Multidetector Computed Tomography 
Myocardial Perfusion Imaging During Adenosine Stress

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OBJECTIVES
The purpose of this study is to validate the accuracy of multidetector computed tomography (MDCT) to measure differences in regional myocardial perfusion during adenosine stress in a canine model of left anterior descending (LAD) artery stenosis, during first-pass, contrast-enhanced helical MDCT.

BACKGROUND
Myocardial perfusion imaging by MDCT may have significant implications in the diagnosis and treatment of coronary artery disease.

METHODS
Eight dogs were prepared with a LAD stenosis, and contrast-enhanced MDCT imaging was performed 5 min into adenosine infusion (0.14 to 0.21 mg/kg/min). Images were analyzed using a semiautomated approach to define the regional signal density (SD) ratio (myocardial SD/left ventricular blood pool SD) in stenosed and remote territories, and then compared with microsphere myocardial blood flow (MBF) measurements.

RESULTS
Mean MBF in stenosed versus remote territories was 1.37 ± 0.46 ml/g/min and 1.29 ± 0.48 ml/g/min at baseline (p = NS) and 2.54 ± 0.93 ml/g/min and 8.94 ± 5.74 ml/g/min during adenosine infusion, respectively (p < 0.05). Myocardial SD was 92.3 ± 39.5 HU in stenosed versus 180.4 ± 41.9 HU in remote territories (p < 0.001). There was a significant linear association of the SD ratio with MBF in the stenosed territory (R = 0.98, p = 0.001) and between regional myocardial SD ratio and MBF <8 ml/g/min, slope = 0.035, SE = 0.007, p < 0.001. Overall, there was a significant non-linear relationship over the range of flows studied (LR chi-square [2 degrees of freedom] = 31.8, p < 0.0001).

CONCLUSIONS
Adenosine-augmented MDCT myocardial perfusion imaging provides semiquantitative measurements of myocardial perfusion during first-pass MDCT imaging in a canine model of LAD stenosis. (J Am Coll Cardiol 2006;48:153–60) © 2006 by the American College of Cardiology Foundation

Myocardial perfusion imaging (MPI) has proven to be a useful and reliable tool in the diagnosis and prognosis of patients with coronary artery disease (CAD) (1). Pharmacologic-induced coronary vasodilation with dipyridamole or adenosine during the infusion of radionuclide tracers (Tl-201 or Tc-99m-sestamibi) has been shown to be as accurate as exercise stress testing with single-photon emission tomography in diagnosing coronary disease (2–6). In addition, MPI can assess the physiologic significance of a stenosis and appropriately risk stratify patients with intermediate stenoses (7).

Multidetector computed tomography (MDCT) is a rapidly evolving technology with growing application in the noninvasive diagnosis of CAD. The rapid advancement of MDCT technology over the past 5 years has greatly improved its spatial/temporal resolution and has expanded its application beyond coronary angiography towards a more comprehensive evaluation of cardiovascular disease, including function, viability, and perfusion (8–10). In its current form, noninvasive coronary angiography by MDCT lacks nuclear stress testing’s ability to assess the functional significance of coronary lesions as supported by a recent study (11).

In light of these observations, a novel method to assess myocardial perfusion during first-pass, contrast-enhanced MDCT would be of great value in the diagnosis and treatment of CAD. The purpose of this study is two-fold: 1) to validate the ability of MDCT to detect a reduction in perfusion in a myocardial territory supplied by a stenosed vessel during adenosine stress; and 2) to correlate MDCT-derived myocardial signal density (SD) with myocardial blood flow (MBF) measurements determined by microspheres.

METHODS
Animal preparation. The Animal Care and Use Committee of the Johns Hopkins University School of Medicine approved all procedures. A total of 8 mongrel dogs (24.5 to 29.5 kg) were anesthetized with intravenous thiopental, intubated, and mechanically ventilated with isoflurane anesthesia during preparation and MDCT scanning. After femoral cut downs, 8-F sheaths were placed in both femoral veins, right femoral artery, and the right internal jugular

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Manuscript received November 9, 2005; revised manuscript received February 28, 2006, accepted March 8, 2006.
Abbreviations and Acronyms

CAD = coronary artery disease
EBCT = electron beam computed tomography
LAD = left anterior descending artery
LV = left ventricle/ventricular
MBF = myocardial blood flow
MBV = myocardial blood volume
MDCT = multidetector computed tomography
MPI = mycardial perfusion imaging
SD = signal density

A left thoracotomy was performed in the fifth intercostal space, and the pericardium was excised. A catheter was then placed into the proximal descending aorta for microsphere sampling, and neutron-activated microspheres (STERIspheres, BioPAL, Inc., Worcester, Massachusetts) were injected using a left atrial catheter to document baseline MBF. The proximal to mid-left anterior descending artery (LAD) was isolated and instrumented with an electromagnetic flow meter, and reactive hyperemia was tested in the vessel with an inflatable external occluder. Suture was then secured around the LAD and tightened to produce a graded stenosis aimed to maintain baseline flow, but attain a 50% or more reduction in hyperemic flow. The thoracotomy was closed, and the animal was transported to the MDCT suite using a portable ventilator.

MDCT imaging protocol. Each animal was placed on an electrocardiographic monitor in a 64-detector MDCT scanner (Aquilion 64, Toshiba Medical Systems Corporation, Otawara, Japan). Animals received intravenous propranolol (5 to 20 mg) to achieve a heart rate <100 beats/min. In order to study a wide range of flows, adenosine was infused for 5 min at 0.14 mg/kg/min in three experiments, 0.21 mg/kg/min in three experiments, and one animal did not receive adenosine. After scout film acquisition, intravenous contrast iodixanol (Visipaque 320 mg iodine/ml, Amersham Health, Amersham, United Kingdom) was infused at a rate of 2.5 ml/s for a total of 100 ml. Using bolus tracking, MDCT scanning was initiated when a threshold of 180 HU was detected in the ascending aorta. Respiration was then suspended with the airway open to air and imaging performed using a retrospectively gated MDCT protocol with the following parameters: gantry rotation time = 400 ms, detector collimation = 0.5 mm × 32 (isotropic voxels = 0.5 × 0.5 × 0.5 mm³ – 13 linepairs/cm), helical pitch = variable depending on heart rate (range: 6.4 to 8.8), beam pitch = variable depending on heart rate (range: 0.224 to 0.275), tube voltage = 120 kV, tube current = 400 mA, and a display field of view = 13.2 cm. Imaging started at the aortic root and stopped caudal to all cardiac structures. Before discontinuation of the adenosine infusion, neutron-activated microspheres were again injected to document MBF during adenosine infusion. A timeline summary of experimental and imaging protocols is shown in Figure 1.

Sample processing. After imaging, the thoracotomy was reopened and the LAD suture was tightened to occlude the vessel. Monastral blue dye was injected into the left atrium to stain myocardium remote to the LAD territory. The animal was then euthanized with a saturated solution of potassium chloride, and the heart was excised and divided into five equal slices perpendicular to the short axis. Myocardial samples (0.87 to 3.24 g) were excised and processed according to the technique described by Reinhardt et al. (12) from the anterior, anteroseptal, lateral, inferolateral, inferior, and inferoseptal walls from base to apex according to the 17-segment system recommended by the American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging (13).

Semi-automated, volumetric regional image analysis. Segmented reconstruction was performed, and images were examined at 10% intervals throughout the R-R interval to determine the optimal phase for reconstruction and analysis. Using multiplanar reconstruction, images were reconstructed in the cardiac short axis at a 4-mm slice thickness. Using hand planimetry, the remote myocardial SD was determined throughout the myocardial volume containing the inferoseptal, inferior, posterior, and inferolateral walls. These results were used to define a perfusion deficit SD threshold as myocardium having an SD one standard deviation below the mean SD of the remote region. Then, using custom cardiac function/perfusion software, with images reconstructed in the cardiac short axis, endocardial and epicardial borders were defined using an automated border detection algorithm (Toshiba Medical, Inc.). The perfusion deficit SD threshold was entered into the custom software that used a step based algorithm to: 1) detect voxels

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Figure 1. Experimental protocol for multidetector computed tomography (MDCT) myocardial perfusion imaging.
within the defined SD range; 2) check for voxel continuity in the X, Y, and Z directions; 3) generate clusters of voxels that meet the perfusion deficit definition; and 4) define the perfusion deficit as the largest cluster detected. Using this method, the software determined the mean SD of the perfusion defect in HU and calculated its volume and mass. Left ventricular (LV) blood pool SD was determined by calculating the mean SD of the entire LV cavity. In order to compare myocardial SD measurements with microsphere MBF measurements, all myocardial signal intensities were normalized as follows:

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\text{Myocardial SD Ratio} = \frac{\text{MeanMYOSD}}{\text{MeanLVSD}}
\]

where MYOSD = myocardial SD and LVSD = LV blood pool SD.

Myocardial SD ratio determined in the perfusion deficit was compared with microsphere-derived MBF. Additionally, myocardial SD ratio of the perfusion deficit and remote myocardium were compared with microsphere-derived MBF over the range of flows studied.

**Slice-by-slice image analysis.** Using segmented reconstruction described above, images were reconstructed in the axial plane with a 4-mm slice thickness and a cardiac phase of 80%. Using hand planimetry, regions of interest were drawn in the stenosed and remote territories for each slice, and the SD was determined. In order to determine if there was SD variation from base to apex secondary to the time the axial slice was acquired, SD for each slice from the base to LV apex was examined to verify that SD did not vary beyond the signal noise (standard deviation) for each slice. Slice-by-slice SD was then normalized to the LV blood pool SD (myocardial SD ratio) as described above. Slice-by-slice myocardial SD ratio was then compared with slice-by-slice microsphere-derived MBF.

**Statistical analysis.** Myocardial blood flow and myocardial SD were expressed as mean ± standard deviation. Volumetric data were expressed as mean and range. Mean MBF and MDCT signal densities were compared using the paired t test. When considering a single SD measurement in the stenosed territory per experiment and its relationship to MBF, linear regression analysis was performed to estimate the slope and statistical significance of the relationship, and a Pearson correlation coefficient was calculated. After the method of Bowman and Waller (14), analyses involving multiple measures at different locations within animals used mixed models to account for the dependence among measures taken from the same animal. In all models, polynomial terms were included when they contributed significantly to model fit based on likelihood ratio tests. Likelihood ratio tests were also used to test whether there were statistically significant associations between SD ratios and MBF. All tests were performed at an alpha level of p < 0.05. Statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, North Carolina).

**RESULTS**

One of eight animals prepared for testing became hemodynamically unstable and could not be imaged. Mean preadenosine MBF by microspheres was 1.37 ± 0.46 ml/g/min in the stenosed territory and 1.29 ± 0.48 ml/g/min in the remote territory (p = NS). During adenosine infusion, MBF increased to 2.54 ± 0.93 ml/g/min in stenosed and 8.94 ± 5.74 ml/g/min in remote territories (p ≤ 0.05). Perfusion deficits showed marked differences in myocardial SD compared with remote regions on visual inspection (Fig. 2). Myocardial SD in stenosed and remote territories measured 92.3 ± 39.5 HU and 180.4 ± 41.9 HU (p = 0.001), respectively, and there were statistically significant differences in myocardial SD in ischemic versus remote regions in

![Figure 2](image_url). Mid-ventricular slice in the axial plane showing a perfusion deficit (arrows) in the anteroseptal, anterior, and anterolateral myocardial territory supplied by the stenosed left anterior descending artery (left). Multiplanar reconstruction showing the extent of the perfusion deficit (arrows) extending from the anteroseptal and anterior walls to the apex (right).
each experiment (Fig. 3). The defect relative mass was on average 14.7% (range 4.1% to 30.0%) of the LV myocardium. Flow reserve, calculated by dividing flow during adenosine infusion by that territory’s baseline flow, was 1.9/1.10060.6 in stenosed versus 7.3/1.10064.7 in remote territories (p/1.10020.05). The ratio of the myocardial SD and the LV cavity blood pool SD (MYO SD/LV SD) was 0.17/1.10060.07 for stenosed versus 0.33/1.10060.08 for remote territories (p/1.10020.01). The semiautomated volumetric analysis algorithm accurately identified the location of the perfusion defect in the myocardial territory supplied by the stenosed LAD in all animals during adenosine infusion (Fig. 4). For the semiautomatic volumetric analysis method, there was a significant linear association of MYO SD/LV SD and microsphere-derived MBF in the stenosed territory, slope = 0.070, SE = 0.007, p < 0.0001 (Pearson R = 0.98, p = 0.001) as shown in Figure 5. There was a significant non-linear relationship between regional SD ratio (MYO SD/LV SD) and absolute MBF in both the ischemic and remote regions over the entire range of flows studied and is shown in Figure 6A (y = −0.00168x² + 0.04701x + 0.07604, LR chi-square [2 degrees of freedom] = 31.8, p < 0.0001). However, when considering absolute MBF < 8 ml/g/min, as shown in Figure 6B, there was a significant linear association between SD ratio and MBF (slope = 0.035, SE = 0.007, p < 0.0001).

A slice-by-slice analysis showed there was no significant variation in SD from slice to slice from the base to the LV apex when restricting the analysis within the remote portion of the myocardial wall. The relationship of SD ratio versus flow in the slice-by-slice analysis was non-linear over the
range of flows studied. We used a novel image analysis method along with objective criteria to define perfusion deficits that eliminated observer bias commonly associated with qualitative and quantitative hand planimetry-based analysis methods. To our knowledge, this is the first study to evaluate the relationship between myocardial SD and MBF using first-pass, helical 64-detector computed tomography.

**DISCUSSION**

**Main findings.** The main findings of this study are:
1) First-pass, contrast-enhanced helical MDCT imaging can detect a LAD territory flow deficit during adenosine stress;
2) MDCT SD ratios of stenosed and remote myocardial beds correlate well with microsphere-derived absolute MBF. These data are the first to demonstrate that myocardial perfusion information can be extracted from imaging protocols designed for first-pass coronary angiography. We used a well-established canine model of LAD stenosis to achieve lesions that were non-flow limiting at rest but flow limiting during pharmacologic stress. This allowed us to compare the sensitivity of relative myocardial MDCT measurements with a proven gold standard for MBF.

**Dynamic versus helical MDCT perfusion imaging.** Our study used MDCT “helical mode” scanning for MPI, which is fundamentally different from “dynamic” or “flow mode” scanning as is performed during electron beam computed tomography (EBCT). Unlike dynamic scanning where images are acquired in four to six fixed slice locations over a predetermined period of time to characterize the wash-in and wash-out of contrast in the myocardium, helical MDCT imaging implements a moving table that transports the subject through the plane of a rotating gantry that contains a grid of detectors opposite a radiation source. Imaging is initiated during first-pass contrast injection when a pre-defined concentration of contrast is detected in the aortic root and continues over a predetermined volume of the chest, starting cranial to the base of the heart and ending caudal to the apex. In this mode, imaging is performed during retrospective gating and generates a stack of 250 to 300 images, each with near isotropic voxel resolution (0.5-mm thickness).

Our study is unique as it aims to measure differences in myocardial perfusion during helical MDCT imaging by capturing myocardial enhancement during a specific phase of the first-pass contrast enhancement curve (Fig. 8). Unlike myocardial perfusion studies using dynamic X-ray imaging, helical MDCT scanning cannot fully measure all phases of myocardial contrast kinetics. Instead, our study is designed to demonstrate that a first-pass helical MDCT coronary angiographic imaging protocol is capable of detecting myocardial perfusion patterns that take place in the early phase of first-pass contrast-enhancement and that relative SD...
analysis of the myocardium provides an accurate surrogate for MBF.

**Microvascular physiology and its implications for MDCT perfusion imaging.** Autoregulation of MBF governed by vasoconstriction/vasodilation of arterioles and venules, in addition to capillary recruitment and derecruitment, is essential for myocyte homeostasis (15–17). In the setting of a normal epicardial coronary artery and myocardial hyperemia secondary to adenosine receptor agonists, arteriole and venule vasodilation decreases the resistance across the coronary microcirculation, increasing MBF (18). Additionally, studies using EBCT and myocardial contrast echocardiography show increased myocardial blood volume (MBV) in myocardium supplied by a normal coronary artery during hyperemia (19,20). Conversely, in the setting of a coronary stenosis, hyperemic MBF begins to decrease with a diameter stenosis >40% to 50%, and capillary derecruitment results in decreased MBV in myocardial territories supplied by a stenosed artery (18,21).

Using X-ray-computed tomography in “dynamic” or “flow” mode, Wang et al. (22) have studied the relationships between MBF and MBV in the coronary microcirculation. In summary, they calculated MBV using the ratio of the area under the curve for contrast-enhanced myocardium and the aortic blood pool. Then MBF was derived using the ratio of MBV and the contrast bolus transit time. Using this method, they accurately estimated MBF compared with microsphere-derived measurements. Furthermore, they demonstrated that MBV increases with increased MBF. In another study that examined MBF and MBV under several hemodynamic conditions, including adenosine infusion, they again concluded that MBV has a predictable relationship to MBF (23). More recently, Möhlenkamp et al. (19), using EBCT and intracoronary Doppler ultrasound, further confirmed that there is a strong correlation between EBCT-derived MBF and MBV and that both increase in response to adenosine.

Our study uses the ratio of myocardial SD and LV blood pool SD, which mathematically more closely resembles the measurement of MBV in these previous studies. While this ratio may not directly measure MBF and more likely represents a measurement of MBV, previous studies show a tight correlation between MBF and MBV and support their use as a surrogate measure of myocardial perfusion.

**Clinical implications.** Multidetector computed tomography has significant unique advantages over other tomographic imaging modalities including unsurpassed spatial resolution, short scanning times, and the ability to image patients with implantable electronic devices. Faster scanning times with 64-detector systems make it possible to assess perfusion during a helical MDCT scan because there is less slice-to-slice variability in the Z axis when scanning from base to apex.

Since the introduction of MDCT, studies have documented improved accuracy for the detection of coronary stenoses >50% (24–29). Multidetector computed tomography MPI could offer a second “lens” of interpretation through which a cardiac MDCT coronary angiogram could be evaluated. An algorithm that determines not only the degree of percent stenosis, but also whether a perfusion defect is present or absent in the corresponding myocardial region would be a valuable tool in the non-invasive diagnosis of CAD.

Our study demonstrates that differences in regional and slice-by-slice myocardial SD reflect differences in myocardial perfusion. While this technique falls short of absolute MBF quantification, the myocardial SD ratio is a robust semiquantitative metric that reflects differences in both MBF and MBV within the clinically important range of flows (up to 8 ml/g/min) as previously defined by positron emission tomography, magnetic resonance, and EBCT at
segments (33,34). Although this effect predisposed our MBF, and this may be more pronounced in ischemic used, which, in turn, have been shown to increase hyperemic ing. To offset the tachycardic effect, beta-blockers were that can significantly degrade the quality of MDCT imag-
sine for stress MDCT MPI is tachycardia and arrhythmias

Study limitations. A potential limitation of using adeno-
sine for stress MDCT MPI is tachycardia and arrhythmias
that can significantly degrade the quality of MDCT imaging.
To offset the tachycardic effect, beta-blockers were
used, which, in turn, have been shown to increase hyperemic
MBF, and this may be more pronounced in ischemic segments (33,34). Although this effect predisposed our hypothesis to failure, significant differences between ischemic and remote myocardial segments were still detected.

Our study demonstrates the feasibility of evaluating myocardial perfusion in a single scan in the setting of an experimental stenosis in the LAD territory only. It is unclear whether we would obtain the same results in patients with stenoses in other territories or who may have multiple stenoses making it difficult to define perfusion deficits indexed or normalized to normal myocardium. Human studies may require either a rest and stress scan or, alternatively, may require defining normal values for contrast-enhanced myocardium normalized to the LV blood pool SD.

Lastly, beam-hardening artifacts can have an MDCT signal appearance that closely resembles a perfusion deficit. In the current study, beam hardening artifacts were easily distinguishable from perfusion deficits because they had several unique characteristics including a triangular, trans-
mural, and hypoenhanced appearance emanating from a structure with a high SD, and they did not follow the distribution of a coronary vascular bed.

Conclusions. Adenosine-augmented MDCT MPI can be successfully performed in a canine model of LAD stenosis using first-pass, contrast-enhanced helical MDCT imaging. Perfusion deficits can be detected visually, and the myocardial SD ratio provides a semiquantitative metric that correlates well with microsphere-derived MBF. The ability to perform MPI during MDCT coronary imaging could have significant implications in the diagnosis and treatment of patients with CAD.

Acknowledgment

The authors thank Jorge Guzman for his technical assistance in this project.

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