USE OF ^{13}N IN STUDIES OF AIRWAY CLOSURE AND REGIONAL VENTILATION

Reginald Greene, Bernard Hoop, and Homayoun Kazemi

Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts

There is a high incidence of chronic obstructive airways disease in the general population as determined by postmortem examination (*1*). In many cases the findings at necropsy are not suspected during life and to a large extent chronic airways disease is not diagnosed clinically until it is rather far advanced.

Pulmonary function studies based on measurements of air flow rates are insensitive detectors of early obstructive airways disease for two reasons: first, the disease is primarily located in small airways of less than 2 mm diam, and second, small airways normally make up less than 10% of total airways resistance (*2,3*). As a result, extensive changes in small airways are necessary before total airways resistance is significantly increased, justifying the term "silent zone" to describe the small airways (*4,5*).

Although obstructive small airways disease results in little increase in overall airways resistance, it probably leads to premature airway closure and significant gas exchange impairment. Thus measurements which rely not on changes of total airways resistance (e.g., $FEV_{1.0}$ and peak flow rate) but on abnormalities of airway closure may detect relatively early obstructive airways disease. The purpose of this report is to describe studies of airway closure using ^{13}N-labeled molecular nitrogen (^{13}N-N_2).

METHODS

Production of ^{13}N-labeled molecular nitrogen. Molecular nitrogen is very insoluble in blood (14 times less soluble than xenon) and is therefore highly suitable for studies of ventilation isolated from blood flow effects (*6*). These studies use high-specific-activity, ^{13}N-labeled molecular nitrogen.

Nitrogen-13, which has a physical half-life of 9.96 min and decays by positron emission resulting in 0.511-MeV gamma radiation, was one of the first artificially produced radioactive elements. It was observed by Curie and Joliot in 1934 after the bombardment of boron with alpha particles (*7*). For clinical application, ^{13}N has been produced by the $^{12}C(d,n)^{13}N$ reaction during the deuteron irradiation of graphite (*8*). It is produced in the Massachusetts General Hospital medical cyclotron by the deuteron irradiation of gaseous carbon dioxide (*9*). A 6-MeV deuteron beam with a cross sectional area of approximately 1×9 cm is directed through a 0.006-mm-thick aluminum window into a 14-cm-deep brass target box of volume 0.75 liters through which a gas mixture of 99.3% carbon dioxide and 0.7% air at 1,000 mmHg pressure is passed. Recoiling ^{13}N atoms undergo an exchange with the nitrogen molecules in the target gas to form ^{13}N-labeled N_2 (*9*). A deuteron beam current of 10 μA and a target gas flow rate of 1.0 liter/min are maintained.

The irradiated gas activity is monitored in a flow-through ionization chamber. The measured ^{13}N yield is approximately 40 mCi/μA-hr. Nitrogen-13 activity is identified by a determination of its half-life. Under the present irradiation conditions no other activity is observed in excess of 0.1%.

For clinical use, small amounts of nitrogen gas are added to the irradiated gas and the remaining CO_2 is absorbed in a NaOH solution to yield high-specific-activity (1–2 mCi/cc) ^{13}N-N_2.

Analysis of the resultant gas mixture is performed using conventional gas radiochromatography. Because of their solubility in aqueous base, NO and NO_2 are effectively removed from the gas phase, and the resulting gas is essentially free of toxic oxides of nitrogen.

No N_2O, labeled or unlabeled, is detected in the resultant gas since the average deuteron beam irradiation dose to the target gas is sufficient to decompose this compound (*9*).

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For reprints contact: Reginald Greene, Massachusetts General Hospital, Boston, Massachusetts 02114.

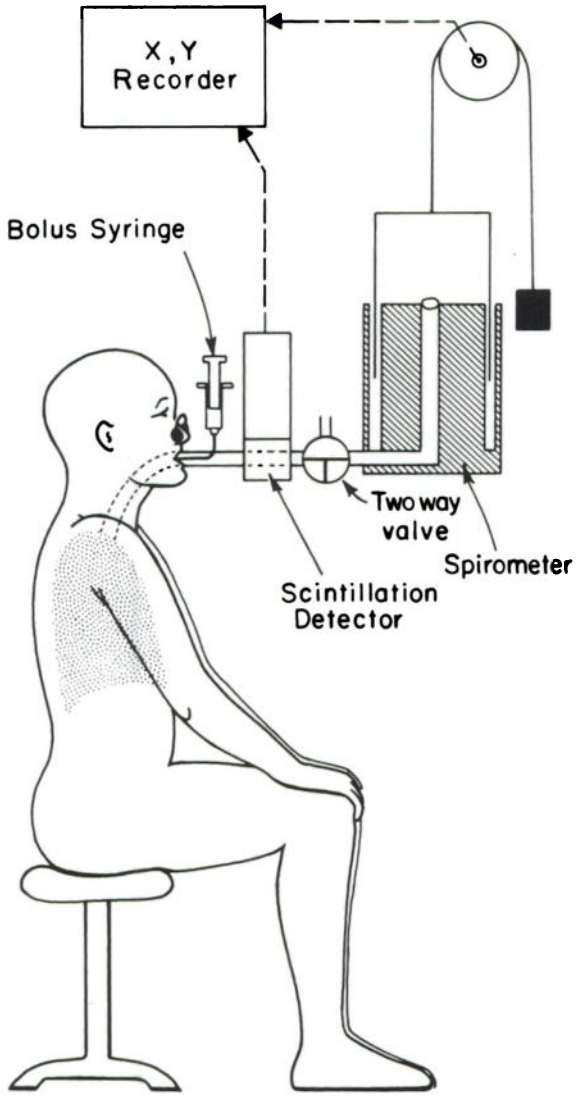

FIG. 1. Diagram of subject and apparatus during airway closure measurement.

Calculations based on a 30-sec breath hold of 1 mCi ^{13}N-N_2 estimate the radiation dose to the lungs and total body to be 15 and 1 mrad, respectively.

Rationale of airway closure measurement. Airway closure occurs because the distending or transpulmonary pressure (TPP) may fall below the critical closing pressure of small airways (about 2 cmH_2O) (*6*). TPP may fall below the critical closing pressure in normal adults breathing at low lung volumes or in older people or bronchitics during normal tidal breathing as a result of increased lung compliance and diminished support of the small airways (*10–15*). The airway closure that results tends to occur first at the lung base because the TPP is less in the dependent than in the superior portions of the lung (*16*).

A 2-ml bolus of 1 mCi ^{13}N-labeled molecular nitrogen (followed by air) which is slowly inhaled after a maximum expiration to residual volume (RV), will be distributed only to airways which remain open. The small airways which close at the lung base at RV will not reopen until a critical opening pressure is exceeded (*4*). The small bolus will be distributed to the periphery of the lung during a slow inhalation before the critical opening pressure is overcome in the closed airways. After complete inspiration with air, an analysis of the radioactivity of the subsequent expirate will indicate the proportion of gas coming from previously open and closed airways. The first few hundred milliliters of the expirate representing the anatomic dead space of the tracheobronchial tree will not contain any radioactivity. The counting rate of the subsequent part of the expirate will rise to a plateau level representing the proportion of expirate coming from previously open airways containing ^{13}N and previously closed airways containing only air. When the TPP again falls below the critical closing pressure at the lung base during the expiration, small airways will again close; the expirate will no longer be diluted by air coming from lung base and the counting rate will suddenly rise. The volume of the lung at which this occurs has been called the "closing volume" of the lung (*16*). With moment-to-moment monitoring of changes in long volume and expired radioactivity the "closing volume" can be determined.

Technique of airway closure measurement. The patient is seated with a nosepiece in place breathing from a mouthpiece attached either to room air or an air-filled, 9-liter spirometer by a two-way tap (Fig. 1). The axis of the spirometer pulley is attached to a potentiometer calibrated to read volume displacement. The analog output of the potentiometer is converted to a form compatible for digital tape and the signal is monitored during the study along the abscissa of an x-y plotter. A thin-walled 2-cm tube runs from the mouthpiece through a shielded 5 × 5-cm NaI(Tl) crystal which is connected to a photomultiplier tube-preamplifier unit. The output of this scintillation detector which monitors expired activity is fed to a magnetic-tape system through a count rate meter, and the signal is monitored during the study along the ordinant of the x-y plotter. The magnetic-tape system allows for storage and retrieval of data.

A 20-gage needle through which the bolus is injected ends in the center of mouthpiece within 2 cm of the oral cavity and is connected to a syringe just proximal to the scintillation detector.

Breathing from room air the patient is instructed to take in a large breath and then expire maximally

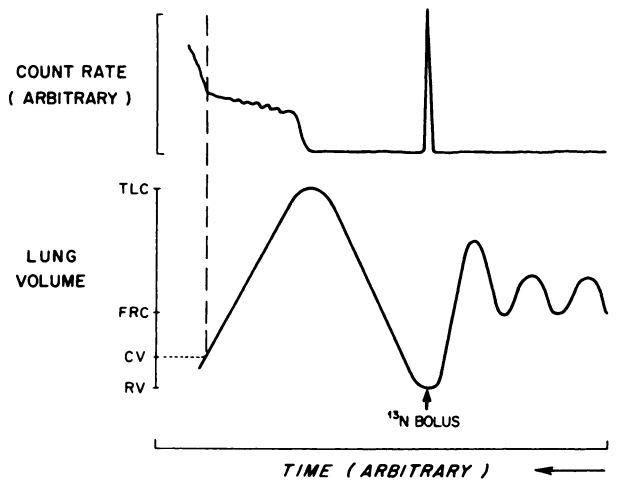

FIG. 2. Diagram of airway closure maneuver and expired radioactivity. Bottom figure shows spirometer trace reading right to left. It shows volume changes during two tidal breaths followed by larger inspiration and maximum expiration to RV. 2-ml ^{13}N bolus is injected during short breath hold at RV and slow steady inhalation to TLC follows. Finally slow exhalation to RV is made. Top figure is simultaneous plot of expired activity against time. Reading from right to left there is low-level background activity until bolus is injected at RV at which time counter registers high counting rate. During inspiration counting rate falls again to background. During subsequent expiration from TLC counting rate increases to rising plateau level until airway closure begins to occur and counting rate suddenly rises; dashed line correlates sudden counting rate rise with volume of lung at which it occurs. CV is "closing volume." FRC is functional residual capacity.

to RV. During a momentary breath hold at RV, the bolus of ^{13}N-N_2 is injected into the mouth and the airway is switched into the air-filled spirometer system. The patient is then instructed to inspire very slowly and steadily to total lung capacity (TLC). The inspiration should take 10–15 sec. After a momentary pause at TLC, the patient then slowly and steadily expires maximally back to RV. During this latter maneuver the expired volume and radioactivity are monitored on the x-y plotter (Fig. 2). The procedure may be repeated after ^{13}N has been washed out of the lungs and the spirometer system.

The volume displacement from TLC to the "closing volume" (CV) is corrected for temperature and expressed as ml (BTPS). It can then be expressed as a fraction of vital capacity (% VC) or as a fraction of total lung capacity (% TLC). The CV may also be related to the volume of the lung after a normal quiet expiration, the functional residual capacity (FRC). This latter relationship is important because FRC is the minimum volume of the lung at which quiet breathing is performed. Airway closure that occurs above FRC can be expected to affect pulmonary gas exchange adversely.

EXAMPLES OF AIRWAY CLOSURE STUDIES

Figure 3 is an x-y plot of an airway closure study in a 32-year-old chemist who was exposed to beryllium dust 2 years before this study. Standard pulmonary function tests and air flow rate measurements were normal. Arterial blood gas tensions were within normal limits except for a fall in arterial oxygen tension (PaO_2) of 8 mmHg during exercise. The "closing volume" was found to be 45.4% of TLC or 330 ml below FRC in the sitting position. During quiet breathing the patient's airways at the lung base remain open, but during deep breathing with wide excursions to very high and to very low lung volumes the airways at the lung base will be closed during part of every breath. This phenomenon may explain the observed fall in PaO_2 with exercise. On assuming the recumbent position FRC falls about 10% of TLC while CV remains the same (*14,18*). Since airway closure occurs in this patient at 45% TLC and FRC falls from 50% to 40% TLC in changing from the seated to the recumbent position, airway closure probably occurs in the supine position during quiet breathing. This study suggests that the patient has small airways disease despite normal air flow rate measurements.

Premature airway closure may also contribute to abnormal gas exchange in diseases generally associated with alterations in the vascular bed. A 39-year-old nonsmoking housewife with dyspnea on exertion and bilateral hilar lymph node enlargement detected on chest radiography had normal pulmonary function tests except for a reduced carbon monoxide diffusing capacity and an increased alveolar-arterial oxygen tension difference. Noncaseating granulomata were found in a liver biopsy, and the patient was presumed to have sarcoidosis. A ^{13}N-N_2 bolus study indicated the presence of airway closure during quiet tidal breathing in the recumbent posi-

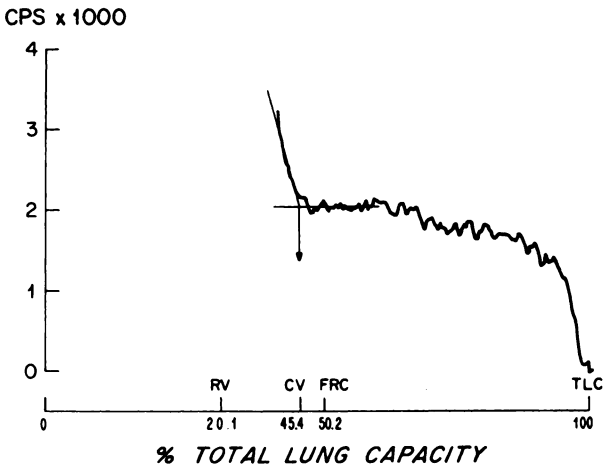

FIG. 3. Airway closure measurement in patient with normal air flow rates. "Closing volume" (CV) is closer to FRC than expected in seated position. Cardiogenic oscillations are evident along plateau (*17*).

tion (Fig. 4). This phenomenon explains at least in part the patient's abnormal gas exchange.

REGIONAL VENTILATION

The regional ventilation of the ^{13}N-N_2 bolus as a proportion of regional lung volume may be used as an indication of the distribution of airway closure in the lungs. Three pairs of appropriately shielded scintillation detectors positioned posteriorly over the upper, mid- and lower lung regions may be used. The output of these detectors can be fed into the magnetic-tape system for retrieval at the end of the study.

The level of activity in a given region after a maximum inspiration is a measure of the regional ventilation ($\dot{V}$) of the bolus. After a maximum expiration maneuver to detect the "closing volume" the patient rebreathes from the spirometer system which is equipped with a soda lime CO_2 absorber and recirculating fan. Oxygen is added continuously in amounts sufficient to match the absorbed CO_2. After equilibration of activity between the lungs and the spirometer as judged by a diminished inspiratory-

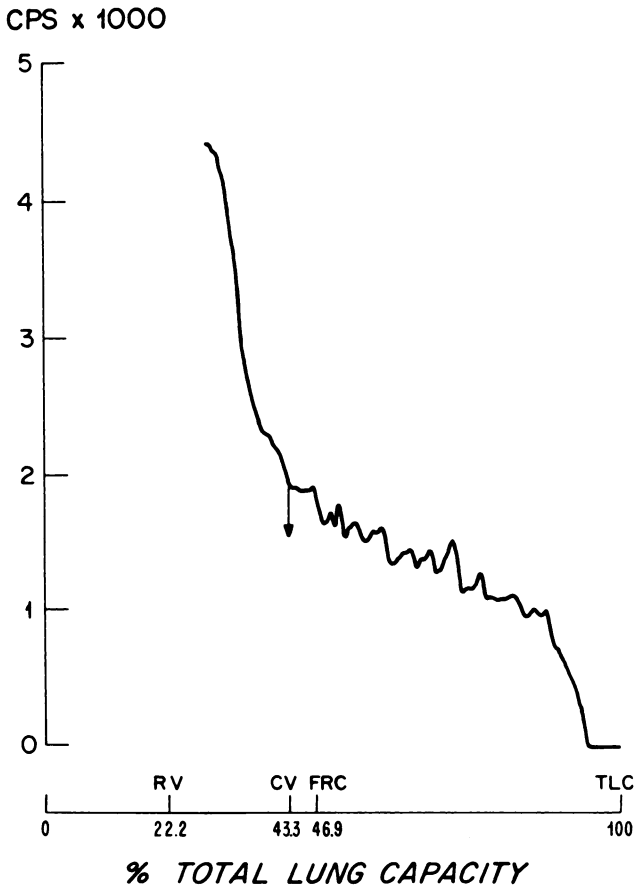

FIG. 4. Airway closure measurement in patient with presumed sarcoidosis. CV is only 3.6% below FRC when seated. Airway closure occurs during quiet breathing in recumbency when FRC falls 10% of TLC.

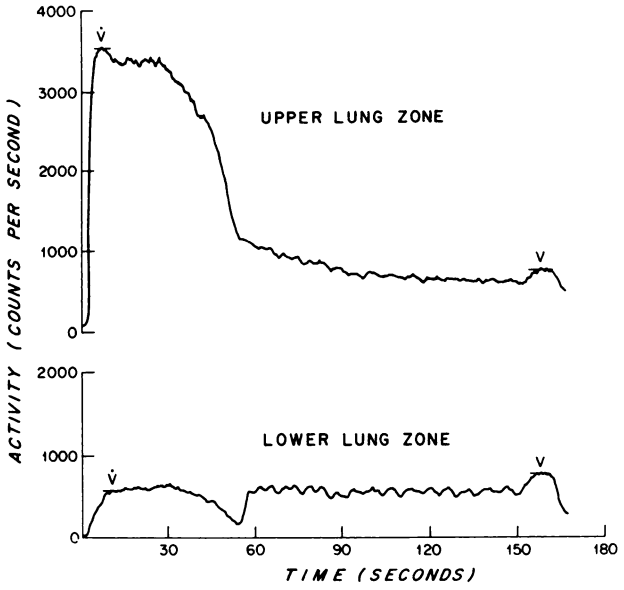

FIG. 5. Upper and lower lung activity after ^{13}N-N_2 bolus study in normal subject. $\dot{V}$ represents activity levels after slow inspiration from RV to TLC. V (corrected for decay) equals level of activity in each zone after equilibration. Ratio $\dot{V}/V$ is proportional to regional distribution of bolus per lung volume. Six times as much of bolus per lung volume is distributed to upper as to lower lung zone.

expiratory activity difference on the expired counter, the patient takes in a maximum breath and holds it for 10 sec. The counting rate (corrected for decay) at this time is proportional to the regional volume of the lungs (V). The ratio of the ventilation and the volume of the bolus gives a measure of the regional distribution of ventilation per unit lung volume ($\dot{V}/V$). The $\dot{V}/V$ for each region is proportional to the number of open airways per unit volume of the region and is an indirect measure of the regional distribution of airway closure.

Figure 5 shows plots of activity versus time in upper and lower lung zones in a normal subject after the inhalation of a ^{13}N-N bolus from RV. The proportion of the counting rate after the inspiration of the ^{13}N-N bolus and after equilibration shows that six times as much of the bolus is distributed to the upper as lower lung zone per volume of lung. The distribution of the bolus is inversely proportional to airway closure, so that the smaller $\dot{V}/V$ in the lower lung zone indicates that airway closure tends to occur at the lung base. These same results would be expected in a patient with small airways disease. Inhalation of the bolus from a higher lung volume (near FRC) would be expected to result in an almost even distribution of $\dot{V}/V$ between the upper and lower lung zones in the normal subject, but the patient with premature airway closure might continue to show evidence of airway closure at the lung base.

DISCUSSION

Peripheral airways (<2 mm in diam) are now recognized as the major site of increased resistance in chronic obstructive airways disease. Measurements of ventilation and airway closure provide potentially more sensitive indications of early small airways disease than tests based on abnormalities of airway resistance.

The physiological importance of airway closure rests on its effect on pulmonary gas exchange. The predominant occurrence of airway closure in the dependent portions of the lung where perfusion tends to be greatest (and ventilation is normally greatest, too) results in ventilation-perfusion mismatch which interferes with the function of the lung as a gas exchanger. Airway closure occurring during tidal breathing therefore can be expected to impair gas exchange. Because normal tidal breathing is performed at a significantly lower lung volume in the recumbent compared with the seated position, airway closure may play a significant role in causing impaired gas exchange in the bedridden patient (*19*).

High-specific-activity ^{13}N-labeled molecular nitrogen is a most convenient radioactive gas with which to make measurements of airway closure and ventilation by virtue of its low solubility in blood. Its energetic radiations produce little self-absorption in the chest during external measurement of regional ventilation. Measurements of airway closure made with nonradioactive gases such as nitrogen and argon do not allow the external detection of regional ventilation. External measurements of airway closure and ventilation may be made with ^{133}Xe, but its much greater solubility in blood than that of nitrogen and its low-energy gamma emissions reduce its usefulness.

SUMMARY

The technique and potential clinical advantages of airway closure and pulmonary ventilation studies with high-specific-activity ^{13}N-labeled molecular nitrogen are presented. External detection of ^{13}N is described in ventilation studies, and the simultaneous monitoring of lung volume changes and of expired ^{13}N boluses are described in airway closure measurements. The application of these studies may be of particular significance in the early detection of obstructive lung disease and pathophysiological mechanisms involving the lung in cardiorespiratory disorders.

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