CLINICAL SIGNIFICANCE OF PULMONARY FUNCTION TESTS

The Volume of Isoflow and Increase in Maximal Flow at 50 Percent of Forced Vital Capacity during Helium-Oxygen Breathing as Tests of Small Airway Dysfunction*

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The purpose of this report is to review the role of helium in the early detection of obstructive pulmonary disease. The underlying physiologic mechanisms of the volume of isoflow (the volume at which flow was the same with the subject breathing air and breathing a mixture of 80 percent helium and 20 percent oxygen) and increases in maximal flow at 50 percent of vital capacity (Vmax50) after breathing helium are reviewed. These tests are able to detect physiologic abnormalities in asymptomatic subjects when the results of other tests are normal; and following cessation of smoking, abnormal results may be reversible. The volume of isoflow is increased when maximal flow is reduced because of loss of elastic recoil or increase in upstream resistance. The increase in Vmax50 after breathing helium appears to be relatively specific for the caliper of the small airways, being uninfluenced by loss of elastic recoil; it can further help to localize the major site of obstruction to either small or large airways. At present, random screening for early unsuspected disease is not warranted, and these tests remain an investigative tool.

It has recently been demonstrated that the major site of physiologic abnormalities in chronic obstructive pulmonary disease occurs in peripheral airways (less than 2 mm in diameter). Furthermore, in early disease, at a time when the process may still be reversible, routine studies of pulmonary function, including airway resistance, forced expiratory volume in one second, (FEV1), and other flow rates at high pulmonary volumes, may be normal or borderline because they do not reflect the peripheral airways which are the site of obstruction. These peripheral airways normally contribute only a small percentage of total airway resistance; however, the contribution of the resistance offered by peripheral airways to total airway resistance increases at low lung volumes. Therefore, flow rates obtained at effort-independent lower lung volumes, such as the mean forced expiratory flow during the middle half of the forced vital capacity (FEF25-75%) may be abnormal in early disease because they better reflect the abnormalities in the peripheral airways.

Newer, more sensitive physiologic tests have been introduced that may detect obstructive pulmonary disease at a time when the patient has few symptoms and when the findings from routine physiologic studies are still normal or borderline. It may be important to detect obstructive airway disease at an earlier time, because when the FEV1 or the ratio of the FEV1 to the forced vital capacity (FEV1/FVC) is markedly abnormal due to chronic bronchitis, the disease is probably irreversible. These new tests include: (1) detection of abnormalities in gas exchange, (2) frequency dependence of dynamic lung compliance (Cdyn); (3) analysis of flow rates at low pulmonary volumes utilizing maximal expiratory flow-volume (MEFV) curves and FEF25-75%; (4) closing volumes; and (5) MEFV curves after helium-oxygen breathing.

Although the frequency dependence of Cdyn has since become the standard by which other tests for small-airway obstruction are judged, determining Cdyn is a technically demanding and somewhat uncomfortable test requiring the subject to swallow an esophageal balloon. Furthermore, there is often poor concordance between abnormalities, such as the frequency dependence of Cdyn and the other tests just described. Moreover, it is only specu-

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lation that abnormalities in any of these tests do represent the early functional abnormalities of the long process that leads to disabling chronic obstructive pulmonary disease.\textsuperscript{5}

Hutcheon et al\textsuperscript{10} introduced the volume of isoflow as a new test for the detection of small-airway obstruction. Maximal expiratory flow-volume curves are obtained in subjects after breathing air, and then after three vital capacity maneuvers with the subject breathing a mixture of 80 percent helium and 20 percent oxygen (Fig 1). The MEFV curves obtained after breathing air and the helium-oxygen mixture are superimposed. They are matched at residual volume (RV) if the values for forced vital capacity (FVC) are unequal.\textsuperscript{19,22} Differences in FVC should be random between RV and total lung capacity and between helium and air curves. Thus, any error that would occur by matching at RV would be random. The lung volume at which flow rates after breathing air and helium are identical are determined and expressed as a percentage of the FVC.\textsuperscript{19} This lung volume is known as the isoflow volume.

It has been shown that the use of a spirometer, which measures changes in volume at the mouth, as compared to a plethysmograph, which measures changes in thoracic gas volume, does not produce a statistically significant difference in determining the volume of isoflow.\textsuperscript{19} Furthermore, breathing helium for ten minutes as compared to three inspiratory maneuvers for vital capacity does not significantly alter the results of tests.\textsuperscript{19}

Early investigators studied the role of gases with a density lower than air, such as helium, in the treatment of asthma and emphysema.\textsuperscript{20-25} Schiller et al\textsuperscript{20} demonstrated the effect of reduced gas density on the MEFV curve, such that after breathing helium the maximal flow at 50 percent of vital capacity (\(V_{\text{max50}}\)) increased about 50 percent. Barnett\textsuperscript{21} demonstrated that with tracheal obstruction, pulmonary resistance was related to density and that flow improved after inhalation of helium. When peripheral airway obstruction was induced with histamine, the airway resistance was not dependent on density.

Wood and Bryan\textsuperscript{22} used the concept of the equal pressure points (EPPs) proposed by Mead et al\textsuperscript{18} to explain the effects of inhalation of helium. According to the theory, maximal expiratory flow at a given lung volume varies directly with the static transpulmonary pressure (elastic recoil) and inversely with the upstream resistance, \(i.e.,\) the resistance offered by noncompressed airways between the alveoli and EPPs.\textsuperscript{23} The EPP is the point in the airway where lateral wall pressure is equal to pleural pressure. During forced exhalation in normal subjects, EPPs remain in the large airways until low lung volumes (about 25 percent of FVC). The major resistance in large airways is due to convective acceleration or turbulence (or both), both of which are dependent on gas density. Therefore, breathing helium will increase flow in subjects whose EPPs are still in large airways. An increase in resistance to flow in small airways or a loss of elastic recoil would cause the EPP to move further upstream toward the alveoli and to locate in small airways at a higher lung volume. In the small airways, laminar flow accounts entirely for the resistance, and losses in pressure are independent of gas density. Reductions in gas density will lower the resistance to convective acceleration or turbulence, or both, and will improve flow but will not affect resistance to laminar flow because it is independent of gas density. Therefore, either in diseases of the small airways where there is increased resistance, or with a loss of elastic recoil as occurs with aging or in emphysema, the EPP would be located in the small airways at a higher lung volume. Flow would not be increased with inhalation of helium, and the volume of isoflow would be increased; however, the finding of an increased volume of isoflow cannot distinguish whether the underlying mechanism is increased resistance or loss of elastic recoil.

\begin{figure}
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\includegraphics[width=0.5\textwidth]{figure1.png}
\caption{Maximum expiratory flow-volume curves after breathing air and helium-oxygen mixture. Solid line represents curve obtained with subject breathing air, and dotted line represents curve with subject breathing helium-oxygen mixture. Volume of isoflow (\(V_{\text{iso}}\)) is determined where flows of helium and air curves are similar and is expressed as percentage of FVC. In addition, increase in \(V_{\text{max50}}\) is determined after breathing helium.}
\end{figure}
As suggested by Despas et al., the response to breathing helium may also be evaluated by determining the flow rates after the subject has breathed air and after he has breathed the helium-oxygen mixture at 50 percent of the MEFV curve, and the increased maximal flow while a subject breathed helium is expressed as a percentage of the flow when he breathed air:

\[ \Delta \text{Vmax}_{50\%_{air}} = \text{Vmax}_{50\%_{air}} - \text{Vmax}_{50\%_{helium}} / \text{Vmax}_{50\%_{air}} \times 100 \]

Dosman et al. have suggested that the ΔVmax50 is not influenced by loss of elastic recoil because aging does not affect ΔVmax50.

Thus, the increase with inhalation of helium at Vmax50 is relatively specific for the caliber of small airways, whereas the volume of isoflow is also influenced by elastic recoil. Upon cessation of smoking, both Vmax50 after breathing helium and the volume of isoflow improved, without any change in elastic recoil. Analyzing MEFV after subjects breathed air and helium, Despas et al. determined that the major site of airway obstruction in patients with asthma and bronchitis occurred with approximately equal frequency in large and small airways. Recently, Mildon et al. using similar techniques, showed that the site of obstruction in exercise-induced asthma was localized to large airways. It appears that the volume of isoflow (as opposed to Vmax50 after breathing helium) is the most sensitive test for small-airway obstruction in asymptomatic smokers when flow at low lung volumes during the breathing of air is normal. Furthermore, these abnormalities appear to be reversible following cessation of smoking. A recent report suggests that the volume of isoflow is more sensitive than the frequency dependence of Cdyn.

While these new techniques appear to provide for early physiologic detection, we do not know whether isolated abnormalities in the results of these tests will predict subsequent progressive functional and symptomatic deterioration. At present, these new tests are being intensively investigated in several medical centers. Random screening for early disease does not appear to be warranted. These tests may be of help in differentiating between large and small airway disease and in dissecting reductions in maximal flow, that is, separating loss of elastic recoil from increased airway resistance.

**References**