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Quantitative myocardial perfusion imaging in a porcine ischemia model using a prototype spectral detector CT system

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Abstract

We optimized and evaluated dynamic myocardial CT perfusion (CTP) imaging on a prototype spectral detector CT (SDCT) scanner. Simultaneous acquisition of energy sensitive projections on the SDCT system enabled projection-based material decomposition, which typically performs better than image-based decomposition required by some other system designs. In addition to virtual monoenergetic, or keV images, the SDCT provided conventional (kVp) images, allowing us to compare and contrast results. Physical phantom measurements demonstrated linearity of keV images, a requirement for quantitative perfusion. Comparisons of kVp to keV images demonstrated very significant reductions in tell-tale beam hardening (BH) artifacts in both phantom and pig images. In phantom images, consideration of iodine contrast to noise ratio and small residual BH artifacts suggested optimum processing at 70 keV. The processing pipeline for dynamic CTP measurements included 4D image registration, spatio-temporal noise filtering, and model-independent singular value decomposition deconvolution, automatically regularized using the L-curve criterion. In normal pig CTP, 70 keV perfusion estimates were homogeneous throughout the myocardium. At 120 kVp, flow was reduced by more than 20% on the BH-hypo-enhanced myocardium, a range that might falsely indicate actionable ischemia, considering the 0.8 threshold for actionable FFR. With partial occlusion of the left anterior descending (LAD) artery (FFR < 0.8), perfusion defects at 70 keV were correctly identified in the LAD territory. At 120 kVp, BH affected the size and flow in the ischemic area; e.g. with FFR $\approx$ 0.65, the anterior-to-lateral flow ratio was 0.29 ± 0.01 , over-estimating stenosis severity as compared to 0.42 ± 0.01 ($p < 0.05$) at 70 keV. On the non-ischemic inferior wall (not a LAD territory), the flow ratio was 0.50 ± 0.04 falsely indicating an actionable ischemic condition in a healthy territory. This ratio was 1.00 ± 0.08 at 70 keV. Results suggest that projection-based keV imaging with the SDCT system and proper processing could enable useful myocardial CTP, much improved over conventional CT.

Keywords

spectral detector CT; beam hardening; myocardial perfusion; mono-energetic images; perfusion modeling; image processing

1. Introduction

Imaging plays an important role in the management of cardiovascular disease. Current imaging options (MRI, ultrasound, SPECT, PET, PET-CT, IVUS, invasive angiography, etc) are costly, incomplete, requiring multiple modalities; and often ineffective. Invasive coronary angiography (ICA) is the clinical standard for the detection of coronary artery disease (CAD). However, correlation between angiographic stenosis and myocardial ischemia is poor (Tonino *et al* 2010) leading to wide use of pressure wire functional flow reserve (FFR). Potential benefit from coronary revascularization depends upon the presence of ischemia rather than the perceived presence of a stenosis (Hachamovitch *et al* 2003, Montalescot *et al* 2013). Hence, current guidelines for stable CAD recommend documenting ischemia with a non-invasive functional test (e.g. SPECT, stress echocardiography, or cardiac MRI) before ICA and revascularization are considered (Montalescot *et al* 2013). Shortcomings are apparent from the frequently inaccurate selection of patients referred to ICA. One report estimates that >60% of patients who underwent elective ICA had insignificant CAD (Patel *et al* 2010). Cardiac single-photon emission CT (SPECT) is currently the preferred non-invasive imaging technique for the functional assessment of myocardial perfusion and the most common option for determining the need to perform ICA. However, SPECT has technical limitations which limit its effectiveness including low correlation with FFR in patients with multi-vessel disease (Melikian *et al* 2010), radiation dose, cost, and examination time. Further, SPECT gives no information about the presence or absence of a treatable obstructive stenosis. With one million ICAs in the US every year (Go *et al* 2014), an effective non-invasive gatekeeper test could reduce a very large number (as many as 600 000 per year) of unnecessary ICAs. Clearly, an ideal gatekeeper would identify ischemia and any stenotic lesions suitable for treatment. With emerging high end CT scanners and analyses, a combination of CTP and CT angiography (CTA) could become the ideal, non-invasive exam prior to ICA.

A great amount of clinical and pre-clinical CTP research has already been published using different scanners and different protocols and corresponding findings have been compared to existing reference standards such as SPECT and cardiac MR. A recent review and summary of current CTP literature can be found in (Rossi *et al* 2014b). However, there are still significant challenges to the clinical use of myocardial CTP, including excessive radiation dose from dynamic scanning, low image contrast-to-noise ratio in the myocardium, partial scan artifacts from fast (180° + fan angle) acquisitions, misregistration, volumetric coverage, and BH artifacts arising from dense iodinated material in the aorta and heart chambers and the polychromatic nature of x-ray beam used in conventional CT. If uncorrected, these artifacts and in particular BH can negatively impact the accuracy of perfusion measurements. Some of these challenges have been addressed with evolving CT technologies. Large multi-detector arrays and high-speed gantry rotation enable rapid,

dynamic, full 360° volumetric imaging of the heart. Several image-based approaches have been proposed to reduce BH artifacts in CTP images (So *et al* 2009, Stenner *et al* 2010). The accuracy of these approaches depends in part on the segmentation of high attenuating objects (e.g. bone and iodine) within the acquisition field of view which is affected by the automatic water BH-correction of the input images (So *et al* 2012a). BH artifacts may also be addressed with energy sensitive CT imaging which is capable of synthesizing monoenergetic (keV) images virtually free of BH (Alvarez and Macovski 1976). There are three x-ray source-based approaches in use to acquire energy sensitive CT data: the single x-ray source with rapid switching between two energies (kVp), the single x-ray source with alternate high and low energy acquisitions between each gantry rotation, and the dual source approach with two x-ray sources using two different energies. These approaches use conventional CT detectors to detect x-ray photons. An alternative is a detector-based approach with a single, polychromatic x-ray source but with spectral detectors which simultaneously discriminate between low- and high-energy x-ray photons. A system implementing this technology is the spectral detector CT (SDCT) scanner (Philips Healthcare, Cleveland, OH). One of the main advantages of the SDCT is that at each view, the high- and low-energy projections are exactly registered with respect to each other both spatially and temporally. This allows material decomposition and generation of keV images to be performed in the projection space without any interpolation. The elimination of the time lag between the high- and low-energy projection data also makes the SDCT system ideal for imaging moving organs such as the heart.

Several myocardial CTP studies, using energy sensitive CT, have already been reported. In (So *et al* 2011), the authors used a kVp switching dual energy CT (DECT) system and showed that projection-based DECT may permit improved quantitative myocardial CTP compared with image-based DECT and conventional CT. However, the effective radiation dose of their pig studies was very high (51 mSv) and perfusion results were not compared to a reference standard. Using ECG-triggering at every other heart beat with rapid kVp switching, the same authors showed in (So *et al* 2012a) that projection-based DECT provided more reproducible myocardial perfusion measurements in a porcine model compared with conventional single energy CT at lower radiation dose (19 mSv) for the same coverage (4 cm) of the heart. There have also been promising clinical CTP studies using DECT. For instance, some used single shot perfusion protocols and dual source CT and found good correlation of stress CTP with SPECT myocardial perfusion imaging (MPI) (Blankstein *et al* 2009), without investigating the BH correction capability. Using dynamic CTP and dual source DECT, others have shown that stress myocardial CTP can detect myocardial perfusion defects in good correlation with SPECT and can identify flow-obstructing stenosis in correlation with stenosis detected in CTA and ICA (Ho *et al* 2010, Wang *et al* 2012).

In this paper, we report the first myocardial CTP imaging study with a new spectral SDCT prototype scanner and an in-house developed image analysis and flow quantification pipeline. Using a two layer detector, the SDCT can acquire energy sensitive image data and create an array of images including virtual mono-energetic (keV) CT images, and iodine and water density images. By combining projection data in the two detector layers, conventional kVp images can also be created from the same SDCT acquisition, giving a unique

opportunity to compare keV and kVp perfusion estimates. We used phantom and preclinical porcine experiments to optimize acquisition and processing. We assessed our ability to make CTP measurements in the porcine model. We compared image quality and perfusion results on keV and kVp images.

2. Materials and methods

2.1. Review of the spectral detector CT system

The SDCT system is a single source dual-layer system for a simultaneous acquisition of spectrally resolved CT data. This idea was first proposed by Brooks and Chiro (Brooks and Di Chiro 1978) in 1978 and was recently modified and implemented by Philips Healthcare (Altman *et al* 2011). In this configuration, one x-ray tube is used to expose a sandwich of two attached scintillator layers directly placed on top of one another. The first layer absorbs most (by design, approximately 50% of the beam) of the low-energy x-ray photons, while the second layer detects the remaining higher-energy x-ray photons (Shefer *et al* 2013). Therefore, the two detected signals correspond to different x-ray spectra with different mean energies. The atomic number and the thickness of the first scintillator layer have been optimized for maximum energy separation and optimal low-energy image noise even for large patients (Shefer *et al* 2013). This compensates for the larger overlap between the low- and high-energy spectra as compared to designs using two separate kVp settings.

Due to its simultaneous acquisition of low- and high-energy data, the SDCT system allows material decomposition to be performed in the projection space. In this space, the knowledge of the physical model (x-ray spectra, detector response, and materials) can be incorporated in the material decomposition process, which allows for BH effect to be inherently reduced, as was previously shown on phantom experiments (So *et al* 2011) for the kV switching system. Contrary to projection-based method, monoenergetic images generated using the image-based method may still contain residual BH artifacts propagated from the low- and high-energy images even after the application of advanced BH correction techniques (Maaß *et al* 2009). Another advantage of the elimination of inter-scan time lag is that CT examinations relying on voxel-by-voxel combination of low- and high-energy images are reliably feasible even for dynamic processes such contrast enhancement which involve pharmacokinetic difference between scans. Furthermore, the use of a single source also eliminates the problem of cross-scatter. Other benefits of the SDCT system over alternative techniques include the ability to image a full 50 cm FOV with no extra radiation dose for both spectral and routine imaging without requiring any *a priori* decision for the type of scan (conventional or spectral) to be performed, making it attractive from a workflow perspective.

Finally, because of its fast gantry rotation (0.27 s), we were able to acquire full 360° dynamic CTP scans with our SDCT scanner to eliminate the shading artifacts. These artifacts arise from partial scan (180° + fan beam angle) acquisitions often used to improve temporal resolution at the expense of introducing temporal CT number variations due to different angular data ranges used to reconstruct images.

2.2. Generation of virtual mono-energetic images

A monoenergetic or keV image at a given energy E depicts how the scanned object would appear if only monochromatic x-ray photons with energy E were produced by the x-ray source during the scanning process. Two different approaches are available to synthesize keV images from data acquired by the SDCT system: projection-based and image-based (Alvarez and Macovski 1976).

In principle, x-ray attenuation in CT imaging is characterized by two main energy-dependent effects, photo-electric (PE) absorption and Compton scattering (CS). In DECT, the contributions of these two effects, along each projection path, is determined by collecting attenuation measurements at two different energies (Alvarez and Macovski 1976). Within the diagnostic x-ray energy range, this decomposition is equivalent to the two basis material decomposition which expresses the linear attenuation coefficient of a voxel, at a given energy, as a linear combination of the mass attenuation coefficients of two basis materials with distinct atomic numbers at the same energy (Lehmann *et al* 1981). In the projection-based approach, which is the only approach considered in this work, two non-linear equations are solved, using the collected measurements and the known relationship of mass-attenuation coefficients in terms of energy to determine the PE and CS sinograms. These sinograms are subsequently de-noised and back-projected to produce PE and CS images, which are linearly combined to synthesize monoenergetic images at different energies. Material selective images, such as water and iodine images, can also be synthesized from linear combinations of the reconstructed PE and CS images, with units given as grams per centimeters cubed. In the image-based approach, monoenergetic images are synthesized as linear combinations of independently reconstructed high- and low-energy conventional kVp images (So *et al* 2011).

2.3. Phantom experiments

We performed phantom experiments to characterize iodine detection and BH artifacts with the SDCT system. The acrylic phantom is a cylinder, 26 cm in diameter and 6 cm high. It can hold up to eight inserts arranged in a circular fashion (figure 3(A)). One tube containing distilled water and seven tubes containing diluted solutions of an iodinated contrast agent (Omnipaque, 350 mg I ml⁻¹) with concentrations ranging from 0.875 mg I ml⁻¹ to 10.5 mg I ml⁻¹, were placed in the insert holes. These concentrations were chosen to produce HU numbers and BH artifacts typical in our porcine CTP protocols. The phantom was scanned at 120 kilo-voltage-peak (kVp) and 100 mAs tube current-time product. Conventional 120 kVp images, projection-based monoenergetic images ranging from 50 to 120 keV at 10 keV increments, and iodine density images were reconstructed. Same size regions of interest (ROI) were drawn in each insert to calculate mean and standard deviations of the pixel values. First, we used iodine density images to compute means of recovered iodine concentrations and compared the results to actual iodine concentrations in each vial. Second, we analyzed the linearity of mean HU values versus iodine concentration, and determined the corresponding regression lines for each reconstruction. Then, we analyzed noise level and sensitivity of iodine detection or iodine contrast to noise ratio (CNR). For each reconstruction (keVs and kVp), the CNR of iodine was computed as the ratio of the corresponding 'HU versus iodine concentration' regression slope and the mean standard

deviation of HU values inside the eight vials. Corresponding keV results were compared against each other and against kVp results. Finally, we evaluated the reduction of BH artifact by scanning the phantom with only two inserts containing specific iodine solution while all of the others holes were sealed with cylindrical acrylic plugs. Iodine concentrations in the two vials were adjusted to produce decrease in attenuation of about 25 HU in an ROI placed between the two iodine-filled tubes, before and after filling the two inserts with the adjusted iodine solutions. This difference in attenuation, due to BH, is approximately equal to that typically measured on the anterior wall of the myocardium in the pig scans before and after the left ventricular (LV) chamber is filled with the iodinated contrast. All phantom images were reconstructed with 2 mm slice-thickness and no overlap.

2.4. Animal model

We used a porcine model to assess our ability to make CTP measurements. The study protocol was approved by Case Western Reserve University's Institutional Animal Care and Use Committee (IACUC). Eleven ($n = 11$) female Yorkshire pigs (40–50 kg, 13–15 weeks of age) were procured from local vendors and were used in this study. In a closed chest procedure, different levels of acute ischemia were induced using a balloon catheter introduced in the femoral artery and implanted in the LAD coronary artery. An FFR wire was used to guide the degree of balloon inflation to match a targeted FFR reading of ischemia. In our experience (Fahmi *et al* 2015), this closed chest model eliminates artifacts due to surgical intervention, allows multiple levels of ischemia on the same animal, enables stable animal handling, and provides reproducible ischemia. To obtain an independent measure of blood flow, we used fluorescent microspheres. The microspheres were injected into the LV cavity over 30 s using a catheter through the femoral artery. Simultaneously, a reference blood sample was collected at a constant rate (5 ml min^{-1}) over three minutes. Red fluorescent microspheres were injected before balloon implantation to obtain the baseline flow, and green microspheres were injected with balloon inflated to $\text{FFR} \approx 0.7$. The animal was then transported to the CT facility under a portable ventilator in order to acquire dynamic CT scans under different hemodynamic conditions. All animals were monitored hemodynamically throughout each experiment.

2.5. CT perfusion data acquisition

Dynamic contrast enhanced CTP scans were acquired under at least three hemodynamic conditions: baseline with the balloon completely deflated ($\text{FFR} = 1$), mild ischemia with balloon inflated to a target $0.6 \leq \text{FFR} \leq 0.8$, and severe ischemia with a target $\text{FFR} \leq 0.45$. During each scan, the animal was positioned on the CT table in a supine, head first position and the respirator was turned off to limit motion artifacts from breathing. Prospective-ECG-triggered scans were acquired at end systole (45% R–R interval) using 20 ml of iodinated contrast agent (Omnipaque, 350 mg-I ml^{-1}) at 5 ml s^{-1} , followed by 20 ml of saline flush at the same flow rate. Baseline scans were acquired first followed by mild and/or severe ischemia scans. Consecutive scans were performed at least 15–20 min apart from each other to allow complete contrast wash out from the heart chambers. Depending on heart rate (HR), scanning was initiated 3–5 s into iodine injection and lasted for less than 25 s to acquire 30–35 volumetric scans of the heart once every heartbeat. Full 360° scans were acquired to avoid partial scan shading artifacts. During image acquisition, heart rate, blood pressures,

body temperature, and FFR values were monitored and recorded. All scans were acquired at 120 kVp and 100 mAs. The effective dose for our dynamic CTP protocol, can be estimated using dose-length product (DLP) multiplied by a conversion coefficient for the chest ($k = 0.014 \text{ mSv mGy}^{-1} \text{ cm}^{-1}$) where DLP (mGy cm) was calculated as the product of CTD_{vol} by the z-coverage of the SDCT scanner of 4 cm. Depending on the number of acquired scans per sequence, the total radiation dose ranged from 15.2–17.6 mSv.

Conventional 120 kVp images were reconstructed using filtered back projection and corresponding monoenergetic images at an optimal keV, as determined by phantom experiments, were generated in the projection domain. Axial mages of the heart were reconstructed with 2 mm slice thickness and no overlap.

3. CTP image processing and flow quantification and analysis

We designed and implemented a comprehensive image processing and blood flow quantification pipeline. Processing includes motion correction through 3D elastic registration, segmentation of the LV myocardium, and singular value decomposition (SVD)-based deconvolution for myocardial blood flow (MBF) estimation.

3.1. Motion artifact correction

To minimize motion artifacts due to breathing in our experiments the respirator was turned off during all image acquisitions. However, prospective ECG-triggered cardiac acquisitions may still suffer from misalignments due to poor ECG synchronizations or irregular heartbeats. Alignment of each acquired 4D sequence is necessary to get accurate arterial and myocardial time activity curves (TACs) which are used for CTP estimations. Each sequence of reconstructed dynamic contrast-enhanced volumes was registered to a common reference time point to minimize residual motion. To this end, a volumetric elastic registration method based on 3D cubic B-splines and normalized mutual information (NMI) was used. The NMI metric was chosen to cope with the dramatic change of the image intensity over time due to the contrast agent kinetics. A three-level multi-resolution approach was adopted for speed and to avoid local minima. Both conventional and 70 keV 4D sequences were each registered to a common reference volume using the parallel implementation of the NMI method in the software NiftyReg (Modat *et al* 2010). For each sequence, the reference volume was automatically chosen as the volume with maximum image energy evaluated as the sum of squared intensity values. In general, this frame corresponds to the time point when large amount of contrast is present in the heart chambers. Visual and quantitative evaluation of registration quality was performed to fine tune some registration parameters.

3.2. Left ventricular myocardial segmentation

For every 4D sequence, we averaged the corresponding motion-corrected 120 kVp images to create a low noise, high contrast average CT map. This allowed us to easily and accurately delineate the LV myocardium, and to generate a corresponding volumetric binary mask. Since all images are registered with each other, this single masking was used to segment the LV myocardium at every time frame in the corresponding 4D sequence. 2D tracing of the epi- and endo-cardial contours was manually performed on the average CT map either in the

axial or short axis plane using an in-house developed interactive contour tracing tool (figure 1). In order to compute mean and standard deviation of MBF and compare results on different LV myocardial segments (figure 1), ROIs were carefully drawn within the segmented myocardium to avoid partial volume averaging and metal artifacts caused by the balloon and the FFR catheters, and to reduce the effects of any residual misalignments.

3.3. Image analysis of myocardial perfusion maps

We developed our own CT perfusion software and used it to quantify blood flow. The two sequences of motion-corrected dynamic contrast-enhanced images, conventional 120 kVp and projection-based 70 keV, were separately analyzed using our perfusion software. TACs measured from ROIs in the LV chamber and from different walls of the LV myocardium for each image sequence were compared to highlight the effect of BH on 120 kVp data. Myocardial tissue TACs were estimated from 2×2 non-overlapping pixel regions or 'superpixels'. To avoid partial volume effects in coronary arteries and metal artifacts in the aorta caused by the FFR catheter, the arterial input function (AIF) was measured from a user-traced ROI within the LV cavity. For each sequence, one global AIF measured from a slice with maximal LV cross section, was used to compute perfusion maps on all analyzed slices in the sequence. These maps were generated by deconvolution of myocardial tissue TACs and the AIF using a model-independent deconvolution method based on singular value decomposition (SVD) with a modified Tikhonov regularization, as described below. Mean 120 kVp and 70 keV perfusion values in different myocardial walls were determined and compared. It is worth noting that, for each experiment, the conventional and the monoenergetic images were reconstructed from the same projections facilitating comparisons. Differences between corresponding groups were compared using paired Student t-test in Matlab (Mathworks Inc., Natick, MA). A p -value ≤ 0.05 was considered to indicate statistical significance.

3.4. Myocardial blood flow quantification

Detailed theoretical basis for determining blood flow from contrast enhanced dynamic functional imaging can be found in (Meier and Zierler 1954). We have developed our own CT perfusion software and used it to quantify blood flow from motion-corrected images. Generally, when a bolus of a contrast agent is intravenously injected, the rate of input of contrast into the tissue is $F C_{\text{art}}(t)$, where F is the blood flow and $C_{\text{art}}(t)$ is the arterial input function, which corresponds to the concentration of contrast in a feeding artery over time. If the flow F is constant over time, then the relationship between the residual concentration of contrast in the tissue of interest, $C(t)$, and the arterial input function $C_{\text{art}}(t)$ can be described by the following convolution as a result of linear superposition:

$$C(t) = 1/\rho_t F \cdot C_{\text{art}}(t) \otimes R(t), \quad (1)$$

where $R(t)$ is the impulse retention or residue function (IRF) which describes the fraction of contrast agent remaining in the tissue, as a function of time, following a unit mass injection of contrast. The convolution operator in (1) is denoted $\otimes$ and ρ_t denotes the tissue density. The estimation of blood flow, F , from measured tissue and arterial time-attenuation curves,

$C(t)$ and $C_{\text{art}}(t)$, is performed through deconvolution of (1) to estimate a flow-scaled IRF, $R_F(t) = F \cdot R(t)$, and then compute F as

$$F = \max_t (R_F(t)).$$

Deconvolution is an ill-posed problem and will not always have a unique solution, which means that some form of regularization is required in order to obtain a numerically stable solution.

For our dynamic myocardial CT perfusion images, we obtain a series of n ECG-triggered volumetric images of the heart acquired a few seconds post injection of the contrast agent. The n volumetric images are acquired with a mean time interval Δt . The tissue and arterial TACs, $C(t)$ and $C_{\text{art}}(t)$ are sampled at times $t = t_i = i \cdot \Delta t$ for $i = 1, \dots, n$. A common algebraic approach to solve for the flow-scaled IRF, $F \cdot R(t)$, is to discretize the convolution integral equation (1) into a system of linear equations using the measured concentration-time curves $C(t)$ and $C_{\text{art}}(t)$ at time points $t_0, t_1, \dots, t_n$. The discretized system can be written in a matrix form as

$$Ax = b, \quad (2)$$

where the n elements of the column vectors b and x are given by $b_i = C(t_i)$, and $x_i = F \cdot R(t_i)$, respectively. The $n \times n$ matrix $A = (a_{ij})_{i,j}$ is given by $a_{ij} = \Delta t \cdot C_{\text{art}}(t_{i-j+1})$ for $0 \leq j < i$ and $a_{ij} = 0$ otherwise (Fieselman *et al* 2011). In order to reduce the influence of time delay between the measured AIF and myocardial TACs, we discretized (1) using a block-circulant matrix of size $2n \times 2n$ assembled using zero-padded time series $C_{\text{art}}(t)$ as was explained in (Fieselman *et al* 2011). This matrix, also noted A here, was decomposed using SVD as

$$A = U \cdot \Sigma \cdot V^T = \sum_{i=1}^r u_i \cdot \sigma_i \cdot v_i^T,$$

where $r = \text{rank}(A)$ is the number of linearly independent rows and columns in A , which corresponds to the highest index of the nonzero singular values. The matrices $U = [u_1, u_2, \dots, u_r]$ and $V = [v_1, v_2, \dots, v_r]$ are unique orthogonal matrices (i.e. $U \cdot U^T = I$ and $V \cdot V^T = I$) whose vector columns, u_i and v_i are referred to as left and right singular vectors, respectively. The diagonal matrix $\Sigma = \text{diag}(\sigma_1, \sigma_2, \dots, \sigma_r)$ contains the singular values σ_i in a non-increasing order, i.e. $\sigma_1 \geq \sigma_2 \geq \dots \geq \sigma_r > 0$. The elements of the singular vectors u_i and v_i have more sign changes as the corresponding singular value becomes smaller, i.e. as the index i increases. The solution of (2) in the least squares sense using the SVD of A is given by

$$x = V \cdot \Sigma^{-1} \cdot U^T b = \sum_{i=1}^r \left(\frac{u_i^T \cdot b}{\sigma_i} \right) \cdot v_i. \quad (3)$$

This solution is equivalent to minimizing the following least-squares problem

$$x_{lsq} = \arg \min_x (\|Ax - b\|_2^2). \quad (4)$$

The block-circulant matrix A is ill-conditioned (Hansen 2002, 2010), causing the solution, x_{lsq} to be very sensitive to noise in the measured data. This makes the least squares problem (4) an ill-posed problem, which requires the use of a regularization method to reduce the effects of small singular values σ_i and obtain a numerically stable solution. A common regularization approach consists of choosing a threshold or truncation index k and setting to zero all σ_i 's such that $i \leq k$. This type of regularization is known as truncated SVD, and the corresponding solution is given by (3) where $1 \leq i \leq k$ in the summation. Different methods exist to appropriately determine the truncation index k such that only desired SVD components are retained in the TSVD solution (Hansen 2002).

An alternative is Tikhonov regularization (Jerosch-Herold *et al* 2002, Fieselmann *et al* 2011) which consists in general of adding the L2-norm of the solution or that of its derivatives as a constraint to the minimization problem (4) as

$$x = \arg \min_x (\|Ax - b\|_2^2 + \lambda^2 \|Lx\|_2^2), \quad (5)$$

where the constraint matrix L is either equal to the identity matrix or is an approximation of the first or second order derivative operators (Hansen 2002, Jerosch-Herold *et al* 2002, Koh and Hou 2002, Koh *et al* 2004), and λ is the regularization parameter which balances the minimization of the residual norm relative to the minimization of the solution norm or that of its derivatives. Often, numerical values of λ are expressed relative to the largest singular value σ_1 , as $\lambda = \lambda_{rel} \sigma_1$ with $\lambda_{rel} \in [0, 1]$ known as the relative regularization parameter. It can be shown that, for a given λ , there is always a unique solution to the above problem (5) (Hansen 2002) which can be calculated in terms of the SVD components of the matrix A as follows

$$x_\lambda = \sum_{i=1}^r f_i \cdot \frac{u_i^T \cdot b}{\sigma_i} v_i, \quad (6)$$

where the quantities $f_i = \sigma_i^2 / (\sigma_i^2 + \lambda^2)$ satisfy $0 \leq f_i \leq 1$ and are called Tikhonov filter factors.

These factors tend to zeros for small σ_i and hence dampen contributions from smaller singular values that can cause instabilities.

The choice of an appropriate λ is crucial since it directly affects the computed flow from the flow-scaled IRF given by the solution x_λ (6). In our perfusion experiments, we noticed that large values of λ led to underestimation of MBF and that small values allowed high frequency noise in the measured data to dominate the solution and produced overestimated MBF values. Different approaches have been proposed to appropriately determine λ for both CT and MR perfusion applications (Sourbron *et al* 2007, Fieselmann *et al* 2011). A simple way is to empirically choose a fixed value for the relative regularization parameter λ_{rel} as was done previously for two commercial perfusion software packages dedicated to brain CT

perfusion ($\lambda_{\text{rel}} = 0.2$) (Kudo *et al* 2009). In this work, we used an automated approach to determine the optimal regularization parameter, λ_{opt} , based on the L-curve criterion (LCC) (Hansen 2002, Jerosch-Herold *et al* 2002, Koh and Hou 2002, Koh *et al* 2004). The LCC provides an automatic way to adaptively specify the regularization parameter in presence of changes in noise level. The L-curve is a log–log plot of the smoothness measure $\|Lx_\lambda\|$ versus the goodness of fit measure $\|Ax_\lambda - b\|$ for different values of λ . A schematic plot of the L-curve is shown on figure 2. The vertical part of the L-curve corresponds to the range of λ values that give rise to small residuals $\|Ax_\lambda - b\|$, and the horizontal part corresponds to values of λ that cause the solution to be sufficiently smooth as indicated by small changes of the constraints norm $\|Lx_\lambda\|$ with λ . The optimal λ corresponds to the point on the L-curve with maximum positive curvature which corresponds to the corner of the L-curve (Hansen 1992, Hansen and O’Leary 1993, Johnston and Gulrajani 2000). Practically, we calculated the Tikhonov regularized solution x_λ given by (6) for a range of λ values. Then, we computed the log values of the corresponding residual norms $\|Ax_\lambda - b\|$, and that of the constraint norms $\|Lx_\lambda\|$, and we fitted a smooth spline to the obtained data points on the L-curve. The optimal regularization parameter λ_{opt} was determined by the point on the fitted spline with maximum curvature.

Due to noise and imaging artifacts, the use of a different optimal λ for every superpixel resulted in flow maps with random spikes. We then made the following modification to the LCC in our CTP experiments. For every processed superpixel p_i in a given 2d slice, we estimated an optimal value of the regularization parameter, λ_k , using the LCC. Then, we calculated a fixed parameter, λ_{opt} , by the following weighted sum and used it for flow computation on the entire cross section

$$\lambda_{\text{opt}} = \sum_{k=1}^K w_k \cdot \lambda_k,$$

where, K is the total number of the allowed values of λ , and $w_k = m_k/M$ is the ratio of the number m_k of superpixels corresponding to λ_k by the total number of processed superpixels, M .

3.5. Comparison of MBF ratio to pressure FFR

We can compare the myocardial blood flow ratio, $\text{MBF}_{\text{ratio}}$, between ischemic and remote myocardium to FFR, as measured with a pressure wire. The MBF ratio is

$$\text{MBF}_{\text{ratio}} = F_{\text{LAD}}/F_{\text{remote}},$$

where F_{LAD} and F_{remote} are mean blood flows in ROIs placed within the ischemic LAD territory and the healthy remote myocardium, respectively. LAD and remote ROIs were placed on the anterior, and the infero- or antero-lateral walls, respectively. FFR, measured with a pressure wire, was the ratio of arterial pressures distal, P_d , and proximal, P_p , to the inflatable balloon, i.e. $\text{FFR} = P_d/P_p$ (De Bruyne and Sarma 2008). To compare FFR and $\text{MBF}_{\text{ratio}}$, we used the circuit analogy, with flow $F = P/R_{\text{myo}}$, where $P = P_a - P_v$ is the

difference between arterial and venous pressures, and R_{myo} is the myocardial resistance, mostly in capillaries (Tuttle and Schottelius 1969, De Bruyne and Sarma 2008). We assume a small venous pressure resulting in $P \approx P_a$. With balloon inflation, there will be a pressure drop across the balloon and MBF in the LAD would correspond to the distal pressure measurement, $F_{\text{LAD}} = P_d/R_{\text{LAD}}$. The remote MBF would correspond to the proximal pressure measurement, $F_{\text{remote}} = P_p/R_{\text{remote}}$. If the myocardial resistance is the same in both instances, i.e. $R_{\text{LAD}} = R_{\text{remote}}$, then $\text{FFR} = P_d/P_p = F_{\text{LAD}}/F_{\text{remote}}$, equivalent to the $\text{MBF}_{\text{ratio}}$ measured in our CT experiments. There are two key assumptions: (1) P_p is the same for both the LAD and unaffected coronary arteries. (2) Myocardial resistance is equal for the territories being compared, i.e. $R_{\text{LAD}} \approx R_{\text{remote}}$. Under these assumptions, we compared $\text{MBF}_{\text{ratio}}$ to measured pressure FFR under baseline ($\text{FFR} = 1.0$) and ischemic ($\text{FFR} < 0.8$) conditions.

4. Results

4.1. Phantom studies

We determined a linear relationship between SDCT signals and iodine concentration, a necessary requirement for any perfusion blood flow measurement. Mean iodine concentrations, measured within ROI's in iodine map images generated from material decomposition with the SDCT system, were compared to actual iodine concentrations in the vials (figure 3(B)). The linear regression line on this plot with near unity slope and zero offset shows that the SDCT system produces accurate estimations of iodine concentration. Rather than using iodine maps, we used projection-based keV images because they had less noise and showed better anatomy. In figure 3(C), mean HU from different keV images show very good linearity with iodine concentration. As 70 keV is approximately equal to the effective energy of the 120 kVp spectrum, the 70 keV intensity (HU) values are close to those measured from the conventional 120 kVp images.

To determine an optimal keV for CTP, we investigated image noise, sensitivity of iodine detection, and residual BH artifact in phantom images. Image noise standard deviation increases at lower keVs (figure 4(A)), especially below 70 keV, while contrast markedly improves at lower energies. Combining measurements, the effect of contrast increase dominates the noise, and iodine CNR increases with decreasing keV (figure 4(B)). The maximum CNR (2.77) was attained at 50 keV, an energy where image noise is substantially higher than at higher energies. Although the SDCT greatly reduces BH, there remain small residual BH artifacts. When measured as described previously, BH artifacts appear in low and high keV images (figure 4(C)). The graph suggests that the residual BH artifact will disappear at around 77 keV. For comparison, the BH artifact in 120 kVp images was 25.01 ± 7.9 HU, about 16 times the value at 70 keV (1.52 ± 6.9 HU). On the one hand, the CNR curve suggests that a low keV value will be best, while the BH artifact curve suggests that one should image at about 77 keV. We chose a compromise at 70 keV. If we were to move from 70 keV to 77 keV to further reduce BH artifact, iodine CNR would be degraded by almost 30%, a substantial penalty. We chose 70 keV as a good operating energy for our pig CTP experiments and corresponding results will be compared against 120 kVp results.

4.2. Myocardial CTP studies

Typical results from a representative healthy and ischemic pig experiments are presented and discussed below.

4.2.1. Non-ischemic (baseline) condition.—In figure 5, we compared image quality, time attenuation curves, and flow maps for both 70 keV and corresponding 120 kVp images. In this case, we imaged a non-ischemic pig (no balloon inflation and FFR = 1), where there should be no perfusion deficit. The 120 kVp images were degraded with a hypoenhancement in the anterior and inferior walls (figure 5(A)). In contrast, the 70 keV image (figure 5(B)) shows relatively uniform enhancement throughout the healthy myocardium. We conclude that BH artifacts at 120 kVp are effectively reduced with the 70 keV reconstruction. The AIF generated from the LV-cavity and the tissue TACs generated from the anterior, lateral, septal, and inferior walls for each reconstruction are plotted in figures 5(C) and (D). During the time interval when the contrast signal is high in the LV, as indicated by the peak of the AIF, BH effects introduced a noticeable dip in the 120 kVp TACs measured from the anterior and the inferior walls (figure 5(C)). In fact, 120 kVp HU values decreased below baseline HU of myocardial tissue, a physical impossibility. These effects were greatly minimized in the 70 keV TACs (figure 5(D)) which exhibit a gradual increase in attenuation over time. These BH-introduced distortions of TACs in the 120 kVp data affected blood flow quantification, leading to an underestimation of MBF in the BH-hypoenhanced areas of the myocardium, as compared to remote areas in the color flow map (figure 5(E)). On the other hand, the 70 keV flow map (figure 5(E)) shows a much more homogeneous distribution of flow throughout the myocardium.

To quantitatively assess the effect of BH artifacts on perfusion estimates for the normal condition (FFR = 1), we computed mean MBF within four ROIs manually drawn in the anterior, lateral, septal, and inferior walls of the LV myocardium. We averaged results across five adjacent apical slices. Corresponding results are plotted in figures 6(A) and (B), where error bars correspond to standard deviation of mean MBF values across the five considered slices. At 120 kVp, mean MBF in the anterior and infero-septal walls were at least 20% lower than that in the septal and lateral walls (figure 6(A)). At 70 keV (figure 6(B)), MBF was much more homogeneous throughout the myocardium, with a mean absolute difference between the four different myocardial walls under 3 ml/min/100 g. Mean MBF value in the anterior, lateral, inferior, and septal walls ranged from 94.02 ± 10.83 to 104.51 ± 14.87 ml/min/100 g for the 70 keV perfusion map and were relatively lower compared to the corresponding 120 kVp values (from 91.92 ± 12.86 to 127.74 ± 18.49 ml/min/100 g). Standard deviations of mean MBF values across adjacent slices were small giving coefficients of variation of 2.7% for 70 keV estimates and 3.71% for 120 kVp, underscoring the consistency of perfusion measurements across different slices.

We also compared relative blood flows to measured FFR using the ratio of mean MBF in the BH-affected areas (anterior and inferior walls) to that in the lateral wall. At 120 kVp, the mean relative flow across six adjacent slices in anterior-to-lateral wall and in inferior-to-lateral wall were 0.75 ± 0.03 and 0.77 ± 0.04 , respectively. This falsely indicates a hemodynamically significant condition for the LAD and the right coronary artery (RCA).

On the other hand, the corresponding 70 keV mean flow ratios were significantly higher 0.95 ± 0.02 ($p < 0.05$) and 0.98 ± 0.05 ($p < 0.05$), respectively on the anterior and inferior walls relative to the lateral wall. The 70 keV flow ratios favorably compared to the measured FFR value (figure 7).

It is worth noting that the heterogeneity of blood flow due to BH artifacts in the 120 kVp flow maps persists across several adjacent slices, which could make it difficult to distinguish between a mere BH effect and a true flow deficit. We also noticed that the 120 kVp flow values were much higher than their 70 keV counterparts over the entire myocardium. This is mainly attributed to BH artifacts, and to noise level, which is about 8% higher in the conventional 120 kVp images compared to 70 keV images.

4.2.2. Ischemic condition.—Under an actionable ischemic condition with recorded $\text{FFR} \approx 0.65$, flow deficits were correctly detected in the ischemic LAD territory in the 70 keV perfusion maps (figure 8—bottom row). We also found that MBF maps in both 120 kVp and 70 keV were quite consistent across several adjacent slices as illustrated by four MBF slices on figure 8. Using the same color bar for each slice, we found that for each reconstruction, flow features were very similar across adjacent slices within healthy and ischemic territories, including the extent of the myocardial ischemia. In addition, we noticed that BH-induced hypoenhancement led to reduction of MBF at 120 kVp in the non-ischemic inferior wall (yellow arrows in figure 8—top row). In areas such as the antero-septal and infero-lateral walls (red arrows in figure 8—top row), BH artifacts induced high flows in 120 kVp maps.

A ROI analysis of blood flow in the ischemia condition is given in figure 9. As for the baseline condition, we computed mean MBF on four different ROIs in the myocardium (anterior, lateral, septal, and inferior walls). Average and standard deviations of flow values within these ROIs across several adjacent slices are plotted in figures 9(A) and (B). Due to BH artifacts, mean 120 kVp perfusion values on the non-ischemic inferior wall was significantly low across several adjacent slices, which appeared as perfusion deficit on the MBF maps. In particular, mean perfusion value in the inferior wall was about 50% lower than that in the lateral wall. In contrast, mean 70 keV flow values were reduced only on the ischemic LAD territories. In this case, the mean flow in the lateral wall was only about 7% higher than that in the inferior wall. Mean MBF value in the lateral and septal walls ranged from 30.41 ± 13.02 to 78.07 ± 14.87 ml/min/100 g for the 70 keV perfusion map and were significantly lower than the corresponding 120 kVp values (from 56.62 ± 13.9 to 96.64 ± 19.7 ml/min/100 g; $p < 0.05$).

As was done for the baseline condition, we computed relative blood flows and compared to the measured FFR for the ischemic case (figure 10). At 120 kVp, the averaged relative flow values across six adjacent slices in anterior-to-lateral wall and in inferior-to-lateral wall were 0.3 ± 0.01 and 0.5 ± 0.04 , respectively. The corresponding 70 keV mean relative flow values were 0.42 ± 0.008 ($p < 0.05$) and 1.0 ± 0.08 ($p < 0.05$), respectively. The 120 kVp perfusion estimates falsely predicted an actionable ischemic condition for the healthy inferior wall, an RCA territory. The 70 keV estimates, on the other hand, correctly indicated a healthy

inferior wall. Relative myocardial perfusion blood flows were less than what one might expect from FFR measurements in the affected LAD (see discussion).

4.2.4. Qualitative assessment.—It is also possible to qualitatively examine myocardial perfusion by examining selected images as has been done in previous studies (Blankstein *et al* 2009). Example of 120 kVp and their corresponding 70 keV slices at peak myocardial enhancement under a baseline (FFR = 1) and an ischemic (FFR $\approx$ 0.65) condition are shown in figure 11. At baseline, 70 keV attenuation values were relatively uniform over the entire myocardium. In the 120 kVp baseline image, dark BH artifacts could be noticed on the anterior and inferior walls, which might be misconstrued as flow deficit. When the LAD artery was partially occluded, lower attenuation values were detected in the LAD region (anterior, antero-lateral and antero-septal walls) as compared to remote myocardial regions, both for 120 kVp and 70 keV images. However, due to BH-induced hypoenhancements in the 120 kVp image, we noticed a widening of the apparent ischemic area in the anterior wall with significant shift in HU values compared to 70 keV images. This suggests that qualitative CTP techniques may also be negatively affected by BH artifacts when using conventional CT scans. Note that since the 120 kVp and the 70 keV images have relatively comparable dynamic ranges, the same window width and level were used for the displays in figure 11.

Finally, it is worth mentioning that the contrast between ischemic and healthy myocardium in monoenergetic images degrades at higher keV's where iodine has relatively less photoelectric absorption. Visual comparison of keV images is confounded because they have different dynamic ranges. We examined images at different window/level settings and concluded that it was relatively difficult to detect ischemia in higher keV images. For an imaging protocol like ours, we found that 70 keV and below were suitable for qualitative visualization of the ischemic defect. However, higher noise levels at lower keV's may compromise visual assessment of perfusion.

5. Discussion

This initial study on myocardial perfusion with a prototype SDCT scanner demonstrates that the SDCT system is well suited to provide useful perfusion assessments, much better than conventional CT. With our porcine, LAD-selective, balloon occlusion model, SDCT perfusion clearly demonstrated perfusion deficits restricted to the LAD territory. When no occlusion was present, dynamic perfusion estimates were relatively constant. Relative flows were nearly 1.0, and would not be confused with the value of 0.8 that might lead to a false positive, actionable result. With conventional CT, the large amount of iodine in the ventricles and aorta, and bone absorption lead to beam hardening artifacts that greatly confound interpretation of myocardial perfusion. These confounds were found in our experiments. As compared to other energy sensitive CT designs, the SDCT system with its dual-layer detector allows one to acquire projections simultaneously, enabling accurate, motion-free, projection-based material decomposition. Since we can reconstruct both energy selective images as well as conventional CT on the SDCT, we have a great experimental system for comparisons. Below, we discuss optimization of SDCT processing; contrast and compare,

energy selective and conventional CT perfusion assessments; and discuss SDCT in the context of other imaging systems.

In phantom experiments, we demonstrated attenuation linearity with iodine concentration, a requirement for any quantitative perfusion assessment. We also determined through these experiments, a proper keV value for projection-based monoenergetic imaging. As keV decreases below 65 keV, noise significantly increases which is a major confound for flow quantification. At that keV range, iodine CNR also increases owing to the increased contrast in the monoenergetic reconstructions. Small residual BH artifacts are minimal at 77 keV and increase at lower keVs. These considerations led us to pick 70 keV as a good compromise for quantitative dynamic cardiac CTP.

To quantify myocardial blood flow, we used a computational pipeline consisting of 4D elastic image registration, noise reduction, and perfusion estimation. The latter step deserves discussion. We used an in-house implemented, model-independent deconvolution method with block-circulant SVD. Due to noise in the measured data, we used Tikhonov regularization to reduce the influence of small singular values and obtain a numerically stable solution. We determined that computed flows greatly depended on the choice of the regularization parameter, and we adopted a modified version of the L-curve criterion to automatically choose the regularization parameter depending on the amount of noise in each scan. Although the L-curve criterion may sometimes fail to compute a reasonable regularization parameter, it was shown to be much more robust than other approaches such as generalized cross-validation (Hansen and O'Leary 1993). Other deconvolution approaches have been used in various perfusion studies, including model-dependent approaches (So and Lee 2011) which assume a certain shape of the impulse residue function and hence reduce its degrees of freedom. Such approaches can make the deconvolution more stable if an appropriate IRF model is used. A theoretical review of these approaches can be found in (Fieselmann *et al* 2011, So and Lee 2011). The SVD-based deconvolution has the advantage of being relatively simple to implement, and when used with Tikhonov regularization, it was shown to be computationally stable and to result in accurate blood flow estimates (Jerosch-Herold *et al* 2002). It has been chosen as a standard method in some clinically available perfusion software packages (Kudo *et al* 2009).

Qualitatively, BH artifacts in conventional 120 kVp pig images resulted in the appearance of dark bands on the myocardium which could be misconstrued as perfusion deficits in a normal heart. In the presence of ischemia, these artifacts led to poor visualization and appreciation of the ischemic region. In contrast, virtual 70 keV images effectively minimized BH artifacts which resulted in a more homogeneous attenuation in normal heart, and led to more reliable assessments of the ischemic defects when the LAD artery was occluded (figures 11(A), (C) versus (B), (D)).

Quantitatively, the 70 keV myocardial blood flow obtained under normal hemodynamic condition ($FFR = 1$) was homogeneous throughout the myocardium, and partial occlusion of the LAD resulted in perfusion maps with correctly identified perfusion deficit in the LAD territory. Due to BH artifact in conventional kVp images, the anterior and inferior myocardial walls were hypo-intense in single images particularly at maximum ventricular

opacity (figure 5(A)). These BH-affected walls lie between the ventricle and other high contrast objects, namely the spine and aorta, respectively. Not only did BH affected single images, it clearly caused dips in tissue TACs (figure 5(C)), which greatly affected blood flow determinations. In particular, mean flow in the anterior and inferior walls in 120 kVp images was down to a level which could be falsely misconstrued as an actionable deficit. That is, the anterior-to-lateral and inferior-to-lateral flow ratios were <0.8 . A value of 0.8 perfusion ratio would roughly correspond to an FFR of 0.8 (see Methods), a common threshold for action. In contrast, virtual 70 keV images were mostly devoid of any BH artifacts leading to more uniform MBF throughout the myocardium. The 70 keV normal MBF measured by us ranged from 90 to 100 ml/min/100 g in most cases. These values are within the range of those reported by others for normal pig (So *et al* 2011). However, MBF was lower in some experiments when arterial blood pressure had dropped and cardiac output decreased following repeated balloon inflations. Under controlled, balloon induced ischemia in the LAD, BH in conventional CT data affected the extent of perfusion defect in the LAD territory and falsely recorded a hemodynamically significant ischemia in the healthy inferior wall, an RCA territory. This could have been falsely interpreted as two vessel disease. The 70 keV MBF maps correctly identified deficits restricted to the LAD territory. These preliminary results suggest that SDCT projection-based keV images will be much better than conventional CT imaging for the assessment of myocardial perfusion.

In this preliminary study, we computed flow ratio, MBF_{ratio} , in affected myocardium relative to remote healthy myocardium and compared them to measured FFR (see Methods). The calculated MBF_{ratio} value in the ischemic and BH-affected anterior myocardium tracked changes in the pressure FFR measurement but often underestimated FFR under induced ischemia. We found that BH artifact in the conventional images contributed to this underestimation, as the 70 keV images had a MBF_{ratio} closer but still lower than the measured FFR. The difference between MBF_{ratio} and FFR could be attributed to flow quantification methods as well as to the breakdowns in the assumptions which relate MBF_{ratio} to FFR. Some potential reasons follow. First, the proximal pressures in both ischemic and remote arteries might not be equal owing to the extra 'hardware' in the LAD. Second, a nonzero venous pressure could lead to up to a 10% over-estimation in measured FFR. Third, a difference in the myocardial resistances of the two territories would cause MBF_{ratio} to differ from FFR. Such a deviation could be obtained if the vascular tone were different in the two territories or if there was a vascular spasm as the result of the sudden occlusion. The exact reasons for the deviation between MBF_{ratio} and the reference FFR will become clearer as more pig experiments and fluorescent microsphere data are analyzed. Given the considerable differences in reported optimal cutoff values of absolute MBF to identify normal and ischemic patients (Huber *et al* 2013, Rossi *et al* 2014a), MBF_{ratio} could be more effective in identifying hemodynamically significant coronary artery stenosis. Recently, Kono *et al* (2014) published a clinical dynamic myocardial CTP study ($n = 42$) showing that MBF_{ratio} correlated better with FFR ($R = 0.76$) than the absolute MBF did ($R = 0.52$).

In addition to SDCT, there are at least two other energy sensitive CT imaging system designs suitable for cardiac CTP, each with advantages and disadvantages. First, the fast kVp switching system has been shown to provide improved perfusion estimates by effectively

reducing BH and improving iodine sensitivity using projection-based monochromatic images (So *et al* 2011). Second, dual source CT has been used for several years for myocardial perfusion (So *et al* 2012b, Vliegenthart *et al* 2012). When there is misregistration between low- and high-energy projections, one has to use image-based material decompositions, which are known to be less accurate than projection based methods (Heismann *et al* 2012). The SDCT design with its dual layer detector has the advantage of acquiring low and high-energy projections that are perfectly aligned in time and space. This gives excellent projection-space material decompositions and BH correction.

Cardiovascular imaging with the SDCT system compares favorably to other non-invasive means of assessing coronary artery disease in the heart. SPECT is the most common way to assess cardiac perfusion, but it suffers from low resolution, radiation dose, cost, examination time, and low correlation with FFR in patients with 2- or 3-vessel CAD (Melikian *et al* 2010). PET is usually regarded as giving the most accurate cardiac perfusion estimates, but it is expensive and is not always readily available. Cardiac magnetic resonance has also established itself as a valuable tool for accurate qualitative and quantitative perfusion imaging. However, none of these three approaches provide the reliable imaging of coronary arteries afforded by CT. Coronary CTA has been shown to be cost-effective in the diagnostic workflow for CAD in low-risk patients when combined with SPECT myocardial perfusion imaging (Zeb *et al* 2014). The ability to measure flow and assess the presence of obstructive CAD in a single non-invasive exam with CT would be powerful as a gateway exam to invasive coronary angiography. Finally, with advancements in low dose CT imaging and specialized acquisitions, it is quite possible that CT will provide dynamic cardiac perfusion at less patient x-ray dose than SPECT, which is typically 9.4–41 mSv (Mettler *et al* 2008) for cardiac rest-stress tests. In our pig studies, we used 15–18 mSv for 4 cm coverage which we speculate could be fairly easily reduced to 3.75–4.5 mSv using advanced iterative reconstruction and reduced sampling rate at later times.

An emerging approach is FFR_{CT}, which has been found to have good correlation with invasive FFR (Nørgaard *et al* 2014). In this approach, blood vessels are segmented and fluid mechanics is used to predict FFR. Potential downsides are sensitivity to CTA image quality, inability to process highly calcified vessels, and offsite processing unsuitable for point of care. Moreover, FFR_{CT} does not actually measure perfusion, giving no opportunity to determine patients suffering from cardiac syndrome X where there is ischemia but no apparent CAD (Kaski 2004). If FFR_{CT} were to become routinely used, then the ideal CT workup could include CTA, FFR_{CT} to predict the severity of a stenosis, and CTP to determine if flow is actually limited.

In conclusion, the SDCT design and appropriate processing appear well suited for making cardiac CT perfusion measurements. The system has eliminated the issue of beam hardening which precludes use of uncorrected conventional CT. Given the unmet need for improved screening prior to cardiac angiography, it appears quite appropriate to continue optimization of methods and determine the reliability of assessments with larger studies.

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References

- Altman A, Shapiro O, Levene S and Wainer N 2011 Double Decker Detector for Spectral CT ed USPTO (Cleveland, OH: Koninklijke Philips Electronics N.V.)
- Alvarez RE and Macovski A 1976 Energy-selective reconstructions in x-ray computerized tomography *Phys. Med. Biol.* 21 733–44 [PubMed: 967922]
- Blankstein R et al. 2009 Adenosine-induced stress myocardial perfusion imaging using dual-source cardiac computed tomography *J. Am. Coll. Cardiol.* 54 1072–84 [PubMed: 19744616]
- Brooks R and Di Chiro G 1978 Split-detector computed tomography: a preliminary report *Radiology* 126 255–7 [PubMed: 619422]
- De Bruyne B and Sarma J 2008 Fractional flow reserve: a review *Heart* 94 949–59 [PubMed: 18552231]
- Fahmi R, Eck BL, Fares A, Levi J, Wu H, Vembar M, Dhanantwari A, Bezerra HG and Wilson DL 2015 Dynamic myocardial perfusion in a porcine balloon-induced ischemia model using a prototype spectral detector CT *SPIE Medical Imaging* (San Diego, CA: International Society for Optics and Photonics)
- Fieselmann A, Kowarschik M, Ganguly A, Hornegger J and Fahrig R 2011 Deconvolution-based CT and MR brain perfusion measurement: theoretical model revisited and practical implementation details *Int. J. Biomed. Imag.* 2011 467563
- Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS and Franco S 2014 Heart disease and stroke statistics—2014 update: a report from the American Heart Association *Circulation* 129 e28 [PubMed: 24352519]
- Hachamovitch R, Hayes SW, Friedman JD, Cohen I and Berman DS 2003 Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography *Circulation* 107 2900–7 [PubMed: 12771008]
- Hansen PC 1992 Analysis of discrete ill-posed problems by means of the L-curve *SIAM Rev.* 34 561–80
- Hansen PC 2002 Deconvolution and regularization with Toeplitz matrices *Numer. Algorithms* 29 323–78
- Hansen PC 2010 *Discrete Inverse Problems: Insight and Algorithms* vol 7 (Philadelphia, PA: SIAM)
- Hansen PC and O'Leary DP 1993 The use of the L-curve in the regularization of discrete ill-posed problems *SIAM J. Sci. Comput.* 14 1487–503
- Heismann BJ, Schmidt BT and Flohr T 2012 *Spectral Computed Tomography* (Bellingham, WA: SPIE)
- Ho KT, Chua KC, Klotz E and Panknin C 2010 Stress and rest dynamic myocardial perfusion imaging by evaluation of complete time-attenuation curves with dual-source CT *JACC Cardiovasc. Imag.* 3 811–20
- Huber AM, Leber V, Gramer BM, Muenzel D, Leber A, Rieber J, Schmidt M, Vembar M, Hoffmann E and Rummeny E 2013 Myocardium: dynamic versus single-shot CT perfusion imaging *Radiology* 269 378–86 [PubMed: 23788717]
- Jerosch-Herold M, Swingen C and Seethamraju RT 2002 Myocardial blood flow quantification with MRI by model-independent deconvolution *Med. Phys.* 29 886–97 [PubMed: 12033585]

- Johnston PR and Gulrajani RM 2000 Selecting the corner in the L-curve approach to Tikhonov regularization IEEE Trans. Biomed. Eng 47 1293–6 [PubMed: 11008433]
- Kaski JC 2004 Pathophysiology and management of patients with chest pain and normal coronary arteriograms (cardiac syndrome X) Circulation 109 568–72 [PubMed: 14769677]
- Koh T and Hou Z 2002 A numerical method for estimating blood flow by dynamic functional imaging Med. Eng. Phys 24 151–8 [PubMed: 11886835]
- Koh T, Wu X, Cheong L and Lim C 2004 Assessment of perfusion by dynamic contrast-enhanced imaging using a deconvolution approach based on regression and singular value decomposition IEEE Trans. Med. Imag 23 1532–42
- Kono AK, Coenen A, Lubbers M, Kurata A, Rossi A, Dharampal A, Dijkshoorn M, van Geuns R-J, Krestin GP and Nieman K 2014 Relative myocardial blood flow by dynamic computed tomographic perfusion imaging predicts hemodynamic significance of coronary stenosis better than absolute blood flow Investigative Radiol. 49 801–7
- Kudo K, Sasaki M, Yamada K, Momoshima S, Utsunomiya H, Shirato H and Ogasawara K 2009 Differences in CT perfusion maps generated by different commercial software: quantitative analysis by using identical source data of acute stroke patients Radiology 254 200–9
- Lehmann L, Alvarez R, Macovski A, Brody W, Pelc N, Riederer S and Hall A 1981 Generalized image combinations in dual KVP digital radiography Med. Phys 8 659–67 [PubMed: 7290019]
- Maaß C, Baer M and Kachelrieß M 2009 Image-based dual energy CT using optimized precorrection functions: a practical new approach of material decomposition in image domain Med. Phys 36 3818 [PubMed: 19746815]
- Meier P and Zierler KL 1954 On the theory of the indicator-dilution method for measurement of blood flow and volume J. Appl. Physiol 6 731–44 [PubMed: 13174454]
- Melikian N, De Bondt P, Tonino P, De Winter O, Wyffels E, Bartunek J, Heyndrickx GR, Fearon WF, Pijls NH and Wijns W 2010 Fractional flow reserve and myocardial perfusion imaging in patients with angiographic multivessel coronary artery disease JACC: Cardiovas. Interventions 3 307–14
- Mettler FA Jr, Huda W, Yoshizumi TT and Mahesh M 2008 Effective doses in radiology and diagnostic nuclear medicine: a catalog 1 Radiology 248 254–63 [PubMed: 18566177]
- Modat M, Daga P, Cash D and Ourselin S 2010 NiftyReg (<http://cmictig.cs.ucl.ac.uk/wiki/index.php/NiftyReg>)
- Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T and Di Mario C 2013 2013 ESC guidelines on the management of stable coronary artery disease The Task Force on the management of stable coronary artery disease of the European Society of Cardiology Eur. Heart J 34 2949–3003 [PubMed: 23996286]
- Nørgaard BL, Leipsic J, Gaur S, Seneviratne S, Ko BS, Ito H, Jensen JM, Mauri L, De Bruyne B and Bezerra H 2014 Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (analysis of coronary blood flow using CT angiography: next steps) J. Am. Coll. Cardiol 63 1145–55 [PubMed: 24486266]
- Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, Brindis RG and Douglas PS 2010 Low diagnostic yield of elective coronary angiography N Engl. J. Med 362 886–95 [PubMed: 20220183]
- Rossi A, Dharampal A, Wragg A, Davies LC, van Geuns RJ, Anagnostopoulos C, Klotz E, Kitslaar P, Broersen A and Mathur A 2014a Diagnostic performance of hyperaemic myocardial blood flow index obtained by dynamic computed tomography: does it predict functionally significant coronary lesions? Eur. Heart J.—Cardiovasc. Imag 15 85–94
- Rossi A, Merkus D, Klotz E, Mollet N, de Feyter PJ and Krestin GP 2014b Stress myocardial perfusion: imaging with multidetector CT Radiology 270 25–46 [PubMed: 24354374]
- Shefer E, Altman A, Behling R, Goshen R, Gregorian L, Roterman Y, Uman I, Wainer N, Yagil Y and Zarchin O 2013 State of the art of CT detectors and sources: a literature review Curr. Radiol. Rep 1 76–91
- So A, Hsieh J, Imai Y, Narayanan S, Kramer J, Procknow K, Dutta S, Leipsic J, Min JK and LaBounty T 2012a Prospectively ECG-triggered rapid kV-switching dual-energy CT for quantitative imaging of myocardial perfusion JACC: Cardiovasc. Imag 5 829–36

- So A, Hsieh J, Li JY and Lee TY 2009 Beam hardening correction in CT myocardial perfusion measurement *Phys. Med. Biol* 54 3031–50 [PubMed: 19398817]
- So A, Hsieh J, Narayanan S, Thibault J-B, Imai Y, Dutta S, Leipsic J, Min J, LaBounty T and Lee T-Y 2012b Dual-energy CT and its potential use for quantitative myocardial CT perfusion *J. Cardiovasc. Computed Tomogr* 6 308–17
- So A and Lee T-Y 2011 Quantitative myocardial CT perfusion: a pictorial review and the current state of technology development *J. Cardiovasc. Computed Tomogr* 5 467–81
- So A, Lee TY, Imai Y, Narayanan S, Hsieh J, Kramer J, Procknow K, Leipsic J, Labounty T and Min J 2011 Quantitative myocardial perfusion imaging using rapid kVp switch dual-energy CT: preliminary experience *J. Cardiovasc. Comput. Tomogr* 5 430–42 [PubMed: 22146502]
- Sourbron S, Dujardin M, Makkat S and Luytbaert R 2007 Pixel-by-pixel deconvolution of bolus-tracking data: optimization and implementation *Phys. Med. Biol* 52 429 [PubMed: 17202625]
- Stenner P, Schmidt B, Allmendinger T, Flohr T and Kachelrie M 2010 Dynamic iterative beam hardening correction (DIBHC) in myocardial perfusion imaging using contrast-enhanced computed tomography *Investigative Radiol.* 45 314–23
- Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leeser MA, Ver Lee PN, Maccarthy PA, Van't Veer M and Pijls NH 2010 Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation *J. Am. Coll. Cardiol* 55 2816–21 [PubMed: 20579537]
- Tuttle WW and Schottelius BA 1969 *Textbook of Physiology* (Maryland Heights, MO: CV Mosby)
- Vliegenthart R, Pelgrim GJ, Ebersberger U, Rowe GW, Oudkerk M and Schoepf UJ 2012 Dual-energy CT of the heart *Am. J. Roentgenol* 199 S54–63 [PubMed: 23097168]
- Wang Y, Qin L, Shi X, Zeng Y, Jing H, Schoepf UJ and Jin Z 2012 Adenosine-stress dynamic myocardial perfusion imaging with second-generation dual-source CT: comparison with conventional catheter coronary angiography and SPECT nuclear myocardial perfusion imaging *AJR Am. J. Roentgenol* 198 521–9 [PubMed: 22357991]
- Zeb I, Abbas N, Nasir K, and Budoff M 2014 Coronary computed tomography as a cost-effective test strategy for coronary artery disease assessment—a systematic review *Atherosclerosis* 234.2 426–35 [PubMed: 24769305]

Figure 1.

Average CT map generated from a registered 4D sequence. High contrast between the right and left ventricles facilitates the delineation of the LV myocardium (enclosed by red and green contours). Dissection, in the axial plane, of the LV myocardium into six segments: anterior, anteroseptal, anterolateral, inferior, inferoseptal, and inferolateral. Flow measurements and comparisons are made within these segments.

Figure 2.

Schematic illustration of the L-curve. A log–log plot of the constraint norm, $\|Lx_\lambda\|$, versus the residual norm, $\|Ax_\lambda - b\|$, for different values of the regularization parameter λ . A smooth spline (red curve) is fitted to the obtained data points (black circles). The optimal regularization parameter λ_{opt} is identified by the location on the L-curve where the fitting spline has maximum curvature (red solid triangle).

Figure 4. Noise (A), iodine CNR (B), and beam hardening artifacts (C) as a function of monochromatic energy ranging from 50 to 120 keV at 10 keV increments.

Figure 5.

Beam hardening (BH) effects on perfusion assessment under baseline condition ($FFR = 1$). (A) 120 kVp and (B) corresponding 70 keV CT slice. (C) 120 kVp and (D) corresponding 70 keV arterial input functions (AIF) and iodine concentrations over time measured as mean HU inside a region of interest in the LV cavity and in the four myocardial walls indicated by red arrows on (A), respectively. Tissue TACs are multiplied by a factor of 3 for better visualization. The green square highlights tissue TACs' distortions caused by BH artifacts. (E) 120 kVp and corresponding (F) 70 keV myocardial flow maps. Color bar corresponds to flow in ml/min/100 g. Blue arrows point to areas of reduced flow caused by BH. Same window width and level used for (A) and (B): 125/35. Abbreviations in (A): Ant = Anterior, Inf = Inferior, Lat = Lateral, Sep = Septal.

Figure 6.

Relative blood flow under baseline condition (FFR = 1). Shown are measured mean MBF ratios in anterior (Ant) and inferior (Inf) walls relative to lateral (Lat) wall, as well as corresponding FFR. Note that, in all experiments, FFR was measured only in LAD. Error bars correspond to standard deviation of relative flow across six adjacent slices.

Figure 7. Relative blood flow under baseline condition (FFR = 1). Shown are measured mean MBF ratios in anterior (Ant) and inferior (Inf) walls relative to lateral (Lat) wall, as well as corresponding measured FFR. Note that, in all experiments, FFR was measured in the LAD only. Error bars correspond to standard deviation of relative flow across six adjacent slices.

Figure 8.

Detection of flow defects and consistency of ischemia features across adjacent slices. Conventional 120 kVp (top row) and projection-based 70 keV (bottom row) myocardial blood flow maps. Shown are four slices of the scanned pig's heart under an ischemic condition with FFR = 0.65. Yellow and red arrows indicate areas with lower and higher flow values on the 120 kVp maps compared to the 70 keV values, respectively.

Figure 9.

Comparison of mean myocardial flow between (A) 120 kVp and (B) 70 keV under an ischemic condition with FFR = 0.65. Measurements were made within ROIs in the anterior, anterior-septal, lateral, and inferior walls. Measured mean MBF values were averaged over seven adjacent slices. Error bars correspond to standard deviation of mean flow in each ROI across the 7 considered slices.

Figure 10.

Relative blood flow under LAD occlusion with measured FFR = 0.65 ± 0.014 for the scan duration. Shown are measured mean MBF ratio in anterior (Ant) and inferior (Inf) walls relative to the lateral (Lat) wall, as well as corresponding FFR. Error bars correspond to standard deviation of relative flow across six adjacent slices. The inferior wall is a right coronary artery territory with no simulated stenosis (FFR = 1).

Figure 11.

Qualitative assessment of perfusion in 120 kVp (left column) and 70 keV (right column) scans. Slices are shown at peak enhancement in the myocardium. (A) and (B) Baseline (FFR = 1) and (C) and (D) ischemic (FFR $\approx$ 0.65) scan. Blue arrows in (A) and (C) indicate hypo-enhancements caused by beam hardening in 120 kVp images. These effects are greatly reduced in corresponding 70 keV images (B) and (D). Same window width and level (120/60 HU) used for all displays.