THE UNIVERSITY of EDINBURGH

Edinburgh Research Explorer

Feasibility of radiation dose reduction using AIDR-3D in dynamic pulmonary CT perfusion.

Citation for published version:
Mirsadraee, S, Weir, N, Connolly, S, Murchison, JT, Reid, JH, Hirani, N, Connell, M & van Beek, EJR 2015, 'Feasibility of radiation dose reduction using AIDR-3D in dynamic pulmonary CT perfusion.' Clinical Radiology, vol. 70, no. 8, pp. 844–851. DOI: 10.1016/j.crad.2015.04.004

Digital Object Identifier (DOI):
10.1016/j.crad.2015.04.004

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Peer reviewed version

Published In:
Clinical Radiology

Publisher Rights Statement:
This is the author's final manuscript as accepted for publication.

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

OPEN ACCESS

Download date: 05. Apr. 2019

Clinical Radiology

Feasibility of radiation dose reduction using AIDR-3D in dynamic pulmonary CT perfusion.

--Manuscript Draft--

Manuscript Number:	CRAD-D-14-00975R1
Full Title:	Feasibility of radiation dose reduction using AIDR-3D in dynamic pulmonary CT perfusion.
Article Type:	Original Paper
Corresponding Author:	Saeed Mirsadraee, PhD, FRCR University of Edinburgh Edinburgh, UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of Edinburgh
Corresponding Author's Secondary Institution:	
First Author:	Saeed Mirsadraee, PhD, FRCR
First Author Secondary Information:	
Order of Authors:	Saeed Mirsadraee, PhD, FRCR
	Nicholas W Weir, PhD
	Stuart Connolly, MBBS
	John T Murchison, PhD FRCR
	John H Reid, FRCR
	Nikhil Hirani, MRCP PhD
	Martin Connell, BSc
	Edwin J van Beek, PhD FRCR
Order of Authors Secondary Information:	
Abstract:	Abstract Aim: To assess the feasibility of radiation dose reduction with Adaptive Iterative Dose Reduction (AIDR-6 3D) reconstruction in dynamic pulmonary CT perfusion (CTP). Materials and Methods: CTP examinations of 10 patients acquired at 100kVp/50mAs were reconstructed with Filtered Back Projection (FBP) and AIDR-3D. Artificial noise was added to raw data (pre-reconstruction projection data) to simulate lower tube current scanning. Hounsfield units (HU), noise, and perfusion values were compared. Results: There was no significant difference in noise between the full and simulated reduced tube current with AIDR-3D reconstruction (p=1). There was significantly lower noise in lung tissue with AIDR-3D images when compared to reconstructions without AIDR-3D (p=0.005) and no significant change in HU (p=1; mean difference <6HU). Mean perfusion values increased significantly at lower tube currents (25 and 12.5mAs), compared to 50mAs (p=0.005). This effect was significantly greater in larger patients compared to thin patients. Conclusion: AIDR-3D produced significantly lower noise images than FBP-based algorithms and maintained consistent noise levels in lung at 12.5mAs, indicating this algorithm is suitable for reduced dose lung perfusion imaging. Iterative reconstruction allows significant radiation dose reduction of up to four fold in smaller patients, and up to 2 fold in the medium/large size patients. The increase in perfusion values at 25% simulated tube currents is attributed to attenuation bias.

Powered by Editorial Manager® and ProduXion Manager® from Aries Systems Corporation

Feasibility of radiation dose reduction using AIDR-3D in dynamic pulmonary CT perfusion.

1. Saeed Mirsadraee, MD PhD FRCR

Senior Lecturer in Radiology

Clinical Research Imaging Centre

Queen's Medical Research Institute

University of Edinburgh

47 Little France Crescent

Edinburgh EH16 4TJ

United Kingdom

2. Nicholas W Weir, PhD

Medical Physicist

Department of Radiology

Royal Infirmary of Edinburgh

51 Little France Crescent, Edinburgh EH16 4SA

3. Stuart Connolly

Medical Student

University of Edinburgh

47 Little France Crescent

Edinburgh EH16 4TJ

United Kingdom

4. John T Murchison, MBBS PhD FRCR

Consultant Radiologist

Department of Radiology

Royal Infirmary of Edinburgh

51 Little France Crescent, Edinburgh EH16 4SA

5. John H Reid, MD FRCR

Consultant Radiologist

Clinical Research Imaging Centre

Queen's Medical Research Institute

University of Edinburgh

47 Little France Crescent

Edinburgh EH16 4TJ

United Kingdom

6. Nikhil Hirani, MD PhD MRCP

Senior Lecturer in Respiratory Medicine

Queen's Medical Research Institute

University of Edinburgh

47 Little France Crescent

Edinburgh EH16 4TJ

United Kingdom

7. Martin Connell, BSc

Image Analysis Scientist

Clinical Research Imaging Centre

Queen's Medical Research Institute

University of Edinburgh

47 Little France Crescent

Edinburgh EH16 4TJ

United Kingdom

8. Edwin J van Beek, MD PhD FRCR

Professor of Radiology

Clinical Research Imaging Centre

Queen's Medical Research Institute

University of Edinburgh

47 Little France Crescent

Edinburgh EH16 4TJ

United Kingdom

Corresponding Author:

Dr Saeed Mirsadraee

Senior Lecturer in Radiology

Clinical Research Imaging Centre

Queen's Medical Research Institute

University of Edinburgh

47 Little France Crescent

Edinburgh EH16 4TJ

United Kingdom

phone +44-131-2427768

fax +44-131-2427773

saeed.mirsadraee@ed.ac.uk

Acknowledgments:

This work is supported by a research grant from Chest, Heart, Stroke Scotland.

Short running head: Low dose CT perfusion using AIDR-3D.

Author Contributions

1. guarantor of integrity of the entire study
2. study concepts and design
3. literature research
4. clinical studies
5. experimental studies / data analysis
6. statistical analysis
7. manuscript preparation
8. manuscript editing

1. Saeed Mirsadraee: 1,2,3,4,5,6,7,8

2. Nicholas: 2,3,5,6,7,8

3. Stuart Connolly: 2,3,4,5,7,8

4. John T Murchison: 2,4,7,8

5. John H Reid: 2,4,7,8

6. Nikhil Hirani: 2,4,7,8

7. Martin Connell: 2,3,4,5,7,8

8. Edwin J van Beek: 2,4,7,8

We truly appreciate comments from the reviewers. Please see the response to the comments and the related changes in the manuscript.

REVIEWER 1

Comment 1: *The use of pvalue >0.05 to establish no significant difference may be a result of the power of the study, this should be addressed.*

Response: Thank you for this valuable comment. In this study, the calculated non-significant p-values ranged between 0.1-1. We have revised the results and exact p-values are included (p-values are highlighted in red).

Comment 2: *Does the increase mean perfusion values pose a problem in perfusion interpretation?*

Response: An increase in calculated mean perfusion can result in under-estimation of perfusion changes that may affect patient management. A comment has been added in the discussion (lines 289-290) to address this important question.

Comment 3: line 69 type "does" - "dose"

Response: Corrected. Line 72

***Comment* 4:** line 232 "sinogram bins" I do not understand this term

Sinogram refers to the array of raw data projection measurements. For clarification, “sinogram bins” is replaced by with “raw data projection sinogram values” (Lines 276 and 283)

REVIEWER 2

Comment 1: *The extremely small sample size confines this investigation to a "proof of concept" investigation at present. It is hard to draw any meaningful comparisons from the statistical analyses, despite the interesting trends. The use of the simulated, rather than actual, different tube currents makes the results harder to extrapolate to clinical practice.*

Response:

We agree with the reviewer that the data used for dose simulation were selected from a relatively small sample group. This potential limitation has been acknowledged in the discussion (line 305).

The application of noise simulation allowed understanding of the effect of tube current reduction on image quality and perfusion quantification. The only alternative to this experimental study would be to perform multiple perfusion scans with different exposure factors. This will expose human subjects to significant risk from radiation exposure and using a validated simulation technique is a logical first step. The phantom study demonstrated little variation in HU of the contrast insert, air hole, and tissue material (fat), when comparing values from the real and simulated low dose studies (differences everywhere < 4 HU) (Lines 188-190 in results section). The results of this study provide researchers with important information that would be used in testing strategies in reducing radiation dose in human subjects.

A sentence has been added to the discussion to further emphasis on the above mentioned points (lines 297-301).

Comment 2: Some questions regarding the validation phase of the simulation are also raised:

-Was the phantom a standard thorax phantom?

Response:

We used a PRM Verification body Phantom, Varian Medical Systems, Palo Alto, USA (37x32cm, medium body size equivalent). We used this phantom since it is designed for checking HU of inserts spanning a range of densities (eg. iodine contrast at predetermine concentration). Details of the phantom are updated in the methods and materials. (Line 97)

-Were ROIs measured at different z-axis (i.e. craniocaudal) positions to account for variation in noise by the adaptive dose reduction strategies used by standard CT, when scanning a real patient? In other words, did the noise filter add noise uniformly to the study or did its model account for variations introduced by adaptive dose modulation. This is important because although no significant difference was found in HU was found in the various measured tissues for the simulated against actual reduced tube current images, there could be variations in the real and simulated scans if different levels were analysed.

Response: Being a volume scan, the tube current was constant and therefore no automatic tube current modulation was used. Therefore the noise addition software did not need to adapt for this factor. This is clarified in the methods section (Lines 86-88).

Comment 3: *Current dose reduction strategies also incorporate reduced tube potential (as acknowledged in the discussion)- this is an important area not explored in this investigation.*

Response: This limitation has been being addressed in the discussion (line 301-303). Currently, there is no noise stimulation software to simulate lower tube voltages.

***Comment* 4:** *With such a small study sample, was it appropriate to use parametric, rather than non-parametric, statistical tests for comparisons?*

Response: We have re-calculated p-values using non-parametric equivalent to paired t-test (Wilcoxon Signed Ranks test). The updated p-values are included in the results. Whilst there are changes in the absolute p-values, statistical significances remain unchanged (p-values are highlighted in red).

The data met the requirement of ANOVA (Shapiro-Wilk normality test p-value >0.3); visualisation of their histograms demonstrated the data was approximately normally distributed).

Comment 5:

Introduction
page 3, line 70: "The aim of this study was to assess the effectiveness of iterative CT image reconstruction techniques?" this is inaccurate; only one method of several IR techniques has been studied here.

Response: Point taken, “iterative CT image reconstruction techniques “ is replaced by the specific type of IR used in this study (AIDR-3D): Line 75.

Comment 6:

Methods
* "Patient size was graded thin, medium, and large when the lower thoracic width was <32cm, 32-38cm , and >38cm, respectively". Were these categorisations arbitrarily decided, or is there precedent for their use?

Response: The patient's lateral width at the level of liver on the CT projection has been used as an index for categorising body sizes and determining exposure fctors (McCollough Radiographics. 2006;26(2):503). The average adult patient in our series was considered to have a lateral width of 34–40 cm. Patients with a lateral width of less than 32 cm were considered thin, and those with a lateral width of more than 38 cm were considered large. This was adapted from the COPDGene study methodology. Please find attached the standard operation procedure used in the COPDGene study. Unfortunately, this was never published in full in any publications, but you will see that COPDGene adopted the IPF-NET protocol when it comes to sizing of patients based on the CT scout film. We have adopted the same principle for our CT perfusion work. (information provided by Prof Edwin van Beek, previously a co-investigator of the COPDGene study).

The paragraph is revised to further clarify (line 152-155). This now reads:

Lateral thoracic width (LTW) was measured on AP scanograms at the cardiac-diaphragm interface (at the level of liver). Based on the average LTW in our cohort, patient size was graded thin, medium, and large, when the LTW was <32cm, 32-38cm, and >38cm, respectively.

Comment 7: *The section on the mean perfusion values (page 9, lines 186-197) is quite confusing and could be better summarised.*

Response: The section is revised as suggested to better project the results (Lines 220-224).

Comment 8: *The term "bias" is used to describe the differences in PA HU values from thin to large patients, in Figure 2. Was this a qualitative interpretation? If not, how was bias calculated?*

Response: To clarify, the word bias is replaced by "the change in Hounsfield units". Please see revised legends for figure 2.

Comment 9: *Discussion*
It would be useful to discuss alternatives for spectral imaging as well, such as dual-energy CT acquisition.

Response: The aim of this study was to investigate the feasibility of dose reduction in pulmonary perfusion imaging by tube current reduction. The perfusion technique used in this study only applies single energy imaging and the discussion of dual energy techniques is less relevant. When publishing the results of the main research data, eg. evaluation of perfusion changes in specific lung pathologies, we will discuss the pros and cons of each imaging technique.

Comment 10:

Highlights

* *The first 2 points are not really highlights of the current investigation.*

Response: The first 2 points are revised to better highlight the aims of this study (please see the relevant section: Highlights).

REVIEWER 3

Well written paper. (Thank you)

Comment 1: *P9 Results "the mean PBF". Abbreviation not clarified earlier in text.*

Response: Abbreviation is now defined in line 220.

Comment 2: *P10 discussion, (3rd line from bottom) - ;an or and an "updated version of the iterative??"*

Sentence is revised: line 265-266.

Comment 3: P11 discussion, 2nd line - add space between to and 50mAs

Response: Space added. (line 271)

***Comment* 4:** Highlights; last line - There is a limit to what/ how low the dose

Response: Revised. The sentence now reads: There is a limit to how low the dose can be reduced before the bias effect falsifies the calculated perfusion values.

Abstract

Aim: To assess the feasibility of radiation dose reduction with Adaptive Iterative Dose Reduction (AIDR-6 3D) reconstruction in dynamic pulmonary CT perfusion (CTP).

Materials and Methods: CTP examinations of 10 patients acquired at 100kVp/50mAs were reconstructed with Filtered Back Projection (FBP) and AIDR-3D. Artificial noise was added to raw data (pre-reconstruction projection data) to simulate lower tube current scanning. Hounsfield units (HU), noise, and perfusion values were compared.

Results: There was no significant difference in noise between the full and simulated reduced tube current with AIDR-3D reconstruction ($p=1$). There was significantly lower noise in lung tissue with AIDR-3D images when compared to reconstructions without AIDR-3D ($p=0.005$) and no significant change in HU ($p=1$; mean difference <6HU). Mean perfusion values increased significantly at lower tube currents (25 and 12.5mAs), compared to 50mAs ($p=0.005$). This effect was significantly greater in larger patients compared to thin patients.

Conclusion: AIDR-3D produced significantly lower noise images than FBP-based algorithms and maintained consistent noise levels in lung at 12.5mAs, indicating this algorithm is suitable for reduced dose lung perfusion imaging. Iterative reconstruction allows significant radiation dose reduction of up to four fold in smaller patients, and up to 2 fold in the medium/large size patients. The increase in perfusion values at 25% simulated tube currents is attributed to attenuation bias.

Feasibility of radiation dose reduction using AIDR-3D in dynamic pulmonary CT perfusion.

Introduction

Dynamic computed tomography pulmonary perfusion imaging is an emerging technology that may be utilised in the evaluation of true pulmonary perfusion in patients with various clinical disorders such as pulmonary hypertension and lung cancer [1,2]. The multiple CT series involved will expose patients to cumulative amounts of ionising radiation and every measure should be undertaken to reduce the dose in these potentially high radiation dose investigations.

Iterative reconstruction algorithms offer the advantage of lowering radiation exposure whilst maintaining image quality [3]. These technologies are more advanced than post-processing image blurring with Gaussian filters, which simply smooth noise and edges indiscriminately, and employ edge-preserving noise reducing algorithms. The most commonly used non-iterative (analytic) image reconstruction technique is filtered back projection (FBP) [4,5]. The acquired projection data are first filtered to compensate for the blurring inherent in the back projection process. However, the projection data from the scanners are noisy and this noise may be further amplified following filtering [5,6]. The characteristics of this reconstruction filter, or kernel, may be chosen to preserve high spatial frequency information to a greater or lesser degree, resulting in sharper or smoother images associated with higher- and lower noise levels respectively.

The major advantage of iterative reconstruction techniques is that they produce much better image quality than FBP in the setting of a very low signal-to-noise ratio at the

detector [5]. As a result, radiation dose may be reduced whilst image quality is maintained [5]. The AIDR-3D (Adaptive Iterative Dose Reduction 3D) iterative reconstruction technique utilises adaptive filtering in the image domain, applied iteratively, together with noise reduction in the raw data domain [7]. Adaptive filtering reduces noise with less blurring than images reconstructed with non-adaptive filtering. It was hypothesised that iterative reconstruction can be used to reduce radiation dose in dynamic contrast enhanced CT perfusion whilst maintaining the perfusion values.

The aim of this study was to assess the effectiveness of AIDR-3D on image noise and to assess the effect on calculated pulmonary CT perfusion parametric map noise and perfusion parameters. Simulation of dose reduction through the addition of noise in pulmonary CT perfusion examinations was performed to determine the subsequent effects on image quality and quantitative interpretation.

Materials and methods:

Image acquisition and reconstruction:

All imaging was performed on a 320-multidetector row CT scanner (Aquilion ONE, Toshiba Medical Systems, Nasushiobara, Japan). Images were obtained using volume scan mode. The tube current was constant and therefore automatic tube current modulation was switched off. AIDR-3D reconstructions were compared with Toshiba's original filtered back projection technique (ORG) which was used both with and without the addition of Quantum Denoising Software (QDS+). QDS+ utilises non-iterative noise reduction in the image domain. The effect of reconstruction techniques on image noise was evaluated in two stages.

Step 1: Validation of noise simulation.

A phantom study was designed to validate the noise simulation function. A phantom (37x32cm, PRM Verification body Phantom, Varian Medical Systems, Palo Alto, USA) with an insert containing water with iodinated contrast agent to achieve a CT attenuation of approximately 600 HU (Iomeron 400, Bracco SPA, Milan, Italy; 400mgI/mL) was scanned using our local lung perfusion CT protocol (100 kVp, 0.5-second gantry rotation time, 512x512 matrix, FC17 kernel, 0.5 mm slice thickness, 0.5 mm slice increment) at 200, 100, 50, and 25 mA, giving tube current- time products of 100mAs, 50 mAs, 25 mAs, and 12.5 mAs, respectively. Artificial noise was added to the raw data from the 100 mAs acquisition to produce simulated reduced current scans at 50, 25 and 12.5 mAs using an experimental software tool (NoiseAdd version 2.3, Toshiba Medical Systems) [6,8,9].

Regions of interests (ROI; 2.6 cm in diameter) were drawn on 4 consecutive slices on exactly the same positions to measure mean HU and standard deviation (SD) within the contrast insert, air holes, and the phantom body (fat attenuation mimicking material). Values from the acquired and simulated low dose studies were compared.

Step 2: Pulmonary perfusion studies.

This is a sub-study from a pool of 50 research patients who prospectively underwent research dynamic first-pass CT to evaluate perfusion changes in emphysema, pulmonary fibrosis, and recent pulmonary embolism (3-6 months following the acute presentation that was proven by CT pulmonary angiography; CTPA). Ten data sets from the above pool were randomly chosen for the purpose of this study (8 with previous PE, 1 emphysema, 1 idiopathic pulmonary fibrosis). The local research ethics committee approved these studies and informed written consents were obtained from all patients.

The scans were performed during a single breath-hold at deep inspiration. Shallow abdominal breathing was permitted at the end stage of acquisition in patients who were unable to hold their breath for the entire perfusion CT data acquisition. Intermittent volume imaging was performed every 1.5 seconds (11 volumes in total) with 3 seconds delay after the start of intravenous contrast injection.

Scans were performed with 16 cm z-axis coverage (320 x 0.5-mm collimation) with the lowest section at the level of the diaphragm, 100 kVp, 0.5s rotation, fixed tube current mA (tube current-time product 50 mAs), and reconstruction parameters as described above. A dual-head power injector (Stellant CT Injection Systems, Medrad, Warrendale, USA) was used for bolus injection of 70 mL iodinated contrast agent (Iomeron 400, Bracco SPA, Milan, Italy; 400mgI/mL) via a 16G antecubital vein catheter at a rate of 9 mL/s, followed by 20 mL of saline solution at the same rate. The dose length product (DLP) for the above protocol was 540 mGy·cm, corresponding to an effective dose of 7.56 mSv (conversion factor 0.014).

All studies were reconstructed and analysed by an image analysis scientist with >20 years experience in image reconstruction and registration techniques, and analysis of pulmonary perfusion studies. All images were reconstructed using QDS+ and AIDR-3D (highest level of iteration used; Strong). An additional reconstruction was made with original filtered back projection technique (ORG) as control. Subsequently, images from the dynamic pulmonary CT perfusion examinations were reconstructed with artificial noise added to raw data (pre-reconstruction projection data) to simulate lower tube current scanning at 25 and 12.5 mAs. This procedure was applied using the NoiseAdd software. These images were then aligned using Body Register software (Toshiba Medical Systems, Nasushiobara, Japan). This process attempts to compensate for any shift in image position caused by anatomical movement during the scan [10]. Parametric

perfusion maps were then produced by single-input maximum slope model [11] using Body Perfusion software (Toshiba Medical Systems, Nasushiobara, Japan).

Patients with various body sizes were included in this study to investigate the effect of patients' body size on images noise and perfusion parameters. Lateral thoracic width (LTW) was measured on AP scanograms at the cardiac-diaphragm interface (at the level of liver) [12]. Based on the average LTW in our cohort, patient size was graded thin, medium, and large, when the LTW was <32cm, 32-38cm, and >38cm, respectively.

Regions of interest (ROI) were placed on the lung CT images generated from the image sets reconstructed with each of the filter methods (ORG, QDS+, AIDR-3D) and also on the resulting perfusion maps. ROI diameter was 10 mm and visible vessels of >1mm diameter were avoided. Six ROIs were placed throughout the lungs of each patient to give a comprehensive assessment of lung perfusion, attenuation, and noise. Mean and SD of HU were recorded for each set of CT images. The mean and SD perfusion values (mL/100g/min) were recorded for each perfusion map. The SD was taken as an indication of image noise in each ROI. Analyze software (AnalyzeDirect, Kansas, USA) was used to define and store identical ROIs for lung tissue CT and perfusion maps in all reconstructions for each patient. The time attenuation curve corresponding to the pulmonary artery ROI was used to define the arterial input function in the perfusion analysis and was stored for each perfusion map analysed. Identical ROIs were used for the pulmonary artery for all reconstructions of a patient by using the store and recall ROI time information.

To identify the potential effect of Gaussian blur function on the calculated perfusion values, mean perfusion values within ROIs on parametric perfusion maps that were produced with weak or medium Gaussian smoothing filter [13,14] were compared.

Statistical analysis:

All results were expressed as mean ± standard deviation (SD) unless indicated otherwise. Noise was calculated as the SD of the HU values within an ROI or, in the perfusion maps, the SD of the perfusion values within an ROI. Noise for each image reconstruction method and image type was compared using Wilcoxon Signed Ranks test or Analysis of Variance (ANOVA). The mean perfusion values were plotted using a Bland-Altman analysis to check for agreement in the means between the different reconstruction techniques and tube current levels [15]. SPSS for Windows (v10.0.1) and MedCalc statistical software (v9.6) were used for all statistical analysis. Statistical significance was established at a p-value of <0.05.

Results

The phantom study demonstrated little variation in HU of the contrast insert, air hole, and tissue material (fat), when comparing values from the real and simulated low dose studies (differences everywhere < 4 HU). There was no statistically significant difference in the measured densities of the contrast, air and fat material, when comparing values at 100 mAs and 50 mAs. There was, however, a significant reduction in the Hounsfield values, when the tube current was reduced from 50 to 25, and 12.5 mAs. Such variation was greater for the measured contrast attenuation (mean difference 134-529 HU), compared to air (13-51 HU), or fatty tissue equivalent (4.6-16 HU) ($p<0.001$; ANOVA) (Table 1).

There was a slight reduction in noise in the simulated images compared to the real reduced tube current images (mean difference: 3.1; range: 0.4-6.3 (Table 1).

When evaluating the 10 CT scans of the thorax, there was no significant difference in the mean HU of lung between AIDR-3D, QDS+, and ORG at various tube currents ($p=1$, ANOVA; mean difference <6HU). There was significantly lower noise in lung tissue with AIDR-3D at simulated 12.5mAs, when compared to QDS+ or ORG at 50 mAs or 25 mAs (mean difference in SD=42-51; $p<0.004$, ANOVA). There was no significant difference in

noise between the 3 tube current groups with AIDR-3D reconstruction (p=0.329, ANOVA) (Table 2).

The mean pulmonary artery HU averaged over all subjects dropped by more than 100HU with a simulated reduction in tube current from 25 mAs to 12.5 mAs for all three algorithms (Figure 1). Although this difference was not significant by analysis of variance, paired test analysis demonstrated a significant difference in HU between 50 mAs and 12.5 mAs (p=0.05, Wilcoxon Signed Ranks test), but not between 50 mAs and 25 mAs (p>0.15, Wilcoxon Signed Ranks test). Close examination of the data demonstrated that the variations were more significant in larger patients (mean difference= 196HU), when compared to medium (mean difference=71HU), and thin patients (mean difference=5HU) (Figure 2).

Image noise level in the parametric perfusion maps was significantly lower with AIDR-3D when compared to QDS+ or ORG reconstructions in all three tube current levels (p<0.05, Wilcoxon Signed Ranks test; Table 3). There was no significant difference in noise level between QDS+ and ORG reconstructions at 50 mAs (p=0.33, Wilcoxon Signed Ranks test). Noise level was not significantly different when comparing AIDR-3D at 25 mAs compared to QDS+ at 50 mAs, and AIDR-3D at 12.5 mAs compared to QDS+ at 50 or 12.5 mAs (p>0.24, Wilcoxon Signed Ranks test).

The mean pulmonary artery blood flow (PBF) in the selected ROIs were 101.6 and 101.5 mL/100g/min with QDS+ and AIDR-3D at 50 mAs, respectively. There was no significant statistical difference in mean perfusion values between AIDR-3D and QDS+ at 50 mAs (p=0.23, Wilcoxon Signed Ranks test) and the level of agreement was considered good (<5% in 9 patients; 25.8% in a large patient). Moreover, there was no significant difference in mean perfusion values with weak or medium Gaussian smoothing filter (p=0.374, Wilcoxon Signed Ranks test).

The mean PBF increased to 105.8, and 126.8 mL/100g/min with AIDR-3D at 25 mAs

and 12.5 mAs, respectively (p=0.005, Wilcoxon Signed Ranks test) (Figure 3). The mean differences between 50 and 12.5 mAs and 25 and 12.5 mAs were 4.3 (0.3-13) and 25.2 mL/100g/min (1.1-71), respectively. The mean difference in perfusion values between 50 mAs and 25 mAs was considered small (<9% increase in 9 patients and 23.8% increase in a large patient). However, the mean difference at 12.5 mAs was significantly larger and ranged between 1-90%. The average PBF changes were 3.5%, 20% and 51% in small, medium and large size patients, respectively (Figure 3-4).

Discussion

Dynamic pulmonary perfusion CT imaging promises a step forward in the investigation of pulmonary embolism and other diseases that affect pulmonary perfusion, such as lung cancer, and pulmonary hypertension [1,2,16]. It offers a comprehensive anatomical and functional examination of the lung parenchyma, pulmonary vessels and perfusion in a single CT examination.

In this study, repetitive CT series exposed patients to a total effective dose of 7.56 mSv. Radiation exposure can increase the lifetime risk of cancer [17]. Computed tomography is the leading cause of radiation exposure in diagnostic imaging and there have been recent technical developments to reduce exposure [18,19].

Iterative reconstruction has been demonstrated to reduce radiation dose while maintaining image quality at low dose. The current study evaluated the effect of iterative reconstruction (AIDR-3D) on image quality compared to traditional filtered back projection techniques (ORG with and without QDS+) and demonstrated significant noise reduction benefit from the application of iterative reconstruction compared to traditional FBP, both in native reconstructed images and derived parametric perfusion maps. Other studies have demonstrated similar results. In a comparison of AIDR- 3D and FBP in coronary CT angiography, AIDR-3D was demonstrated to reduce noise by an additional 22% compared to FBP [20]. In a lung CT study, AIDR-3D allowed for a dose

reduction of 64.5% whilst still reducing noise when compared to FBP filtration in higher dose scans [21].

A recent study into the effectiveness of a previous version of the iterative algorithm, AIDR, in hepatic perfusion showed that AIDR was significantly better at reducing noise than the filtered back projection method, but not significantly better than QDS+ in either a standard dose group or a low dose (approximately 45% lower dose) group [22]. In comparison, the results of our study showed that AIDR- 3D significantly reduces noise in non-perfusion contrast enhanced CT images, whilst preserving agreement in the mean HU against the previous standard QDS+. The results of the two studies, however, are not directly comparable due to study design differences. The updated version of the iterative reconstruction which we used (AIDR-3D vs AIDR in previous study) has potential advantages compared to the previous version. Differences in the characteristics of the liver and lung are also factors which should be further investigated.

In this study, there was a significant difference in the perfusion values from perfusion maps generated with AIDR-3D at 12.5 mAs, when compared to 50 mAs or 25 mAs. This differs from a study by Negi et al. which reported similar perfusion values in parametric perfusion maps in both low and high dose groups [20]. In our study, a significant reduction in Hounsfield units was demonstrated at tube current of 12.5 mAs in the pulmonary artery (but not in the lung tissue) which is thought to be CT number bias related to the increased percentage of non-positive raw data projection sinogram values at very low tube currents [23]. This effect can be expected to be greater for more highly attenuating structures. The phantom study also demonstrated similar reduction in HU at lower tube current, the reduction in values were far greater in dense contrast, compared to air and fat attenuation material. The bias effect can be seen in both the real and simulated low dose images. A greater noise variance in absolute terms must be added by the software to higher mAs data in order to simulate low mAs scanning and this can be

243 expected to produce a similar number of non-positive raw data projection sinogram
244 values as the real low mAs data.
245
246 The reduction in pulmonary artery peak HU would result in increased perfusion values
247 by maximum slope technique, which is calculated by dividing the maximum
248 enhancement slope in the target tissue (lung) by the peak of input function (pulmonary
249 artery) [11]. An increase in calculated mean perfusion can result in the under-
250 estimation of perfusion reduction that can potentially affect patient management. The
251 current study also demonstrated much smaller variations in pulmonary artery peak
252 enhancement and perfusion values at low tube current in patients with small thoracic
253 width. This may indicate that very low dose perfusion studies are feasible in thin
254 patients but further phantom studies or larger cohorts are necessary to define a dose
255 regimen based on patients' body habitus.
256
257 The application of noise simulation allowed understanding of the effect of tube current
258 reduction on image quality and perfusion quantification. Only alternative to this
259 approach would be to perform multiple perfusion scans with different exposure factors.
260 This will expose human subjects to significant risk from radiation exposure and using a
261 validated simulation technique is a logical first step in testing our hypothesis. A
262 limitation of the image noise addition technique used in this study is that it only
263 simulates reduction of the tube current and not tube potential. The benefits from AIDR-
264 3D in reduced tube potential examinations need to be investigated in other studies.
265 Another limitation to this study is the sample size. Larger cohorts would be necessary
266 before a dose saving regimen can be recommended for dynamic pulmonary CT
267 perfusion studies.
268
269 **Conclusions**

This study demonstrated that AIDR-3D significantly reduces noise in contrast enhanced CT images and parametric perfusion maps compared to conventional FBP techniques. However, lowering tube current resulted in an overestimation of perfusion values due to HU bias effects associated with photon starvation. In order to avoid this effect, a reduced dose lung perfusion CT protocol would therefore need to take into account the patient's body habitus. Designing patient specific imaging protocols with AIDR- 3D is feasible and according to this preliminary experience, would result in significant ionising radiation reduction, especially in small patients, enabling the application of this technique beyond the purely research environment within more routine clinical practice.

Figure and Table legends:

Figure 1. Mean HU values and image noises in pulmonary artery by tube currents and image reconstruction technique.

Mean HU was significantly lower in the 50 mAs and 25 mAs images compared to 12.5 mAs, irrespective of reconstruction technique (p-value <0.05; paired t-test).

AIDR-3D: adaptive iterative dose reduction- 3 dimensional; HU: Hounsfield unit; QDS+: quantum de-noising; ORG: Original (non-filtered); SD: standard deviation of mean HU values.

Figure 2. The effect of patients' body size on mean pulmonary artery (PA) Hounsfield units at low tube currents.

A. The plot shows the changes in PA HU for each patient with various thoracic diameters at low tube currents (as compared to 50 mAs) for AIDR3D. The plot illustrate that the the change in Hounsfield units is dependent on both patient size and mAs. B. This plot shows the divergence in HU in the PA for the two groups of patients, large and small, as tube current is decreased in simulation. The change in Hounsfield units is less when images are reconstructed with AIDR3D than with QDS+ or ORG.

LTW: lateral thoracic width (cm).

Figure 3. Example of parametric pulmonary perfusion maps at various tube currents in a thin (top row) and large patient (bottom row).

In the parametric map, black/dark blue, yellow/green, and red colour codes represent low, moderate, and high pulmonary blood flow. Arrows show areas with apparent perfusion abnormality in the posterior segment of the left lower lobe at 50mAs (A&D), 25mAs (B&E), and 12.5mAs (C&F), respectively. Note that the severity of perfusion

abnormality remains unchanged at low mAs in the thinner patient. In contrast, there is apparent over-estimation of perfusion at lower current in the larger patient.

Figure 4. Analysis of agreement between pulmonary artery blood flow (PBF) measurements obtained following QDS+ and AIDR-3D reconstructions.

A: AIDR-3D (50mAs) vs. QDS+ (50mAs); B: AIDR-3D (50mAs) vs. AIDR-3D (25mAs); C: AIDR-3D (50mAs) vs. AIDR-3D (12.5mAs); D: AIDR-3D (25mAs) vs. AIDR-3D (12.5mAs). The solid line shows the mean difference and the dotted lines show the 2 SD limits of agreement. SD: standard deviation.

The limits of agreement were considered acceptable for clinical purposes when comparing AIDR-3D and QDS+ at same tube voltage (50mAs), and AIDR-3D at 50mAs vs. AIDR-3D at 25mAs. The difference between the mean perfusion values for AIDR-3D at 50mAs or 25mAs and the 12.5mAs was much greater and clinically unacceptable in large patients. The analysis demonstrated overestimation of perfusion values at lower mAs.

Table 1. Phantom validation of noise addition software.

A: Hounsfield values (SD); B: image noise values (SD).

All real and noise simulated studies were reconstructed with AIDR-3D. Mean values were measured within ROIs drawn in the same position on multiple sections (n=4) within contrast insert, air hole, and fat mimicking material.

Whilst the above results shows acceptable variation in the measured Hounsfield units and image noise in the real and simulated images, there were significant reduction in the Hounsfield units (iodinated contrast and fat material), when the tube current was reduced below 50mAs ($p<0.001$; ANOVA). The change was more obvious with the dense contrast.

AIDR-3D: adaptive iterative dose reduction- 3 dimensional. SD: standard deviation; SD:

334 standard deviation; ROI: region of interest.

335

336

337 Table 2. Mean HU values and image noises in 10 regions of interest in lung tissue by tube
338 currents and image reconstruction technique.
339 AIDR-3D: adaptive iterative dose reduction- 3 dimensional; QDS+: quantum de-noising;
340 ORG: Original (non-filtered); HU: Hounsfield unit; SD: standard deviation of HU values.

341

342 Table 3. Mean perfusion value (±SD) for lung tissue perfusion (mL/100g/min) by tube
343 currents and image reconstruction technique.
344 AIDR-3D: adaptive iterative dose reduction- 3 dimensional; HU: Hounsfield unit; QDS+:
345 quantum de-noising; ORG: Original (non-filtered); SD: standard deviation of HU values.

346

347

348

References

1. Pienn M, Kovacs G, Tscherner M, et al. Non-invasive determination of pulmonary hypertension with dynamic contrast-enhanced computed tomography: a pilot study. Eur Radiol. 2014;24(3):668-76.

2. Harders SW, Madsen HH, Nellemann HM, et al. Dynamic contrast-enhanced CT in suspected lung cancer: quantitative results. Br J Radiol. 2013;86(1031):20130257.

3. Gervaise A, Osemont B, Lecocq S, et al. CT image quality improvement using Adaptive Iterative Dose Reduction with wide-volume acquisition on 320-detector CT. Eur Radiol. 2012;22(2):295-301.

4. Fleischmann D, Boas FE. Computed tomography—old ideas and new technology. Eur Radiol 2011;21:510–517

5. Willemink MJ, de Jong PA, Leiner T, et al. Iterative reconstruction techniques for computed tomography Part 1: technical principles. Eur Radiol. 2013;23(6):1623-31.

6. Chen MY, Steigner ML, Leung SW, et al. Simulated 50 % radiation dose reduction in coronary CT angiography using adaptive iterative dose reduction in three-dimensions (AIDR3D). nt J Cardiovasc Imaging. 2013;29(5):1167-75.

7. R. Irwan, S. Nakanishi, A. Blum. AIDR 3D - Reduces Dose and Simultaneously Improves Image Quality. [Toshiba-medical.eu website] 2011. Available at: http://www.toshiba-medical.eu/upload/TMSE_CT/White%20Papers/White%20Papers/Toshiba_White%20paper%20CT_nov11.pdf?epslanguage=en. Accessed 22 September 2014.

8 . Schultz K, George E, Mullen KM, et al. Reduced Radiation Exposure for Face Transplant Surgical Planning Computed Tomography Angiography. PLoS One. 2013;8 (4): e63079.

9. Fan Y, Zamyatin A, Nakamishi S. Noise simulation for Low-dose Computed Tomography. IEEE Nucl Sci Symposium and Medical Imaging Conference. 2012: 2641-2643.

10. Piper J, Ikeda Y, Fujisawa Y, et al. Objective evaluation of the correction by non-rigid

registration of abdominal organ motion in low-dose 4D dynamic contrast-enhanced CT. Phys Med Biol. 2012; 57 (6):345 1701-15.

11. Brix G, Zwick S, Griebel J et al. Estimation of tissue perfusion by dynamic contrast-enhanced imaging: simulation-based evaluation of the steepest slope method. Eur J Radiol 2010; 20: 2166-2175.

12. McCollough CH, Bruesewitz MR, Kofler JM Jr. CT dose reduction and dose management tools: overview of available options. Radiographics. 2006;26(2):503-12.

13. Zhu F, Carpenter T, Rodriguez Gonzalez D, et al. Computed tomography perfusion imaging denoising using gaussian process regression. Phys Med Biol. 2012; 21;57(12):N183-98.

14. W Burger and MJ Burger. Digital Image Processing: An algorithmic introduction using Java (1st Ed). Springer, 2010.

15. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;327:307–10.

16. Ohno Y, Koyama H, Matsumoto K, et al. Differentiation of malignant and benign pulmonary nodules with quantitative first-pass 320-detector row perfusion CT versus FDG PET/CT. Radiology. 2011;258(2):599-609.

17. Sodickson A, Baeyens PF, Andriole KP, et al. Recurrent CT, cumulative radiation exposure, and associated radiation-induced cancer risks from CT of adults. Radiology. 2009; 251(1):175-84.

18. National Council on Radiation Protection and Measurements. Ionizing radiation exposure of the population of the United States. Report 160. Bethesda, Md: National Council on Radiation Protection and Measurements, 2009.

19. Thrall JH. Radiation exposure in CT scanning and risk: where are we? Radiology. 2012;363 264(2):325-8.

20. Tatsugami F, Matsuki M, Nakai G, et al. The effect of adaptive iterative dose reduction

403 on image quality in 320-detector row CT coronary angiography. Br J Radiol. 2012; 85
404 (1016): e378-82.
405 21. Yamada Y, Jinzaki M, Hosokawa T, et al S. Dose reduction in chest CT: Comparison of
406 the adaptive iterative dose reduction 3D, adaptive iterative dose reduction, and filtered
407 back projection reconstruction techniques. Eur J Radiol. 2012; 81(12):4185-95.
408 22. Negi N, Yoshikawa T, Ohno Y, et al. Hepatic CT perfusion measurements: A feasibility
409 study for radiation dose reduction using new image reconstruction method. Eur J Radiol.
410 2012;81(11):3048-54.
411 23. Xia T, Alessio A, Kinahan PE. Limits of ultra-low dose CT attenuation correction for
412 PET/CT IEEE Nucl Sci Symposium Conf Rec 2009: 3074-3079.

Figure 1
Click here to download high resolution image

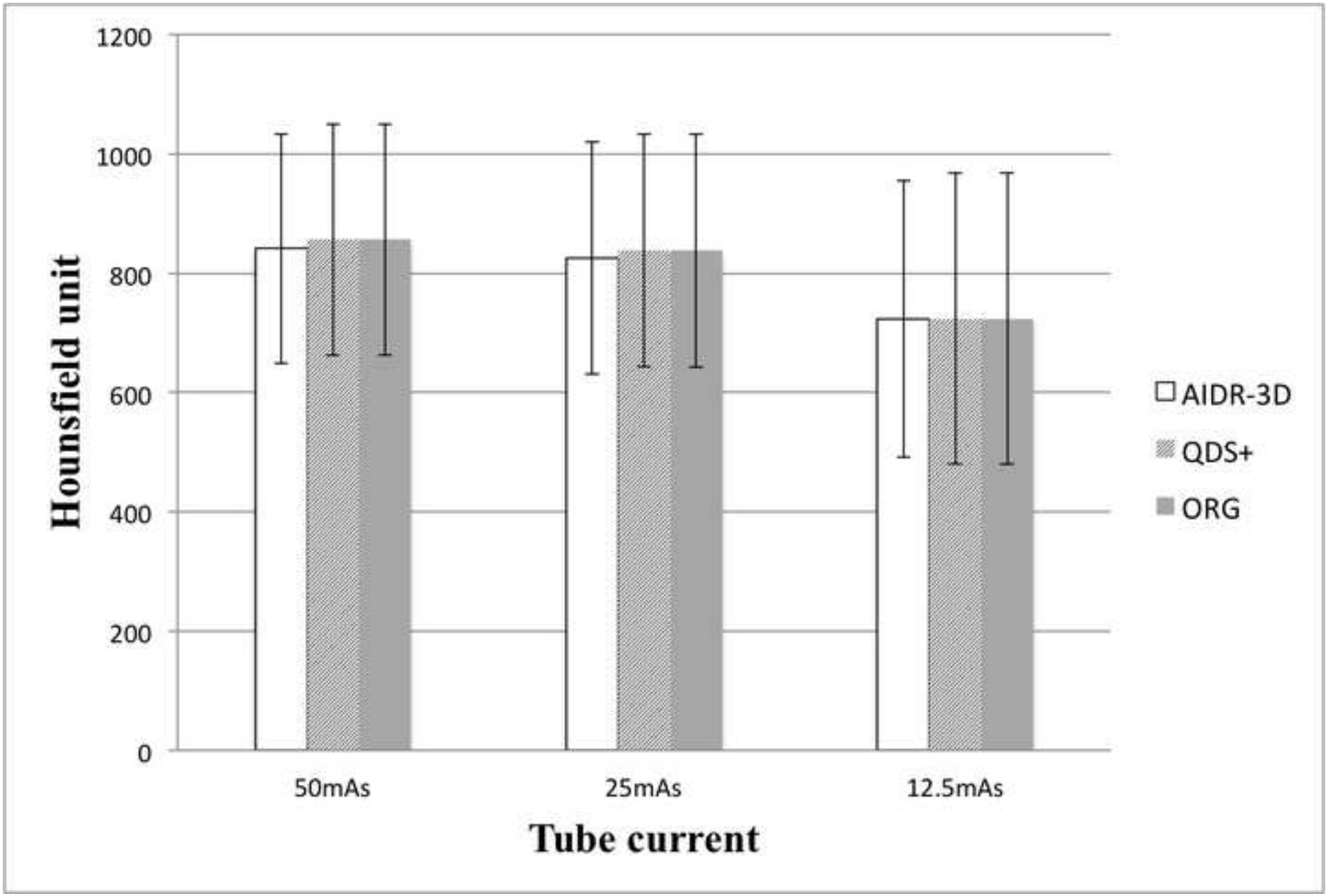


Figure 2a
Click here to download high resolution image

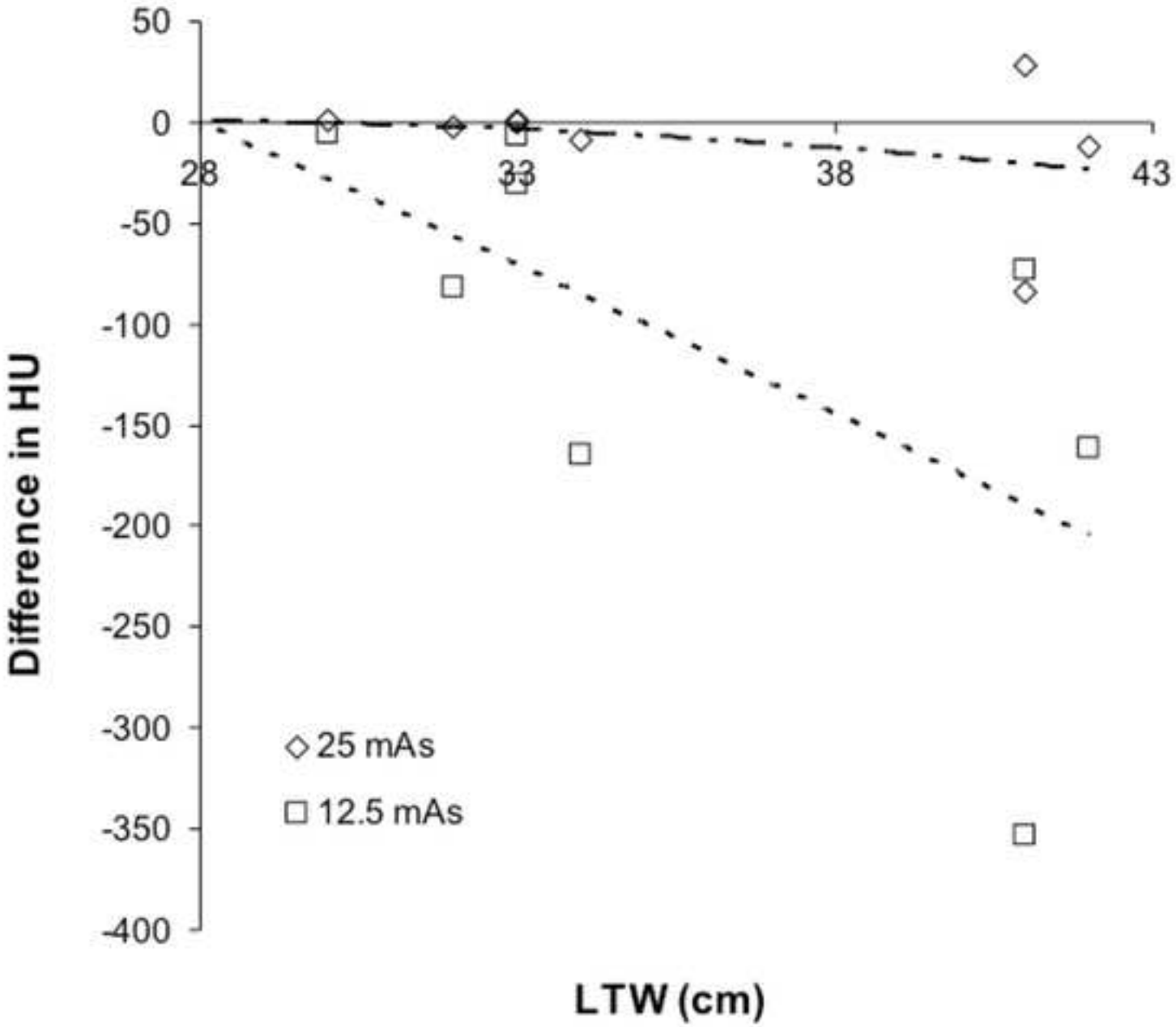


Figure 2b
Click here to download high resolution image

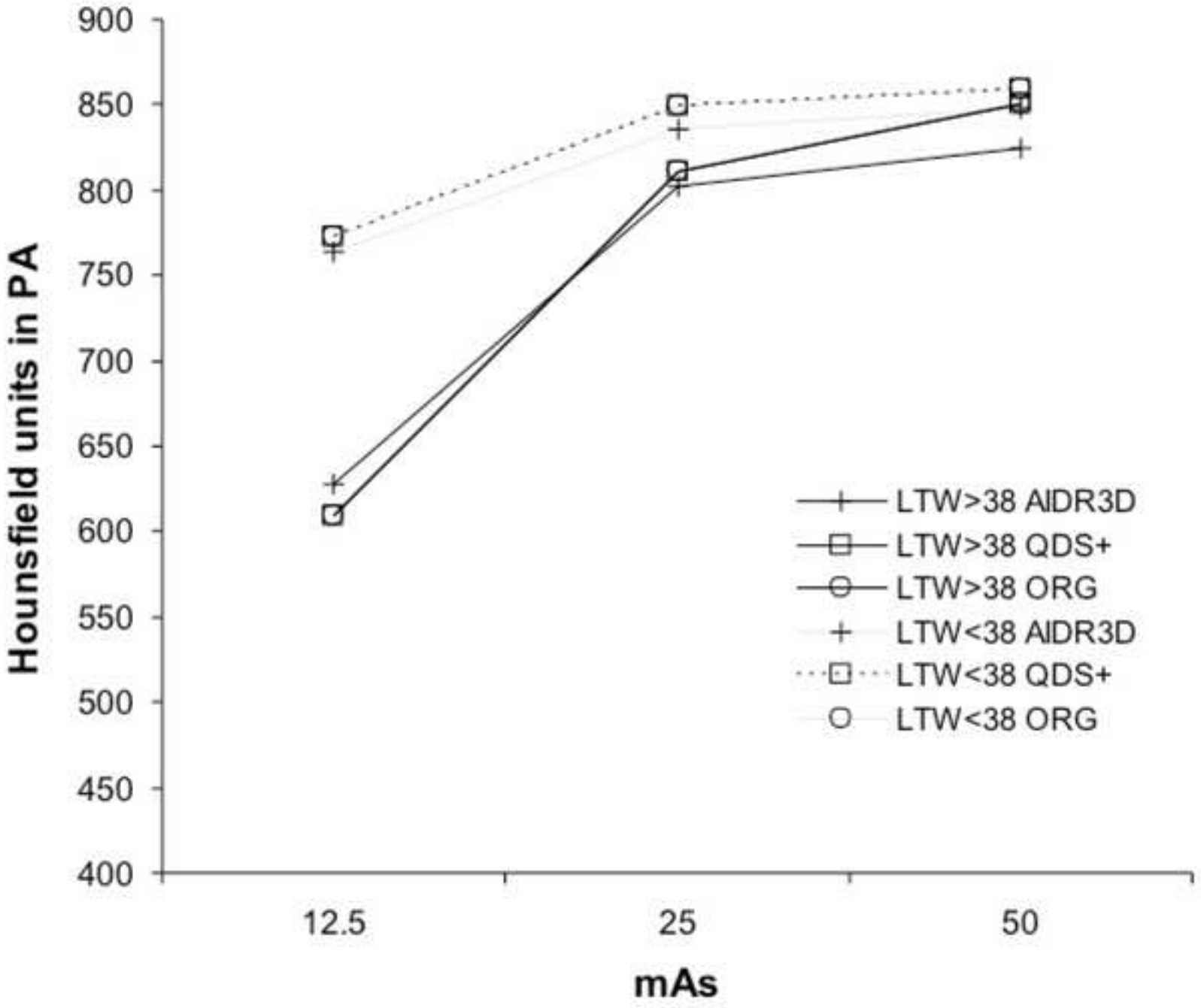


Figure 3
Click here to download high resolution image

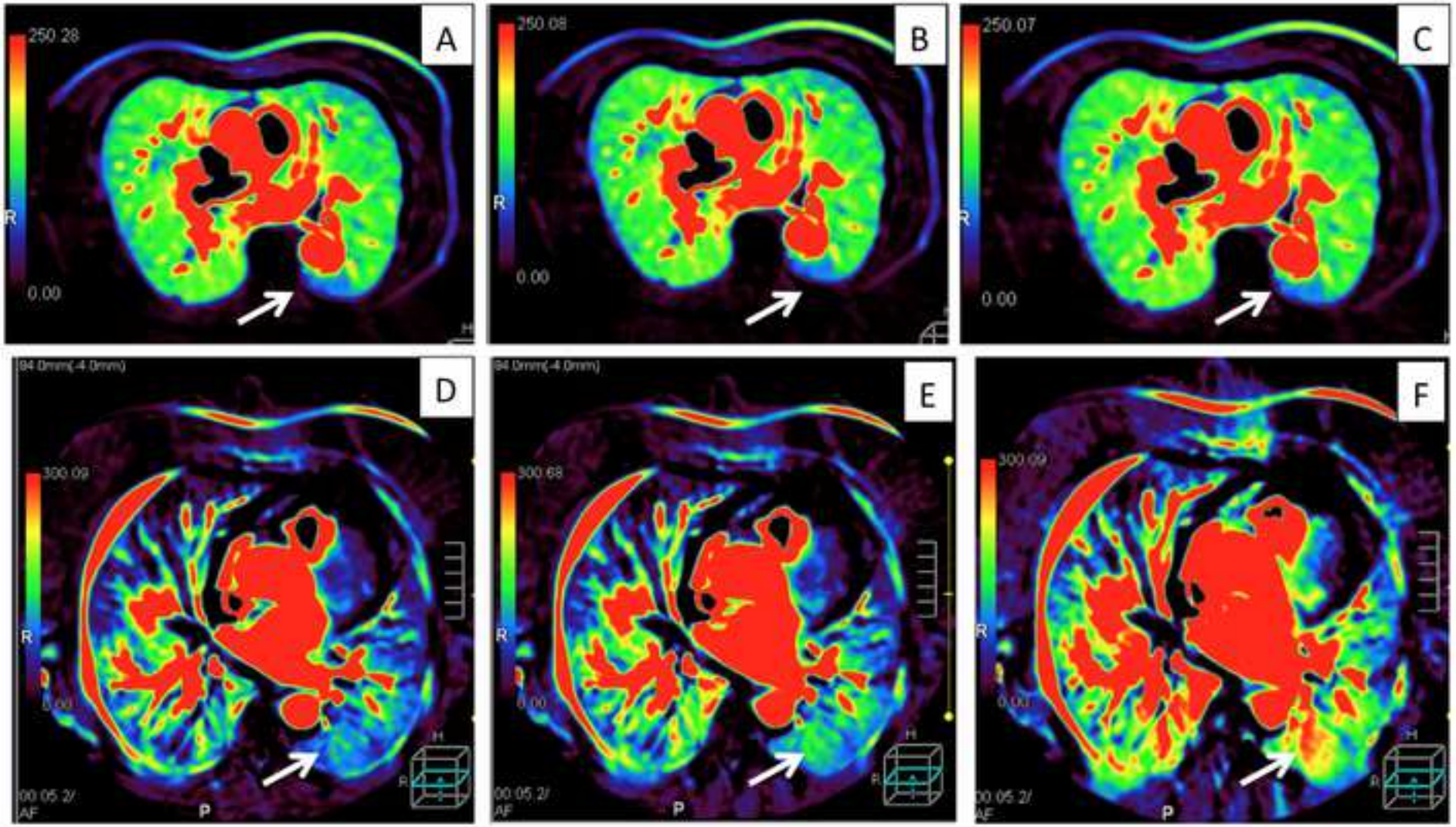
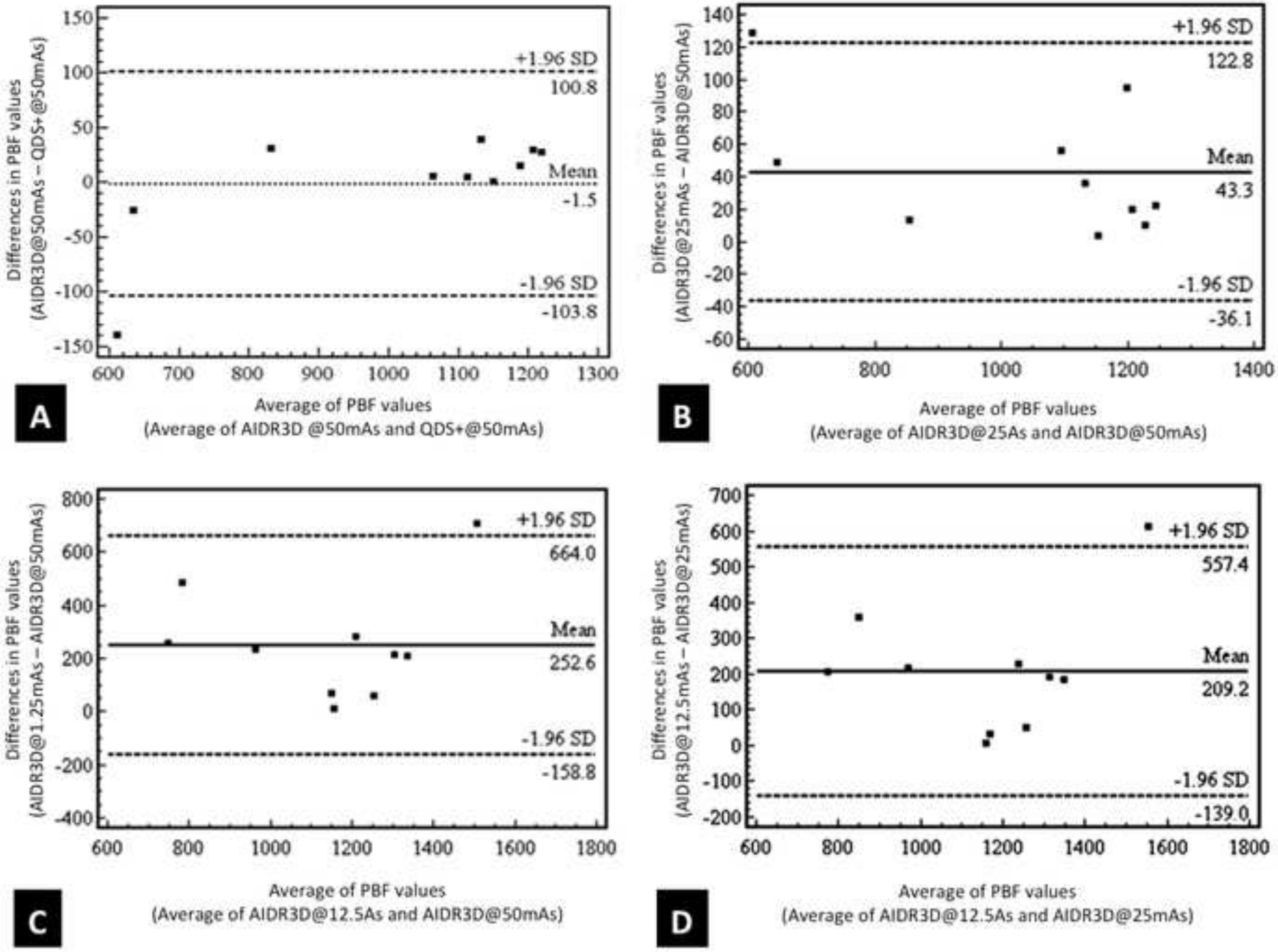


Figure 4
Click here to download high resolution image



Tables

	100mAs	50mAs	Simulated 50mAs	25mAs	Simulated 25mAs	12.5mAs	Simulated 12.5mAs
Contrast insert	1180 (3)	1176 (1)	1176 (3)	1042 (4)	1040 (2)	679 (1)	647 (2)
Air	-998 (1)	-997 (1)	-997 (1)	-983 (1)	-982 (1)	-950 (1)	-946 (1)
Soft tissue (fat)	-99 (2)	-99 (1)	-99 (1)	-104 (1)	-104 (1)	-114 (2)	-115 (1)

A

	100mAs	50mAs	Simulated 50mAs	25mAs	Simulated 25mAs	12.5mAs	Simulated 12.5mAs
Contrast insert	39.8 (2)	44.0 (3)	41.5 (2)	63.6 (2)	63.2 (2)	65.3 (2)	59.0 (2)
Air	15.0 (1)	17.5 (3)	16.7 (1)	24.5 (1)	20.7 (2)	28.4 (1)	23.8 (1)
Soft tissue (fat)	20.2 (1)	24.8 (0)	22.0 (1)	28.0 (1)	22.9 (0)	32.2 (1)	27.2 (1)

B

Table 1. Phantom validation of noise addition software.

A: Hounsfield values (SD); B: image noise values (SD).

All real and noise simulated studies were reconstructed with AIDR-3D. Mean values were measured within ROIs drawn in the same position on multiple sections (n=4) within contrast insert, air hole, and fat mimicking material.

Whilst the above results shows acceptable variation in the measured Hounsfield units and image noise in the real and simulated images, there were significant reduction in the Hounsfield units (iodinated contrast and fat material), when the tube current was reduced below 50mAs ($p<0.001$; ANOVA). The change was more obvious with the dense contrast.

AIDR-3D: adaptive iterative dose reduction- 3 dimensional. SD: standard deviation; SD: standard deviation; ROI: region of interest.

Tube Current		AIDR-3D	QDS+	ORG
50 mAs	HU	-815.5 ± 53.8	-816.9 ± 53.5	-816.7 ± 53.5
	SD	48.8 ± 8	85.9 ± 21.4	95.1 ± 28.2
25 mAs	HU	-810.3 ± 54.9	-813.7 ± 53.8	-816.2 ± 52.1
	SD	46.2 ± 7.5	101.8 ± 26.8	110.8 ± 32.5
12.5 mAs	HU	-805.7 ± 54	-807.9 ± 54.2	-803.2 ± 58.1
	SD	43.8 ± 6.7	118.4 ± 26	129.1 ± 32

Table 2. Mean HU values and image noises in 10 regions of interest in lung tissue by tube currents and image reconstruction technique.

AIDR-3D: adaptive iterative dose reduction- 3 dimensional; QDS+: quantum de-noising; ORG: Original (non-filtered); HU: Hounsfield unit; SD: standard deviation of HU values.

Tube Current	AIDR-3D	QDS+	ORG
50 mAs	101.5 ± 174	101.6 ± 213	101.8 ± 214
25 mAs	105.8 ± 212	107.6 ± 256	107.6 ± 264
12.5 mAs	126.8 ± 275	133 ± 364	144.5 ± 386

Table 3. Mean perfusion value (±SD) for lung tissue perfusion (mL/100g/min) by tube currents and image reconstruction technique.

AIDR-3D: adaptive iterative dose reduction- 3 dimensional; HU: Hounsfield unit; QDS+: quantum de-noising; ORG: Original (non-filtered); SD: standard deviation of HU values.

COPD GENETIC EPIDEMIOLOGY
CT IMAGE ACQUISITION AND PROCESSING

Revised:
January 4, 2007

CT ACQUISITION AT STUDY SITES

A. Site survey

An initial site survey (Appendix) will be performed to identify responsible personnel, CT scanner models, and image transmission preferences.

B. Technologist training

A Powerpoint training set will be implemented for technologists at the Clinical Centers to assure understanding of the outline of the study, and compliance with the radiology protocols. Each technologist involved in the acquisition of scans must be certified as having reviewed the training set.

C. Scanner quality assurance

At each study site, each CT scanner used in the study will be calibrated on a monthly basis, using the Catphan 600 phantom (to be purchased by each site), scanned using the study protocol parameters for small-size patients. The following parameters will be measured using this phantom: slice thickness; spatial resolution, low contrast resolution; image uniformity and noise; high-contrast spatial resolution accuracy of CT attenuation values for air, low density polyethylene, water, Teflon. These values will be reported to the Radiology core laboratory.

D. Patient preparation

Prior to the study, patient's identity will be confirmed according to institutional policy. The patient will be informed of the importance of compliance with the breathing instructions. Ability to comply with instructions should be assessed, and conditions which might impair compliance such as deafness, breathlessness, or mental impairment should be noted. At least one rehearsal of the end-inspiratory breathhold should be performed.

E. CT acquisition

All CT scans will be obtained using the enclosed protocol (Protocols for GE 64-detector scanners and for Phillips scanners to be developed). Minimal criteria for study entry will include

availability of a set of contiguous CT images obtained on inspiration, using scanners with 16 or more detector rows, and ≤ 1.25 mm thickness of reconstructed slices. Contiguous end-expiratory CT images will also be obtained where possible. Additional reconstructions may be performed as required at study site, but only the contiguous thin section 1.25 mm images should be sent to the Core Laboratory.

The responsible CT technologist should complete the CT acquisition form, and sign off on the quality of the study.

F. Scan transmission

All potentially identifying material should be removed from the DICOM header, and replaced with the participant's study ID. The anonymized scan data, consisting of contiguous thin-section 1.25 mm images should be written to CD or DVD, and sent to the Radiology Core Laboratory using express mail. An image shipment form (enclosed) should be faxed to the core laboratory, and a copy should be enclosed with the shipped images.

IMAGE PROCESSING AT RADIOLOGY CORE LABORATORY

A. PROCESSING/QUALITY ASSURANCE

Anonymized images will be submitted on CDs to the image registry in DICOM format, using a study ID as the only identifier. Upon arrival at the radiology core laboratory at National Jewish Medical and Research Center, CT media will be processed by the research staff, to verify anonymization and appropriate identification of study information, protocol compliance, image quality, and image count. If quality issues are identified, the staff will complete a quality form and will contact the site to attempt resolution.

B. QUANTITATIVE CT ANALYSIS

Image segmentation

Scans will be loaded to the image analysis workstation (Dell Precision Workstation 670 with dual Intel® Xeon™ Processors operating at 3.60GHz, 2MB L2 memory cache, 8 GB RAM, 250 GB SATA hard drive, and 20 inch monitor) for quantitative image analysis. Anonymized DICOM images will be segmented using the VIDA image analysis system developed at University of Iowa (http://www.vidadiagnostics.com). The software will be used to divide the right lung from the left lung, and each lung will be divided into two craniocaudal zones of equal height. Individual lung lobes will also be segmented. Images will be visually inspected for quality of segmentation.

Quantification of emphysema

The following analyses will be performed on the segmented lung images, and results provided to the DCC:

- total inspiratory lung volume
- mean lung attenuation
- % lung area with attenuation coefficient < -950, -910 and -856 HU
- % LAA (<-950 HU) in upper lungs and lower lungs
- % LAA (<-950 HU) in upper lobes and lower lobes
- % LAA (<-950 HU) in peripheral 50% of lung

- % LAA (<-950 HU) in central 50% of lung
- Hounsfield Unit values at each percentile from 1 to 16
- α value (negative slope from the log-log relationship of hole size vs percentage of holes) (with hole membership defined as voxels at -950 HU, -910 HU, or -850 HU)
- α value in upper lobes and lower lobes

Analysis of airway abnormality

The VIDA software will be used to generate a skeletonized model of the airways, following seed placement in the upper trachea. An automated iterative process will be used to correct defects in the segmented airway tree. Using a 3D curve-thinning algorithm, a centerline of the airway tree will be generated, then pruned and smoothed. The following airway analyses will be performed and reported:

- Mean % wall area for third generation bronchi
- Mean % wall area for fourth generation bronchi
- Mean % wall area for fifth generation bronchi
- Mean % wall area for sixth generation bronchi
- For each patient, the square root of wall area of all bronchi will be plotted against the internal perimeter, to identify the intercept corresponding to a bronchus of 10 mm internal perimeter. The resultant value for square root of wall area will be the primary measure of airway wall thickness.

C. STORAGE

Validated studies received by the core laboratory will be archived to a Dell Windows Server 2003 RAID 5 (1.5 TB), with 6 GB memory, dual processors, and a gigabyte network interface. This server will be backed up to tape on a weekly basis, and backup tapes will be transported to an offsite location, For document storage, we will use a FireKing fireproof locking filing cabinet.

D. QUALITY ASSURANCE

The consistent high quality acquisition of CT images is critical to the success of this study. Quality will be achieved in the following ways:

A. Review of phantom scan data from clinical sites

B. Visual evaluation of a subset of scans by a core laboratory radiologist for image quality, using the enclosed form. Specific attention will be paid to adequacy of inspiration, absence of motion artifact, or excessive noise, and adherence to study protocol, The first 10 scans from each site will be reviewed, followed by a 5% sample of scans. Quality problems will be communicated directly to the study site radiologist by the core laboratory. Persistent quality problems will mandate re-training of technologists at the study site.

C. For quality assurance of the quantitative image analysis, 10% of scans will be re-analyzed at University of Iowa using the same software, and the same subset will also be analyzed at Brigham and Women's Hospital using the 3-D SLICER program.

E. IMAGE ANALYSIS AT OTHER SITES

The primary VIDA analysis will be performed at National Jewish; however, we also will take advantage of the extensive developmental work on airway imaging and quantification being done at the University of Iowa and at Brigham and Women's Hospital. The collaborative interactions of these three image analysis groups will be used for: 1) quality control, 2) comparisons to nonsmoking and smoking control subjects (without airflow obstruction), and 3) development and validation of novel techniques for quantification of airway characteristics. A subset of CT scans will be reanalyzed at both the University of Iowa (using the VIDA program) and at Brigham and Women's (using the 3D-SLICER program) for quality control purposes. CT-determined airway wall parameters have been well established on two-dimensional CT images to be correlated with COPD physiology and pathology. Three-dimensional assessment of airway wall dimensions offers the opportunity to quantitate greater numbers of airways with greater reliability and potentially lower cost. The collaboration between these three programs will allow our proposed COPD cohort to be analyzed with state-of-the-art CT image analysis techniques. The segmented image data will be available for re-analysis as new techniques are developed.

F. DATA REPORTING:

The following data will be reported to the DCC, preferably electronically:

- Receipt of complete and technically adequate scan
- Quantitative parameters outlined above
- Quality assurance data

G. APPENDICES

1. **SITE RADIOLOGY SURVEY**
2. **CT PROTOCOL SHEET**
3. **IMAGE ACQUISITION WORKSHEET**
4. **IMAGE TRANSMISSION WORKSHEET**
5. **IMAGE QUALITY WORKSHEET**
6. **IMAGE TRACKING WORKSHEET**

Genetic Epidemiology of COPD

Radiology Site Survey Form

Please Complete the Form and Fax to COPD Imaging Lab at 303 270 XXXX

Personnel Contact Information

Imaging Site name: _____

Imaging Site number: _____

Site address: _____

_____

_____

Fax Number: _____

Coordinator: _____

Telephone _____ Email _____

Primary Radiologist: _____

Telephone _____ Email _____

Backup Radiologist: _____

Telephone _____ Email _____

Primary CT Technologist: _____

Telephone _____ Email _____

Backup CT Technologist: _____

Telephone _____ Email _____

Physicist: _____

Telephone _____ Email _____

PACS Supervisor: _____

Telephone _____ Email _____

CT information

Number of CT scanners: 1☐; 2☐; 3☐; >3☐

_____

Genetic Epidemiology of COPD

Radiology Site Survey Form

CT Information

Please list each scanner separately.

Scanner 1

Scanner Manufacturer: GE☐, Siemens☐, Philips☐, ☐other_____

CT Model or Name (e.g.,Lightspeed, Sensation, etc.) _____

Number of detectors: 4☐, 8☐, 16☐, 40☐, 64☐, ☐other _____

Current Software Version: _____

Scanner 2

Scanner Manufacturer: GE☐, Siemens☐, Philips☐, ☐other_____

CT Model or Name (e.g.,Lightspeed, Sensation, etc.) _____

Number of detectors: 4☐, 8☐, 16☐, 40☐, 64☐, ☐other _____

Current Software Version: _____

Scanner 3

Scanner Manufacturer: GE☐, Siemens☐, Philips☐, ☐other_____

CT Model or Name (e.g.,Lightspeed, Sensation, etc.) _____

Number of detectors: 4☐, 8☐, 16☐, 40☐, 64☐, ☐other _____

Current Software Version: _____

Scanner 4

Scanner Manufacturer: GE☐, Siemens☐, Philips☐, ☐other_____

CT Model or Name (e.g.,Lightspeed, Sensation, etc.) _____

Number of detectors: 4☐, 8☐, 16☐, 40☐, 64☐, ☐other _____

Current Software Version: _____

Are there any planned upgrades or new scanner purchases within the next 4 years?
Yes__ No _____

Please provide details

Genetic Epidemiology of COPD

Radiology Site Survey Form

Please return via fax to

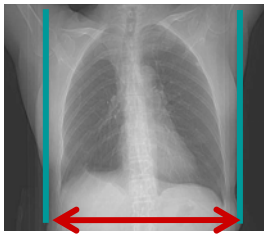
COPD Imaging Lab at 303 270 XXXX

IPF-NET STUDY Volumetric HRCT Protocols

GE / SIEMENS

GENERAL: This study consists of 2 scouts (topograms) and 3 scans. All scans use the same parameter grid. For the GE scanners the mA is set according to patient size, defined as follows:

Lateral Thickness at Level of Liver	Size Definition
< 32 cm.....	Small (S)
32-38 cm.....	Medium (M)
>38 cm.....	Large (L)



CONTRAST: **Oral/IV.** None.

SUPINE SERIES

GE SCOUT: **Supine** PA S0-I450; Scan from top of shoulder through mid-liver.
SIEMENS TOPOGRAM: **Supine** PA, 512mm. **STOP SCAN** when through lungs.

SUPINE INSPIRATION: Start at **bottom** of lungs, end at **top** of lungs. **Instruct the patient to breathe as follows:**

"For the first part of this study you will be asked to hold your breath in for about 20 seconds. If you cannot hold your breath that long, try the best you can and then take very shallow, slow breaths if you need to."

"For now, take several easy, deep breaths and relax while we prepare to take a CT scan of your lungs."

Allow patient to breathe and relax for at least 15 seconds.

"I am now going to give you specific breathing instructions. Try to follow as best you can."
"Take in a deep breath….and let it out."
"Take in another deep breath….and let it out."
"Take in another deep breath, and hold your breath in. Keep holding your breath!"

Scan the patient in one breath-hold at full-inspiration.

When the scan is completed, tell the study participant to "Breathe and relax!"

SUPINE EXPIRATION: (Required only for baseline study- may either do continuous volumetric acquisition or 1 mm scans every 2 cm)

Same protocol as **SUPINE INSPIRATION**. Start at **bottom** of lungs, end at **top** of lungs.

Instruct the patient to breathe as follows:

"For the second part of this study you will be asked to blow out your breath and hold it out for about 20 seconds. This is usually more difficult than holding your breath in, but do the best that you can. If you cannot hold your breath out that long, take a very slow shallow breath in if you need to."

"For now, take several easy, deep breaths and relax while we prepare to take the last CT scan of your lungs."

Allow patient to breathe and relax for at least 15 seconds.

"I am now going to give you more specific breathing instructions. Try to follow as best you can. "
"Take in a deep breath….and let it out."
"Take in another deep breath….and let it out."
"Take in another deep breath, let it out and hold your breath all the way out! Do not breathe!"

Scan the patient in one breath-hold at full-expiration as quickly as possible.

When the scan is completed, tell the study participant to "Breathe and relax!"

PRONE SERIES

Reposition Patient into Prone position on table.
GE SCOUT: **Prone** PA S0-I450; Scan from top of shoulder through mid-liver.
SIEMENS TOPOGRAM: **Prone** PA, 512mm. **STOP SCAN** when through lungs.

PRONE INSPIRATION: (Required only for baseline study- may either do continuous volumetric acquisition or 1 mm scans every 2 cm)

Same protocol as **SUPINE INSPIRATION**. Start at bottom of lungs, end at top of lungs.

Instruct the patient to breathe as follows:

"For the first part of this study you will be asked to hold your breath in for about 20 seconds. If you cannot hold your breath that long, try the best you can and then take very shallow, slow breaths if you need to."

"For now, take several easy, deep breaths and relax while we prepare to take a CT scan of your lungs."

Allow patient to breathe and relax for at least 15 seconds.

"I am now going to give you specific breathing instructions. Try to follow as best you can."
"Take in a deep breath….and let it out."
"Take in another deep breath….and let it out."
"Take in another deep breath, and hold your breath in. Keep holding your breath!"

Scan the patient in one breath-hold at full-inspiration.

When the scan is completed, tell the study participant to "Breathe and relax!"

SCAN TECHNIQUES:

GE	LS Ultra-8	LS 16	Sensation-16	Sensation-64	SIEMENS
Scan Type	Helical	Helical	Spiral	Spiral	Scan Type
Rotation Time (s)	0.5	see mA	0.5	0.5	Rotation Time (s)
Det. Configuration	8 x 1.25	16 x 0.625	*16 x 0.75*	*64 x 0.6*	*Collimation*
Pitch	1.35	1.375	*1.1*	*1.1*	*Pitch*
Speed (mm/rot)	13.5	13.75	13.2	21.1	Feed (mm/rot)
kVp	140	140	140	140	kVp
mA	S: 130 M: 255 L: 380	S:150 @ 0.5s M:300 @ 0.5s L:375 @ 0.6s	110	110	Quality ref mAs
Auto-mA	OFF	OFF	ON	ON	CARE Dose 4D
Breath-hold time for 280 mm (sec)	11	S or M:10.8 L:12.9	10.6	7.44	Breath-hold time for 280 mm (sec)
RECON 1					**RECON JOB 1**
Algorithm	STD/FULL	STD/FULL	B40f	B40f	Kernel
Thickness (mm)	5	5	5	5	Slice (mm)
Interval (mm)	5	5	5	5	Recon Incr. (mm)
DFOV (cm)	Patient	Patient	Patient	Patient	FOV (mm)
RECON 2					**RECON JOB 2**
Algorithm	BONE /FULL	BONE /FULL	B46f	B46f	Kernel
Thickness (mm)	1.25	1.25	1.0	1.0	Slice (mm)
Interval (mm)	10	10	10	10	Recon Incr. (mm)
DFOV (cm)	Lungs*	Lungs*	Lungs*	Lungs*	FOV (mm)
RECON 3					**RECON JOB 3**
Algorithm	BONE /FULL	BONE /FULL	B46f	B46f	Kernel
Thickness (mm)	1.25	1.25	1.0	1.0	Slice (mm)
Interval (mm)	0.625	0.625	0.5	0.5	Recon Incr. (mm)
DFOV (cm)	Lungs*	Lungs*	Lungs*	Lungs*	FOV (mm)
		Additional Information			
CTDIvol (mGy)	*15.0*	*17.3*	*13.1*	*11.33*	*CTDIvol (mGy)*
Effective Dose (mSv)	6.6	8.3	*6.4*	*6.1*	*Effective Dose (mSv)*

*** Set DFOV for Recon 2 and 3 "Lungs*" to include outside edge of the ribs.**

AXIAL HIGH-RESOLUTION CHEST (IPF-NET) STUDY (LIMITED PROTOCOL)

CONTRAST: **Oral.** None.
IV. None.

SERIES 1: **GE Scout**: **Supine** AP S0-I450; Scan from top of shoulder through mid-liver.
Siemens Topogram: **Supine** AP, 512mm. **STOP SCAN** when through lungs.

SERIES 2: Start at bottom of lungs, end at top of lungs. End-inspiration.

GE	CT/i-1	LS QX/i-4	LS Plus-4	Volume Zoom	SIEMENS
Scan Type	Axial	Axial	Axial	Sequential	Scan Type
Rotation Time (s)	1	0.8	0.8	0.75	Rotation Time (s)
Det. Configuration	1 x 1	1 x 1.25	1 x 1.25	*1 x 1*	*Collimation*
Table Increment (mm)	10	10	10	10	Feed (mm/rot)
kVp	140	140	140	140	kVp
mA	240	330	330	200 ?	Quality ref mAs
Breath-hold (s)	10	10	10	10	Breath-hold (s)
Breathe Time (s)	12	12	12	12	Breathe Time (s)
RECON					**RECON**
Algorithm	BONE	BONE	BONE	B46f	Kernel
Thickness (mm)	1.0	1.25	1.25	1.0	Width (mm)
Interval (mm)	10	10	10	10	Interval (mm)
DFOV (cm)	Patient	Patient	Patient	Patient	DFOV (mm)
Additional Information					
CTDI-vol (mGy)	*1.9*	*10.1*	*10.1*	*3.1 ?*	*CTDI-vol (mGy)*
Effective Dose (mSv)	0.9	4.7	4.7	*1.3 ?*	*Effective Dose (mSv)*

Genetic Epidemiology of COPD

IMAGE ACQUISITION FORM

This form is to be completed for each subject exam and submitted with the image data.

Site #	Subject ID[1]	Subject Initials
__ __	__ __ __	__ __ __

[1]For phantom scans, include your site # and write 'phantom' in the Subject ID field.

CT Scan Date:_____

CT Technologist: _____

Scanner manufacturer _____ Scanner model: _____

Number of detectors _____

CT IMAGE ACQUISITION

Completed	Scan	Reconstructed collimation	
☐	Scout		
☐	INSPIRATION		
☐	EXPIRATION		

CT IMAGE QUALITY

Adequate inspiration
Motion artifact
Inclusion of all parts of lungs

TECHNOLOGIST SIGNATURE: _____

Genetic Epidemiology of COPD

IMAGE SHIPMENT FAX NOTIFICATION FORM

TO: Radiology core laboratory
National Jewish Medical and Research Center
1400 Jackson Street
Denver, CO 80206

FAX # 1-303-270-XXXX

FROM: Site # _____

P. I. _____

Contact Person: _____

FAX # _____

Date Faxed: _____

COPD Imaging Research Laboratory Use Only

☐ Approved
☐ Conditional Approval (see attachments)
☐ Not Approved (see attachments)

Subject ID[1]	Subject Initials	Shipment Type	
		CD	DVD
__ __ __	__ __ __	☐	☐
__ __ __	__ __ __	☐	☐
__ __ __	__ __ __	☐	☐
__ __ __	__ __ __	☐	☐
__ __ __	__ __ __	☐	☐

[1]For test scans (non-patient), write 'TEST' in the Subject ID field.

The above data is being sent to you today _____ (today's date)

Airbill # (FedEx, Airborne, DHL shipments only) _____

Form completed by _____

Email _____

Telephone _____

Genetic Epidemiology of COPD

CT QUALITY ASSURANCE WORKSHEET

Patient ID _____ Date of study _____

Reviewer ID _____

Exam quality

	No quality issue	Minor quality issue	Substantial impairment of quality	Non-diagnostic scan	Comments
Adequate inspiration					
Motion artifact					
Inclusion of all parts of lungs					
Adherence to study acquisition parameters:					
mA					
kVp					
Slice collimation					

Genetic Epidemiology of COPD

IMAGE TRACKING WORKSHEET

SITE ID	STUDY ID	DATE FAX NOTIFICATION RECEIVED	DATE CT RECEIVED	DATE QA COMPLETE	DATE OF IMAGE ANALYSIS	IMAGES ARCHIVED	DATA SENT TO DCC

Highlights:

Dynamic CT examinations provide functional information but at the cost of a higher radiation dose.

Doses can be reduced by decreasing tube current but increases image noise.

This study demonstrates that significant dose reduction is feasible when images are reconstructed with iterative reconstruction (AIDR-3D), especially in smaller patients.

There is a limit to how low the dose can be reduced before the bias effect falsifies the calculated perfusion values.