Validation of Therapeutic Bronchoscopic Bronchial Washing in Cystic Fibrosis*

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Validation of rigid-tube bronchoscopy with small-volume (5-ml increments not to exceed 300 ml) bronchial washing as a therapeutic adjunct was performed on six patients with cystic fibrosis, using serial tests of pulmonary function as a yardstick for assessment of efficacy. Two patients did not undergo the procedure and served as control subjects. All patients were characterized as having varying severity of pulmonary involvement. Large central airways were severely obstructed, and older patients had more trapped gas in their lungs. Hypoxemia and large alveolar-arterial oxygen pressure differences \( [P(A-a)O_2] \) were due to inhomogeneity of alveolar ventilation. Results indicated that up to ten days to two weeks, bronchoscopic bronchial washing may in some instances improve maximal expiratory flow-volume curves and specific airway conductance and decrease \( P(A-a)O_2 \) towards normal. Distribution of alveolar gas became more homogeneous. We conclude that bronchoscopic bronchial washing may be effective in the management of patients with cystic fibrosis, by augmentation of their inadequate cleansing function of the conducting airways.

The pulmonary pathophysiologic findings in cystic fibrosis are considered to be a result of bronchial mucoid impaction.† Included among the conventional accepted therapies for the pulmonary involvement of cystic fibrosis are the inhalation of mucolytic and hydrating agents, the use of antibiotic therapy, and chest physiotherapy, to aid in the evacuation of mucopurulent respiratory tract secretions.‡ Di Sant’Agnese and Talamo§ characterized the bronchial obstruction in cystic fibrosis as “often reversible.” Refractory to therapy with bronchodilator drugs, the obstruction in cystic fibrosis is more effectively reversed by mechanical means. Reversibility has been demonstrated when bronchoscopic bronchial washing, formerly known as bronchoscopy and bronchial lavage, has been employed in patients with cystic fibrosis who have accumulating pulmonary secretions.

The evacuation of thick mucous casts and plugs is accomplished with the patient under light general anesthesia, so as not to depress the cough reflex. Introduction of a rigid bronchoscope is followed by instillation of small increments of a washing solution consisting primarily of a 5-percent solution of N-acetylcysteine (Mucomyst) in saline and by dispersion via positive pressure from the anesthesia bag. Application of suction for aspiration, with the patient coughing, completes the procedure.

The present study was undertaken in order to demonstrate whether objective improvement in ventilatory function may be attributable to bronchoscopic bronchial washing.

**Materials and Methods**

The subjects were eight adult and adolescent patients with cystic fibrosis, whose vital statistics are given in Table 1. Six were treated with bronchoscopic bronchial washing, and two controls were not. Other than bronchoscopic bronchial washing, all patients were subjected to the same regimen in the hospital. This included intravenous therapy with antibiotics (gentamicin and carbenicillin), administration of mucolytic aerosols with N-acetylcysteine (Mucomyst), followed by postural drainage four times daily, and therapy with pancreatic enzymatic supplements (Viokase or Cotazym, or both).

Following the suggestion of Beier et al., a variable-pressure body plethysmograph (Collins) was used, in order to determine the thoracic gas volume, which includes the non-communicating air spaces. The volume of trapped gas was estimated by comparing the patient's end-inspiratory vital capacity with the predicted normal value for the patient's age and height. The difference between the two volumes was considered to be the volume of trapped gas.

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calculated as the arithmetic difference between the thoracic gas volume measured at functional residual capacity (FRC) and the FRC measured by the seven-minute nitrogen-washout method.

Airway resistance was expressed as its reciprocal, conductance per liter of lung volume (specific conductance, [Gaw/VL], in L/sec/cm H2O/L). With each subject breathing 100 percent oxygen, the minute ventilation and mean tidal volume (TV) were computed by electronic integration of the flow signal of a hot-wire anemometer and were compared with values obtained with each subject breathing ambient air, on an automated pulmonary function laboratory (SRL Medical).

Maximal expiratory flow-volume curves were automatically plotted on an x-y plotter at one-fourth velocity to avoid the pen-slewing artifact. The fractional concentration of nitrogen in the expired air (as percent nitrogen) during a slow maximal expiratory maneuver was plotted in relation to lung volume, following a single breath of oxygen, and was found to be a reproducible test in only one of the patients studied. Single-breath tests of carbon monoxide diffusing capacity (Dab) were performed by each subject, with calculation of Krogh's constant, "the lung permeability." Single-stick samples of arterial blood were obtained from five subjects treated with bronchoscopic bronchial washing and from one control subject, reclining at rest and breathing ambient air. Blood was analyzed for arterial oxygen pressure (PaO2), arterial carbon dioxide tension (PaCO2), and arterial pH by polarographic electrodes (IL model 213), and the alveolar-arterial oxygen pressure difference [P(A-a)O2] was calculated from an assumed respiratory exchange ratio of 0.8 and zero arterial-alveolar carbon dioxide tension difference.

Each of the six patients treated with bronchoscopic bronchial washing was studied before and at least once following the washing. Each of the two control patients was studied twice, once upon admission to the hospital and again at discharge, an interval not exceeding ten days. From the Shwachman-Kulczycki scores in Table 1, it is evident that the patients studied manifested varying degrees of pulmonary pathologic abnormality.

**RESULTS**

Table 2 shows the volumes of trapped gas present in the lungs prior to bronchoscopic bronchial washing in the subjects with cystic fibrosis who were studied. Only in the youngest subject was no trapped gas detected. In the others, there was an almost perfect correlation between age and the volume of trapped gas found, ranging from 0.39 L in a 13-year-old to 5.06 L in a 45-year-old subject (r = 0.97; P < 0.001). No consistent change was observed in this measurement following bronchoscopic bronchial washing.

Table 3 compares the minute ventilation and depth of respiration in the patients with cystic fibrosis who were studied before bronchoscopic bronchial washing. Large increases in minute ventilation and TV were detected in all but the two youngest patients studied, when breathing 100 percent oxygen. These data suggest a hypoxemic drive to respiration, which, like the volumes of trapped gas found, seem to be related to age, with inconsistent changes following bronchoscopic bronchial washing.

Figure 1 depicts the improved Gaw/VL following
bronchoscopic bronchial washing. It is evident that all initial values for Gaw/Vt fall below the lower limit of normal (0.13 L/sec/cm H2O/L). The two patients treated with bronchoscopic bronchial washing who had the lowest values failed to show improvement in this measurement. Three patients responded to bronchoscopic bronchial washing by an increase in Gaw/Vt. In fact, on the tenth day following bronchoscopic bronchial washing, two patients' values for Gaw/Vt increased to the normal range; however, values for the control subjects showed no change in one and worsening Gaw/Vt in the other.

Figure 2 depicts improvement in flow-volume relations which were observed following bronchoscopic bronchial washing. Improvement is indicated by simultaneous increases in peak flow rate (Vmax) and forced vital capacity (FVC).

In Figure 3, expired nitrogen curves obtained from single-breath oxygen tests of alveolar gas uniformity in a patient treated with bronchoscopic bronchial washing indicate decrements in the height and slope of the phase-3 alveolar plateaus both 7 and 13 days following bronchoscopic bronchial washing, as compared with the baseline study. Reproducibility of this test was obtainable on this patient only; however, tests in this patient indicate better distribution of inspired gas following bronchoscopic bronchial washing. Distribution of alveolar ventilation was so nonuniform that closing volumes were not discernible.

Within ten days after the washing procedure, major decreases in the P(A-a)O2 were observed in four or five subjects treated with bronchoscopic bronchial washing. After the tenth day, the P(A-a)O2 was still significantly lower than baseline values in two or three subjects treated with bronchoscopic bronchial washing whose blood gas levels were studied. In one control and one subject treated with bronchoscopic bronchial washing, increases in the P(A-a)O2 were detected.

**Discussion**

The technique of bronchoscopic bronchial washing is unique among other applications of therapeutic pulmonary washing, especially with regard to the volume of washing solution utilized. In bronchoscopic bronchial washing, small increments (5 ml) are instilled to a total amount of not more than 300 ml in both lungs during one procedure. In 1965, Ramirez-R and associates reported a procedure of segmental lavage applied to the treatment of pulmonary alveolar proteinosis, utilizing from 1 to 2 L of solutions. This technique was modified by Kylistra et al and became known as volume-controlled lavage, which was reported to have improved ventilation and gas exchange in five of ten patients with cystic fibrosis who were subjected to a total of 33 unilateral lavages on degassed lungs. Bronchoscopic bronchial washing is also unlike other procedures of "small-volume lavage," such as that reported by Thompson et al, who utilized 800 to 1,500 ml of saline solution. Bronchoscopic bronchial...
washing is a pulmonary washing technique which should not be confused with the historical concept of lavage, which has implied use of a lung-flooding procedure.

The importance of postprocedural medical care to the outcome of bronchoscopic bronchial washing cannot be overemphasized. Following induction of a successful bronchorrhea by bronchoscopic bronchial washing, bronchopulmonary drainage must be continued noninvasively via postural drainage and suctioning. Oxygen therapy is generally contraindicated, except on an intermittent basis in emergencies. Our studies indicate that adolescent and adult patients with cystic fibrosis may have a significant hypoxemic drive to respiration. During the bronchorrhea following bronchoscopic bronchial washing, therapy with oxygen can reduce effective alveolar ventilation, producing acidemia via retention of carbon dioxide. Further depression of mucociliary escalatory function may result. This can create a positive feedback loop in which respiratory tract secretions accumulate and obstruct airways.

In an attempt to validate volume-controlled lavage in patients with cystic fibrosis, Kylstra et al utilized routine procedures for pulmonary function testing, including helium-dilution methods. Fortunately, at an earlier date, Beier et al documented the pitfalls of applying dilutional methods to patients with cystic fibrosis and recommended the use of a body plethysmograph. Data which rely on dilutional methods greatly underestimate the relationship of residual volume to total lung capacity (RV/TLC), which was found to provide the best test correlation to progression of the disease. Progression of the total obstruction of pulmonary units, which is responsible for the errors of dilutional measurements, is represented in our studies by the proportionality between age and the volumes of trapped gas detected.

Differences in techniques have made the effectiveness of pulmonary lavage difficult to evaluate. Lober and associates reported a volume-controlled lavage as beneficial as an adjunct in treatment of a 22-year-old patient with cystic fibrosis. A 24-year-old patient with cystic fibrosis was shown to have an increased RV/TLC and decreased vital capacity following a 12-L lavage, indicating increased airway obstruction after lavage by inert-gas dilutional techniques for measurement of FRC. The admitted difficulty in explaining clinical improvement in terms of an increase in ventilatory function may have been related to the measurements and the methods chosen to evaluate the responses. Dilutional methods of determining lung volume and maximal expiratory flow rates are not the methods that are likely to characterize what is known about the pulmonary pathophysiologic findings in cystic fibrosis.

The disease seems to progress from smaller to larger airways. Since 20 to 30 percent of the total airway resistance can be attributed to airways less than 2 mm in diameter, the large airways provide the site for limitation of flow rate, especially when large airway obstruction is superimposed on small airway obstruction. Increased airway collapsibility, as suggested by the marked concavity of the effort-independent portion of maximal expiratory flow-volume curves may be the source of limitation of flow. Therefore, it seems that the tests best suited to characterize the pulmonary pathophysiologic findings in the airways of the adolescent and adult patient with cystic fibrosis are those designed to measure the resistance of the airways to flow, such as body plethysmography. In addition, the rigid bronchoscope used in bronchoscopic bronchial washing is limited by its size to the large airways. Thus, it was
not surprising to find the most consistent ventilatory changes, following bronchoscopic bronchial washing, in studies of large airway function, ie, Gaw/Vl.

All patients studied returned to either school or work and were considered to be improved from a clinical standpoint. Increases in FVC and maximal voluntary ventilation (MVV) were documented in all but one patient, indicating greater activity tolerance, even without bronchoscopic bronchial washing. The one patient in which neither increased FVC nor increased MVV were shown also had the lowest Shwachman-Kulczycki x-ray score, and no change in Gaw/Vl was able to be detected.

Nevertheless, increases in Gaw/Vl were detected in three of five patients treated with bronchoscopic bronchial washing. The fact that the two patients treated with bronchoscopic bronchial washing who had with the lowest initial values for Gaw/Vl (below 0.04 L/sec/cm H2O/L) failed to show such increases suggests that in patients with cystic fibrosis who have the most severe pulmonary pathologic abnormalities, airway obstruction may be irreversible. Since, by experimental design, patients treated with bronchoscopic bronchial washing were limited to one procedure, we could not determine whether repetition of bronchoscopic bronchial washing could have resulted in improved airway function in the two patients who failed to respond to one procedure. Our clinical experience in younger patients indicates that improvements in the radiographic appearance of the chest and in the FVC may occur only after repeated procedures in some patients. Among six patients with cystic fibrosis whose blood gas levels were studied, baseline values for P(A-a)O2 were similar in order of magnitude to those previously reported.15,16 In addition, measurements of Dsb made on all patients studied were normal when values were adjusted to account for restricted lung volumes obtained by spirometric studies. Values for Krogh's constant also fell within the normal range. The fact that the integrity of the alveolar-capillary membrane was preserved in these patients eliminates a defect in diffusion as a significant source of the increased P(A-a)O2.

The P(A-a)O2 was labile in patients treated with bronchoscopic bronchial washing. The decreases detected were temporary in at least two patients. The apparently beneficial effect, like that of Gaw/Vl, occurred within the first ten days after washing in most of the patients studied. In one of the patients treated with bronchoscopic bronchial washing whose Gaw/Vl did not increase, an increased P(A-a)O2 was found. It may be significant that this patient was the only subject who required mechanical ventilation after the washing. In the other of the two patients treated with bronchoscopic bronchial washing whose Gaw/Vl did not increase, a decreased P(A-a)O2 was accompanied by an increased PaCO2 and an unchanged PaO2. This decreased P(A-a)O2 was 16 mm Hg, and the increased PaCO2 was 14 mm Hg. A Bohr shift in the oxyhemoglobin dissociation curve was responsible for lowering the oxygen content of the arterial blood by an amount equal to the decreased oxygen content of the ideal alveolar gas, resulting in no net change in the P(A-a)O2. Thus, in this subject, a decreased P(A-a)O2, when expressed in terms of gas tensions, indicated improved pulmonary function, ie, more evenly distributed ventilation-perfusion relationships; however, when the data were expressed in terms of oxygen content, the effect was interpreted as being a result of less effective blood arterIALIZATION, due to increased retention of carbon dioxide following bronchoscopic bronchial washing. All other decreases in P(A-a)O2 following bronchoscopic bronchial washing, were accompanied by normalization of the PaO2 or PaCO2, or both, indicating improved blood arterIALIZATION.

In conclusion, data indicate that a major improvement in large airway function may be attributable to bronchoscopic bronchial washing. Increased values for Gaw/Vl in patients with cystic fibrosis whose baseline values were near the lower limit of normal were accompanied by decreased values for P(A-a)O2, although in one patient, values of Gaw/Vl progressively increased in spite of a return of the P(A-a)O2 to the baseline value.

These studies are the first to use body plethysmographic studies in the validation of therapeutic bronchoscopic bronchial washing. In addition, body plethysmographic studies should be employed in the pulmonary function testing procedures of patients with cystic fibrosis because the tests are highly reproducible, even in severely disabled patients. The requirements of breathing at FRC and panting against a closed shutter for a few seconds represent a comparatively small expenditure of energy, compared to the yield of meaningful information about the conducting characteristics of the large airways, which appear to be the major site of benefit from the employment of bronchoscopic bronchial washing in patients with cystic fibrosis.

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REFERENCES
2 Di Sant'Agnese PA, Talamo RC: Pathogenesis and physiopathology of cystic fibrosis of the pancreas. N Engl...

Symposium on Cardio-Graphics

The Symposium of Cardiographics (electrocardiography, echocardiography, His-bundle electrocardiography) will be held at the Grand Bahama Hotel, Grand Bahama Island May 28-29, 1977. For further information, contact Ms. Billie N. Chiles, Tampa Tracings, PO Box 1245, Tarpon Springs, Florida 33589. The group will also present a nurse-clinician series: Acid-base, Blood Gases and Electrolyte Disorders at the Sheraton-Sand Key Hotel, Clearwater Beach, Florida, June 18-18.