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Comparison of quantitative myocardial perfusion imaging CT to fluorescent microsphere-based flow from high-resolution cryo-images

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Abstract

Myocardial perfusion imaging using CT (MPI-CT) has the potential to provide quantitative measures of myocardial blood flow (MBF) which can aid the diagnosis of coronary artery disease. We evaluated the quantitative accuracy of MPI-CT in a porcine model of balloon-induced LAD coronary artery ischemia guided by fractional flow reserve (FFR). We quantified MBF at baseline (FFR=1.0) and under moderate ischemia (FFR=0.7) using MPI-CT and compared to fluorescent microsphere-based MBF from high-resolution cryo-images. Dynamic, contrast-enhanced CT images were obtained using a spectral detector CT (Philips Healthcare). Projection-based mono-energetic images were reconstructed and processed to obtain MBF. Three MBF quantification approaches were evaluated: singular value decomposition (SVD) with fixed Tikhonov regularization (ThSVD), SVD with regularization determined by the L-Curve criterion (LSVD), and Johnson-Wilson parameter estimation (JW). The three approaches over-estimated MBF compared to cryo-images. JW produced the most accurate MBF, with average error 33.3 ± 19.2 mL/min/100g, whereas LSVD and ThSVD had greater over-estimation, 59.5 ± 28.3 mL/min/100g and 78.3 ± 25.6 mL/min/100g, respectively. Relative blood flow as assessed by a flow ratio of LAD-to-remote myocardium was strongly correlated between JW and cryo-imaging, with $R^2=0.97$, compared to $R^2=0.88$ and 0.78 for LSVD and ThSVD, respectively. We assessed tissue impulse response functions (IRFs) from each approach for sources of error. While JW was constrained to physiologic solutions, both LSVD and ThSVD produced IRFs with non-physiologic properties due to noise. The L-curve provided noise-adaptive regularization but did not eliminate non-physiologic IRF properties or optimize for MBF accuracy. These findings suggest that model-based MPI-CT approaches may be more appropriate for quantitative MBF estimation and that cryo-imaging can support the development of MPI-CT by providing spatial distributions of MBF.

Keywords

Myocardial perfusion imaging; CT; perfusion modeling; myocardial blood flow; microsphere-based blood flow

1. INTRODUCTION

Imaging plays an important role in the screening and diagnosis of coronary artery disease (CAD). The current standard work up is a noninvasive functional test, such as ECG, echocardiogram, or myocardial perfusion imaging SPECT (MPI-SPECT), prior to invasive diagnostic testing. MPI-SPECT remains the most common functional imaging test to screen for CAD with over 10 million exams per year in the United States. If functional defect is suspected, patients are then referred to invasive coronary angiography (ICA), performed under x-ray fluoroscopy, which provides the final diagnosis. While noninvasive screening for CAD is highly sensitive and can rule out disease, over 60% of patients referred to ICA procedures are false positives, not having hemodynamically significant stenosis¹. These many unnecessary procedures add significant cost to the health care system and include an added risk to the patient. Thus, a more effective noninvasive gatekeeper exam for ICA is needed.

With the addition of myocardial perfusion imaging CT (MPI-CT), CT could become an ideal noninvasive gatekeeper for referral to ICA. MPI-CT can provide functional information for the diagnosis of coronary artery disease which could combine with the anatomic information from coronary CT angiography. For most patients, qualitative blood flow images or relative blood flow estimates may be sufficient to identify single-vessel coronary disease. However, in the case of balanced ischemia as in multi-vessel disease or microvascular disease, quantitative evaluation of myocardial blood flow (MBF) could enable more accurate diagnosis. In order for MPI-CT to become a quantitative tool, validation of MBF measurements and spatial MBF distributions is required. In this work we use cryo-imaging, a fluorescence imaging cryomicrotome technique, to assess spatial MBF distributions from fluorescent microspheres in a porcine heart. This technique has been previously limited to small animal models^{2,3} with large animal models using physical slicing and tissue digestion techniques⁴. We compare quantitative measurements of MBF from three MPI-CT analysis methods to the cryo-imaging reference. We then analyze the MPI-CT solutions to identify potential causes of deviation from the reference microsphere MBF.

2. METHODS

2.1 Animal model and balloon-induced ischemia

We used a porcine ischemic model (Yorkshire female, weight: 40–50kg, age: 13–15 weeks) with percutaneously induced ischemia guided by fractional flow reserve (FFR)^{5–7}. Under fluoroscopy, a pigtail catheter for fluorescent microsphere injection was introduced in the femoral artery and placed in the left ventricle cavity. A balloon catheter was then implanted in the left anterior descending (LAD) coronary artery and FFR wire placed with one pressure sensor proximal and the other distal to the balloon to measure the extent of

ischemia in real-time. The balloon was inflated to induce the desired level of stenosis as determined by FFR, with targeted values of $FFR=1.0$ (baseline, deflated) and $FFR=0.7$ (ischemic, inflated). Three baseline cases and three ischemic cases were analyzed in this study, giving a total of six data sets. Microsphere injections for both hemodynamic conditions were performed in the animal surgery suite followed by CT imaging in the CT scanning room. FFR was recorded for both microsphere injection and CT acquisition and used for relative blood flow comparisons.

2.2 Fluorescent microsphere injection

Fluorescent microspheres are a reliable, commonly-used technique for regional organ perfusion⁸. Fluorescent microspheres were injected to obtain reference myocardial blood flow for baseline and ischemic conditions. First, 9 million red fluorescent microspheres (15 μ m, excitation 625nm/emission 645nm, Molecular Probes, Inc.) were injected in the left ventricle cavity via a pigtail catheter at baseline ($FFR=1.0$) over 30s, followed by a saline flush. A blood sample was collected from the femoral artery at a constant rate of 5mL/min for 3min starting 5s prior to injection. Second, the balloon was inflated to obtain a stable moderate ischemia ($FFR=0.7$) and 9 million green fluorescent microspheres (15 μ m, excitation 495nm/emission 525nm, Triton Technology, Inc.) were injected. A separate blood sample was collected in a similar way as for the red microspheres.

2.3 CT image acquisition

After microsphere injections in the surgical suite, the animal was transported to the CT scanning room for dynamic myocardial perfusion imaging CT (MPI-CT). CT images were acquired using a spectral detector CT system (SDCT, Philips Healthcare)^{7, 9}. The SDCT simultaneously acquires high- and low-energy projections using a dual-layer detector design, enabling projection-based material decomposition for mono-energetic image reconstruction even at high gantry rotation speeds^{10, 11}. In this work, the dynamic MPI-CT protocol included 45 ECG-gated scans acquired at 45% R-R cycle (end systole), 4cm z-coverage, 120kVp, 100mAs, full 360deg acquisitions and reconstruction, and 0.27s rotation speed. During CT scans the ventilator was turned off to reduce respiratory motion effects. Mono-energetic images at 70keV were reconstructed with 2mm slice thickness, 2mm increment, and 120mm field of view. The advantage of mono-energetic images is their negligible beam hardening artifact as compared to conventional poly-energetic reconstruction^{7, 9, 11}. Iodinated contrast agent (Omnipaque 350, GE Healthcare) was injected intravenously at 5mL/s for 4 seconds and imaging was initiated at 2 seconds. Baseline scans ($FFR=1.0$) were obtained first and were followed by a 15 minute wait for contrast wash-out. For the ischemic case, the LAD balloon was inflated to obtain a stable FFR value (targeted $FFR=0.7$) and CT scans were repeated.

2.4 Dynamic MPI-CT processing

For any given hemodynamic condition, monoenergetic 4D sequences were analyzed using an in-house developed dynamic MPI-CT analysis pipeline⁵. The analysis includes nonrigid registration, cardiac short axis reformatting, myocardium segmentation, and myocardial blood flow (MBF) quantification. MBF was quantified using three approaches: model-independent deconvolution with SVD with a fixed Tikhonov regularization parameter

(ThSVD)^{12, 13}, SVD with Tikhonov regularization determined in an automated fashion by the L-curve criterion (LSVD)^{7, 9, 14}, and parameter estimation using the Johnson-Wilson physiologic model for capillary exchange of contrast agent (JW)^{15, 16}. For ThSVD, we selected a Tikhonov parameter of $\lambda=0.09$ based on our previous studies¹². For LSVD, λ is determined automatically using the L-curve criterion which provides a balance between the noise in the deconvolved impulse response function and the goodness-of-fit to the CT data¹⁴. Average MBF was computed over large regions of interest (ROIs) in the LAD and remote myocardial territories, giving MBF_{LAD} and MBF_{remote} , respectively. The same ROIs were used for all three MPI-CT methods for exact comparison, and corresponding ROIs were drawn in cryo-image MBF maps. We compared relative blood flow from MPI-CT to cryo-imaging using the flow ratio, $FlowRatio = MBF_{LAD} / MBF_{remote}$, evaluated at corresponding FFR wire conditions. The relationship between the Tikhonov regularization parameter (λ), MBF, and the L-curve was evaluated to test whether the L-curve is optimized for MBF accuracy. Tissue impulse response functions for each model were assessed for validity with regards to physiology.

2.5 Cryo-imaging and microsphere-based blood flow

At the end of the experimental procedure, the animal was sacrificed and the heart was sliced into three cardiac short axis segments: base, mid, and apex. The mid and apex segments were approximately 2cm thick and distal to the induced stenosis. Sliced sections were embedded in "Optimal Cutting Temperature" compound (OCT, Tissue Tek) and flash frozen with liquid nitrogen. Cryo-imaging of the apex and mid segments was performed using the CryoViz system (BioInVision, Cleveland, OH) which acquires block-face microscopic images in sequential slices with a cryomicrotome^{3, 17}. Brightfield and fluorescence images were acquired with 10.724um in-plane resolution and 100um slice thickness. Cryo images enable the detection of individual microspheres in the myocardial tissue which distribute in proportion to blood flow.

Myocardial blood flow in the cryo-images can be computed by quantifying microsphere density using the following equation, which is derived from the assumption of no venous outflow^{3, 8}:

$$\left(\frac{\text{Flow}}{\text{Volume}} \right)_{\text{tissue}} = \frac{\left(\frac{\text{Count}}{\text{Volume}} \right)_{\text{tissue}}}{\text{Count}_{\text{blood}}} * \text{Rate}_{\text{blood}}$$

where $\left(\frac{\text{Count}}{\text{Volume}} \right)_{\text{tissue}}$ is the microsphere count density in the myocardium as obtained from cryo-imaging, $\text{Count}_{\text{blood}}$ is the microsphere count in the withdrawn blood sample obtained from flow cytometry, and $\text{Rate}_{\text{blood}}$ is the withdraw rate of the blood sample. Low autofluorescence and high fluorescence signal enables detection of green and red microspheres by thresholding. Two sets of binary images are produced for detected green and red microspheres. The detected microsphere images are loaded as a 3D volume and used to count microspheres over sub-volumes in the myocardium using connected components. We used non-overlapping sub-volumes of dimension 5×5×10mm (Fig 1). A tissue mask is

manually segmented from the anatomic, brightfield images and used to compute microsphere counts/volume. Calibration with 20 μ m slices was used to estimate a correction factor for microspheres missed in the thicker 100 μ m slices¹⁸, although most microspheres are detected at a 60–120 μ m tissue depth. A 10% correction factor was applied to account for the known effect of tissue expansion after freezing¹⁹.

3. RESULTS

Examples of cryo-images and MPI-CT data are shown in figures 1 and 2. Figure 1 shows brightfield and fluorescence cryo-images which are processed to obtain MBF maps which serve as a reference for MPI-CT. Figure 2 shows a cardiac short axis CT image and typical time-attenuation curves (TACs) in dynamic MPI-CT. The arterial input function and 2 $\times$ 2 voxel TACs are used to generate MBF maps using JW parameter estimation, with similar processing to generate MBF maps from LSVD and ThSVD.

Comparisons between MPI-CT and cryo-imaging at the same FFR condition are shown in figures 3 and 4. Figure 3 shows a baseline case with the LAD artery balloon completely deflated, giving an FFR=0.95. The MBF maps from JW and cryo-imaging were qualitatively similar, with relatively uniform perfusion throughout the myocardium. Figure 4 shows an ischemic case with the LAD artery balloon inflated to achieve FFR=0.70. Clear under-perfusion can be seen in the LAD territory, the anterior and antero-septal wall, in the MPI-CT map, also seen in the cryo-imaging MBF map.

Comparisons of absolute and relative MBF measurements from MPI-CT and cryo-imaging are shown in figures 5 and 6. In figure 5, MBF measurements from MPI-CT (Fig 5a, y-axis) are compared to MBF measurements from cryo-imaging (Fig 5a, x-axis) for corresponding myocardial regions and FFR conditions. Overall, MPI-CT over-estimated MBF as compared to cryo-imaging. JW was most accurate, with average error of 33.3 $\pm$ 19.2mL/min/100g, followed by LSVD with average error of 59.5 $\pm$ 28.3mL/min/100g and ThSVD with average error of 78.3 $\pm$ 25.6 mL/min/100g. Correlation (R^2) of MPI-CT to cryo-imaging MBF was 0.61, 0.55, and 0.26 for JW, LSVD, and ThSVD, respectively. MBF measures from MPI-CT were better correlated between techniques than compared to cryo-imaging (Fig 5b). Correlation (R^2) of LSVD and ThSVD to JW was 0.86 and 0.36, respectively, higher than the corresponding correlation to cryo-imaging. Relative blood flow showed a stronger correlation to cryo-imaging as shown in figure 6. Correlation between MPI-CT and cryo-imaging was 0.97, 0.88, and 0.78 for JW, LSVD, and ThSVD, respectively. However, correlation of the flow ratio between JW and LSVD and ThSVD was not improved. Note, one ThSVD case was not included as $\lambda=0.09$ was insufficient for regularization leading to extremely high flow values, although this case was sufficiently regularized with the LSVD technique.

Impulse response functions (IRFs) from MPI-CT techniques were analyzed to assess potential sources of errors. Figure 7 shows a typical L-curve for the LSVD technique. As regularization, λ , is increased, the solution norm shrinks and the residual norm grows. Regularization damps the oscillations, “noise”, in the IRF, decreasing the solution norm. However, greater regularization worsens the goodness of fit to the original CT data, causing

the residual norm to grow. In LSVD, the optimal λ is considered to be the one which balances these two effects and is determined by the maximum curvature¹⁴. Selection of λ has a direct effect on the estimated MBF, as MBF is determined by the maximum of the flow-scaled IRF. Increasing λ reduces the peaks in the noisy IRF, thus reducing the estimated MBF. In figure 8, representative IRFs are shown from JW, LSVD, and ThSVD for healthy (FFR=1.0) and ischemic (FFR=0.7) voxels along with corresponding curve fits to CT time attenuation curves (TACs). The IRF from JW plateaus after a time delay and smoothly decays, corresponding to contrast passing through small sub-voxel vessels, extravasation from vessels, and then wash out from the tissue. Conversely, the IRF from ThSVD shows non-physiologic properties: strong oscillations and negative values. SVD methods appear to fit noise in the TACs, as seen in figure 8d. The L-curve generally improved the IRFs obtained from LSVD as compared to ThSVD, as it is more adaptive in the presence of different noise levels. However, it does not constrain the IRF to physiologically valid forms and also does not optimize for blood flow accuracy, as LSVD still produced less accurate MBF estimates compared to microspheres than JW.

4. DISCUSSION

In this work, we demonstrated the use of high-resolution cryo-imaging for measurement of myocardial blood flow and its usefulness in developing quantitative MPI-CT analysis methods. Cryo-imaging enables the detection of individual microspheres in tissue which can then be digitally “sliced” into sub-volumes for assessing spatial MBF distributions. In contrast to conventional microsphere-based MBF measurement techniques, cryo-imaging can be analyzed in numerous ways after acquisition whereas conventional techniques require physical slicing of myocardial tissue into large segments. While the comparisons in this work are at the coronary territory level and similar to conventional methods^{8, 20}, cryo-imaging can enable analysis at multiple resolutions on the same data. This technique would be useful for assessing flow distributions such as transmural perfusion gradient, physiologic flow heterogeneity, ischemic volume, etc. A limitation of this approach is that the number of microsphere counts decreases as smaller sub-volumes are used, leading to increased noise following the Poisson distribution²¹. The resolution limit for MBF assessment using the cryo-imaging method will depend upon the level of uncertainty required for an application. This effect can be mitigated by injecting a greater number of microspheres, suggesting that one could anticipate the number of microspheres required for their specific application and plan an optimal experiment. Overall, cryo-imaging can serve as a powerful tool for assessment of spatial MBF distributions and development of MPI-CT techniques in large animal models.

In the three animals used in this study, we found that CT over-estimated MBF as compared to cryo-imaging. These errors could be due to either to physiologic changes during the experiment or MPI-CT processing. Since microspheres were injected in the surgical room before CT imaging, hemodynamics may have changed between microsphere injection and CT imaging. One could address such changes by normalizing by mean arterial pressure from the FFR wire recordings and converting measured MBF to an intrinsic property such as myocardial resistance which should not vary between cryo-imaging and MPI-CT. Regarding MPI-CT analysis, we found better correlation between SVD methods and JW, despite

significant differences in their approach, rather than to cryo-imaging. Relative flows from JW were strongly correlated with cryo-imaging, whereas ThSVD and LSVD were more varied. In this work, we did not account for bolus dispersion of the contrast agent between the LV cavity and the myocardium which is known to affect flow estimates²². However, we do account for other sources of error which can significantly degrade MPI-CT: the SDCT nearly eliminates beam hardening artifacts through mono-energetic reconstruction, ECG gating and turning the ventilator off during CT scanning reduces motion effects, and full scan acquisition and reconstruction avoids partial scan artifact. We selected 70keV reconstruction in this work based due to its high MBF contrast-to-noise ratio from our previous experience^{7, 9}, however noise reduction in mono-energetic reconstruction could enable improved iodine signal enhancement at lower keVs. Overall, the CT data itself is of relatively good quality, so we are confident that errors in MBF estimates stem either from physiologic changes or perfusion processing.

We note the advantage of JW over LSVD and ThSVD due to its physiologic constraints. Although there are no assumptions about contrast agent kinetics in LSVD and ThSVD, both suffer from non-physiologic IRFs exhibiting negative values and oscillations. We found that LSVD does have an advantage over ThSVD when compared to cryo-imaging and JW, owing to its ability to adapt to differing levels of noise. Non-negativity and other constraints from the literature could be applied to SVD, but tend toward those same constraints already provided by a physiologic model. Aside from physiologic constraints, parameter estimation approaches also offer the opportunity to include prior information, such as prior probabilities for parameters. Additionally, anatomic and physiologic clustering strategies could be incorporated under a hierarchical processing paradigm^{23, 24}. This could make the parameter estimation more robust to CT image noise while not sacrificing quantitative accuracy, enabling x-ray dose reductions.

5. CONCLUSION

In this work, we compared quantitative blood flow estimates from MPI-CT to fluorescent microsphere cryo-images. The cryo-imaging method enables direct visualization of spatial myocardial blood flow distributions and can be analyzed in multiple ways (length scales, ROIs, tissue segments), advantageous over standard tissue digestion techniques. We found that the tested MPI-CT analysis methods, model-independent deconvolution with SVD and parameter estimation with the Johnson-Wilson model, generally over-estimated blood flow as compared to fluorescent microspheres from cryo-imaging. Johnson-Wilson was the best matched to blood flow from microspheres. Further analysis of the impulse response functions showed that SVD produced non-physiologic properties including oscillations and negative values. Lastly, we found that the L-curve does improve MBF estimates as compared to ThSVD but does not optimize for accurate blood flow as compared to microspheres or JW, nor does it remove all non-physiologic oscillations from the solution. These findings suggest that improvements can be made to MPI-CT analysis methods to better match the reference microspheres.

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Figure 1.

Example cryo-images and processing for microsphere-based blood flow quantification. (a) Brightfield image used for anatomic information and tissue segmentation. (b) Fluorescent image of red (FFR=1.0) and green (FFR=0.7) microspheres, integrated over 10 consecutive slices. (c) Detected red microspheres. (d) Detected green microspheres. MBF maps obtained by cryo-imaging for (e) FFR=1.0 and (f) FFR=0.7. A flow deficit can be seen in the antero-septal wall in the FFR=0.7 MBF map (10–12 o'clock), not evident in the FFR=1.0 map.

Figure 2.

Example MPI-CT data for MBF quantification. (a) Cardiac short axis CT image at peak enhancement in healthy myocardium, showing hypo-enhancement in the LAD territory. ROIs correspond to time-attenuation curves (TACs) shown in (b) for the arterial input function (red), ischemic myocardium (blue), and healthy myocardium (green) which (c) are processed by JW to produce MBF maps.

Figure 3.

Example baseline (FFR=1.0) case. (a) FFR pressure wire trace indicates no occlusion in the LAD coronary artery. (b) MBF map from MPI-CT and (c) MBF map from cryo-imaging indicate relatively uniform perfusion.

Figure 4.

Example ischemic (FFR=0.7) case. (a) FFR pressure wire trace indicates hemodynamically significant stenosis in the LAD. (b) MBF map from MPI-CT and (c) MBF map from cryo-imaging indicate reduced perfusion in the affected LAD territory.

Figure 5.

Correlation of MBF measurements from MPI-CT and cryo-imaging in corresponding ROIs (LAD and remote) at corresponding conditions (FFR=1.0 and FFR=0.7). (a) MBF from CT compared to MBF from cryo-imaging. MPI-CT typically over-estimated MBF as compared to cryo-imaging, ranging from JW (most accurate) to ThSVD (least accurate). (b) MBF from SVD methods compared to JW. MBF estimates from SVD methods tended to be greater than those from JW, but were better correlated to JW than cryo-imaging.

Figure 6.

Correlation of relative flow measurements from MPI-CT and cryo-imaging using the flow ratio at corresponding hemodynamic condition (FFR=1.0 and FFR=0.7). (a) Flow ratio from CT compared to cryo-imaging. (b) Flow ratio from SVD methods compared to JW. Flow ratio from JW was strongly correlated with cryo-imaging whereas LSVD and ThSVD were more weakly correlated with both JW and cryo-imaging.

Figure 7.

L-curve and MBF as related to Tikhonov regularization. (a) As lambda increases, more regularization occurs, decreasing the solution norm and increasing the residual norm, giving the “L-curve”. (b) As lambda increases, noise in the IRF is reduced, leading to lower MBF estimates as a function of lambda. Changes in estimated MBF as a function of lambda (b, left y-axis) follow the same trend as changes in the solution norm (b, right y-axis).

Figure 8.

Typical shapes of flow-scaled impulse response functions (IRFs) obtained from JW, LSVD, and ThSVD methods with corresponding curve fits to CT data in an ischemic, FFR=0.7 case. Shown are IRFs determined by each method for the same 2×2 voxel TACs. TACs are shown after subtraction of an averaged pre-contrast myocardium HU value. (a) IRFs in healthy remote myocardium. (b) Corresponding healthy TAC and curve fits from each processing method. (c) IRFs in ischemic LAD myocardium. (d) Corresponding ischemic TAC and curve fits. IRFs from the SVD techniques exhibit non-physiologic properties including oscillations and negative values although appear to share a similar shape with JW. SVD methods appear to fit the noise spikes in the TACs, particularly evident in (d). LSVD reduces these effects as compared to ThSVD and more closely matches JW.