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Abstract. Cardiac computed tomography (CT) acquisitions for perfusion assessment can be performed in a dynamic or static mode. Either method may be used for a variety of clinical tasks, including (1) stratifying patients into categories of ischemia and (2) using a quantitative myocardial blood flow (MBF) estimate to evaluate disease severity. In this simulation study, we compare method performance on these classification and quantification tasks for matched radiation dose levels and for different flow states, patient sizes, and injected contrast levels. Under conditions simulated, the dynamic method has low bias in MBF estimates (0 to 0.1 ml/min/g) compared to linearly interpreted static assessment (0.45 to 0.48 ml/min/g), making it more suitable for quantitative estimation. At matched radiation dose levels, receiver operating characteristic analysis demonstrated that the static method, with its high bias but generally lower variance, had superior performance ($p < 0.05$) in stratifying patients, especially for larger patients and lower contrast doses [area under the curve (AUC) = 0.95 to 0.96 versus 0.86]. We also demonstrate that static assessment with a correctly tuned exponential relationship between the apparent CT number and MBF has superior quantification performance to static assessment with a linear relationship and to dynamic assessment. However, tuning the exponential relationship to the patient and scan characteristics will likely prove challenging. This study demonstrates that the selection and optimization of static or dynamic acquisition modes should depend on the specific clinical task. © 2016 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: 10.1117/1.JMI.3.2.024001]

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1 Introduction

Cardiac computed tomography (CT) imaging is currently primarily performed for anatomical assessment of the lumen of epicardial coronary arteries (CT angiography). Visual assessment of epicardial disease can infer the presence of myocardial ischemia with only fair diagnostic accuracy.^{1,2} The addition of CT perfusion to CT coronary artery angiography may improve diagnostic accuracy; the perfusion information could provide information for two primary tasks: blood flow quantification or patient classification. These are arguably overlapping tasks, but do have distinct roles, and consequently distinct metrics for objective assessment of image quality (one is an estimation task and the other a detection task). This paper explores the performance of the two common cardiac CT acquisition modes on these tasks and argues that the mode should be selected and optimized based on the desired task.

The two acquisition techniques for CT perfusion assessment rely on contrast agent enhancement and are performed in either dynamic (e.g., see Ref. 3) or static (e.g., see Ref. 4) mode. There is an open debate regarding the preferred mode, and the only direct comparison to date has a very small sample size and limited patient population.⁵ Considered on its own, static CT myocardial perfusion assessment has been shown to have incremental value in improving the specificity and positive predictive

value when combined with anatomical stenosis information from cardiac CT angiography (CCTA) and correlates with rest and stress single photon emission computed tomography myocardial perfusion imaging (SPECT MPI)⁶ and with cardiac magnetic resonance imaging perfusion assessment.⁷ Previous animal studies have demonstrated that dynamic CT myocardial perfusion assessment is strongly correlated with gold standard microsphere perfusion measurements⁸ and coronary flow probe measurements.⁹ Likewise, patient dynamic CT studies have demonstrated added incremental value to CCTA stenosis information¹⁰ and the ability to independently outperform stenosis-based evaluations in identifying functionally significant lesions¹¹ and to correlate well with SPECT identification of perfusion defects.^{12,13} While there have been many preliminary studies using static and/or dynamic perfusion approaches, there remain open questions about the relative tradeoffs of these approaches for myocardial perfusion assessment.

In this work, we present a simulation experiment to evaluate the performance of static and dynamic CT perfusion acquisitions under matched conditions. In particular, we matched the contrast dose, radiation dose, and numerous patient characteristics. We performed simulations of the kinetics of iodine contrast and of CT acquisitions of the heart during pharmacologic stress. Stressed myocardium is essential to characterize relevant perfusion abnormalities.¹⁴ We report performance on two clinically

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Table 1 Conditions varied in simulations.

Condition varied	Values examined	Notes
Acquisition method	Static, dynamic	Static method uses one 480 mAs image; dynamic method uses fifteen 30 mAs images; total effective radiation dose from either method is ~4.3 mSv
Injected contrast agent volume	50 ml, 100 ml	Injection rate held constant (5 ml/sec)
Patient size	70 kg, 115 kg	Digital phantoms have identical internal organs; larger patient has additional superficial layer of fat
Independent acquisitions	5 noise realizations	Simulates the effect of re-scanning the same patient multiple times
ROI location	10 myocardial ROIs	Five endocardial and five epicardial ROIs from a single 2.5-mm thick axial slice. Image ROI areas varied from 1.3 cm ² to 1.5 cm ²
Static method acquisition time	4, 6, 8, or 10 s after peak opacification of left ventricle	When timing variation is included, static acquisitions are simulated at each of these time points, and evaluated separately. Otherwise, static acquisition is at 6 s after peak LV opacification
True perfusion level	0.5, 1, 2, 3 ml/min/g	Covering the range from severely reduced to healthy stressed MBF

appropriate perfusion assessment tasks: (1) grading severity of perfusion defects (estimation task) and (2) binary detection of perfusion defects (classification task). In this controlled experiment, we provide performance metrics for the detection of reduced myocardial blood flow (MBF) and describing the bias and variance of quantitative estimation of flow. While simulations are not a perfect reflection of reality, they do allow a direct head-to-head comparison of these two methods, which otherwise would be difficult to perform with patient data, given radiation and contrast administration concerns.

2 Methods

2.1 Simulation System

We use the simulation system that we developed previously.¹⁵ A detailed physiological model of cardiac contrast bolus dynamics was treated as ground truth for simulated patients and drives iodine concentrations over time in a modified XCAT digital phantom.¹⁶ A polyenergetic simulator was used to generate the CT projection data from the dynamic phantoms. The spectrum, photon flux levels, and the system parameters were matched to a CT scanner at the University of Washington (GE Lightspeed 16-slice, GE Healthcare, Waukesha, Wisconsin). The specific scanner parameters used were: number of bins = 888, number of views = 984, detector width = 90.9 cm, focal length = 54.1 cm, and source to detector distance = 94.9 cm. Water-based beam hardening correction was performed on the projection data using a polynomial correction, with the calibration function estimated from simulated scans of a uniform water phantom. Image reconstruction was performed on the simulated projection data using filtered back-projection with a Hann filter and a cutoff of 0.94 times the Nyquist frequency. The reconstructed images have a pixel size of 0.67×0.67 mm². All simulations were performed with end-diastolic images under the assumption of no respiratory motion and ideal end-diastolic gating.

In previous work, we generated a large database of these simulated scans under a wide variety of conditions, including variations in patient cardiac output, x-ray tube current, beam hardening correction algorithm, temporal sampling frequency, and myocardial perfusion levels. In this work, we use the

same basic system, but add variation in contrast injection volume, patient size, and examine more and larger myocardial regions of interest (ROIs; Table 1). Axial slice myocardial ROIs were chosen by dividing the identified myocardial wall into five approximately equal arc segments, and then dividing each segment into epicardial and endocardial halves. Image ROI areas varied from 1.3 to 1.5 cm² (on 2.5 mm slices). For iodinated contrast agent, we simulate a 50 ml and a 100 ml injection. The 50 ml injection at a rate of 5 ml/s was simulated with recirculation parameters designed to fit patient data (see in Figure A2 of Ref. 15). The 100 ml injection was constructed using a gamma variate with double the area of the 50 ml injection and using the same recirculation parameters. The gamma variate parameters were chosen such that the initial slope matches between the 50- and 100-ml bolus volumes, mimicking the effect of increasing volume while maintaining injection rate.¹⁷

Static images (Fig. 1) were generated using the same system as the dynamic images (Fig. 2), but simply used a single frame with higher tube current than dynamic imaging (to perform radiation dose matched comparison). For beam hardening correction, the dynamic image series used the temporal information to segment the image and iteratively correct errors from iodine

Fig. 1 Example CT images of simulated static acquisitions. (a) Images from 0.5 ml/min/g and (b) 3.0 ml/min/g true perfusion levels for 6 s following left ventricular cavity peak enhancement for the 70 kg patient injected with 100 ml of contrast are presented. Higher CT numbers are apparent in the myocardium on the higher flow (b) image.

Fig. 2 Example CT images of simulated dynamic acquisitions. Images at (a) 4, (b) 14, and (c) 24 s post-injection of 100 ml of contrast for the 70 kg patient with a true flow of 3.0 ml/min/g are presented.

and bone (as described in Ref. 18); this ability to use temporal information to improve the beam hardening correction is one of the potential advantages of the dynamic approach. The static image series followed conventional clinical processing and are only beam hardening corrected for water components.

Our physiological driving model¹⁵ and CT simulation produced images with myocardial CT numbers at different time points postcontrast injection and at different perfusion levels. Since static cardiac CT acquisition timing is usually based on a timing bolus acquisition monitoring arterial enhancement, we specified the timing of our static acquisition as a delay from the peak opacification of the left ventricular (LV) cavity, which is within 1 to 3 s of peak aortic opacification. Unless otherwise indicated, simulated static acquisitions were 6 s following the LV peak. For some results, we examined the effect of varying this acquisition timing to 4, 6, 8, or 10 s following the LV peak opacification to evaluate the impact of suboptimal acquisition timing.

When overall performance comparisons were made between static and dynamic methods of perfusion assessment, the data were based on 800 data points per method (4 true perfusion levels $\times$ 5 noise realizations $\times$ 10 myocardial ROIs $\times$ 2 patient sizes $\times$ 2 contrast volumes). The CT simulations were performed to have dynamic and static acquisitions with matched total absorbed radiation dose (effective dose of $\sim$ 4.3 mSv) to provide insight into our key question: “given a fixed radiation dose allowance, is it better to perform static or dynamic imaging?”

2.1.1 Comparison of patient computed tomography numbers with simulation predictions

In order to evaluate whether our simulation system (encompassing the digital phantom, the simulated CT acquisition physics, image reconstruction, and the contrast dynamics model) produced images with realistic CT numbers, we collected the mean myocardial CT number from 339 myocardial segments ($N = 20$ patients) from conventional CT angiography images. Segments were selected that were found to have normal perfusion based on a matched rest-stress SPECT study, CT angiography, or static CT assessment.⁴ We assume that these patients have a distribution of normal resting flows of 1.00 ± 0.25 ml/min/g, matching the normal resting flow distributions suggested by Danad et al.,¹⁹ who quantified a large population ($N = 330$ patients) using $[O^{15}]H_2O$ positron emission tomography (PET). Combining this population prevalence of true flows with flow-dependent bias and standard deviation kernels derived from our simulation, we generated a probability density function that describes the myocardial CT numbers that our simulation system would generate if given a population with true flows distributed as in Danad. This allows a direct comparison between CT numbers observed

in real patients and the corresponding CT numbers generated through our simulation system.

2.2 Quantification of Myocardial Perfusion

2.2.1 Dynamic method

The dynamic method involves fitting a flow model to a time attenuation curve with the flow model directly providing a quantitative MBF estimate.

2.2.2 Linear static method

The static method, on the other hand, employs CT numbers from a single time point, is typically interpreted qualitatively by visual inspection, and therefore, does not produce a quantitative MBF estimate. In order to make direct quantitative comparisons between the two methods, we needed to formalize the relationship between the interpreted CT number and estimated MBF. We assumed that viewers interpret CT numbers as visual ratios of apparent enhancement. Furthermore, we assume that (1) the viewer sets the top of the viewing window at the most enhanced region of the myocardium, (2) this region has normal stress perfusion at exactly 3 ml/min/g, and (3) the viewer assumes a linear relationship between apparent enhancement and MBF. The only remaining element necessary to fix a relationship between CT number and MBF is to assign a CT number corresponding to an MBF of 0 ml/min/g. The baseline CT number at 0 ml/min/g MBF is estimated for each condition examined by finding the mean CT number for myocardial regions perfused at 1 and 0.5 ml/min/g and extrapolating that linear relationship down to zero flow. Thus, all static quantification bias curves are guaranteed to have zero mean bias at a MBF of 3 ml/min/g because those points are used to anchor the assumed linear relationship between CT number and MBF estimates. In equation form:

$$F = \frac{F_3}{H_3 - H_0} (H - H_0), \quad (1)$$

where F is the MBF estimate, H is the myocardial CT number, H_3 is the mean myocardial CT number associated with an MBF of 3 ml/min/g, F_3 is 3 ml/min/g, and H_0 is the myocardial CT number associated with unenhanced, zero-flow myocardium.

This approach mimics the condition where a color window for interpretation has its maximum set at a truly well-perfused region and minimum set at truly unenhanced myocardium; given that such information may not be readily available, this approach can be interpreted as the “best case” scenario for a static acquisition.

In one case, we examine problems with failing to subtract the baseline myocardial CT number. This is equivalent to assuming that the baseline CT number of a myocardial region with a flow of 0 ml/min/g (H_0) is 0 HU.

2.2.3 Refinements to static computed tomography interpretation (exponential static method)

Functional form relating computed tomography numbers and blood flow. We examined an approximation of the relationship between CT number and MBF of the form:

$$F = A \cdot B^H - C, \quad (2)$$

where F is the MBF, H is the myocardial CT number, and A , B , and C are constants that parameterize the fit. Optimal parameter values were found by adjusting A , B , and C until the squared CT number residuals were minimized. Points with flows <0.1 ml/min/g were omitted because that portion of the curve was not approximately exponential, and including them reduced the quality of the fit to the rest of the curve.

Normalization of computed tomography numbers and flows. Since static perfusion assessment is generally interpreted in a relative sense, we transformed the absolute CT number versus blood flow relationship into a relative relationship relating percent decrease in CT number (toward baseline) ($\tilde{H}$) to percent decrease in MBF ($\tilde{F}$) from a reference flow:

$$\tilde{F} = \left(1 - \frac{F}{F_{\text{ref}}}\right) \times 100\%, \quad (3)$$

$$\tilde{H} = \frac{H_{\text{ref}} - H}{H_{\text{ref}} - H_0} \times 100\%, \quad (4)$$

where H is the myocardial CT number, F is the MBF, F_{ref} is the reference MBF, H_{ref} is the myocardial CT number associated with F_{ref} , and H_0 is the myocardial CT number associated with unenhanced myocardium (or, equivalently, a flow of 0 ml/min/g). As blood flow to a myocardial ROI decreases from the reference flow toward zero, $\tilde{F}$ rises from 0% reduction toward 100% reduction and $\tilde{H}$ rises from 0% reduction to 100% reduction in enhancement. This normalization does not require that $\tilde{F}$ and $\tilde{H}$ are equal in general, however, which would be equivalent to proposing a linear relationship.

2.2.4 Comparing quantification between methods

To compare quantification performance between static and dynamic assessment methods, we find the MBF estimation residuals. Averaging these residuals gives estimate bias and taking the standard deviation of the residuals gives a measure of estimate error variability. Bias differences between static and dynamic assessment for matched patient size and contrast injection size were tested for statistical significance using two-sample t -tests. Estimate error standard deviation differences were tested for statistical significance using two-sample F -tests. To avoid unfairly favoring the static linear method, which has zero bias by construction at a true MBF of 3 ml/min/g, the bias entries in Table 2 omit these points, including only those estimates where the true MBF was 0.5, 1, or 2 ml/min/g.

2.3 Classifying Myocardial Regions

2.3.1 Population prevalence of perfusion estimates

Ziadi et al.²⁰ report a mean $\pm$ standard deviation stressed MBF of 2.24 ± 0.93 ml/min/g for a large patient population ($N = 677$) assessed for myocardial ischemia via quantitative PET. For the purposes of constructing a reasonable approximation of the distribution of true perfusion levels, we assume that this population is Gaussian and representative of typical cardiac patients, who might be assessed for perfusion defects via CT.

We leveraged our large database of simulated CT images at MBF values of 0.5, 1, 2, and 3 ml/min/g to estimate the bias and standard deviation of flow estimates (from dynamic acquisitions) and mean regional myocardial CT numbers (from static acquisitions) for each of these MBF values under a wide variety of CT acquisition scenarios. For example, for a true flow of 1 ml/min/g, using dynamic assessment, we have MBF estimates for 10 myocardial ROIs over five noise realizations, yielding 50 measures of bias and a standard deviation of MBF estimates at 1 ml/min/g. Likewise, we can calculate a mean bias and standard deviation at each of the other true MBF levels (0.5, 2, and 3 ml/min/g). Between these values, we can linearly interpolate to have a continuous estimate of expected mean bias and standard deviation of MBF estimation at any true perfusion level. For true MBF levels <0.5 ml/min/g and over 3 ml/min/g, the closest interpolated line segment is extrapolated to provide reasonable estimates of MBF estimate bias and standard deviation between 0 and 4 ml/min/g. For the dynamic flow performance, at 0.01 ml/min/g increments, we construct an approximate measurement kernel (a Gaussian curve with mean of the projected MBF estimate bias and standard deviation corresponding to projected MBF estimate standard deviation) that represents the expected distribution of MBF estimates. At each increment, we convolve the approximate measurement kernel with the population prevalence at that flow level (according to Ziadi et al.²⁰) to determine the measurements for all stressed patients. Similarly, for static flow performance, we interpolate mean and standard deviation of regional CT numbers from simulated measurements to each increment level to determine a similar set of convolution kernels that allow calculation of the distribution of mean regional CT numbers from static acquisitions for all stressed patients. Sweeping a threshold across these distributions allows a receiver operating characteristic (ROC) analysis over an essentially continuous population of patients. These approaches effectively estimate the measurement performance of static and dynamic imaging across an essentially continuous population of patients.

2.3.2 Classification and ROC analysis

For the classification task (ischemia versus no ischemia), we first needed to define the prevalence of “normal” and “impaired” stress flows. We use the population prevalence of flows derived above and use a threshold of 2.0 ml/min/g (Ref. 2) to separate the total population into normal and impaired flow populations. The true populations are, therefore, distinct, but after convolution with the flow-dependent kernels described above, the dynamic flow estimate prevalences for the two populations overlap. Varying the threshold for the classification of normal versus impaired flow enables construction of the ROC curve. Specifically, for dynamic perfusion, this classification threshold is the flow estimate; for static perfusion, the threshold is the

Table 2 Estimation bias and classification performance for radiation dose-matched dynamic and static acquisitions.

Acquisition method	Patient size (kg)	Contrast injection volume (ml)	Classification		Quantification		
			Classification AUC [95% CI]	Optimal classification threshold	Flow estimate bias ^a (ml/ min /g)	Standard deviation of flow estimate error (ml/ min /g) ^a	H ₀ /H ₃ ^b
Dynamic (30 mAs × 15 frames)	70	100	0.976 [0.970, 0.982]	1.9 ml/ min /g	−0.01	0.25	—
		50	0.971 [0.962, 0.980]	1.9 ml/ min /g	−0.00	0.26	—
	115	100	0.892 [0.863, 0.924]	2.1 ml/ min /g	0.16	0.53	—
		50	0.865 [0.830, 0.905]	2.1 ml/ min /g	0.11	0.63	—
Static (480 mAs × 1 frame)	70	100	0.981 [0.977, 0.987]	99 HU	0.46 ^d	0.27	37.1/104.9
		50	0.979 [0.974, 0.984]	72 HU	0.45 ^d	0.27	34.9/76.1
	115	100	0.972 ^d [0.967, 0.978]	94 HU	0.47 ^d	0.30 ^d	36.8/99.4
		50	0.966 ^d [0.959, 0.974]	70 HU	0.45 ^d	0.31 ^d	35.1/73.5
Static (incl. timing variation) ^c	70	100	0.967 ^d [0.963, 0.971]	99 HU	0.48 ^d	0.31 ^d	38.7/104.2
		50	0.967 ^d [0.963, 0.971]	71 HU	0.47 ^d	0.31 ^d	35.9/74.8
	115	100	0.960 ^d [0.956, 0.964]	94 HU	0.47 ^d	0.33 ^d	38.8/98.7
		50	0.953 ^d [0.948, 0.958]	69 HU	0.47 ^d	0.35 ^d	36.4/72.1

^aFlow estimate bias table entries are the average of estimate biases for true MBF values of 0.5, 1, and 2 ml/ min /g, omitting the true MBF of 3 ml/ min /g to avoid unfairly favoring the static linear method (see Sec. 2). The average standard deviation of flow estimate error is across all four simulated true MBF values. Bias and standard deviation values for static rows use the linear interpretation. Bias numbers are based on 150 data points and standard deviation numbers are based on 200 data points (5 noise realizations × 10 ROIs × 3 or 4 true flow levels).

^bH₀ is the estimate of baseline CT number; H₃ is the mean myocardial CT number corresponding to a true flow of 3 ml/ min /g. Numbers reported are the means of simulated data points (5 noise realizations × 10 myocardial ROIs = 50 points).

^c“Timing variation” means that in addition to static acquisitions at 6 s after left ventricular peak opacification, we also simulated independent static acquisitions at 4, 8, and 10 s after left ventricular opacification. This variation explicitly accounts for uncertainty in acquisition timing (since acquisition is typically gated to the cardiac cycle), and can also be viewed as a proxy for other types of patient heterogeneity (e.g., variation in cardiac output).

^dA statistically significant difference ($p < 0.05$) between a value and the corresponding value for dynamic assessment, matched for patient size and contrast injection volume.

apparent CT number. ROC curves are used to determine AUC measurements and also to find “optimal” thresholds, where the optimal point is defined as the point on each ROC curve with the minimum Euclidean distance to perfect sensitivity and specificity (i.e., the point [0,1] on an ROC plot). The statistical significance of AUC differences were evaluated using a bootstrapping approach. The set of ROI MBF estimates (for dynamic) or ROI mean CT number (for static) values for each true MBF value was resampled with replacement, and the full ROC analysis rerun on the resampled data. This was repeated 1000 times, and the reported 95% confidence interval is the range of AUC values, which cover 950 of the bootstrapped values. Static method table entries are marked as statistically significantly different from the corresponding dynamic method table entry if the AUC values lie outside of each other’s 95% confidence interval.

3 Results

3.1 Simulation Output

The simulation-derived CT images are qualitatively similar to clinical images and exhibit realistic beam hardening artifacts and quantum noise. Calibration of detector noise was validated using a uniform phantom and varying clinical scanner tube

current.¹⁵ Simulated myocardial time activity curves had peaks which varied with MBF and occurred within the same time window as clinical CTA acquisitions (~4 to 8 s after peak opacification of the left ventricle). All of the following results are for radiation dose-matched static and dynamic simulated acquisitions resulting in an approximate effective dose of 4.3 mSv.

3.1.1 Comparing patient computed tomography numbers and simulation predictions

The simulation system produced CT numbers for resting myocardial flows that were similar to, but less variable than CT numbers measured on images from actual patients. For 339 normal resting myocardial segments in 20 patients, the mean ± standard deviation is 100.6 ± 25.9 HU (2.4% coefficient of variation), whereas the simulation system predicts 76.2 ± 8.5 HU (0.8% coefficient of variation). A difference in mean is inconsequential for flow estimation purposes, since all computations involve comparisons with a baseline rather than usage of a raw CT number.

3.2 Quantification of Myocardial Perfusion

One of the key advantages of dynamic assessment of perfusion is the ability to produce a quantitative estimate of MBF. Static

Fig. 3 Perfusion estimation bias as a function of true perfusion level and assessment method. Symbols are mean and error bars standard deviation of bias in MBF estimates. Dashed lines show the change in static exponential MBF estimate bias due to normalizing by a region with true MBF 41% below (upper line) or above (lower line) 3 ml/min/g, highlighting reference region selection as a major source of possible error for the static methods. Each mean and standard deviation formed from 50 flow estimates (10 myocardial regions and 5 noise realizations). Points are jittered in x slightly so that error bars are adjacent rather than overlapping.

assessment, as typically interpreted, produces only a relative measure of perfusion. To reiterate the method introduced in Sec. 2.2, we translated the relative measure of static perfusion into quantitative estimates by applying two assumptions: (1) contrast enhancement is linearly related to perfusion and (2) there is a myocardial region with a normal stressed flow of 3 ml/min/g, which can be identified and used as a reference for the rest of the heart. Assumption 2 is quite optimistic and can be viewed as a “best case scenario” for static assessment. Even in this optimal case, static MBF estimates are significantly more biased than dynamic MBF estimates (Fig. 3, “static-linear” curve, circle symbols). The positive bias of the linear interpretation of static perfusion myocardial CT numbers apparent in Fig. 3 arises because assumption 1 is incorrect: there is a non-linear relationship between contrast enhancement and perfusion.

We explored the nature of this nonlinear relationship between contrast and MBF using our physiologically realistic driving model. The relationship between myocardial CT number at this time point and the true MBF as predicted by the driving model is shown in Fig. 4 (dotted curves). Except at extremely low flows (MBF < ~0.2 ml/min/g, see inset of Fig. 4), this relationship is very well approximated by an exponential curve. The parameters of the best fit exponential relationship to the noisy simulated data depend most strongly on the contrast agent dosage and more weakly on other factors (e.g., the patient mass, myocardial ROI, and noise realization).

By creating an exponential fit curve using the noisy simulated data for each condition (where “condition” is defined as a combination of contrast injection volume and patient size),

Fig. 4 Predicted relationship between MBF and myocardial CT number in a static acquisition. Dotted lines are predictions of the ground truth model in our simulations for myocardial CT number at the time of a static acquisition (6 s after the peak opacification of the left ventricle), blue dots are for a 50-ml contrast agent bolus and orange dots are for a 100-ml contrast bolus. Dashed and dash dot lines are fits of the exponential equation shown to the dotted curve ($[A, B, C] = [0.096, 1.041, 0.22]$ for 50 ml contrast and $[0.162, 1.024, 0.24]$ for 100 ml contrast). Inset shows area at low blood flow where exponential fits and truth curves diverge.

we can convert every CT number directly in to an estimated MBF value. This method produces MBF values with essentially no bias on average (Fig. 3, yellow–orange curve, “x” symbols). Like the static linear method, the bias values plotted for the static exponential method assume that a region with a true MBF of 3 ml/min/g is correctly identified and is used for normalization of CT number values. The effect of relaxing this assumption can be seen in the dashed yellow–orange lines in each panel of Fig. 3. These represent the change in MBF estimate bias for the static exponential method due to normalizing by a region with a true MBF, which is >3 ml/min/g (lower line) or <3 ml/min/g (upper line) by 41%, the coefficient of variation of stress flows in Ziadi et al.²⁰ Similar envelopes could be drawn around the static linear data but would decrease the readability of the figure. The dynamic method does not rely on normalization to a healthy region with known MBF.

Comparing the three methods, it is clear that the linear static method performs least well from the perspective of estimation bias, that dynamic assessment outperforms linear static, and that our new exponential static method, at least when properly normalized, has the least bias. From a variability standpoint, the linear static method has a standard deviation of estimate error that is essentially constant across flow levels, whereas the exponential static and dynamic methods increase in estimate variability with increasing true perfusion. For the larger patient digital phantom, MBF estimates from the dynamic method are consistently more variable than the exponential static method; for the smaller patient, they are similarly variable.

Figure 3 presents quantification results separated by digital phantom size, contrast dosage, and true MBF. Table 2 presents quantification results combined across true MBF values, as well as classification results.

3.2.1 Normalized flow versus computed tomography number relationship is also approximately exponential

By selecting a reference perfusion level and replotting the relationship as percent reduction in CT number versus percent

reduction in blood flow, the relationship remains exponential and is the same whether 50 or 100 ml of contrast agent is used [Fig. 5(a)]. It is also clear from Fig. 5(a) why the linear model has a positive bias (Fig. 3) in flow estimation. The linear model would predict that a 50% reduction in CT number toward baseline corresponds to a 50% reduction in flow from the reference flow. However, our simulations and fitted exponential relationships reveal that a 50% CT number reduction is associated with a 71% true reduction in flow when using a reference flow of 3 ml/min/g (Table 3). While this relationship appears to be independent of contrast agent dosage, it does depend on the reference flow [Fig. 5(b)], with lower reference flows leading generally to lower difference between a linear model and the true relationship.

In general, reference flow rates will be unknown in static assessment. That is, a reference myocardial region can be selected and other regions compared with it, but the true MBF associated with the reference region will not be known to the reader. This will limit the ability of the reader to precisely interpret relative flow reductions using the relationships identified in Fig. 5 (see Table 3).

The last row of Table 3 also highlights the importance of using a baseline subtraction before calculating % CT number reduction. Using absolute CT number percent change neglects that myocardium without contrast still attenuates x-rays more than water, and this false assumption skews interpretation. Applying a linear model to no baseline subtraction, CT numbers would compound the errors and lead to the assumption that a 50% reduction in CT number corresponds to a 50% reduction in flow, when in fact it would correspond to an 88% reduction in flow. Furthermore, without baseline subtraction, the actual % reduction in flow with % reduction in CT number will depend on the contrast bolus volume, with larger contrast boluses leading to larger errors.

3.3 Classifying Myocardial Regions

In a dose-matched comparison, the static method outperforms the dynamic method in classifying large (115 kg) patients

Fig. 5 (a) Normalized relationship is the same for two different contrast levels. Blue curve and orange dots are from the ground truth driving model with two different contrast bolus sizes, 50 and 100 ml, respectively, both with a reference flow of 3 ml/min/g. Black dashed line is a linear model for comparison. (b) Effect of varying reference flow. Blue curve is the same as in panel A, the dark orange and light orange curves represent the same data, only using $F_{ref} = 2$ ml/min/g or $F_{ref} = 1$ ml/min/g, respectively, rather than $F_{ref} = 3$.

Table 3 Percent flow reduction with percent CT number reduction demonstrating problem with linear assumption of flow and CT number.

		% CT number reduction after baseline subtraction				
		10%	25%	50%	75%	90%
% MBF reduction	Assuming reference flow of 3 ml/min/g	21%	45%	71%	86%	92%
	With unknown reference flow in the range of 1 to 3 ml/min/g	13 to 21%	31 to 45%	53 to 71%	73 to 86%	84 to 92%
	With no CT number baseline subtraction ^a ; reference flow of 3 ml/min/g	32%	62%	88%	>100%	>100%

^aWithout baseline subtraction, % CT number reduction is simply the CT number/reference CT number $\times 100\%$, equivalent to assuming a baseline of 0 HU. In this case, CT numbers less than that for unenhanced myocardium would suggest negative flows, and therefore flow reductions of greater than 100%. Also, without baseline subtraction, the percentage values in the last table row depend on the contrast dosage; values shown are based on 50 ml of contrast agent.

into normal MBF and impaired MBF categories (Table 2 and Fig. 6), with AUCs of ~ 0.98 for static and ~ 0.88 for dynamic MBF estimates. MBF classification for lighter (70 kg) patients is not statistically different between the two methods, with an overall AUC of ~ 0.98 for static and ~ 0.97 for dynamic MBF estimates. With some additional heterogeneity in the static data (Table 2, last four rows), performance of the static method declines, such that it underperforms the dynamic method for high signal to noise data (100 ml contrast and 70 kg patients), but still outperforms the dynamic method for low signal to noise data (50 ml contrast and 115 kg patients). Of note, the best threshold for successfully dividing patients into healthy and impaired flow categories is close to 2 ml/min/g for the dynamic method, independent of the contrast dosage used. For the static method, the optimal CT number threshold depends strongly on the contrast dosage (Table 2). This suggests that even where the static method outperforms the dynamic method

by AUC, the dynamic method may have a practical advantage in that a global threshold could be adopted and used consistently, whereas the static method threshold would need to be adapted based on conditions. Also note that there is no distinction between static linear and static exponential methods here, because classification thresholds for static are applied directly to CT numbers, not to MBF interpretations of CT numbers.

4 Discussion

There is an open debate regarding whether static or dynamic CT acquisitions should be used to assess myocardial ischemia. A majority of prior work evaluates the ability of CT myocardial perfusion assessment to identify physiologically significant epicardial disease.^{5,10,11,21–23} Several studies have shown that CT perfusion can improve the specificity and positive predictive value of CT angiography (for static,²³ and for dynamic^{10,11}). However, not all perfusion defects are linked to a focal stenosis. For example, patients with microvascular disease may have poorly perfused myocardial regions without visible epicardial narrowing. CT perfusion evaluation has also been compared against established measures of perfusion, including nuclear SPECT studies. Okada et al.⁶ had 42 patients who underwent both rest and stress static CT perfusion and rest and stress SPECT, finding a good correlation between modalities on a per-segment, per-vessel, and per-patient basis. For dynamic CT perfusion, Wang et al.¹² used the combination of an invasive angiography-identified stenosis and a downstream SPECT-identified perfusion defect as the gold standard against which to assess dynamic CT perfusion, which was found to have excellent sensitivity and negative predictive value and greater specificity and negative predictive value than CTA-identified stenosis alone.

As shown from this prior work, evaluations of static or dynamic myocardial perfusion assessment have generally been carried out separately. In one notable exception, Huber et al.⁵ directly compared dynamic and static performance for the detection of hemodynamically relevant coronary stenoses. Consistent with our findings, these authors concluded that static and dynamic methods have similar detection performance. However, their work did not provide insight into absolute quantitation performance and was limited by the small sample size, motivating future work to compare performance across a larger patient population.

Fig. 6 ROC curves comparing patient classification performance between dynamic and static assessment methods and under selected conditions. For each method, the best-performing (smaller 70 kg patient and larger 100 ml contrast agent volume) and worst-performing (larger patient and smaller contrast agent volume) conditions are shown. Circles are the closest point to perfect sensitivity and specificity on each curve and correspond to thresholds of 101 HU (blue curve), 1.9 ml/min/g (dark orange dashed curve), 71 HU (light orange dash-dot curve), and 2.1 ml/min/g (purple dotted curve). All curves represent the same underlying population of true perfusion levels.

Our goal was to evaluate static and dynamic CT perfusion assessment at matched radiation dose levels to allow direct comparison between them in a context where true MBF is known and where the contribution of numerous CT parameters to MBF measurement error can be identified and quantified. We chose to evaluate CT perfusion performance on two different tasks: (1) quantitative perfusion estimation in ml/min/g of myocardial tissue and (2) binary perfusion classification into normal (no ischemia) or abnormal (ischemia). We compared simulations of static acquisitions with simulations of dynamic acquisitions to ensure that comparisons were not complicated by differences between patients, scanners, and so on, but were direct evaluations of the acquisition schemes. Our results indicate that the static method can outperform the dynamic method for correct classification of myocardial regional perfusion to either normal (no ischemia) or abnormal (ischemia) despite producing highly biased MBF estimates. This may seem counter-intuitive, but it arises naturally from the fact that estimating variance from static acquisitions is lower considering that the single static CT acquisition is acquired with higher radiation dose (higher signal-to-noise) than any single frame of the dynamic acquisition. Therefore, in an ROC analysis, the superior resolving power of the static method yields a greater classification AUC. It is important to note that optimal classification thresholds for static perfusion assessment are both patient and protocol dependent, especially on the contrast volume, whereas dynamic classification could use a single MBF estimate threshold across patients.

If the goal is absolute quantification of MBF, such as in patients with multivessel or microvascular coronary disease, the dynamic method yields MBF estimates with very low bias in the most relevant perfusion range (<3 ml/min/g) and significantly outperforms even the most optimal linear relationship chosen for the static method (which assumes perfect identification of background and perfect identification of 3 ml/min/g true flow). The fundamental nonlinearity in the relationship between CT number and MBF means that any estimation method based simply on ratios between CT numbers will produce biased MBF estimates. In addition, the necessity for normalization in static methods is another large source of potential error, even for the improved exponential static interpretation, so the fact that dynamic assessment does not require normalization is a significant advantage.

These findings could inform workflow solutions for CT evaluation of myocardial ischemia. For example, this study would be supportive of the logic that for most patients, CT angiography would be performed first and if multivessel coronary disease was not seen or suspected, static perfusion would be preferential, providing decent detection performance for regional ischemia. In patients with discovered or known multivessel disease, or in patients with suspected microvascular disease, dynamic perfusion would be preferable to quantify and grade severity of flow limitations.

Additional limitations to these findings should also be mentioned. Our simulation system produces CT numbers for resting myocardial segments with a lower mean and less variability than we observe in patient CT data. The reduced variability could have many causes. First, we made the assumption that patient resting flows followed a published distribution; these patient cohorts were not matched. Although we simulated major factors such as variation in CT acquisition triggering time, beam hardening, and patient size, we did not include all sources of

variability. Notably, we did not include patient respiratory or cardiac motion, inpatient heterogeneity, partial scan artifacts, or variations in contrast delivery speed or shape. In general, we expect that additional variability and artifacts will be more detrimental to the static method, which derives all of its data from a single frame, than to the dynamic method, which can partially compensate for errors in a single frame with information from other frames. The shift in mean CT number between patients and simulations is of less concern, since it is unlikely to affect the validity of the comparisons we are making in this study. Also, there are numerous approaches to improving the image quality of CT images and dynamic imaging (e.g., filtering strategies,²⁴ iterative reconstruction, and so on) that were not considered here. Finally, our simulation environment imposed the assumption that contrast reductions result from reduced blood flow. In practice, there may be physiologic states, other than just reduced flow, that could cause relative contrast variations such as severe fibrosis and inflammatory disease (both leading to different baseline attenuation of tissue). Due to all these limitations, our study does not definitively establish the superiority of one method over the other for a particular clinical task. The intention of this study was not to derive absolute measures of performance, but rather to explore trends and rankings in a head-to-head comparison.

In order to reduce the computational load for the simulations, we simulate a single 2.5-mm axial slice through our digital phantoms and use myocardial ROIs within this slice. This does not correspond directly to clinical use, where at least 4 cm of tissue is likely to be acquired at a time, but the important effects (e.g., realistic quantum noise, tomographic reconstruction structured noise, differential beam hardening between frames and around the myocardium) are included. Because of our choice to use a single axial slice, we do not label our myocardial ROIs according to the standard AHA 17 segment model, but rather choose 10 approximately equal sized ROIs within the slice.

While our results may appear to recommend the use of the static methods for clinical classification tasks, it is important to recall that this is a simulation study, and a number of real world factors could degrade the performance of the static method in actual practice. The first, and most important, is that ROC analysis is based on a complete sweep of a threshold parameter, but in clinical practice, an actual particular threshold would need to be chosen, and the best CT number threshold to apply will vary with a number of conditions, most notably with the volume of contrast injected (and more generally the bolus size and shape), the timing of the single acquisition, and the patient size. In theory, it may be possible to determine a function relating the optimal threshold to the contrast dosage, but such an approach would need to assume that other factors contributing to the quantitative inaccuracy of CT imaging (e.g., variable beam hardening contributions in the presence of varying contrast distributions and patient body habitus) can be neglected. The dynamic method avoids many of these problems by measuring the ventricular or aortic input function directly and fitting a time delay term as well as the flow term and should generally be viewed as more robust. That acknowledged, the requirement for low-dose dynamic acquisitions means that its resolving power is less for classification tasks. In general, this study should be viewed as exploratory rather than conclusive regarding static versus dynamic myocardial perfusion assessment.

A significant outcome of this work is that analysis of the predicted true relationship between myocardial enhancement and

myocardial flow at the time point of static acquisition suggests that this relationship is nonlinear and that the form of the non-linearity is approximately exponential except at very low flows (<0.2 ml/min/g). This method, using an optimized exponential relationship for interpreting myocardial CT numbers, produces quantitative MBF estimates with essentially zero mean bias and lower variability than dynamic MBF estimation. However, this accuracy depends critically on using the correct exponential curve for interpretation. In this simulation study, we could calibrate the exponential curve parameters by using known MBF values; in clinical patients, this relationship will be much more challenging to determine. It is clear that the correct parameters will depend critically on the volume of contrast injected and will also depend on other factors, such as patient size, cardiac output, and contrast injection rate. In application to qualitative interpretation of static images, our results suggest that a normalized exponential interpretation of % flow reduction as a function of % CT number reduction toward baseline has the ability to remove interpretation dependence on contrast agent dosage, though not a dependence on selected reference flow. Exploring these relationships further has the potential to reduce the inherent bias in the linear interpretation of reductions in static acquisition enhancement as directly proportional to reductions in flow.

5 Conclusions

At matched radiation dose levels, our simulations suggest that static cardiac CT perfusion assessment under a linear enhancement-to-flow interpretation scheme yields MBF estimates with high bias but relatively low variability, whereas dynamic cardiac CT perfusion assessment yields estimates with low bias but higher variability. Under the matched conditions explored, these characteristics led to linear static perfusion generally matching or outperforming dynamic perfusion on a binary perfusion classification task (normal/abnormal) and dynamic outperforming linear static on an absolute perfusion quantification task. Variation in the timing of the static acquisition ($\sim \pm 3$ s around optimal post contrast injection time) does not dramatically reduce the classification performance of static CT. In addition, our study proposes an improved interpretation of CT number reduction on static CT based on the exponential relationship between CT number and MBF reduction. This novel method can produce unbiased MBF estimates from static images but relies on a patient and acquisition protocol dependent calibration, which is not yet available for clinical patients. This work concludes that both static and dynamic cardiac CT acquisitions have a role in perfusion assessment and the method should be selected and optimized for the particular clinical task.

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