Quantitative Evaluation of Regional Pulmonary Ventilation Using PET and Nitrogen-13 Gas

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A new quantitative method, "Simultaneous Exponential Equation method" (SEE), has been developed for the analysis of pulmonary ventilation studies using ^{13}N-labeled nitrogen gas and positron emission computed tomography. This method uses Kety's model assuming insolubility of nitrogen gas in blood or tissues. Activity in poorly ventilated regions does not reach the equilibrium in the so-called equilibrium scan (EQ) performed following 3 or 4 min of washin. Therefore EQ images do not represent lung volume images nor do they provide the initial value of washout phase. Our method corrects for these transient phenomena observed during EQ scan and yields idealistic equilibrium state images (lung volume images) as well as more accurate regional ventilatory time constants than a modified Stewart-Hamilton (A/H) method and tomograms of high resolution.

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Xenon-133 (^{133}Xe) gas has been widely used for the assessment of regional pulmonary ventilatory parameters including lung volume and ventilatory turnover rate (specific ventilation) (*1–5*). These parameters are calculated using an appropriate physiologic model to describe the process, such as Kety's model (*6*). However, due to the solubility of xenon in blood and tissues (*7*), significant errors can be introduced in those estimated values (*8,9*). Furthermore, low-energy photons (81 keV) of ^{133}Xe make it difficult to evaluate deeper regions due to increased photon attenuation. Accordingly, emission computed tomography is hardly feasible.

Recently we have introduced a new method to evaluate regional pulmonary ventilation using ^{13}N-labeled nitrogen gas (^{13}N gas) and positron emission computed tomography (PET) (*10*). We took advantage of the insolubility of nitrogen gas and excellent resolution and quantitative capability of PET in order to estimate regional ventilatory parameters more accurately.

Compared with planar imaging, far more count statistics are necessary for the image reconstruction to make the most of PET's good resolution. Ultra-high sensitivity and temporal resolution are necessary to obtain fast serial dynamic tomograms in high resolution and S/N ratio which can generate good time-activity curves pixel by pixel. Therefore, we did not adopt a curve fitting method that is used in planar studies (*5*). In our protocol only two scans were carried out in a study, the so-called equilibrium phase scan (EQ scan) performed following 3 or 4 min of closed circuit inhalation, and the washout phase scan (WO scan) performed during the washout phase.

A modified Stewart-Hamilton (A/H) method has been accepted as a simple and useful means to compute regional ventilatory clearance from these EQ and WO images in ^{133}Xe studies (*3,4*). In the A/H method, the EQ images are considered to represent the equilibrium images and are adopted as the initial value of the washout phase. Our PET studies revealed, however, that the activity in poorly ventilated regions did not reach the equilibrium by the end of the washin phase and still increased during the EQ scan. Therefore, the EQ scan cannot be used as initial value of washout phase, nor does it provide lung volume images.

In this paper, we propose a new method, "Simultaneous Exponential Equation method" (SEE), to calculate relative pulmonary volume (V) and ventilatory time constant (T) pixel by pixel from the EQ and WO images. This method describes the washin and the washout process with Kety's model, which was formulated as single exponential functions for an insoluble gas such as ^{13}N. We integrated the equation over the

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scanning period of the EQ and WO, respectively, and solved the equations simultaneously to obtain V and T pixel by pixel. Hence the name SEE method. Thus, we corrected for the transient phenomenon observed during the EQ scan and obtained these parameters more accurately with high resolution.

In this paper we evaluate the errors involved in the A/H method and compare our SEE method with the A/H method in clinical studies. We placed a special emphasis on whether the accurate ventilatory clearance could be determined and whether the pathological loss of ventilated volume observed in pulmonary fibrosis or nonventilated bullae could be properly evaluated.

MATERIALS AND METHODS

Protocol

Nitrogen-13 (^{13}N) gas was produced in a baby cyclotron* by bombarding a gas target containing carbon dioxide and 10% helium with protons involving the $^{16}O(p, \alpha)^{13}N$ nuclear reaction. The radiochemical purity of the product was >99.99%. The radioactive nitrogen gas was diluted with 30 *l* of oxygen gas and guided into a lead-shielded bag, where the activity concentration was 1.5–2.5 mCi/l. The remaining carbon dioxide had been absorbed in soda lime, so that the final concentration of CO_2 in the bag was <0.5%.

The devoted PET machine† (*11*) had four detector rings providing seven slices at the interval of 16 mm. The detectors were arranged at irregular intervals along the ring based on the principle of "positology" (*12*) and the rings rotate continuously acquiring data from all projections simultaneously. The spatial resolution was 7.6 mm full width half maximum (FWHM) (Shepp-Logan filter) and the axial resolution was 12 mm FWHM at the center of the field.

The subject, in a supine position in the gantry, put on a mask that was connected to the bag through a soda lime column. The system dead space was 50 ml. First, the subject inhaled ^{13}N gas in a closed-circuit. When the PET count rate reached equilibrium in 3 or 4 min, the so-called equilibrium phase scan (EQ scan) was performed for 3 min. Then the radioactive gas was washed out by the room air during which the washout phase scan (WO scan) was performed for 5 min (Fig. 1). A time lag of about 15 sec existed between EQ and WO (interval between t_2 and t_3), which stemmed from the data transfer time required in our PET system. Both EQ and WO images were reconstructed with a Shepp-Logan filter convoluted with 2 mm sigma Gaussian in a 64 × 64 matrix within 32 cm diam field. The pixel size was 5 × 5 mm. Further data manipulations were performed in another 16-bit minicomputer.

Model

Because ^{13}N gas is almost insoluble in blood or tissues, Kety's model is reduced to a single compartment model. When this model is applied to our protocol, the dynamics of the count rate in pixel i is described as follows, if we assume the constant decay-corrected concentration of the inspired gas in washin phase. In washin phase

$$N_i(t) = N_{ieq}(1 - e^{-k_i t})e^{-\lambda t} \quad (0 \le t \le t_3) \qquad (1)$$

and in washout phase

$$N_i(t) = N_i(t_3)e^{-(k_i+\lambda)t} \quad (t > t_3) \qquad (2)$$

where k_i is the ventilatory turnover rate, N_{ieq} is the count rate in the ideal equilibrium state decay-corrected to t = 0, and λ is the decay constant. $N_i(t_3)$ denotes the count rate at the time the washout begins (Fig. 1).

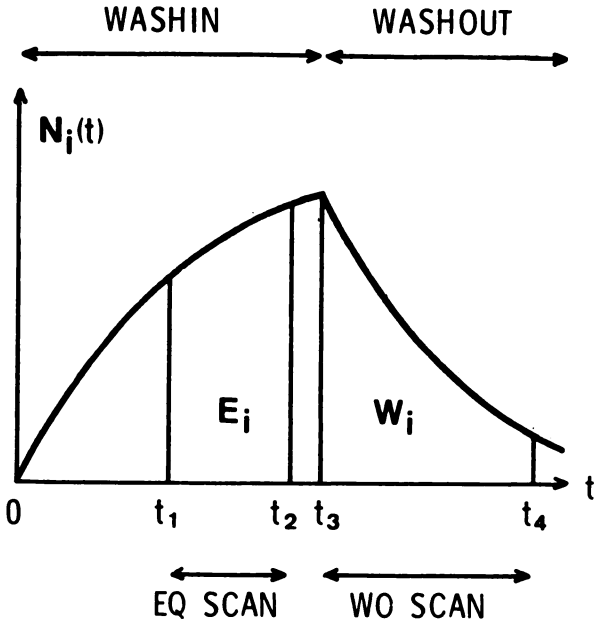

FIGURE 1
Dynamics of count rate in pixel i in our protocol. Subject inhales ^{13}N nitrogen gas in closed circuit until time t_3, followed by washout with room air. EQ scan is performed from t_1 to t_2 and WO scan from t_3 to t_4. Regional count in each scan is calculated by integrating count rate during respective scan period

Simultaneous Exponential Equation (SEE) Method

The regional counts in the EQ and WO scan are

$$E_i = \int_{t_1}^{t_2} N_i(t)dt \quad \text{and} \quad W_i = \int_{t_3}^{t_4} N_i(t)dt, \qquad (3)$$

respectively, where t_1, t_2, t_3, and t_4 stand for the time when the EQ and WO scan begins and ends (Fig. 1). We solved these equations simultaneously using Newton's method (*13*) to obtain N_{ieq} and k_i pixel by pixel. Then we made the functional images of the relative lung volume (V) which is proportional to N_{ieq} and the ventilatory time constant (T) which is equal to $1/k_i$. The absolute regional lung volume depends on the total activity and cannot be determined in our protocol.

Stewart-Hamilton (A/H) Method

The regional turnover rate is derived simply by

$$k_{i(A/H)} = E_i/W_i(t_2 - t_1) - \lambda. \qquad (4)$$

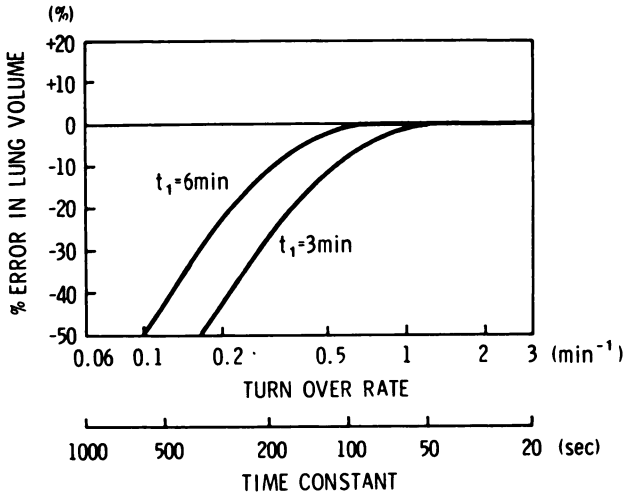

FIGURE 2
Percent errors in value of lung volume obtained by A/H method in varying k_i values. In A/H method, EQ images corrected for decay were considered to represent lung volume. EQ scan was performed from t_1 (shown in figure) for 3 min

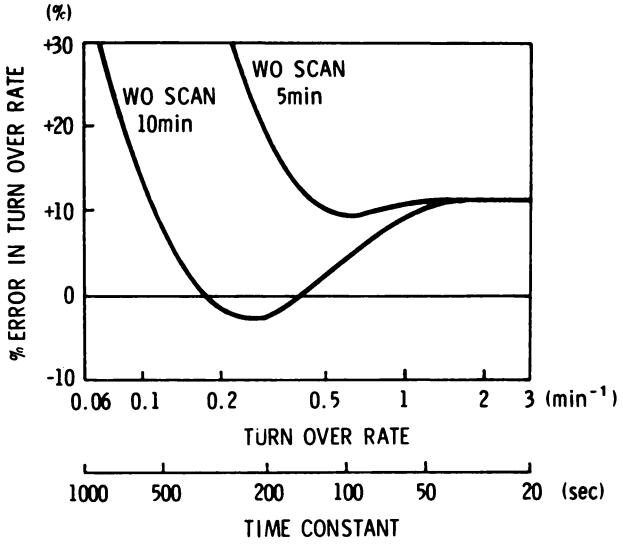

FIGURE 3
Percent errors in k_i calculated with A/H method in varying k_i values, in which t_1 = 3 min, t_2 = 6 min, t_3 = 6 min, and WO scan length was 5 min or 10 min

In the A/H method, the EQ image is considered to represent the relative regional volume. In the following theoretical evaluation, however, the regional EQ counts (E_i) were decay-corrected so as to yield accurate N_{ieq} in sufficiently well-ventilated regions.

Theoretical Evaluation of Errors in A/H Method

We assume that the pixel count rate follows Eqs. (1) and (2), and calculated E_i and W_i in various values of k_i and in different conditions of sampling periods. We thereby theoretically evaluated the errors in the lung volume and the turnover rate calculated with the A/H method described above.

Clinical Studies

A pulmonary ventilation study was performed in three cases according to the protocol described above. Case 1 was a 31-yr-old nonsmoking normal male volunteer. Case 2 was a 56-yr-old man with emphysema. The x-ray computed tomograms showed bullae in the left dorsal lung fields. $FEV_{1.0}$% was 30 and %VC was 95. Case 3 was a 68-yr-old man with pulmonary fibrosis. His chest x-ray film indicated fibrotic shadows in the dorsal lung fields and %VC was 42.2.

RESULTS

Theoretical Evaluation

Figure 2 indicates the errors in the value of lung volume calculated with the A/H method. Where t_1 = 3 min, the EQ scan provided accurate values when the ventilatory turnover rate was more than 1.5 min^{-1}. When the turnover rate was lower, the counts of EQ decreased significantly, resulting in large errors. Delaying t_1 to 6 min allowed more time for equilibration and decreased the errors to some extent, still leaving large errors in poorly ventilated regions.

Figure 3 indicates the errors in the value of the turnover rate calculated with the A/H method, which was evaluated by comparison of $k_{i(A/H)}$ and k_i. In well-ventilated regions, $k_{i(A/H)}$ was 11% larger than k_i due to decay during the EQ scan. When the sampling time of the WO scan was 5 min, significant overestimation was observed in the regions with k_i <0.5 min^{-1}, and the errors increased as k_i became smaller. This was because the radioactive gas was not washed out completely by the end of the WO scan. Such errors due to the early termination of the WO scan were decreased by increasing WO scan length to 10 min, although overestimation still occurred in extremely poorly ventilated regions. On the other hand, some underestimation occurred when k_i = 0.25 min^{-1}, because the count rate did not reach the equilibrium by t_1, making the EQ counts smaller than the initial value of the washout process. This transient phenomenon during the EQ scan could result in significant underestimation of k_i, if the decay during the EQ scan is corrected to provide accurate k_i in well ventilated regions. At any rate, the application of the EQ images to the initial values of the washout process could induce errors of more than 10% in calculated k_i value.

Clinical Studies

Figures 4, 5, and 6 show EQ, WO, ventilatory time constant (T) and relative lung volume (V) images obtained by SEE method in Case 1 (normal), Case 2 (emphysema), and Case 3 (pulmonary fibrosis), respectively.

In the normal volunteer, both EQ and V images show homogeneous activity distribution throughout the lung fields, indicating that the activity has reached equilibrium in the EQ scan and that the lung volume is uniform. The time constant (T) images show gravity-induced gradient in ventilation. The time constant ranges 15–20 sec (Fig. 4).

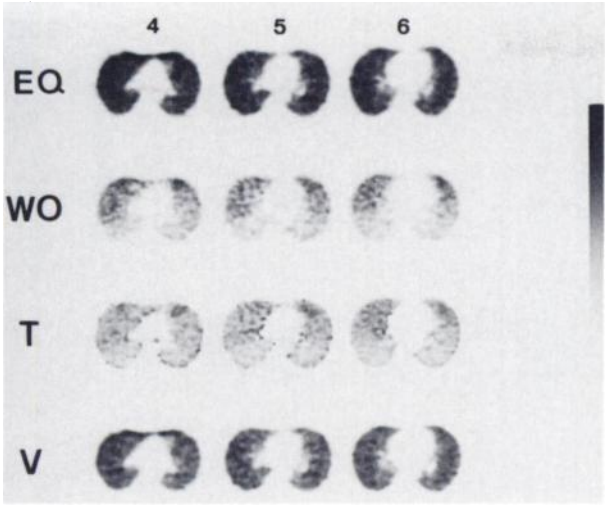

FIGURE 4
EQ, WO, ventilatory time constant (T) and lung volume (V) images of normal volunteer obtained by our SEE method

In the patient with emphysema, poorly ventilated regions show decrease activity in the EQ images and increased values in WO and T images. Our volume images (V) reveal that their ventilated lung volume did not decrease, indicating that they were not in the equilibrium state in the EQ scan. On the other hand, the bullous lesions show low activity in the EQ images and decreased volume, indicating that they were barely ventilated (Fig. 5).

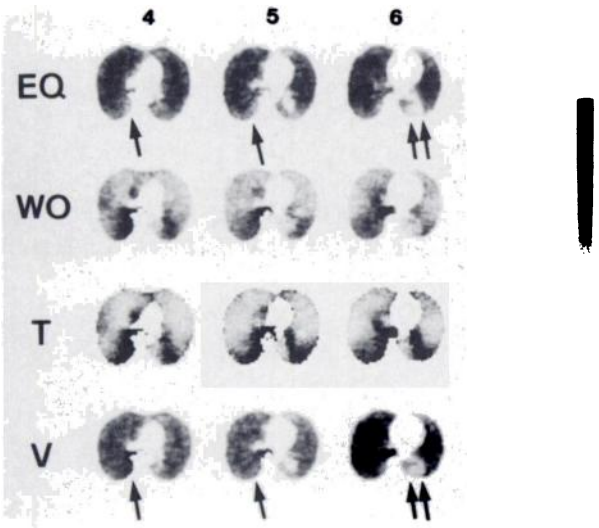

FIGURE 5
EQ, WO, ventilatory time constant (T) and lung volume (V) images of patient with emphysema obtained by our SEE method. Single arrows indicate poorly ventilated regions, which show decreased counts in EQ and normal values in V images. Double arrows indicate bullous lesions demonstrated in x-ray computed tomograms, which have decreased values in both EQ and V images. t_1 = 186 sec, t_2 = 366 sec, t_3 = 398 sec and t_4 = 712 sec

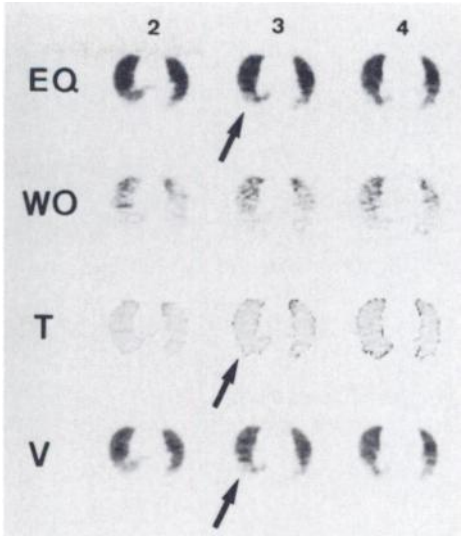

FIGURE 6
EQ, WO, ventilatory time constant (T) and lung volume (V) images of patient with pulmonary fibrosis obtained by our SEE method. Arrows indicate diseased regions showing decreased values in EQ and V images with normal T values. t_1 = 131 sec, t_2 = 311 sec, t_3 = 344 sec, and t_4 = 644 sec

In the patient with pulmonary fibrosis, diseased regions show low activity in the EQ and WO images. Our SEE method revealed that they had normal ventilatory time constant (T) and decreased lung volume (V), indicating the absence of airway obstruction and the presence of volume loss due to the substitution of the air space by fibrotic tissues (Fig. 6).

When decreased activity was observed in a region in EQ images, they alone could not tell whether the region had poor ventilation, volume loss, or both. Our SEE method provided T and V images that could distinguish them quantitatively.

The ventilatory time constant images obtained by the A/H and SEE method were compared in Case 1 (Fig. 7), and in Case 2 (Fig. 8). The A/H and the SEE method provided qualitatively similar images. Quantitatively, however, the time constant computed with the A/H method was smaller than the SEE by about 10% in the normal volunteer and by 10–50% in the case with emphysema.

It took 2 min to compute the T and V images from the EQ and WO images in a slice with a 64 × 64 matrix.

DISCUSSION

The Stewart-Hamilton (A/H) method is a simple and useful method to obtain regional ventilatory turnover rates and has been used in xenon-133 (^{133}Xe) studies (*3,4*). Our theoretical evaluation disclosed, however, that several inherent errors were involved in the A/H method. First, activity in poorly ventilated regions did not reach the equilibrium in the so-called equilibrium (EQ) scan performed following 6 min of washin, which has been considered sufficient for equili-

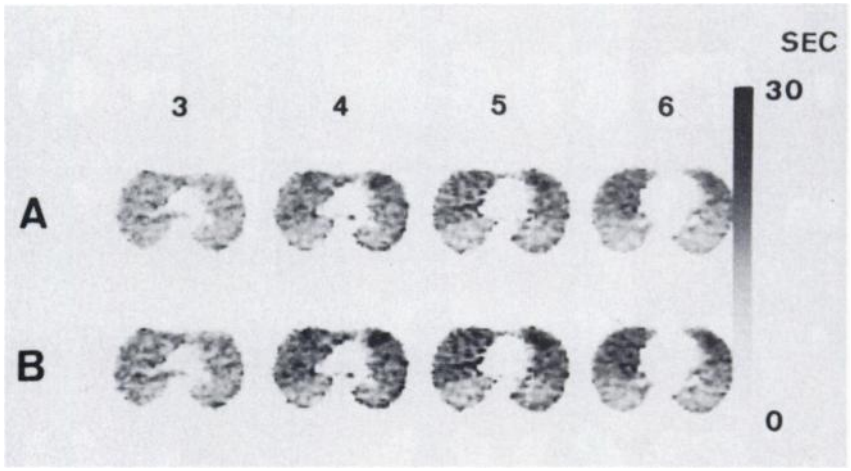

FIGURE 7
Time constant images of normal volunteer calculated by A/H method (A) and SEE method (B)

bration in ^{133}Xe studies (*4*). Therefore, the EQ scan does not provide volume image. Second, the EQ image could not represent the initial value of the washout because of the activity changes during the EQ scan due to the physical decay and the transient phenomenon observed in the poorly ventilated regions. Third, the activity in poorly ventilated regions was not washed out completely by the end of the WO scan performed for 10 min. Therefore, the time constant obtained by the A/H method has considerable errors. Those inherent errors in the A/H method are eliminated in our SEE method, which corrects for decay and transient phenomenon in the EQ scan as well as the sampling interval of each scan.

In our clinical studies, the EQ images found low activity both in the regions of poor ventilation and volume loss. The EQ and WO images alone could not determine whether the decrease in the EQ was due to volume loss or poor ventilation or both. Our SEE method provided the V and T images which could quantitatively distinguish these two factors.

The apparently homogeneous activity distribution in the EQ images reported in earlier ^{133}Xe studies in the patients with obstructive disease may be attributed to the poorer resolution and the low sensitivity in deep regions. Our results have demonstrated that the EQ images are far from the equilibrium images.

Our comparative study suggests that the A/H method provides qualitatively valid information about regional ventilation. However, when comparing two cases or in the follow-up of a patient, quantitative information is required, and the A/H method suffers inherently large errors.

Our SEE method uses a single-compartment model which is based on the following assumptions:

1. The subject maintains constant ventilation during whole span of the study.

2. The decay-corrected activity concentration of the inspired gas is constant during the washin phase. This assumption does not hold strictly for a closed system although the errors may be small for a well-mixed large bag. In order to keep the inspired gas concentration constant, an open system is recommended (*14,15*).

3. Nitrogen-13 gas is insoluble in blood or tissues. This assumption is acceptable, because the blood-gas partition coefficient of nitrogen gas is 0.014, which is 13

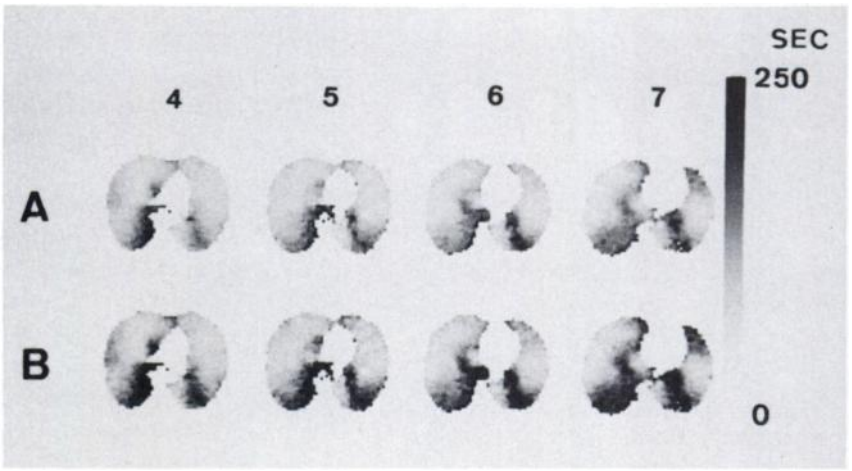

FIGURE 8
Time constant images of patient with emphysema calculated by A/H method (A) and SEE method (B)

times less soluble than xenon (0.15), although some authors still point out the errors due to the solubility of ^{13}N gas (*16*).

4. Deadspace is ignored. Rebreathing the expired gas remaining in the anatomical deadspace may decrease the turnover rate, especially when nonuniform ventilation exists. Although this point has never been discussed in ^{133}Xe studies, it may induce some errors in a highly quantitative study such as ours. Further investigations may be necessary.

5. The ventilatory clearance is uniform within a pixel volume. This is far more acceptable than the ^{133}Xe study when one considers the high resolution of PET. Whether the assumption is true or false, the estimated parameters are the average values within and around the pixel volume, because the respiratory movement is ignored.

Thus we believe that our model is reasonable for a quantitative study using PET and ^{13}N gas.

CONCLUSIONS

We have developed a new method to evaluate quantitatively the regional pulmonary ventilatory turnover rate and the ventilated lung volume using ^{13}N nitrogen gas and PET. Because nitrogen gas is almost insoluble in blood or tissues and PET has high resolution and quantitation, our method yields far more reliable regional parameters than ^{133}Xe studies.

The so-called equilibrium phase (EQ) scan by no means provides equilibrium images. Our SEE method provides idealistic equilibrium phase images, which are valuable for evaluation of pathological changes with volume loss. The regional turnover rate obtained by the Stewart-Hamilton (A/H) method suffers considerable inherent errors in poorly ventilated regions. Our SEE method perfectly corrects for those errors and yields more accurate estimates of the regional parameters.

FOOTNOTES

* Sumitomo, Tokyo, Japan (Cypris, Model 325).

† Positologica III, Hitachi, Tokyo, Japan.

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