

Logan Hubbard, Ph.D.[1], **Shant Malkasian, B.S.**[1], **Yixiao Zhao, M.S.**[1], **Pablo Abbona, M.D.**[1], **Jungnam Kwon, M.D.**[1], **Sabee Molloi, Ph.D**[1]

[1]Department of Radiological Sciences, University of California - Irvine, Irvine, California, 92697, USA

Abstract

Objectives—To assess the feasibility of a prospective first-pass analysis (FPA) dynamic CT perfusion technique for accurate low-radiation-dose stress global stress perfusion measurement.

Materials and Methods—The prospective FPA technique was evaluated in ten swine (42 ± 12 kg) by direct comparison to a previously validated retrospective FPA technique. Of the ten swine, three had intermediate stenoses with fractional flow reserve severities of 0.70 – 0.90. In each swine, contrast and saline were injected peripherally followed by dynamic volume scanning with a 320-slice CT scanner. Specifically, for the reference standard retrospective FPA technique, volume scans were acquired continuously at 100 kVp and 200 mA over fifteen to twenty seconds, followed by systematic selection of only two volume scans for global perfusion measurement. For the prospective FPA technique, only two volume scans were acquired at 100 kVp and 50 mA for global perfusion measurement. All prospective global stress perfusion measurements were then compared to the corresponding reference standard retrospective global stress perfusion measurements through regression analysis. The $CTDI_{vol}^{32}$ and size-specific dose estimate (SSDE) of the prospective FPA technique were also determined.

Results—All prospective global stress perfusion measurements (P_{PRO}) at 50 mA were in good agreement with the reference standard retrospective global stress perfusion measurements (P_{REF}) at 200 mA (P_{PRO} = 1.07 P_{REF} - 0.09, r = 0.94, RMSE = 0.30 mL/min/g). The $CTDI_{vol}^{32}$ and SSDE of the prospective FPA technique were 2.3 and 3.7 mGy, respectively.

Conclusions—Accurate low-radiation-dose global stress perfusion measurement is feasible using a prospective FPA dynamic CT perfusion technique.

Keywords

Coronary artery disease; Myocardial perfusion imaging; Dynamic computed tomography; Dose reduction

Address for Correspondence: Sabee Molloi, Ph.D., Department of Radiological Sciences, Medical Sciences I, B-140, University of California, Irvine, CA 92697, Telephone: (949) 824-5904, Fax: (949) 824-8115, symolloi@uci.edu.

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Introduction

Coronary artery disease (CAD) is a major global health concern. While computed tomography (CT) angiography is a powerful tool for non-invasive assessment of CAD, it is an imperfect guide for percutaneous coronary intervention (PCI) as downstream PCI and optimal medical therapy outcomes are often equivalent(1). Such discrepancies stem from the fact that CT angiography alone can only assess the morphological severity of segmental stenosis, i.e., it cannot resolve the functional severity of concurrent multi-vessel, diffuse, and microvascular disease. Hence, guidelines recommend additional flow-based assessment of CAD to appropriately stratify patient risk and guide downstream intervention(2–4). Nevertheless, the primary modalities used for flow-based assessment of CAD, i.e., single-photon emission computed tomography (SPECT), cardiac magnetic resonance, static positron emission tomography (PET), and static CT perfusion only provide metrics of relative perfusion(5–10). As a result, they cannot resolve the true functional severity of multiform CAD. Only absolute stress perfusion measurement in mL/min/g can overcome these limitations, where the vessel-specific distribution of stress perfusion combined with physiologic cutoff thresholds(11) may be used to more reliably stratify patient risk and more properly guide downstream intervention.

Absolute stress perfusion is most commonly measured with dynamic PET(4). However, limited radiotracer access and high cost preclude its routine clinical use(12). Fortunately, recent research suggests that absolute stress perfusion measurement is also feasible with dynamic CT(13–15), is more capable of determining the functional significance of intermediate severity of CAD than CT angiography alone(16), and can be used in conjunction with CT angiography for improved comprehensive workup of multiform CAD(13, 17). Nevertheless, despite positive correlation with quantitative microsphere perfusion, current upslope-based dynamic CT perfusion techniques are known to underestimate absolute perfusion(18–20). More specifically, to maintain high spatial resolution, these techniques derive perfusion in small myocardial tissue volumes(18–20). Given the rapid hyperemic transit from coronary artery to coronary sinus(21), contrast material unavoidably exits these small tissue volumes during the measurement time, leading to perfusion underestimation(18–20). Small tissue volumes also suffer from poor signal-to-noise ratio (SNR) and are more susceptible to artifacts; hence, smooth curve fitting of data over many cardiac cycles is necessary to improve measurement reliability, leading to high effective radiation doses(~10 mSv)(5). In combination, these factors have limited the clinical adoption of dynamic CT perfusion; thus, there is a need for an improved accurate low-radiation-dose dynamic CT perfusion technique.

Fortunately, a new dynamic CT perfusion technique based on first-pass analysis (FPA) addresses the problems of perfusion underestimation and high radiation dose via the use of 320-slice CT technology for whole-heart imaging within a single cardiac cycle. More specifically, rapid whole-heart imaging allows the entire myocardial tissue volume to be used as a single large perfusion compartment with an extended contrast material transit time window. As a result, dynamic volume scan acquisition can be performed prior to contrast material exit; thus, the problem of perfusion estimation can be solved. More importantly, given the large compartment size and extended transit time window, the accumulation of

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contrast material over time is also large; hence, the number of dynamic volume scans necessary for accurate vessel-specific perfusion measurement can be reduced to a minimum of two, i.e., radiation dose reduction is feasible, as previously validated retrospectively versus invasive fractional flow reserve (FFR), quantitative microsphere perfusion, and ultrasonic flow probe measurement(22–24). That said, no prospective assessment of the FPA technique has been performed to date. Hence, the purpose of this study was to assess the feasibility of prospective implementation of the FPA technique for accurate low-radiation-dose global stress perfusion measurement(22–24). The central hypothesis was that global stress perfusion measurement was feasible using only two whole-heart volume scans that were prospectively acquired at a reduced tube current.

Materials and Methods

FPA Dynamic CT Perfusion Theory

As previously described(22–24), first-pass analysis (FPA) and conservation of mass(25) state that the average perfusion (P_{AVE}) within the entire myocardium (C_{MYO}) is proportional to the first-pass entry of contrast material mass into the myocardium (dM_C/dt), normalized by the incoming contrast material concentration (C_{in}) and myocardial tissue mass (M_T), prior to contrast material outflow. By extension, the average perfusion (P_{AVE}) is also proportional to the first-pass contrast material concentration change within the myocardium; i.e., the average change in myocardial enhancement (ΔHU_{AVE}) over time. Hence, the integrated change in myocardial enhancement (dM_C/dt), the average change in myocardial enhancement (ΔHU_{AVE}), the average aortic blood pool enhancement (C_{in}), the change in myocardial enhancement (ΔHU), and the total myocardial mass (M_T) may be used in combination to derive perfusion (P_{FPA}), as described by Equation 1 and Figure 1a and 1b. Given such a theory, only two whole-heart volume scans, labeled V1 and V2 in Figure 1b, are mathematically necessary for accurate global or vessel-specific perfusion measurement, as previously validated retrospectively versus invasive fractional flow reserve (FFR), quantitative microsphere perfusion, and ultrasonic flow probe measurement(22–24). Specifically, V1 is defined as the first volume scan after the aortic enhancement exceeds 140 HU above the baseline blood pool enhancement, while V2 is defined as a volume scan that approximates the peak of the aortic enhancement. Such an acquisition strategy maximizes the contrast material mass difference between V1 and V2, while also avoiding false triggering of V1 by the blood pool noise.

$$P_{FPA} = \left(M_T^{-1} C_{in}^{-1} \frac{dM_c}{dt} \right)_{AVE} \cdot \frac{\Delta HU}{\Delta HU_{AVE}} \quad (1)$$

General Methods

The study was approved by the Animal Care Committee and was performed on a total of ten male Yorkshire swine (42 ± 12 kg) with all experiments successfully completed. First, repeat retrospective global perfusion measurements were performed in two of the swine under rest conditions at 100 kVp and 100, 50, 25, and 10 mA, and were compared to corresponding

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reference standard retrospective global perfusion measurements at 100 kVp and 200 mA(22–24). The aim was to determine the minimum tube current necessary for accurate global perfusion measurement with the FPA technique. Using this minimum tube current, the accuracy of prospective, two-volume global perfusion measurement was then assessed in the remaining eight swine under maximal IV stress conditions (240 μg adenosine/kg/min, Model 55–2222, Harvard Apparatus, Holliston, MA), where three of those eight swine had intermediate stenoses with FFR severities of 0.7 – 0.9. Specifically, prospective global perfusion measurements were made in all eight swine at 100 kVp and 50 mA and were compared to corresponding reference standard retrospective global perfusion measurements which were made at 100 kVp and 200 mA, again as previously validated(22–24). The aim was to determine if accurate prospective global perfusion measurement was feasible with the FPA technique using only two whole-heart volume scans that were acquired at a reduced tube current.

Swine Model Preparation

For all ten swine, anesthesia was induced with Telazol (4.4 mg/kg), Ketamine (2.2 mg/kg), and Xylazine (2.2 mg/kg), and was maintained with 1.5–2.5% Isoflurane (Highland Medical Equipment, Temecula, CA and Baxter, Deerfield, IL). Sheaths were placed (AVANTI®, Cordis Corporation, Miami Lakes, FL) in both femoral veins and were used for IV fluid and contrast material administration, with adenosine also infused for stress perfusion conditions in eight of the swine (240 μg adenosine/kg/min). Additionally, in the last three swine, another sheath was placed in the right carotid artery and was used to pass a Judkins Right (JR) catheter (Cordis Corporation, Miami Lakes, FL) into the left coronary ostium. A pressure wire (PrimeWire PRESTIGE® Pressure Guide Wire, Volcano Corp, Rancho Cordova, CA) was then advanced through the JR catheter into the distal left anterior descending (LAD) coronary artery, and a balloon was passed over the wire into the mid LAD. The balloon was used to generate several sub-occlusive stenoses with fractional flow reserve (FFR) (ComboMap, Volcano Corp., Rancho Cordova, CA) severities of 0.7 – 0.9 at maximal IV stress (240 μg adenosine/kg/min).

Retrospective FPA Perfusion Protocol

For the first two swine, reference standard perfusion acquisitions were performed under rest conditions. Specifically, contrast material (1 mL/kg, Isovue 370, Bracco Diagnostics, Princeton, NJ) was injected peripherally via a femoral vein sheath (5 mL/s, Empower CTA, Acist Medical Systems, Eden Prairie, MN) followed by a saline chaser (0.5 mL/kg) at the same rate. Whole-heart volume scans were then acquired dynamically at 100 kVp and 200 mA (Aquilion One, Canon Medical Systems, Tustin, CA) over fifteen to twenty seconds to completely capture the aortic enhancement curve, where all volume scans were ECG-gated full projection scans with a 0.35 second rotation time with 320 × 0.5 mm collimation. Two volume scans (V1 and V2) were then systematically selected at approximately the base and peak of the aortic enhancement, as described above, for each reference standard retrospective global perfusion measurement, as previously validated(22–24). The reference standard retrospective FPA perfusion protocol is shown in Figure 1c.

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A minimum ten-minute delay was then employed to allow for adequate recirculation and redistribution of contrast material within the blood pool and interstitium, prior to beginning retrospective global perfusion measurement at reduced tube current. Following the delay, contrast material and a saline chaser were then injected as described above, and whole-heart volume scans were acquired dynamically at 100 kVp and 100, 50, 25, and 10 mA, with a minimum ten-minute delay employed between all acquisitions at reduced tube current. From each acquisition series, two volume scans (V1 and V2) were again systematically selected at approximately the base and peak of the aortic enhancement (22–24) for each retrospective global perfusion measurement at reduced tube current. The entire acquisition scheme was then repeated, such that duplicate reference standard and reduced tube current perfusion measurements were made in each swine, for a total of four retrospective global perfusion measurements at each reduced tube current and four reference standard retrospective global perfusion measurements. The $CTDI_{vol}^{32}$ of global perfusion measurement was recorded in each case. Finally, the minimum tube current necessary for accurate retrospective global perfusion measurement with the FPA technique was determined.

Prospective FPA Perfusion Protocol

For the next eight swine, reference standard perfusion acquisitions were again performed at 100 kVp and 200 mA, as described above, but under maximal IV stress conditions (240 μg adenosine/kg/min). A minimum ten-minute delay was again employed during each acquisition delay. Of note, during each delay, the time (Δt) between V1 and V2 was estimated from the prior reference acquisition using automatic time-density-curve analysis (Acquilion One, Canon Medical Systems, Tustin, CA) and was used, in place of a diluted test bolus(26) or an empirically derived time delay(27), for proper timing of the subsequent prospective two-volume FPA perfusion acquisition. Following each delay, contrast material and a saline chaser were injected as described above, and low-dose, 2-mm slab, dynamic bolus tracking at (SureStart, Aquilion One, Canon Medical Systems, Tustin, CA) was performed, where V1 was acquired after the aortic enhancement exceeded 140 HU above the baseline blood pool intensity while V2 was acquired after V1 using the previously estimated time delay, Δt. Of note, both volume scans were acquired at 100 kVp and 50 mA, i.e., at the previously determined reduced tube current necessary for accurate global perfusion measurement. After each acquisition, V1 and V2 were used for prospective global perfusion measurement. The entire acquisition scheme was then repeated, such that two to three global stress perfusion measurements were made in each swine, for a total of 18 prospective global stress perfusion measurements and 18 corresponding reference standard retrospective global stress perfusion measurements. Finally, the $CTDI_{vol}^{32}$ for all prospective global stress perfusion measurements was recorded, with a size-specific dose estimate (SSDE) also determined(28) to account for the small effective diameter of the swine used in the study. The prospective FPA perfusion protocol is shown in Figure 1d.

Image Processing

All volume scans were first reconstructed from full projection data at 75% of the R-R interval using AIDR 3D reconstruction(29) and a voxel size of 0.43 × 0.43 × 0.50 mm. The volume scans of interest, i.e. V1 and V2, from each acquisition were then deformably

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registered using a mutual information metric(30) and combined into maximum intensity projection (MIP) image volumes with the same voxel raster as above. Each MIP was then segmented semi-automatically (Vitrea fX version 6.0, Vital Images, Inc., Minnetonka, MN), yielding the entire myocardium as a binary mask. Using each mask, perfusion measurements were then computed according to Equation 1 and were averaged within the entire myocardium to yield global perfusion measurements. All retrospective global perfusion measurements at reduced tube current and all prospective two-volume global perfusion measurements at 50 mA were then quantitatively compared to their corresponding reference standard retrospective global perfusion measurements at 200 mA. Additionally, as a proof-of-concept in one swine, the prospective stress perfusion maps in the presence of intermediate severity stenoses with FFR severities of 0.7 – 0.9 were automatically clustered using predefined physiologic cutoff thresholds to yield the amount of myocardial tissue with normal stress perfusion (>2.39 mL/min/g), minimal stress perfusion reduction (1.76 – 2.39 mL/min/g), mild stress perfusion reduction (1.20 – 1.76 mL/min/g), moderate stress perfusion reduction (0.91 – 1.20 mL/min/g), and definite ischemia (0.00 – 0.91 mL/min/g) (11).

Dose-Modulated FPA Dynamic CT Perfusion Protocol

The impact of dose-modulation on the $CTDI_{vol}^{32}$ of the prospective FPA technique was also assessed over a range of effective diameters. The automatic exposure control settings (SureExposure, Acquilion One, Canon Medical Systems, Tustin, CA) were first tuned to match the image noise characteristics from the swine at 100 kVp and 50 mA. Water phantoms with effective diameters of 24 cm, 34 cm, and 42.5 cm were then imaged with the noise-matched dose-modulated implementation of the prospective FPA technique. The resulting $CTDI_{vol}^{32}$ data was then used to estimate the $CTDI_{vol}^{32}$ of global perfusion measurement as a function of effective diameter.

Statistical Approach

First, student's T-tests were performed to determine if the retrospective global perfusion measurements at reduced tube current were significantly different from the corresponding reference standard retrospective global perfusion measurements at 200 mA. Second, the prospective global perfusion measurements were quantitatively compared to the corresponding reference standard retrospective global perfusion measurements through regression, root-mean-square-error (RMSE), root-mean-square deviation (RMSD), and Lin's concordance correlation coefficient (CCC)(31). Student's T-tests were also performed to determine if the prospective global stress perfusion measurements were significantly different from the corresponding reference standard retrospective global stress perfusion measurements. All fit parameter data were reported with 95% confidence intervals displayed in brackets. All other data were reported as mean ± standard deviation. P-values less than 0.05 indicate significant differences. Statistical software was used for all analyses (MatLab 2013a, MathWorks, Natick, MA; PS, Version 3.0, Vanderbilt University, Nashville, TN; SPSS, Version 22, IBM Corporation, Armonk, NY).

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Results

Accuracy and Precision Results

The heart rate and mean arterial pressure of the ten swine were 94 ± 9 beats per minute and 74 ± 9 mmHg, respectively. Retrospective global rest perfusion at 100 and 50 mA were 0.79 ± 0.37 mL/min/g and 0.69 ± 0.25 mL/min/g, respectively, which were not significantly different from the reference standard retrospective global rest perfusion of 0.71 ± 0.33 mL/min/g at 200 mA ($p = 0.33$ and $p = 0.43$). while retrospective global rest perfusion at 25 and 10 mA were 0.43 ± 0.31 mL/min/g and 0.27 ± 0.22 mL/min/g, respectively, which were significantly different from reference standard retrospective global rest perfusion ($p = 0.04$ and $p = 0.00$). All other tube current reduction and perfusion data are reported in Table 1.

The average prospective global stress perfusion at 50 mA was 2.01 ± 0.88 mL/min/g, which was not significantly different from the average reference standard retrospective global stress perfusion of 1.96 ± 0.77 mL/min/g ($p = 0.55$) at 200 mA. All other prospective perfusion data are reported in Table 2. Additionally, prospective global stress perfusion (P_{PRO}) and reference standard retrospective global stress perfusion (P_{REF}) measurements were related by $P_{PRO} = 1.07\ P_{REF} - 0.09$ (Slope, 95% CI: 0.86 – 1.27; Intercept, 95% CI: −0.52 – 0.35), with a Pearson's correlation of $r = 0.94$ (95% CI: 0.84 – 0.98), a concordance correlation of $\rho = 0.93$ (95% CI: 0.82 – 0.97), a root-mean-square-error of 0.30 mL/min/g, and a root-mean-square deviation of 0.29 mL/min/g, as shown in Figure 2. Prospective stress perfusion maps are also displayed in the absence and presence of a LAD stenosis with a FFR severity of 0.7, as shown in Figure 3. In each case, the amount of myocardial tissue with normal flow (>2.39 mL/min/g), no ischemia but minimal flow reduction (1.76 – 2.39 mL/min/g), no ischemia but mild flow reduction (1.20 – 1.76 mL/min/g), moderate flow reduction (0.91 – 1.20 mL/min/g), and definite ischemia (0.00 – 0.91 mL/min/g) is also reported in Table 3.

Dose Reduction Results

The $CTDI_{vol}^{32}$ of retrospective global rest perfusion measurement at 100, 50, 25, and 10 mA was 4.60, 2.30, 1.15, and 0.46 mGy, while the $CTDI_{vol}^{32}$ of reference standard retrospective global rest perfusion measurement was 9.20 mGy. The $CTDI_{vol}^{32}$ and SSDE for prospective two-volume global stress perfusion measurement were estimated to be 2.3 and 3.7 ± 0.43 mGy. All other dose-reduction data are reported in Table 1 and Table 2. Finally, for the noise-matched dose-modulated implementation of the prospective FPA technique, the $CTDI_{vol}^{32}$ of global perfusion measurement as a function of effective diameter (cm) was $CTDI_{vol}^{32} = 0.09e^{0.13\ cm}$, as shown in Figure 4, where the $CTDI_{vol}^{32}$ in a CAD patient with an average effective diameter of 34 cm(32) was estimated to be 7.5 mGy.

Discussion

Indication of Results

The results of retrospective rest global perfusion measurement at 100 and 50 mA were in good agreement with reference standard retrospective global rest perfusion measurement at

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200 mA, while retrospective global rest perfusion measurement at 25 and 10 mA significantly underestimated reference standard retrospective global rest perfusion measurement. Hence, the results of the reduced tube current measurement analysis suggest that accurate global perfusion measurement is feasible with the retrospective FPA technique at a tube current as low as 50 mA. Moreover, the results of the prospective measurement analysis demonstrate that accurate prospective global perfusion measurement at 50 mA is also feasible with the prospective FPA technique, as compared to the previously validated reference standard retrospective FPA technique at 200 mA. First, there were no significant differences between average prospective global stress perfusion measurement and average reference standard retrospective global stress perfusion measurement. Second, prospective global stress perfusion measurements agreed well with reference standard retrospective global stress perfusion measurements, demonstrating near unity slope, minimal offset, negligible bias, good concordance correlation, and small RMSE and RMSD. Third, the qualitative spatial distribution of stress perfusion also agreed well with the induced flow conditions, where stress perfusion without a stenosis appeared normal, while stress perfusion distal to a LAD stenosis with FFR severity of 0.7 appeared markedly reduced. The fractional breakdown of stress perfusion throughout the myocardium also appeared to be in agreement in each case, although the quantitative accuracy of such data could not be assessed. In combination, these findings suggest that accurate global stress perfusion measurement with the prospective FPA technique is feasible at a $CTDI_{vol}^{32}$ and SSDE as low as 2.3 and 3.7 ± 0.43 mGy, respectively.

Such results are ultimately enabled by 320-slice CT technology, mass conservation, and first-pass analysis (FPA). More specifically, by maximizing the size of the myocardial tissue compartment assessed, while simultaneously minimizing the number of volume scans acquired, accurate low-radiation-dose global and vessel-specific perfusion measurement is feasible with the FPA technique(22–24). As such, the prospective FPA technique could help to increase clinical utilization of combined stress and rest dynamic CT perfusion protocols, such that coronary flow reserve (CFR) may also be assessed(11). Moreover, given the unique two-volume acquisition protocol of the prospective FPA technique, V2 has the potential to be used for CT angiography during rest perfusion measurement(22, 23) or for cardiac functional analysis (CFA) during stress perfusion measurement(33, 34), provided the tube current and exposure time are increased, respectively. Hence, the prospective FPA technique has further potential to provide morphological and functional assessment of multiform CAD into a single comprehensive CT exam, although further validation is still necessary.

Limitations

This study is not without limitations. First, a small number of swine were used for validation; two swine in the retrospective tube current reduction cohort and eight swine in the prospective cohort. While multiple measurements were made in each animal, additional studies in more animals may still be necessary. Moreover, for the purposes of validation, the global perfusion between the retrospective reduced tube current or prospective acquisitions and their corresponding reference standard retrospective acquisitions was assumed to be unchanged. However, fluctuations in the swines' vitals between paired acquisitions may

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have contributed to measurement variance. Therefore, considerable effort was made to tightly control ventilation, anesthesia, IV fluid administration, and hemodynamics between acquisitions. As an alternative solution, artificial noise could have been added to the raw data projections of the reference standard retrospective acquisitions to simulate reduced tube current acquisitions(35), but raw data projection access was not possible in this study. Of additional note, the swine had high heart rates; a common impediment to accurate dynamic CT perfusion measurement. Fortunately, the prospective FPA technique relies on the integrated change in HU within the entire myocardium to derive perfusion. Hence, the absolute error due to heart-rate-dependent motion artifact was negligible(22–24), with further error reduction achieved through deformable registration of V1 and V2(30).

Another limitation was proper prospective acquisition of V2 at approximately the peak of the aortic enhancement(23, 24, 26). For the purposes of this study, the optimal time delay (Δt) between V1 and V2 to capture V2 at the peak was estimated from the reference standard retrospective acquisition prior to each subsequent prospective acquisition. While such a scheme is clinically unrealistic, fortunately, the optimal time delay can also be derived through the preemptive use of a low-dose diluted test bolus acquisition, as previously validated(26). Specifically, the geometry of a diluted test bolus emulates that of a true bolus(26); hence, the time delay can be predicted in advance and used for proper prospective acquisition of V2, albeit with increased contrast and radiation dose per exam. Alternately, recent work also suggests that the optimal time delay between V1 and V2 is simply a function of the contrast injection time plus a fixed dispersion time(27). Given such a relation, the optimal time delay can also be predicted in advance, without the use of a preemptive low-dose diluted test bolus acquisition.

The swine used in the study also had a small 25 cm effective diameter as compared to the average 34 cm effective diameter of patients with CAD(32). When using a fixed tube current, a patient with a large effective diameter will have lower photon flux as compared to a patient with a small effective diameter. Such a relation is problematic at very low tube currents, as photon starvation leads to attenuation bias which leads to perfusion measurement inaccuracy(35). Fortunately, work by Mirsadraee et al. suggests that a tube current as low as 50 mA may be used over a large range of effective diameters with minimal attenuation bias(35), although measurement noise increases for larger effective diameters. That being said, adequate noise reduction may still be achieved using model-based iterative reconstruction algorithms such as FIRST(36). Additionally, dose-modulated techniques (SureExposure, Acquilion One, Canon Medical Systems, Tustin, CA) can enable automatic adjustment of the tube current necessary to maintain the same measurement noise at any effective diameter. Therefore, dose modulation in water phantoms was used to approximate the $CTDI_{vol}^{32}$ of prospective global perfusion measurement with the FPA technique as a function of effective diameter. Unfortunately, such phantoms cannot truly emulate the noise characteristics of a bony thorax; hence, the $CTDI_{vol}^{32}$ estimates remain a limitation.

Additionally, tube current reduction was performed at a single kVp, i.e., the impact of reducing the incident X-ray energy on prospective triggering, measurement accuracy, and radiation dose was not assessed. Hence, additional work to assess the performance of the FPA technique at different mA and kVp setting combinations is still necessary. Nevertheless,

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the effective radiation dose of the prospective FPA technique is still expected to be markedly low, even for large effective diameter patients, as only *two* whole-heart volume scans are necessary for accurate prospective global perfusion measurement.

Another limitation of the study was that global perfusion measurements were used for validation, in the absence of CT angiography. Specifically, the vessel-specific distribution of stress perfusion combined with physiologic cutoff thresholds(11) and CT angiographic data are necessary for reliable risk stratification and proper downstream intervention of CAD. Hence, the value of global perfusion measurement alone is limited. Fortunately, if prospective FPA perfusion data is acquired in combination with a CT angiogram(22, 23, 26), the coronary tree data can be used in combination with minimum-cost-path myocardial assignment(37, 38) to generate coronary vessel-specific territories, i.e., perfusion measurements can be averaged within each territory to yield vessel-specific or branch-specific perfusion measurement, as previously validated(22, 23). Nevertheless, CT angiography data was not acquired in this study; hence, perfusion territory assignment could not be performed.

One final limitation of the study is that the accuracy and dose of the prospective FPA technique are a function of the volume of myocardial tissue assessed. More specifically, as radiation dose is task dependent, the minimum dose necessary for accurate global perfusion measurement, by definition, must be less than the minimum dose necessary for accurate vessel-specific perfusion measurement, assuming equivalent diagnostic parameters. Hence, additional work to determine the minimum dose necessary for accurate prospective vessel-specific FPA perfusion measurement is still necessary.

Conclusion

In conclusion, the prospective FPA technique enables accurate measurement of global stress perfusion using only two whole-heart volume scans that are prospectively acquired at reduced tube current. The results indicate that the tube current can be reduced to as low as 50 mA, while maintaining global perfusion measurement accuracy. Moreover, the results indicate that prospective global perfusion measurement is also feasible, i.e., only two volume scans need to be acquired for accurate prospective global perfusion measurement as compared to the previously validated retrospective FPA technique(22–24). Hence, the prospective FPA technique can dramatically reduce the radiation dose associated with dynamic CT perfusion-based assessment of global stress perfusion.

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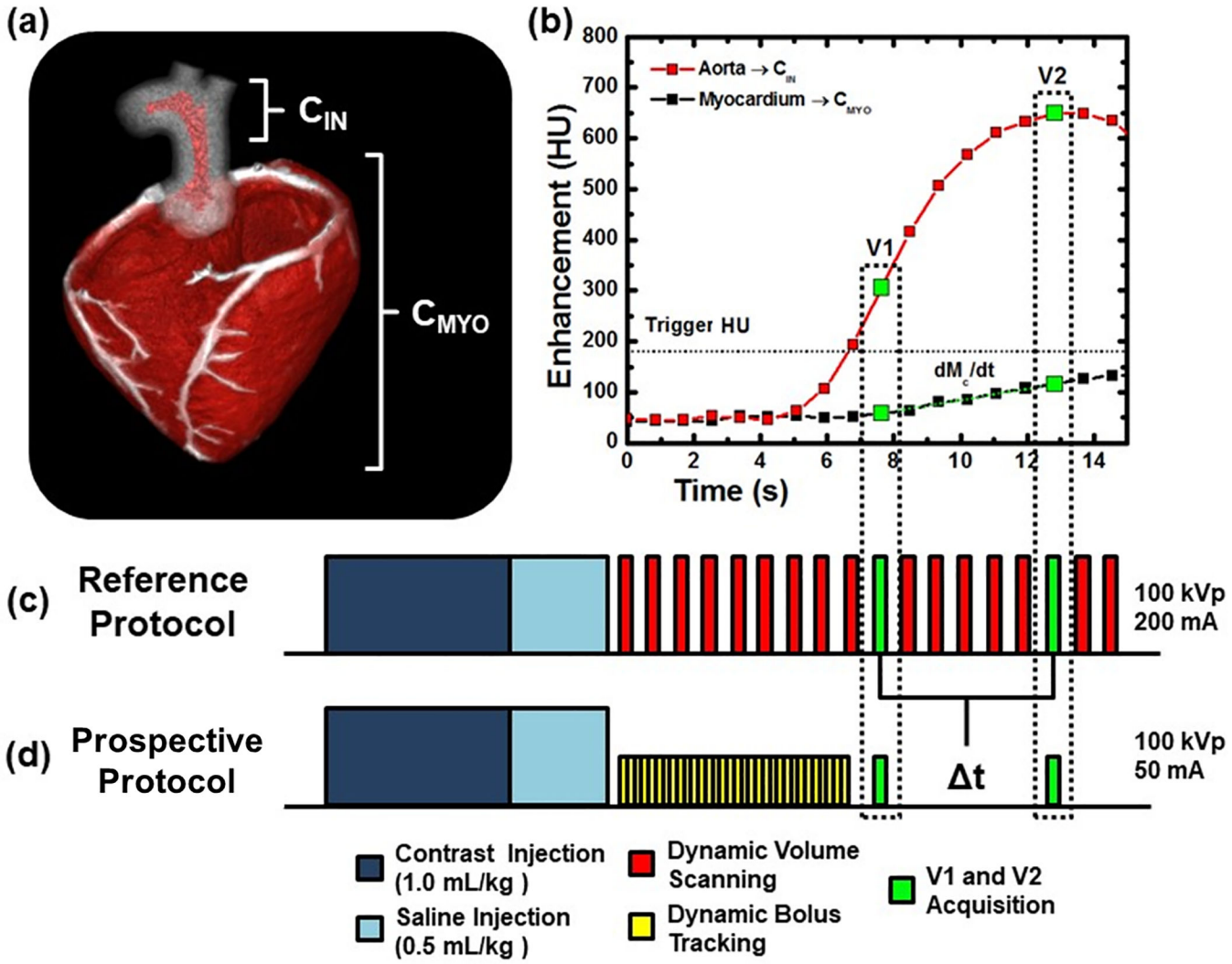

Figure 1: First-pass analysis theory and implementation.

(a) Whole-heart myocardial perfusion compartment (C_{MYO}) and input concentration (C_{IN}) used for first-pass-analysis dynamic CT perfusion measurement. (b) The first-pass enhancement within the aorta and entire myocardium following contrast and saline injection are shown in red and black, respectively. Two first-pass volume scans, V1 and V2 denoted in green, are used for both reference standard retrospective and prospective global perfusion measurement, respectively. (c) The reference standard retrospective FPA dynamic CT perfusion protocol is comprised of contrast injection and dynamic volume scan acquisition at 100 kVp and 200 mA over fifteen to twenty seconds, followed by systematic selection of the V1 and V2 volume scans for global perfusion measurement. (d) The prospective FPA dynamic CT perfusion protocol is comprised of contrast injection followed by 2-mm slab dynamic bolus tracking at 100 kVp and 50 mA, triggering at 140 HU above the baseline blood pool enhancement HU, then dynamic volume scan acquisition of two volume scans, V1 and V2, at 100 kVp and 50 mA for global perfusion measurement.

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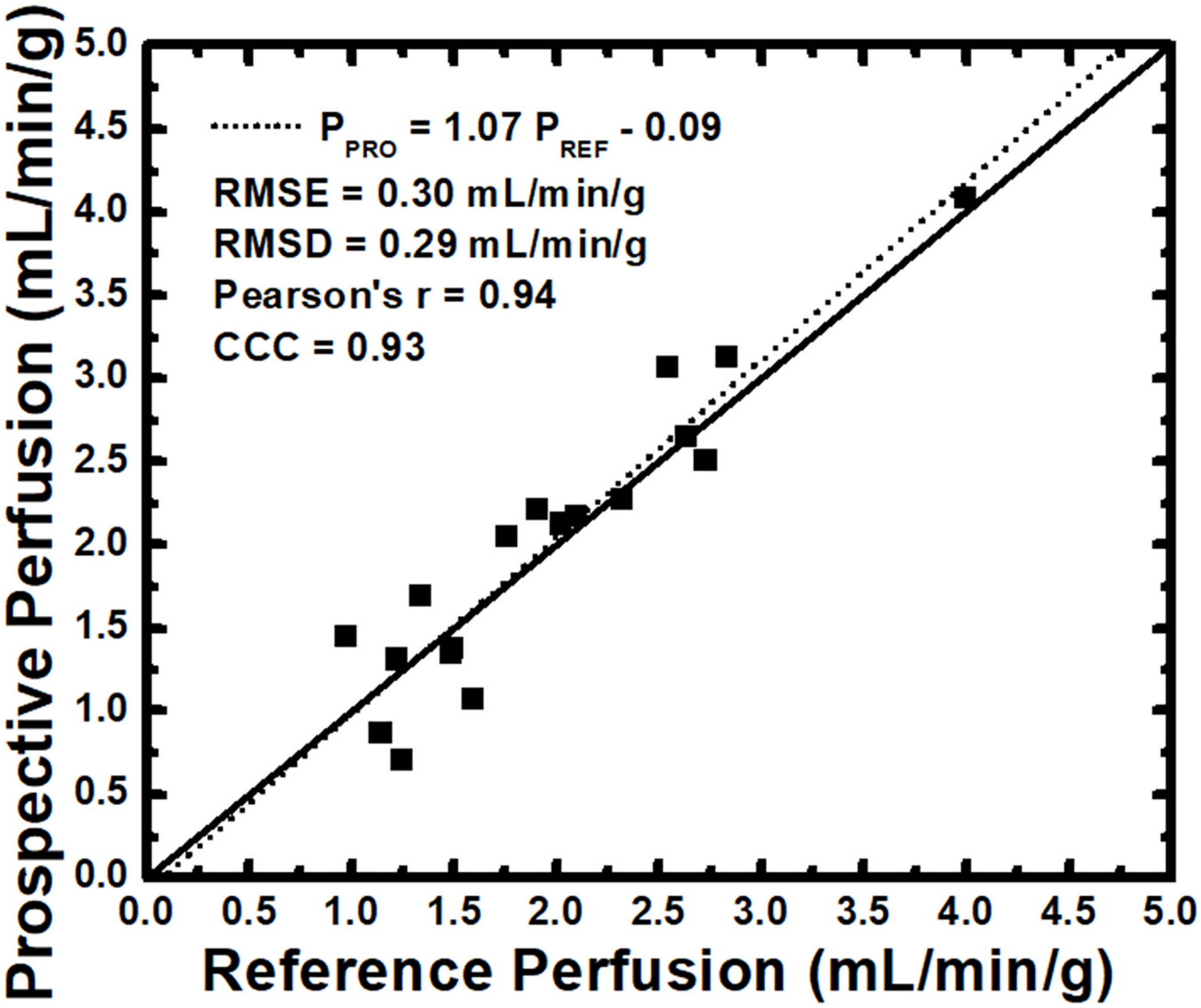

Figure 2: Prospective global stress perfusion measurement analysis.

Two to three global stress perfusion conditions were assessed in each swine, for a total of 18 prospective global stress perfusion measurements and 18 reference standard retrospective global perfusion measurements. The regression analysis compares prospective global stress perfusion measurements at 50 mA (P_{PRO}) to corresponding reference standard retrospective global stress perfusion measurements at 200 mA (P_{REF}). RMSE indicates root-mean-square-error; RMSD, root-mean-square-deviation; CCC, Lin's concordance correlation.

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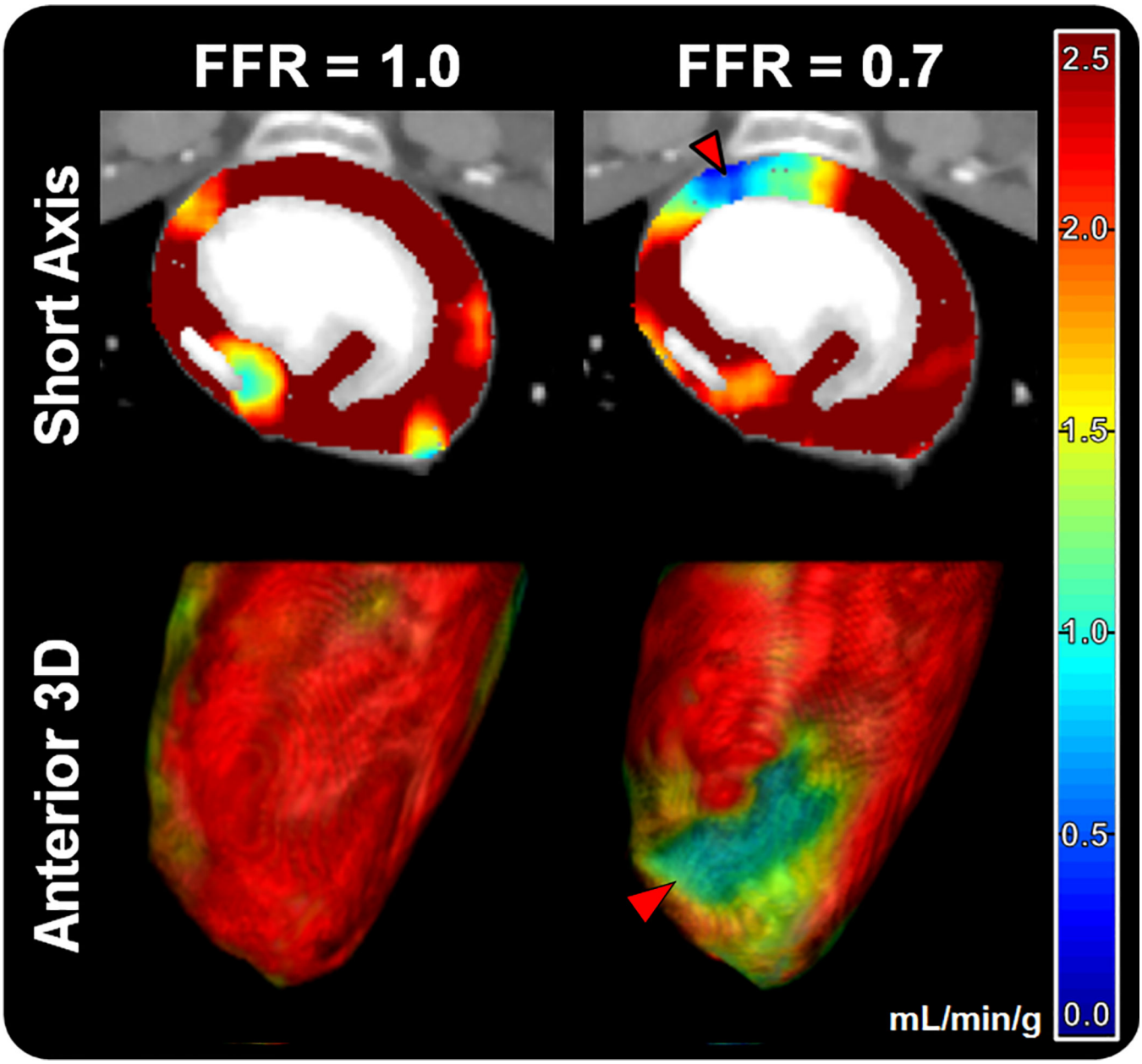

Figure 3: Qualitative prospective stress perfusion measurement distribution in the absence and presence of a significant left anterior descending (LAD) coronary artery stenosis in one swine.

The perfusion deficit displayed in the short axis view (top row) and anterior 3D view of the left ventricle (bottom row) had an FFR severity of 0.70. The red arrow in the short axis and anterior 3D view of the left ventricle indicates the perfusion defect in the LAD territory. The color bar indicates prospective stress perfusion measurement in mL/min/g. Red = normal perfusion (>2.39 mL/min/g); orange = no ischemia but minimally reduced perfusion (1.76 – 2.39 mL/min/g); yellow = no ischemia but mildly reduced perfusion (1.20 – 1.76 mL/min/g); green = moderately reduced perfusion capacity (0.91 – 1.20 mL/min/g); blue = definite ischemia and/or myocardial steal (0.00 – 0.91 mL/min/g)(11).

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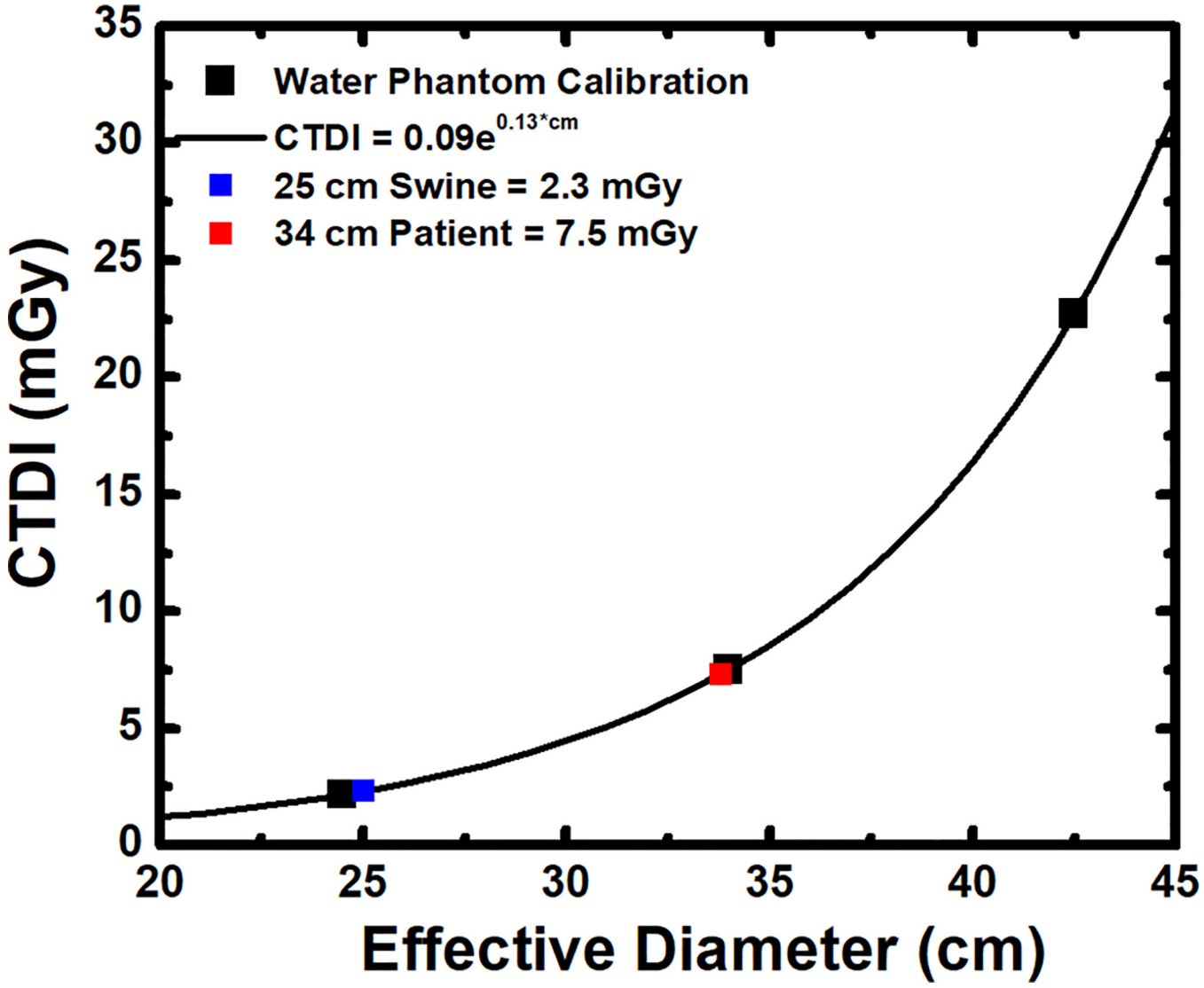

Figure 4: $CTDI^{32}_{vol}$ of global stress perfusion measurement with the prospective FPA technique using dose-modulation.

The $CTDI^{32}_{vol}$ estimates are shown for a range of effective diameters, where prospective global stress perfusion measurement in an average 34 cm effective diameter patient is also displayed.

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Table 1.

Global rest perfusion measurement at reduced tube current and reference standard global rest perfusion measurement mean comparison with corresponding dose metrics in two swine

Perfusion Metric	200 mA Reference	100 mA	50 mA	25 mA	10 mA
REST (N = 4)					
GLOBAL (mL/min/g)	0.71 ± 0.33	0.79 ± 0.37 (p = 0.33)	0.69 ± 0.25 (p = 0.43)	0.43 ± 0.31 (p = 0.04)	0.27 ± 0.22 (p = 0.00)
$CTDI_{vol}^{32}$ (mGy)	9.20	4.60	2.30	1.15	0.46

Duplicate reference standard and reduced tube current global perfusion measurements were made in each swine, for a total of four global perfusion measurements at each reduced tube current and four reference standard retrospective global perfusion measurements. P-values less than 0.05 indicate significant mean differences in global rest perfusion. mA indicates the tube current setting; N, the total number of perfusion measurements at each tube current setting in two swine; GLOBAL, the entire myocardium; $CTDI_{vol}^{32}$, CT dose index per perfusion measurement.

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Table 2.

Prospective global stress perfusion measurement and reference standard retrospective global stress perfusion measurement mean comparison with corresponding prospective global stress perfusion dose metrics

Perfusion Condition	Prospective Perfusion (mL/min/g)	Reference Perfusion (mL/min/g)	P-value($\alpha < 0.05$)	$CTDI^{32}_{vol}$ (mGy)	SSDE (mGy)
STRESS (N = 18)					
GLOBAL	2.01 ± 0.88	1.96 ± 0.77	0.55	2.30	3.74 ± 0.43

Two to three global stress perfusion conditions were assessed in eight swine, for a total of 18 prospective global stress perfusion measurements and 18 reference standard retrospective global perfusion measurements. P-values less than 0.05 indicate significant mean differences. N indicates the total number of global perfusion measurements in eight swine; GLOBAL, the entire myocardium; CTDI, CT dose index; SSDE, size-specific dose estimate.

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Table 3.

Prospective stress perfusion distribution in the left ventricle of one swine in the absence and presence of functionally significant LAD stenosis(11)

Stress Perfusion Cutoff Thresholds (mL/min/g)	FFR = 1.0 LV Mass (%)	FFR = 0.90 LV Mass (%)	FFR = 0.80 LV Mass (%)	FFR = 0.70 LV Mass (%)
0.00 – 0.91 Definite ischemia	5.98	8.98	19.89	25.45
0.91 – 1.20 Moderate reduction	4.60	3.45	3.51	5.69
1.20 – 1.76 Mild reduction	11.67	11.02	9.10	12.47
1.76 – 2.39 Minimal reduction	10.86	19.78	8.87	16.72
2.39 < Normal flow	66.88	56.77	58.64	39.66

All stress perfusion cutoff thresholds are outlined by Johnson and Gould(11). LAD indicates the left anterior descending coronary artery; FFR, fractional flow reserve; LV, left ventricle.