Reproducibility of intensity-based estimates of lung ventilation

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Purpose: Lung function depends on lung expansion and contraction during the respiratory cycle. Respiratory-gated CT imaging and image registration can be used to estimate the regional lung volume change by observing CT voxel density changes during inspiration or expiration. In this study, the authors examine the reproducibility of intensity-based estimates of lung tissue expansion and contraction in three mechanically ventilated sheep and ten spontaneously breathing humans. The intensity-based estimates are compared to the estimates of lung function derived from image registration deformation field.

Methods: 4DCT data set was acquired for a cohort of spontaneously breathing humans and anesthetized and mechanically ventilated sheep. For each subject, two 4DCT scans were performed with a short time interval between acquisitions. From each 4DCT data set, an image pair consisting of a volume reconstructed near end inspiration and a volume reconstructed near end exhalation was selected. The end inspiration and end exhalation images were registered using a tissue volume preserving deformable registration algorithm. The CT density change in the registered image pair was used to compute intensity-based specific air volume change (SAC) and the intensity-based Jacobian (IJAC), while the transformation-based Jacobian (TJAC) was computed directly from the image registration deformation field. IJAC is introduced to make the intensity-based and transformation-based methods comparable since SAC and Jacobian may not be associated with the same physiological phenomenon and have different units. Scan-to-scan variations in respiratory effort were corrected using a global scaling factor for normalization. A gamma index metric was introduced to quantify voxel-by-voxel reproducibility considering both differences in ventilation and distance between matching voxels. The authors also tested how different CT prefiltering levels affected intensity-based ventilation reproducibility.

Results: Higher reproducibility was found for anesthetized mechanically ventilated animals than for the humans for both the intensity-based (IJAC) and transformation-based (TJAC) ventilation estimates. The human IJAC maps had scan-to-scan correlation coefficients of 0.45 ± 0.14 , a gamma pass rate 70 ± 8 without normalization and 75 ± 5 with normalization. The human TJAC maps had correlation coefficients 0.81 ± 0.10 , a gamma pass rate 86 ± 11 without normalization and 93 ± 4 with normalization. The gamma pass rate and correlation coefficient of the IJAC maps gradually increased with increased smoothing, but were still much lower than those of the TJAC maps.

Conclusions: The transformation-based ventilation maps show better reproducibility than the intensity-based maps, especially in human subjects. Reproducibility was also found to depend on variations in respiratory effort; all techniques were better when applied to images from mechanically ventilated sheep compared to spontaneously breathing human subjects. Nevertheless, intensity-based techniques applied to mechanically ventilated sheep were less reproducible than the transformation-based applied to spontaneously breathing humans, suggesting the method used to determine ventilation maps is important. Prefiltering of the CT images may help to improve the reproducibility of

the intensity-based ventilation estimates, but even with filtering the reproducibility of the intensity-based ventilation estimates is not as good as that of transformation-based ventilation estimates.

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I. INTRODUCTION

Lung function depends on tissue material properties and respiratory system mechanics. Since many disease processes and injury conditions can alter lung function, it is useful to be able to reliably calculate indices of lung function at the global and regional levels. Regional pulmonary ventilation is the term used to characterize the volume of fresh air per unit time that enters or exits the lung at the acinar (gas exchange) level. Regional pulmonary ventilation can reflect physiological and pathological changes in the airways, parenchymal mechanics, respiratory muscles, body posture effects, and inhaled gas properties. While some characteristics of global lung function can be assessed using spirometry and pulmonary function testing, regional pulmonary ventilation is more difficult to estimate.

Noninvasive imaging approaches have been developed to assess regional pulmonary ventilation, such as positron emission tomography (PET),¹⁻³ single photon emission computed tomography (SPECT),⁴⁻⁶ hyperpolarized noble gas MR imaging,⁷⁻¹¹ and xenon-enhanced CT.¹²⁻¹⁴ Recent advances in multidetector-row CT (MDCT), 4DCT respiratory gating methods, and image registration algorithms now enable us to obtain a regional lung expansion map for the lung, which in turn can be used as an index of regional lung ventilation.^{15,16}

Before the registration-based assessments of regional tissue expansion can be trusted to provide clinically meaningful estimates and be used to track pulmonary function change, for example, during radiation therapy (RT) course,¹⁷ it is necessary to understand the variabilities of the techniques and establish technique uncertainty. Several factors can influence these calculations, such as subject motion, respiratory rate, and breathing effort variations, image acquisition artifacts and noise, the image registration algorithm, associated regularization and similarity criteria, and image registration errors. In Ref. 18, Du *et al.* examined the reproducibility of lung expansion estimates computed from the Jacobian of the registration displacement field aligning a CT image of the lungs at end inspiration to an image acquired at end expiration. Yamamoto *et al.*¹⁹ investigated the reproducibility of lung ventilation using a transformation-based volume change metric and 4DCT imaging over two different time frames and reported moderate voxel-based correlation between two ventilation images (Spearman rank correlation 0.50 ± 0.15).

In this paper, we evaluate the reproducibility of three different techniques for computing regional pulmonary ventilation. All three techniques utilize the same 4DCT as the input data for computations, which have been acquired as repeat scans for a cohort of spontaneously breathing human subjects

and anesthetized and mechanically ventilated sheep. The first technique is based on computing the specific air volume change (SAC), which is computed directly from the intensity value (Hounsfield unit) of each voxel within the lung.¹⁶ For the second technique we derive the relationship between the SAC and the local volume change of each voxel, again derived from the CT voxel intensity, which we call the intensity-based Jacobian (IJAC). Finally, we derive the local volume change from transformation field required to register the CT acquired at the end of inspiration with that at the end of expiration, which we call the transformation-based Jacobian (TJAC).¹⁸ Since SAC and the Jacobian represent different physical phenomena and have different units, they are difficult to compare directly. Therefore, we introduce the IJAC, which estimates the same local volume change as the TJAC. We propose using reproducibility as the metric to assess which of these approaches provide the most sensitive estimate of ventilation change following medical intervention (e.g., radiation therapy), and to quantify the amount of change that can be attributed to the intervention and not from the inherent uncertainty produced by the technique. We also analyze the effects of variation in respiratory effort and the impact of CT noise on the different approaches for computing pulmonary ventilation.

As an extension of our previous work in Ref. 18, this paper continues and expands the analysis on the reproducibility of registration-based estimates of lung ventilation in the following aspects: (1) developing IJAC to make an intensity-based ventilation estimate comparable with transformation-based ventilation estimate, and clarifying the relationship between IJAC and SAC; (2) deriving analytic models to study the impact of noise from CT images on intensity-based ventilation maps; (3) introducing an additional comparison metric, the gamma index; (4) comparing the reproducibility of the intensity-based ventilation estimates with the transformation-based ventilation estimates presented in Ref. 18; (5) using the same normalization scheme as in Ref. 18 on the intensity-based ventilation estimates and studying the reproducibility before and after normalization; and (6) investigating improvement in IJAC reproducibility with increasing levels of denoising on the CT images.

II. BACKGROUND

One approach to estimate regional ventilation is to apply the principles of continuum mechanics on the displacement field produced by a deformable image registration. The Jacobian determinant, or simply the Jacobian, is the determinant of the deformation gradient tensor as shown in Eq. (1), where

$\mathbf{h}(\mathbf{x})$ represents registration deformation field,¹⁵

$$J(\mathbf{h}(\mathbf{x})) = \begin{vmatrix} \frac{\partial h_1(\mathbf{x})}{\partial x_1} & \frac{\partial h_1(\mathbf{x})}{\partial x_2} & \frac{\partial h_1(\mathbf{x})}{\partial x_3} \\ \frac{\partial h_2(\mathbf{x})}{\partial x_1} & \frac{\partial h_2(\mathbf{x})}{\partial x_2} & \frac{\partial h_2(\mathbf{x})}{\partial x_3} \\ \frac{\partial h_3(\mathbf{x})}{\partial x_1} & \frac{\partial h_3(\mathbf{x})}{\partial x_2} & \frac{\partial h_3(\mathbf{x})}{\partial x_3} \end{vmatrix}. \quad (1)$$

In this paper, we will refer to the Jacobian calculated using Eq. (1) as the TJAC. The Jacobian provides a surrogate of local volume change in a region, and can include contributions due to both tissue volume change and air volume change. Castillo *et al.*¹⁶ demonstrated the equivalence of the Jacobian computed using Eq. (1) and a geometrical approach based on computing the volume change of a 3D polygonal region.²⁰ Reinhardt *et al.*¹⁵ compared registration-based estimates of regional lung function using the Jacobian with xenon-CT estimates of specific ventilation and reported average r^2 of 0.73. Ding *et al.*¹⁷ used the Jacobian to quantitatively estimate the regional ventilation before and after a course of radiation therapy.

An alternative to the Jacobian-based approach for computing a ventilation map was described by Guerrero *et al.*,²¹ who characterized regional ventilation in subjects utilizing the relationship between local air fraction and CT intensity values, following the approach suggested by Simon.²² Assuming that a lung region consists only of air and tissue, the air fraction F can be calculated directly from the CT voxel values^{23,24}

$$F = -\frac{HU}{1000}, \quad (2)$$

where HU represents the mean CT value in the region of interest. Now suppose an image registration algorithm registers two images (called the *fixed* and *moving* images) acquired at different lung volumes. The change in fractional air content, or specific air volume change (SAC), within a region is then²²

$$SAC = \frac{\Delta V}{V_f} = \frac{F_2 - F_1}{F_1(1 - F_2)}, \quad (3)$$

where ΔV is local volume change in the region, and V_f is the volume of air in the region the fixed image. F_1 is the fraction of air in the region in the fixed image, and F_2 is that fraction in the corresponding region in the moving image. If we assume that local volume change is due only to the increase or decrease of air (flow in or flow out), and assume the intensity of air is -1000 HU and tissue is 0 HU, the SAC can be computed from the image intensity values and the image registration transformation $\mathbf{h}(\cdot)$,

$$SAC = \frac{\Delta V}{V_f} = 1000 \frac{I_m(\mathbf{h}(\mathbf{x})) - I_f(\mathbf{x})}{I_f(\mathbf{x})(I_m(\mathbf{h}(\mathbf{x})) + 1000)}, \quad (4)$$

where $I_f(\mathbf{x})$ is the CT intensity (HU) at location $\mathbf{x}$ in the fixed CT image and $I_m(\mathbf{h}(\mathbf{x}))$ is the CT intensity of corresponding voxel in the moving CT image.¹⁶ In Ref. 16, Eq. (4) was applied to all lung voxels with a CT intensity between -999 and -250 HU.

Castillo *et al.*¹⁶ compared the TJAC [computed using Eq. (1)] and intensity-based specific air ventilation [computed using Eq. (4)] with ventilation from ^{99m}Tc -labeled aerosol SPECT/CT, and found higher correlation between intensity-based ventilation and SPECT/CT based ventilation

than correlation between transformation-based Jacobian and SPECT/CT based ventilation. Yaremko *et al.*²⁵ proposed using the intensity-based ventilation map to identify regions of highly functional lung for avoidance in intensity modulated radiation therapy (IMRT) planning in nonsmall-cell lung cancer. Vinogradskiy *et al.*²⁶ used the intensity-based specific air volume change [Eq. (4) in this paper] calculated from weekly 4DCT data to study ventilation change throughout radiation therapy as a function of radiation dose. Recently, Ding *et al.*²⁷ compared three registration-based ventilation estimates, specific air volume change calculated from the Jacobian (SAJ), specific air volume change calculated by the corrected Jacobian (SACJ), and specific air volume change by intensity change (SAI), where SAI can be derived from SACJ by assuming that tissue volume is preserved during deformation. The SACJ was found better correlated with Xe-CT than the other two estimates.

III. MATERIAL AND METHODS

III.A. Method overview

Figure 1 shows a block diagram of the entire process. Two 4DCT scans (denoted as scan one and scan two) are acquired for each subject with a short time interval between acquisitions. This so-called “coffee break” acquisition is intended to capture two separate 4DCT image sets of the lung depicting the same anatomy and physiological condition. For each 4DCT scan, two volumes are selected and reconstructed: an image near full inspiration (denoted as 100%IN) and an image near end exhalation (denoted as 0%EX). Three-dimensional B-spline deformable image registration is used to deform the 100%IN image to the 0%EX image, producing a registration deformation field. Following the process in Ref. 16, the 0%EX and 100%IN images involved in the registration are smoothed to reduce noise and then the intensity-based ventilation is computed from the displacement field and the

FIG. 1. Block diagram shows the processing dataflow for reproducibility of intensity-based ventilation metrics. Two complete 4DCT scans are acquired with a short time interval in between acquisitions. The intensity-based ventilation maps for scans one and two are calculated from the original CT images 0%EX, 100%IN, and the corresponding registration displacement fields. The ventilation maps for scan two are transformed to the space of scan one for reproducibility assessment.

TABLE I. Summary of the image registrations performed to calculate intensity-based ventilation. Names of images and transformations refer to those given in Fig. 1.

Transformation name	Image transformed	Transformation is used to
T0	Scan two 0%EX $\rightarrow$ scan one 0%EX	Transform the scan two ventilation map into the scan one 0%EX coordinate, producing $IJAC_{T2 \circ T0}$
T1	Scan one 100%IN $\rightarrow$ scan one 0%EX	Calculate scan one ventilation map $IJAC_{T1}$
T2	Scan two 100%IN $\rightarrow$ scan two 0%EX	Calculate scan two ventilation map $IJAC_{T2}$

aligned CT image pair. An additional spatial averaging of the resulting ventilation map is performed to generate the final ventilation map. This process is performed for both the scan one and scan two data, producing registration transformations T1 and T2 and final intensity-based ventilation images SAC_{T1} and SAC_{T2} or $IJAC_{T1}$ and $IJAC_{T2}$ (see Table I).

Other than transformations T1 and T2 defined between the 100%IN and 0%EX respiratory phase points on 4DCT, one additional transformation, T0, mapping scan two 0%EX to scan one 0%EX, is used to convert the ventilation maps into a common coordinate system for comparison. T0 transformation is computed using the same image registration algorithm as that used for T1 and T2. The coordinate system of scan one 0%EX is used as the reference coordinate system for all comparisons. Because the intensity-based ventilation maps may have zero and missing values,¹⁶ the application of a voxel-by-voxel ratio or difference is not appropriate for comparison. In this paper, we use a gamma index metric to compare the two maps with tolerance for differences in ventilation value and location.

III.B. Image data sets

III.B.1. Animal subjects

Appropriate animal ethics approval was obtained for these protocols from the University of Iowa Animal Care and Use Committee and the study adhered to NIH guidelines for animal experimentation. Data from three adult male sheep, with weights 44.0, 37.8, and 40.4 kg, were collected. The sheep were anesthetized using intravenous pentobarbital and pancuronium to ensure adequate sedation and to prevent spontaneous breathing. Animals were positive pressure ventilated during experiments using a custom built dual Harvard apparatus piston ventilator designed for computer control. Respiratory rate for animals ranged from 15 to 18 breaths per minute. Two 4DCT images were acquired for each animal with a short (less than 10 min) time interval in between scans. The animals were not moved between scans. Images were acquired in the prone position using the dynamic imaging protocol with a pitch of 0.1, slice collimation of 0.6 mm, rotation time of 0.5 s, slice thickness of 0.75 mm, slice increment of 0.5 mm, 120 kV, and 400 mAs. The airway pressure signal was simultaneously recorded with the x-ray projections and images were reconstructed retrospectively using the B30f kernel to produce a full inspiration image (100%IN) and end exhalation

image (0%EX). These are the same data sets previously analyzed in Ref. 18.

III.B.2. Human subjects

All data from human subjects were gathered under a protocol approved by the University of Iowa Institutional Review Board. The human data consist of 4DCT data from ten human subjects about to undergo radiation therapy for lung cancer. While 13 human subjects enrolled in the study, data were not analyzed for three (two withdrew prior to data acquisition and one experienced substantial coughing during the 4DCT scan making the images unusable). The subjects included five males and five females, with ages ranging from 31 to 78 years, with an average age of 59 ± 17 (mean $\pm$ standard deviation) years. These subjects, with the exception of H-15, are the nine subjects evaluated in Ref. 18.

Prior to imaging, each subject was trained using a biofeedback system (RESP@RATE, Intercure Ltd., Lod, Israel) to identify and support maintaining their nominal breathing rate. Musical cues were used to pace respiration during imaging, using a technique developed at our institution previously shown to have high success.²⁸

Two 4DCT scans were acquired for each subject with a short time between scans (see Table III). The subjects left the scanner table between scans. Images were acquired in the supine position using the dynamic imaging protocol with a pitch of 0.1, slice collimation of 0.6 mm, rotation time of 0.5 s, slice thickness of 2 mm, slice increment of 0.5 mm, 120 kV, and 700 mAs. The pressure signal was simultaneously recorded with the x-ray projections and images were reconstructed retrospectively with the B30f kernel to produce a full inspiration image (100%IN) and end exhalation image (0%EX).

III.C. Data processing

III.C.1. Preprocessing

After image acquisition and reconstruction, all images were examined for evidence of severe breathing artifacts or other acquisition problems. Such artifacts may disrupt the image registration process and lead to poor registration results and erroneous lung expansion estimates. For the ten human cases and three animal cases considered here, no significant image artifacts or other problems were detected.

TABLE II. Summary of lung volumes for scans 1 and 2 in 0%EX and 100%IN images for three animal subjects. The “Tidal Vol.” column shows the volume difference from 0%EX to 100%IN. All volumes are in liters.

Subject	Scan	0%EX (L)	100%IN (L)	Tidal vol. (L)
S-1	1	2.79	3.14	0.38
	2	2.87	3.24	0.37
S-2	1	2.50	2.88	0.38
	2	2.62	3.01	0.39
S-3	1	2.80	3.34	0.54
	2	2.93	3.49	0.56

Prior to image registration, the images of the animal subjects were resampled to size $288 \times 288 \times 352$ with voxel size $1 \text{ mm} \times 1 \text{ mm} \times 1 \text{ mm}$. Images of the human subjects were resampled to the same voxel size but with image size $304 \times 304 \times 320$. The Pulmonary Workstation 2.0 software (VIDA Diagnostics, Inc., Iowa City, IA) was used to identify the lung regions in the CT images. Blood vessels and the bronchial tree were included in the lung segmentation. The binary whole lung mask obtained from the segmented lung was used to limit the spatial domain of the image registration and subsequent transformation-based lung function analysis. As in Ref. 16, we limited the intensity-based ventilation analysis to segmented lung voxels in the range $[-999, -250]$ HU. The lung volume was calculated by counting the number of voxels in the lung region and multiplying by the voxel volume. Tables II and III list the lung volumes calculated for the subjects in this study.

III.C.2. Deformable image registration

For each subject, the 100%IN image was registered to the 0%EX image using tissue volume preserving nonrigid registration algorithm developed by our group.^{18,29–31} The algorithm uses a cubic B-spline transformation model and multi-resolution optimization procedure to minimize the sum of squared tissue difference (SSTVD),³² subject to a Laplacian regularization constraint. Subvoxel accuracy of the registration algorithm compared to manually identified landmarks has been previously reported for transformations T0, T1, and T2 for the same set of subjects in this paper except subject H-15.¹⁸ All ventilation images in this study were subsequently derived from this registration algorithm with the same registration parameters.

III.C.3. Intensity-based estimates of ventilation

With the CT image intensities and spatial correspondence between the registration pair 0%EX and 100%IN, SAC can be computed via Eq. (4), estimating specific air volume change. In addition, the Jacobian of the registration displacement field [Eq. (1)] calculates the local volume change in a region. Both SAC and the Jacobian are widely used as ventilation estimates, but they represent different physical phenomena. SAC estimates the fraction of air volume change,

TABLE III. Summary of lung volumes for scans one and two in 0%EX and 100%IN images for ten human subjects. The “Tidal vol.” column shows the volume difference from 0%EX to 100%IN. All volumes are in liters. The “Time between scans” column gives the approximate time between the scans one and scan acquisition.

Subject	Scan	0%EX (L)	100%IN (L)	Tidal vol. (L)	Time between scans
H-1	1	1.24	1.72	0.48	54 min
	2	1.26	1.94	0.68	
H-2	1	5.24	5.86	0.62	61 min
	2	5.34	5.91	0.57	
H-4	1	2.90	3.39	0.49	20 h
	2	2.83	3.41	0.58	
H-7	1	5.26	5.72	0.46	33 min
	2	5.69	6.37	0.68	
H-8	1	3.02	3.79	0.77	7 days
	2	3.12	4.35	1.23	
H-9	1	3.65	4.50	0.85	35 min
	2	3.81	4.33	0.52	
H-10	1	2.09	2.63	0.54	64 min
	2	2.14	2.61	0.47	
H-11	1	3.51	4.09	0.58	33 min
	2	3.54	4.22	0.67	
H-12	1	3.95	5.11	1.16	29 min
	2	3.91	5.14	1.23	
H-15	1	2.51	2.87	0.36	23 min
	2	2.49	2.85	0.36	

while the Jacobian calculates the relative regional volume change.²⁷ In addition, the two estimates have different quantities, for example, a 5% change in SAC and a 5% change in the Jacobian represent different quantities of physiological volume change. In this section, we will show that an intensity-based Jacobian, which estimates the same local volume change as the transformation-based Jacobian, can be calculated from the intensity change in registered CT image pair. The intensity-based Jacobian enables a direct comparison between the intensity-based and transformation-based methods.

SAC is defined by Castillo *et al.*¹⁶ as

$$\text{SAC} = \frac{f_2 - f_1}{f_1(1 - f_2)}, \quad (5)$$

where f_1 and f_2 are the air fractions in a region in two different inflation conditions. We can write

$$f_1 = \frac{V_{\text{air},1}}{V_1}, \quad f_2 = \frac{V_{\text{air},2}}{V_2},$$

where $V_{\text{air},1}$ and $V_{\text{air},2}$ are the air volumes in conditions 1 and 2 and V_1 and V_2 are the volumes of the region in conditions 1 and 2.

From Hoffman’s work,³³ we also know that if we assume the lung is composed of only air and tissue, then

$$f_1 = -\frac{\text{HU}_1}{1000}, \quad f_2 = -\frac{\text{HU}_2}{1000}, \quad (6)$$

where HU_1 and HU_2 are the mean CT values in the region in conditions 1 and 2.

Note that

$$\text{SAC} + 1 = \frac{\frac{f_2}{1-f_2}}{\frac{f_1}{1-f_1}} = \frac{\frac{V_{\text{air},2}}{V_{\text{tissue},2}}}{\frac{V_{\text{air},1}}{V_{\text{tissue},1}}}.$$

If we assume that there is no tissue volume change between conditions 1 and 2, then $V_{\text{tissue},1} = V_{\text{tissue},2}$. In that case, we can write

$$\text{SAC} + 1 = \frac{V_{\text{air},2}}{V_{\text{air},1}}.$$

If we define the volume ratio, VR, as

$$\text{VR} = \frac{V_2}{V_1},$$

it is straightforward to show that

$$\text{SAC} + 1 = \frac{f_2}{f_1} \text{VR}$$

or

$$\text{VR} = \frac{f_1}{f_2} (\text{SAC} + 1). \quad (7)$$

From Eq. (5) we have

$$f_2 = \frac{f_1 (\text{SAC} + 1)}{1 + f_1 \text{SAC}},$$

which, if substituted into Eq. (7) and combined with $\frac{V_{\text{air},1}}{V_1} = \frac{-\text{HU}_1}{1000}$, produces

$$\text{VR} = -\frac{\text{HU}_1}{1000} \text{SAC} + 1, \quad (8)$$

where HU_1 is the CT intensity at a voxel of interest in the fixed image. Compared to Eq. (7), the form in Eq. (8) is easier to compute.

Substituting Eq. (5) into Eq. (7) yields

$$\text{VR} = \frac{1 - f_2}{1 - f_1}, \quad (9)$$

which can be written using Eq. (6) as

$$\text{IJAC} = \text{VR} = \frac{1000 + \text{HU}_1}{1000 + \text{HU}_2}. \quad (10)$$

Thus, VR, which estimates the same volume ratio as the transformation-based Jacobian, can be calculated directly from the Hounsfield unit change within the region. We will refer to the volume ratio calculated using Eq. (10) as the IJAC. An alternate derivation of Eqs. (7) and (10) based on the definitions of SAC and IJAC is given in Appendix A.

An advantage of using IJAC [Eq. (10)] rather than SAC is that a direct comparison between IJAC and TJAC [Eq. (1)] is possible. Thus, with Eq. (10), we can directly compare IJAC vs TJAC reproducibility and compare to previous work using the transformation-based Jacobian (such as Refs. 15 and 18). Comparisons to SAC-based work (such as Refs. 16, 21, and 34) are also possible using Eq. (7) or (8).

For the intensity-based ventilation analysis in each scan, lung voxels from the CT images of scan one 0%EX and scan two 0%EX were delineated by an intensity-based segmentation algorithm with HU values in the range $[-999, -250]$ representing pulmonary parenchyma.^{16,21,34} The spatial transformation established from the image registration linked the

fixed image (0%EX) and moving image (100%IN). The warping function $\mathbf{h}(\mathbf{x})$ interpolates the moving image and maps the set of moving voxels to the corresponding location in the fixed image. The resulting intensity-based Jacobian maps in the coordinate system of 0%EX, representing fractional change in air content during lung expansion.

Following the approaches from Refs. 16, 21, 34, each CT input image was smoothed by local averaging with kernel size $3 \times 3 \times 3$, to suppress noise in the original CT images and reduce the effects of image registration error, we then performed an additional $9 \times 9 \times 9$ local averaging on the preliminary IJAC results to generate the final ventilation maps. In contrast to TJAC, which is directly computed from the displacement field from image registration, the calculation of IJAC also involves the intensity information of the registered CT images at 0%EX and 100%IN. Consequently, the increased noise in the intensity-based ventilation maps and poorer reproducibility may come from two sources: noise in original CT images and image registration error. To test how different levels of filtering affect reproducibility, we processed the data for all human subjects with different amounts of low-pass filtering applied to the CT images prior to registration. We tested the change of IJAC reproducibility for CT images without smoothing and with different scales of smoothing using local average kernels $3 \times 3 \times 3$, $7 \times 7 \times 7$, $11 \times 11 \times 11$, and $15 \times 15 \times 15$ voxels. Results for effects of filtering on reproducibility are presented in Sec. IV.C.

Because of the use of the thresholds $[-999, -250]$, not every voxel in the lung region is assigned a ventilation value. Therefore, when we warp IJAC_{T2} back to the coordinate of scan one 0%EX, nearest neighborhood interpolation was used to warp voxels outside of the threshold range, instead of the usual linear interpolation.

III.C.4. Analytical analysis of noise in intensity-based estimates of ventilation

As shown in Eqs. (4) and (10), the intensity-based SAC and intensity-based Jacobian are computed from the CT values of the 0%EX and 100%IN images and the registration transformation. Therefore, the ventilation calculations are vulnerable to CT image noise and registration errors. In Ref. 16, noise filtering was used to reduce these effects. The error in the intensity-based SAC and intensity-based Jacobian ventilation estimates caused by the perturbation in CT HU values can be computed analytically from Eq. (4) using the propagation of error theory.³⁵ Details of the derivation of the coefficient of variation for the intensity-based SAC and the Jacobian are described in Appendixes B and C.

Equation (11) shows the impact of CT noise standard deviation σ_{CT} on the coefficient of variation (CV) of SAC estimates

$$\frac{\sigma_{\text{SAC}}}{\mu_{\text{SAC}}} = \sigma_{\text{CT}} \frac{\sqrt{I_f^2(I_f + 1000)^2 + I_m^2(I_m + 1000)^2}}{I_f(I_m - I_f)(I_m + 1000)}, \quad (11)$$

FIG. 2. Error propagation to coefficient of variation for intensity-based SAC (left) and IJAC (right). Vertical axis shows $\frac{\sigma_x}{\mu_x \sigma_{CT}}$, where x represents either SAC or intensity-based Jacobian. EE represents the mean CT value in a region of interest at end expiration, while EI represents the mean CT value in that same region at end inspiration.

where μ_{SAC} is the mean of SAC, and I_f and I_m are the CT intensity values at a voxel of interest in the 0%EX and 100%IN images.

Similarly, from Eq. (10), we can perform a similar noise analysis for the intensity-based Jacobian, which yields

$$\frac{\sigma_{IJAC}}{\mu_{IJAC}} = \sigma_{CT} \frac{\sqrt{(I_m + 1000)^2 + (I_m - I_f)^2}}{(I_f + 1000)(I_m + 1000)}, \quad (12)$$

where μ_{IJAC} is the mean of IJAC.

The curves in Fig. 2 plot the error propagation from CT noise to CV of intensity-based ventilation estimates for several fixed EI HU values. The vertical axis is $\frac{\sigma_x}{\mu_x \sigma_{CT}}$ where x represents either SAC or intensity-based Jacobian. For example, for an EE-EI pair with EE = -600 HU and EI = -975 HU, Fig. 2 shows $\frac{\sigma_{SAC}}{\mu_{SAC}} = 0.043 \sigma_{CT}$ and $\frac{\sigma_{IJAC}}{\mu_{IJAC}} = 0.038 \sigma_{CT}$. If we assume $\sigma_{CT} = 10$ HU,³⁶ this produces a coefficient of variation in the SAC of 43% and a coefficient of variation in the IJAC of 38%, indicating the intensity-based ventilation calculations are noisy. Even with local averaging to reduce noise in the CT images, the impact of CT noise on the final intensity-based ventilation may be large and should not be neglected. Additionally, any registration error will further increase variability of ventilation estimates.

III.C.5. Reproducibility analysis

After calculating the intensity-based ventilation maps from two separate 4DCT data sets, a metric is needed to compare these two ventilation maps regionally and quantitatively. In our previous work,¹⁸ we introduced the Jacobian ratio map, the colored 2D kernel density scatter plot, and the modified Bland-Altman plot to show the voxel-by-voxel relationship of ventilation in two scans, and calculated statistical parameters such as the mean and standard deviation of Jacobian ratio map, the correlation coefficient between two Jacobian maps, and the slope of linear regression line. However, in this paper since the SAC map calculated from Eq. (4) and IJAC map calculated from Eq. (10) may not be defined at all lung

voxels, we propose to use a modified gamma index to allow for approximate matching.

The gamma index was developed in quantitative dose evaluation for RT dose delivery.³⁷ In addition to considering the ventilation difference, the gamma index adds a term to tolerate possible spacial misalignment, which may result from subject motion, image acquisition problems, and image registration errors. The gamma index is defined as

$$\begin{aligned} \gamma(\vec{r}_2, \vec{r}_1) &= \min_{\vec{r}_2} \{\Gamma(\vec{r}_2, \vec{r}_1)\} \\ &= \min_{\vec{r}_2} \left\{ \sqrt{\left(\frac{\vec{r}_2 - \vec{r}_1}{\Delta d_0} \right)^2 + \left(\frac{S_2(\vec{r}_2) - S_1(\vec{r}_1)}{\Delta S_0} \right)^2} \right\}, \end{aligned} \quad (13)$$

where $\vec{r}_1$ and $\vec{r}_2$ are the voxel positions of IJAC_{T1} and IJAC_{T2} points, respectively. $S_1(\vec{r}_1)$ and $S_2(\vec{r}_2)$ are IJAC values in two scans. Δd_0 is the criteria for spatial offset tolerance and ΔS_0 is the IJAC difference criteria. For any given location in IJAC_{T1}, there are as many Γ as there are evaluated points in the search space in IJAC_{T2}. The minimum value of Γ is the final γ value.

Since breathing effort, and thus ventilation, may vary subject to subject, we have modified Eq. (13) so that ventilation values are compared on a percentage difference basis, depending upon a tolerance Δp_0 ,

$$\begin{aligned} \gamma(\vec{r}_2, \vec{r}_1) &= \min_{\vec{r}_2} \left\{ \sqrt{\left(\frac{\vec{r}_2 - \vec{r}_1}{\Delta d_0} \right)^2 + \left(\frac{S_2(\vec{r}_2) - S_1(\vec{r}_1)}{S_1(\vec{r}_1) \times \Delta p_0} \right)^2} \right\}. \end{aligned} \quad (14)$$

In this paper, we use $\Delta d_0 = 4$ mm and $\Delta p_0 = 0.1$ (i.e., 10% tolerance) as default parameters. The gamma index tries to balance between differences in specific ventilation and the distance between matching voxels. The pass threshold of the γ test is $\gamma = 1$. A voxel with $\gamma \leq 1$ passes the test,

implying that there is a matching voxel in the other ventilation map with less than 10% ventilation difference within a distance of 4 mm. The pass region percent rate is computed by counting all passed voxels divided by total number of pulmonary parenchyma voxels.

III.C.6. Compensating for variations in respiratory effort

As described in Ref. 18, even with training and audio guidance, for some subjects the level of breathing effort varied between the two pairs of scans gathered to assess reproducibility. In Ref. 18, the authors used differences in lung volume to normalize for breathing effort differences. As shown in Table III, some subjects had a significantly higher or lower breathing efforts in scan two than scan one. In this case, the gamma metric above would probably draw a low pass percentage because it becomes harder to find a similar ventilation value in the certain search space. The normalized gamma is introduced to normalize the $IJAC_{T_2 \circ T_0}$ to the scale of $IJAC_{T_1}$. As described in Ref. 18, since the average Jacobian should reflect the global volume change in the lung, the 0%EX and 100%IN lung volumes can be used as a global linear normalization factor to adjust for lung volume differences between scans one and two.

By definition, the Jacobian is the ratio of 100%IN volume and 0%EX volume in a specified region. Therefore for corresponding locations in scan one and scan two, we have the relation

$$\frac{JAC_1}{JAC_2} \sim \frac{\left(\frac{100\%INvolume}{0\%EXvolume}\right)_{scan1}}{\left(\frac{100\%INvolume}{0\%EXvolume}\right)_{scan2}}, \quad (15)$$

where JAC_1 and JAC_2 are Jacobian values at corresponding locations in $IJAC_{T_1}$ and $IJAC_{T_2 \circ T_0}$.

Then, the normalized gamma can be computed by Eq. (17) as

$$\hat{\gamma}(\vec{r}_2, \vec{r}_1) = \min_{\vec{r}_2} \left\{ \sqrt{\left(\frac{\vec{r}_2 - \vec{r}_1}{\Delta d_0}\right)^2 + \left(\frac{\hat{S}_2(\vec{r}_2) - S_1(\vec{r}_1)}{S_1(\vec{r}_1) \times \Delta p_0}\right)^2} \right\}, \quad (16)$$

where

$$\hat{S}_2 = S_2 \times \frac{\left(\frac{100\%INvolume}{0\%EXvolume}\right)_{scan1}}{\left(\frac{100\%INvolume}{0\%EXvolume}\right)_{scan2}}. \quad (17)$$

IV. RESULTS

IV.A. Pulmonary function estimates in animal model

Table II lists the lung volumes and the tidal volumes in two scans calculated for the three animal subjects in this study.

Figure 3 shows IJAC and TJAC color maps of the scan one ventilation estimate, the scan two ventilation estimate, the ratio map, and the gamma map for animal S-1. In the lung regions, nonpulmonary voxels outside the range [−999,

FIG. 3. IJAC (top) and TJAC (bottom) color maps of (left to right) scan one Jacobian, scan two Jacobian, Jacobian ratio, and gamma map for animal subject S-1. Parts of this figure were reproduced by permission from Du *et al.*, Med. Phys. 39, 1595–1608 (2012). Copyright 2012 American Institute of Physics.

−250] HU were not processed. As illustrated in Fig. 1, the ventilation map from scan two is transformed through the T_0 transformation to be converted into the coordinate system of scan one. The T_0 transformation allows the two ventilation images to be directly compared in the same coordinate framework and allows us to compute the voxel-by-voxel gamma comparison.

Figure 4(a) shows 2D kernel density estimates for the voxel-by-voxel scatter plot of the scan one and scan two IJAC data for one animal subject. The scatter plot is displayed with a color overlay that shows the density of joint cumulative distribution of the $IJAC_{T_1}$ and $IJAC_{T_2}$ data. Marginal histograms of the $IJAC_{T_1}$ and $IJAC_{T_2}$ data are plotted along the top and right side of the figures. Pearson's correlation coefficient was computed. Averaged across all animal subjects, the correlation coefficient is 0.367. Figure 4(b) is the Bland-Altman plot which shows the ratio of the two estimates versus the geometrical mean of two estimates. The solid line is the reference line that equals to one, representing perfect agreement in the two estimates. The dashed line is the average ratio in IJAC estimates. The scatter plot and Bland-Altman plot of TJAC for the same subject S-1 are shown in Figs. 4(c) and 4(d), adapted from Ref. 18. The axis of the scatter plots for IJAC and TJAC was set with the same scale for easier comparison. The statistical parameters for animal subjects are summarized in Table IV.

IV.B. Pulmonary function estimates in human subjects

Similar to Table II, Table III lists the lung volumes, tidal volumes in two scans for the ten human subjects in this study. Breathing effort variation is more apparent in the free-breathing humans compared to mechanically ventilated animals. The time intervals between two scans are also listed. Note that subject H-8 received the second scan 7 days after the first scan, which is substantially longer than the time difference for the other subjects.

Figures 5 and 6 show the coronal view of IJAC and TJAC for scan one ventilation, scan two ventilation, the ratio map and the gamma comparison map for human subjects H-2 and

FIG. 4. Reproducibility results for animal S-1. (a) IJAC density scatter plot and marginal histograms. (b) IJAC modified Bland-Altman plot. (c) TJAC density scatter plot and marginal histograms. (d) TJAC modified Bland-Altman plot. Parts of this figure were reproduced by permission from Du *et al.*, Med. Phys. **39**, 1595–1608 (2012). Copyright 2012 American Institute of Physics.

H-8. As with the animal subjects, the scan two ventilation image has been transformed into the coordinate system of scan one using the T0 transformation. Subjects H-2 and H-8 were selected to illustrate cases with good and poor reproducibility when comparing the scan one to scan two results, as in Ref. 18.

Similar to Fig. 4, Figs. 7 and 8 show the 2D kernel density estimates for the voxel-by-voxel scatter plot and Bland-Altman plot of the scans one and two for the two human subjects H-2 and H-8. Pearson's correlation coefficient was computed with an average correlation of 0.478 in all ten human subjects. For comparison purposes, we use identical scales in all of the plots for a given subject. All figures for the transformation-based ventilation in this paper were reproduced from Ref. 18.

Figure 9 shows one example subject to illustrate the differences between the inconsistent ventilation map ($\gamma > 1$) for

the IJAC and TJAC methods. Both maps are calculated after respiratory effort correction and use the same color scale. Regions that passed the gamma test ($\gamma \leq 1$) were not overlaid with color. Figure 9 shows the TJAC inconsistent ventilation regions are more focal and fewer in number than the IJAC inconsistent ventilation regions. Similar results were observed for the other nine human data sets. In several cases, TJAC defects were limited spatially to the lower lobes of the lung, while in all cases we observed IJAC inconsistent ventilation regions throughout the lung. In other words, TJAC reported changes in ventilation between scanning sessions that were physiologically clustered, primarily in the lower lobes where ventilation is greatest. Alternatively, IJAC reported changes in ventilation that were small in volume and distributed randomly in all lobes of the lung.

If the subject, image acquisition, image registration, and ventilation analysis were perfectly reproducible, the

TABLE IV. Summary of reproducibility statistics for three animal subjects and ten human subjects, for the intensity-based Jacobian, and the transformation-based Jacobian. The “Corr. Coef.” column shows correlation coefficients of two ventilation images, the “Pass” column shows the percentage of pass voxels in the gamma map, the “Pass Norm.” column shows the pass rate in normalized gamma map, and “JacRatio Std” column shows standard deviation of the Jacobian ratio map.

Subject	Intensity-based JAC				Transformation-based JAC			
	Corr. coef.	Pass (%)	Pass norm. (%)	JacRatio std	Corr. coef.	Pass (%)	Pass norm. (%)	JacRatio std
S-1	0.369	93.18	93.05	0.0628	0.922	100	100	0.0139
S-2	0.338	88.74	88.78	0.0737	0.843	99.63	99.60	0.0226
S-3	0.350	86.37	86.17	0.0628	0.887	99.84	99.84	0.0264
H-1	0.473	53.24	85.37	0.1206	0.937	69.74	99.09	0.0565
H-2	0.327	74.04	73.78	0.2037	0.811	99.05	99.10	0.0359
H-4	0.688	76.78	78.95	0.1363	0.860	85.28	90.48	0.0681
H-7	0.247	74.13	76.30	0.1869	0.570	92.80	94.55	0.0515
H-8	0.347	56.34	78.11	0.2281	0.894	67.80	90.99	0.0757
H-9	0.260	62.84	68.38	0.1832	0.772	79.10	93.41	0.0527
H-10	0.469	71.21	71.93	0.1319	0.820	88.53	90.59	0.0635
H-11	0.399	72.04	71.94	0.1564	0.755	88.29	89.56	0.0666
H-12	0.483	72.98	72.25	0.1675	0.850	87.82	88.11	0.0747
H-15	0.536	76.95	77.19	0.1083	0.849	97.47	97.46	0.0399

ventilation values computed from scan one and scan two would match exactly at each voxel, the gamma maps would be equal to zero, the correlation coefficients would be equal to one, and the standard deviation of the ratio map would be equal to zero. Table IV lists the statistics for intensity-based Jacobian, and transformation-based Jacobian. It summarizes statistical parameters including Pearson’s correlation coefficients, gamma pass rate, gamma pass rate after effort normalization, and standard deviation of the ratio map. Compared to the statistics table in Ref. 18, Table IV adds the gamma pass rates for the transformation-based Jacobian. Due to the thresholding of pulmonary parenchyma voxels, the ventilation map may have “holes,” therefore the standard deviation is calculated only for those voxels where $IJAC_{T1}$ and $IJAC_{T2}$ both have ventilation values. The reproducibility of the transformation-based Jacobian is described more completely in Ref. 18.

In Eq. (14), Δp_0 is the value tolerance criterion and Δd_0 is the distance tolerance criterion in the gamma metric. Both

relaxed Δp_0 and relaxed Δd_0 will increase the possibility for one voxel to find a similar ventilation value in the other map within a given neighborhood. Figure 10 shows the gamma pass percent for different Δp_0 for TJAC and IJAC with $\Delta d_0 = 4$ mm.

IV.C. Effects of low-pass filtering on reproducibility

To test how different levels of filtering affect reproducibility, we processed the data for all human subjects with different amounts of low-pass filtering applied to the CT images prior to registration. Figure 11 shows the effects of different levels of low-pass filtering on reproducibility for subject H-8. The top row shows the sagittal view of $IJAC_{T1}$ and the bottom row shows the smoothed color density scatter plots. Ordered left to right, the smoothing kernel sizes for filtering on the original CT images are $7 \times 7 \times 7$, $11 \times 11 \times 11$, and $15 \times 15 \times 15$ voxels.

FIG. 5. IJAC (top) and TJAC (bottom) color maps of (left to right) scan one Jacobian, scan two Jacobian, Jacobian ratio, and gamma map for human subject H-2. Parts of this figure were reproduced by permission from Du *et al.*, Med. Phys. **39**, 1595–1608 (2012). Copyright 2012 American Institute of Physics.

FIG. 6. IJAC (top) and TJAC (bottom) color maps of (left to right) scan one Jacobian, scan two Jacobian, Jacobian ratio, and gamma map for human subject H-8. Parts of this figure were reproduced by permission from Du *et al.*, Med. Phys. **39**, 1595–1608 (2012). Copyright 2012 American Institute of Physics.

FIG. 7. Reproducibility results for human subject H-2. (a) IJAC density scatter plot and marginal histograms. (b) IJAC modified Bland-Altman plot. (c) TJAC density scatter plot and marginal histograms. (d) TJAC modified Bland-Altman plot. Parts of this figure were reproduced by permission from Du *et al.*, Med. Phys. **39**, 1595–1608 (2012). Copyright 2012 American Institute of Physics.

Figure 12 shows change of average gamma pass percent and average correlation coefficient for all human subjects with different levels of low-pass filtering on the original CT images. The horizontal axis shows the neighborhood radius in local averaging. The solid line in blue shows the gamma pass percent for IJAC, and the gamma pass percent for TJAC is also drawn in blue dashed line for comparison. The green dotted line shows the correlation coefficient for IJAC, and the green dashed line on the top shows the correlation coefficient for TJAC.

V. DISCUSSION

In this study, we examined the reproducibility of the intensity-based estimate of ventilation using two separate 4DCT image sets within a short interval between acquisitions. We compared these results to those from a transformation-

based estimate of ventilation. Mechanically ventilated sheep and human subjects prior to receiving radiation therapy were studied. Since neither the ratio nor difference is appropriate for reproducibility evaluation of intensity-based ventilation, we introduced the gamma indices which consider both ventilation differences and distance to agreement. A normalization strategy was used to compensate for different breathing efforts in the two 4DCT acquisitions. In both intensity-based and transformation-based ventilation, we found the reproducibility obtained in anesthetized, mechanically ventilated animals is slightly better than for the spontaneously breathing humans. All statistical parameters, including correlation coefficients, gamma pass percentage, and standard deviation of ratio map, indicate the reproducibility of intensity-based ventilation is worse than that of transformation-based ventilation. The reproducibility of the human IJAC maps showed as correlation coefficients 0.45 ± 0.14 , gamma pass rate 70 ± 8

FIG. 8. Reproducibility results for human subject H-8. (a) IJAC density scatter plot and marginal histograms. (b) IJAC modified Bland-Altman plot. (c) TJAC density scatter plot and marginal histograms. (d) TJAC modified Bland-Altman plot. Parts of this figure were reproduced by permission from Du *et al.*, Med. Phys. **39**, 1595–1608 (2012). Copyright 2012 American Institute of Physics.

without normalization and 75 ± 5 with normalization. The reproducibility of the human TJAC maps showed as correlation coefficients 0.81 ± 0.10 , gamma pass rate 86 ± 11 without normalization, and 93 ± 4 with normalization. To study the impact of noise from the original CT images on the final intensity-based ventilation map, we developed analytical models and investigated reproducibility improvement with increased filtering on the CT images. We found that the low-pass filtering in intensity-based ventilation calculation can help to remove extreme ventilation values, however the increase of reproducibility is limited, and the spatial resolution of the resulting ventilation map is reduced.

Figure 3 shows the reproducibility of the calculated intensity-based Jacobian in the animal model. Though the patterns appear similar, there are still considerable regional differences between $IJAC_{T1}$ and $IJAC_{T2 \circ T0}$. The original-repeat scan voxel-by-voxel correlation coefficients for IJAC range

from 0.369 to 0.350 for these animals. Figure 4 compares the reproducibility of IJAC and TJAC. We can see the scatter plot of IJAC is more dispersed than that of TJAC. While the scatter distribution of TJAC converges well to the regression line, the linearity of IJAC almost disappears. Since these subjects are anesthetized and mechanically ventilated animals, they likely represent the best possible case in terms of ventilation map reproducibility.

Figures 5 and 6 show examples of data from human subjects with good and poor reproducibility based on the statistical parameters in Table IV. Table III shows that subject H-2 has more consistent lung volumes and tidal volumes than subject H-8. If H-8 has poor reproducibility because of variations in lung volumes and tidal volumes, it may reveal that ventilation regions are not consistently distributed under different pressures. Figures 7 and 8 show the IJAC vs TJAC comparison of scatter plots for subject H-2 and H-8. As shown in Table III,

FIG. 9. Colored panel shows the differences between the scattered distribution of inconsistent ventilation estimate in IJAC and the clustering of those inconsistencies in TJAC for subject H-7. The gamma maps were calculated after respiratory effort normalization. Color scales are shown on the right.

subject H-8 had a greater expansion in scan two than in scan one, and it is easy to see that this respiratory effort difference is clearly reflected in mass center of scatter points over the reference line $y = x$ in both IJAC and TJAC. These scatter plots and histograms clearly show that the reproducibility of IJAC is worse than that of TJAC. With the same data, processing, and registration algorithm, the poor reproducibility performance of intensity-based ventilation may be due to the high noise sensitivity of the calculation itself.

Table IV lists statistical parameters for evaluating reproducibility. From Table III, we see that H-4 had an inter-scan interval of 20 h and H-8 had an inter-scan interval of 7 days,

which is much longer than that for any of the other subjects. However, we do not see any noticeable difference in reproducibility for these two subjects compared to the others. The global linear normalization using lung volumes¹⁸ can offset the effects of different respiratory efforts in the two 4DCT scans and scale the ventilation values of scan two to the same range of scan one. Higher gamma pass rate is found after normalization as shown in Table IV. The correlation coefficient between two Jacobian maps and the standard deviation of Jacobian ratio map for IJAC are several times worse than those for TJAC. For all subjects, the gamma pass percentage of IJAC is lower than that of TJAC even after breathing effort normalization. Even though it is known that lung expansion and contraction are not uniform apex to base and ventral to dorsal,¹⁸ the subject-specific normalization used to compensate for varying effort between studies in Eq. (17) is a useful normalization scheme in this situation to compare ventilation maps across scans and calculate gamma indices across subjects. More sophisticated approaches for normalizing for differences in tidal volume may provide even better results, and this is an area of active research.

Recently Yamamoto *et al.*¹⁹ also investigated the reproducibility of ventilation, using two cohorts of patients imaged over two different inter-scan intervals. A transformation-based metric ($\text{TJAC} - 1$) was used to represent volume change. Moderate voxel-based correlation was reported between two ventilation images (Spearman rank correlation 0.50 ± 0.15). However, we reported correlation coefficients 0.81 ± 0.10 for the human TJAC ventilation estimate. We speculate that reproducibility can be influenced by many factors, such as image acquisition parameters, patient motion control, variations in respiratory rates and pattern, image registration, and ventilation metrics. They found respiratory variation during 4DCT scans would deteriorate the reproducibility, which is consistent with our observation.

Figure 9 shows that regions of inconsistent ventilation are more numerous and spatially distributed for the

FIG. 10. The gamma pass percent changes with different Δp_0 in Eq. (14) for the intensity-based Jacobian, IJAC, and, the transformation-based Jacobian, TJAC. (a) Average of three sheep data sets with normalization; (b) Average of ten human data sets with normalization.

FIG. 11. Effects of increased low-pass filtering on reproducibility for subject H-8. The top row shows the sagittal view of $IJAC_{T1}$ and the bottom row shows the smoothed color density scatter plots. Ordered left to right, the local average kernel sizes for filtering on the original CT images are $7 \times 7 \times 7$, $11 \times 11 \times 11$, and $15 \times 15 \times 15$ voxels. Histograms and summary statistics are given along the top and right side of each plot. Colorscale is same as in Fig. 4.

intensity-based Jacobian compared to the transformation-based Jacobian. In addition, the data in Table IV and Fig. 10 show that the total number of voxels with $\gamma > 1$ is less for the transformation-based approach compared to the intensity-based approach. This may be due to the increased noise sensitivity of the intensity-based method compared to the transformation-based approach. Upon visual inspection of Fig. 9 it appears substantial disagreement is near the blood vessels and airways, which suggests that careful segmentation of blood vessels and airways may reduce the inconsistencies in the ventilation map for the IJAC method. To track changes in ventilation in a longitudinal study, it is important for the ventilation estimate methods to be reproducible and as robust to noise as possible. While we observed similar results to those as shown in Fig. 9 for all human subjects, a more complete and quantitative evaluation of the spatial distribution of the inconsistent ventilation regions needs to be performed before drawing any final conclusions.

Compared to transformation-based ventilation, which is directly calculated from the deformation gradient tensor, the intensity-based ventilation approach is derived from both the deformation and intensities of involved CT images. Castillo *et al.*¹⁶ showed visual and quantitative differences between TJAC and intensity-based SAC. They also concluded that the intensity-based method showed better spatial correction with the clinical standard of nuclear medicine exams. Mathematically, both ventilation approaches make use of deformable image registration. After the displacement field is estab-

lished, the transformation-based Jacobian is directly calculated, while the intensity-based method uses the original CT images for intensity information, which may introduce additional noise. Therefore, the TJAC is influenced by image registration error; however, intensity-based method is influenced by both registration error and CT intensity noise. The analytical error analysis of the SAC and IJAC shows the impact of CT noise on these ventilation estimates may be large and should not be neglected. As shown in Table IV, for all subjects the gamma pass rate of the TJAC maps is much higher than that of the IJAC maps.

Equation (8) provides a way to link the SAC and Jacobian, which have different definitions and quantities to show tissue expansion as described in Sec. II. The conversion from SAC to IJAC puts the intensity-based ventilation into the same units as TJAC and makes it easier for direct comparison. Since the intensity-based ventilation metrics can be converted from one to another, the reproducibility results of the SAC and IJAC in this paper are representative of all ventilation metrics using the intensity-based strategy.

Due to the overlay of pulmonary parenchyma mask $[-999, -250]$ to the ventilation computation, not all lung locations are allocated a ventilation value. Combined with this nonlinearity and existence of zero values, these restrictions limit the application of ratio or difference metric for direct validation of regional ventilation. We introduce the gamma index to address the problem of mismatch by considering neighborhood voxels in a certain distance. From Fig. 10, we can see for

FIG. 12. Change of mean gamma pass percent and mean correlation coefficient for ten human subjects with low-pass filtering on original CT images with different smoothing kernel sizes. The horizontal axis shows the neighborhood radius for filtering, where smooth radius 0 means no filtering, radius 3 means kernel size $7 \times 7 \times 7$, etc. The solid line in blue shows the gamma pass percent for IJAC, and the gamma pass percent for TJAC is also drawn as the blue dashed line for comparison. The green dotted line shows the correlation coefficient for IJAC, and the green dashed line on the top shows the correlation coefficient for TJAC.

both sheep and human subjects, the gamma pass percentage of IJAC is always lower than that of TJAC for different criterion Δp_0 . Take the human subjects in Fig. 10(b), for example, to achieve as good pass percentage as TJAC at $\Delta p_0 = 0.1$, the criterion Δp_0 for IJAC has to be relaxed to as high as 0.3, indicating the worse reproducibility of IJAC. When Δp_0 changes from zero to infinitely large, the gap between IJAC and TJAC gamma pass percentage first increases and then decreases. The Δp_0 that corresponds with the maximum gap may represent the fluctuation percentage of intensity-based ventilation caused by CT HU noise. Another noteworthy phenomenon can be found in Figs. 10(a) and 10(b) when Δp_0 is extremely small, e.g., less than 0.02, the gamma pass percentage of IJAC is higher than that of TJAC. This might be explained that in the case of when Δp_0 is small, in fact the fluctuation in IJAC map helps the gamma index algorithm find similar ventilation values in the neighborhood in the other map, if we imagine scans one and two ventilation maps as two distributions of values with slightly biased centers.

Figure 11 shows IJAC_{T1} ventilation map and scatter plots after different levels of local averaging on original CT images involved in IJAC computation. Compared to Fig. 6, the IJAC map appears more smooth with heavier smoothing. However, the pattern of scatter plots does not change much except noise is suppressed partly with increased smoothness. As shown in Fig. 12, the gamma pass percentage and correlation coefficient of IJAC did increase gradually with smoothing, but still much lower than the parameters of TJAC even with ex-

tremely heavy smoothness like kernel size $15 \times 15 \times 15$. When increasing the smoothing radius from 1 to 7 voxels, the pass rate and correlation coefficient of intensity-based ventilation estimates increased modestly, i.e., only 25% of the difference between them and the transformation-based results. Moreover, increased filtering may cause that small, but important, variations in regional ventilation are lost by the filtering operation.

VI. CONCLUSION

In this paper, we examined the reproducibility of two intensity-based ventilation metrics as an estimate of lung function and compared them with a transformation-based estimate of ventilation. The transformation-based ventilation maps show better reproducibility than the intensity-based maps, especially in human subjects, when comparing the correlation coefficients and the gamma index. Reproducibility was also found to depend on changes in respiratory effort; all techniques were better when normalization for changes in tidal volume were applied to images from mechanically ventilated sheep compared to spontaneously breathing human subjects. Nevertheless, intensity-based techniques applied to mechanically ventilated sheep were less reproducible than the transformation-based applied to spontaneously breathing humans, suggesting the method used to determine ventilation maps is important. We have developed an analytical model of how CT image noise affects the intensity-based ventilation. Prefiltering of the CT images may help to improve the reproducibility of the intensity-based ventilation estimates, but even with filtering the reproducibility of the intensity-based ventilation estimates is not as good as that of transformation-based ventilation estimates. When increasing the smoothing radius from 1 to 7 voxels, the pass rate and correlation coefficient of intensity-based ventilation estimates increased modestly, i.e., only 25% of the difference between them and the transformation-based results. The pass rate of gamma index, which is specially designed for validation of intensity-based ventilation, and other statistical parameters show transformation-based Jacobian is more reproducible than intensity-based Jacobian. The superior reproducibility of the transformation-based technique appears to allow smaller changes in ventilation to be detected; a 10% change in ventilation was observed between estimates of ventilation derived from repeat scans <10% of the voxels, compared to $\sim 30\%$ of the voxels when intensity-based techniques are used.

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APPENDIX A: ALTERNATE DERIVATION METHOD OF INTENSITY-BASED JACOBIAN AND ITS RELATION WITH SAC

First, we are going to show the alternate derivation of Eq. (7). From the definition of SAC, we have

$$\begin{aligned} \text{SAC} &= \frac{\Delta V_{\text{air}}}{V_{\text{air},1}} \\ &= \frac{V_{\text{air},2} - V_{\text{air},1}}{V_{\text{air},1}} \\ &= \frac{V_{\text{air},2}}{V_{\text{air},1}} - 1 \\ &= \frac{V_2 f_2}{V_1 f_1} - 1. \end{aligned}$$

If we define the volume ratio, VR, as

$$\text{VR} = \frac{V_2}{V_1}.$$

We can get the same result as Eq. (7),

$$\text{SAC} + 1 = \frac{f_2}{f_1} \text{VR}.$$

We can explore further about this. From Simon's and Hoffman's work,²²⁻²⁴ if we assume that there is no tissue volume change between conditions 1 and 2, then $V_{\text{tissue}} = V_{\text{tissue},1} = V_{\text{tissue},2}$, we have

$$\begin{aligned} f_1 &= \frac{\text{HU}_{\text{tissue}} - \text{HU}_1}{\text{HU}_{\text{tissue}} - \text{HU}_{\text{air}}} \\ f_2 &= \frac{\text{HU}_{\text{tissue}} - \text{HU}_2}{\text{HU}_{\text{tissue}} - \text{HU}_{\text{air}}} \end{aligned}$$

then from Eq. (B1), we have

$$\text{SAC} + 1 = \frac{\text{HU}_{\text{tissue}} - \text{HU}_2}{\text{HU}_{\text{tissue}} - \text{HU}_1} \text{VR}.$$

If we assume the air is -1000 HU and the tissue is 0 HU, then

$$\text{SAC} + 1 = \frac{\text{HU}_2}{\text{HU}_1} \text{VR}.$$

Second, we will show the alternate derivation of Eq. (10).

If we assume $V_{\text{tissue}} = V_{\text{tissue},1} = V_{\text{tissue},2}$, then

$$\begin{aligned} \text{VR} &= \frac{V_2}{V_1} \\ &= \frac{V_{\text{tissue}} + V_{\text{air},2}}{V_{\text{tissue}} + V_{\text{air},1}} \\ &= \frac{1 + \frac{V_{\text{air},2}}{V_{\text{tissue}}}}{1 + \frac{V_{\text{air},1}}{V_{\text{tissue}}}} \\ &= \frac{1 + \frac{V_2 \left(-\frac{\text{HU}_2}{1000} \right)}{V_2 \left(1 - \left(-\frac{\text{HU}_2}{1000} \right) \right)}}{1 + \frac{V_1 \left(-\frac{\text{HU}_1}{1000} \right)}{V_1 \left(1 - \left(-\frac{\text{HU}_1}{1000} \right) \right)}} \\ &= \frac{1000 + \text{HU}_1}{1000 + \text{HU}_2}, \end{aligned}$$

which is exactly the same as Eq. (10).

APPENDIX B: ANALYTICAL ANALYSIS OF NOISE IN INTENSITY-BASED SAC

The propagation of errors for the general function $x = f(u, v)$ is given by the relation³⁵

$$\sigma_x^2 = \sigma_u^2 \left(\frac{\partial x}{\partial u} \right)^2 + \sigma_v^2 \left(\frac{\partial x}{\partial v} \right)^2 + 2\sigma_{uv}^2 \left(\frac{\partial x}{\partial u} \right) \left(\frac{\partial x}{\partial v} \right). \quad (\text{B1})$$

We can evaluate the propagation of CT image noise to the noise of intensity-based SAC using Eq. (B1). To simplify the analysis, we assume the transformation from the fixed image to the moving image is the identity transformation. Since I_f and I_m are images obtained from two separate acquisitions, they can be assumed to be independent, and thus the covariance term in Eq. (B1) is zero.³⁵ In fact, even if I_f and I_m are not truly independent, the covariance terms are usually one to two orders of magnitude smaller than the variance terms.³⁵

From Eq. (4), if we let $u = I_f$, $v = I_m$, and $x = \frac{\Delta V}{V_f}$, then we have

$$x = \frac{1000(v - u)}{u(v + 1000)},$$

and then,

$$\begin{aligned} \frac{\partial x}{\partial u} &= \frac{-1000u(v + 1000) - 1000(v - u)(v + 1000)}{(u(v + 1000))^2} \\ &= \frac{-1000v}{u^2(v + 1000)}, \end{aligned}$$

$$\begin{aligned} \frac{\partial x}{\partial v} &= \frac{1000u(v + 1000) - 1000(v - u)u}{(u(v + 1000))^2} \\ &= \frac{1000(u + 1000)}{u(v + 1000)^2}. \end{aligned}$$

If we assume the CT noise variance in the fixed image and the moving image to be the same, we have $\sigma_u^2 = \sigma_v^2 = \sigma_{\text{CT}}^2$, and,

$$\begin{aligned} \sigma_{\text{SAC}}^2 &= \sigma_x^2 = \sigma_u^2 \left(\frac{\partial x}{\partial u} \right)^2 + \sigma_v^2 \left(\frac{\partial x}{\partial v} \right)^2 \\ &= \sigma_{\text{CT}}^2 \left(\left(\frac{\partial x}{\partial u} \right)^2 + \left(\frac{\partial x}{\partial v} \right)^2 \right) \\ &= \sigma_{\text{CT}}^2 \left(1000^2 \frac{u^2(u + 1000)^2 + v^2(v + 1000)^2}{u^4(v + 1000)^4} \right). \end{aligned}$$

The impact of CT noise on the CV of SAC is

$$\begin{aligned} \frac{\sigma_x}{\mu_x} &= \frac{\sigma_{\text{CT}} \sqrt{1000^2 \frac{u^2(u + 1000)^2 + v^2(v + 1000)^2}{u^4(v + 1000)^4}}}{\frac{1000(v - u)}{u(v + 1000)}} \\ &= \sigma_{\text{CT}} \frac{\sqrt{u^2(u + 1000)^2 + v^2(v + 1000)^2}}{u(v - u)(v + 1000)}. \end{aligned}$$

APPENDIX C: ANALYTICAL ANALYSIS OF NOISE IN INTENSITY-BASED JACOBIAN

Similar to the analytical analysis of noise in intensity-based SAC in Appendix B, we can use the same error propagation theory on intensity-based Jacobian. Similarly, we assume the transformation from the fixed image to the moving image is the identity transformation to ignore the covariance term in Eq. (B1). From Eq. (10), if we let $u = I_f$, $v = I_m$, and use IJAC as the intensity-based Jacobian, then we have

$$\text{IJAC} = \frac{u + 1000}{v + 1000},$$

and then,

$$\frac{\partial \text{IJAC}}{\partial u} = \frac{1}{v + 1000},$$

$$\begin{aligned} \frac{\partial \text{IJAC}}{\partial v} &= \frac{(v + 1000) - (u + 1000)}{(v + 1000)^2} \\ &= \frac{v - u}{(v + 1000)^2}. \end{aligned}$$

If we assume the CT noise variance in the fixed image and the moving image to be the same, we have $\sigma_u^2 = \sigma_v^2 = \sigma_{\text{CT}}^2$, and,

$$\begin{aligned} \sigma_{\text{IJAC}}^2 &= \sigma_u^2 \left(\frac{\partial \text{IJAC}}{\partial u} \right)^2 + \sigma_v^2 \left(\frac{\partial \text{IJAC}}{\partial v} \right)^2 \\ &= \sigma_{\text{CT}}^2 \left(\left(\frac{\partial \text{IJAC}}{\partial u} \right)^2 + \left(\frac{\partial \text{IJAC}}{\partial v} \right)^2 \right) \\ &= \sigma_{\text{CT}}^2 \left(\frac{(v + 1000)^2 + (v - u)^2}{(v + 1000)^4} \right). \end{aligned}$$

The impact of CT noise on the CV of IJAC is

$$\begin{aligned} \frac{\sigma_{\text{IJAC}}}{\mu_{\text{IJAC}}} &= \frac{\sigma_{\text{CT}} \sqrt{\frac{(v+1000)^2 + (v-u)^2}{(v+1000)^4}}}{\frac{u+1000}{v+1000}} \\ &= \sigma_{\text{CT}} \frac{\sqrt{(v+1000)^2 + (v-u)^2}}{(u+1000)(v+1000)}. \end{aligned}$$

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