Comparison of ^{133}Xe Xenon Ventilation Equilibrium Scan (XV) and $^{99\text{m}}\text{Tc}$ Technetium Transmission (TT) Scan for Use in Regional Lung Analysis by 2D Gamma Scintigraphy in Healthy and Cystic Fibrosis Lungs

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Abstract

Background: Quantification of particle deposition in the lung by gamma scintigraphy requires a reference image for location of regions of interest (ROIs) and normalization to lung thickness. In various laboratories, the reference image is made by a transmission scan (^{57}Co or $^{99\text{m}}\text{Tc}$) or gas ventilation scan (^{133}Xe or ^{81}Kr). There has not been a direct comparison of measures from the two methods.

Methods: We compared $^{99\text{m}}\text{Tc}$ transmission scans to ^{133}Xe equilibrium ventilation scans as reference images for 38 healthy subjects and 14 cystic fibrosis (CF) patients for their effects on measures of regional particle deposition: the central-to-peripheral ratio of lung counts (C/P); and ROI area versus forced vital capacity. Whole right lung ROI was based on either an isocontour threshold of three times the soft tissue transmission (TT) or a threshold of 20% of peak xenon ventilation counts (XV). We used a central ROI drawn to 50% of height and of width of the whole right lung ROI and placed along the left lung margin and centered vertically.

Results: In general, the correlation of normalized C/P (nC/P) between the two methods was strong. However, the value of nC/P was significantly smaller for the XV method than the TT method. Regression equations for the relationship of nC/P between the two methods were, for healthy subjects, $y=0.75x+0.61$, $R^2=0.64$ using rectangular ROIs and $y=0.76x+0.45$, $R^2=0.66$ using isocontour ROIs; and for CF patients, $y=0.94x+0.46$, $R^2=0.43$ and $y=0.85x+0.42$, $R^2=0.41$, respectively.

Conclusions: (1) A transmission scan with an isocontour outline in combination with a rectangular central region to define the lung borders may be more useful than a ventilation scan. (2) Close correlation of nC/Ps measured by transmission or gas ventilation should allow confident comparison of values determined by the two methods.

Key words: scintigraphy, regions of interest, aerosol deposition, C/P

Introduction

GAMMA CAMERA SCINTIGRAPHY is useful for studying the deposition of particles within the respiratory airways and their subsequent clearance.^(1,2) Usually in deposition studies, the liquid or powder substance under study is admixed with a radioactive atom or moiety and aerosolized. The aerosolized admixture is then inhaled with defined breathing patterns to deposit in airways of interest. However, the resulting deposition pattern measured by two-dimensional (2D) gamma scintigraphy may not necessarily coincide with the

actual boundary and thickness of the lung, making interpretation of the image difficult. Therefore, another reference image capable of defining the lung boundary is needed to determine these parameters. The reference image is then co-registered with the particle deposition image for definition of lung boundary and correction of lung thickness.

Typically, two types of reference images have been considered: radioactive gas ventilation and transmission through the subject from a radioactive source. Each has its particular advantages and disadvantages. On the one hand, a gas fills the lung to produce an image with pixel counts nearly

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proportional to the thickness of the lung, with points of emission within the lung similar to that emitted by the particles measured. This is valid when the ventilated gas is at equilibrium at all points within the lung airspace. But this may not always be the case. For example, a gas with a short half-life ($^{81\text{m}}\text{Kr}$) will decay before equilibrating into the distal volume or into poorly ventilated lung regions. Even a gas with a longer half-life (^{133}Xe) may not quickly equilibrate into lung regions with obstructed airways or with very high compliance compartments. On the other hand, transmission of a radioactive source through the subject produces a density image through the entire thickness of the chest, independent of gas-flow heterogeneities, proportional only to the density of the tissue through which it attenuates. This includes attenuation through both chest walls, whereas the labeled particles used for deposition measurements emit through only one.

The Product Quality Research Institute and the International Society for Aerosols in Medicine have recently advocated for the development of standardized protocols for acquisition and analysis of the distribution of particle deposition in the respiratory tract for both scientific and regulatory purposes. Standardization would also allow for laboratories to better compare results and to collaborate on multisite studies. There has not been a systematic paired comparison of the two methods, gas ventilation and transmission, by which to make a considered decision as to which is more useful and practical to be part of such a standardized protocol.

For over 20 years, this laboratory and others have used the xenon ventilation equilibrium scintigraphy scan as the basis for determining lung outline and for normalization to lung volume in measures of regional lung deposition and mucociliary clearance. With the advent of recent studies performed in our newer facilities that preclude the use of the gaseous xenon method, the transmission scan was substituted for the xenon scan. Many arguments pro and con for each method have been discussed, but there has been no direct evidence collected for the two methods for making an objective comparison. How, and to what degree, the two methods affected the calculations for regional particle deposition and clearance were unknown. Additionally, researchers in the field of imaging lung deposition and clearance have been setting the stage for developing a standardized method for the determination of lung outline and normalization to volume. Therefore, this study was proposed to provide the data to enable a better comparison of the two methods for a decision of standardizing the method. However, it was not designed to select which method would be best for standardizing protocols. Regulatory and advisory committees for which these methods might provide supporting data for approval of orally inhaled products and their devices must reach consensus on such recommendations.

This study directly compares the two methods in a pairwise fashion using ^{133}Xe equilibrium gas ventilation images (XV) and $^{99\text{m}}\text{Tc}$ transmission images (TT) in a group of healthy subjects and a group with impaired lung function [mild cystic fibrosis (CF)]. Comparisons included: a central-to-peripheral ratio of particles deposited in the right lung (C/P) as an index of regional heterogeneity, and a comparison of 2D area of lung determined from

scintigraphic images versus subjects' lung volume measured by spirometry [forced vital capacity (FVC)].

Materials and Methods

Subjects

Thirty-eight nonsmoking healthy volunteers (H) (27 male, 11 female) aged 18–44 years (mean 26) and 14 subjects with diagnosed CF (9 male, 5 female) aged 21–37 years (mean 25 years) were recruited to participate in the study.

All subjects received a medical exam on a separate screening day prior to beginning the study and were free of upper or lower respiratory tract infections for 4–6 weeks prior to beginning the study. Forced expiratory volume in 1 sec (FEV₁) and FVC were obtained by spirometry (Pulmo-Screen IIE System, model VRS2000; S&M Instrument Company, Doylestown, PA). The healthy subjects had an FEV₁ greater than 80% of predicted values (average $103 \pm 13\%$). The CF patients had an FEV₁ greater than 50% of predicted (average $77 \pm 17\%$). The study protocol was approved by the University of North Carolina's Committee on the Protection of Rights of Human Subjects, and informed consent was obtained from each subject. After the initial screening and evaluation visit, the subjects returned for a separate experimental visit to include a ^{133}Xe equilibrium ventilation scan, a $^{99\text{m}}\text{Tc}$ transmission scan, and a $^{99\text{m}}\text{Tc}$ -radiolabeled aerosol deposition scan described below.

$^{99\text{m}}\text{Tc}$ Technetium reference transmission scans (TT)

The subject was seated upright with back against a BodyScan (MieAmerica, Forest Hills, IL) 400 mm width by 610 mm height gamma camera face while the gamma camera acquisition was operated in persistence mode at 128×128 resolution. To keep the subject's position constant, a pencil laser pointer mounted on a far wall was directed as a spot on a marked area near the subject's sternal notch. A mirror was placed within view of the subject to observe the spot for maintaining position. To develop the transmission image, a double-walled Lucite container with a circular space between the walls 43 cm in diameter and 1.3 cm thick was filled with water containing 2 mCi/74 MBq of $^{99\text{m}}\text{Tc}$ and placed in front of the subject approximately 15 inches from, and parallel to, the gamma camera face. A static image approximately 90 sec in duration was acquired by the camera. The amount of $^{99\text{m}}\text{Tc}$ used in the phantom and the time of exposure were chosen to approximate the resolution of the lower range of the xenon ventilation exposure. After acquisition, the $^{99\text{m}}\text{Tc}$ source was removed to a shielded location away from the camera. The transmission scan was performed first to preclude any interference from dissolved xenon in the bloodstream.

Xenon ventilation reference scans (XV)

The subject was seated and marked by location similarly as with the transmission scan. The subject was placed on a mouthpiece attached to a Pulmonex model 130-502 xenon ventilation system (Shirley, NY). The contents of one or two 1-mL vials of ^{133}Xe gas (typically 10 mCi/370 MBq total) were injected into the breathing circuit and allowed to circulate until equilibrium mixing was inferred by observation of constant count rates in the lungs by the camera in

persistence mode, usually around 10 breaths (30 sec).⁽¹⁾ At equilibrium, the gamma camera was switched from persistence to dynamic acquisition (32 frames at 6 sec each). At the end of the fourth frame, the xenon ventilation system valve was switched to washout mode to remove the ^{133}Xe gas from the circuit and replace it with clean air. The subject continued to breathe clean air until the 32 frames were completed. After completion, the xenon ventilation system was removed to a location away from the camera.

Radioaerosol inhalation

The $^{99\text{m}}\text{Tc}$ transmission scan and ^{133}Xe equilibrium ventilation scan were obtained prior to a radiolabeled aerosol inhalation. A background image (in the $^{99\text{m}}\text{Tc}$ energy window) of the subject was taken immediately following the ^{133}Xe scan. Sulfur colloid particles radiolabeled with $^{99\text{m}}\text{Tc}$ ($^{99\text{m}}\text{Tc}$ -SC) were prepared from Technescan Sulfur Colloid Kits (CIS-Sulfur Colloid, CIS-US, Inc., Bedford, MA) at the UNC Hospitals, Chapel Hill, NC, radiopharmacy following the procedure provided by the manufacturer. The sub-micrometer [$0.22\ \mu\text{m}$, geometric stand deviation (GSD) 1.75] $^{99\text{m}}\text{Tc}$ -SC particles⁽³⁾ are insoluble and suspended in a normal saline solution for delivery by DeVilbiss 646 jet nebulizers (DeVilbiss Healthcare, Somerset, PA). Breathing patterns during aerosol inhalation were controlled after training the subjects to follow feedback signals. Two milliliters of the $^{99\text{m}}\text{Tc}$ -SC particle suspension (5 mCi/185 MBq) were placed in a DeVilbiss 646 jet nebulizer [aerosol size of $5.4\ \mu\text{m}$ mass median aerodynamic diameter (MMAD), GSD 1.8 by Malvern Mastersizer S (Malvern Instruments USA, Westborough, MA)] for the controlled inhalation by the subjects.

To deposit the radiolabeled particles, the subjects inhaled from the nebulizer by mimicking a shallow cyclic breathing pattern of 0.5 L/sec peak flow rate at a frequency of 30 breaths/min, 50% duty cycle, following a lighted graduated flow signal and metronome. The breathing pattern was displayed and recorded from a pneumotachograph attached directly downstream to the nebulizer. Further downstream of the pneumotachograph, a 12-inch tubing was connected to a Spira Electro2 Inhalation Dosimeter (Respiratory Care Center, Hämeenlinna, Finland). Nebulizer operation and a lighted display of the flow rate to the subject were provided by the dosimeter. The dosimeter directed the compressor actuation air (DeVilbiss Pulmo-Aide, Model 5610D) to the nebulizer for 0.7-sec duration after a 100-mL delay of inhalation onset at the beginning of each 50% duty cyclic breath (see Zeman *et al.*⁽⁴⁾ for schematic of equipment configuration). Inhalation continued until approximately 30–40 μCi /1–1.5 MBq of $^{99\text{m}}\text{Tc}$ was detected within the field of a single 2-inch NaI single crystal scintillation detector placed at the back (less than approximately 2 min of continuous breathing). Activity deposited in the mouth was swallowed to the stomach by a small drink of water prior to camera acquisition. This was followed immediately, less than 2-min delay from end of inhalation, by a 2-min gamma camera scan of the subject's lungs to measure regional particle deposition. Subject's inhalation and imaging were performed seated upright. The laser pointer was positioned on the subject's chest similar to the xenon and transmission scans to provide a visual cue to help maintain a constant position in the camera field.

Image analysis

Gamma camera counts were determined from the DICOM images using ImageJ 1.45s image analysis software (Wayne Rasband, National Institutes of Health, Bethesda, MD) and Excel (Microsoft Excel for Mac 2011, v.14.14). For all images, the camera acquisition resolution was set at 128 by 128, physical pixel size 4.77 by 4.77 mm. Regions of interest (ROIs) were manually drawn independently for the XV and TT methods using a rectangular and an isocontour ROI around the whole right lung. For these paired comparisons, attenuation and scattering corrections of the deposition images were not used.

To investigate the effect of using filtered image processing, the 14 CF patients were independently analyzed after a single-pass smoothing of the raw images.

For the XV analysis, the first four images of the xenon scan representing 24 sec were summed. An isocontour whole right lung ROI was drawn at 20% of the right lung peak pixel value (average of highest three pixels) with the medial edge of the ROI limited to four pixels to the midline. A rectangular whole right lung ROI was drawn that circumscribed the isocontour ROI. From this ROI, a central rectangular ROI was derived that was half-height and half-width (expanded to include whole pixel) and centered vertically on the medial border, *i.e.*, 25% of the whole right lung ROI. This central ROI was used for both the isocontour and rectangular ROI analysis.

For the TT analysis (see Fig. 1), a small (approximately 5 cm wide by 3 cm height) ROI was centered over the lower abdomen to obtain the soft tissue-attenuated counts (soft body background) for locating the lung edges. The mean pixel count within this region was multiplied by 3 and rounded to next highest integer to obtain the pixel value needed to draw an isocontour ROI of the whole right lung. Due to the ragged noisy nature of the isocontour at the lung edges, "islands" and "peninsulas" of counts extending inside and outside a smooth continuous isocontour line were ignored. The medial edge of the ROI was set at four pixels from the midline. Due to the small distance between the upper lateral border of the right lung and the edge of the shoulder, counts passing over the shoulder interfere with the lung counts near this area. A lung border was estimated through this area by tracing through a "valley" of minimum

FIG. 1. A $^{99\text{m}}\text{Tc}$ transmission image from a healthy subject (01CFS) illustrates the derivation of whole lung ROIs for $^{99\text{m}}\text{Tc}$ transmission (TT) analysis. (A) A small ROI over the lower abdominal region is used to find typical soft tissue values. (B) An isocontour ROI with a lower cutoff value three times above the soft tissue value is made around the right whole lung. (C) A whole lung rectangular ROI circumscribes the isocontour ROI.

FIG. 2. Example of xenon equilibrium ventilation scan (A), technetium transmission scan (B), and deposited labeled sulfur colloid particles (C). Upper row images are from a healthy subject; lower row images are from a CF patient.

counts. A rectangular whole right lung ROI that circumscribed the isocontour ROI was drawn. From this ROI, a central rectangular ROI was derived that was half-height and half-width (expanded to include whole pixel) and centered vertically on the medial border, *i.e.*, 25% of the whole right lung ROI. This central ROI was used for both the isocontour and rectangular ROI analysis.

The criteria for drawing of the XV ROIs were based on a 20% drop from peak lung value; for TT, it was three times ($3\times$) soft body background. The criteria were estimated based on the first few subjects to keep the two ROIs approximately similar for the two approaches. The ROI sizes diverged somewhat as the sample size increased. Thus, the lower area for TT may have been simply due to the *a priori* criteria we used to define the lung outlines.

The C/P of the ^{99m}Tc -labeled particles was divided by the C/P derived from the xenon ventilation image for the XV method, or the transmission image for the TT method, resulting in a normalized C/P (nC/P):

$$\text{nC/P} = (\text{C/P}_{99\text{mTc-SC}}) / (\text{C/P}_{\text{XV or TT}}) \quad (1)$$

Statistical analysis

Values for groups are given as means and standard deviations. Statistical significance is set to less than 0.05 using

Student's *t* distribution unless otherwise noted. Regressions and *t* tests were calculated using functions in Excel for Mac version 14.2.2.

Results

Figure 2 illustrates an example of ROIs created from XV and TT in a healthy subject and a patient with CF using the methods described above.

Relationship of ROI area to lung volume

The area of the right lung ROI was investigated for its relationship to lung volume using FVC as a surrogate for total lung capacity. Mean FVC for the healthy subjects (H) and CF patients was 4.97 ± 0.98 mL and 4.14 ± 1.28 mL, respectively. A power function was fit on the relationship of ROI area with FVC to calculate the equation of the ROI versus lung volume, and the Spearman correlation coefficient, R^2 . Table 1 lists the equations for the relationships and associated values. For the healthy subjects, ROI area and FVC were significantly correlated regardless of the method of XV or TT. There was no correlation for the CF patients of ROI area and FVC, except for a slight improvement in the relationship using the TT over the XV method. In both the healthy subjects and patients with CF, the ROI areas based on the TT method were significantly smaller, by 12–17% ($p < 0.001$), than the ROI areas based on the XV method for both rectangular and isocontour ROIs. There was no change in the ROI areas after a single-pass smoothing of the images when compared with the unsmoothed images (data not shown).

Central-to-peripheral ratio of counts (C/P)

In the healthy subjects, the normalized ratio of central to peripheral right lung counts (nC/P) based on XV or TT was significantly different when using rectangular ROIs (Table 2) but not when using the isocontour ROIs. nC/P between the two methods, XV and TT, was highly correlated (Fig. 3) for both rectangular and isocontour boundaries. Regression equations for the relationship of nC/P between the two methods were $y = 0.75x + 0.61$, $R^2 = 0.64$ using rectangular ROIs and $y = 0.76x + 0.45$, $R^2 = 0.66$ using the isocontour ROIs.

In the CF patients, nC/P was significantly greater for TT versus XV for both rectangular and isocontour ROIs, but were also well correlated. However, the correlation was less so than in healthy subjects (Fig. 4). The nC/P values of the TT method were 12% higher (using rectangular ROIs) and

TABLE 1. RELATIONSHIP OF ROI AREA (cm^2) TO LUNG VOLUME (L)

	XV rectangular	XV isocontour	TT rectangular	TT isocontour
Relationship H	$y = 92.9^* x^{0.67}$	$y = 67.5^* x^{0.72}$	$y = 73.3^* x^{0.73}$	$y = 62.0^* x^{0.69}$
Relationship CF	$y = 206^* x^{0.13}$	$y = 174^* x^{0.12}$	$y = 138^* x^{0.31}$	$y = 115^* x^{0.28}$
R^2/p value H	0.49 / <0.001	0.53 / <0.001	0.54 / <0.001	0.52 / <0.001
R^2/p value CF	0.10 / 0.67	0.10 / 0.28	0.22 / 0.09	0.22 / 0.09
ROI area (cm^2) H	273 ± 49^a	213 ± 38^a	237 ± 47	188 ± 35
ROI area (cm^2) CF	249 ± 32^a	208 ± 26^a	216 ± 42	173 ± 32

Values are given for the regression equations fit to the association of ROI area and FVC for healthy subjects (H) and cystic fibrosis patients (CF). Variables for regression are ROI area (*y*) and FVC (*x*). ROI area is mean for the group. R^2 is Spearman coefficient, and *p* value is for difference from no relationship.

^a $p < 0.001$ when comparing rectangular XV vs. TT, and isocontour XV vs. TT.

TABLE 2. NORMALIZED C/P VALUES FOR THE TWO METHODS

	XV rectangular	XV isocontour	TT rectangular	TT isocontour
nC/P H	1.60±0.37 ^a	1.58±0.37	1.82±0.35 ^a	1.65±0.35
C/P dep H	0.91±0.22	0.97±0.24	0.81±0.18	0.90±0.20
C/P ref H	0.57±0.05	0.62±0.06	0.45±0.06	0.55±0.08
nC/P CF	1.51±0.26 ^b	1.51±0.26 ^c	1.89±0.37 ^b	1.70±0.34 ^c
C/P dep CF	0.90±0.16	0.94±0.16	0.78±0.15	0.86±0.16
C/P ref CF	0.60±0.08	0.63±0.08	0.41±0.02	0.51±0.03

Relationship of regional analysis of particle deposition comparing the normalized C/P (nC/P) analysis using xenon ventilation or transmission as reference images for lung size and volume. "dep" and "ref" are values of C/P from the deposition image and the respective reference xenon or transmission image used for determining nC/P.

^a $p < 0.001$.

^b $p = 0.002$.

^c $p = 0.017$.

4% higher (using isocontour ROIs) than those of the XV method in healthy subjects. For the CF patients, nC/P using the TT method was 25% higher (using rectangular ROIs) and 13% higher (with isocontour ROIs) than that using the XV method. The TT method resulted in higher values of nC/P due to lower values of the C/P of the transmission reference image when compared with the xenon equilibrium ventilation reference image (Table 2). There was no difference in the nC/P values after a single-pass smoothing of the images (installed ImageJ function) when compared with the unsmoothed images. Regression equations of the relationship of nC/P between the two methods were $y = 0.94x + 0.46$, $R^2 = 0.43$ using rectangular ROIs and $y = 0.85x + 0.42$, $R^2 = 0.41$ using isocontour ROIs.

Effect of ROI shape on nC/P

The shape of the whole right lung ROI in healthy individuals tended to be similar for the XV and TT methods (Fig. 2, top row). The border definition of 20% of peak lung counts for XV and $3 \times$ soft body background for TT produced similar outlines with similar height and width ROI parameters, as evidenced by similar areas (Table 1). As the central ROI is based on a fixed fraction of the whole right lung ROI at its furthest extent, it tended to be similar for both XV and TT as well. Similar central and peripheral regions for the isocontour ROIs resulted in similar un-normalized particle de-

position ratio (C/P dep) in the healthy subjects for both the XV and TT method: 0.97 ± 0.24 and 0.90 ± 0.20 , respectively (Table 2). The difference was reduced by normalizing to the reference image: 1.58 ± 0.37 and 1.65 ± 0.35 , respectively. In addition, normalizing to the reference image reduced the difference in C/P dep between the rectangular and isocontour shapes for both the XV and TT methods (Table 2). Figure 5 illustrates the good relationship between nC/P derived from the rectangular versus the isocontour lung outlines for both the XV and TT methods.

On the other hand, for the CF patients (Fig. 2, bottom row), there tended to be a loss of area in the apices with the XV method in some individuals, due to incomplete ventilation, that was corrected with the TT method, which is ventilation-independent. As the peripheral region was calculated from the difference between the reduced size of the ROI of the whole right lung and its central region, the peripheral region of the ROIs became smaller on average and more variable between individuals. Therefore, there was an increase in nC/P from XV to TT: 1.51 ± 0.26 to 1.70 ± 0.34 . Also observed was a larger variation in the average nC/P for the TT method over the XV method when comparing the rectangular [standard deviation (SD) 0.26] and isocontour (SD 0.37) ROIs. This variation was greater than that seen with healthy individuals (Table 2 and illustrated in Fig. 6). This is reflected in the lower association of nC/P between the XV and TT methods using isocontour ROIs for the CF patients

FIG. 3. Normalized ratio of central to peripheral counts (nC/P) in the healthy right lung for XV and TT methods. XV=analysis using a lung reference image obtained by a xenon equilibrium ventilation scan; TT=analysis using a ^{99m}Tc transmission scan. $y = 0.75x + 0.61$, $R^2 = 0.64$ using rectangular ROIs shown on left; and $y = 0.76x + 0.45$, $R^2 = 0.66$ using the isocontour ROIs shown on right.

FIG. 4. Central-to-peripheral ratio of counts in the right lung of CF patients normalized to a reference image (nC/P). XV=analysis using a lung reference image obtained by a xenon equilibrium ventilation scan; TT=analysis using a ^{99m}Tc transmission scan. Regression equations are $y = 0.94x + 0.46$, $R^2 = 0.43$ using rectangular ROIs shown on left, and $y = 0.85x + 0.42$, $R^2 = 0.41$ using isocontour ROIs shown on right.

FIG. 5. Comparison of normalized C/P (nC/P) for the healthy subjects when using rectangular or isocontour ROIs for the xenon ventilation (XV) and transmission (TT) methods. $y = 1.0x - 0.02$, $R^2 = 0.99$ for the XV method shown on left, and $y = 0.97x - 0.11$, $R^2 = 0.94$ for the TT method shown on right.

than for healthy subjects: $R^2 = 0.41$ versus 0.66 , respectively (Figs. 3 and 4).

Discussion

This study has found that there is a good correlation of normalized regional particle deposition (nC/P) by gas ventilation versus transmission scan for both healthy ($>80\%$ FEV₁ predicted) and CF lungs ($>50\%$ FEV₁ predicted), even though there was an absolute difference in values. Although the absolute values for nC/P with both groups of subjects were different for the two methods, XV and TT, the good correlation indicates that, for most of the 2D scintigraphic analyses performed using either gas equilibrium ventilation images or radioactive transmission images as references for lung and chest geometry, direct comparisons between the two may be made using simple corrections. For example, it should be possible to use the regression equations found in Figures 3 and 4 to relate nC/P data generated from the use of the XV or TT methods, such as for a meta-analysis, if the definition for lung outlines used in the analysis are similar to those presented here. Some deviation from these ROI definitions should still result in a good correction due to the insensitivity of nC/P to ROI shape and size.⁽⁵⁾ Based on the two arguments presented and discussed below, *i.e.*, normalizing C/P and the tight correlation between XV and TT methods, we propose that the equations of Figures 3 and 4 can be used to compare population data of regional lung deposition generated from either of the two methods.

Although the size of the ROIs in this study tended to be less for TT versus XV scans for either the healthy subjects or CF patients, it should be emphasized that our patients had relatively mild lung disease (mean FEV₁ % predicted = 77). In patients with more severe disease where ventilation may be almost absent from large portions of the lungs, the size of ROIs determined by TT may, in fact, be larger than by XV, being more representative of the true lung outline. As shown in Figure 2A, apices in CF patients can have reduced ventilatory capacity in that region of the lung. This may reduce the size of the ROI by truncating or attenuating the edges, although in this case there was still sufficient activity for the ROI to include much of this region. Transmission imaging is somewhat less sensitive to the ventilation reduction, as seen in Figure 2B. As our ROIs were set at boundaries of 20% of peak xenon counts or at $3 \times$ soft tissue background in transmission images, the TT ROIs averaged smaller than the XV ROIs.

FIG. 6. Comparison of normalized C/P (nC/P) for the CF patient when using the rectangular or isocontour ROIs for the xenon ventilation (XV) and transmission (TT) methods. $y = 0.98x + 0.02$, $R^2 = 0.97$ for the XV method shown on left, and $y = 0.89x + 0.02$, $R^2 = 0.94$ for the TT method shown on right.

It is interesting to note that the nC/P values of regional particle deposition for the two methods correlate so well despite the density patterns of the reference images being very different. The C/P of the reference image for the TT method was lower than that for the XV method for both study groups (Table 2), indicating a much more curved structure by gas ventilation, or alternatively, a flatter TT structure, yet the nC/P for the deposition images for the two methods correlates very well. This is likely due to the fact that the difference in nC/P is predominately due to differences in the reference C/P, whereas the C/P for the deposition images is very similar between the two methods (Table 2).

For the normal subjects, the area of the ROI was highly correlated with FVC, nearly to the same degree for both the XV and TT methods. In contrast, the ROIs for the CF patients were poorly associated with FVC, most likely due to the degradation of lung function with the disease, but a stronger correlation was observed for the TT method. For these subjects, poor lung function results in poor xenon gas ventilation that alters the XV outlines due to nonequilibrium conditions. For this reason, if the results can be inferred to other subjects with compromised lung functions such as asthma and chronic obstructive pulmonary disease, the TT method would be a better choice for defining lung outline and calculating a regional deposition parameter such as C/P in patients with lung disorders.

The use of the isocontour outline of the lung periphery, rather than a rectangular outline, reduced the variability in nC/P between the XV and TT method, especially in lungs of CF patients whose ventilation is compromised, making a better comparison between the two methods. The higher variability with the rectangular ROI using the TT method is presumably due to the high variability associated with the nonlung corners, which is eliminated when using the isocontour outline.

Compared with gas ventilation scans, transmission scans with either ^{57}Co or $^{99\text{m}}\text{Tc}$ are the easiest and most accessible method for defining the lung borders, because all laboratories undertaking deposition studies should have access to a flood-field source for quality control purposes. An additional advantage of the transmission scan over the xenon ventilation scan is the lower radiation dose received by the subject. Our estimation of radiation dose to the lungs for the xenon scan for 5 min of ventilation with 10 mCi of ^{133}Xe is approximately 65 mRem. For the 90-sec transmission scan with 2 mCi of $^{99\text{m}}\text{Tc}$, it is estimated to be less than 3 mRem. Although the results

presented here used ^{99m}Tc rather than ^{57}Co for the transmission scans, differences between ^{57}Co and ^{99m}Tc transmission scans are expected to be negligible, with linear attenuation coefficients changing from 0.15 to 0.14 cm^{-1} , respectively.⁽⁶⁾

The C/P values reported here are specific to the shapes and sizes of ROIs derived from the criteria of our analysis technique. The method for determining the rectangular central ROI was chosen to allow for reproducibility. The counts in the central region, with its high mean count per pixel, may be very sensitive to which pixels are included. The ambiguity of central ROI shape and position is reduced by making the central ROI a simple geometric fraction of its rectangular whole right lung ROI with unambiguous placement in relation to the whole right lung ROI. In this study, the same rectangular central ROI defined for each subject was used for both the rectangular and isocontour whole right lung analysis. As seen in the values in Table 2, the difference in values for nC/P for the two methods can be minimized by choosing a whole right lung isocontour outline in combination with a rectangular central region. However, differences between the XV isocontour method and the TT isocontour method persist in the data based on the CF population. Biddiscombe *et al.*⁽⁵⁾ have recently shown that the size of the central (C) versus whole lung (WL) ROI can clearly affect the magnitude of the C/P for the deposition image alone (*i.e.*, non-normalized C/P). But when the nC/P is determined by Equation 1 (normalized to a reference image), the relative size of C versus WL is much less important, emphasizing the importance that the C/P indices be normalized by reference images (either gas or transmission scans). The tight correlation of nC/P between the differently sized rectangular and isocontour outlines, for either XV or TT method, shown in Figures 5 and 6, confirms this observation.

The determination of the lung boundary in a 2D image created by a radioactive gas that fills the lung, such as ^{133}Xe in our XV method, is based on where the gas-containing region meets the solid tissue. In a logical sense, this is a determination based on where the "lung is detected," *i.e.*, a top-down determination with respect to counts. On the other hand, a transmission image detects the lung by passing a planar radiation source through the whole body, attenuating most where the denser body tissue is located and less in the gas-containing regions. Therefore, our method for determining the boundary from a transmission scan is based on the assumption that "the lung is where the solid tissue is not," *i.e.*, a bottom-up determination, with respect to counts, to locate the tissue boundary. Complicating the generation and comparison of XV and TT lung boundaries is the fact that the XV counts from the lung are attenuated by one layer of body tissue, and the TT counts pass through two layers of tissue. Were it not for the fact that the lungs are tapered around the edges, setting the boundary would be elementary. However, a limit must be set at where the taper ends. We have used 20% of peak lung count as the isocontour limit for lung boundary for the gas ventilation method and $3\times$ abdominal count as the isocontour for tissue boundary. Many studies set the limit even lower, *e.g.*, where the "radioactive counts decreased to background levels."⁽⁵⁾ These are well used but somewhat arbitrary values and may need further evaluation in future studies.

Our findings show that transmission scans are similar to and can be easily related to gas ventilation scans for defining lung borders and lung thickness required for measuring re-

gional particle deposition. Based on the results of this study, the following conclusions can be drawn: (1) using a transmission scan instead of a ventilation scan to define the lung borders may limit problems associated with poorly ventilated lung regions; (2) choosing a right lung isocontour outline in combination with a rectangular central region appears to be more precise in terms of defining the nC/P compared with choosing a right lung outline based on the rectangular method; and (3) using simple corrections based on the appropriate regression equations of similarly generated data may allow direct comparison between nC/Ps based on ventilation versus transmission scans. These suggestions should be appropriate to other deposition parameters, such as nP/C or penetration index.

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Author Disclosure Statement

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