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FURTHER CLINICAL AND RESEARCH APPLICATIONS OF A COMPUTERIZED METHOD FOR INSTANTANEOUS AND CONTINUOUS MEASUREMENTS OF EXPIRED NITROGEN

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The experiments reported herein were conducted according to the "Guide for Laboratory Animal Facilities and Care," 1965 prepared by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences – National Research Council.

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FOREWORD

During the period 1964-1966 a method for instantaneous and continuous measurements of expired nitrogen was developed at the University of Vermont College of Medicine under Contract No. AF33(615)-2262 for the Aerospace Medical Research Laboratories, Wright-Patterson Air Force Base. These developmental studies were reported in Technical Report AMRL-TR-67-77 dated September 1967.

In September 1967 a proposal was submitted for a 2-year no-cost contract to continue clinical studies with the nitrogen washout computer. This contract was approved (Contract F33615-68-C-1111), and the present report summarizes results of investigations made during this 2-year period, 1967-1969. (Contract monitor - Dr. Michael McCally)

Partial support of the projects was also obtained from the following sources: USPHS: National Heart Institute (grants HE-04010, HE-10,585) National Institute of Allergy and Infectious Diseases (AI07958); Association for the Aid to Crippled Children, New York City; Vermont Heart Association.

This technical report has been reviewed and is approved.

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SECTION I

EVALUATION OF INTRAPULMONARY GAS DISTRIBUTION BY COMPUTERIZED NITROGEN WASHOUT TECHNIQUE.

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Introduction:

The degree of uniformity of alveolar ventilation may be evaluated by measuring the distribution of inspired gas in the lung. Of the measurements now available for this variable, none is free of influence by other factors such as respiratory pattern, patient cooperation, and size of lung volumes. Because of this, quantitation of maldistribution is difficult and at best tedious.

This report describes an index of inspired gas distribution which is very simply calculated from a digital computer-based nitrogen washout curve. It is not influenced by patient cooperation or by the absolute size of the functional residual capacity as measured during the test. This is possible since the computer measures and compensates for anatomic dead space, therefore negating the effects of naturally occurring variations in dead space - tidal volume ratio during a determination.

As a result, this index has narrow physiologic variation in normal persons and is sensitive to changes in distribution which occur in disease states. It is particularly useful in detecting early distribution changes where visual perusal of the nitrogen washout curve may not be conclusive.

Methods and Theory:

A digital computer technique for on-line study of pulmonary nitrogen washout with 100% oxygen has been devised in this laboratory (9,10). Using

a multiple breath, open technique, expired gas nitrogen (N_2) concentration is plotted logarithmically against a linear display of cumulative alveolar ventilation (V_c). The "anatomic dead space" is calculated from the first 4 breaths and subsequently subtracted from each tidal volume. Functional residual capacity, (FRC), is also calculated and displayed. The breath-by-breath decrease in expiratory N_2 concentration is exponential and is directly plotted on semi-log paper as a function of alveolar ventilation. If a single, uniformly-ventilated space is being measured, a single straight line is obtained and the slope of the N_2 concentration line is related solely to the size of the space being ventilated. Any deviation of the slope from a straight line represents non-uniform distribution of inspired gas.

With even distribution of inspired gas, the volume of cumulative alveolar ventilation which reduces the alveolar N_2 concentration is a linear function of FRC volume. The N_2 concentration and cumulative alveolar ventilation may be expressed as: $\text{Log } F_N = -(V_c/FRC) \times (1/\ln 10)$, where F_N = alveolar nitrogen concentration, V_c = theoretical volume of cumulative alveolar ventilation required, FRC = functional residual capacity and 1 is assumed to be 80% nitrogen (inspired air).

It follows that the cumulative alveolar ventilation (V_c) required to reduce the alveolar N_2 concentration to 1% in an evenly ventilated single space is: $\log 1/80 \times FRC \times \ln 10 = -V_c$. Therefore, $V_c = FRC \times 4.38$. For purposes of this test, end tidal N_2 is taken to represent alveolar N_2 concentration. The Inspiratory Gas Distribution Index (IDI), when washout is carried to 1% end-tidal nitrogen, is: $IDI = V_c'/FRC \times 4.38$, where V_c' is the measured cumulative alveolar ventilation required to reduce measured end-tidal N_2 concentration to 1%. It is read off the abscissa of the N_2 washout plot. Hence, the IDI of an evenly ventilated

single space, where $V_c' = V_c$, equals 1.0. Any non-uniformity of distribution yields an IDI greater than 1.0. Since even the most normal lung is not a single anatomic space one would not expect a measured IDI to reach the theoretical level of 1.0. However, it has been useful conceptually to relate measurements in both normal and disease states to this unity rather than an arbitrary normal value.

The selection of an end-tidal N_2 concentration of 1% instead of the conventional 2% as end point has meant that in cases of severe obstructive pulmonary disease, terminal N_2 concentration of 1% may not be reached because of severe maldistribution. The washout is then arbitrarily stopped at 64L cumulative alveolar ventilation. This yields an IDI which is underestimated although exceedingly high. This sacrifice of accuracy at the extremely abnormal end of the spectrum of values was made in order to increase sensitivity to minor distribution abnormalities since it clinically is more useful to quantitate small and inapparent abnormalities than gross and obvious ones. This is particularly true in the early detection of disease.

Computer measurements of pulmonary nitrogen washout were made in 41 normal subjects, 63 patients with diffuse obstructive pulmonary disease, 16 patients with restrictive pulmonary disease, and 15 patients with regional underventilation. Analysis of these measurements and comparison of the calculated IDI's form the basis of this report. Clinical diagnoses were made on the basis of history, physical examination and complete clinical pulmonary function testing.

Results:

Normal Subjects

IDI was measured in 41 normal subjects without evidence of pulmonary

disease, (Table 1 and Fig. 1). Ages ranged from 15 to 70 years. The mean IDI for all normal subjects was 1.77 with a standard deviation of $\pm$ 0.21. There was a small increase in mean IDI with age: under 21 years: 1.64 $\pm$ 0.24; 21 - 50 years: 1.76 $\pm$ 0.20; and over 50 years: 1.91 $\pm$ 0.11. The difference of IDI for subjects younger than 21 years and those between 21 and 50 years was not significant ($p>0.2$), but the oldest group was statistically different from the others, ($p<0.01$). Since this difference, though statistically significant, is very small, and since the abnormal patients tested were not selected according to age, we have used the mean for all normal subjects (1.8 $\pm$ 0.2) for comparison with the various patient populations.

The effects of different tidal volumes on the IDI were examined during positive pressure breathing. Eleven normal subjects were studied at several different tidal volumes. Tidal volumes and flow were kept constant during each N_2 washout by a flow and volume regulated BIRD®, Mark IV - VII positive pressure respirator. Respiratory rate and regularity were voluntarily regulated by the subjects. The volume of alveolar ventilation per breath was varied between 185 cc. and 1190 cc. but was kept constant during each washout. The tidal volume, per se, was not measured during these experiments. Values for mean IDI at different tidal volumes were essentially the same (Table 2). Although there was some variation within individual subjects, there was no trend noticeable within these limits.

Studies using stricter control of respiratory frequency, tidal volume and flow rate indicate that minor distribution changes are detectable with changes in these parameters (see Section V). The significance of the studies reported here in is that for changes in tidal volume alone such as might occur due to subject variability during a N_2 washout determination, the dead space

compensating mechanisms prevent the introduction of gross error in distribution estimation.

Diffuse Obstructive Pulmonary Disease:

IDI was measured in 63 patients with known chronic diffuse obstructive disease, (Table 3, Fig. 1). The mean index and its standard deviation for this group is 3.4 $\pm$ 0.9. The difference between these patients and normal subjects was very highly significant, ($p<0.0001$). Twenty-two of these patients did not attain a 1% terminal N_2 level after prolonged O_2 breathing and IDI was calculated when cumulative alveolar ventilation reached 64 liters, thus underestimating the IDI. This situation occurred only in physically-limited patients.

The patients were divided into four classes on a functional basis:

Class I - no limitation of physical activity and minimal or no symptoms.

Class II - mild limitation of physical activity.

Class III - marked limitation of activity, but tolerated mild or sedentary activity.

Class IV - inability to carry on any physical activity without discomfort.

Many of the Class I patients were detected during pulmonary function testing as control subjects or for complaints not specifically of pulmonary origin. Several were asthmatics. The mean IDI for this group was 2.6 $\pm$ 0.7. Three of these 10 patients had an IDI within the 95% range of normal (i.e. 1.8 $\pm$ 0.4), although all were above average. Two of these normal values were obtained in asthmatic patients between attacks. The group mean, however, was significantly greater than the normal controls, ($P<0.001$).

The remaining 53 symptomatic patients with chronic bronchitis and/or emphysema were classified according to degree of disability, II, III, and

IV. The calculated group IDI's were 3.3 ± 0.7, 3.7 ± 0.6, and 4.3 ± 1.1 respectively. Significance of the differences between the group means was: classes I and II, $P<0.01$; classes II and III, $P<0.05$; and classes III and IV, $P>0.1$, (not significant). Only one of these 53 patients' IDI fell within the 95% range of normal, being at the upper limits of normal, 2.2.

From this data, it is apparent that there is good separation between normals and Class I obstructed patients and essentially no overlap of normal with physically limited patients (Figure 1). There is also a general correlation between the degree of functional impairment and abnormality of IDI, especially in the mild to moderate cases of diffuse obstructive disease. It is clear from the wide spread of values within each class, however, that the IDI cannot be used to predict the functional status of a particular patient.

Restrictive Pulmonary Disease:

Sixteen patients with primarily restrictive disease and no evidence of obstruction also demonstrated distribution abnormalities as reflected in an average IDI of 2.5 ± 0.8, (Table 3). Most of these patients had exogenous restrictive disease such as thoracic deformity or myasthenia gravis. As might be expected, there is a wide range of abnormality and there is some IDI overlap between these patients and normals, 6 of 16 being <2.2. The group mean, however, is significantly different from normal ($p<0.001$). There is also a significant difference ($p<0.0001$) between these patients and the obstructed patients who in general show a greater degree of maldistribution.

Regional Hypoventilation:

Fifteen patients were studied who showed an obvious underventilated area on x-ray such as atalectasis, bullae, and segmental airway obstruction

(Table 3). The severity of their functional impairment was generally only mild to moderate. Average IDI was 2.8 $\pm$ 0.5. The mean value significantly exceeded normal, ($p<0.0001$), but was significantly less abnormal than the mean IDI of the diffuse obstructive disease group ($p<0.001$).

Discussion:

A variety of methods has been designed to evaluate the uniformity of alveolar ventilation utilizing analysis of expired gases. In the closed circuit, multiple breath technique (1), a known quantity of a relatively insoluble gas, such as helium, is introduced into a closed system and equilibrium with intrapulmonary gas is reached within a certain time. From the inert gas concentration at equilibrium, the FRC can be calculated, and the time required to reach equilibrium provides an index of the evenness of distribution. The dependence on time fails to take into consideration the effects of various rates and depths of respiration. Mild to moderate maldistribution may be overlooked by this technique.

The single breath, open circuit, technique (3) uses the continuous measurement of expired N_2 concentration during a single, slow expiration following inhalation of 100% O_2. After 750 cc. of gas have been expired, the increase of N_2 concentration during the next 500 cc. is measured. If N_2 concentration does not increase more than 1.5% during this period, the result is interpreted as normal. This method does not indicate unevenness of alveolar ventilation if the rates of expiration from differently ventilated regions of the lung are the same during the measured portion of the breath. The normal range is 0.3% - 0.7% for the younger population and 1.0% - 1.8% for older normal subjects. This is a 5-fold variation within the normal range. Neither of these problems is encountered with this N_2 washout technique.

In the multiple breath, open circuit technique (4) the patient inspires 100% O_2 for seven minutes and by forced expiration delivers a final end-expiratory sample for N_2 analysis. If this sample contains less than 2.5% N_2, the result is interpreted as normal. It can be seen from our data that many patients with significant maldistribution wash out their FRC to 1% in less than seven minutes. In addition to such insensitivity, the method's validity can be reduced by a small hypoventilated area such as a bulla which may contribute a high N_2 concentration during forced expiration. Thus, it is not possible to quantitate the degree of maldistribution with this technique.

When breath-to-breath N_2 concentration is measured using the preceding method, and plotted on semi-log paper as a function of time or number of breaths, the so-called nitrogen washout curve is derived (5,8). Deviation from a straight line (exponential fall of N_2 concentration) is interpreted as representing uneven alveolar ventilation. It is clear that when either time or number of breaths is used, variation of rate and depth of breathing may influence the shape of the curve. In addition, there can be no numerical expression of the degree of uneven ventilation.

Using the multiple breath open technique and measuring total ventilatory volume one can calculate the Lung Clearance Index (L.C.I.) (2,7). This is: liters ventilation required to wash 90% FRC free of N_2. This index is thus very similar to the one proposed in this paper except for measuring total ventilation instead of alveolar ventilation and the use of a higher end-tidal N_2 for end point. In Becklake's series (2) L.C.I. averaged 7.02 with S.D. 1.68. One standard deviation was 24% of the value for mean L.C.I. while one standard deviation was 11% of the mean IDI. This indicates a narrower physiological range for IDI. In that series there was only fair separation

of normals and emphysematous patients, since 8 of 27 emphysematous patients fell within the normal range and 4 were borderline. The author states "if allowances were made for anatomic dead space, the results might have fallen within the emphysematous range".

In essence, the IDI is a modification of Becklake's L.C.I. in which computer techniques have allowed an on-line plot of expired N_2 concentration against cumulative alveolar ventilation. This eliminates significant effects of variations in tidal volume and the resultant variations in dead space/tidal volume ratios during the examination. This result, we believe, accounts for narrowing of the range of normal and increased sensitivity.

More recently, an index of alveolar ventilation (IAV) has been proposed by Lichtneckert (6). Using a mathematical analysis of the nitrogen washout curve, it is possible to derive an index based on the comparison of ideal clearance coefficient to measured clearance coefficient without measuring FRC or alveolar ventilation. It is, therefore, necessary to make certain assumptions such as synchrony of alveolar emptying and constant volumes of lungs and tidal air during the determination for the mathematical theory to be valid. It is well known that these assumptions and prerequisites are not always valid or possible when dealing with patients with respiratory disease. Since the computer technique upon which our IDI is based allows actual measurement of FRC, anatomic dead space, and cumulative alveolar ventilation, it has seemed reasonable to make use of these facts rather than assumed values in evaluating the uniformity of alveolar ventilation.

Summary:

Based on computer techniques, an accurate and simple index of inspired pulmonary gas distribution (IDI) is described. This relates FRC volume to the on-line determination of cumulative alveolar ventilation (V_c) required

to reduce end-tidal N_2 concentration to 1% while breathing 100% O_2. This is expressed as IDI=V_c/(FRC x 4.38). The value for an ideally ventilated single space is 1.0. The mean IDI in 41 normal subjects was 1.8 $\pm$ 0.2. There is a clear separation from patients with obstructive lung disease whose mean value in 63 cases was 3.4 $\pm$ 0.9. In these patients the elevation in IDI increased with the severity of functional impairment. Abnormal values were found in patients with restrictive disease and regional hypoventilation.

The relative freedom from distortion by variations in dead space - tidal volume ratio, the effects of aging, the relationship to other quantitative measurements of intrapulmonary distribution and the ease of applicability of this index are discussed.

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TABLE 1

THE EFFECTS OF AGE ON IDI IN NORMAL SUBJECTS

Age Group	Number	Average Age	IDI*	Significance of the difference of the mean
21 years old	7	17	1.64 ± 0.24	p<0.2
21 - 50 years old	27	31	1.76 ± 0.20	p<0.01
50 years old	7	59	1.91 ± 0.11	
all normals	41	33	1.77 ± 0.21	

* mean ± S.D.

TABLE 2

THE EFFECT OF TIDAL VOLUME ON IDI IN NORMAL SUBJECTS

Alveolar ventilation per breath, cc.	185-499	500-749	705-1190
Number of determinations	13	12	14
IDI*	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.3

* mean ± S.D.

TABLE 3

CHARACTERISTICS OF THE PULMONARY NITROGEN WASHOUT IN NORMAL SUBJECTS AND PATIENT GROUPS

Diagnosis	Number of Subjects	Mean Age, yrs.	Mean* FRC, liters	Mean Wash-+ out Time, minutes	Mean+ V_c, Liters O_2	IDI**
1. Normal subjects, total	41	33	2.37	2.5	18.7	1.8 ± 0.2
2. Diffuse obstructive pulmonary disease:						
Class I	10	41	3.51	4.8	41.3	2.6 ± 0.7
Class II	30	52	4.29	7.5	55.9	3.3 ± 0.7
Class III	15	51	4.34	7.4	60 +	3.7 ± 0.6
Class IV	8	54	4.53	8.8	64 +	4.3 ± 1.1
Total	63					3.4 ± 0.9
3. Restrictive Pulmonary Disease	16	46	1.90	4.2	19.7	2.5 ± 0.8
4. Regional Under-ventilation	15	52	3.05	4.5	37.2	2.8 ± 0.5

* FRC = Functional Residual Capacity

+ Time required to wash FRC to 1% N_2

+

+ V_c = Cumulative Alveolar Ventilation to 1% N_2

Many patients did not washout to 1% N_2 even after 64 L.

**Mean ± S.D.

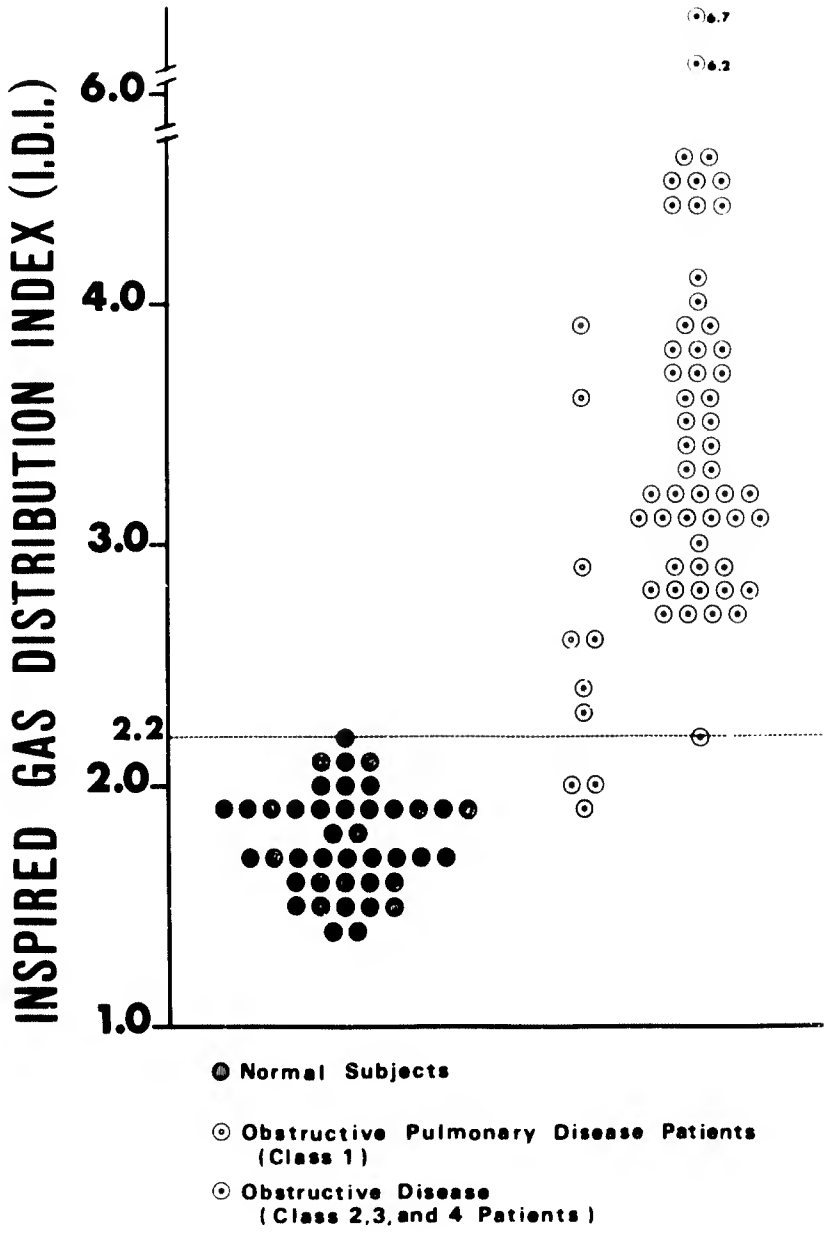

Figure 1: I.D.I. values are shown for normal subjects and patients with obstructive pulmonary disease. Three functional Class I patients exhibit values within normal limits; all 3 were asthmatics. One patient in functional Class II or higher showed an I.D.I. at the upper limit of normal. The remainder are clearly abnormally elevated.

SECTION II

INTRAPULMONARY GAS DISTRIBUTION CHARACTERISTICS OF PATIENTS WITH CARDIAC DISEASE AS DETERMINED BY THE NITROGEN WASHOUT COMPUTER. Richard A. Anderson, M.D.

Sixty-five nitrogen washouts with determination of functional residual capacity and calculation of IDI were performed on 48 patients with cardiac disease but without evidence of pulmonary disease by history, physical examination or chest x-ray. Twenty-four patients underwent cardiac catheterization during the same hospital admission, and 25 had measurement of vital capacity as well. The patients' ages ranged from 17 to 67 years, mean 46. They had predominantly rheumatic valvular heart disease and are categorized by anatomic diagnosis in Table 1.

Most patients exhibited signs and/or symptoms of congestive heart failure and are categorized according to functional class (AHA and NYHA) in Table 2.

Data from the pulmonary studies were compiled and compared with the descriptive patient material and with the hemodynamic data obtained at catheterization to determine:

1) if an intrapulmonary distribution abnormality could be found in patients with cardiac disease (predominantly valvular), and
2) if the type and degree of distribution abnormality was related to the type and severity of disease or to the pulmonary vascular hemodynamics. The mean values for data obtained are listed in Table 3.

The mean IDI of 2.32 $\pm$ 0.85* for all cardiac patients was significantly

* $\pm$ 1 standard deviation

higher ($p<0.002$) than for our normal controls (1.77 ± 0.21) indicating a measurable maldistribution of inspired air in these patients. IDI did not vary significantly between diagnostic categories or by functional class indicating a pulmonary maldistribution characteristic of these patients in general and not unique to one structural abnormality or to only very sick patients. IDI could not be significantly correlated either with vital capacity or with pulmonary artery pressures, resistance or cardiac output. However, IDI correlated negatively with arterial hemoglobin saturation ($p<0.05$) and positively with advancing age ($p<0.05$), a trend also seen in our normal controls.

The remainder of the measured data was cross-correlated and also related to patient descriptive data. Several interesting statistically significant relationships were noted. The number of breaths required to reach the 1% end-expiratory N_2 level increased with degree of C.H.F.: Class II (40 breaths) vs. Class IV (58 breaths), $p<0.05$. Number of breaths also varied with diagnosis: mitral stenosis (53 breaths) vs. mitral insufficiency (37 breaths), $p<0.05$. This would indicate a varying tidal volume between these categories since neither FRC nor IDI varied significantly.

Determined vital capacity (V.C.) and, more importantly, percent of predicted vital capacity decreased with increasing severity of disease: Class II, 79% V.C.; Class III, 73% V.C.; Class IV, 57% V.C. with $p<0.05$. Percent vital capacity also varied between one pair of diagnostic groups: mitral insufficiency (82% V.C.) and aortic insufficiency (69% V.C.), $p<0.05$.

As one would expect from the natural history of left heart disease, pulmonary artery pressures and wedge pressures rose progressively with increasing severity of heart failure. Also, as expected, the degree of

pulmonary artery pressure elevations varied between diagnostic categories, e.g. mitral stenosis, pulmonary artery pressure 48/22, "wedge" 21 mm. Hg. vs. corresponding pressures with aortic stenosis, 28/11 and 12 mm. Hg.

Oxygen saturation decreased with increasing severity, but this was not significant at the 0.05 probability level.

End-tidal N_2 elevation correlated with an increased number of breaths to reach 1% ($p<0.05$). This may represent the effects of small tidal volume. Both parameters would be elevated together in patients who exhibit the greatest degree of distribution abnormality and are, therefore, related statistically.

The size of vital capacity was correlated positively with oxygen saturation ($p<0.02$) indicating conversely measurable hypoxia in those patients with the most restricted V.C. These are, as stated above, those patients with worst functional classification.

Cardiac output decreased with advancing age ($p<0.02$).

The percent of predicted vital capacity was nearest 100% in those patients with the largest FRC ($p<0.005$). Since none of these patients was emphysematous, excluding very large FRC's, these pulmonary volumes would be expected to be related.

Summary:

A group of patients with cardiac disease primarily characterized by left heart failure due to valvular or myocardial disease and tending to have secondary pulmonary hypertension were studied by N_2 washout techniques and cardiac catheterization. A widespread and significant abnormality of intrapulmonary gas distribution was found with IDI averaging 2.3 ± 0.9. There was considerable overlap within the normal range. The IDI abnormality was not directly statistically relatable to diagnosis, severity as expressed by functional classification, vital capacity, or hemodynamic measurements

despite the fact that other variables measured separated the diagnostic and functional groups into groups with different vital capacities and hemodynamics. It must be concluded that the factors leading to maldistribution of inspired air in these cardiac patients were not characterized by the hemodynamic or pulmonary function studies done in these patients. This has led us to an investigation of distribution in acute animal experiments with pulmonary overload (see Section III).

TABLE 1

Primary Diagnosis	Number of Patients
Mitral Stenosis	14
Mitral Insufficiency	7
Aortic Stenosis	14
Aortic Insufficiency	5
Combined Valvular Disease	2
Atrial Septal Defect	2
Ventricular Septal Defect	2
Arteriosclerotic Heart Disease	2
Miscellaneous	5

TABLE 2

Functional Class	Number of Patients
I	14
II	17
III	15
IV	7

TABLE 3

Variable	Mean Value
IDI	2.32
FRC (determined)	2.13 L
FRC (predicted)	1.96 L
A.V. to 1%	21.9 L
End Tidal N_2	1.6%
Breaths to 1%	45
Vital Capacity (determined)	2.04 L
Vital Capacity (predicted)	2.94 L
Cardiac Output	6.08 L/min
Pulmonary Artery Pressure (systolic)	47 mm. Hg.
Pulmonary Artery Pressure (diastolic)	21 mm. Hg.
Pulmonary Artery Pressure (mean)	32 mm. Hg.
Pulmonary Artery Pressure (wedge)	18 mm. Hg.
Pulmonary Vascular Resistance	2.7 mm. Hg./L/min.
Arterial Oxygen Saturation	94.4%
Age	46 years

SECTION III

INTRAPULMONARY DISTRIBUTION OF RESPIRED GAS AND PULMONARY MECHANICS DURING INDUCED PULMONARY VASCULAR CONGESTION IN THE RABBIT. Edgar J. Caldwell, M.D. and Richard A. Anderson, M.D.

Introduction:

The intrapulmonary distribution of respired gas in patients with clinical heart disease and without clinical evidence of pulmonary disease has been under investigation in this laboratory, as discussed in the previous section. In an effort to gain more insight concerning the factors operative in the maldistribution of inspired gas in the heart disease patient, an animal respiratory model system has been adapted to examine this question.

Methods:

New Zealand white rabbits are used in this study. Intravenous pentabarbital (25 mgm/kg) is used to anesthetize all animals. Following anesthesia the trachea was cannulated and special catheters placed in the esophageal space for measurement of intrathoracic pressure, the right jugular vein directed through the right heart into the pulmonary artery for pressure measurement, and the left jugular vein for delivery of homologous blood for vascular volume expansion. Animals were then prepared for studying pulmonary mechanics, static and dynamic, and N_2 washout characteristics.

Static lung volumes and static expiratory compliance of the parenchymal meshwork of the lung were measured. Continuous measurement of lung volume, gas flow and indirect transpulmonary pressure during varied forced vital capacity expiratory efforts provide isovolume pressure-flow and flow (maxima)-

volume relationships of the lung. Respiratory flow and instantaneous lung volume were measured using a small body plethysmograph consisting of a rigid cylindrical plastic chamber and suitable transducers. Volume measurement by plethysmography eliminates gas compression phenomena which might occur during expiratory maneuvers of considerable force and be unobserved if volume were otherwise measured by integration from a pneumotachograph placed at the mouth. Volume changes are sensed by an electrical recording caliper attached to the spirometer bell. It is linear, free of hysteresis and has a uniform ($\pm$5%) dynamic response through 20 cps.

Flow is measured with a specially designed linear flow meter interposed between the plethysmograph and the spirometer. Differential pressure across the flow meter is measured with a Statham PM97 transducer.

An indirect estimate of transpulmonary pressure was obtained from the output of a Sanborn 267B pressure transducer which measures intra-esophageal pressure through a fluid-filled end-and-side hole PE 200 polyethylene catheter on the positive side and tracheal pressure is transmitted to the negative side. The instantaneous values of intra-esophageal pressure have been correlated against the simultaneous values of the intrathoracic pressure at three different degrees of instantaneous lung inflation. The correlation coefficient at all three volumes was greater than 0.99. One concludes from these data that the intra-esophageal pressure may be used as a good index of intrathoracic pressure in rabbits.

The unidirectional valve developed to adapt the N_2 washout computer to small animals is shown in Figure 1. All signals were recorded on an Electronics for Medicine DR-8 recorder.

At the completion of the foregoing maneuvers the total blood volume was increased by 50% slowly over a 15-20 minute period.

Total blood volume was taken as 65.6 cm.^{3}/kg., the mean value of those values given for the rabbit in the Handbook of Circulation prepared under the direction of the committee on the Handbook of Biological Data. Homologous blood with ACD solution (15 parts/100 parts of blood) and Achromycin (1.25 mgm.) was used for blood volume expansion. Preliminary studies had shown that homologous blood was far superior in raising blood volume and pulmonary artery pressure when compared to the plasma volume expanders, i.e. 10% Dextran solution. After a 50% increase in blood volume had been achieved and spontaneous respiration returned, the N_2 washout clearance studies and pulmonary mechanics were repeated.

Immediately following the completion of these studies, the animal was sacrificed and the heart and lungs removed en bloc for anatomic examination.

Histologic Preparation:

Following sacrifice of the animal, the heart and lungs were removed en bloc and fixed by intrabronchial perfusion of 10% buffered formaldehyde at a pressure head of 10 cm. of water. After adequate fixation, usually 24 hours, the lungs were sectioned grossly and examined under a dissecting microscope for gross anatomic architecture. Routine tissue blocks were taken from the left upper and right lower lobe, sectioned at 6 micron thickness and stained with hematoxylin and eosin for assessment of the normal histology and changes associated with vascular overloading.

Results:

Preliminary data show that following 50% increase in calculated total blood volume, an average increase of 31% is observed in the mean pulmonary artery pressure. In association with the rise in pressure of the pulmonary

circulation, no significant change was measured in the functional residual capacity (FRC), inspired gas distribution index (IDI) or lung and total compliance. Flow-maxima were essentially unchanged from control measurements following blood infusion. Further analysis of experimental data is currently in progress.

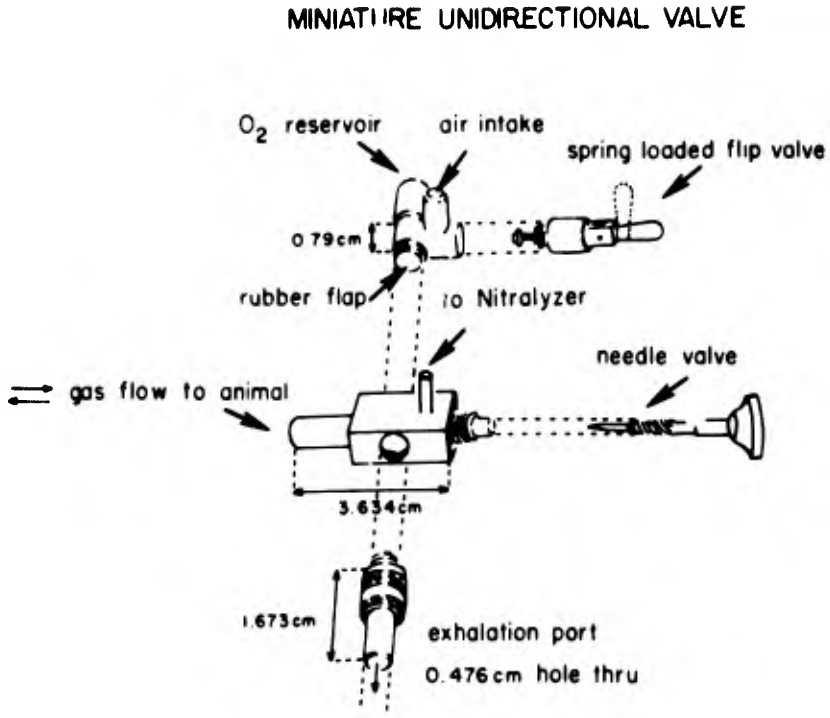

Figure 1: Miniature unidirectional valve developed for adaptation of nitrogen washout computer to small-animal studies.

SECTION IV

PULMONARY MECHANICS AND INTRAPULMONARY GAS DISTRIBUTION IN THE RABBIT: PHYSIOLOGIC CHANGES MEASURED FOLLOWING PAPAIN DESTRUCTION OF THE LUNG'S PARENCHYMAL MESHWORK.

Edgar J. Caldwell, M.D.

Introduction:

Papain applied intrabronchially to the rabbit lung causes alveolar wall disruption and distention with associated bronchiolar and alveolar duct distention. These anatomic changes alter the configuration of the isovolume pressure-flow relationship characteristic of the normal lung. The maximum expiratory flow-volume curve is depressed in the papain lung as compared to the normal lung. These phenomena are accentuated when a viscous gas mixture is respired. The purpose of this study was: 1) to present the changes observed in pulmonary mechanics and intrapulmonary gas distribution after destruction of pulmonary architecture with intrabronchial papain, 2) to evaluate the rabbit as an experimental model system for chronic obstructive lung disease in man.

Methods:

Twenty-one mature white rabbits were studied. Baseline static pulmonary lung volumes and expiratory pressure-volume curves of the lung and total pulmonary system were measured, as were the isovolume pressure-flow and maximum flow-volume relationships for each animal. Nitrogen washout curves were recorded in each animal. Observations were repeated after a total of 10 mgm. of intrabronchial papain given in 1 mgm. serial applications every two weeks.

Preliminary Results:

The flow maxima on isovolume pressure-flow curves with air breathing were reduced throughout the vital capacity following intrabronchial papain. These findings were more pronounced during breathing of a more viscous helium-oxygen gas mixture, particularly at the lower lung volumes. It is felt that this observation reflects flow limitation of peripheral airways at the bronchiolar level which have lost tethering properties of alveolar walls. The results thus far calculated are shown in Table 1. The values for IDI pre- and post-papain have not yet been derived, but the papain-induced increase in FRC is shown in the Table.

TABLE 1

Mean values ± std. dev. for the static lung volumes and compliance measurements obtained were as follows:

	Before Papain	After Papain
Body weight (kg.)	3.49 ± 0.49	4.30 ± 0.75
Tidal volume ($cm.^3$)	24.1 ± 4.83	25.4 ± 4.44
Inspiratory capacity ($cm.^3$)	86.7 ± 12.9	104.7 ± 29.4
Vital capacity ($cm.^3$)	104.0 ± 13.4	111.1 ± 27.8
Functional residual capacity ($cm.^3$) (n=18)	38.5 ± 12.1	49.7 ± 10.9
Total lung capacity ($cm.^3$) (n=17)	125.6 ± 17.5	155.8 ± 35.9
Static compliance [illegible] (n=21):		
Lung	10.2 ± 2.68	13.0 ± 4.33
Total	7.48 ± 1.10	9.10 ± 2.34
Thoracic wall	51.1 ± 59.35	37.2 ± 37.28

SECTION V

VARIATIONS IN INTRAPULMONARY GAS DISTRIBUTION DURING ASSISTED VENTILATION: EFFECTS OF VARYING TIDAL VOLUME FLOW RATE AND FREQUENCY. John S. Hanson, M.D. and Tamotsu Shinozaki, M.D.

Introduction:

As previously reported from this laboratory (1-5), numerous physiologic studies have been conducted in normal subjects employing an artificial expiratory airway obstruction. The effects of such airway impedance on minute oxygen uptake, lung volumes and pulmonary mechanics have been described. In attempting to develop further a model of obstructive airway disease in normal subjects, it was regarded essential that the effects on intrapulmonary gas distribution of the expiratory airway impedance be investigated. Previously, only indirect indication of such changes has been obtained through use of the Lung Clearance Index as employed by Becklake (6). Because the expiratory airway obstruction causes very significant alterations in respiratory frequency, tidal volume and probably expiratory gas flow rates, it was necessary to define the effects of variations in these variables themselves on nitrogen washout patterns and the IDI. Only in this manner could the particular influence of the airway impedance be isolated. Accordingly, the changes in nitrogen washout characteristics of normal subjects effected through changes of respiratory frequency, tidal volume and inspiratory flow rates were studied.

Materials and Methods:

Five normal subjects were employed for the study, 4 males and 1 female, ranging in age from 20 to 41 years of age. In each subject 10 normal, un-

assisted nitrogen washouts were performed to establish individual variations in the cumulative alveolar ventilation required to reach expired nitrogen concentration of 1%, functional residual capacity, anatomical dead space, tidal volume, IDI, and the number of breaths necessary to reach the 1% expired nitrogen level. Mean values for these variables for each subject were then adopted as baselines against which the subsequent machine-assisted washouts would be compared.

Varying respiratory frequency, tidal volumes and flow rates were achieved through use of a Mark 4 Bird volume controlled respirator. Subjects completely suspended all spontaneous respiration and breathed only passively in response to the respirator. A total of 10 nitrogen washouts was performed in each subject while being breathed by machine. The protocol involved various combinations of the following: 1) a "normal" tidal volume approximating 750 ml. and a "high" tidal volume of 1,000-1,200 ml.; 2) respiratory frequencies of 6, 10 and 15/min.; and 3) "low", "normal" and "high" inspiratory flow rates of 9.8, 22.2 and 32.0 L/min., respectively.

Instrumentation, in addition to the Bird respirator, included an improved and updated version of the original nitrogen washout computer. A uniquely stable nitrogen analyzer and improved logic circuitry comprise the alterations.

Pictorial representation of the experimental equipment is depicted in Figure 1.

Results:

Mean values for the parameters studies during both spontaneous and assisted nitrogen washouts are presented in Tables 1 and 3. It will be noted that the standard deviations of the means for each variable measured

during unassisted nitrogen washouts are considerably lower than the corresponding figures originally reported employing the prototype nitrogen washout computer. Accordingly, more precise definition of normal limits for the IDI has been established.

Comparison of the mean values for all variables obtained under the ten conditions of assisted ventilation with the corresponding means obtained from spontaneous washouts reveals no statistically significant differences. There are, however, detectable trends. As seen in Table 3, IDI increased with a low respiratory frequency in conjunction with both normal and high tidal volumes. The latter combination, low frequency and high tidal volume, produced the greatest IDI increase which proved significantly different from two other sets of conditions (Table 4). Inspiratory flow rate also affected IDI, a lower flow producing a considerably lower value for his parameter than a high flow when frequency and tidal volume were constant.

Summary:

From these observations it is concluded that varying conditions of inspiratory flow rate, frequency and tidal volume during mechanically assisted nitrogen washouts in normal subjects do not significantly affect the IDI or the variables measured to derive it. Low respiratory frequency and high inspiratory flow rate are less well tolerated than normal or high frequencies at normal or low flow rates.

It may thus be reasonably asserted that if significant effects on FRC, V_c and/or IDI are detected during nitrogen washout with the artificial expiratory airway obstruction, these alterations will be a consequence of the obstruction and not the factors discussed above.

Further implications of the present study results can be recognized in relation to treatment of chronic obstructive pulmonary disease with IPPB. The

determinations presented above will be repeated in patients with varying severities of emphysema in an attempt to define some rationale for "tailoring" respirator therapy to the individual for maximum effectiveness.

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TABLE 1

Subject No.	V_c	FRC	IDI	DS	n
1.	13.2 ± 0.77	1.30 ± .07	1.81 ± .11	189.5 ± 11.3	17.2 ± 2.7
2.	16.8 ± 0.50	2.24 ± 0.06	1.72 ± 0.07	192.5 ± 6.7	32.9 ± 2.2
3.	25.4 ± 1.47	2.50 ± 0.13	2.26 ± 0.10	207.6 ± 5.3	39.3 ± 5.8
4.	17.9 ± 0.85	2.34 ± 0.11	1.74 ± 0.09	194.2 ± 10.9	30.3 ± 3.0
5.	12.6 ± 0.84	1.68 ± 0.07	1.72 ± 0.12	177.7 ± 5.5	21.4 ± 2.5
6.	16.2 ± 0.70	1.91 ± 0.09	1.52 ± 0.05	170.1 ± 5.5	14.3 ± 1.1
7.	18.8 ± 1.05	2.41 ± 0.11	1.78 ± 0.07	183.2 ± 8.5	33.1 ± 5.7
Mean:	17.28	2.05	1.79	188.3	26.9
Mean S.D.:	± 0.88	± 0.09	± 0.08	± 7.68	± 3.3

V_c = cumulative alveolar ventilation to reach 1% end-expiratory nitrogen; FRC = functional residual capacity; IDI = inspired air distribution index; DS = dead space; n = no. breaths to reach 1% end-expiratory nitrogen concentration.

TABLE 2

Protocols for Assisted Washouts

	Inspiratory Flow	Frequency/Min.	Tidal Volume
1.	Normal[1]	10	Normal[2]
2.	Normal	15	Normal
3.	Normal	6	Normal
4.	Normal	10	High[3]
5.	Normal	15	High
6.	Normal	6	High
7.	Low[4]	10	Normal
8.	Low	10	High
9.	High[5]	10	Normal
10.	High	10	High

[1]22.2 L/Min.
[2]approximately 750 ml.
[3]approximately 1,000-1,200 ml.
[4]9.8 L/Min.
[5]32.0 L/Min.

TABLE 3

Mean values of variables measured and calculated during mechanically assisted washouts in 5 subjects.

Assisted Washout No.	V_C	FRC	IDI
1.	21.0	2.55	1.85
2.	19.7	2.34	1.89
3.	22.2	2.52	1.96
4.	20.3	2.42	1.90
5.	19.8	2.42	1.86
6.	24.8	2.55	2.22
7.	19.2	2.43	1.76
8.	20.4	2.43	1.89
9.	22.3	2.48	2.00
10.	20.5	2.50	1.86

TABLE 4

Statistical significance of differences in IDI calculated from washouts performed under various conditions.

Comparison	Variable	P Value
N-6-N vs. L-10-N	IDI	<.05
N-6-H vs. L-10-N	IDI	<.05
N-6-H vs. H-10-H	IDI	<.02
L-10-N vs. H-10-N	IDI	<.01

Key: "N-6-N" = Normal flow, frequency = 6, Normal tidal volume.
N = normal
L = low
H = high

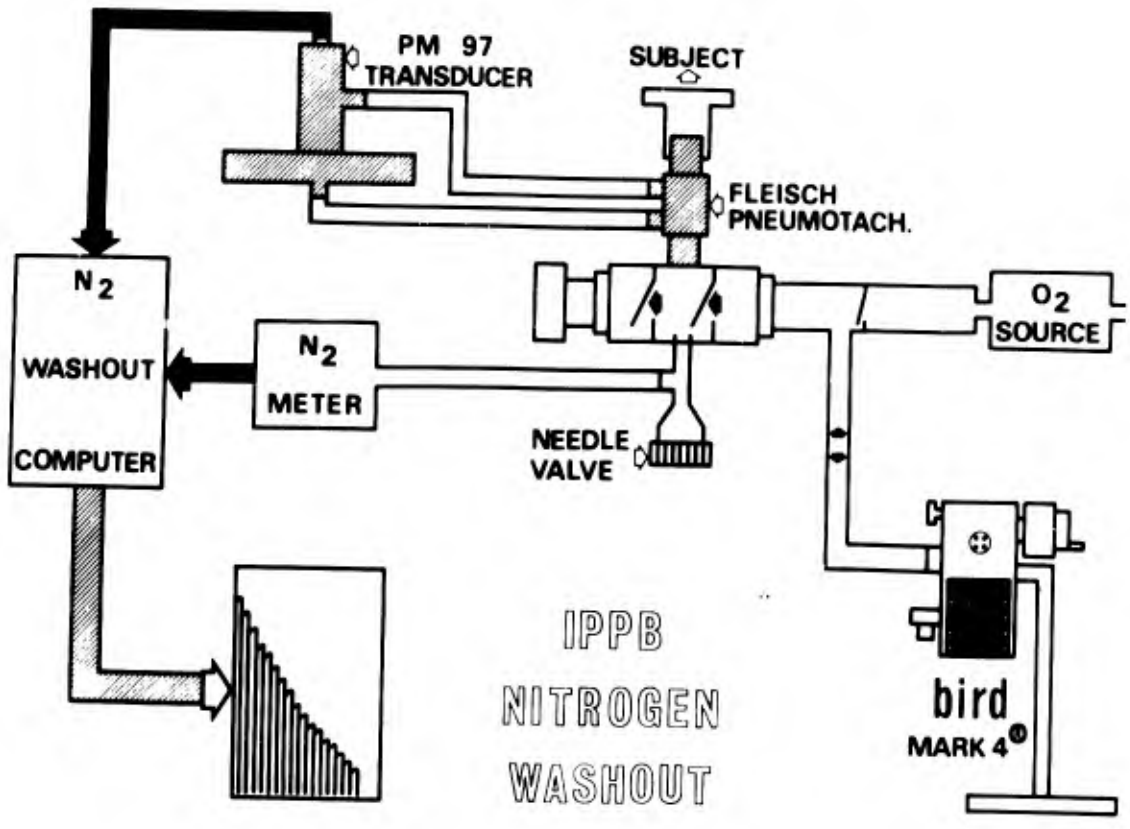

Figure 1: Orientation of equipment employed for respirator-controlled nitrogen washout studies to evaluate effects of varying tidal volume, respiratory frequency and inspiratory flow rates on washout characteristics and the I.D.I.

SECTION VI

THE NITROGEN WASHOUT COMPUTER IN STUDIES OF NORMAL NEWBORN INFANTS' RESPIRATORY PHYSIOLOGY AND THE NEONATAL RESPIRATORY DISTRESS SYNDROME.

John S. Hanson, M.D., Tamotsu Shinozaki, M.D., and Burton S. Tabakin, M.D.

Introduction:

The neonatal respiratory distress syndrome, representing a lethal combination of circulatory and respiratory aberrations, accounts for 25,000 annual newborn deaths in this country alone. Defects which have been previously defined in this disease include pulmonary vascular hypoperfusion, alterations of ventilation perfusion, and abnormalities of pulmonary mechanics and lung volumes. It remains ill-defined what the relative contributions are of these respiratory defects and circulatory right-to-left shunting of blood. The characteristic occurrence of profound hypercapnia would suggest a major role for the pulmonary factors.

Previous investigations have studied respiratory status through a combination of fairly simple direct and indirect approaches. No attempt has been made to evaluate intrapulmonary gas distribution through a nitrogen washout technique. Since the development of the nitrogen washout computer and its subsequent adaptation for use in small experimental animals, this direct approach to evaluation of both the normal and sick newborn human's respiratory physiological status is now feasible.

The relatively recent emergence of neonatology as a pediatric subspecialty has been coincident with intense investigative efforts to characterize all aspects of this "most hazardous period of one's life". Because initiation and subsequent maintenance of respiration represent such an integral portion of extra-uterine adaptation, post-partum pulmonary physiology has been a major area for this research. The incidence and consequences of neonatal respiratory distress have further intensified such studies.

Application of "modern" investigative technology to this field might properly be considered to have been initiated 15-20 years ago with the work of Smith et al. Elucidation of newborn respiratory rate, tidal volume, lung volumes, pulmonary mechanics and other respiratory variables has been accomplished. The important aspect of ventilatory efficiency and ventilation/perfusion relationships, however, has of necessity usually been examined indirectly until now.

The present communication describes methodology for and results of direct, breath-by-breath assessment of the newborn's alveolar ventilatory efficiency with simultaneous measurement of functional residual capacity. Longitudinal time-course changes in these parameters during the first 128 hours of life are described.

Materials and Methods

The technique of pulmonary nitrogen washout was employed. This consists basically of replacing, through breathing of 100% oxygen, the nitrogen contained in the lungs. The nitrogen washout curve shows for each breath the relationship between expired nitrogen concentration as a function of the ventilatory volume, time or the number of breaths to reach a certain

nitrogen concentration. Rapidity and hence slope of the curve is strictly a function of the size of the space being washed out (functional residual capacity, FRC) and the uniformity of inspired gas distribution as reflected in total alveolar ventilation. More detailed theoretical and mathematical considerations are given in Appendix I.

Although this technique is a time-honored procedure for evaluation of adult pulmonary function, it has only rarely been applied to the study of infants. The present investigation was conducted with a special-purpose, hybrid computer devised and constructed in this facility to produce breath-by-breath, on-line analysis of nitrogen washout. This instrument has been described in great detail elsewhere and evaluation made of its clinical application. Despite the fact that the original computer was designed for adult function testing, relatively simple logic modifications have allowed its application to infant studies. Net effect of these changes has been the capability of sensing and calculating extremely small ventilatory flows and volumes with maintenance of the original instrument's overall accuracy (3%).

The following description applied to the original hardware as modified for use in infant studies. Components consist of: Fleisch #00 pneumotachograph, Statham PM97 pressure transducer, Vertek 3000 nitrogen analyzer, heaters, computer logic, appropriate inspiratory-expiratory valve and patient airway adapter, and X-Y plotter*. The pneumotachograph, respiratory valve and nitrogen sampling needle are heated to obviate moisture condensation. The block diagram of Figure 1 shows the equipment configuration. The glass inspiratory-expiratory valve (A, Fig. 1) is connected to the patient via a milled nylon adapter with neoprene O-ring seal (B). This adapter contains

*Hewlett-Packard Model 7004A

the nitrogen sampling needle (D). These valves are available* in several sizes and have found application in other neonatal respiratory studies. Patient attachment is made with a soft plastic Y-tube fitted with tapered rubber tips (C) which are applied to the infant's nose sealing off the nares from external atmosphere. Total dead space of the airway-valve system is 0.76 ml. Inspiratory side of the valve is connected to a 3-way stopcock (E) allowing switching between atmosphere and the 100% oxygen source.

During performance of a washout the tapered rubber tips are positioned carefully but firmly in the infant's nares. Following confirmation of a good volume signal, the infant is switched from room air to oxygen breathing. An atmospheric leak due to improper nasal valve positioning or an oral leak is immediately detectable by nitrogen concentration spikes at each breath's peak. Expiratory flow is measured by the pneumotachograph (F) and its transducer (G), output of the latter being integrated by the computer to volume information. Nitrogen concentration is continuously monitored and relayed to the computer. Logic systems in the latter calculate from this information average anatomical or airway dead space on the basis of the first four breaths (Appendix I). This volume is subsequently subtracted from each breath's total volume giving nominal alveolar ventilatory volume which is plotted as the X-axis of output. Nitrogen percentage of expired gas constitutes the Y-axis. Characteristic on-line nitrogen washout plots are illustrated in Figure 2.

Functional residual capacity is continuously calculated on the basis of expired nitrogen volume. The washout may be terminated at any arbitrarily set point, usually an expired nitrogen concentration of 2% or 1%.

*F. F. Anderson, Madison, N.J.

The FRC value is then read directly from Nixie^{R} tubes which register this progressively incremental value.

In order to express the uniformity of alveolar ventilation in terms of the variables measured during washout, the Inspired Gas Distribution Index (I.D.I.) was devised. This consists essentially of the ratio between the theoretical and actual cumulative alveolar ventilations required to reduce alveolar nitrogen concentration of the FRC to a given level during 100% oxygen breathing. A single, uniformly ventilated space will have an I.D.I. of 1.0. a value both theoretically and practically unattainable for the human lung. Normal values for adult humans are 1.8 $\pm$ 0.1. Theory and actual computation of the I.D.I. are given in the Appendix.

Subjects:

A total of 40 newborn infants was studied. Ages ranged from 1 3/4 to 128 hours and birth weights from 1,899 to 4,338 grams. Four subject groups were established according to age, weight and number of examinations. Group I consists of 5 babies studied 2-4 times during the first 24 hours of life. In Group II are 10 infants examined at least twice during their nursery stay, the first study having taken place within 24 hours post-partum. Group III contains 20 subjects who were studied on only one occasion and at variable ages. Five infants with birth weights less than 2500 grams comprise Group IV.

With the exception of Group I subjects in whom the first feeding was given at age 12 hours, and 3 members of Group II whose studies were made prior to 12 hours age, washouts were always performed within 2-3 hours following feeding. No sedation was employed. Subjects were wrapped in their usual nursery blankets and placed in the study bassinette on their

sides or backs. No infants were studied in whom persistent problems of temperature regulation existed. Pre- and post-study checks of rectal temperature confirmed that this variable was maintained practically constant during the procedures. Four babies with initially low temperature (35.2^{0}-36.0^{0}) at the time of the first study became normothermic during the procedure. Determinations were not initiated until the infant was obviously deeply asleep with a regular respiratory pattern and was undisturbed by positioning of the nasal adapters.

Results:

It has become obvious that the establishment of norms for FRC and I.D.I. require that the measured variables be related to the infant's size and age. Despite such intra-group correlation, it is also apparent that the initial FRC size, its subsequent alterations, and the state of alveolar ventilatory uniformity are highly individualized and frequently modulating characteristics for any given infant. In the discussion below it should thus be kept in mind that grouping of results into mean values for categories of weight, surface area and age represents a somewhat artificial classification which ignores individual variability and unpredictable time factors.

Functional residual capacity:

In all subject groups FRC exhibited a significant correlation with birth weight and body surface area (Figures 3, 4 and 5). For Groups II and III the relationship of FRC and birth weight was better expressed by a second degree polynomial correlation (Figure 3) rather than the linear association seen for Group IV (Figure 4) or for BSA (Figure 5). When

mean FRC values were obtained through classification of Group II and III infants according to weights alone, the following distribution pertained: 2500-3000 gm: 46.8 ml; 3000-3500 gm: 58.2 ml; 3500-4000 gm: 65.9 ml; 4000-4500 gm: 66.7 ml. Statistically significant differences were established between the first and second weight group ($P<.001$) as well as the second and third groups ($P<.05$). Thus, for birth weights greater than 4000 grams, the subjects of Groups II and III did not evidence larger FRC's than those measured in the 3500-4000 gram range.

Examination of sequential FRC measurements in Groups I and II revealed progressive expansion of this volume with time in approximately 50% of babies. This phenomenon was therefore evident not only during the first 24 hours of life, but also during the course of the day following (Tables I and II). The point at which FRC expansion occurred could be closely approximated for one Group I baby (Subject 4, Table I) in whom a period of lusty crying during bathing was followed by a 44% FRC increase (Figure 6).

Uniformity of ventilation and I.D.I.:

As seen in Figure 7, the I.D.I. bore no correlation to birth weight. Time course changes in this variable were, however, impressive during the first day (Group I, Figure 8) and up to the sixth day of life (Group II, Figure 9). Figure 6 indicates the improvement in ventilatory uniformity seen in a Group I baby between the 12th and 24th hours, I.D.I. decreasing from greater than 2.0 to 1.72 despite a large expansion of FRC occurring during the first 12 hours. This trend toward a lower I.D.I. 24 hours following birth was also noted in the 20 subjects of Group III who were studied on only one occasion (Table III).

Mean values for I.D.I. derived from age-grouping of Groups II and III also indicate a temporal reduction of this variable: <24 hours: 2.09; 24-48 hours: 1.97; 48-72 hours: 1.94; >72 hours: 1.90. None of the changes between consecutive age rankings was statistically significant at the 0.05 probability level, however.

That the observed improvement in ventilatory efficiency with increasing age was independent of initial body weight can be seen in Figure 10 where the 3 variables' relationships are shown for Group II.

Discussion:

Analysis of the results herein reported is currently in progress. However, several obvious conclusions can be drawn from the material at this point.

Contrary to some previous indications, it would appear that uniformity of inspired gas distribution and hence ventilatory "efficiency" does not reach its most optimal or even stable levels during the first 24 hours of life. Indeed, longitudinal time course changes have been observed over 6 days.

Relatively large changes in the inspired gas distribution index may occur abruptly over the period of a few hours. There is some evidence that this occurs in close temporal relation to alterations in lung volume.

Uniformity of inspired gas distribution is not a function of birth weight, but must be interpreted from the standpoint of the infant's age and lung volume changes.

The functional residual capacity was seen to be closely correlated with birth weight and body surface area in the range of weights 1,900 - 4,400 grams. There are also temporally related increments in this variable

which can be observed over relatively short intervals. A documented example of lung volume expansion related to crying occurring in a 1-hour period has been illustrated.

Summary:

The applicability of an on-line, breath-by-breath nitrogen washout technique to respiratory studies in newborn infants has been demonstrated. Reproducibility and accuracy of the system is entirely comparable to that previously established in studies of adults.

The methodology allows for relatively simple, direct assessment of a newborn infant's functional residual capacity, the uniformity of inspired gas distribution, and longitudinal time changes in these parameters. Coupled with hemodynamic and blood gas studies, results obtained by this technique can provide a thorough evaluation of an infant's cardiopulmonary status. Such application will be made in a study of the respiratory distress syndrome. It is anticipated that the nitrogen washout technique will also provide valuable help in assessing ventilatory assistance and pharmacologic interventions in this disease.

TABLE I

Group I

Subject	Birth Weight (gm)	BSA (m^2)	Age (hrs)	FRC (ml)	I.D.I.
1.	3175	.2024	4	55	1.93
			24	56	2.16
2.	3232	.2040	6	48	2.29
			25	63	1.67
3.	2722	.1362	4	51	2.48
			12	48	1.92
			24	51	1.53
4.	3260	.2045	2	36	2.17
			3	52	2.02
			12	53	2.08
			24	55	1.70
5.	2438	.1711	3	46	1.47
			13	49	1.30
			26	52	1.16

TABLE II

Group II

Subject	Birth Weight (gm)	BSA (m^2)	Age (hrs)	FRC (ml)	I.D.I.
1.	3204	.2033	14	67	1.71
			19	64	1.72
			43	71	1.59
			62	71	1.59
2.	3629	.2144	6	71	2.29
			30	68	1.97
3.	3374	.2115	20	61	2.31
			32	61	2.31
			128	58	1.94
4.	3629	.2220	15	58	2.02
			43	69	1.85
5.	3260	.2010	21	61	2.06
			45	69	2.19
6.	3175	.1951	21	68	2.14
			45	63	2.16
			68	69	2.19
7.	2438	.1677	17	49	1.77
			36	44	1.75
8.	3374	.2078	22	53	2.02
			51	63	1.63
			75	63	1.49
9.	3175	.2024	4	55	1.93
			24	51	2.16
			76	46	2.02
10.	3232	.2040	6	48	2.29
			25	63	1.67

TABLE III

Group III

Subject	Birth Weight (gm)	BSA (m^2)	Age (hrs)	FRC (ml)	I.D.I.
1.	3544	.2122	44	60	1.93
2.	2722	.1757	96	46	1.90
3.	4338	.2477	70	74	2.31
4.	3742	.2326	120	76	1.86
5.	4224	.2410	67	67	2.18
6.	2523	.1736	54	50	1.94
7.	2778	.1843	48	39	2.13
8.	2863	.1867	60	55	1.64
9.	2977	.1898	96	43	1.73
10.	2948	.1962	57	43	1.64
11.	3515	.2153	42	56	1.51
12.	2835	.1895	51	46	1.81
13.	2665	.1776	35	50	2.22
14.	3090	.2002	24	57	2.38
15.	2722	.1897	24	49	2.05
16.	3856	.2278	23	72	1.89
17.	4338	.2395	42	59	1.69
18.	3175	.1989	46	49	2.28
19.	3940	.2299	56	54	2.27
20.	3997	.2233	25	75	2.14

TABLE IV

Group IV

Subject	Birth Weight (gm)	BSA (m^2)	Age (hrs)	FRC (ml)	I.D.I.
1.	1899	.1477	113	26	1.51
2.	2041	.2041	65	33	1.95
3.	2098	.1604	10	39	2.39
4.	2211	.1672	43	47	1.61
5.	2438	.1677	17	49	1.77

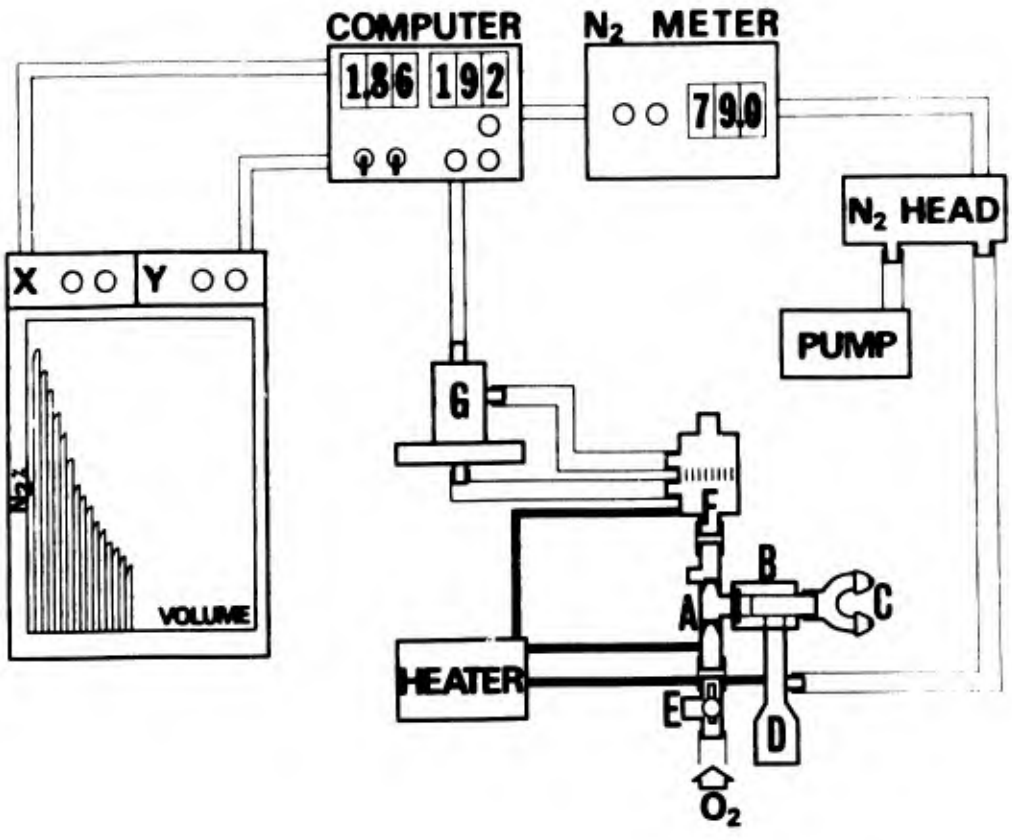

Figure 1: Diagrammatic representation of components employed for nitrogen washout studies in newborn infants.

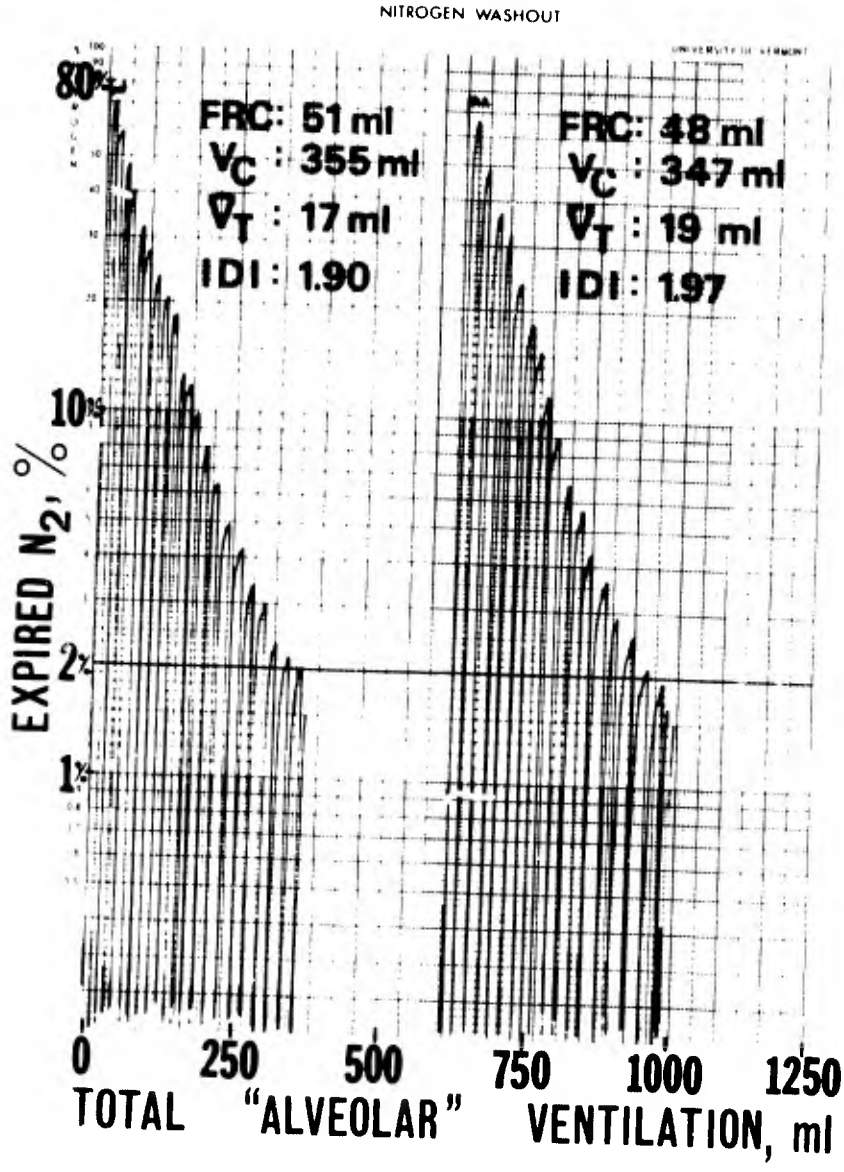

Figure 2: On-line, breath-by-breath nitrogen washouts in a newborn to emphasize reproducibility.

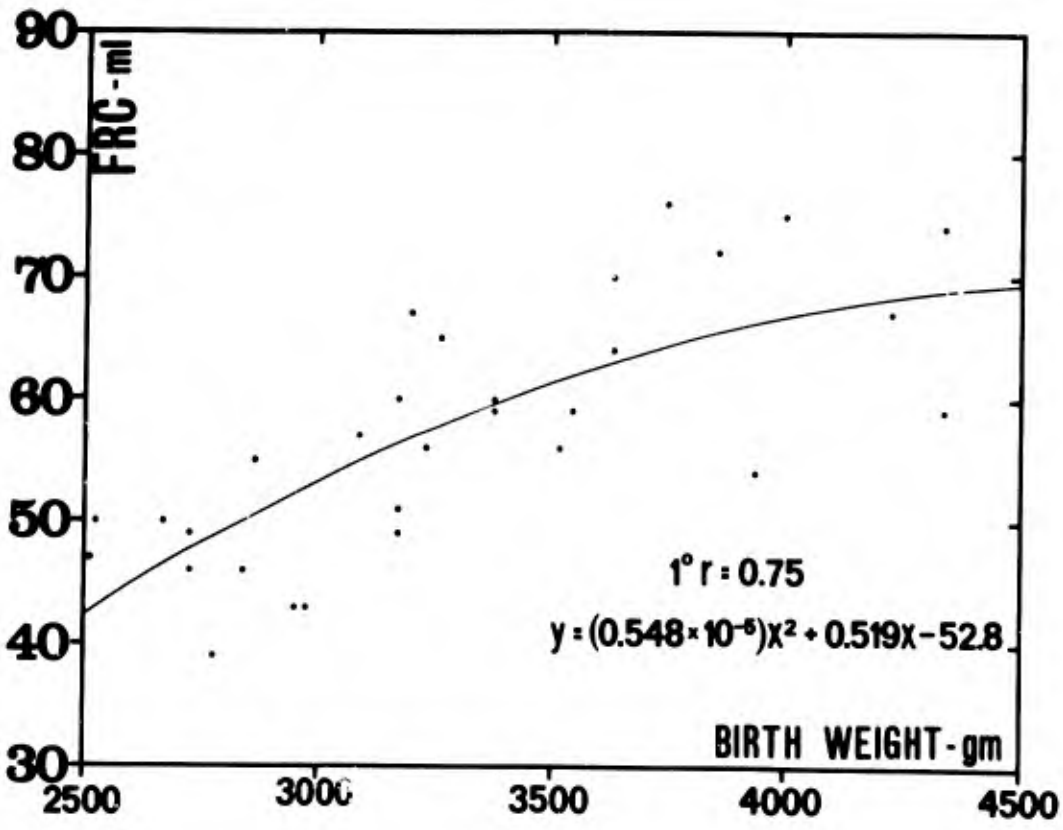

Figure 3: Relationship between birth weight and FRC in 30 newborn infants comprising Groups II and III. The correlation is best expressed by a second degree polynomial equation.

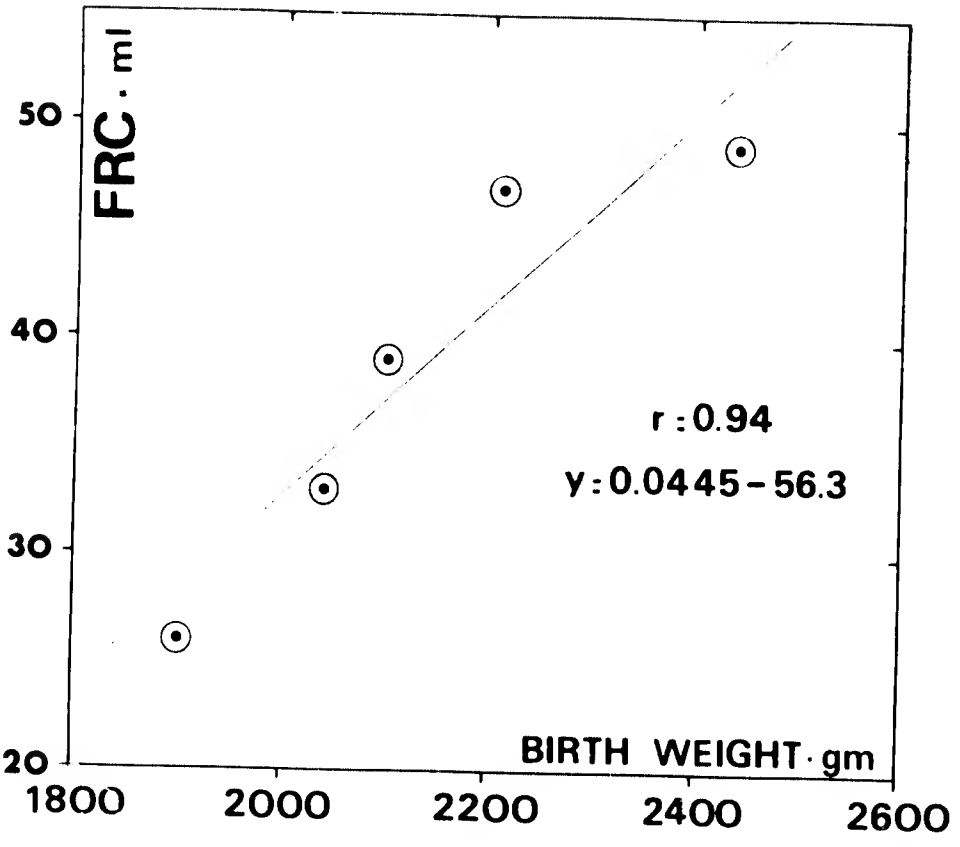

Figure 4: Correlation of birth weight with FRC in 5 newborn infants weighing less than 2500 grams.

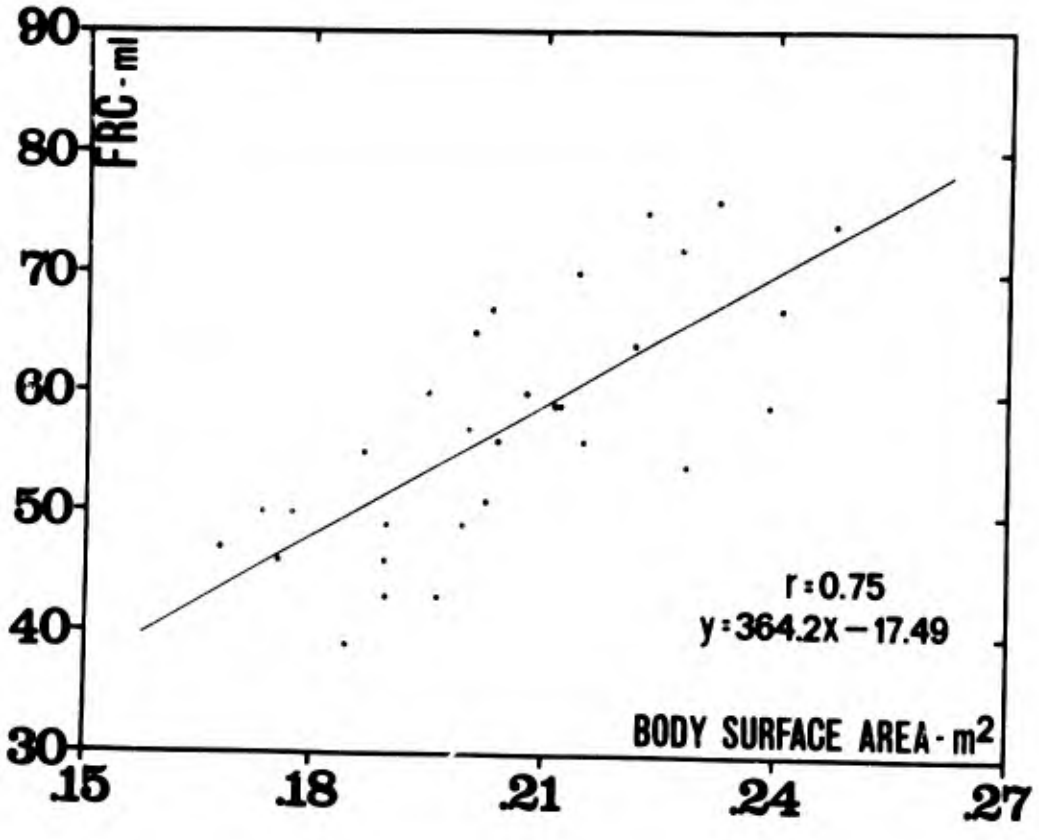

Figure 5: Relationship of body surface area at birth and FRC in 30 newborn infants of Groups II and III.

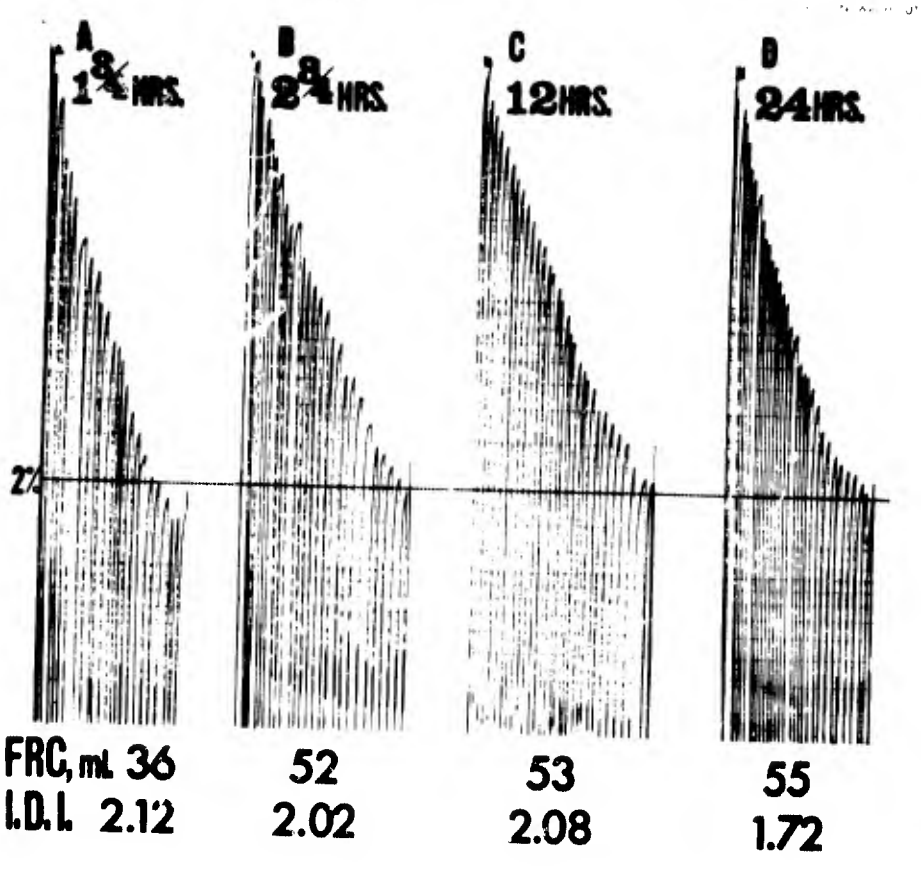

Figure 6: Sequential nitrogen washouts in a newborn infant during the first 24 hours of life. Note increase in FRC following crying at age 1 3/4 hours and improvement in ventilatory efficiency between 12 and 24 hours.

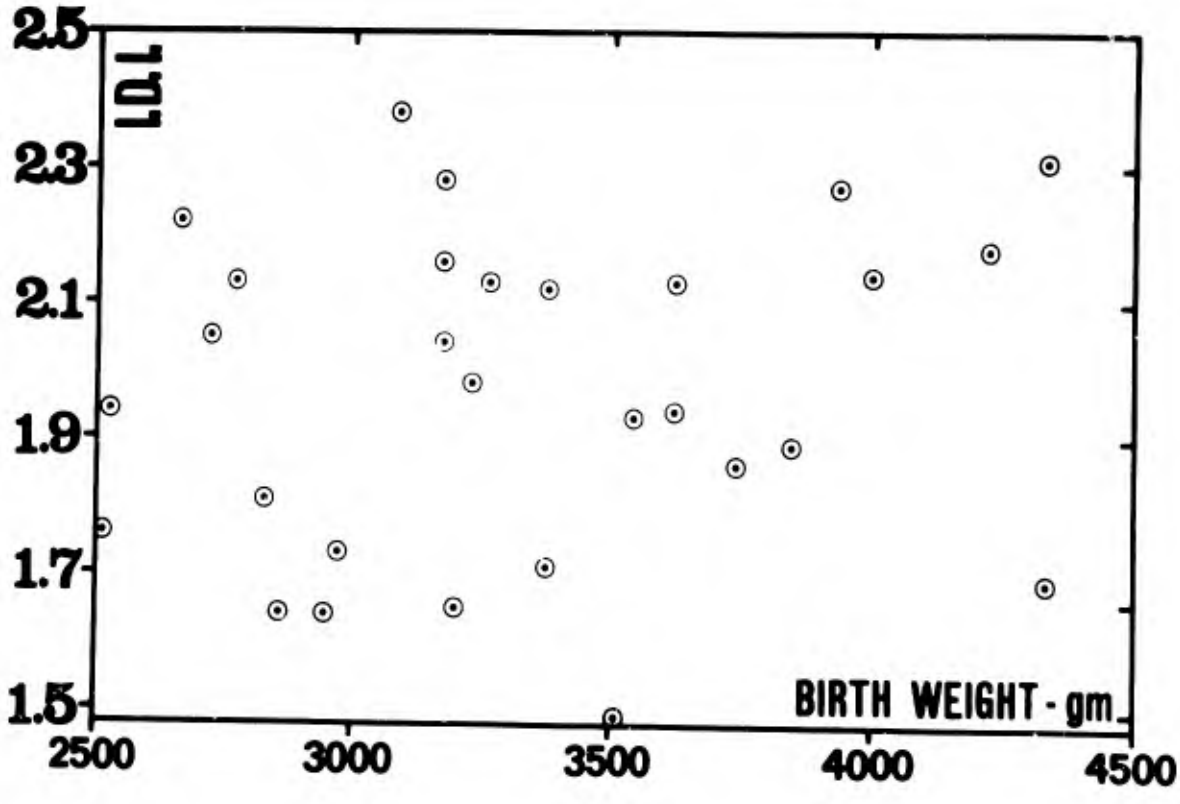

Figure 7: I.D.I. related to birth weight in 30 newborns of Groups II and III. Ventilatory efficiency is completely unrelated to an infant's birth size.

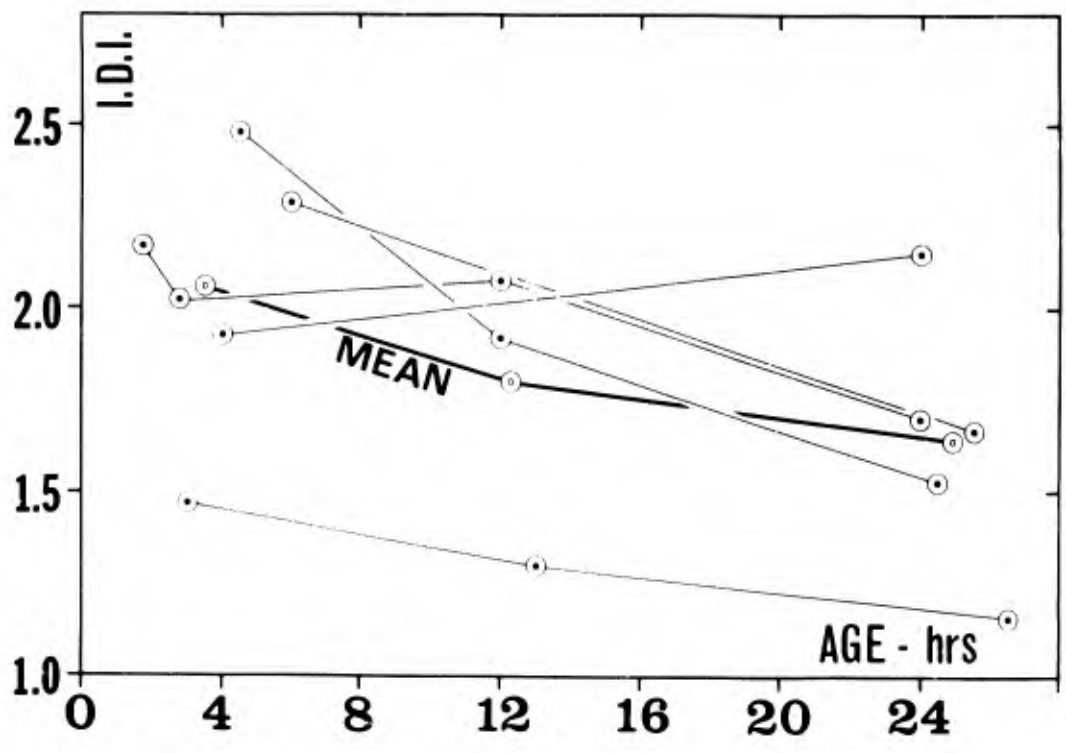

Figure 8: Time course changes in ventilatory efficiency during the first 24 hours of life. Group I.

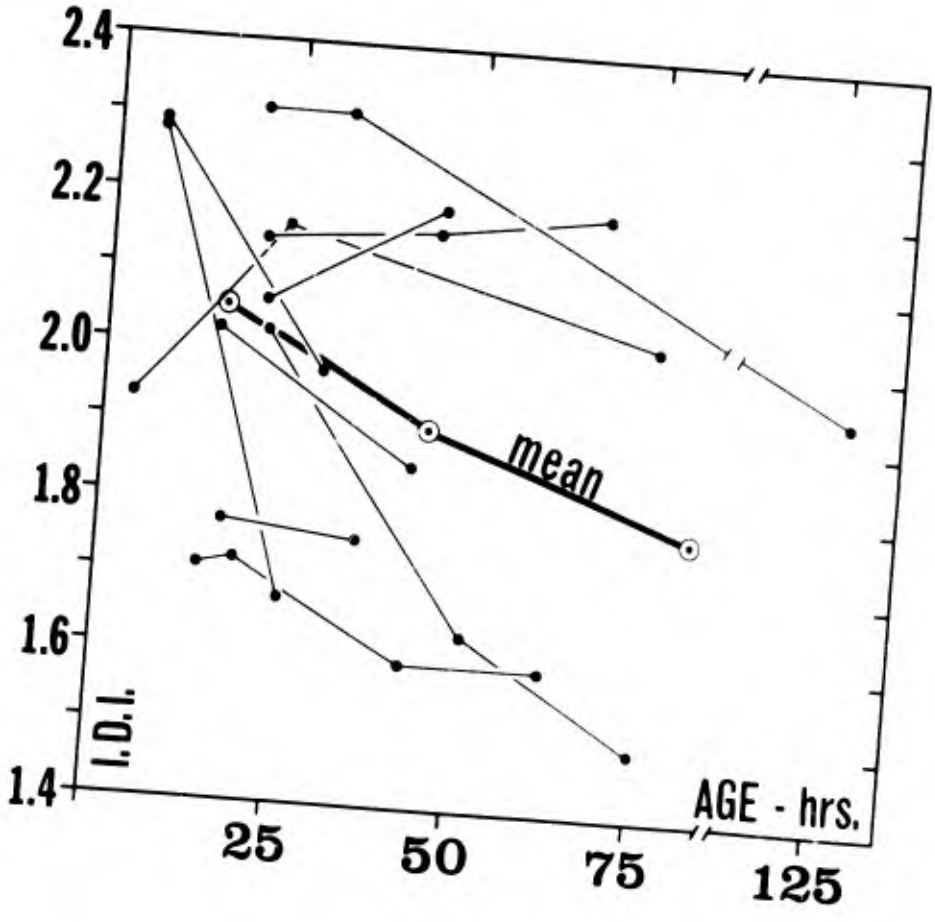

Figure 9: Longitudinal time changes in I.D.I. between the first and sixth days of life in 10 newborns comprising Group II.

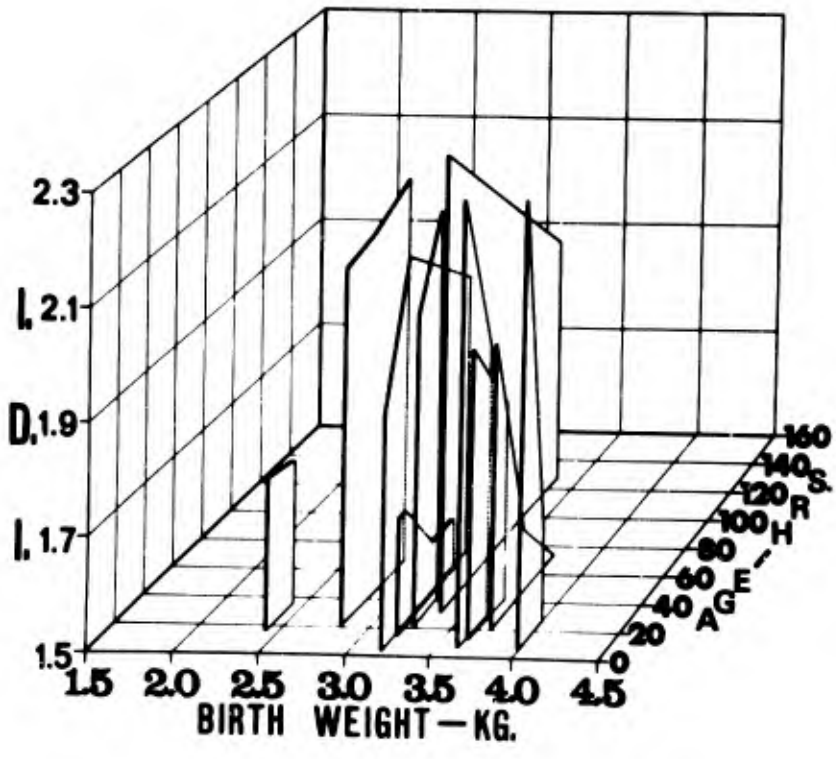

Figure 10: Relationships between birth weight, age and ventilatory efficiency in repeated nitrogen washouts for Group II.

SECTION VII

NITROGEN WASHOUT COMPUTER AS A TOOL FOR LONGITUDINAL STUDY OF CHRONIC BRONCHITIS.

For the past 18 months the Cardiopulmonary Laboratory has taken part in a USPHS-supported study entitled "Infection and Immunity in Chronic Bronchitis", Ben R. Forsyth, M.D., Principal Investigator. The over-all aim of this project is to study a limited population of chronic bronchitics over a prolonged period of time in regard to the following factors: 1) investigation of the role of viruses, mycoplasma, L-forms and bacteria in the etiology of chronic bronchitis and its exacerbations; 2) examination of the possible synergistic role of viral and bacterial infections; 3) determination of the significance of antibody secreted in nasal, salivary and bronchial locations and study of the relationship between such antibodies and serum antibodies; 4) study of the natural history of chronic bronchitis, particularly as related to the development of chronic obstructive emphysema; 5) definition of the role of cellular defense mechanisms; 6) definition of antibiotic distribution, effects and effectiveness.

At the present time, 25 patients are enrolled in this study and have been evaluated through pulmonary function testing in the Cardiopulmonary Laboratory. These evaluations have included nitrogen washout studies, lung volume determinations, spirometry, arterial blood gas studies at rest and during exercise, and steady-state carbon monoxide diffusing capacity determinations.

The study subjects are being followed on a weekly basis by the Infectious Disease Group. Repeat pulmonary function testing is being carried out at 6-12 month intervals and will continue in this manner for the duration of the study.

Due to the relatively short period of time during which this study has been conducted, no definitive or significant results have yet been obtained. It is anticipated, however, that over a period of years we will build up very valuable data relating to the natural history of chronic bronchitis and the development of chronic obstructive pulmonary disease. Because of the variety of function testing being employed, significant correlations between nitrogen washout characteristics and other indicators of respiratory dysfunction should be obtained. A minimum of 5 years will probably be required before meaningful deductions can be made from this longitudinal study.

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13. ABSTRACT

Current research applications of a computerized method for instantaneous and continuous measurements of expired nitrogen are presented. Projects already completed, now in progress and being implemented include: (1) evaluation of intrapulmonary gas distribution in patients with various types of pulmonary disease; (2) definition and classification of nitrogen washout patterns in patients with various types of cardiac disease; (3) study of intrapulmonary distribution of respired gas and pulmonary mechanics during induced pulmonary vascular congestion in the rabbit; (4) investigation of pulmonary mechanics and washout patterns in the rabbit following papain destruction of the lung's parenchymal meshwork; (5) delineation of changes in washout patterns during assisted ventilation with varying tidal volume, respiratory frequency and inspiratory flow rates; (6) definition of newborn infants' nitrogen washout patterns and lung volumes; the defects of intrapulmonary gas distribution encountered in the respiratory distress syndrome of the newborn; and (7) longitudinal study of washout characteristics in a group of patients with chronic bronchitis with particular reference to development of chronic obstructive emphysema.

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papain destruction						
tidal volume						
ventilation						
respiratory physiology						
neonatal respiratory distress syndrome						
chronic bronchitis						