Physiological evaluation of a new quantitative SPECT method measuring regional ventilation and perfusion

Johan Petersson, Alejandro Sánchez-Crespo, Malin Rohdin, Sven Nyrén, Hans Jacobsson, Stig A. Larsson, Sten G. E. Lindahl, Dag Linnarsson, Robb W. Glenny, and Margareta Mure. Physiological evaluation of a new quantitative SPECT method measuring regional ventilation and perfusion. J Appl Physiol 96: 1127–1136, 2004. First published November 14, 2003; 10.1152/japplphysiol.00092.2003.—We have developed a new quantitative single-photon-emission computed tomography (SPECT) method that uses 113mIn-labeled albumin macroaggregates and Technegas (99mTc) to estimate the distributions of regional ventilation and perfusion for the whole lung. The multiple inert-gas elimination technique (MIGET) and whole lung respiratory gas exchange were used as physiological evaluations of the new SPECT method. Regional ventilation and perfusion were estimated by SPECT in nine healthy volunteers during awake, spontaneous breathing. Radiotracers were administered with subjects sitting upright, and SPECT images were acquired with subjects supine. Whole lung gas exchange of MIGET and respiratory gas exchange were found to be well predicted from SPECT distribution. Correlations (r²) between SPECT-predicted and measured inert-gas excretions and retentions were 0.99. The method offers a new tool for measuring regional ventilation and perfusion in humans. single-photon-emission computed tomography; multiple inert-gas elimination technique; gas exchange

EFFICIENT GAS EXCHANGE in the lungs is the result of intimate matching of regional alveolar ventilation and perfusion. Regional distributions of ventilation and perfusion in human subjects have previously been analyzed by use of a number of techniques, many of which have used external detection of radioactive markers for ventilation and perfusion (3, 15, 21, 29, 32, 36, 39, 42, 57, 58). Measurement of regional distributions of ventilation and perfusion provides insights into how different treatment regimes (e.g., positioning) influence gas exchange. To explain such mechanisms, a method is needed that provides simultaneous quantitative measures of both regional ventilation and perfusion for the whole lung. To meet these needs, we developed a new dual-isotope quantitative single-photon-emission computed tomography (SPECT) method that simultaneously measures the distributions of regional alveolar ventilation and regional lung perfusion in the whole lung. The method has previously been evaluated by using phantom studies (47). In the present study, the multiple inert-gas elimination technique (MIGET) (54, 55) and respiratory gas exchange were used as physiological evaluations of the new SPECT method. We evaluated not only the ability of the method to depict the distributions of radioactivity in the subject, but also how well the method, including the methods of administering the isotopes, describes the actual distributions of regional ventilation and regional perfusion in human subjects.

METHODS

Subjects

Ten healthy volunteers (5 men and 5 women), aged 20–40 yr, were studied. All subjects were of normal weight (range 57–70 kg), height (range 160–175 cm), and body mass index (range 20–26). We recruited subjects <180 cm in height to ensure that all lung regions would fit into the scanning field of the SPECT camera. None of the subjects had a history of pulmonary disease, all were nonsmokers, and all had normal spirometry and lung volumes. The subjects received written information about the procedure, and informed verbal consent was obtained. Under sterile conditions and after infiltration of local anesthetics, an arterial line was inserted into each subject’s radial artery at the wrist. An intravenous catheter was inserted into the antecubital vein of the same arm. Results from one of the subjects had to be excluded from the study because of technical problems with the transmission source causing artifacts in the SPECT results. The study was approved by the local ethical committee and the local radiation safety committee.

SPECT Imaging

Radiopharmaceuticals. Regional distribution of ventilation was marked by using inhaled Technegas, microscopic graphite particles labeled with radioactive technetium (99mTc) (11). Regional distribution of perfusion was marked by use of macroaggregates of albumin (LyoMAA, Mallinckrodt Medical, Petten, The Netherlands) labeled with radioactive indium (113mIn). Both radiotracers were administered to subjects in the sitting upright posture. The principal photon energy of 99mTc is 140 keV and for 113mIn 392 keV. Labeling of the macroaggregates was performed according to Watanabe et al. (56) with a few modifications. 99mTc was obtained from a 99Mo/99mTc generator (Nycomed/Amersham), whereas 113mIn was obtained from

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a $^{113m}$Sn-$^{113m}$In generator (Radioisotope Center, Polatom, Otwock Swierk, Poland). Technegas was inhaled during quiet tidal breathing from a Technegas generator (Tetley Manufacturing, Sydney, Australia). This was done through a box that mixed Technegas (initially 100% argon) with air. Pulse oximetry was monitored during the Technegas inhalation to demonstrate normal hemoglobin oxygen saturation. During the Technegas inhalation, a radiation protection monitor (Proportional chamber, Bertold, Bad Widbad, Germany) was used to register the counts over the lung regions. Inhalation was terminated when the counts in the lower dorsal fields reached a level of 200 counts/min. Immediately after inhalation of Technegas, 100 MBq of $^{113m}$In-LyoMAA was injected via the peripheral venous catheter followed by a flush of normal saline. The subjects were estimated to receive a total effective dose of $\sim 5$ mSv.

**SPECT.** The dual-isotope SPECT technique used in this work has previously been presented in detail (47). In brief, SPECT images are obtained with a three-headed gamma camera (TRIAD XLT 20, Trionix Research Laboratory, Twinsburg, OH) equipped with medium energy general-purpose parallel-hole collimators. SPECT scans are performed in 72 projections, 62 s per projection, by use of a four-energy window acquisition protocol. Thus four images ($128 \times 128$ pixels with a pixel size of $3.56 \times 3.56$ mm$^2$) are obtained at each data-acquisition angle. An additional transmission tomography with a moving $^{133}$Cs line source is performed to obtain data for the attenuation correction routine. The two sets of projected images, one for each principal photon energy (140 and 392 keV), are corrected for photon scattering and attenuation as well as for the contribution of high-energy photons in the lower photon-energy window and the radioactive decay before image reconstruction. The lung areas are delineated in the reconstructed transverse transmission images by using a previously described edge-detection algorithm (47). To verify that only lung tissue was included in the images, they were reviewed by a radiologist. In a few of the images, a small number of peripheral pixels were considered nonlung tissue and therefore removed. All images were obtained with subjects in the supine posture while breathing against an expiratory pressure of 2.5 cmH$_2$O to compensate for the reduction in functional residual capacity (FRC) when changing from the sitting to the supine position.

**Assessment of Global Ventilation and Perfusion**

Quantitative SPECT data represent regional ventilation and perfusion only in relative terms. Prediction of gas exchange from SPECT requires separate measurements of global lung ventilation and perfusion.

**Global alveolar ventilation.** Whereas excretion and retention of MIGET gases depends on total minute ventilation, Technegas distribution only describes alveolar ventilation. Estimation of gas exchange from SPECT results therefore requires measurement of alveolar ventilation. Anatomic dead space was measured with the Fowler method (13), and alveolar ventilation was estimated from the total minute ventilation minus the anatomic dead space ventilation. CO$_2$ concentration and flow at the mouth were recorded during several slow expirations by using a calibrated in-line infrared capnometer (model 14360 A, Hewlett-Packard, Palo Alto, CA) and a volume-calibrated pneumotachograph (Fleisch no. 2, Siemens-Elema, Solna, Sweden, linear for flows up to 3 l/s). Data from the capnometer and the pneumotachograph were digitally recorded with a sampling frequency of 50 Hz by using the software program Workbench (Strawberry Tree, Sunnyvale, CA). Measured flow was corrected for the difference between gas temperature at the point of measurement and body temperature. The data were converted to text files and analyzed with the use of Microsoft Excel. The same equipment was used for registration of respiratory rate and minute ventilation during MIGET sampling and during the administration of the radiopharmaceuticals (during these recordings, the sampling frequency was reduced to 20 Hz). Alveolar ventilation was calculated by using the minute ventilation, the measured anatomic dead space, the apparatus dead space (different for each situation, measured with water), and the respiratory rate. Minute ventilation, alveolar ventilation, and tidal volumes were adjusted to BTPS (body temperature and pressure, water vapor saturated gas).

**Cardiac output.** Cardiac output was measured with a total rebreathing technique using Freon 22 (CHClF$_2$) (6, 45, 46). Gas flow was measured with a pneumotachometer (type 3813, Hans Rudolph, Kansas City, MO) and gas concentrations with a quadrupole mass spectrometer (AMIS 2000, Innovision A/S, Odense, Denmark). Before and after each experiment, the mass spectrometer was calibrated against gases of known composition, and the flowmeter was calibrated with a 3-liter syringe within the experimental flow range. The response latency of the mass spectrometer was determined from a sudden, simultaneous change of gas composition and flow direction at the inlet of the sampling capillary. During the rebreathing maneuver, pulmonary capillary blood flow was estimated from the uptake of Freon 22, and cardiac output was considered to equal pulmonary capillary blood flow. Each subject performed five rebreathing maneuvers, and the mean value of the three most consistent measurements was used to estimate cardiac output.

**Regional Alveolar Ventilation and Perfusion**

Coordinates and number of events per voxel within the total delineated lung region were extracted from original reconstructed transverse SPECT $^{113}$m-In-LyoMAA and $^{99m}$Tc-Technegas image data. Because of a limitation in the number of voxel data that could be handled by the software used in the subsequent calculations of gas exchange, the original set of $128 \times 128 \times 128$ voxels was converted into a smaller number ($32 \times 32 \times 32$) of larger voxels ($1.4 \times 1.4 \times 1.4$ cm$^3$ pixels).
1.4 cm$^3$), by adding $4 \times 4 \times 4$ original voxels together. Figure 1 illustrates the increment in voxel size in relation to lung size. Indium and technetium counts per voxel were converted to ventilation and perfusion (both ml/min) per voxel by multiplying the fraction of the total number of counts for each isotope in that voxel by the total cardiac output and total alveolar ventilation, respectively.

Arterial blood gases. Arterial blood samples were obtained at the start and finish of both the collection of expired gases and the MIGET sampling. The mean values of these two samples were used as the arterial blood-gas values during each situation. One arterial blood sample was obtained immediately before the administration of the radioactive isotopes. The samples were analyzed with a AVL OMNI 1-9 blood-gas analyzer (Roche Diagnostics, Graz, Austria).

MIGET

A continuous intravenous infusion of a standard solution of six inert gases (sulfur hexafluoride, ethane, cyclopropane, enflurane, diethyl ether, and acetone) was administered to the subjects and allowed to equilibrate for 60 min. Inert-gas concentrations in arterial and mixed exhaled gas were measured with a gas chromatograph (Star 3400 CX GC, Varian Chromatography Systems, used with a Varian 4400 Integrator) by using previously described techniques (54). Mean values from duplicate samples of both expired gases and arterial blood were used for the calculations. Retentions and excretions for the inert gases were calculated without measured mixed venous concentrations of the inert gases according to Gale et al. (14). Excretions were corrected for anatomic dead space.

Mixed Venous Oxygen and Carbon Dioxide Content

Prediction of respiratory gas exchange requires estimates of mixed venous oxygen and carbon dioxide content. Because a pulmonary catheter was not used, contents were calculated from arterial blood content, oxygen consumption, and carbon dioxide elimination. Arterial blood oxygen content was calculated from blood hemoglobin concentration and the percentage of oxyhemoglobin in arterial blood by use of a standard equation. Mixed venous oxygen content was estimated from arterial oxygen content, cardiac output, and oxygen consumption. Arterial carbon dioxide content was estimated from the arterial PCO$_2$ (Pa$_{CO_2}$), according to Douglas et al. (12), and mixed venous carbon dioxide contents were subsequently estimated from the arterial contents, cardiac output, and carbon dioxide elimination for each subject. A value 0.04 below the arterial pH was used as the mixed venous pH.

Oxygen consumption and carbon dioxide production. Expired gases were collected in a Douglas bag while the number of breaths during 10 min were counted. After thorough mixing, the content of the bag was analyzed by use of the same mass spectrometer as used for the cardiac output measurements. Expired volume was measured by use of a standard gas meter (AB Nordgas, Stockholm, Sweden). Oxygen consumption and carbon dioxide elimination were calculated, and oxygen consumption was corrected for the difference between inspired and expired volume by Haldane transformation of the expired volume (35).

Comparison of SPECT and MIGET

By using the method of Altemeier et al. (1), regional measurements of ventilation and perfusion obtained by SPECT were used to estimate arterial PO$_2$ (Pa$_{O_2}$), Pa$_{CO_2}$, and retentions and excretions of the MIGET gases. These calculations were performed with a Microsoft Excel spreadsheet with macros written with Visual Basic for Applications; input data consist of ventilation and perfusion (in ml/min per voxel), barometric pressure, blood hemoglobin concentration, cardiac output, mixed venous pH, Pa$_{O_2}$ and Pa$_{CO_2}$, and the inert gas blood solubilities. Finally, SPECT-derived estimates of Pa$_{O_2}$, Pa$_{CO_2}$, and retentions and excretions of the MIGET gases were compared with measured values. Parameters derived from the 50-compartment model of the MIGET method were compared with the ventilation and perfusion distributions estimated by the SPECT method.

Experimental Protocol

Figure 2 provides an overview and timeline for the experiments. The subjects sat in the upright posture until administration of the radiopharmaceuticals was completed. Before each data collection, the subjects rested undisturbed for a minimum of 5 min to attain as stable conditions as possible throughout the experiments. Heart rate and invasive blood pressure were monitored from the start of the physiological measurements until the administration of the radioactive isotopes was completed. Pulse oximetry was monitored during rebreathing maneuvers and during Technegas administration by use of an Ultima S device (Datex, Helsinki, Finland). Respiratory rate and tidal volume were monitored during the MIGET sampling and during the administration of the radiopharmaceuticals. After administration of the radiotracers, subjects were transported to the gamma camera in a wheelchair. Subjects were told to refrain from any movements during image acquisition. Physiological measurements and isotope administration lasted 2–3 h, and image acquisitions in the SPECT camera required another 1–2 h.
MEASUREMENTS

General physiological descriptors of the subjects are summarized in Table 1. Cardiac output was 4.3 ± 0.6 l/min, oxygen consumption 280 ± 30 ml/min, and carbon dioxide elimination 240 ± 40 ml/min (volumes in STPD, standard temperature and pressure, dry gas). At the first measurements of the protocol, the average minute ventilation was 7.4 ± 1.7 l/min, alveolar ventilation was 5.7 ± 1.4 l/min, and tidal volume was 690 ± 140 ml (all volumes BTPS). The stability of physiological measurements during the course of the study protocol is summarized in Table 2. The variability, expressed as the mean of all intraindividual coefficients of variation, was less than 15% for all parameters. The lowest pulse oximetry reading recorded during Technegas administration was 95%.

SPECT

Subjects received 86–105 MBq (mean 96 MBq) of 113mIn, corresponding to 270,000–360,000 LyoMAA particles. Technegas breathing required 120–387 s (mean 208 s). There was a good agreement between the volume of SPECT lung masks (mean 3,184 ml, range 2,215–4,237 ml) and measured FRC in the sitting posture (mean 3,219 ml, range 2,150–4,180 ml). Unlike the FRC, the SPECT lung mask does not include the anatomic dead space. The volumes also differ in that the SPECT lung mask represents not only the gas volume in the lungs but also the total volume of the lungs, including tissue and the intravascular blood volume. The number of voxels used for the gas-exchange calculations ranged from 751 to 1,476 voxels/subject. Average radioactivity counts per voxel varied from 1,383 to 6,148 for indium and for technetium from 5,835 to 26,954.

Physiological SPECT evaluation. The precision of the arterial blood gases predicted from regional ventilation and perfusion as measured with the SPECT method is shown in Fig. 3. Mean SPECT-estimated \( \text{PaO}_2 \) was 107 Torr, and mean SPECT-estimated \( \text{PaCO}_2 \) was 37 Torr. Corresponding measured values for \( \text{PaO}_2 \) and \( \text{PaCO}_2 \) were 100 and 38 Torr, respectively. The agreements between measured and SPECT-derived inert gas retentions and excretions are shown in Figs. 4 and 5. The correlation between measured and calculated excretions for all subjects and all inert gases grouped together was 0.99 (Fig. 4). The correlation between measured and calculated retentions of the inert gases was equally high, 0.99 (Fig. 5). In none of the subjects did SPECT data demonstrate blood flow to regions without ventilation (shunt) nor ventilation of regions without blood flow (alveolar dead space). Analysis of the measured MIGET data demonstrated no or insignificant shunt in eight subjects. In one subject, the estimated shunt corresponded to 7% of cardiac output. Compared with the SPECT measurements, the MIGET method demonstrated a larger fraction of the total ventilation going to regions with very high ventilation-to-perfusion ratio (\( V_A/Q \)), i.e., dead space. The difference between the SPECT and MIGET methods in this regard was expected because the SPECT method only identifies alveolar dead space, whereas the MIGET method identifies total dead space. The heterogeneity of SPECT-estimated regional ventilation and perfusion was less than the heterogeneity of the MIGET \( V_A/Q \) distributions (Table 3).

![Fig. 3. Comparison of measured and SPECT-estimated arterial PCO₂ (PaCO₂) and PO₂ (PaO₂) plots according to Bland and Altman (5). X-axis: mean of measured and estimated arterial blood gases. Y-axis: difference between measured and estimated arterial blood gases. Solid lines mark mean differences between measured and estimated gases; dashed line corresponds to a perfect agreement between measured and estimated arterial blood gases.](http://jap.physiology.org/)

Table 1. Circulatory and respiratory parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Value</th>
<th>Mean CV, %</th>
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<tbody>
<tr>
<td>CO, l/min</td>
<td>4.3±0.6</td>
<td></td>
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<tr>
<td>HR, beats/min</td>
<td>76±10</td>
<td></td>
</tr>
<tr>
<td>VO₂, ml/min</td>
<td>280±50</td>
<td></td>
</tr>
<tr>
<td>VCO₂, ml/min</td>
<td>240±40</td>
<td></td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>130±17</td>
<td></td>
</tr>
<tr>
<td>Ve, l/min</td>
<td>7.4±1.7</td>
<td></td>
</tr>
<tr>
<td>VA, l/min</td>
<td>5.7±1.4</td>
<td></td>
</tr>
<tr>
<td>Vt, ml</td>
<td>690±140</td>
<td></td>
</tr>
<tr>
<td>RR, breaths/min</td>
<td>11±2</td>
<td></td>
</tr>
<tr>
<td>PaO₂, Torr</td>
<td>98±3</td>
<td></td>
</tr>
<tr>
<td>PaCO₂, Torr</td>
<td>38±5</td>
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</tr>
</tbody>
</table>

Values are means ± SD for all subjects at the first measurement of each parameter. CO, cardiac output; HR, heart rate; VO₂, oxygen consumption; VCO₂, carbon dioxide elimination (VO₂ and VCO₂ are ml s⁻¹); SBP, systolic blood pressure; Ve, expired minute volume; VA, alveolar ventilation; Vt, mean tidal volume during the registration (all ventilatory volumes as BTPS); RR, mean respiratory rate during the registration; PaO₂, measured arterial PO₂; PaCO₂, measured arterial PCO₂.

Statistics

All data, unless otherwise stated, are presented as means ± SD. The agreements between measured retentions and excretions of the MIGET gases and arterial blood gases were compared with those estimated from the SPECT data by using plots of linear correlation and by the method of Bland and Altman (5).

RESULTS

Physiological Measurements

The precision of the arterial blood gases predicted from regional ventilation and perfusion as measured with the SPECT method is shown in Fig. 3. Mean SPECT-estimated \( \text{PaO}_2 \) was 107 Torr, and mean SPECT-estimated \( \text{PaCO}_2 \) was 37 Torr. Corresponding measured values for \( \text{PaO}_2 \) and \( \text{PaCO}_2 \) were 100 and 38 Torr, respectively. The agreements between measured and SPECT-derived inert gas retentions and excretions are shown in Figs. 4 and 5. The correlation between measured and calculated excretions for all subjects and all inert gases grouped together was 0.99 (Fig. 4). The correlation between measured and calculated retentions of the inert gases was equally high, 0.99 (Fig. 5). In none of the subjects did SPECT data demonstrate blood flow to regions without ventilation (shunt) nor ventilation of regions without blood flow (alveolar dead space). Analysis of the measured MIGET data demonstrated no or insignificant shunt in eight subjects. In one subject, the estimated shunt corresponded to 7% of cardiac output. Compared with the SPECT measurements, the MIGET method demonstrated a larger fraction of the total ventilation going to regions with very high ventilation-to-perfusion ratio (\( V_A/Q \)), i.e., dead space. The difference between the SPECT and MIGET methods in this regard was expected because the SPECT method only identifies alveolar dead space, whereas the MIGET method identifies total dead space. The heterogeneity of SPECT-estimated regional ventilation and perfusion was less than the heterogeneity of the MIGET \( V_A/Q \) distributions (Table 3). An example of measured MIGET result and MIGET results derived from the SPECT-estimated \( V_A/Q \) distribution from one subject is presented in Fig. 6.

![Fig. 3. Comparison of measured and SPECT-estimated arterial PCO₂ (PaCO₂) and PO₂ (PaO₂) plots according to Bland and Altman (5). X-axis: mean of measured and estimated arterial blood gases. Y-axis: difference between measured and estimated arterial blood gases. Solid lines mark mean differences between measured and estimated gases; dashed line corresponds to a perfect agreement between measured and estimated arterial blood gases.](http://jap.physiology.org/)
DISCUSSION

The principal finding of this study is the good agreement between measured gas exchange and gas exchange predicted from SPECT-derived estimations of regional ventilation and perfusion. This supports the use of the SPECT method to measure regional perfusion and ventilation in small volume units of lung in healthy human volunteers. Several methodological aspects of our study deserve comments. The following discussion details the limitations of the study design, limitations of the SPECT method, and differences between the SPECT and MIGET methods.

Limitations of the Study Design

In this study, our objective was to develop and evaluate a method to measure regional ventilation and perfusion in humans. Validating or proving measurements of regional ventilation and perfusion require gold standards for comparison. Lacking an applicable gold standard, we have employed a strategy comparing multiple indirect assessments that are each “necessary but insufficient” to validate our method. A further limitation of the present study is that only healthy subjects were studied. In normal lungs, the heterogeneity of regional ventilation and perfusion distributions is small, and the correlation between these distributions is high. Gas exchange estimated from these distributions is, therefore, mostly dependent on the measurement of global alveolar ventilation and global lung perfusion, with regional ventilation and perfusion data making little contribution to the results of the calculations. In fact, gas exchange calculated by using a single-compartment model, i.e., using only global measurements of cardiac output and minute ventilation, predicts arterial blood gases and inert-gas retentions and excretions very similar to those predicted by the SPECT method. Although the ability to predict whole lung gas exchange supports the accuracy of our measurements, it cannot prove that they are correct. However, if we could not predict gas exchange, it would prove that our measurements are not valid. Accurate prediction of arterial blood gases from SPECT studies of patients with abnormal ventilation and perfusion distributions, producing gas-exchange abnormalities, would provide stronger evidence that our method accurately estimates regional ventilation and perfusion. Despite that, we considered it reasonable to include only healthy volunteers in this first study of a new method. Our results include multiple measures of ventilation and perfusion distributions and of whole lung gas exchange. Neither alone can validate our methods, but the fact that all are in agreement is evidence that our method may have merit. Prior validations of new imaging methods for regional ventilation and perfusion have solely compared their distributions with previous results with similar techniques. Other than Tokics et al. (51), we believe this is the only other study to attempt validation of an imaging technique with independent methodologies.

Limitations of the study protocol. Ideally, physiological measurements and MIGET should have been performed simul-
MIGET and SPECT methods are not comparable. Ventilation is omitted from the table because the fractions obtained with the anatomic and apparatus dead space ventilation. The dead space fraction of total ventilation and excretion estimated from SPECT data. 

Table 3. Characteristics of the \( V/Q \) distributions

<table>
<thead>
<tr>
<th></th>
<th>MIGET</th>
<th>SPECT</th>
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<tr>
<td>Mean ( V_{a}/Q ) of ( Q )</td>
<td>1.44±0.33</td>
<td>1.38±0.34</td>
</tr>
<tr>
<td>log SD ( Q )</td>
<td>0.62±0.41</td>
<td>0.23±0.05</td>
</tr>
<tr>
<td>Qs/Qt</td>
<td>0.01±0.02</td>
<td>0±0</td>
</tr>
<tr>
<td>Mean ( V_{a}/Q ) of ( V_{a} )</td>
<td>1.88±0.37</td>
<td>1.46±0.38</td>
</tr>
<tr>
<td>log SD ( V_{a} )</td>
<td>0.37±0.12</td>
<td>0.27±0.07</td>
</tr>
<tr>
<td>DISP R-E*</td>
<td>4.07±3.78</td>
<td>0.89±0.39</td>
</tr>
<tr>
<td>Predicted PaO(_2)</td>
<td>89±12.6</td>
<td>107±7.0</td>
</tr>
<tr>
<td>Predicted PaCO(_2)</td>
<td>37±3.0</td>
<td>37±2.9</td>
</tr>
</tbody>
</table>

Values are means ± SD. MIGET, parameters derived from the 50-compartment model of the multiple inert-gas elimination technique method. SPECT, actual ventilation and perfusion distributions as estimated by the single-photon-emission computed tomography method. Mean \( V_{a}/Q \) of \( Q \), mean of the perfusion (Q) distribution with reference to log \( V_{a}/Q \); log SD, standard deviation of the Q distribution with reference to log \( V_{a}/Q \); Qs/Qt, shunt blood flow as fraction of total blood flow (cardiac output); mean \( V_{a}/Q \) of \( V_{a} \), mean of the \( V_{a} \) distribution with reference to log \( V_{a}/Q \); log SD, standard deviation of the \( V_{a} \) distribution with reference to log \( V_{a}/Q \); DISP R-E*, MIGET dispersion index, corrected for apparatus and anatomic dead space. The dispersion index is defined as the root square differences between the retention and excretion (R-E) for the 6 inert gases. Correction for apparatus and anatomic dead space is necessary to make it comparable with dispersion index calculated from SPECT-derived Q/Q distributions. The differences in mean \( V_{a}/Q \) of \( V_{a} \) caused by different minute ventilation during MIGET sampling and Technegas inhalation and by minute ventilation during MIGET, including anatomic and apparatus dead space ventilation. The dead space fraction of total ventilation is omitted from the table because the fractions obtained with the MIGET and SPECT methods are not comparable.

Fig. 6. Results from 1 subject. A: inert-gas retention and excretion estimated from SPECT data. B: ventilation-to-perfusion ratio (V/Q) distribution of SPECT-measured regional ventilation and perfusion. C: measured retention and excretion of inert gases. Measured inert-gas excretion was corrected for anatomic dead space. D: V/Q distribution of regional ventilation and perfusion derived from measured inert-gas exchange. Dead space estimated by MIGET includes anatomic and apparatus dead space; in contrast, the SPECT method only estimates alveolar dead space, hence the difference in the dead space in the V/Q distributions.

Taneously with the administration of the radiotracers. Additionally, a pulmonary catheter providing mixed venous blood samples would have eliminated the need to measure oxygen uptake and carbon dioxide elimination. Also, cardiac output could have been measured simultaneously with MIGET sampling and administration of radiopharmaceuticals. Any error in these measurements and calculations may contribute to the differences between measured and calculated values. Because it is used several times in the calculations, the estimates of cardiac output have an especially great influence on estimates of respiratory and inert-gas exchange, and also on measured MIGET retentions and excretions. Right heart catheterization was not considered justified in the present study of healthy volunteers because alternative techniques were available.

The data analysis assumes that cardiac output, oxygen uptake, and carbon dioxide elimination remained unchanged during the study. Any deviations from this assumption may reduce the agreement between measured and SPECT-estimated arterial blood gases and MIGET indexes. To maintain as stable conditions as possible, the subjects remained seated all through the first part of the protocol, and each measurement was preceded by a 5-min period of inactivity. Although not completely stable, the variability of the physiological measurements during the course of the experiment was relatively low. In animal studies, regional ventilation and perfusion in the same posture have been demonstrated to be stable over time (17, 18, 43).
Changes in the distributions of ventilation and perfusion between MIGET measurements and administration of radiotracers are, therefore, unlikely to have influenced the agreement between measured and estimated values. For the same reason, we believe that the sequential, rather than simultaneous, administration of the radiotracers did not affect the results.

Limitations of the SPECT Method

Correction for scatter and attenuation. The SPECT method uses a gamma camera to externally detect photons emitted from radiotracers within the body. Because of interaction with matter along its pathway through the body, only part of the radiation emitted from a certain volume unit of the lung will be detected by the gamma camera. When two different tracers are present simultaneously, scattered photons originating from the isotope with the higher energy adds to the counts detected in the energy window of the other isotope (known as downscatter). These phenomena must be taken into account when SPECT is used for quantitative physiological measurements. The SPECT method used in this study incorporates new methods of correcting for attenuation, scatter, and downscatter. In phantom studies, these methods have been shown to allow an accurate retrieval of the true regional radioactivity, with mean differences between SPECT data from a low-density phantom and corrected value in a thorax phantom of \(-0.9\%\) for \(^{111m}\)In and \(-1.9\%\) for \(^{99m}\)Tc (47).

Spatial resolution. The resolution of imaging equipment is characterized by the full-width half-maximum (FWHM). The FWHM for our SPECT system is 16 mm. This measure means that 50% of the counts of one lung voxel will be counted in a voxel of another lung region 16 mm from the first one. Consequently, the radioactivity measured within one voxel is not independent of the activity in the surrounding voxels. This is the partial volume effect. The movements of the lung during breathing and movements caused by the pulsations of the heart and the large vessels further reduce the spatial resolution. The partial volume effect also causes a gradual attenuation of the radioactivity measured at the lung edges.

Macroaggregates as markers of regional perfusion. With SPECT, imaging of regional blood flow is accomplished by microembolization of radionuclide-labeled particles in the arterial pulmonary circulation. It is based on the principle that the number of particles trapped in a particular lung volume is proportional to regional blood flow. Both macroaggregates of albumin and 15-\(\mu\)m microspheres have been shown to faithfully measure regional pulmonary blood flow compared with other measurement methods (4, 19, 38).

Technegas as marker of regional ventilation. Technegas is a dispersion of ultrafine graphite particles labeled with \(^{99m}\)Tc (11). Although determination of the particle size with different techniques has yielded somewhat different results (10, 11, 26, 27, 33, 34, 48, 49), most authors seem to agree that the diameter of the majority of particles is \(<200\) nm, a particle size that is associated with predominating alveolar deposition (7, 50). Isawa et al. (24) reported that 84.9\% of Technegas retained in the lung was deposited in alveoli. Several studies using both planar imaging and SPECT have found minor discrepancies between the distributions of true radioactive gases and Technegas. Isawa et al. (25), using planar imaging, compared the distributions of Technegas and radioactive krypton (\(^{81m}\)Kr) in both healthy subjects and patients and found that the two tracers produced somewhat different ventilation distributions. In contrast, Amis et al. (2), also using planar imaging, compared the distribution of Technegas with the distribution of radioactive xenon (\(^{133}\)Xe) and found no differences. Hartmann et al. (22) compared \(^{81m}\)Kr and Technegas as the marker of regional ventilation for SPECT diagnosing pulmonary embolism: in 15 of 92 patients, the \(^{81m}\)Kr and Technegas examinations produced different diagnostic conclusions. We are not aware of any study quantitatively comparing the distribution of Technegas with that of a true gas at the level of spatial resolution used in this study. Pellegrino et al. (41) used Technegas and SPECT to study regional airflow limitation during methacholine-induced bronchoconstriction. In this study, Technegas deposition in larger airways increased with increasing bronchoconstriction. It is thus possible that in diseased lung there is a larger discrepancy between the distribution of Technegas and the distribution of regional ventilation. Obviously, the estimates of regional ventilation obtained with the SPECT method will suffer from any failure of the deposition of the Technegas particles to mimic the true distribution of alveolar ventilation. The duration of the image acquisition also requires the radiotracer distributions in the lung to be stable over an extended period of time. The hydrophobic nature of the Technegas particles is claimed to be important to lung imaging, preventing deposition in the airways and thereby preventing the distribution to be influenced by mucociliary clearance. Amis et al. (2) found no change in the distribution of Tc activity in the lung after Technegas inhalation when imaging was repeated after 20 min. Again, this evaluation used planar imaging and comparing lung regions much larger than the voxels used in the present study. Xu et al. (59) observed an unintentional contamination of Technegas with Pertechegas, which is produced by transformation of Technegas in the presence of moisture. This is an important observation because Pertechegas is rapidly cleared into the blood with a half-life of \(~10\) min. Thus, in quantitative studies using Technegas, the absence of Pertechegas needs to be verified. These results were published after the completion of the present studies. We have not been able to exclude the possibility that the Technegas used in this study was contaminated in this manner, but, because the minimum time from Technegas administration to image acquisition was 30 min, we believe that any contamination will not have influenced our results.

Differences Between the SPECT and MIGET Methods

Although they are fundamentally different, the MIGET and SPECT methods share the ability to produce information on ventilation and perfusion distributions. MIGET uses measured global gas exchange to estimate the distributions of perfusion and ventilation to 50 compartments with different \(V/A/Q\). The method produces no data on regional ventilation and perfusion because it does not include any spatial information; there is no defined anatomic counterpart to the 50 \(V/A/Q\) compartments. MIGET, therefore, cannot be used to explore the factors that determine the spatial distribution of regional ventilation and perfusion. In contrast, the SPECT method results in estimates of regional spatial distributions of ventilation and blood flow. These data can be transformed to \(V/A/Q\) distributions similar to those obtained with MIGET. Furthermore, the SPECT method...
can be used to identify anatomic lung regions with V\textsubscript{A}/Q mismatch. We believe this spatial information to be crucial if the goal is not only to describe but also explain the cause of gas-exchange impairment or differences in gas exchange in different situations. For example, localizing blood flow through low V\textsubscript{A}/Q regions might provide insights into mechanisms causing difficulties in oxygenation.

The SPECT method did not detect any intrapulmonary shunt in any of the subjects, whereas the MIGET results indicated that there was a small shunt in several of the subjects. These discrepancies could be explained by the fundamental differences between the methods. The shunt flow measured by the MIGET method corresponds to the sum of all blood flow differences between the methods. The shunt discrepancies could be explained by the fundamental differences that there was a small shunt in several of the subjects. These in any of the subjects, whereas the MIGET results indicated causing difficulties in oxygenation.

Approximately 3–5 h were required to complete the experimental protocol. The SPECT study in itself required 1–2 h (most studies were completed in 1 h). Thus in future studies 1–2 h should be adequate for each experiment, if relative quantitative measures of regional ventilation and perfusion are considered sufficient. Absolute values of regional ventilation and perfusion (ml/min) require measurement of anatomic dead space, which in this study took ~10 min to perform, and measurements of global ventilation and cardiac output. The time required for the latter measurements, of course, depends on the chosen methodologies. Our subjects found it somewhat difficult but still possible to avoid movements during the image acquisition.

Repeated studies. In this study, the subjects were estimated to receive an effective dose of 5 mSv. The limits for acceptable radiation exposure of healthy individuals vary worldwide. The radiation dose used in this study is of the same magnitude as the effective annual dose from radon and background radiation for the average Swedish individual and is accepted by the local Radiation Safety Committee for studies of volunteers and patients; 5 mSv is about one-half of what is obtained from a clinical computed tomography (CT) examination to diagnose pulmonary embolism. In the present examinations, the signal-to-noise ratio was adequate, indicating that a reduction of the administered radioactivities is possible. Reducing the doses by 50% would probably not distort the information too much, but allow for a repeated examination to study some clinical or physiological variable without increasing the radiation dose. However, the second examination should not be performed until after at least 2 days because of the physical half-life of 6 h for 99mTc.
method over prior methods is the ability to analyze simultaneous distributions of ventilation and perfusion for whole lung. Another advantage is that the radiopharmaceuticals can be administered outside the camera, which means that the distribution of ventilation and perfusion during conditions different from those during imaging (e.g., a different posture) can be studied. In this situation, the interpretation of regional distributions is complicated by any changes in the distribution of lung tissue within the thorax. It is also an advantage that SPECT imaging does not require any special respiratory maneuver, which might affect both the distribution of both regional ventilation and perfusion. The disadvantages of the SPECT method are mostly related to the spatial resolution, which is lower than for some of the other methods, and the partial volume effect. Time required for image acquisition is longer for SPECT than for CT- and PET-based methods. The radiation dose is an obvious disadvantage, which limits the number of examinations that can be performed in the same individual. Although some PET techniques use a radiation dose much lower than the doses used in this study (40), dose restriction applies to a similar or even greater extent to other CT and PET techniques.

In this study, we found a good agreement between measured gas exchange and estimates of regional and whole lung gas exchange from SPECT measurements. Despite the limitations of our study design and the SPECT method, we remain optimistic about the potential for this new method to provide new insights into the mechanisms responsible for the distributions of regional ventilation and perfusion in humans. In addition, this method offers a tool for measuring regional ventilation and perfusion under physiological conditions not amenable for CT, PET, and MRI methods.

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