INTERRELATIONSHIP OF AIRFLOW LIMITATION AND

VENTILATION INHOMOGENEITY

IN OBSTRUCTIVE LUNG DISEASE

by

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ABSTRACT

The purpose of this study was to investigate the
interrelationship between airflow limitation and ventilation
inhomogeneity in individuals with asthma and cystic fibrosis.
Tests of forced expiration [the forced expiratory volume in one
second (FEV_1) and the forced expiratory flow during 25-75% of
the vital capacity ($FEF_{25-75\%}$)] and the single-breath nitrogen
test [slope of Phase III ($SBN_2/L\%$)] were conducted in fourteen
control subjects [mean age 24 years], fourteen individuals with
asthma [mean age 23 years] and seven individuals with cystic
fibrosis [mean age 20 years]. The tests were conducted
according to the standards and procedures of the American
Thoracic Society and the National Heart and Lung Institute. A
questionnaire assessing activity level and subjective rating of
symptoms was also administered. All subjects were tested on
two occasions within a seven month period, from July to
February. The subjects were able to complete all of the test
procedures without difficulty. The control group had the
highest mean values of 102% and 95% predicted for FEV_1 and
$FEF_{25-75\%}$ respectively. The asthmatic group fell between the
control and cystic fibrosis groups with mean FEV_1 and $FEF_{25-75\%}$
values of 80% and 59% predicted respectively. In the cystic
fibrosis group, the mean FEV_1 was 44% predicted and the mean
$FEF_{25-75\%}$ was 24% predicted. The $SBN_2/L\%$ mean values followed
a similar trend with the lowest percent predicted values in the
control group [115%] followed by the asthmatic group [153%] and

the cystic fibrosis group with the highest mean [937%]. In the cystic fibrosis group, the $SBN_2/L\%$ was disproportionately impaired in comparison to the severity of airflow limitation. Over all groups, the coefficients of variation for the $SBN_2/L\%$ averaged less than 10%. Within a given test session, the tests of airflow limitation and ventilation inhomogeneity were correlated, however, the change in these test values between the two test sessions did not correlate. The difference in mean test values between the asthmatic and cystic fibrosis groups could be explained on the basis of the underlying mechanisms of airway obstruction in these diseases. The moderately impaired test performance in the asthmatic group may reflect the variable bronchoconstriction and airway inflammation in this disease, whereas the severely impaired test performance in the cystic fibrosis group is likely due to the greater degree and severity of obstruction from mucus plugging and bronchiectasis. In all groups, the lack of correlation of the change in test values in individuals between test sessions reflects the different pathophysiologic phenomenon that influences each test, and also the different time courses of recovery of airflow rates and ventilation homogeneity towards baseline levels. Thus, on different occasions, ventilation inhomogeneity can be more severe than expected from assessment of airflow limitation. In addition, within a test session in the cystic fibrosis group, the $SBN_2/L\%$ was more severely impaired than expected on the basis of spirometry. Since more severe ventilation inhomogeneity may exist in cystic fibrosis and asthma compared to airflow

limitation, it may well be that the inclusion of the SBN_2 test [which this study has shown to have a satisfactory coefficient of variation] might be useful in the management of these chronic diseases. Further research is necessary to determine whether the SBN_2/L% can predict the rate of decline in spirometry in these individuals.

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INTRODUCTION

PURPOSE

The purpose of this study was to investigate the
interrelationship between airflow limitation and ventilation
inhomogeneity in two examples of obstructive lung disease. In
healthy subjects and subjects with asthma or cystic fibrosis
[CF], the slope of Phase III of the single-breath nitrogen test
and tests of forced expiratory volume and forced expiratory
flow were measured in the same session to assess ventilation
inhomogeneity and airflow limitation respectively. In
addition, the tests were repeated on a second occasion to
examine the relationship of the change in these variables
between two test sessions.

PURPOSE OF THE SINGLE BREATH NITROGEN TEST

The single breath nitrogen [SBN_2] test was introduced by
Fowler [1949] as a useful test for detecting abnormalities in
intrapulmonary gas mixing and the distribution of ventilation.
The sensitivity and relative simplicity of this test permitted
its extensive application both clinically and epidemiologically
since that time [Buist, 1975].

In 1968, Anthonisen et al and Woolcock et al demonstrated
that conventional lung function tests such as: lung volumes,

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forced expiratory volume in one second [FEV_1], maximal expiratory flow rate, airway resistance and measures of elastic recoil, were too insensitive to detect the early stages of small airway disease. Although other more sensitive tests [radioactive gas technics and frequency dependence of compliance] were able to detect peripheral airway obstruction, the difficulty in conducting these tests rendered them unsuitable for routine or wide scale studies [McCarthy et al, 1972]. Further, McCarthy et al [1972] and Buist et al [1973] concluded that the single breath test was simple to perform and considerably more sensitive in detecting early peripheral airway disease than conventional lung function tests. These conclusions were based on their respective investigations of both smokers and nonsmokers in a group of 112 subjects from the general population [using an Argon bolus technic], and 1,073 subjects at an emphysema screening center [using the SBN_2 method].

The work of Cosio et al [1978] made a significant contribution to the body of literature supporting the SBN_2 test. They performed routine spirometry and the SBN_2 test on 36 patients prior to thoracotomy for localized pulmonary lesions. Following this they quantified the amount of airway disease in the excised specimens and designated those having the greatest proportion of normal airways as Group 1 and those having the greatest proportion of diseased airways as Group 4. They then compared these groups to the preoperative pulmonary function test [PFT] results. Only the SBN_2 test was

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statistically different between Groups 1 and 2, which indicated that this test was more sensitive in detecting early airway disease-when pathological changes were still potentially reversible. Baile et al [1982] extended this work in their investigation of the effect of acute peripheral airway inflammation on tests of small airway function. The inflammation was induced in a dog model by nebulization of 0.25% HCl to the small airways preferentially. The slope of Phase III of the SBN_2 test increased significantly and dynamic lung compliance decreased significantly immediately after nebulization, and these changes persisted throughout the experiment. These investigators concluded that minimal acute inflammation of the peripheral airways results in physiologic abnormalities that can be detected with these tests of small airway function.

COMPONENTS OF THE SBN_2 TEST

The SBN_2 test is performed with the subject wearing a noseclip and connected to a mouthpiece, while usually in a sitting position. The subject takes two deep inspirations of ambient air then exhales to residual volume [RV] prior to taking a vital capacity [VC] breath of 100% oxygen. As the subject exhales this breath at a regulated flow rate, the nitrogen [N_2] concentration in the expirate is continuously monitored at the mouth and plotted against lung volume. The plot of lung volume on the abscissa and N_2 concentration on the

ordinate produces a characteristic 4-phase graph shown in Figure 1.

Each phase of the SBN_2 plot is representative of the extent of ventilation of a specific lung region, and thus of the concentration of N_2 contained within. Phase I appears as a horizontal line as the anatomical dead space containing 100% oxygen is emptied, with a zero concentration of N_2. A sharp upward deflection of the line occurs at the onset of Phase II which represents the exhalation of the interface gas between dead space and alveolar air. Since there is diffusion across this interface, the line has a slope rather than a step-like pattern [Schachter, 1986]. This slope is followed by the shallower slope of Phase III which represents alveolar emptying. The slope of Phase III is determined by the homogeneity of alveolar ventilation and thus may vary from a relative plateau in normals to a prominent slope in subjects with pulmonary disease [Schachter, 1986]. Phase IV occurs as another upward deflection from the slope of Phase III and in the normal seated subject occurs because airway closure prevents further emptying from dependent regions, and the expired gas comes increasingly from upper lung zones. The volume above residual volume at which the onset of Phase IV occurs is termed the closing volume [CV] or the closing capacity when referring to the absolute lung volume.

The SBN_2 test has therefore been used as a test of dependent airway closure and as an index of small airways
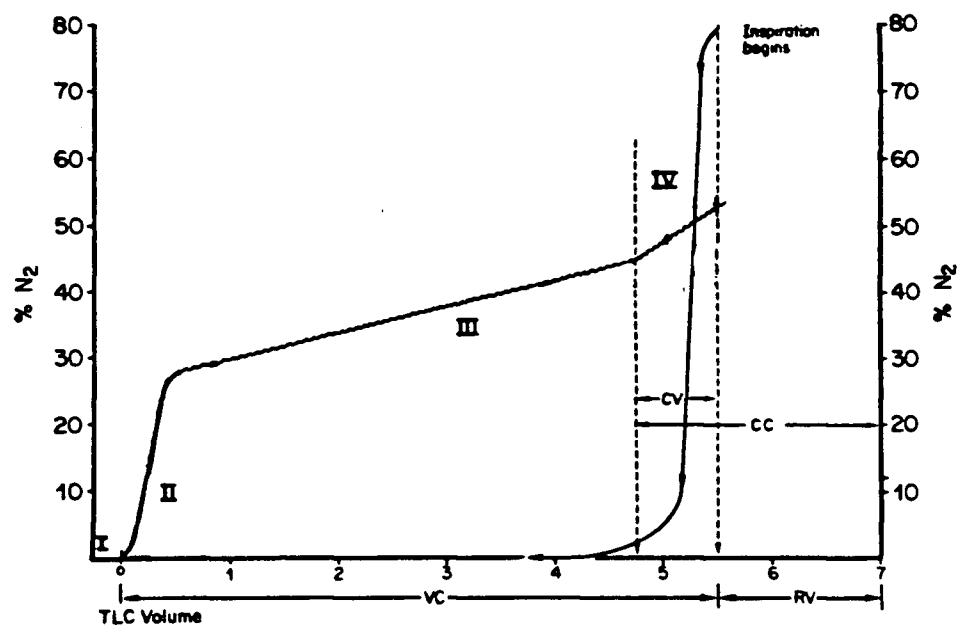
Fig. 1. X-Y recording of the single-breath nitrogen test. Percent nitrogen is displayed on the y-axis and exhaled volume is on the x-axis. Phase I represents dead space gas. Phase II represents a mixture of dead space and alveolar gas. Phase III represents true alveolar gas, and Phase IV represents the closing volume.

disease [McCarthy et al, 1972]. Coincident with the increasing use of the closing volume test, several attempts were made to clarify the specific underlying mechanism responsible for the occurrence of Phase IV. The physiologic mechanism could theoretically be explained by any of the following: 1. airway closure, 2. decreased alveolar compliance, 3. alveolar collapse or, 4. expiratory flow limitation [Engel et al, 1975].

In 1967 Dollfuss et al concomitantly measured the xenon [Xe] concentration in sequential lung regions using scintillation counters arranged vertically on the posterior thorax and one also located at the mouth. A bolus of Xe was introduced at the mouth during inspirations starting from different lung volumes ranging from RV to 90% VC. Throughout the range of inspirations starting from 26-95% VC, these authors concluded that regional ventilation inhomogeneity existed and could be explained by the effect of gravity. This resulted in a linear increase in Xe concentration from apex to base. At low lung volumes [between residual volume and 25% VC], regional ventilation inhomogeneity was attributed to the occurrence of airway closure, resulting in sequential emptying and reversal of the normal Xe gradient. The occurrence of airway closure was further supported by the measures of expired Xe concentration at the mouth. The Xe concentration showed little change until between 20-15% VC at which point there was an abrupt change which the authors attributed to the progressive base to apex airway closure. Hyatt and Rodarte [1975] attributed the onset of Phase IV of the SBN_2 test to

dynamic airway compression rather than airway closure. They suggested that the sudden rise in N_2 concentration toward the end of the VC occurred at a time when the lung reached flow limitation. This would cause the dependent lung regions to empty early and reach flow limitation; airway closure need not be postulated. They observed that the volume at which Phase IV occurred could be changed by varying the expiratory flow rate; they considered that this observation strengthened their theory of expiratory flow limitation.

The most definitive experiments to clarify the closing volume mechanism were conducted by Engel et al in 1975. Their normal subjects were partially equilibrated with N_2O, then held their breath while a bolus of Xe was delivered at the mouth or injected intravenously. As the N_2O was absorbed into the circulation it set up a pressure gradient between the mouth and alveoli, producing gas flow. The Xe carried in by this gas flow was distributed proportionally to the N_2O absorption into the circulation [assuming patent airways], and thus in proportion to the regional blood flow. Since there is greater perfusion of basal zones, the Xe concentration would have a base to apex vertical gradient. The authors compared the distribution of Xe as it was carried in by the N_2O with the intravenous [IV] bolus, at lung volumes both above and below CV. At FRC the N_2O bolus distribution closely matched that of the IV bolus. However, close to RV there was a greater amount of the N_2O bolus distributed to the apex than the base while the IV bolus distribution remained unchanged. The authors

concluded that this must indicate that airway closure in the dependent airways was occurring, since the pressure gradient set up by N_2O absorption into the circulation would fail to produce a flow of Xe into the alveoli only if airways leading to them became completely obstructed. Narrowing of dependent airways as proposed by Hyatt and Rodarte [1975] could not explain their results.

In addition, the other proposed theories to explain the CV were not supported by the results of Engel et al [1975]. These authors observed that the N_2O bolus distribution of Xe at RV was similar to that which occurred when a bolus of Xe was inhaled from RV-even though the flow rate [0.2-0.5 L/s] was ten fold greater than that during N_2O absorption. If the distribution of the N_2O bolus was determined by regional resistance, then it would be flow sensitive and would not have displayed a similar distribution when the two flow rates were so different. These authors also ruled out alveolar collapse in the dependent lung regions based on their finding that the IV bolus did not change its distribution at RV as the N_2O bolus had, indicating the presence of air filled perfused dependent alveoli which did not exchange gas with the trachea. They considered that the similarity of distribution of the N_2O bolus near RV, to that of a Xe bolus inhaled from RV, constituted substantial evidence that airway closure completely accounted for the distribution of ventilation at that lung volume. They further concluded that a potential decrease in compliance at low lung volumes would not influence the distribution of

ventilation.

LIMITATIONS OF THE CLOSING VOLUME MEASUREMENT

Despite the valuable applications of the CV measurement,
it was found to be limited in cases of airflow obstruction as
shown by Abboud and Morton [1975]. These investigators
observed a low incidence of abnormal CV measures in subjects
with mild airflow obstruction. Marcq and Minette [1980]
observed a decrease or absence of CV in subjects with airflow
obstruction and concluded from their results that phase IV was
predominantly determined by intraregional gas gradients in
these subjects. This conclusion was further explained by
Andersen and Rasmussen [1981] who stated that the range of
airway opening pressures in airway disease widens, so that open
and closed airways now occur within regions as well as between
regions. The consequence of this is that the distance between
regions with different N_2 concentrations decreases, so that
equalization of the normal interregional gradient may occur
either by molecular diffusion or cardiogenic mixing. In
addition, the development of enhanced collateral ventilation
contributes to the reduction of the N_2 gradient between open
and closed lung units so that the normal interregional gradient
will be underestimated and may appear normal or disappear
completely. The net result would be a continuous rising slope
of Phase III with a normal or absent Phase IV. Therefore
Andersen and Rasmussen [1981] concluded that although the

measurement of CV is sufficiently sensitive to reveal the
structural abnormalities in peripheral airways during the early
stages of airflow limitation, this sensitivity decreases as
generalized airflow obstruction increases. They suggested that
CV measurements would only be useful in asymptomatic subjects
or patients with near normal spirometry.

DEVELOPMENT OF THE SLOPE OF PHASE III MEASUREMENT

While the incidence of invalid measures of CV in subjects
with airway obstruction was being investigated, the ability of
the slope of Phase III of the SBN_2 test to detect ventilation
inhomogeneity in these subjects was given further attention.
Andersen and Rasmussen [1981] reported that in subjects with
airflow obstruction, the slope of Phase III [SBN_2/L%] revealed
abnormal test values in the presence of normal CV values. They
concluded that the progression and remission of peripheral
airway dysfunction is more likely to be revealed by the SBN_2/L%
[which continues to increase with the development of airway
obstruction] than spirometry. Oxhoj et al [1977] also
concluded that the SBN_2/L% was more sensitive than flow
recordings and routine spirometry in their investigation of
lung disease in middle aged smokers. They obtained abnormal
SBN_2/L% values in 40-60% of the smokers while CV and FEV_1
measures were approximately equally sensitive, with abnormal
values in 10-30% of the smokers. These authors concluded that
the SBN_2/L% was the most valid single measurement for detection

of small airway abnormality related to smoking in the 50 and 60 year aged subjects they studied.

Morphologic studies conducted by Cosio et al [1980] and Petty et al [1980] found minor morphologic and functional abnormalities in the small airways or alveoli of subjects who had demonstrated normal spirometry and a steep SBN_2/L%. They suggested that these abnormalities may precede overt airflow limitation in the course of development of chronic airway disease. Berend et al [1984] also associated an increased SBN_2/L% with functional derangements such as changes in elasticity in non-emphysematous lungs.

The SBN_2/L% has also been investigated in longitudinal studies as a predictor of the rate of decline in FEV_1. Olofsson et al [1986] randomly selected two groups by their birthdate, conducted PFT initially and then again after a seven year interval. These investigators found that the steeper the SBN_2/L% was on initial assessment, the faster was the rate of decline in FEV_1 during the follow-up. This relationship persisted even when only the subjects with a normal FEV_1 on initial assessment were analyzed. Their findings agreed with the earlier work of Beaty et al [1984] and Buist et al [1984]. However, in middle-aged smokers, Stanescu et al [1987] recently concluded that the SBN_2/L% did not accurately predict the decline in FEV_1. All of these studies were limited by the two data points-the initial and final measures, and a high variability of FEV_1 rate of decline between subjects. Thus,

Buist et al [1988] studied 734 subjects [smokers and nonsmokers] selected randomly from county employees and an emphysema screening center over a nine to eleven year period; during which the SBN_2 test and spirometry were assessed three to five times. They found that only the CC/TLC measure of the SBN_2 test was significantly related to the rate of decline of FEV_1 when adjustments were made for smoking, age, sex and height. However, the CC/TLC was not able to consistently identify the smoker who will progress to an abnormal FEV_1, which the investigators partially explained on the basis that many smokers do not progress to develop chronic airflow limitation and thus may never produce an abnormal FEV_1. Buist et al thus concluded that the SBN_2 test was limited in its ability to predict the smoker or nonsmoker who would develop chronic airflow limitation.

PHYSIOLOGIC IMPLICATIONS OF THE SLOPE OF PHASE III

The literature has thus clearly demonstrated the significant role of the SBN_2/L% in detecting ventilation inhomogeneity-often when tests of airflow limitation were normal. The physiologic mechanisms underlying the SBN_2/L% and thus the ventilation inhomogeneity, have been the topic of considerable investigation and have led to the development of several theories.

Buist and Ross [1973] described the occurrence of regional [parallel] inhomogeneity and stratified [series] inhomogeneity as the most likely explanation for the $SBN_2/L\%$. Regional inhomogeneity was attributed to differences in time constants between different lung regions as discussed by Otis et al [1956], and to gravity-determined differences in volume change of alveoli in different lung zones [Anthonisen et al, 1970]. Stratified inhomogeneity was attributed to incomplete diffusion mixing in the most distal alveoli [Krogh and Lindhard, 1917; Engel et al, 1973]. Buist and Ross [1973] concluded that a positive $SBN_2/L\%$ was a result of sequential emptying of dependent regions with low a N_2 concentration followed by non-dependent regions with a higher N_2 concentration. In addition, areas with a high regional volume and thus a high N_2 concentration and incomplete diffusion mixing, would contribute late in the expiration. They further suggested that any disease which resulted in airway obstruction would accentuate either regional or stratified inhomogeneity, or both, thus increasing the positive slope of Phase III.

Engel et al [1974] investigated the intrinsic mechanical determinants of ventilation. They used an open-chested dog preparation to eliminate the influence of gravity on ventilation, and compared these results with an intact preparation. With catheters, they measured the N_2 concentration at various locations. They observed an upward $SBN_2/L\%$ in both preparations, and related this to intrinsic mechanical properties in the open-chested model. This was

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consistent with previous work where significant differences in elastic properties between the upper and lower lobes of the dog were documented [Faridy et al, 1967]. The positive $SBN_2/L\%$ was obtained irrespective of the sampling site, which indicated a fixed emptying pattern in all lung units such that well ventilated units emptied prior to poorly ventilated units. The authors found no significant difference in the $SBN_2/L\%$ when measured in the trachea and bronchi. They thus suggested that the $SBN_2/L\%$ is determined within lung units smaller than those with 3 mm airways leading to them. This was confirmed by their finding of relatively large variations in ventilation/unit volume within small units, ie significant ventilation inhomogeneity. These authors were thus able to partition the $SBN_2/L\%$ measured in the trachea of a supine intact dog into three components: 52% due to the large variation in ventilation/unit volume within terminal units, 34% due to the effects of gravity and 14% due to the different elastic properties between upper and lower zones.

Engel et al [1974] also considered the implications of the relative proportions of the $SBN_2/L\%$ components that they had determined. They suggested that during the Xe bolus technic, the large vertical Xe gradient which is established by gravity may mask the contribution of the other components, and thus may account for some of the variation in theories of the physiologic basis for the slope of Phase III. This concept of masking had been demonstrated by Anthonisen et al [1970] who studied subjects after they inhaled a Xe bolus at the onset of

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a 100% VC inspiration from RV. These investigators were able to reverse the Xe slope of Phase III by tilting the subject head down on inspiration and upright on expiration. With this technic the Xe was distributed to the non-dependent base when inverted and then following return to upright, expired first from the dependent base. Thus the early expirate would have a high Xe concentration which would decrease over the course of expiration as the apex increased its contribution to the expirate. However, when the SBN_2 test was performed with this invert-upright technic, the SBN_2/L% was not changed. The authors concluded that this indicated the presence of a non-gravity dependent intraregional inhomogeneity which was too great to be masked by the induced interregional N_2 gradient between apex and base. They further concluded that diffuse lung disease would have a major influence on the SBN_2/L% by increasing the intraregional inhomogeneity. Marcq and Minette [1980] added to the work of these investigators when they studied the effect of gravity reversal on Phase III and IV measured with the SBN_2 test and bolus technics. These investigators concluded that the slope of Phase III of the bolus test was primarily related to interregional inhomogeneities and that of the SBN_2 test primarily related to non-gravity determined intraregional inhomogeneities.

Macklem [1979] explained ventilation inhomogeneity on the basis of the influence of enlarged airspaces, characteristic of emphysema. He theorized that the diffusion pathways would be too long for complete mixing to occur so that intraregional

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sequential emptying, thus ventilation inhomogeneity, would result. The pressure-volume behavior and thus the ventilation/unit volume of some airspaces would also be altered, contributing further to sequential emptying. In addition, Macklem suggested that airway disease could contribute to ventilation inhomogeneity on the basis of differing time constants between parallel units. Since the expiratory flow rate for the SBN_2 test is less than 0.5 L/s this factor would unlikely have an influence. However, as flow is increased, the degree of sequential emptying and thus ventilation inhomogeneity would increase due to the influence of units with long time constants. Macklem thus suggested that one can differentiate between volume and flow dependent sequential emptying by observing the effect of increasing expiratory flow rate on expired N_2 concentration. If volume dependent sequential emptying predominates, due to either incomplete diffusion mixing or changes in ventilation/unit volume, it would not be influenced by expiratory flow. Therefore, flow dependence of the N_2 concentration would suggest that the sequential emptying which was present, primarily depended on differences in time constants.

Paiva and Engel [1981] examined the influence of anatomic asymmetry on the interaction of convection and gas-phase diffusion within the lung acinus and used their findings to explain the SBN_2/L%. They studied a model consisting of two trumpet shaped units joined at a branch point and whose relative lengths and volumes could be varied. When the two

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units were symmetrical, the unit gas concentrations were constant at end inspiration and expiration so that the SBN_2/L% was horizontal. However, when the two units were asymmetrical, the oxygen concentration at end inspiration was greater in the shorter unit due to more rapid diffusion despite the equivalent conductive flow per unit volume to the two units. The gas between the two units did not equilibrate due to the interdependence of gas transport along parallel paths. On expiration the oxygen concentration fell in the short unit and caused a progressive decrease in expired oxygen as expiration proceeded. Some of the expired N_2 from the larger unit diffused back into the shorter unit from the branch-point which resulted in a lower expired N_2. Then in late expiration as the N_2 concentration in the shorter unit increased, there was less retrograde diffusion and thus an increase in expired N_2-creating the rising SBN_2/L%. These authors thus concluded that neither stratification or sequential emptying of parallel units is necessary to produce a rising SBN_2/L%; and further that intra-acinar airway asymmetry could account for part of the SBN_2/L%. In addition, they reported that asymmetrical pathways which had a proximally located branch-point, contributed significantly to the SBN_2/L% and thus the more peripheral the asymmetry [ie distal to 20th generation] the less of an effect it would have on the SBN_2/L%.

Cormier and Belanger [1981a] investigated the influence of gas exchange on the slope of Phase III. They demonstrated that the slope of Phase III was greater during the SBN_2 test than

the reversed SBN_2 test which used 100% oxygen as the resident gas. They explained their findings on the basis of gas exchange occurring during the slow VC expiration required for the SBN_2 test. The N_2 concentration increased with expiratory time so that the SBN_2/L% would be steeper in the SBN_2 test and flatter in the reversed SBN_2 test which has a negative slope. These investigators also demonstrated that compared with rest, exercise resulted in a steeper SBN_2/L% during the SBN_2 test and a greater flattening of the SBN_2/L% during the reverse SBN_2 test [Cormier and Belanger, 1981b]. They explained these findings on the basis of the increased oxygen uptake during exercise which would increase the N_2 concentration. In addition, Cormier and Belanger [1983] were able to quantify the contribution of gas exchange to the SBN_2/L% and found this to be 10.2% in normal subjects at rest.

Petty et al [1980] attempted to differentiate between the loss of elastic recoil and small airway pathology as determinants of an abnormal SBN_2/L% and closing capacity [CC]. They conducted SBN_2 tests on whole lung specimens with less than 10% of the parenchyma involved in acute or chronic disease, and then studied the morphology of these specimens. They could not find a difference in elastic recoil between a group of lungs with a normal CC and another group with an abnormal CC. However they found that occlusion of the airways by cells and mucus, mural inflammation and increased airway smooth muscle thickness all correlated with an increased SBN_2/L%. They concluded that the abnormal CC and SBN_2/L% were

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associated with pathologic changes in small airways and not with changes in elastic recoil.

Berend et al [1984] further investigated the relative importance of the inhomogeneity of elastic properties of lung units and the presence of small airway lesions in determining the magnitude of $SBN_2/L\%$. They performed SBN_2 tests and determined pressure-volume curves on 11 emphysematous free and 17 emphysematous excised human lungs and on two groups of 23 smokers and 24 nonsmokers. Their results showed that in emphysematous free lungs, the $SBN_2/L\%$ was better correlated with elastic properties of the lungs as compared to bronchiolar inflammation. They suggested that increasing inhomogeneity of lung elastic properties resulted in the increased slope of Phase III. In the emphysematous lungs however, they were unable to demonstrate any significant correlations, which they attributed to the interplay between airway obstruction and inflammation, airway and parenchymal destruction and inhomogeneity of elastic properties. The group of smokers demonstrated a significant relationship between $SBN_2/L\%$ and lung elastic properties, which was not present in the nonsmokers. However, the authors reported that the degree of peripheral airway inflammation was unknown in these subjects and may have influenced their results.

The characteristics of ventilation inhomogeneity were further studied in the investigation of cardiac oscillations and the effect of breath-holding. Cardiac oscillations are

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seen as oscillations in the N_2 concentration during Phase III of the SBN_2 test. They are considered to be the result of pressure waves created by the heart which act downstream of bifurcations to displace the gas from poorly ventilated areas into the common stream of expired air [Langer et al, 1960]. Engel et al [1974] concluded that this cardiac action provided a dynamic component to gas mixing on inspiration, expiration and during breath holding. Verhamme et al [1982] demonstrated a decrease in amplitude of these oscillations in relation to increasing severity of airway obstruction. They explained this finding on the basis of long time constants in the areas of severe airway obstruction, which would dampen the effect of the cardiac action. Breath-holding had a similar effect in damping these oscillations in peripheral airways [Engel et al, 1974]. The breath-hold enabled equalization of intraregional N_2 gradients by molecular diffusion and cardiogenic mixing, so that the cardiac oscillations were decreased in amplitude. These investigators also reported a flattening of the SBN_2/L% following breath-holding. They could not demonstrate any difference in the interregional N_2 concentration after breath holding, which they attributed to the long bronchial path for diffusion between lobes. They thus concluded that the intraregional gas mixing proceeds more rapidly and is responsible for the flattening of the SBN_2/L% following breath-holding.

The discussion of regional and stratified ventilation inhomogeneity can best be concluded by considering the

suggestion of Engel and Macklem [1977] that these two categories may not be distinct entities. For example, collateral ventilation of an obstructed unit in parallel with another unit would result in serial inhomogeneity. Thus, many factors must be considered before the ventilation distribution and the resultant SBN_2/L% can be interpreted.

MEASUREMENT OF EXPIRATORY FLOW RATE

This study compared measurement of the SBN_2/L% to two routine tests of airflow limitation-the forced expiratory volume in one second [FEV_1] and the forced expiratory flow during 25-75% of the VC [$FEF_{25-75\%}$].

The FEV_1 is the maximum volume that can be expired from a full inspiration in one second. At high lung volumes [ie at the onset of the test] the FEV_1 is flow and thus effort dependent. This disadvantage was felt to be outweighed by the high reproducibility that the FEV_1 test exhibits, which enables interpretation of relatively small changes in airway resistance [Anthonisen, 1986]. The coefficient of variation has been determined as 3% in normals and 8.1% in those with obstructive disease [Pennock et al, 1981]. The FEV_1 is often reported as a ratio to the forced vital capacity [FVC] to indicate the portion of the FVC that is expired in one second. The expression of this ratio permits some differentiation between obstructive and restrictive disease patterns where both FVC and

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FEV_1 are decreased. Normal values for the FEV_1 are weighted by sex, age and height and are considered to be within 1.65 x SEE of the predicted value [Crapo et al, 1981].

Leuallen and Fowler [1955] introduced the $FEF_{25-75\%}$ as a test for airway obstruction that was more sensitive than the FEV_1. This flow rate is calculated as the slope of the line drawn between the points at which 25% and 75% of the vital capacity has been delivered. The representative volume is thus the middle half of the FVC and the time to deliver this volume is the later, effort-independent part of the FVC maneuver. Normal values are determined similar to the FEV_1 as described by Crapo et al [1981]. In obstructive disease, the $FEF_{25-75\%}$ falls to a lower percent of predicted normal than the FEV_1 [Anthonisen, 1986]. However, this increased sensitivity is offset by the fact that the $FEF_{25-75\%}$ has a greater coefficient of variation, being 8% in normals and 14% in those with obstructive disease [Pennock et al, 1981].

Neither of these pulmonary function tests are sensitive to early peripheral airways disease. Macklem and Mead [1967] in their classic study, used an intraluminal catheter to measure airway pressure in open-chested living dogs and in excised lungs. They were able to separate airflow resistance into peripheral resistance [ie that from the catheter to the alveoli] and central resistance [ie that from the catheter to the trachea]. Their results showed that between 80-100% VC almost all of the airflow resistance was central in origin and

between 10-80% VC peripheral resistance increased to a maximum of only 15%. These investigators commented that since the peripheral airways contributed such a minor component of the total resistance, [because of their very large cross-sectional area], there could be considerable disease present resulting in a considerable increase in peripheral resistance, but leading to a very small effect on total airway resistance. It is the total airway resistance that primarily determines the FEV_1 and $FEF_{25-75\%}$ and therefore they have limited sensitivity to early peripheral airways disease.

However, characteristics other than resistance may be more readily detectable in these peripheral airways. Alveoli distal to obstructed small airways would have increased time constants, and thus display ventilation inhomogeneity. Thus the $SBN_2/L\%$ would be expected to detect small airways disease through its assessment of ventilation homogeneity, before the FEV_1 and $FEF_{25-75\%}$ show abnormal values. As noted earlier, this has been shown to occur. But what has not so far been studied is the variation in both ventilatory indices and the $SBN_2/L\%$ in the same individuals as their condition varies either spontaneously or as a consequence of treatment.

Thus the present study was designed to compare and contrast changes in the FEV_1 and $FEF_{25-75\%}$, to variations in the $SBN_2/L\%$ in patients with obstructive airways disease-specifically asthma or cystic fibrosis [both diseases in which variations commonly occur]. The information obtained may give

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insight into the occurrence and magnitude of airflow limitation and ventilation inhomogeneity in small airways disease, and permit the interrelationship between these two types of measurement to be examined.

RATIONALE FOR THE SELECTED TESTS IN ASTHMATIC SUBJECTS

Asthma is difficult to define and can best be described as 'non-specific airway reactivity' [Bates, 1989]. Individuals may present with variable degrees of bronchial obstruction and wheezing dating from childhood or early adulthood, airway hyperreactivity, and hyperinflation without destructive changes. Airway hyperreactivity is the predominant feature of asthma, and is often not clearly related to an allergic mechanism [Bates, 1989]. Hyperreactivity may also present as a consequence of an inflammatory reaction in the airways [Holtzman et al, 1983] induced by a specific antigen [Ishizaka and Ishizaka, 1970], upper respiratory tract infections [Empey et al, 1976] or non-specific irritants such as ozone [Golden et al, 1978]. In mild asthma [characterized by reversible airflow limitation] smooth muscle contraction predominates, whereas airway inflammation and mucous plugging are also prevalent in more severe states [Bates, 1989]. This leads to thickening of the basement membrane and hyperplasia of the bronchial smooth muscle cells. Destructive changes in the alveoli and the surrounding capillary beds seen in emphysema are not present in asthma.

Asthma often presents as a course of exacerbations and remissions and as defined by Bates [1989], asthmatics may present in five stages from complete remission to status asthmaticus. This author summarized the pulmonary function changes common to each of these stages and they are presented as follows. During complete remission the individual has completely normal pulmonary function. The occurrence of this phase is likely less often than is assumed on the basis of resolution of the patient's symptoms alone. Several studies have demonstrated impaired PFTs during the asymptomatic phase which Bates [1989] refers to as the state of partial remission [Bates, 1952; Beale et al, 1952; Cade and Pain, 1973; McCarthy and Sigurdson, 1980]. This stage of partial remission may be characterized by intra and interregional ventilation inhomogeneity, frequency dependence of compliance, ventilation-perfusion [V/Q] mismatch, an increase in functional residual capacity, residual volume and total lung capacity, and a decrease in VC and inspiratory capacity.

The PFT abnormalities in the stages of moderate and severe bronchospasm reflect the prominence of airway obstruction. Therefore, in addition to worsening of the PFTs from the previous stage there is a decrease in FEV_1, $FEF_{25-75\%}$, peak flow rate and maximal breathing capacity.

The underlying pathology and altered mechanics that are responsible for the PFT changes in asthma have been investigated at the different stages of disease. Loke et al

[1981] investigated the site of airway obstruction in asymptomatic asthmatic children. They found that the site of airway obstruction could be central, peripheral or both. Thurlbeck [1984] suggested that altered function in chronic airflow obstruction should be considered as involving abnormalities in the various components of the lung, the central and peripheral airways and the parenchyma. He concluded that the co-existence of various causes of flow-limitation would render the use of one test to detect airflow limitation inappropriate.

The reversibility of PFT changes with disease remission or treatment has been a focus of study in attempt to elucidate the underlying pathologic mechanisms in asthma. Engstrom [1964] studied asthmatic children from an acute attack to symptom free status. He found that although airway obstruction [determined by calculation of pulmonary flow resistance] would reverse rapidly in 1-2 days, ventilatory impairment [measured by static lung volumes and forced expiratory volumes] did not reverse as rapidly or completely. Both VC and FEV_1 continued to increase after complete normalization of airway resistance. Further, he found that hyperinflation would remain even after resolution of obstruction. On the basis of these observations he suggested that some minor peripheral obstructions remained and that the normal balance of opposing forces between the thorax and lungs was disturbed-possibly due to parenchymal changes. Gold et al [1967] investigated elastic recoil in asthma more thoroughly to determine whether persistent hyperinflation was due to changes

in lung elastic recoil. They demonstrated that prolonged airway obstruction is associated with a decrease in elastic recoil and leads to hyperinflation. This would account for the persistent hyperinflation despite resolution of airway obstruction. These investigators could not define the cause of the decrease in recoil but indicated that it develops slowly and persisted for 1-2 wk after relief of obstruction. However, prolonged relief of obstruction resulted in a normal elastic recoil which eliminates emphysematous destructive changes as a causative factor. These investigators supported the conclusions of Fry and Hyatt [1960] that decreased flow rates in chronic asthma are probably related to abnormal elastic recoil, bronchoconstriction and airway inflammation. Further investigation into the static elastic properties of asthmatic lungs was conducted by Woolcock and Read [1968] who observed a decrease in elastic recoil that persisted into remission in some patients. They concluded that the mechanism responsible was complex and not clearly related to airway obstruction. However, Martin et al [1980] stated that changes in lung elastic recoil could not completely account for hyperinflation, since it is possible to reach an end-expiratory lung volume that is above the resting volume of the chest wall. These investigators examined the mechanism of hyperinflation in asthmatics by observing lung and chest wall mechanics following induction of progressive bronchoconstriction. They observed persistent activity of the inspiratory muscles [intercostals and accessories] throughout expiration, and recruitment of the abdominals. The inspiratory muscle activity increased with

progressive bronchoconstriction and acted to limit the development of positive pleural pressures-thus expiratory flow limitation, and to promote hyperinflation. These investigators suggested that the abdominal muscle activity was coordinated with the inspiratory muscles to optimize diaphragmatic function, by increasing the abdominal pressure and thus restoring the diaphragmatic length. They thus concluded that sustained inspiratory muscle activity during expiration is a major determinant of hyperinflation.

The persistence of abnormal pulmonary function during the asymptomatic stage indicates a need for close monitoring of these patients at all phases of their disease process. Beale et al [1952] indicated that the occurrence of marked PFT changes in the symptom-free asthmatic was significant in that the underlying pathology responsible for these changes could lead to hypoxemia and more irreversible airway obstruction if not recognized and managed effectively. Zapletal et al [1971] indicated that airway obstruction was one of the main features of asthma and cystic fibrosis, and that its accurate assessment is important for clinical diagnosis and management. However, Woolcock and Read [1965] observed variability in the extent of FEV_1 changes during recovery from an acute episode of asthma due to the influence of coincident changes in lung volumes on airway caliber, which may limit the usefulness of this test in monitoring airway obstruction.

RATIONALE FOR THE SELECTED TESTS IN CYSTIC FIBROSIS SUBJECTS

Cystic fibrosis, like asthma, is a disease in which airflow obstruction is a major cause of symptoms. It is a hereditary condition which affects the function of exocrine glands and involves the membrane transport of sodium, chloride and other ions. It is usually diagnosed in infancy or early childhood. Diagnosis is based on a high salt content in sweat, the presence of viscid bronchial mucus and radiological changes, and deficiency in pancreatic enzymes. The mucus plugs in the lung are tenacious and effectively obstruct the airways leading to airflow obstruction, inhomogeneous ventilation [and thus V/Q mismatch and hypoxemia], and increased work of breathing to overcome the increased airway resistance. The sequence of airway obstruction leading to air trapping and loss of elastic recoil has been demonstrated by Featherby et al [1970] with further confirmation of the loss of lung recoil by Mansell et al [1974]. This loss of lung recoil may occur without the development of morphologic emphysema [Bates, 1989]. Pulmonary infection is a classic feature of CF since the viscid mucus plugs become purulent and often develop staphylococcal and pseudomonal infections [Scanlin, 1988]. This often leads to the development of bronchiectasis and pneumonia. Cystic fibrosis is a terminal disease as these patients succumb to cor pulmonale secondary to the chronic hypoxemia and pulmonary hypertension [Beier et al, 1966].

Mellins et al [1968] compared the characteristics of airway obstruction in CF and asthma. They observed that CF patients demonstrated effort dependent flow at high lung volumes whereas asthmatics are limited by the mechanical properties of their lungs throughout expiration. They suggested that at high lung volumes some airways function normally in CF and that the smaller volume of normally functioning lung would account for the peak flows being less than normal. However, Mansell et al [1974] suggested volume displacement from bronchiectatic airways as a more likely explanation for the effort dependent flow in CF. Mansell et al [1974] demonstrated decreased elastic recoil in CF and at high lung volumes they observed the paradox of a decreased elastic recoil associated with a decrease in compliance. At low to moderate lung volumes, compliance was relatively normal and thus this phenomenon could not be attributed to progressive gas trapping during expiration. They concluded that the decreased compliance observed at high lung volumes was compatible with a deficiency in lung units which had previously been reported by Esterly and Oppenheimer [1968]. Therefore, although airway obstruction is a prominent feature of CF and asthma, the characteristics of the obstruction are different in these two diseases.

Sobonya and Taussig [1986] studied the lung morphology post-mortem and compared it to controls who had died from causes other than CF. They described a course of mucopurulent plugging with enlargement of bronchial glands leading to acute

and chronic airway inflammation. Over time this developed into bronchiectasis, but did not lead to significant alveolar destruction or emphysema. They observed varying types of pathology in the different age groups. Those who died at an early age had a predominance of bronchiectasis and small airway dilation with mucus plugging. The older patients had small airway stenoses with less dilation, and no sign of worsening bronchiectasis with increasing age. Although there was mild alveolar enlargement in most cases, the internal surface area was shown to be well preserved. However, three patients in their 20s had morphologic evidence of mild emphysema, demonstrated by small lesions around small bronchi and bronchioles. Thus small airway disease was predominant with either dilation, stenosis or both. Mucus gland enlargement was not a universal finding despite markedly increased mucus in the lungs. The small amount of pneumonia present was given less significance than the mucus plugs and airway inflammatory changes.

Therefore, airway obstruction is the prominent pulmonary manifestation of CF and as Beier et al [1966] emphasized, worsening airway obstruction is significantly associated with chronic hypoxemia and the development of cor pulmonale-thus end-stage disease.

SPECIFIC PURPOSES OF THIS STUDY

The purposes of this study can thus be summarized:

1. To investigate the interrelationship between airflow limitation and ventilation inhomogeneity as they are measured by the FEV_1 and $FEF_{25-75\%}$ tests and the $SBN_2/L\%$ respectively, in asthmatic and cystic fibrosis subjects.

2. To determine whether either of these tests correlates with the individual's subjective report of symptoms and exercise capacity.

3. To determine whether the slope of Phase III of the single breath N_2 test is likely to be a useful addition to routine spirometry in following the course of these two diseases.

METHODS

RESEARCH DESIGN

Three groups of subjects participated in the study; specifically two patient groups-one consisting of asthmatic patients and the other consisting of cystic fibrosis patients, and a control group of healthy subjects. A within subject experimental design was used to examine the interrelationships of the following four dependent variables: FEV_1, $FEF_{25-75\%}$, $SBN_2/L\%$ and subjective rating of symptoms. All subjects were tested on two occasions within a seven month period, from July to February. On each of these occasions, three acceptable measures of the pulmonary function variables FEV_1 and $FEF_{25-75\%}$ were obtained and the 'best' measures from each session were used as the two repeated trials for statistical analysis. Three acceptable tracings of the SBN_2 test were obtained at each session and an average $SBN_2/L\%$ value was determined from the three measured values. A questionnaire assessing subjective rating of symptoms and exercise capacity was completed by each subject during each visit. The questionnaires were scored in a standardized manner for data analysis.

Subjects ranged from 18 to 26 years of age. The lower limit of this age criterion was chosen to ensure that the subjects would be able to perform the required pulmonary function tests accurately and reproducibly, and to control for developmental changes in the lungs. The upper limit was determined to eliminate the inclusion of cystic fibrosis subjects with end-stage disease and potential emphysematous changes as observed by Sobonya and Taussig [1986]. Subjects in the patient groups were recruited from the populations of asthmatic and cystic fibrosis subjects in the Lower Mainland. The control group was free of respiratory disease and recruited from the general population.

Subjects in both the experimental and control groups were non-smokers, free of heart failure, and did not present with other medical pathology unrelated to their disease process. No attempt was made to control for the stage or acuteness of disease process-other than to ensure that their symptoms did not limit their ability to perform the tests. A minimum endurance capacity was required so that subjects could travel to the laboratory and perform the SBN_2 tests and spirometry without excessive shortness of breath. Individual medications were recorded but not altered for the purposes of the study.

During the first testing session, subjects were assessed in terms of their ability to perform the tests accurately and

reproducibly after an appropriate learning period. Prior to the study it was decided that if a subject was unable to achieve this performance level or became excessively short of breath during the procedures, that individual would be excluded from the study. If the subject was unable to meet these conditions at the second test session, testing was delayed until they could reach this performance level.

PROCEDURES

General Procedures:

The subjects were requested not to participate in any exercise or heavy physical activity on the day of a test session, to minimize the influence of fatigue and the incidence of exercise induced bronchospasm. They were requested to avoid eating a heavy meal within two hours of the test and to wear comfortable non-restrictive clothing. The subjects followed their usual medication regimen but were asked to withhold the use of their bronchodilator inhaler six hours prior to testing.

The subjects arrived at the laboratory 15 minutes prior to the commencement of testing procedures to allow for familiarization with the environment and tester, and to establish a resting state. During this time a brief history or update from the first session was taken and their height and weight were determined. All testing procedures were explained

to the subjects prior to their [or their parent's] written consent to the study. The order of testing [ie spirometry and SBN_2 test] was randomized amongst all subjects and upon re-assessment, each individual performed the opposite sequence to the original session. Subjects were required to perform a minimum of three acceptable tests of both the FEV_1 [$FEF_{25-75\%}$] and SBN_2/L%. Each test session was completed within 90 minutes, including three to five minute rest periods between trials and ten minutes between tests. In the rest period between tests, the subjects completed a questionnaire regarding the presence and severity of their symptoms, and their exercise tolerance.

As recommended in the American Thoracic Society [ATS] guidelines [1987], all testing was carried out by the same experienced individual to control for potential tester variability. All procedures and interactions with the subjects were carried out in a standardized manner.

Specific Procedures:

1. Calibration of the Spirometer.

An Ohio 842® dry-rolling-seal spirometer connected to a Hewlett Packard 7046A® X-Y recorder was used to perform the spirometric tests [Fig. 2]. The spirometer was calibrated prior to each period of testing. The spirometer maintained its calibration between subjects and was thus recalibrated only if

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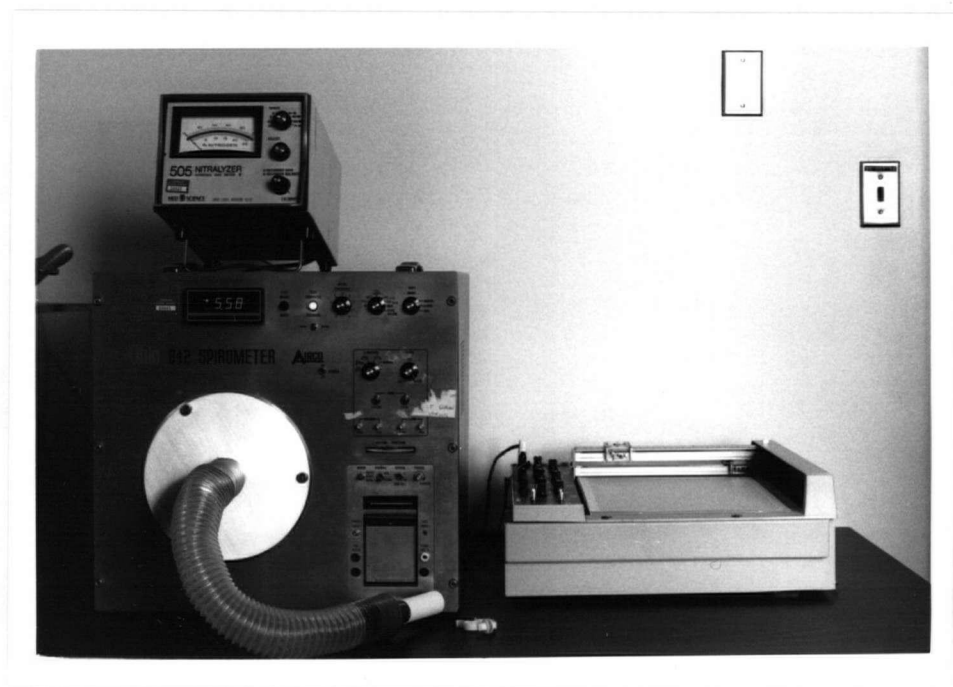
Fig. 2. Equipment set up for the spirometry tests. All equipment
was arranged on a table. The spirometer is on the left with the
nitrogen analyzer ontop and the remainder of the single-breath
nitrogen equipment [out of the picture] located to the left. The
x-y recorder is to the right of the spirometer.

it was shut off between testing sessions. Calibration was performed following 15 minutes of warm-up, using a three liter calibration syringe. Three verification lines were obtained for each channel of the x-y recorder that would record volume. Following this procedure, the BTPS correction switch on the spirometer was set according to the ambient temperature which ranged from 20-28 degrees Celsius.

2. Calibration of the Nitrogen Analyzer.

A 505 Nitralyzer Nitrogen Gas Meter[®] and Sargent-Welch DirecTorr 8805[®] vacuum pump were used to perform the SBN_2 tests [Fig. 3]. The analyzer was calibrated prior to each period of testing and recalibrated only if it was shut off between testing sessions. Calibration was performed following 30 minutes of warm-up. The sampling needle valve was opened to achieve a maximal deflection on the analyzer. The analyzer was then adjusted to read 79.6% N_2, reflecting room air. Following this, the needle valve was slightly closed until the analyzer dropped by 3% N_2 according to the operating instructions. The analyzer was finally adjusted to again display 79.6% N_2. The x-y recorder was then calibrated with the analyzer and three verification lines were obtained.

A linearity check of the nitrogen analyzer was performed at the onset and end of the study, and at monthly intervals during the study. A deflection on the recorder was obtained for each of the six different concentrations of N_2 [ranging
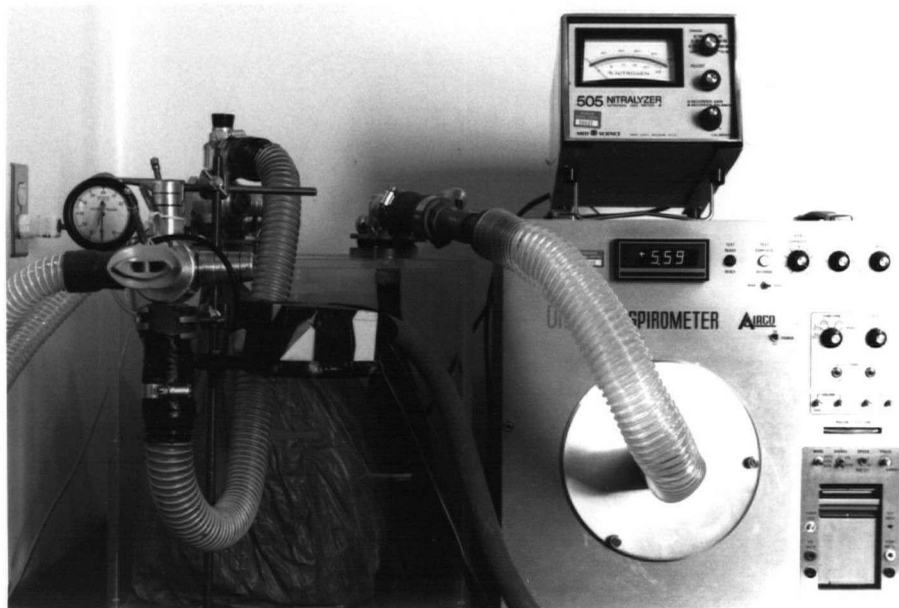
Fig. 3. Equipment set up for the single-breath nitrogen test. All equipment was arranged on a table. The mouthpiece assembly is on the left with the expiratory flow gauge to its left and the nitrogen sensor at the base of the rubber mouthpiece. The mouthpiece assembly is connected to the oxygen bag and the sealed volume box which contains the bag. The volume box is connected to the spirometer located to its right. The vacuum pump [under the table] and x-y recorder [to the right of the spirometer] are out of the picture. The nitrogen meter is ontop of the spirometer.

from 0.2% to 79.6%] that were analyzed. To determine linearity, the N_2 concentration was plotted on the abscissa against the recorder deflection in centimeters on the ordinate.

3. Performance of the Spirometry Tests.

The spirometry tests were conducted according to the ATS guidelines [1987]. The subject was seated upright in a chair and monitored to prevent alterations in posture. Following detailed explanation of the test, the subject performed repeated maximal forced expiration maneuvers until three acceptable tracings were obtained. The subject rested three minutes between trials to enable maximal performance. The tester coached the subject in a standard manner to ensure optimal and consistent effort.

Acceptable tracings for the FEV_1 were selected according to ATS [1987] criteria. The results were analyzed with the back extrapolation method wherein zero time was determined by extrapolating the steepest portion of the expiratory tracing back to where it intersected the time axis. From this point the one second point on the time axis was determined and its vertical intercept with the curve represented the forced expiratory volume in one second. The greatest volume achieved was then compared to age, sex and height matched predicted values. The spirometric reference values and normal limits [1.65 x standard error of the estimate (SEE)] reported by Crapo et al [1981] were used.

The $FEF_{25-75\%}$ was obtained from the single 'best-test' curve as per the ATS [1987] guidelines. This curve is represented by that with the largest sum of FVC and FEV_1. The $FEF_{25-75\%}$ was determined from the slope of the line drawn through the two points where 25% and 75% of the VC had been expired. This value was then compared to the spirometric reference values and normal limits [1.65 x SEE] reported by Crapo et al [1981].

4. Performance of the SBN_2 Tests.

The SBN_2 tests were conducted according to the procedures outlined by Martin and Macklem [1973], using the method of Buist and Ross [1973]. This method differed from the standardized test described by Kjellmer et al [1959] in that the subject inspired a VC breath of oxygen from RV instead of FRC, and the slope of Phase III was calculated from the best fit line through the last two-thirds of the curve, rather than from the increase in N_2 between 750-1250 ml expired volume. The test values in this study were then compared with the reference values of Buist and Ross [1973].

The subject was seated on an adjustable stool so that the mouth was aligned with the mouthpiece. The subject sat upright and was monitored to prevent alterations in posture. Following detailed explanation of the procedure the subject was connected to the system via a mouthpiece and noseclip, and performed a period of tidal breathing. The subject then performed two slow

VC maneuvers before inhaling a slow VC breath of oxygen. An internal resistor on the expiratory port of the breathing valve was used to assist the subject in maintaining a flow rate of 0.3-0.4 L/s during the final VC expiration, as done previously by Abboud and Morton [1975]. DeGroodt et al [1983] have reported that the effect of inspiratory flow rate on the SBN_2/L% is controversial and that there is more agreement on the effect of expiratory flow rate on the SBN_2/L%. With increasing expiratory flow rate, the SBN_2/L% flattens and airway closure occurs sooner. At higher flow rates there may also be influence from dynamic airflow limitation. Thus the standard flow rate of 0.3-0.4 L/s was adopted in the present study. Andersen and Rasmussen [1981] and DeGroodt et al [1983] have also reported that the SBN_2/L% was not affected by an internal resistor and recommended its use.

The subject repeated these single breath nitrogen tests until three acceptable tracings were obtained. The subject rested five minutes between trials to restore the normal nitrogen gradient. The examiner coached the subjects in a standard manner to ensure VC breaths and adherence to slow flow rates.

The acceptance criteria for the SBN_2 tracings set by Martin and Macklem [1973] included: the mean expiratory flow [after the first 500 ml is expired] must be less than or equal to 0.5 L/s; differences in VC between tests must not exceed 10%; the difference between inspired and expired VC must be

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less than 5%; and there must not be a step change in the N_2 concentration with continuing cardiogenic oscillations. Once these criteria were met, intra-session reproducibility was measured and the $SBN_2/L\%$ was calculated. The $SBN_2/L\%$ was determined by the 'best-fit' line drawn through the tracing between 70% of the expired VC and the onset of Phase IV. This method was based on the work of Buist et al [1979] to avoid the potential overshoot in flow at the onset of expiration. Furthermore, Dunning and Allam [1976] reported that patients with severe airway obstruction may exhibit a normal $SBN_2/L\%$ early in the expiration, which then appears markedly abnormal later in the expiration. The mean of three acceptable slopes was then calculated.

5. Completion of the Questionnaire.

A questionnaire was developed to assess the subjects' symptoms and physical endurance. The questionnaire [Appendix A] included categories pertaining to cough, sleep patterns, and current activity level. The Medical Research Council [1960] standardized questionnaire on respiratory symptoms was used to rate dyspnea, and a standardized metabolic equivalent table [Ford, 1986] was used to rate endurance. The subject was orientated to the questionnaire and then completed the questionnaire without assistance between tests, at each test session. The questionnaires were scored based on a coding system with the total possible score ranging from 0 [no symptoms and satisfactory endurance] to 29 [severe symptoms and

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limited endurance]. The total score on the questionnaire that the subject achieved at each test session was included in the data analysis.

DATA ANALYSIS

Calculations for the spirometry and SBN_2 tests from all the tracings and tabulation of the questionnaires were performed during the same period. The tracings were coded and arranged in a random order, and then analyzed by an investigator blind to the coding system.

The data were analyzed in six stages using nonparametric methods. First, descriptive statistics were calculated for age, height and weight of the subjects in each group. Descriptive statistics were also calculated for the four primary variables of interest namely, FEV_1, $FEF_{25-75\%}$, $SBN_2/L\%$ and scores on the questionnaire, for each group. For the calculation of the descriptive statistics, FEV_1, $FEF_{25-75\%}$ and $SBN_2/L\%$ were expressed as a percentage of the predicted value for each variable for each subject.

For statistical analysis, the data for FEV_1, $FEF_{25-75\%}$ and $SBN_2/L\%$ were further expressed as a percentage of the 95th percent confidence interval [one tail], ie 1.65 x SEE, for each variable. This was done to control for differences in coefficients of variation between the spirometric and SBN_2

tests. In the case of the FEV_1 and $FEF_{25-75\%}$, this product was subtracted from the predicted mean for each subject in order to determine the lowest acceptable normal limit. In the case of the $SBN_2/L\%$, this product was added to the predicted mean for each subject in order to determine the highest acceptable normal limit.

All statistical tests were performed on data expressed as described above, thus the results and discussion similarly present and discuss the data in this form. A significance level of p less than 0.05 was selected for all statistical tests.

Second, Wilcoxon matched pairs tests were used to determine whether any differences existed between the two test sessions for each of the four primary variables for each group.

Third, to establish the reproducibility of the data, coefficients of variation [CV] were calculated using the three repeated measures of the $SBN_2/L\%$ for each subject within each group. Further, Spearman rank correlation coefficients [R] were calculated within each variable between sessions for the control group.

Four, the interrelationships of the variables with each other were examined using Spearman rank correlation coefficients.

Five, frequency tables were constructed within each group to examine the relationship of normal or abnormal values in one variable with the occurrence of normal or abnormal values in another variable within one session. These frequency tables, however, could not be statistically analyzed because of the limited cell sizes.

And six, to determine the relationship of change observed within one variable compared with the change in another variable between the two test sessions, change scores were calculated by subtracting the value for each variable in session two from that in session one. Spearman rank correlation coefficients were then calculated using these change scores.

SUBJECT CHARACTERISTICS

The characteristics of the control and experimental groups including gender, age, height and weight are summarized in Table I. Thirty-five subjects in total were included in the study; 14 in the control group, 14 in the asthmatic group and 7 in the CF group. The average weight was lower in the CF group, otherwise the age and height characteristics were similar amongst the groups.

CHARACTERISTICS OF GROUP PERFORMANCE

Spirometry:

All subjects who satisfied the criteria for inclusion in the study were able to complete both test sessions. The interval between test sessions ranged from one to four months. Three acceptable FEV_1 [$FEF_{25-75\%}$] and SBN_2 tracings were obtained without difficulty in each session. The descriptive statistics for the questionnaire, FEV_1, $FEF_{25-75\%}$ and $SBN_2/L\%$ for each of the two sessions are summarized for each group in Tables II-IV. The descriptive statistics were based on the percent of the predicted values achieved by each subject. The control group had the highest mean values for FEV_1 and

TABLE I

SUBJECT CHARACTERISTICS: DESCRIPTIVE STATISTICS [Mean ± SD]

	CONTROL GROUP	ASTHMATIC GROUP	CYSTIC FIBROSIS GROUP
	N=14	N=14	N=7
Female:	14	11	6
Male:	0	3	1
AGE [years]			
Female:	23.6 ± 1.91	23.3 ± 2.69	21.2 ± 1.83
Male:	–	22.0 ± 2.00	19.0
HEIGHT [cm]			
Female:	166.8 ± 3.88	162.7 ± 5.43	164.3 ± 3.96
Male:	–	179.0 ± 1.00	178.0
WEIGHT [kg]			
Female:	57.2 ± 2.98	58.8 ± 8.61	52.0 ± 7.68
Male:	–	72.0 ± 4.73	79.5

TABLE II

DESCRIPTIVE STATISTICS FOR THE DEPENDENT VARIABLES
FOR THE CONTROL GROUP [N=14] IN BOTH TEST SESSIONS

	SESSION 1	SESSION 2
VARIABLE		
QUESTIONNAIRE*:		
Mean ± SD	1.2 ± 1.48	1.2 ± 1.19
Median	0.5	1.0
Range	0.0 - 4.0	0.0 - 3.0
FEV_1:**		
Mean ± SD	102.0 ± 11.72	97.6 ± 7.21
Median	102.6	96.2
Range	88.1 - 126.8	86.3 - 113.4
$FEF_{25-75\%}$:**		
Mean ± SD	95.2 ± 21.65	92.3 ± 21.69
Median	100.6	90.9
Range	65.3 - 142.6	61.2 - 135.6
$SBN_2/L\%$*:**		
Mean ± SD	114.5 ± 27.34	116.0 ± 28.08
Median	112.6	100.8
Range	62.2 - 186.4	89.5 - 176.6

*   Questionnaire scores range from 0 - 29: zero = minimal symptoms and satisfactory endurance, 29 = severe symptoms and limited endurance.

**   Data expressed as percent of predicted [Crapo et al, 1981]

***   Data expressed as percent of predicted [Buist and Ross, 1973]

TABLE III

DESCRIPTIVE STATISTICS FOR THE DEPENDENT VARIABLES
FOR THE ASTHMATIC GROUP [N=14] IN BOTH TEST SESSIONS

	SESSION 1	SESSION 2
VARIABLE		
QUESTIONNAIRE*:		
Mean $\pm$ SD	7.1 $\pm$ 4.44	5.9 $\pm$ 3.83
Median	7.5	5.5
Range	1.0 - 18.0	0.0 - 12.0
FEV_1**:		
Mean $\pm$ SD	80.0 $\pm$ 18.46	83.2 $\pm$ 21.98
Median	85.7	84.7
Range	56.0 - 108.9	44.4 - 114.8
$FEF_{25-75\%}$**:		
Mean $\pm$ SD	59.0 $\pm$ 29.48	65.2 $\pm$ 34.02
Median	69.7	70.4
Range	21.8-97.0	14.0 - 115.9
$SBN_2/L\%$***:		
Mean $\pm$ SD	152.8 $\pm$ 124.43	132.1 $\pm$ 94.19
Median	109.6	109.8
Range	66.0 - 514.2	39.8 - 405.5

*   Questionnaire scores range from 0 - 29: zero = minimal symptoms and satisfactory endurance, 29 = severe symptoms and limited endurance.

**   Data expressed as percent of predicted [Crapo et al, 1981]

***   Data expressed as percent of predicted [Buist and Ross, 1973]

TABLE IV

DESCRIPTIVE STATISTICS FOR THE DEPENDENT VARIABLES
FOR THE CYSTIC FIBROSIS GROUP [N=7] IN BOTH TEST SESSIONS

	SESSION 1	SESSION 2
VARIABLE		
QUESTIONNAIRE*:		
Mean ± SD	10.7 ± 6.52	11.4 ± 6.58
Median	9.0	12.0
Range	5.0 - 24.0	0.0 - 22.0
FEV_1**:		
Mean ± SD	44.2 ± 20.14	48.1 ± 11.03
Median	46.1	44.8
Range	18.5 - 70.8	32.1 - 66.2
$FEF_{25-75\%}$**:		
Mean ± SD	23.6 ± 15.06	22.9 ± 6.27
Median	25.5	21.0
Range	7.2 - 47.4	14.5 - 33.8
$SBN_2/L\%$***:		
Mean ± SD	936.6 ± 393.44	788.2 ± 256.29
Median	948.8	693.5
Range	452.4 - 1427.3	505.7 - 1090.9

*   Questionnaire scores range from 0 - 29: zero = minimal
      symptoms and satisfactory endurance, 29 = severe symptoms
      and limited endurance.

**   Data expressed as percent of predicted [Crapo et al, 1981]

***   Data expressed as percent of predicted [Buist and Ross,
      1973]

$FEF_{25-75\%}$. For example in session one, the FEV_1 and $FEF_{25-75\%}$ were 102.0 and 95.2% predicted respectively. The asthmatic group fell between the control and CF groups with FEV_1 and $FEF_{25-75\%}$ values of 80.0 and 59.0% predicted respectively. In the CF group the FEV_1 was 44.2% predicted and the $FEF_{25-75\%}$ was 23.6% predicted. The $SBN_2/L\%$ values followed a similar trend with the lowest percent predicted mean in the control group [114.5%], followed by the asthmatic group [152.8%] and the CF group with the highest mean [936.6%]. In session two the same trends were observed for both the spirometry and $SBN_2/L\%$ mean values.

Spirometry and SBN_2 Tracings:

The spirometry tracings differed markedly in their appearance amongst groups, being smallest in magnitude and more gently sloped in the severe asthmatic subjects and all CF subjects. The SBN_2 tracings of the severe asthmatics and all CF subjects also had a characteristic appearance which differed significantly from the control group as well as each other. A representative SBN_2 tracing from the control group is displayed in Figure 4. Phase IV was less evident amongst the younger subjects in this group. The SBN_2 tracings of the mild asthmatics approximated those of the control subjects. The SBN_2 tracings of the severe asthmatics displayed a concavity during Phase III [Figure 5], while the CF subjects displayed a steep and continuous slope [Figure 6]. In these subjects, the

Fig. 4. X-Y recording of the single-breath nitrogen test from a
control subject. Percent nitrogen is displayed on the y-axis and
exhaled volume is on the x-axis.
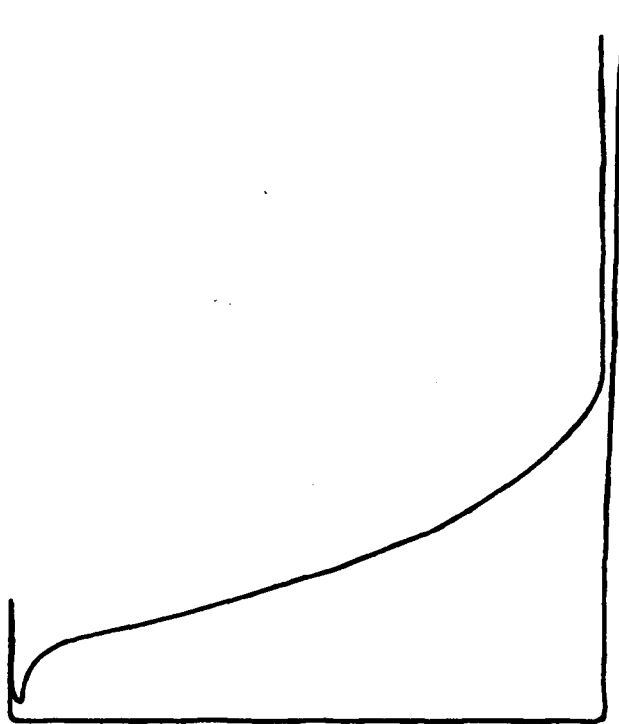
Fig. 5. X-Y recording of the single-breath nitrogen test from a severe asthmatic subject. Percent nitrogen is displayed on the y-axis and exhaled volume is on the x-axis.
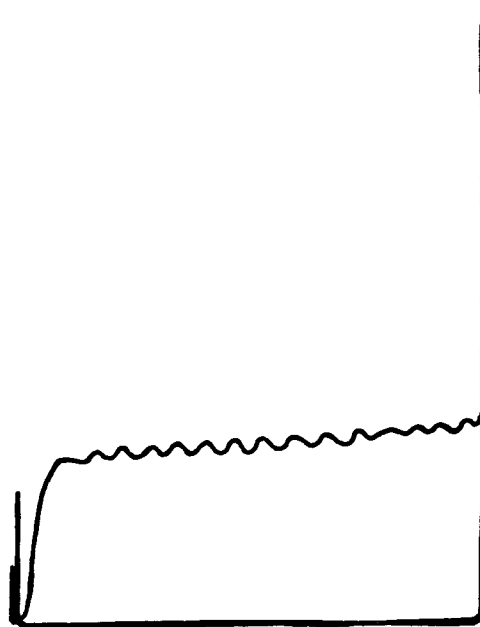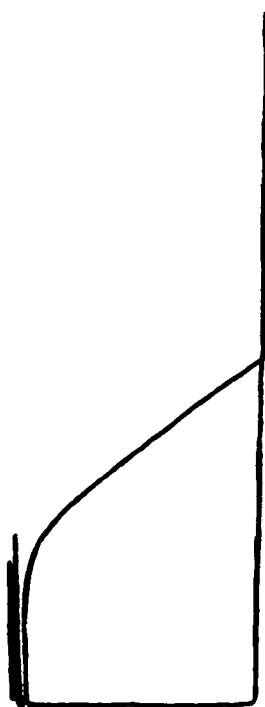
Fig. 6. X-Y recording of the single-breath nitrogen test from a
cystic fibrosis subject. Percent nitrogen is displayed on the
y-axis and exhaled volume is on the x-axis.

cardiac oscillations were absent and Phase IV was typically indistinguishable.

REPRODUCIBILITY OF THE TEST RESULTS

Within the control group, spirometry and $SBN_2/L\%$ values and questionnaire scores [expressed as a %predicted lower/upper limit] between session one and two were highly correlated [Table V]. Table VI shows the coefficients of variation [CV] for each test session within each group for the $SBN_2/L\%$. Over all groups, the CV for the $SBN_2/L\%$ averaged less than 10%.

INTERRELATIONSHIP AMONGST VARIABLES WITHIN A SESSION

Using the Wilcoxon matched pairs test, no significant differences were observed for any variable [expressed as a %predicted lower/upper limit] within groups, between session one and session two [p> 0.05]. Therefore, analysis of the interrelationship between variables was conducted using one single session.

The Spearman rank correlations for all three groups between FEV_1, $FEF_{25-75\%}$, $SBN_2/L\%$ and the questionnaire scores appear in Table VII. The correlations for FEV_1 vs $SBN_2/L\%$ and $FEF_{25-75\%}$ vs $SBN_2/L\%$ appear in Figures 7-12. At the p< 0.05 level, FEV_1 correlated positively with $FEF_{25-75\%}$ and both

TABLE V

REPRODUCIBILITY OF VARIABLES OVER THE TWO SESSIONS FOR THE
CONTROL GROUP [N=14]: SPEARMAN RANK ORDER CORRELATIONS [R]

VARIABLE	SPEARMAN R	p LEVEL
Questionnaire	0.59	0.03
FEV_1	0.75	0.01
$FEF_{25-75\%}$	0.88	<0.01
$SBN_2/L\%$	0.65	0.02

TABLE VI

REPRODUCIBILITY OF THE SBN_2/L%: COEFFICIENTS OF VARIATION
[SD/MEAN %] WITHIN SUBJECTS FOR EACH GROUP

	SESSION 1	SESSION 2
GROUP:		
CONTROL [N=14]		
Mean ± SD	7.5 ± 5.14	5.9 ± 3.47
Median	6.0	6.0
Range	2 - 17	0 - 12
ASTHMATIC [N=14]		
Mean ± SD	9.8 ± 4.84	8.4 ± 3.97
Median	9.5	7.5
Range	3 - 19	2 - 16
CYSTIC FIBROSIS [N=7]		
Mean ± SD	3.6 ± 2.64	7.9 ± 2.50
Median	3.0	8.0
Range	1 - 8	4 - 10

TABLE VII

INTERRELATIONSHIP AMONG VARIABLES FOR EACH GROUP WITHIN ONE SESSION: SPEARMAN RANK CORRELATIONS [R]

	SPEARMAN R		
	CONTROL GROUP [N=14]	ASTHMATIC GROUP [N=14]	CYSTIC FIBROSIS GROUP [N=7]
COMPARISON			
Questionnaire vs			
FEV_1	-0.39	0.14	-0.41
$FEF_{25-75\%}$	-0.12	-0.07	-0.20
$SBN_2/L\%$	0.17	0.20	0.63
FEV_1 vs $FEF_{25-75\%}$	0.58*	0.82**	0.96*
$SBN_2/L\%$	-0.54*	-0.63*	-0.93*
$FEF_{25-75\%}$ vs $SBN_2/L\%$	-0.63*	-0.54*	-0.86*

* $p<0.05$
** $p<0.01$

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%PRED FEV1 vs %PRED SBN2/L%

CONTROL GROUP

Fig. 7. Relationship between the %predicted FEV1
[mean - 1.65xSEE] and the %predicted SBN2/L% [mean + 1.65xSEE]
for the control group.

%PRED FEF25-75% vs %PRED SBN2/L%

CONTROL GROUP

Fig. 8. Relationship between the %predicted FEF25-75%
[mean - 1.65xSEE] and the %predicted SBN2/L% [mean + 1.65xSEE]
for the control group.

%PRED FEV1 vs %PRED SBN2/L%

ASTHMATIC GROUP

Fig. 9. Relationship between the %predicted FEV1
[mean - 1.65xSEE] and the %predicted SBN2/L% [mean + 1.65xSEE]
for the asthmatic group.

%PRED FEF25-75% vs %PRED SBN2/L%

ASTHMATIC GROUP
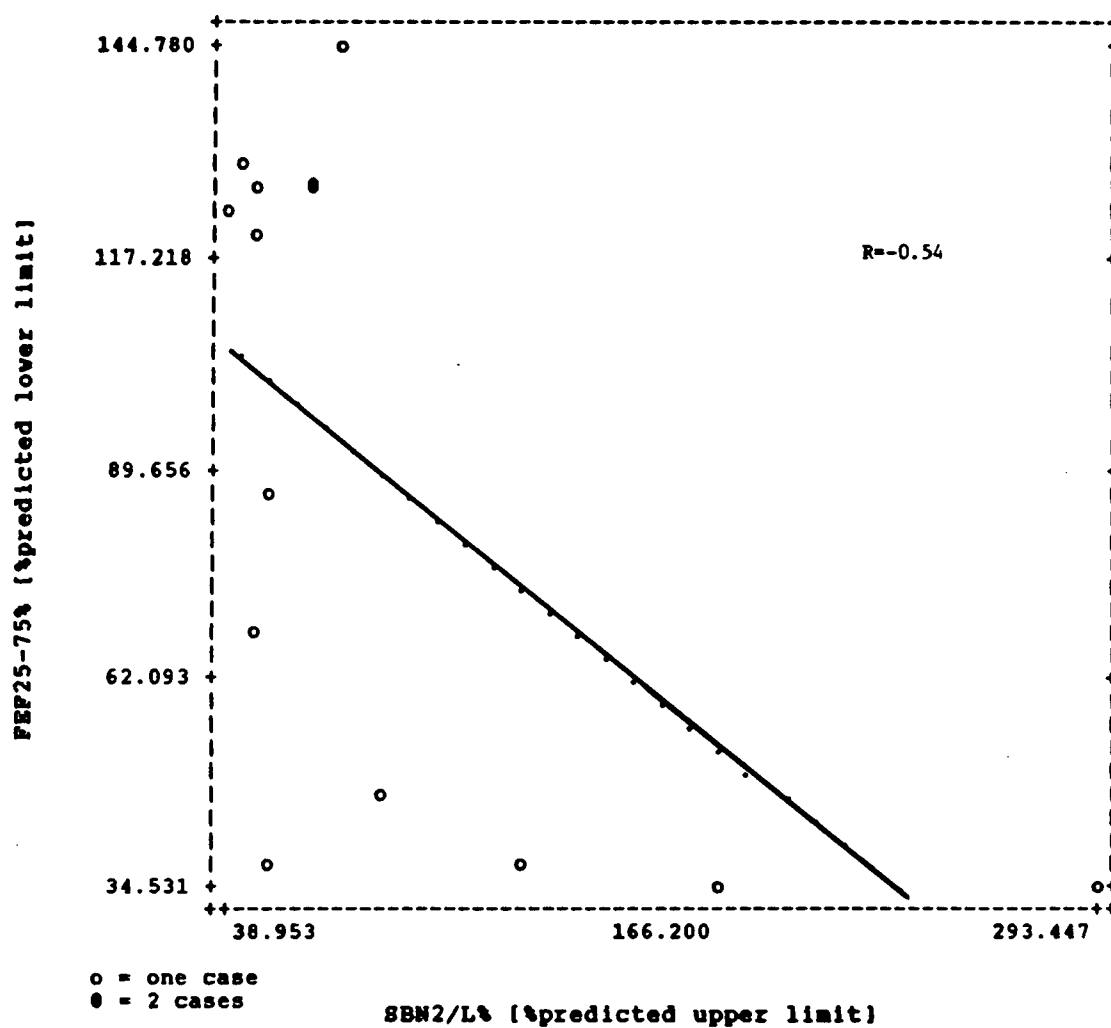
Fig. 10. Relationship between the %predicted FEF25-75%
[mean - 1.65xSEE] and the %predicted SBN2/L% [mean + 1.65xSEE]
for the asthmatic group.

%PRED FEV1 vs %PRED SBN2/L%
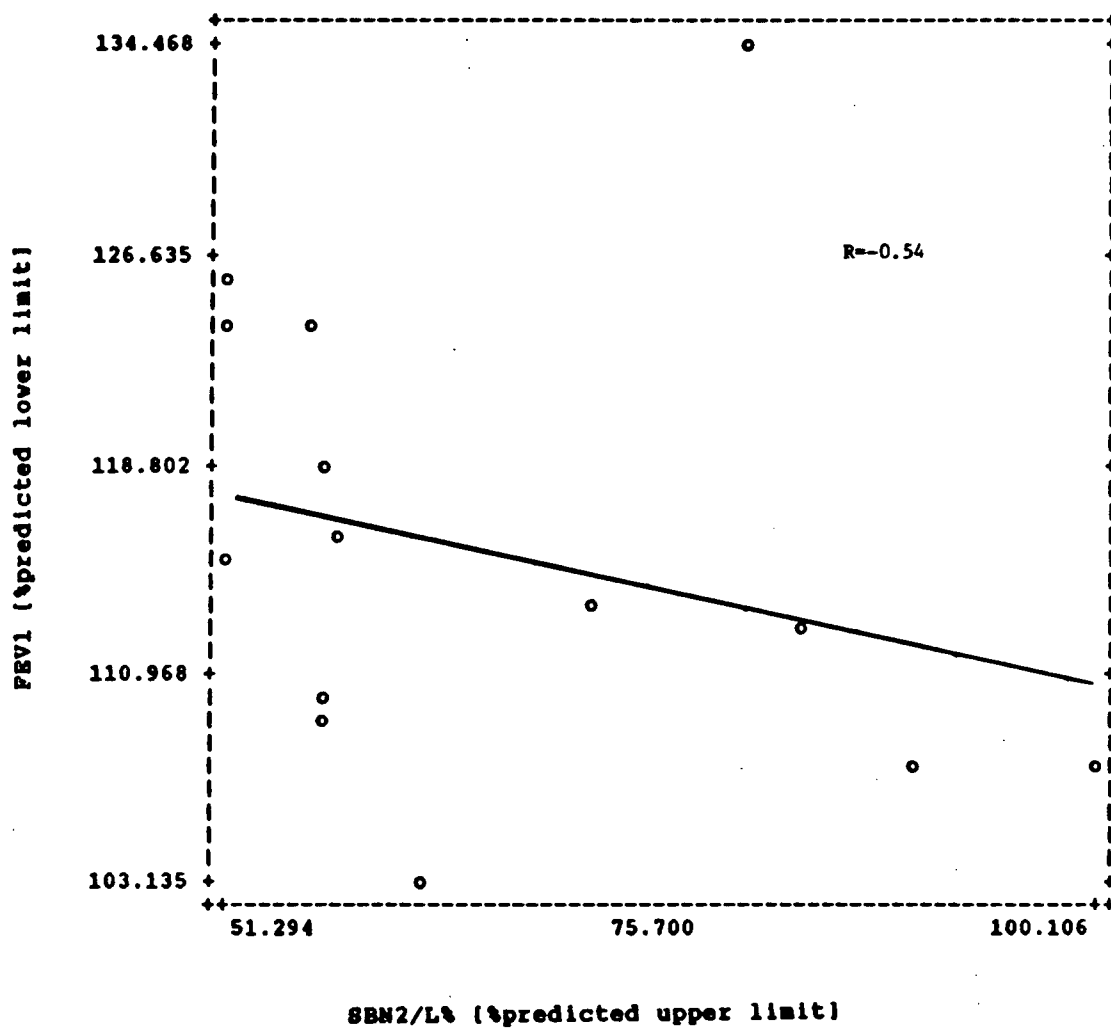
CYSTIC FIBROSIS GROUP
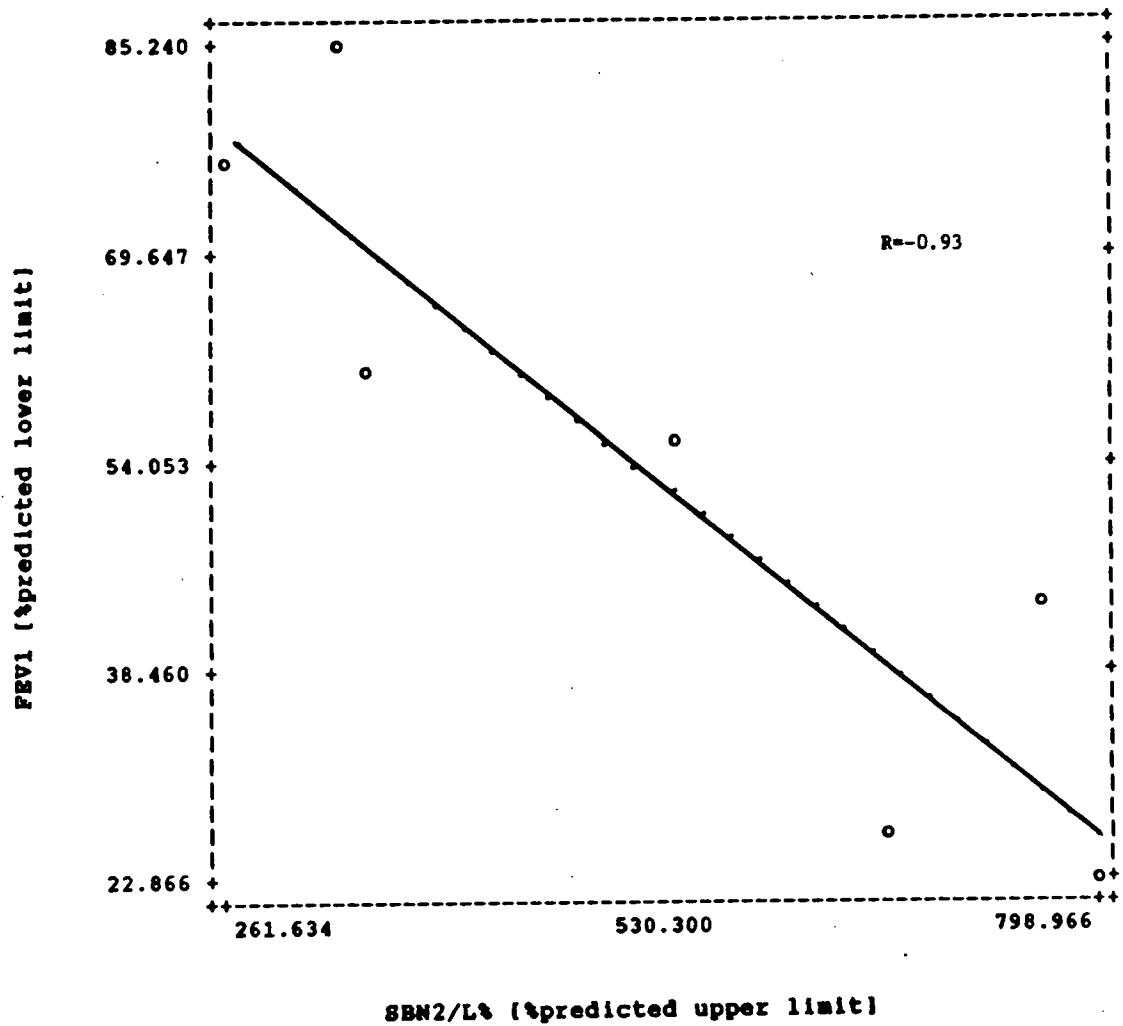
Fig. 11. Relationship between the %predicted FEV1
[mean - 1.65xSEE] and the %predicted SBN2/L% [mean + 1.65xSEE] for
the cystic fibrosis group.

%PRED FEF25-75% vs %PRED SBN2/L%
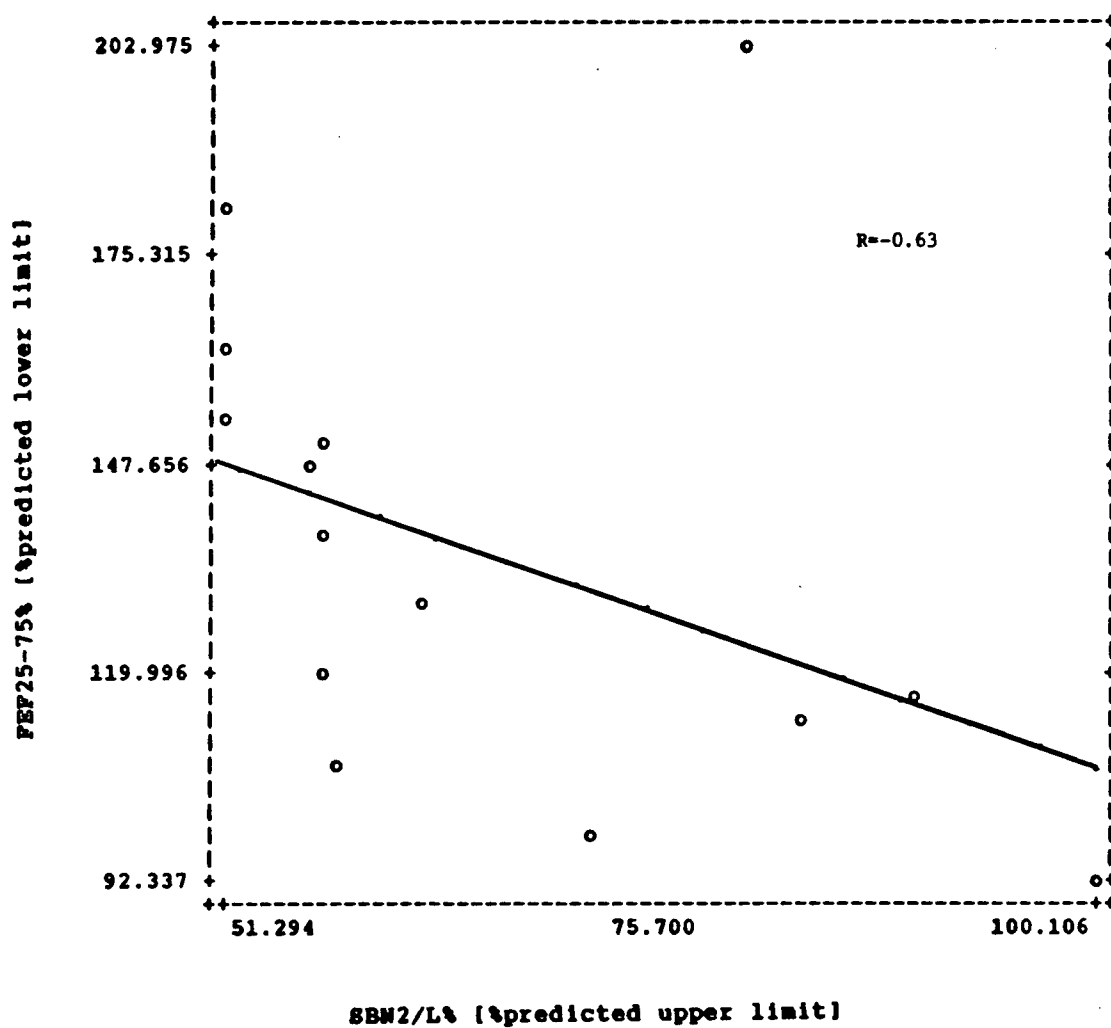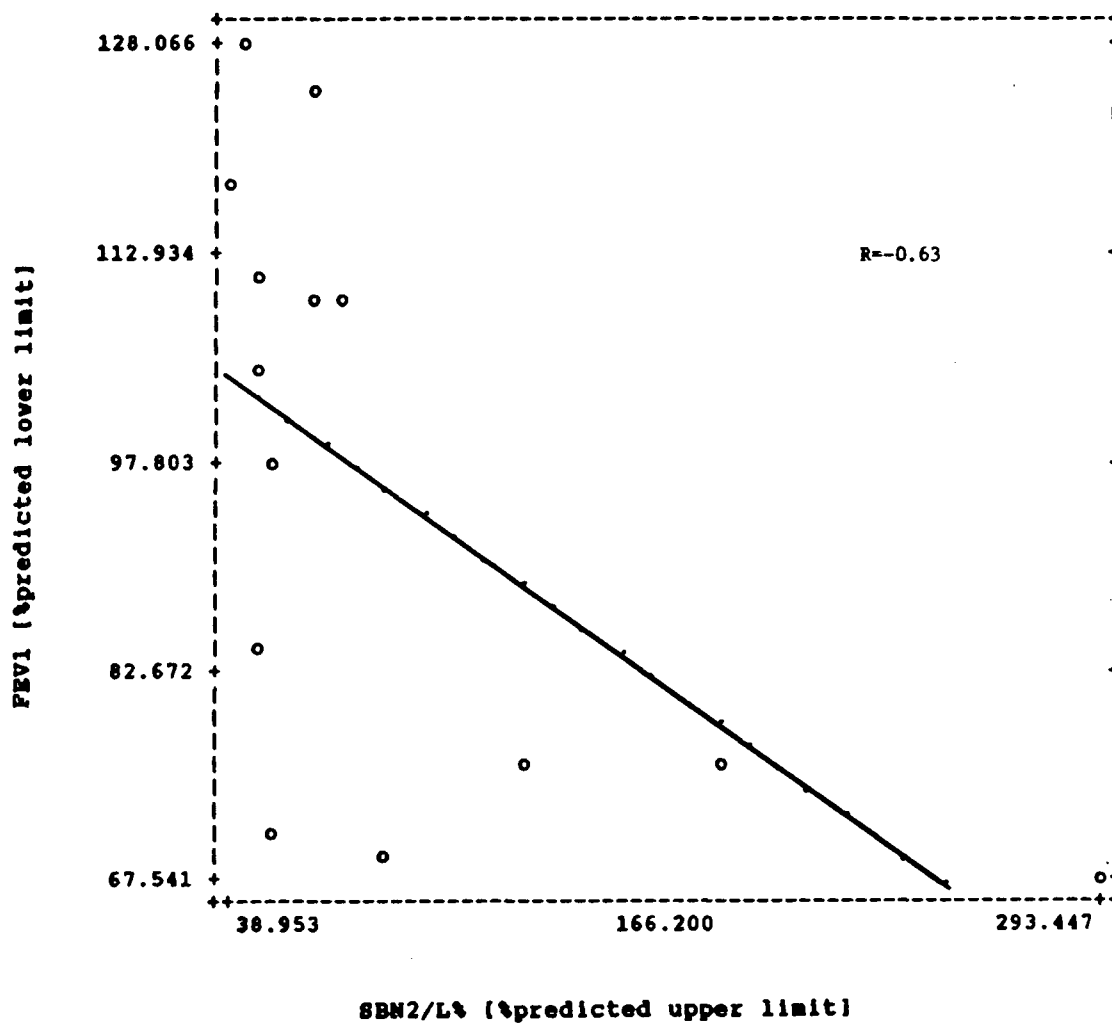
CYSTIC FIBROSIS GROUP
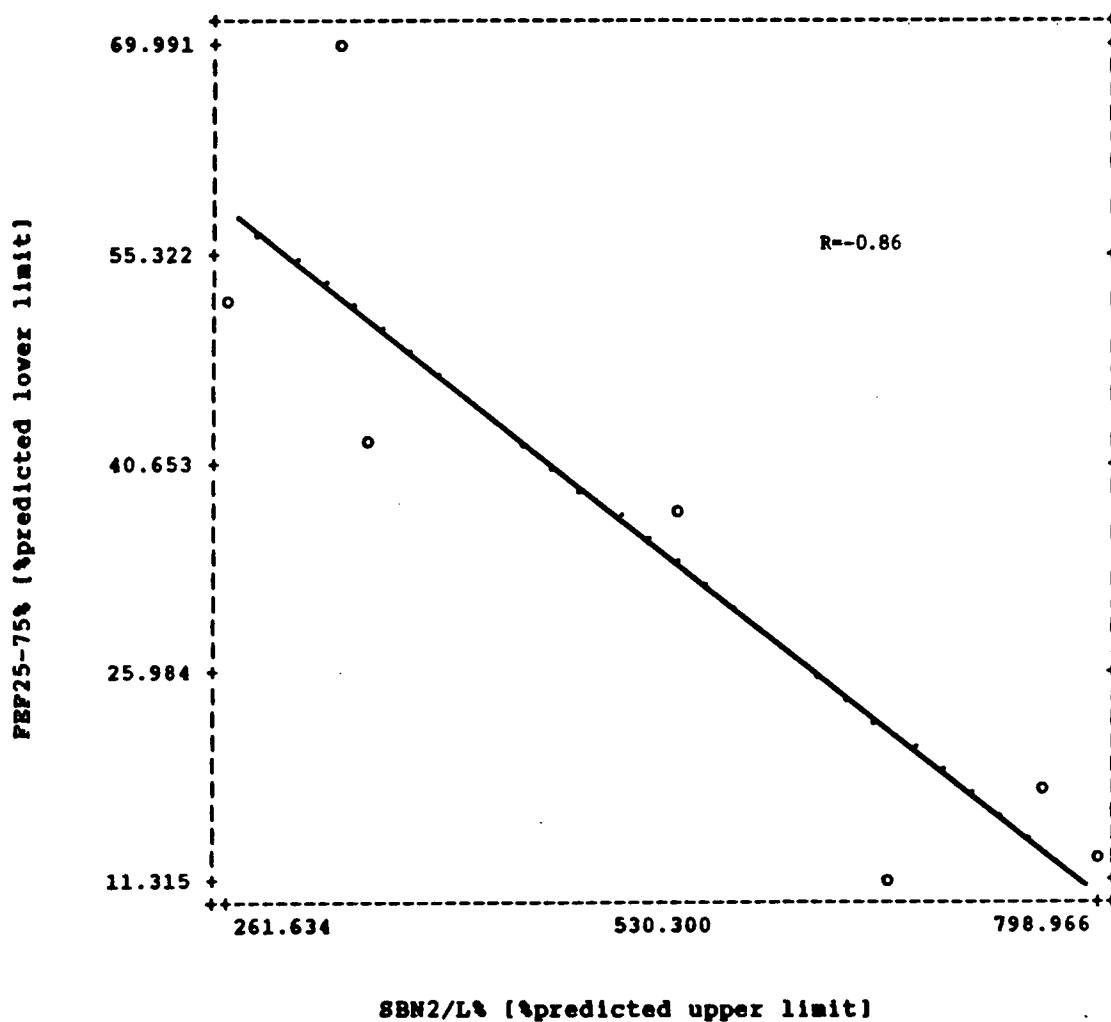
Fig. 12. Relationship between the %predicted FEF25-75%
[mean - 1.65xSEE] and the %predicted SBN2/L% [mean + 1.65xSEE]
for the cystic fibrosis group.

correlated negatively with the $SBN_2/L\%$. The questionnaire did not correlate with any of the variables. The same pattern of correlations was observed in the asthmatic and CF groups.

The association between FEV_1, $FEF_{25-75\%}$ and the $SBN_2/L\%$ is further presented in a summary of frequency tables [Table VIII] relating normal and abnormal values for all three groups. In the control group, tests were normal for all subjects except one who had an abnormal $FEF_{25-75\%}$ with a normal $SBN_2/L\%$. In the asthmatic group seven subjects had a normal FEV_1 and $SBN_2/L\%$, while four subjects had an abnormal FEV_1 with a normal $SBN_2/L\%$, and three subjects had both an abnormal FEV_1 and $SBN_2/L\%$. The $FEF_{25-75\%}$ values followed a similar relationship with the $SBN_2/L\%$ in this group. In the CF group all of these values were abnormal.

INTERRELATIONSHIP OF THE CHANGE IN VARIABLES BETWEEN TWO SESSIONS

The interrelationship of the change in the variables [expressed as a %predicted lower/upper limit] from test session one to session two is presented in Table IX for the three groups. The correlations for FEV_1 vs $SBN_2/L\%$ and $FEF_{25-75\%}$ vs $SBN_2/L\%$ appear in Figures 13-18. In all three groups, the change in FEV_1 was positively correlated [Spearman rank order correlation] with the change in $FEF_{25-75\%}$ [$p< 0.05$]. The change in $SBN_2/L\%$ did not correlate with the change in the

TABLE VIII

INTERRELATIONSHIP OF VARIABLES WHEN CATEGORIZED AS NORMAL OR
ABNORMAL: FREQUENCY DATA FOR EACH GROUP FOR ONE SESSION

	CONTROL GROUP [N=14]	ASTHMATIC GROUP [N=14]	CYSTIC FIBROSIS GROUP [N=7]
CATEGORY			
Normal FEV_1*			
normal SBN_2/L%**	14	7	0
abnormal SBN_2/L%	0	0	0
Abnormal FEV_1			
normal SBN_2/L%	0	4	0
abnormal SBN_2/L%	0	3	7
- - - - - - - - - - - - -	- - - - - - - - -	- - - - - - - - -	- - - - - - - - -
Normal $FEF_{25-75\%}$*			
normal SBN_2/L%	13	7	0
abnormal SBN_2/L%	0	0	0
Abnormal $FEF_{25-75\%}$			
normal SBN_2/L%	1	4	0
abnormal SBN_2/L%	0	3	7

---

* Normal FEV_1 $\geq$ %predicted minus 1.65 x SEE [Crapo et al, 1981]

** Normal SBN_2/L% $\leq$ %predicted plus 1.65 x SEE [Buist and Ross, 1973]

*** Normal $FEF_{25-75\%}$ $\geq$ %predicted minus 1.65 x SEE [Crapo et al, 1981]

TABLE IX

INTERRELATIONSHIP OF THE CHANGE IN VARIABLES BETWEEN TWO
SESSIONS: SPEARMAN RANK ORDER CORRELATIONS [R]
FOR THE THREE GROUPS

| | SPEARMAN R | | |
	CONTROL GROUP [N=14]	ASTHMATIC GROUP [N=14]	CYSTIC FIBROSIS GROUP [N=7]
COMPARISON OF CHANGE AMONGST VARIABLES			
Questionnaire vs			
FEV_1	0.17	-0.11	-0.78*
$FEF_{25-75\%}$	-0.01	-0.02	-0.80*
$SBN_2/L\%$	-0.11	0.20	0.55
FEV_1 vs $FEF_{25-75\%}$	0.78**	0.94**	0.89*
$SBN_2/L\%$	-0.48	-0.12	-0.75 [*]
$FEF_{25-75\%}$ vs $SBN_2/L\%$	-0.44	-0.17	-0.64

[*] approaching $p<0.05$
 * $p<0.05$
** $p<0.01$

CHANGE FEV1 vs CHANGE SBN2/L%

CONTROL GROUP
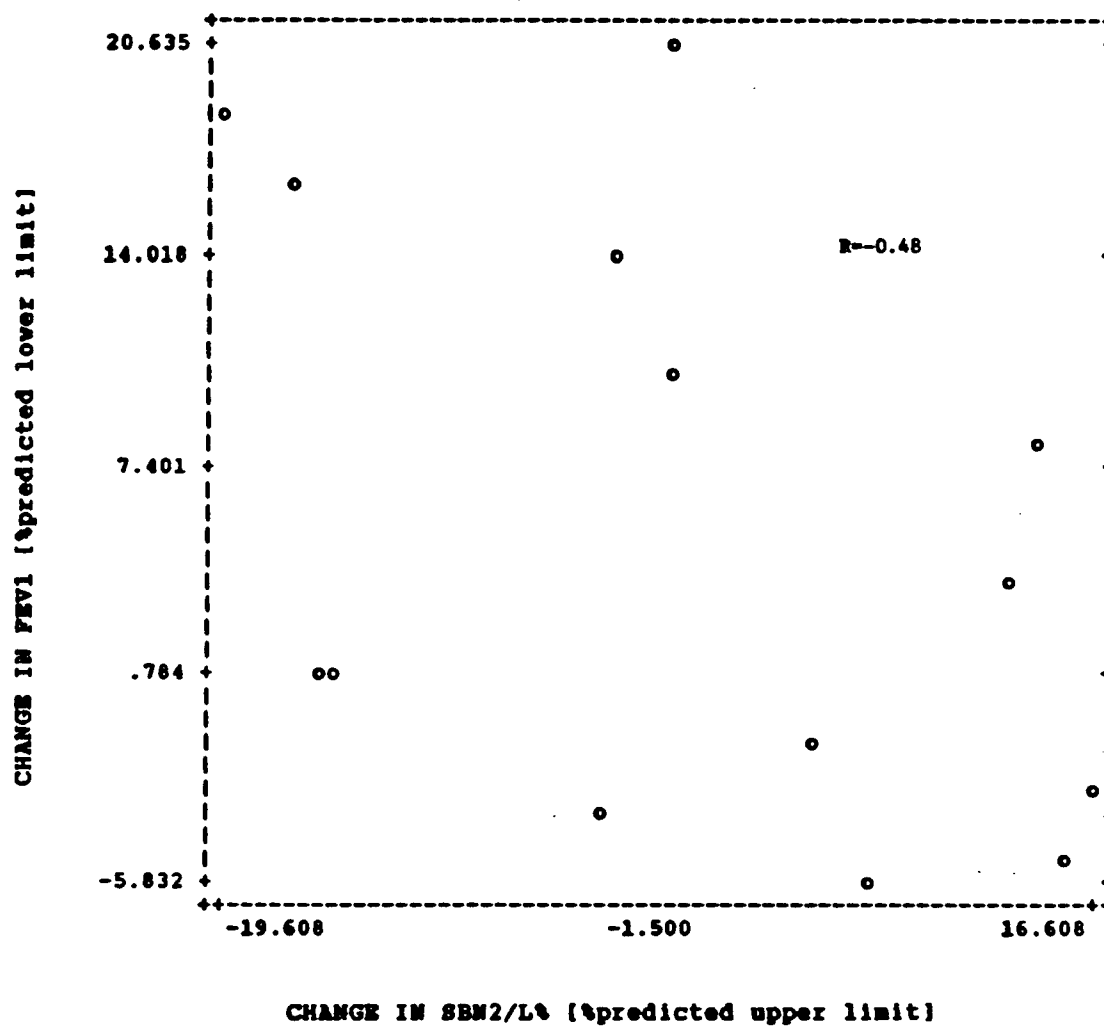
Fig. 13. Relationship between the change in %predicted FEV1
[mean - 1.65xSEE] and the change in %predicted SBN2/L%
[mean + 1.65xSEE] for the control group.

CHANGE FEF25-75% vs CHANGE SBN2/L%

CONTROL GROUP
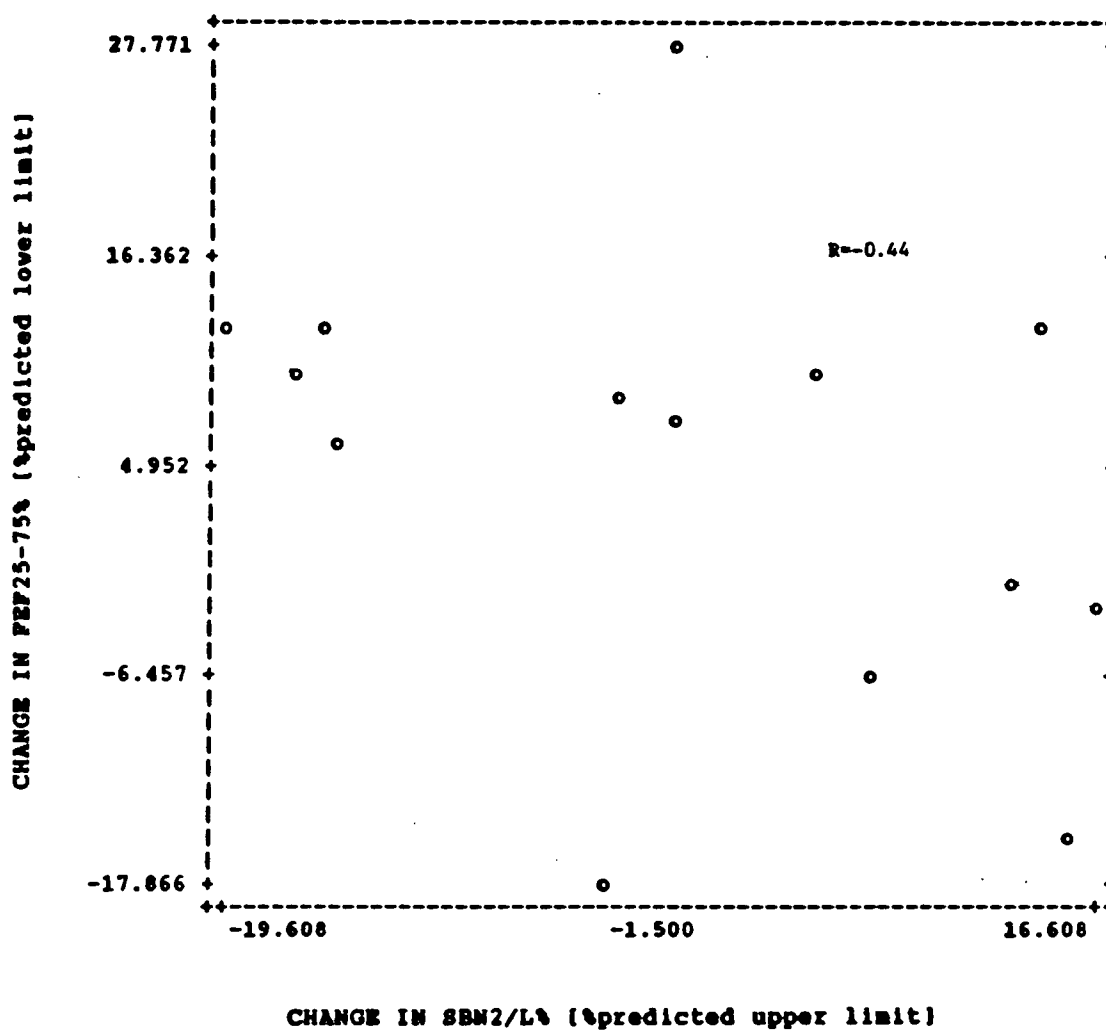
Fig. 14. Relationship between the change in %predicted FEF25-75% [mean - 1.65xSEE] and the change in %predicted SBN2/L% [mean + 1.65xSEE] for the control group.

CHANGE FEV1 vs CHANGE SBN2/L%

ASTHMATIC GROUP
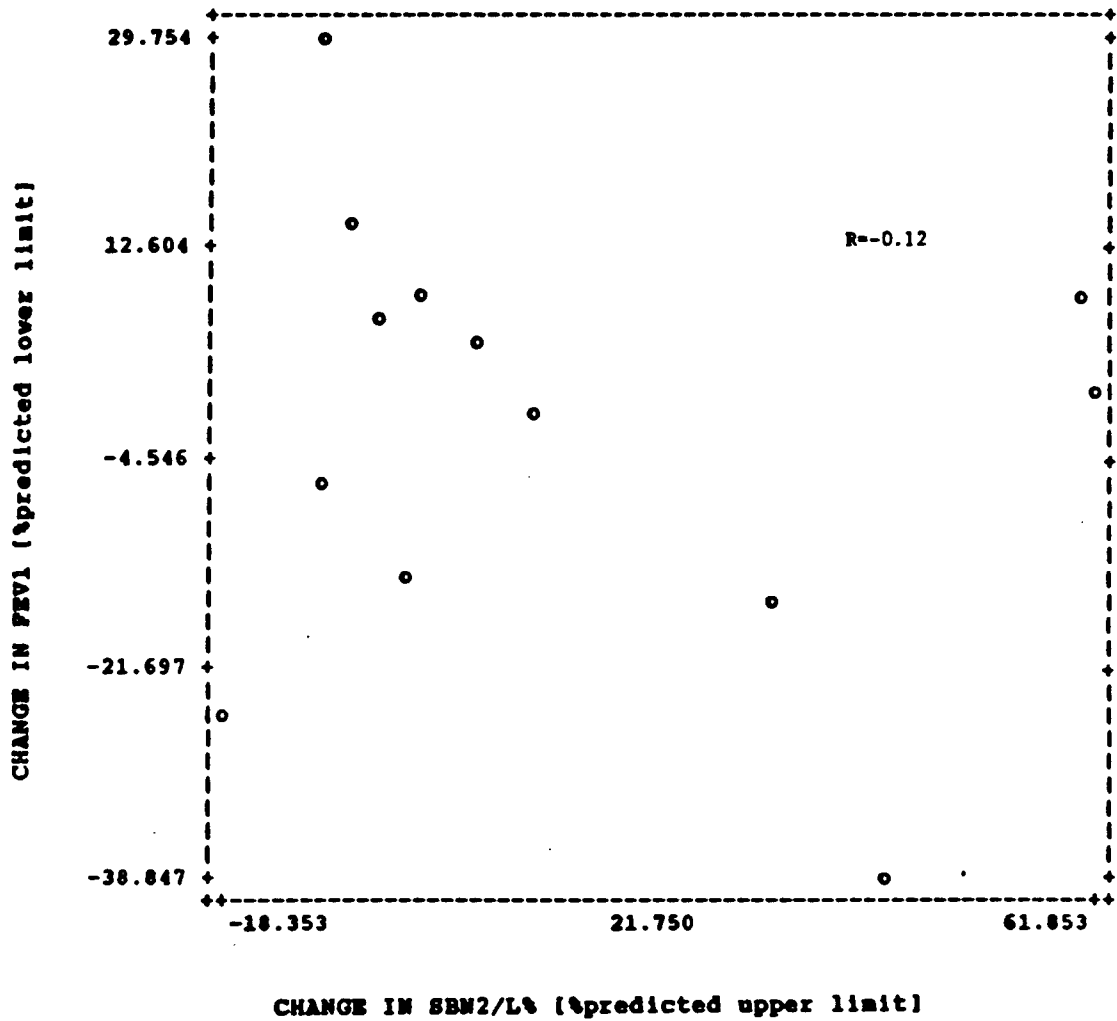
Fig. 15. Relationship between the change in %predicted FEV1
[mean - 1.65xSEE] and the change in %predicted SBN2/L%
[mean + 1.65xSEE] for the asthmatic group.

CHANGE FEF25-75% vs CHANGE SBN2/L%

ASTHMATIC GROUP
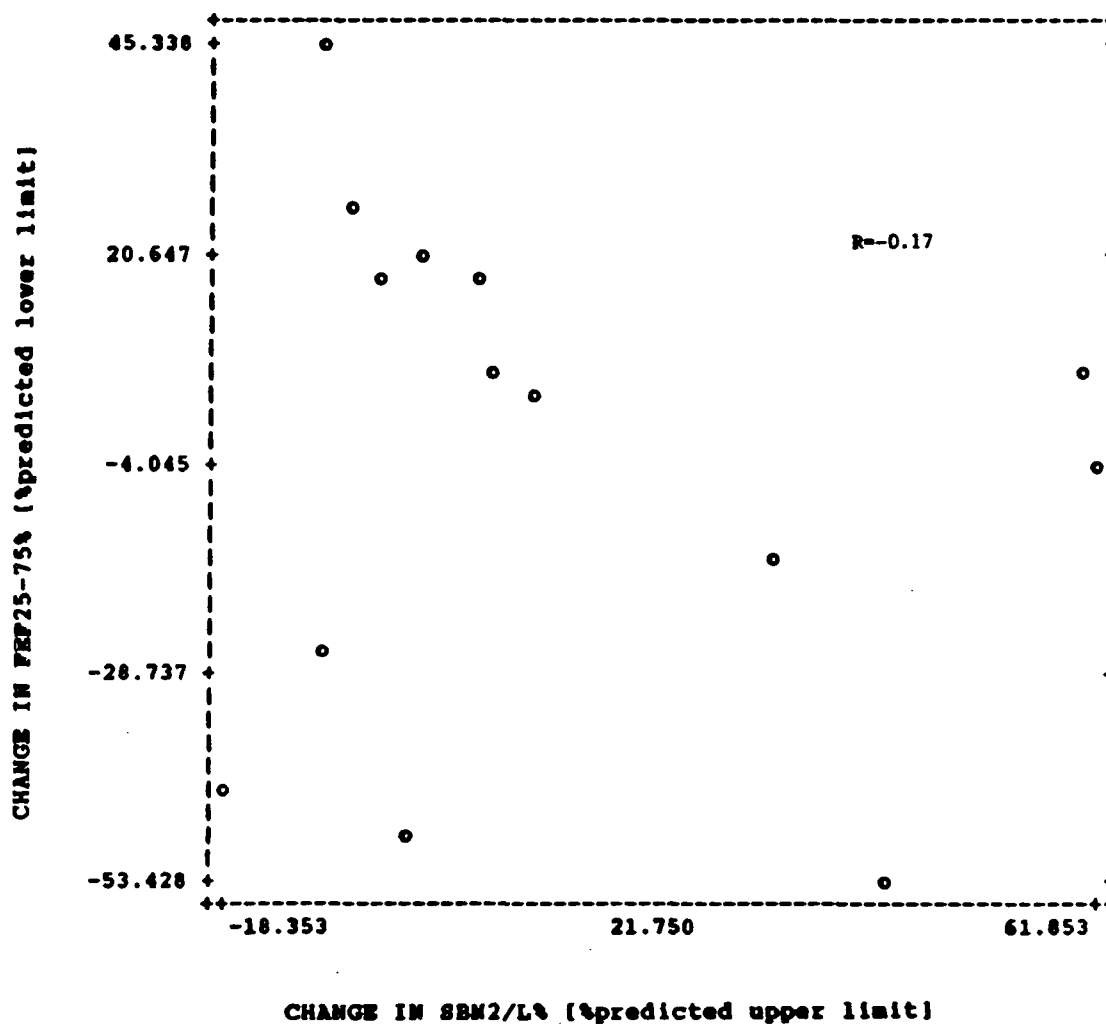
Fig. 16. Relationship between the change in %predicted FEF25-75%
[mean - 1.65xSEE] and the change in %predicted SBN2/L%
[mean + 1.65xSEE] for the asthmatic group.

CHANGE FEV1 vs CHANGE SBN2/L%

CYSTIC FIBROSIS GROUP
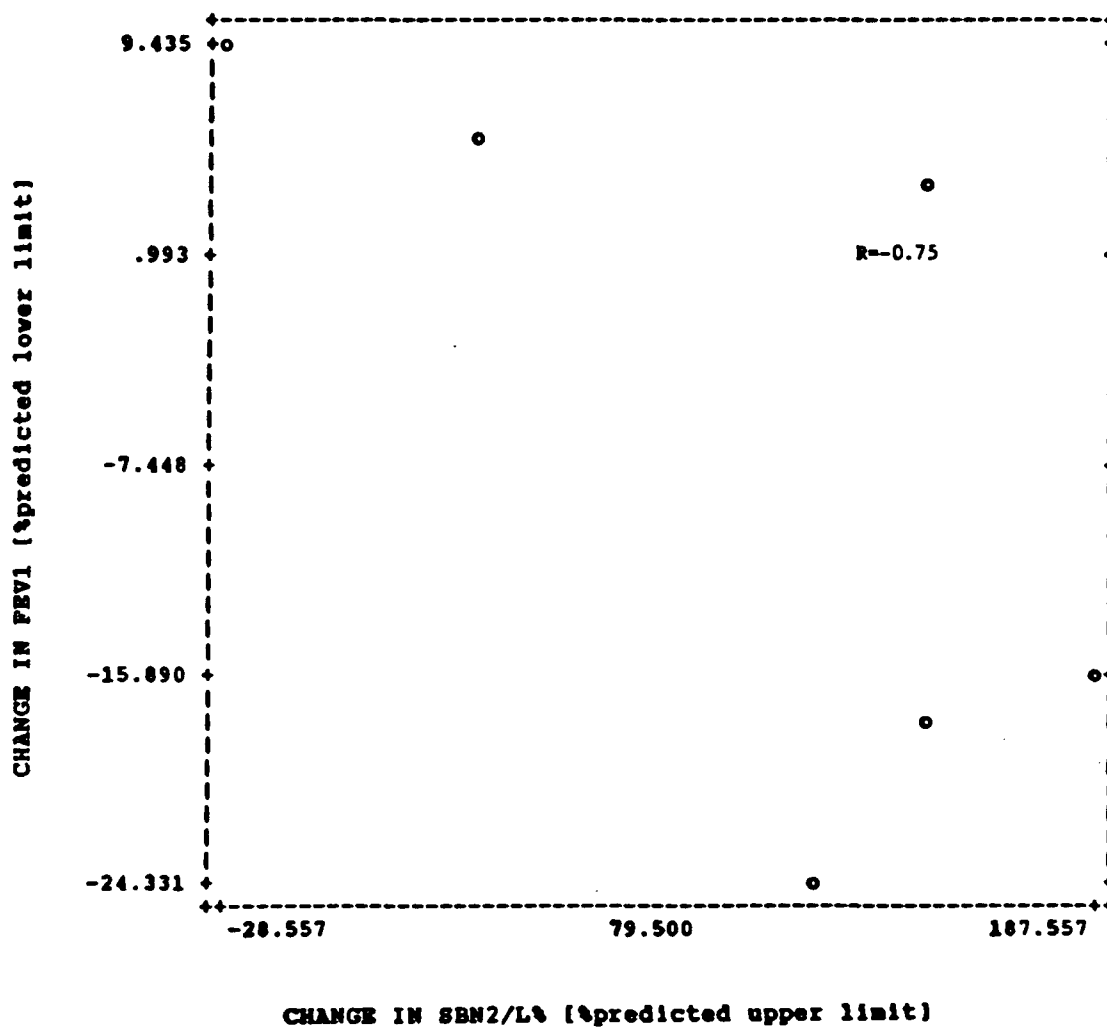
Fig. 17. Relationship between the change in %predicted FEV1
[mean - 1.65xSEE] and the change in %predicted SBN2/L%
[mean + 1.65xSEE] for the cystic fibrosis group.

CHANGE FEF25-75% vs CHANGE SBN2/L%

CYSTIC FIBROSIS GROUP
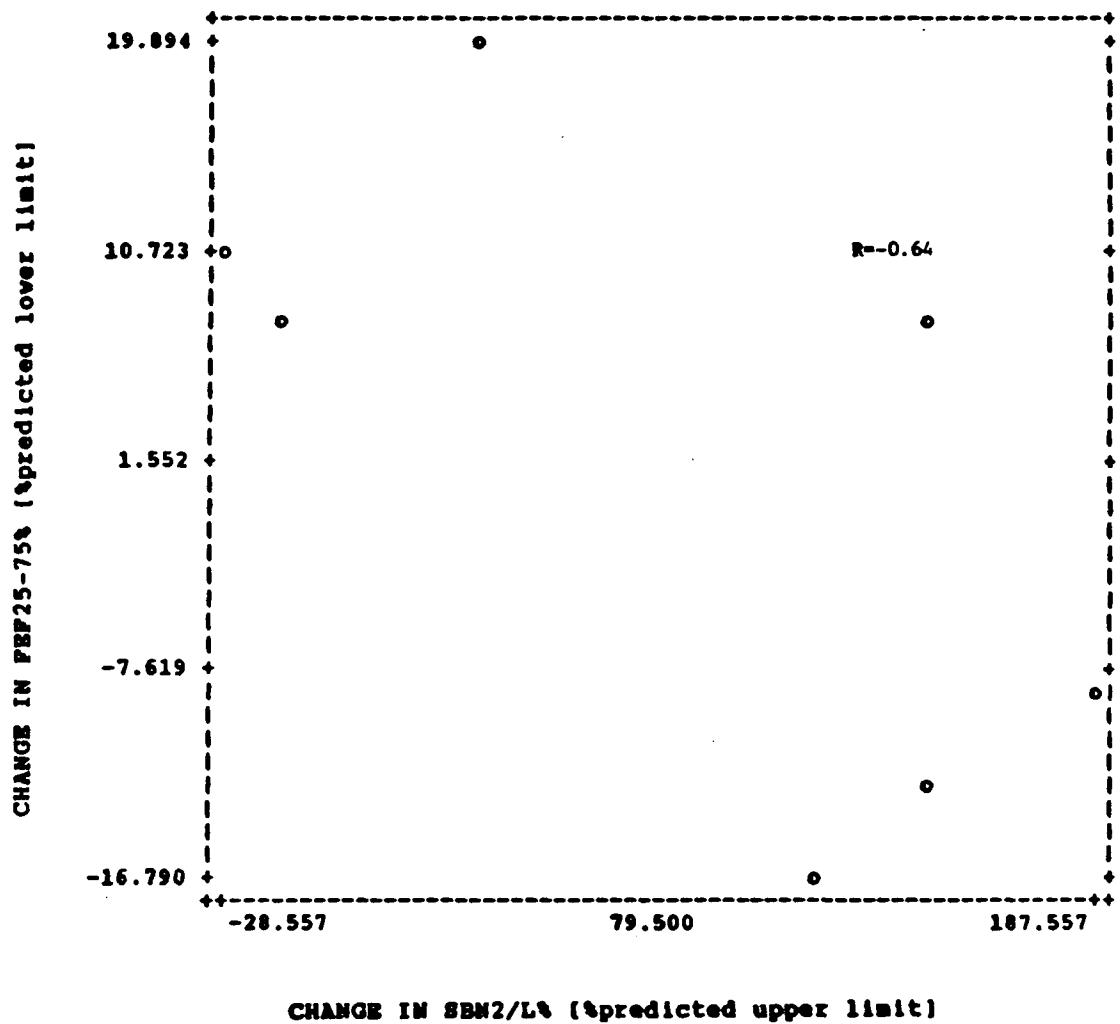
Fig. 18. Relationship between the change in %predicted FEF25-75%
[mean - 1.65xSEE] and the change in %predicted SBN2/L%
[mean + 1.65xSEE] for the cystic fibrosis group.

other variables in any group, although the correlation between $SBN_2/L\%$ and FEV_1 was approaching significance in the CF group [p=0.06]. In the CF group, the change in questionnaire scores correlated negatively with the change in FEV_1 and $FEF_{25-75\%}$ [p< 0.05]. A low score on the questionnaire reflected minimal symptoms and a satisfactory endurance capacity.

This study investigated the interrelationship between airflow limitation and ventilation inhomogeneity as measured by spirometry and the $SBN_2/L\%$ respectively, in subjects with asthma and cystic fibrosis. The results of this study quantified the airflow limitation and ventilation inhomogeneity in each of these groups, and determined the interrelationship between them. Based on these findings and their implications, conclusions can be made about the role of the $SBN_2/L\%$ in the assessment and management of individuals with asthma and cystic fibrosis over the course of disease.

DIFFERENTIATING THE PERFORMANCE OF THE CYSTIC FIBROSIS AND ASTHMATIC GROUPS

Spirometry and SBN_2 Test Results:

In the descriptive statistics shown in Tables II-IV, the mean test scores of the asthmatic group fell between those of the control and CF groups, which were highly normal and abnormal respectively. These findings are consistent with the presentation of asthma and CF, wherein asthma presents with variable degrees of airway obstruction over time, and is not relentlessly progressive in its course [Bates, 1989; McFadden, 1988]. Cystic fibrosis however, is characterized by a gradual

and persistent decrease in pulmonary function, with more rapid declines during exacerbations [Scanlin, 1988]. Amongst the asthmatic and CF groups, there were only a few subjects who exemplified moderate disease severity. This bimodal distribution is also reflected in the frequency data of Table VIII where only eight subjects fell in a category reflecting mild to moderate disease-when one test score was normal and the other was abnormal.

In the CF group, the mean $SBN_2/L\%$ [936.6% predicted] was significantly more impaired than the mean FEV_1 [44.2% predicted] or mean $FEF_{25-75\%}$ [23.6% predicted]. This indicates that in the CF group, more severe ventilation inhomogeneity was present than would be expected from the degree of airflow limitation detected by spirometry. Thus, these results suggest that inclusion of the $SBN_2/L\%$ is necessary to accurately determine the degree of ventilation inhomogeneity in individuals with cystic fibrosis.

Differences in the SBN_2 Tracings:

The variation in test results amongst groups is also reflected in the actual SBN_2 tracings illustrated in Figures 4-6. In the asthmatic group, the tracings of the mild asthmatics were qualitatively similar to the controls, again exemplifying the variable degree of airway obstruction in asthma. The tracings of the severe asthmatics however, had a concave $SBN_2/L\%$. Tomioka et al [1988] described a similar

concavity during Phase IV of the SBN_2 test in their examination of the relationship between airway closure and collateral ventilation. They used a dog and pig model since these animals have a well developed and poorly developed collateral ventilation respectively. They observed the greatest concavity in the dog model and attributed this finding to ventilation of closed units through collateral channels which would decrease the concentration of the tracer gas in the expirate. Woolcock and Macklem [1971] have previously reported that resistance through collateral channels is greater than that through small airways, thus limiting collateral ventilation. However, with the onset of airway closure there would be greater potential for collateral ventilation [Tomioka et al, 1988]. Andersen and Rasmussen [1981] have reported that the development of enhanced collateral ventilation in disease may contribute to the reduction of the N_2 gradient between open and closed lung units. Therefore, it is possible that collateral ventilation distal to obstructed airways may be responsible for the curvature seen during Phase III in the severe asthmatics of the present study. Furthermore, Phase IV was difficult to distinguish in these tracings, as predicted by Andersen and Rasmussen [1981] on the basis of a decreased interregional N_2 gradient secondary to significant intraregional inhomogeneity.

The SBN_2/L% concavity was not seen in the tracings of the CF group, which displayed a steep and continuous slope without a clearly distinguishable Phase IV. This may be explained by the differences in underlying pathology between these two

diseases. Although small airway obstruction is prevalent in both CF and asthma, the underlying mechanisms differ. Airway obstruction in asthma results predominantly from bronchoconstriction and airway inflammation of variable location and severity [Gold et al, 1967; Bates, 1989]. The persistent airway obstruction in CF is characterized primarily by mucus plugging and the development of bronchiectasis [Scanlin, 1988]. These differences were exhibited in the findings of Mansell et al [1974] who observed effort dependence of flow at high lung volumes in individuals with CF, but not in asthmatics. They attributed their findings to volume displacement from bronchiectatic airways in CF individuals. Thus, the steep and continuous $SBN_2/L\%$ seen in the CF subjects in the present study may reflect a more significant and permanent pathology than in the asthmatic subjects. Furthermore, the small vital capacity observed in the CF subjects relative to the asthmatics, may also contribute to a greater degree of ventilation inhomogeneity. If collateral ventilation was a factor in producing the concave $SBN_2/L\%$ in the asthmatic group, it is possible that collateral ventilation was not as prominent in the CF group, or that its effect was masked by the significant intraregional inhomogeneity. Since adjacent alveolar units may be subtended by a common bronchiole that is bronchiectatic or obstructed by tenacious mucus plugs, ventilation would be impaired to all of these units and collateral ventilation amongst them would be ineffective.

In the SBN_2 tracings of both the severe asthmatic and CF
subjects, the cardiac oscillations were absent. Since a
breath-hold did not occur during the procedure, the damping of
the oscillations can not be explained by equalization of the
intraregional N_2 gradients previously reported by Engel et al
[1974]. Thus it is more likely that these results can be
explained on the basis of increased time constants in the areas
of severe airway obstruction, which would dampen the pressure
waves generated by the cardiac action, as suggested by
Verhamme et al [1982]. Increased time constants are
characteristic of asthma and CF primarily due to the increased
airway resistance, although a decrease in elastic recoil may
also contribute in the later stages of disease [Gold et al,
1967; Featherby et al, 1970].

INTERRELATIONSHIP BETWEEN AIRFLOW LIMITATION AND VENTILATION
INHOMOGENEITY

Relationship between Normal and Abnormal Test Results:

In the spirometry and SBN_2 tests, the asthmatic subjects
displayed normal or abnormal results, while the CF subjects had
consistently abnormal results, as shown in Table VIII. This
may reflect the differences in disease severity between the
groups. In the asthmatic group there was a predominance of
subjects who were in complete remission and a few subjects who
were severe, while the CF group had a predominance of subjects

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with severe disease and two moderately severe subjects.
Another factor which may account for the differences between
groups is the variability of airway obstruction in asthma;
which may present as central or peripheral airway obstruction,
or both [Loke et al, 1981]. The prevalence of central airway
obstruction in asthma has gained recent attention in the
investigation of laryngeal and glottal constriction during
bronchoconstriction [Collett et al, 1983; Collett et al, 1986].
These investigators observed glottal and laryngeal constriction
during histamine induced bronchospasm, with a resultant
decrease in flow rates to 35% of their initial value. The
effect of central and peripheral obstruction on spirometry and
the SBN_2/L% was investigated by Simonsson and Malmberg [1964].
They studied subjects with central airway obstruction due to a
tumor or tracheal stenosis, and subjects with the same
pathology in addition to chronic obstructive pulmonary disease
[COPD]. They observed that both groups had airflow
obstruction, but only the COPD group with peripheral airway
obstruction had an abnormal SBN_2/L%. Antic and Macklem [1976]
reported that the airway obstruction in asthmatics is
predominantly central in the absence of factors such as
smoking, chronic bronchitis and recurrent respiratory tract
infections. These factors were not present in the majority of
the asthmatic subjects in the present study, suggesting a
predominance of central airway obstruction which may explain
why in some cases the SBN_2/L% was normal when the FEV_1 was
abnormal, contrary to results previously reported in the
literature [Beale et al, 1952; Cade and Pain, 1973]. The

SBN_2/L% is sensitive to peripheral airway disease characteristic of smokers, in whom it often detects abnormality in pulmonary function when spirometry is normal [McCarthy et al, 1976; Hogg et al, 1985; Bates, 1989].

Relationship of Test Results Within a Session:

1. Spirometry and the SBN_2/L%.

The distribution of ventilation is one of the determinants of ventilation-perfusion [V/Q] matching [West, 1985], and the V/Q mismatch seen in asthma has been largely attributed to uneven peripheral airways obstruction [Roca et al, 1988; West, 1982]. Thus, the results of the present study of airflow limitation and ventilation inhomogeneity are consistent with the work of Roca et al [1988]. These investigators studied the relationship between spirometry and V/Q inequality in ten acute asthmatics who were refractory to bronchodilator therapy. They studied these subjects from admission to discharge, and again 3-4 weeks post-discharge. They observed simultaneous improvement in spirometry and V/Q matching in only one subject. Overall, spirometry returned to baseline at discharge, but recovery in V/Q was not complete until 3-4 weeks later-the point at which the spirometry and V/Q matching correlated. In the present study, any subject who was hospitalized during the study, was tested a minimum of three weeks post discharge. Consistent with the findings of Roca et al [1988], the spirometry and SBN_2/L% correlated within each group

[Figures 7-12, Table VII]. The lack of correlation between spirometry and V/Q matching in the study of Roca et al [1988] was explained on the basis of airflow rates being largely determined by large airway properties, and gas exchange being more related to peripheral airway obstruction from edema or mucus plugging [Rodriguez-Roisin et al, 1984; Rubinfeld et al, 1978; Wagner et al, 1978]. This hypothesis can also be extended to the present study wherein the SBN_2/L% of the CF group was highly abnormal compared to the asthmatic group, reflecting the more permanent airway changes in cystic fibrosis.

2. Effect of Bronchodilation on Spirometry and the SBN_2/L%.

Roca et al [1988] also suggested that persistent V/Q mismatch as a consequence of peripheral airway changes may explain why the subjects in their study were unresponsive to bronchodilator treatment. Deychakiwsky et al [1985] bronchodilated asthmatic subjects with antigen-induced bronchoconstriction, and observed ventilation inhomogeneity which did not always return to baseline when the spirometry returned to normal. Similar results were achieved in our laboratory when spirometry and the SBN_2 test were conducted on an asthmatic subject pre and post bronchodilation [unpublished findings-see Appendix B]. Following bronchodilation, the subject had a 34% increase in FEV_1, 45% increase in $FEF_{25-75\%}$ and an 11% increase in SBN_2/L%. Based on similar findings, Siegler et al [1976] concluded that the effect of a

bronchodilator on the $SBN_2/L\%$ is difficult to predict for a given patient. They suggested that the bronchodilator may act to increase the interregional N_2 gradient by increasing the gradient in regional volume, or decrease the intraregional inhomogeneity by narrowing the range of critical opening pressures.

3. Subjective and Objective Findings.

Although the pulmonary function tests correlated within each group, there was no correlation between them and the questionnaire scores [Table VII]. The questionnaire assessed the presence and severity of symptoms, the activity level and endurance capacity. Thus, a subject who maintained a high activity level regardless of symptoms, would score lower on the questionnaire than expected. This may have been a factor in both the asthmatic and CF groups who tended to report a greater activity level than would be anticipated from their test results. Boyle et al [1976] have previously observed that adults with CF were more active than might be expected by their disease severity. In addition, denial of symptoms and overestimation of exercise tolerance may have been prevalent in the CF group in the present study. One CF subject for example, denied any shortness of breath and reported participation in a 20 minute exercise program 3 times a week, although she was unable to slowly walk a short distance to the laboratory without obvious shortness of breath. In the asthmatic group, the lack of correlation could also be explained by a diminished

perception of changes in pulmonary function. Rubinfeld and
Pain [1977] observed significant changes in airflow and
residual volume before symptoms were reported by their
subjects. However, Burki et al [1978] reported that asthmatics
were more perceptive of inspiratory loads than normals. In
addition to these known influences on an individual's
subjective report, the questionnaire may not have been
sufficiently sensitive to accurately reflect the abnormalities
in pulmonary function.

Relationship of the Change in Test Results Between Sessions:

1. Spirometry and the $SBN_2/L\%$.

Although the change in FEV_1 correlated with the change in
$FEF_{25-75\%}$ in each group, there was no correlation between the
change in spirometry and $SBN_2/L\%$, as shown in Figures 13-18 and
Table IX. However, in the CF group this correlation was
approaching significance, which may be a reflection of the
greater severity and permanence of the pathology in this group.
These findings are consistent with the work of Deychakiwsky et
al [1985] who observed a correlation between spirometry and
ventilation inhomogeneity that was not maintained after a
change in status when bronchospasm was induced. In addition,
the results of the present study are consistent with the
conclusions of Roca et al [1988]. These investigators had
concluded from their observations of a lack of correlation
between airflow limitation and gas exchange in acute asthmatics

until 3-4 weeks post discharge, that spirometry and V/Q inequality indicate different pathophysiologic phenomena. They further concluded that impairment of V/Q matching can not be inferred from spirometric results during acute severe asthma, and that both should be assessed during acute and asymptomatic disease states. As previously discussed, the results of the present study also demonstrated a correlation between spirometry and the $SBN_2/L\%$ within a single session at a subacute disease state. However, the lack of correlation of change in spirometry and $SBN_2/L\%$ between two sessions suggests that these two tests do not change in a similar manner over time. This is consistent with the different time courses for recovery of airflow rates and V/Q matching reported by Roca et al [1988] during an acute disease state. It is plausible that a subject could have an exacerbation of disease following a testing session, and that the recovery of airflow and ventilation homogeneity would be at different stages upon reassessment at the next testing session. The subjects in the present study were seen over a one to four month interval, and often reported a change in status during that time interval. Therefore, the results of the present study extend the observations and conclusions of Roca et al [1988] over a longer period of time, and during a less acute disease state.

2. Subjective and Objective Findings.

The change in questionnaire scores and test results between sessions did not correlate except for the change in

spirometry scores in the CF group [Table IX]. The lack of correlation may be explained as per the previous discussion of the findings within one test session. In the CF group, the correlation between the change in questionnaire scores and spirometry results may be explained by the substantial work of breathing in these individuals who had the greatest severity of disease. Both the increased resistance to airflow and increased elastic work due to hyperinflation contribute significantly to the work of breathing [Collett et al, 1988]. Thus, an improvement or deterioration in their airflow obstruction would likely be recognized as a change from the previous test. In addition, the observation that the change in $SBN_2/L\%$ was not similarly correlated with the change in questionnaire score could be explained by the observations of Roca et al [1988]. These investigators observed that limitations in maximal expiratory flow were related to symptoms of dyspnea and wheezing, while V/Q mismatch was a more silent manifestation of pathology that was less related to symptoms. Therefore, even though the CF individuals appeared to have underestimated their symptoms and exercise limitation, the questionnaire was able to detect the change in these subjective findings.

IMPLICATIONS OF THE STUDY

The results of the present study support the inclusion of the SBN_2/L% in pulmonary function testing as suggested by others [Andersen and Rasmussen, 1981; Beale et al, 1952; Buist et al, 1984; Olofsson et al, 1986; Oxhoj et al, 1977]. Determination of the SBN_2/L% provides assessment of the 'quiet zone' of the lung defined by Mead [1970], where significant pathology can develop before it is often detected by tests of airflow limitation.

More specifically, in individuals with asthma or cystic fibrosis, the ventilation inhomogeneity can be more severe than expected from assessment of airflow limitation. Thus, this suggests that the inclusion of the SBN_2 test in the management of these chronic diseases would be beneficial. Deychakiwsky et al [1985] and Roca et al [1988] largely attributed the impaired gas exchange seen in these diseases to V/Q mismatch, which emphasizes the necessity of monitoring the ventilation inhomogeneity in these individuals.

Further research is needed to confirm and extend the results of this study. To delineate the interrelationship between airflow limitation and ventilation inhomogeneity further, it would be beneficial to perform the procedures in this study every three months, over a two year period. During this greater time interval, the airflow limitation and ventilation inhomogeneity could be characterized during more

subtle and frequent changes in disease state.   In addition, such a longitudinal study could determine whether the $SBN_2/L\%$ can predict the rate of decline in spirometry in these individuals, which would be of great prognostic value.

CONCLUSIONS

The conclusions from this study are:

1. The slope of Phase III of the single-breath nitrogen test was relatively easy to perform and well tolerated by the subjects. Repeated measures within subjects were more reproducible than previously reported in the literature. Specifically, the coefficients of variation over all groups for the $SBN_2/L\%$ averaged less than 10%. Thus, this non-invasive procedure was a simple and reliable test of ventilation inhomogeneity in individuals with asthma or cystic fibrosis.

2. In this study, the indices of airflow limitation and ventilation inhomogeneity in the asthmatic group showed a range of values from normal to abnormal; but were consistently abnormal in the cystic fibrosis group. This could be explained by differences in the underlying mechanisms of airway obstruction in these diseases; asthma being characterized by variable bronchoconstriction and airway inflammation, and cystic fibrosis causing a more severe obstruction and inhomogeneity as a result of mucus plugging and bronchiectasis.

3. In the cystic fibrosis group, the severity of ventilation inhomogeneity was greater than would be expected by the severity of airflow limitation during the same test session. This suggests that inclusion of the $SBN_2/L\%$ is necessary to determine the degree of ventilation inhomogeneity in these individuals.

4. At a given test session, tests of forced expiration were correlated with the slope of Phase III in all groups [R values for the $SBN_2/L\%$ vs FEV_1 and $FEF_{25-75\%}$ correlations respectively were -0.54 and -0.63 in the control group, -0.63 and -0.54 in the asthmatic group, and -0.93 and -0.86 in the cystic fibrosis group]. However, between two different test sessions, the changes in the two tests [spirometry and $SBN_2/L\%$] were not inter-correlated. This may reflect the different pathophysiologic phenomenon that influence each test, tests of forced expiration being predominantly influenced by large airway properties and the single-breath nitrogen test being more influenced by peripheral airway properties. In addition, these results reflect the different time courses of recovery of airflow rates and ventilation homogeneity towards baseline levels. Since more severe ventilation inhomogeneity may exist in asthma and cystic fibrosis compared to airflow limitation, it may well be that the inclusion of the SBN_2 test might be useful in the management of these chronic diseases.

5. The interpretation of pulmonary function tests is limited by the degree of variability associated with the particular tests; the coefficients of variation being greater for the slope of Phase III than those for spirometry. Despite the greater variability inherent in the measurement of the $SBN_2/L\%$, this study has indicated a role for its inclusion with routine spirometry in the management of individuals with asthma and cystic fibrosis.

6. The prognostic significance of a disproportionate impairment of ventilation homogeneity in these diseases has yet to be determined.

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VENTILATION AND AIRFLOW OBSTRUCTION STUDY

SCHOOL OF REHABILITATION MEDICINE
UNIVERSITY OF BRITISH COLUMBIA

Name:
Date:

Please complete this questionnaire with the most suitable response as it applies to you at this time. Place a check mark or answer on the line next to the most appropriate response.

1. If you had a **cough** in the last 24 hours, when did it occur?

        _____   no cough at present
        _____   only in the morning [when you first got up]
        _____   with activity such as 2 flights of stairs
        _____   with activity such as 1 flight of stairs
        _____   during the day [not related to activity]

2. Was this cough **productive of phlegm?** ____ Yes   ____ No

    When was it productive? _____

    Was the **amount:**   _____   less than usual
                           _____   the same as usual
                           _____   greater than usual

3. In the last 24 hours, how would you best describe your **shortness of breath:**

        _____   Not troubled with breathlessness except with strenuous exercise.

        _____   Troubled by shortness of breath when hurrying on the level or walking up a slight hill.

        _____   Walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at own pace on the level.

        _____   Stop for breath after walking about 100 yards or after a few minutes on the level.

        _____   Too breathless to leave the house or breathless when dressing or undressing.

4. Over the last 3 days, how many hours of **continuous sleep** did you usually get in a night:

        _____   7 hours or more
        _____   6 hours
        _____   5 hours
        _____   4 hours or less

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5. Over the last 3 days, when you slept at night, did you use:

    _____   1 pillow or less
    _____   2 or more pillows

6. Over the last 3 days, when you got up in the morning, did you feel

    _____   rested
    _____   tired

7. Over the last 24 hours, how far could you walk on the level at a comfortable pace and in good weather:

    _____   1 block or less
    _____   2 blocks
    _____   3 blocks
    _____   4 blocks
    _____   5 or more blocks

8. In this past week, did you participate in exercise that involved:

    _____   no specific exercise

    _____   recreational activities

    _____   a regular program once a week for at least 10-20 minutes

    _____   a regular program 2 times a week for at least 10-20 minutes

    _____   a regular program 3 times a week for at least 10-20 minutes

9. Circle the category which best describes the maximal level of activity that you could perform on average over the last 3 days:

    a. self-care
        reading or watching TV
        desk work
        driving a car
        walking at 1 mph

    b. cooking
        car repair
        walking at 2 mph
        bicycling at 5 mph
        bowling
        golfing with motorcart

    c. general housework
        pushing light powermower
        walking at 3 mph
        bicycling at 6 mph
        golfing with handcart
        badminton [doubles]

    d. heavy housework or repairs
        raking leaves or grass
        golf [carrying clubs]
        dancing
        slow swimming
        tennis [doubles]

    e. digging in the garden
        walking at 4 mph
        bicycling at 10 mph
        hiking or skating

    f. mowing lawn with hand mower
        walking or jogging at 5 mph
        bicycling at 11 mph
        light downhill skiing
        tennis [singles]

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APPENDIX B

INTERRELATIONSHIP OF VENTILATION INHOMOGENEITY AND AIRFLOW
LIMITATION IN AN ASTHMATIC SUBJECT PRE AND POST BRONCHODILATION

Introduction:

Asthmatics are commonly prescribed bronchodilators to
decrease their airflow limitation in the management of their
disease. The effect of bronchodilators on airflow obstruction
has been well documented [Paterson et al, 1979]. Since an
abnormal FEV_1 [$FEF_{25-75\%}$] and $SBN_2/L\%$ are determined by
different pathophysiologic processes, it is of interest to
follow the effect of bronchodilation on these tests and the
pathophysiology that influences them. Thus, these tests were
conducted in an asthmatic subject pre and post bronchodilation.

Methods:

1. Subject Characteristics.

The subject was a 22 year old male, 178 cm in height and
77.3 kg in weight. He was diagnosed as a child and experienced
frequent respiratory infections throughout his childhood, but
was able to attend school on a regular basis and keep up with
his peers. At the time of the study, he was working full time
as a carpenter and participated in recreational activities. On

the questionnaire, he reported that he was not troubled with breathlessness except with strenuous exercise and that he was capable of the maximum activity level on the questionnaire [6-7 METS]. He used a Ventolin® inhaler, 2 puffs bid, on a regular basis. He reported that although his inhaler gave him relief, it was limited in degree and duration.

2. Procedure.

During one test session this subject repeated the complete test protocol as outlined in the methods [with the exception of the questionnaire] following the use of his bronchodilator. He used two puffs of his Ventolin® inhaler and then rested for 15 minutes. Following this, he repeated the test sequence in the same order as he had initially.

Results:

The subject completed both of the test protocols without any difficulty. Throughout the test session he exhibited a prominent wheeze at rest which was accentuated during the tests. Although this wheeze was less pronounced post-bronchodilation, it was still clearly evident.

The subjects test results pre and post bronchodilation, and the percent change, are summarized in the Table. The FEV_1 improved by 34.2% and the $FEF_{25-75\%}$ improved by 44.8%, while the $SBN_2/L\%$ appeared to worsen by 10.9%.

TABLE

SPIROMETRY AND SBN$_2$/L% RESULTS* PRE AND POST BRONCHODILATION
IN AN ASTHMATIC SUBJECT

	FEV$_1$	FEF$_{25-75\%}$	SBN$_2$/L%
Pre-bronchodilator**	56.7	30.8	147.3
Post-bronchodilator	76.1	44.6	163.4
% change	34.2	44.8	10.9

*   Values expressed as % predicted.

** Bronchodilation was performed with a Ventolin® Salbutamol
    inhaler [2 puffs].

Discussion:

Previous work in asthmatics has shown that the FEV_1 consistently increases and SBN_2/L% consistently decreases following bronchodilation [Olofsson et al, 1985]. However, the VC had increased by almost as much as the FEV_1 in these subjects. Deychakiwsky et al [1985] had observed a poor correlation between changes in airflow limitation and ventilation distribution following bronchoconstriction. Thus, Sackner et al [1977] concluded that the FEV1 is a more sensitive indicator of change following bronchodilation than the SBN_2/L%. This conclusion may account for the results seen in this subject wherein the SBN_2/L% increased somewhat in comparison to the increase in FEV_1 and $FEF_{25-75\%}$. The findings in the present study may also be explained by the relative contributions of central and peripheral airway obstruction. It is possible that the bronchodilator acted to relieve a significant portion of the central airway obstruction and less of the peripheral obstruction. In addition, the relief of the peripheral obstruction may have been non-uniform, which would contribute to ventilation inhomogeneity. These explanations can only be hypothesized however, since the discussion is based on the results of only one subject. Thus, the relationship between indices of airflow limitation and ventilation inhomogeneity requires further study.