THE UNIVERSITY OF MANITOBA

NON - INVASIVE ANALYSIS OF BREATHING PATTERNS IN PATIENTS WITH CHRONIC AIRWAYS OBSTRUCTION

by

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A THESIS

Submitted to the Faculty of Graduate Studies in Partial Fulfillment of the requirements for the Degree of Doctor of Philosophy.

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To My Family

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NON-INVASIVE ANALYSIS OF BREATHING PATTERNS IN PATIENTS WITH CHRONIC AIRWAYS OBSTRUCTION:

B. LOVERIDGE

We used the respiratory inductance plethysmograph (RIP) to analyze breathing pattern in patients with chronic airways obstruction (CAO) and in age and sex matched controls. Since we intended to use the RIP to study breathing pattern in a single body position, we developed a method to calibrate it in one position (seated), and verified the stability of this calibration for periods up to 60 minutes. The technique was verified in 8 young normal, 8 old normal and 12 CAO subjects. The subjects breathed spontaneously through a pneumotachygraph for 1 minute during all calibration and verification runs. All inspiratory data from the abdomen (ABD) and ribcage (RC) RIP transducers were analyzed using multiple linear regression analysis to derive calibration factors for the ABD and RC transducers. The correlation coefficients were > .93 for all subjects, and the slopes and intercepts describing the relationship of the RIP volume to the pneumotachygraph volume were not significantly different between calibration and verification runs in any of the groups. This calibration method allowed a spirogram to be generated from the RIP signals.

We analyzed breathing patterns in the same 12 CAO and 8 age and sex matched normal subjects. Following calibration of the RIP as described above, the subjects remained in the seated position and the RC and ABD RIP signals were collected for a 45 minute period. The timing components of the spirograms were compared between the CAO and control groups. Breathing pattern from the 1 minute calibration on the mouthpiece was also compared to breathing pattern measured with the RIP above.

Inspiratory time (Ti) and expiratory time (Te) were significantly shorter, and mean inspiratory flow (Vt/Ti), frequency (f) and minute ventilation ($\dot{V}e$) were all significantly increased in CAO subjects. As well, there was less variability in Ti, Ti/Ttot (cycle duration) and $\dot{V}e$ in CAO subjects even after removal of breaths > 30% FVC predicted from the data of both groups. The increased $\dot{V}e$ in CAO subjects was due to increased f as tidal volume (Vt) was the same in both groups. There was no difference in the correlation coefficients of any variables compared between the CAO and controls. The Vt and Ti correlation was strongest. Vt and f were negatively correlated. $\dot{V}e$ varied mainly by varying Vt and it appeared that Te was not closely associated with the preceeding Ti in both groups. CAO subjects took significantly fewer sighs than did controls. No correlation was found between severity of disease in CAO subjects assessed by $FEV_{1.0}$ and any variable. Breathing pattern and particularly inspiratory timing appears to be more fixed in CAO subjects. The alterations cannot be explained on the basis of either mechanical loading or increased drive alone and suggests that neural adjustments to breathing in excess of these demands have occurred in patients with CAO. Mouthpiece breathing significantly increased Vt and decreased f in both groups as compared to the RIP. Vt/Ti was also significantly increased in controls on a mouthpiece. It appears that the mechanism of increased Vt induced by the mouthpiece was different between the two groups and that mouthpiece effects may not be non-specific.

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I INTRODUCTION

The respiratory system is vital to life, and yet, the understanding of breathing patterns, an important reflection of the integration of the system, remains extremely limited. The nature of normal patterns as well as respiratory dysrhythmias in patients with chronic lung disease still have to be explored.

Clinical observations suggest that breathing patterns in patients with chronic airways obstruction (CAO) are significantly altered from normals (West 1909, Cherniack et al 1972, Ashutosh et al 1975). All authors describe diminished chest movements and increased use of accessory muscles of respiration in these patients. Many patients with advanced disease exhibit paradoxical motion of the lower intercostal spaces and of the abdomen during respiration (Ashutosh et al 1975), and roentgenographic examination reveals a flattened diaphragm with decreased excursion (Kryger,1981).

Although clinical impressions have been recorded for considerable period of time, the ability to quantitate accurately and to analyze breathing patterns in patients with CAO is still in its developing stages. Early attempts to analyze the components of a respiratory cycle relied on studies using mouthpiece and noseclips, or facemasks to collect data on respiration. These studies provided the necessary basis for subsequent development, but it was discovered that the apparatus itself induced changes in breathing patterns (Gilbert et al,1972). Noninvasive methods of measuring breathing are still in the developmental stages which has limited their usefulness as research tools.

The respiratory inductance plethysmograph (RIP) is an example of one such noninvasive technique for monitoring ventilation(Watson,1980).

It has been used mainly to record tidal volume (Vt) and minute ventilation ($\dot{V}e$) in normal adults (J.D. Sackner et al,1980 a and b), in children (Tabachnik et al,1981) and in infants (Duffty et al,1981), in smokers (Sackner et al,1982, Cohen et al,1982) and in conscious sheep (Abraham et al,1981). However, the methods currently employed in calibrating the RIP have not been adequately evaluated.

We were unable to obtain consistent results using the 2 position calibrating technique which is the one most often reported. Since we intended to use RIP to study breathing patterns in a single position, we developed an alternate method of calibration which could be carried out in one position.

Subsequently, we used this single position calibration method to analyze resting breathing in patients with CAO and compared their breathing patterns to those of an age and sex matched control population.

II GENERAL OBJECTIVES

1. To verify the accuracy and precision of the Respiratory Inductance Plethysmograph (RIP) for recording breathing.
2. To quantitate and to analyze breathing patterns with the RIP in patients with chronic airways obstruction (CAO) as compared to normal subjects.

III BACKGROUND AND RATIONALE

A. Relevance of Breathing Pattern Analysis to Control of Breathing

Information on the control of breathing in man has been provided through the study of breathing patterns and the effects of various interventions on the components of a respiratory cycle. Two variables have

been considered to be important indices of respiratory neural drives. They are the mouth occlusion pressure measured 0.1 seconds after the onset of inspiration with the airway occluded ($P_{O\ .1}$) (Whitelaw et al, 1975) and the mean inspiratory flow rate [tidal volume (Vt)/inspiratory time (Ti)] (Milic Emili and Grunstein,1976).

Other indices of neuronal output, diaphragmatic electromyographic (EMG) activity (Onal et al,1981) and phrenic nerve activity,(Von Euler, 1970, Clark and Von Euler,1972, Remmers et al,1975 and Pack et al,1981) are also a reflection of respiratory drives and have been employed in both animal and human studies. However, their use in clinical experimentation is limited. Phrenic nerve outputs cannot be measured directly in man, and diaphragmatic EMG activity (recorded with surface or esophageal electrodes) is only a crude and indirect assessment of total muscle activity.

$P_{O\ .1}$ is considered to be an index of inspiratory drive, and more specifically, the neuromuscular inspiratory drive. It represents the potential pressure available for inspiration and a major advantage in using $P_{O\ .1}$ is that it is independent of lung mechanics. However, it assumes that the pattern of development of pressure in the respiratory muscles does not vary. Considerable inter animal variability in the shape of the occlusion pressure wave has been demonstrated by Siafakas et al (1981). This suggests that inspiratory drive is not constant during inspiration and therefore, $P_{O\ .1}$ may not be an accurate reflection of inspiratory neural events. In spite of these limitations $P_{O\ .1}$ has been a useful clinical tool in assessing inspiratory neuromuscular drive. $P_{O\ .1}$ has been found to be increased in patients with CAO with and without hypercapnia (Grassino et al,1978; Sorli et al,1978). Both authors found

that part of the increased $P_{0.1}$ in these patients was due to hypoxemia, but even when the hypoxemia was relieved, $P_{0.1}$ did not return to normal levels. Aubier et al (1980) in CAO patients in acute respiratory failure also found $P_{0.1}$ to be elevated to levels as high as those found in young normals breathing 50-70 l/min. Administration of oxygen in these patients markedly decreased $P_{0.1}$.

The spirogram represents the integrated output of the respiratory system. Analysis of the timing components and pattern have provided a further means of investigating control of breathing in man. Conventionally minute ventilation ($\dot{V}e$) is expressed by the following equation:

$$\dot{V}e = Vt \text{ (tidal volume)} \times f \text{ (frequency)}$$

Both Vt and f are time dependent and little information is provided about factors which affect Vt and f in this type of analysis.

Milic-Emili and Grunstein (1976) suggested an alternate approach to better describe the factors contributing to $\dot{V}e$:

$$\dot{V}e = Vt/Ti \times Ti/Ttot \times 60$$

Vt,Ti (inspiratory time) and Ttot (cycle duration) can all be measured directly from the spirogram and then the Vt/Ti and Ti/Ttot ratios are calculated. Vt/Ti represents mean inspiratory airflow and is considered to be an index of the firing of inspiratory neurons and thus an index of the inspiratory drive. Vt may be altered by altering the rate of rise of inspiration (Vt/Ti) and by changing the duration of Ti. Therefore, changes in these parameters provides information about inspiratory drive. Ti/Ttot is considered to be an index of respiratory timing. Milic Emili (1976) viewed the breathing cycle as the result of a driving mechanism (assessed by Vt/Ti) turned on and off by a cyclic timing mechanism (assessed by Ti/Ttot).The values of these components of the spirogram

will vary with neural events, and therefore, analysis of the spirogram provides insight into control of breathing in man.

Many studies on control of breathing have involved measuring the responses to chemostimulated respiration.

Hey et al (1966) studied the relationship between Vt,f and $\dot{V}e$ under quiet breathing and during cardon dioxide (CO2) or exercise induced hyperpnea and found that the relation between $\dot{V}e$ and Vt was linear up to a Vt approximately half the vital capacity (VC). Further increases in ventilation were achieved by increasing f. These findings were reproducible for position changes, wide variations in alveolar carbon dioxide tension and alveolar oxygen tension, acidemia, and infusion of noradrenalin. However, increasing the core body temperature resulted in an increase in f at all levels of $\dot{V}e$.

Von Euler et al (1970) examined the effects of CO2 rebreathing and vagotomy on anesthetized cats. They found that as CO2 concentrations were increased, $\dot{V}e$ increased by an increase in Vt and f, but at a Vt of approximately half the VC, the further increased $\dot{V}e$ was achieved by increased f only. Bilateral vagotomy resulted in a decrease in f and a loss of the f accelerating effect of CO2. Increased $\dot{V}e$ was achieved by increased Vt, but the slope of the $\dot{V}e$/Vt relationship was shifted downwards. The linear $\dot{V}e$/Vt relationship found in cats was comparable to that Hey et al (1966) found in humans. Von Euler et al concluded that the acceleration of f in response to an increased chemical drive required intact vagi. They suggested that some critical distension of the lungs at Vt of approximately half the VC may provide the afferent input to the vagi necessary for this effect.

Clark and Von Euler (1972) studied the regulation of breathing

in cats and in humans during CO2 breathing. They examined the volume and time relationships of breathing cycles. In cats, phrenic nerve activity was used to plot Ti, and in man Ti was estimated from the volume records. They proposed a vagal threshold which was stimulated at a critical Vt. In intact cats, as Vt increased, Ti decreased. With vagotomy, Ti was prolonged and independent of Vt or CO2. Because there was no volume feedback to the central nervous system, the termination of inspiration was fixed. In intact man breathing through a mouthpiece,Ti remained constant as Vt was increased to 2-3 times normal. Further increases in Vt were associated with decreased Ti. This effect was attributed to vagal volume related feedback which was thought to be effective only after a threshold Vt of 2-3 times the resting value was reached. These data were supported by the careful studies of Gardner (1977). Clark and Von Euler found that expiratory duration was linearly dependent upon the preceeding inspiratory duration. Volume inflations during the expiratory phase in cats produced a prolongation of Te and a disruption of the normal relationship between Ti and Te. Clark and Von Euler suggested that this distension of the lungs was not important under normal conditions but questioned if this mechanism might become important in subjects with increased expiratory airways resistance.

They postulated that breathing pattern was almost entirely dependent on inspiratory events: central respiratory drive which determined the rate of inspiration, or Vt/Ti, and an "off switch" which terminated inspiration in response to volume related signals from the vagus. The sensitivity of the "off switch" increased with time after the onset of inspiration, so that long after onset, breaths were terminated at low Vt, and large Vt's were needed to terminate inspiration shortly after onset. Thus Vt and Ti were

inversely related and breaths characterized by intense inspiratory drive (large Vt/Ti), had short Ti and large Vt, while the opposite was true during states of low central inspiratory drive (small Vt/Ti). Central timing factors determine Ti in vagotomized cats and in intact humans during resting breathing when vagal influences are thought to be weak. Subsequent work has shown that the duration of expiration (Te) is not entirely dependent on Ti, as postulated by Clark and Von Euler. Gardner (1977) found an inverse relationship between Vt and Te and suggested that most changes in f in man are brought about by changes in Te rather than Ti.

Hey et al (1966) did not demonstrate a fixed Ti at low Vt's, f increased as soon as $\dot{V}e$ increased. Clark and Von Euler had subjects hyperventilate prior to recording ventilation and the decreased respiratory drive resulted in subjects starting to breathe at Vt less than resting Vt. This may be the reason for the discrepancy between these authors.

The problem inherent in analyzing pattern is that it depends both on neural drive and lung mechanics. The complexity of integration of neural processes and the mechanical events resulting in the development of the spirogram, make separation of these two components difficult. Vt/Ti is a result of both drive and mechanics. $P_{0.1}$ provides information about inspiratory drive which is independent of lung mechanics, but does so only insofar as the first 0.1 second of inspiration represents the remainder. The spirogram provides the ability to assess drive (Vt/Ti) as well as to assess the relationship between the other timing components.

B. Measurement of Breathing Patterns

1. Study of Breathing Patterns Using Invasive (Mouthpiece or Facemask) Techniques.

As early as 1909 recordings of ventilatory patterns can be found in the literature. West (1909) illustrated a spirogram comparing a patient with emphysema to a normal subject. The pattern from the emphysematous patient showed a shorter, steeper inspiratory limb, and an irregular, oscillatory and lengthened expiratory limb.

Priban (1963) studied breathing patterns in normal males at rest, in the supine position, wearing a facemask connected to a spirometer to record respiratory cycles continuously. During resting breathing he found small changes with time in Vt and f but $\dot{V}e$ remained relatively constant. Vt and f were negatively correlated. He suggested that a controlling mechanism existed which was tightly coupled to ventilation, so that Vt and f may vary, but do so in opposite directions to maintain a fairly constant $\dot{V}e$.

Dejours et al (1966) investigated the breath to breath variations in gas exchange in normal subjects at rest. They recorded respirations using a facemask and pneumotachograph whose flow signal was then integrated to provide a volume output. Subjects were studied in a semi supine position. They found a positive correlation between Vt and cycle duration. Vt and f varied in such a manner as to maintain a fairly stable $\dot{V}e$.

Lenfant (1967) studied 12 normal subjects at rest in the sitting position. Subjects breathed through a mouthpiece and wore noseclips. A spirogram was generated by electrical integration of the pneumotachograph signal. He found that all respiratory variables showed an oscillatory pattern about the mean. Vt correlated positively with the duration of the breath.

Hlastala et al (1973) confirmed the positive correlation between Vt and respiratory cycle duration in normal subjects.

Newsom Davis and Stagg (1975) investigated breathing patterns in resting man in the greatest detail. They studied normal subjects in the supine position wearing a facemask, and recorded ventilation for 20-25 minutes. They incorporated a computer based analysis of the volume and time components of individual breaths. This allowed Vt, inspiratory time (Ti) and expiratory time (Te) to be measured for more than 200 breaths. They confirmed the negative correlation between Vt and f, and the positive correlation between Vt and cycle duration (Ttot) found by earlier investigators. The correlation between Vt and Ti was found to be stronger than between Vt and Ttot. Furthermore, they found that the constancy of ventilation from breath to breath depended on the tendency for mean inspiratory flow rate (Vt/Ti) to remain constant. Changes in Vt/Ti were more consistently related to changes in ventilation than either Vt,Ti or Te. With inhalation of both 1.5 and 3.0% CO2 in room air in normals, Davis and Stagg observed that Vt increased, Te shortened and Ti remained unchanged. They observed no gross changes in the distribution of the histograms of these variables but found that the coefficients of variation tended to decrease with CO2 inhalation. Vt showed a progressive increase with increasing levels of inhaled CO2. They concluded that regulating the rate of inspiratory airflow is an important mechanism controlling ventilation.

Sorli et al (1978) and Grassino et al (1978) compared ventilatory variables between hypercapnic and normocapnic patients with CAO at rest and in the supine position. They found that Vt was decreased ($p < 0.01$) and f increased in hypercapnic subjects. Ti was also shorter

in this group, but both groups maintained similar $\dot{V}e$. Vt/Ti was the same in both groups. They suggested that the decreased Ti might be due to increased activity of stretch and/or irritant receptors in the lung and that this led to a decreased Vt and, therefore, to rapid shallow respiration. Ti/Ttot was also decreased ($p < 0.01$) in hypercapnic subjects. The authors suggested that this reflected dynamic compression on expiration which in turn might elicit vagal reflexes prolonging the duration of expiration.

Bradley et al (1979) confirmed the findings of Sorli et al (1978) that $\dot{V}e$ and Vt/Ti were the same in patients with CAO irrespective of hypercapnia, and further found the same was true of patients with hypoxemia. They also showed that patients with CAO and hypoxemia displayed a decreased Ti ($p < 0.05$) compared to patients without significant hypoxemia. This finding was similar to that of Sorli et al in hypercapnia and it was suggested that hypoxemia was the determining factor in variations in breathing patterns. Bradley et al found that the rapid shallow breathing pattern found in the hypoxemia group occurred in patients with and without accompanying hypercapnia.

Javaheri et al (1981) also studied patients with CAO with and without hypercapnia and confirmed the findings of Sorli et al (1978). They studied patients in the sitting position as well and found no difference in any of the parameters.

Parot et al (1980) studied a large group (91 patients) with CAO and hypercapnia or normocapnia. The experiments were conducted with patients in the sitting position. They found Vt was lower in the hypercapnic group ($p < 0.001$) which resulted in a decreased $\dot{V}e$ ($p < 0.001$) and a significantly higher deadspace/Vt ratio (VD/Vt). The authors suggested

hypoventilation led to hypercapnia in this group. The scatter in individual Vt's was large and therefore a large sample was necessary to see these results.

Burki (1979) divided patients with asthma and/or CAO into two groups; one group complained of shortness of breath and were objectively dyspneic at rest, the other group exhibited no dyspnea at rest. He compared ventilatory parameters, f, Ti, Vt/Ti, and Ttot between these groups. Subjects breathed into a spirometer and a minimum of 50 consecutive breaths were recorded. There were no significant differences in any of the parameters between the dyspneic and nondyspneic patients. $P_{0.1}$ was also measured and found to be elevated ($p < 0.001$) in the group with breathlessness. However, the group with dyspnea had significantly worse airways obstruction. They suggested that increased inspiratory neuromuscular drive as estimated by $P_{0.1}$ was an important contributor to the genesis of breathlessness. However, $P_{0.1}$ would have had to have been higher in this group to maintain ventilation.

2. Inadequacy of Studying Breathing Using Invasive Techniques

Many investigators have compared breathing patterns when subjects breathed through a mouthpiece or a facemask to those measured with less invasive methods such as magnetometers or RIP. These less invasive methods will be discussed in the next section.

The apparatus,mouthpiece,or facemask,was found to alter breathing in a significant and consistent manner. Vt was found to be significantly increased when subjects breathed in a mouthpiece (Gilbert et al,1972, Sackner et al 1980, Askanazi et al 1980, Tabachnik et al 1981, and Hirsch and Bishop 1982) and to a lesser but significant degree on a facemask (Askanazi et al 1980, Hirsch and Bishop 1982). Frequency was found

to be unchanged (Askanazi et al 1980, Tabachnik et al 1981) or decreased (Gilbert et al 1972, Hirsch and Bishop 1982). In the studies where Vt increased and f decreased, $\dot{V}e$ remained constant. However where Vt was shown to increase without changes in f, a significant increase in $\dot{V}e$ was also reported.

Tabachnik et al (1981) found that the mean increase in Vt was approximately equal to the apparatus deadspace. Gilbert et al (1972) suggested that the decreased frequency may be due to irritation of the nasal and oral mucosa by the noseclips and mouthpiece. However, Bishop and Hirsch (1982) found that when subjects wore noseclips under the face-mask, breathing patterns did not change from that found in mask breathing alone. They suggested that the effects of breathing apparatus on pattern are not simply due to a shift from mouth to nose breathing. Tabachnik also suggested that breathing pattern appeared more regular when subjects used a mouthpiece as compared to breathing measured with RIP.

Hirsch and Bishop (1982) also compared the effects of mouthpiece versus facemask in chemostimulated ventilation. Increased CO2 and decreased O2 resulted in increased $\dot{V}e$, f, and Vt/Ti in all subjects wearing a mouthpiece. It was suggested to be due to a significantly shortened Te. The responses on the mask varied; during hypoxic stimulated breathing, Vt increased but f remained unchanged.

3. Study of Breathing Patterns Using Noninvasive Techniques

Two of the earliest systems attempting to analyze respiration noninvasively were mercury strain gauges used to record pressure changes resulting from chest wall motion, and surface electrodes placed on various aspects of the chest wall to record changes in impedance as a result of respiration.

Wade (1954) was the first to look at the separate contributions of ribcage and diaphragmatic movements to respiration. He used four mercury-in-rubber strain gauges to record chest movement during quiet and forced ventilation in ten normal subjects in the supine and erect postures. He also simultaneously measured diaphragmatic excursion under fluoroscopy and recorded the vertical motion of the thorax. The tension developed by the strain gauges was linear over a wide range of lengths and the frequency response of the system was accurate up to a frequency of 60 cycles/sec. He assumed that the sum of diaphragmatic movement and chest movement equalled the volume ventilated and calculated the contribution of each component. His results suggested that in a vital capacity maneuver one quarter of the ventilation was due to chest expansion and three-quarters was due to the diaphragm's contribution. The assumptions inherent in these observations were that total ventilation can be expressed simply in terms of diaphragmatic and chest movement; that the relationship is linear; and that other factors affecting volume changes contribute negligibly. He failed to consider that the diaphragm contributes to both ribcage and abdominal movements during respiration.

Agostoni et al (1965) studied normal male subjects in standing, sitting and supine positions and confirmed the findings of Wade (1954).

Bendixin et al (1964) used a strain gauge pneumograph to study breathing patterns in 28 young adults. They recorded respiration with the subjects in a semisitting position in an adjustable hospital bed. The strain gauge was applied at the level of the xyphoid process and breathing was recorded for 1 hour. The phases of respiration and the frequency were assessed during 50 consecutive breaths. Frequency

gradually decreased with time. The mean frequency was 19.2/min, and 17.0/min for females and males respectively. The average inspiratory duration was 35.2% of the total cycle. The ratio of inspiration to expiration varied greatly between subjects and individuals changed the expiratory phase when they altered frequency. Vt varied considerably from breath to breath. Sighing which was defined as a Vt three times greater than the mean Vt occurred in all subjects. Frequency decreased by approximately 2 breaths/min in the first 10 breaths following a sigh ($p < 0.01$).

Shapiro and Cohen (1965) employed mercury strain gauges to record changes in thoracic circumference and relate them to tidal volume changes. They assumed that the volume of the chest changed only as a result of air flowing in and out of the trachea and that the volume of the abdomen remained constant. The relationship of the analog signal from the mercury gauge to the volume as recorded using a spirometer was reported as being linear over a 4 litre volume range. They observed however that change in position and the use of accessory muscles of respiration resulted in less accurate measurements of volume using this system.

Most investigators using mercury strain gauges only measured changes in RC circumferences, and the volume estimates were very dependent on the position of the strain gauges on the thorax. As well, strain gauges consist of a coil with a small diameter and therefore, only look at circumference changes over a small area. These factors coupled with the lack of an adequate calibration technique has limited the usefulness of strain gauges in analyzing breathing.

Impedance plethysmography was another method used widely to measure Vt (Allison et al, 1964; Kubicek et al, 1964; Hamilton et al,1965; Wadhwani and Longini, 1972; Ashutosh et al, 1974). This procedure involved

placing surface electrodes on the thorax at various sites and recording the changes in electrical impedance as a result of changes in volume of the thorax. All authors calibrated their impedance system against a known volume from a spirometer. The ratio of the impedance signal to the spirometer signal could be calculated, and subsequent impedance signals could then be multipled by this calibration coefficient and expressed as a volume. The major problem with this technique was that impedance is also affected by blood in the chest.

Allison et al (1964) found impedance plethysmography to be inaccurate in estimating volume during vital capacity maneuvers. They suggested that the redistribution of blood during this procedure resulted in an increased blood volume in the thorax which in turn increased the conduction and reduced the peak inspiratory impedance recorded. Kubicek et al (1964) observed that variations in breathing patterns resulted in nonlinearity of the impedance system. In contrast, Hamilton et al (1965) found that their system was linear up to 1.5-2 litres in all body positions and when the contribution of the ribcage and abdomen was voluntarily altered. Vt varied within 6% of Vt as recorded on a spirometer. The variations in size and position of the electrodes, and artifacts at the electrode contact surfaces with the chest wall were thought to contribute to the differences between these results.

Wadhwani and Longini (1973) employed electrical impedance plethysmography to look more specifically at breathing patterns and individual wave forms in normal subjects and subjects with chronic airways obstruction. Previous workers had only been able to grossly quantitate Vt. Wadhwani and Longini measured the duration and amplitude of inspiratory and expiratory phases and calculated the expiratory time/inspiratory

time (E/I) ratio. They stated that deviation from a numerical value of 1.2 for the E/I ratio would indicate an abnormal breathing pattern. The patients with CAO exhibited larger E/I ratios than normals. The impedance system underestimated E/I ratios as compared to spirometric measurements because breathing cycles as recorded by the impedance system showed a shorter expiratory phase and a longer inspiratory phase. They also found the site of electrode placement was of paramount importance to monitoring respiration accurately.

Ashutosh and associates (1974) used both the impedance pneumograph system and magnetometer method (see below) to monitor Vt in normal subjects and patients with CAO in the supine position. Both systems were comparable in their ability to record ventilation if the subject's position did not change. However, they both became inaccurate as measuring devices when the head of the bed was elevated or when subjects turned onto their sides. The authors stated that even in a stable supine position the results of both systems in patients with CAO were less accurate than those in the normal group. However there was large scatter in their data and no statistically significant difference was reported.

Magnetometers, which are electromagnetic sensors, have been employed to obtain Vt measurements from movements of the chest wall and abdomen. A set of magnetic coils are placed opposite each other on the anterior and posterior aspects of the chest wall and abdomen. An alternating current sent to the exciter coils produces a magnetic field and induces a voltage in the receiver coils which is inversely related to the distance between the coils. This voltage signal is calibrated with the use of a spirometer to result in a volume equivalent to the voltage signal. The relative amplification of the chest and abdominal signals is vital to ensure that the total signal represents Vt over a wide range of breathing

patterns. This has been accomplished by use of the isovolume maneuver (Konno and Mead,1967) by a linear equation method (Gilbert et al,1971) and by computer analysis of breathing cycles (Stagg et al,1978).

Konno and Mead (1967), considered that the chest wall had two degrees of freedom of movement, the volume change of the ribcage accounting for one, and the volume change of the abdomen for the second. They demonstrated that the volume displacements of the ribcage and abdomen were linearly related to their antero-posterior diameters as measured by magnetometers in the standing position, and the relationship was slightly curvilinear in supine. The output from the abdomen and ribcage were summed and their gains were adjusted so that at a constant lung volume, the summed output remained constant. This was checked by having each subject with his airway closed voluntarily shift fixed volumes back and forth between the ribcage and abdomen (isovolume maneuver). They found that the abdomen contributed more to Vt in supine than in standing and suggested that the more caudal direction of the central portion of the diaphragm in supine favours a greater contribution of it to abdominal displacement. However, these relationships were derived on normal subjects experienced in respiratory techniques and who had to perform isovolume maneuvers.

Mead et al (1967), studied 5 normal subjects in the upright posture with magnetometers. They compared the Vt recorded with magnetometers to that recorded when subjects breathed into a spirometer, and found comparable results for volume estimation between both techniques. The results were maintained not only for quiet breathing but also for carbon dioxide rebreathing experiments.

Gilbert et al (1971) also used magnetometers as did previous investigators to obtain Vt measurements. However, they did not employ an isovolume maneuver to calibrate the system. Instead, they had subjects take one breath primarily using the abdomen, and one primarily using the ribcage. Three signals were recorded during those breaths, the chest, abdominal and spirometer signal. Each breath was then expressed as a linear equation with two unknowns, the scaling factors for the ribcage and abdomen. This method necessitated two quantitatively different breaths to solve the equations. Gilbert and coworkers found this technique very time consuming and altered the method of calibration. They recorded abdominal, ribcage and spirometer signals on an X-Y plotter and the resulting signal formed a closed loop. The abdominal signal gain was then altered until the signal was superimposed in the ribcage signal. The scaling factors were then optimally adjusted to accurately reflect the volume measured. This alternate method resulted in a linear relationship between the spirometer signal and the magnetometer signal and the standard error of estimate ranged from 33.4 - 93.7 ml. They studied 17 normal subjects at rest and rebreathing various percentages of CO2 via a mouthpiece or Venturi mask. Values for Vt, f, and $\dot{V}e$ were determined from magnetometer measurements. The $\dot{V}e$ versus Vt relationship was found to be curvilinear. No relationship between $\dot{V}e$ and f could be established. Vt and $\dot{V}e$ were greater in all subjects rebreathing on a mouthpiece as compared to a Venturi mask.

Stagg and coworkers (1978) used magnetometers to record Vt and suggested a third method of calibration. They proposed a computer program to yield 30 to 40 paired observations for a single breath. Each breath could then be described by a matrix of 30-40 linear equations in

2 unknowns which were solved by the computer for the best fit estimates. They employed this method with 3 normal subjects at rest and in the supine position. The correlation coefficients for measurement of Vt ranged between 0.99 and 0.995 in the 3 subjects. The magnetometer estimates of Vt were within 10% of that obtained from the integrated airflow signal.

Ashutosh et al (1975) studied patients with CAO in the supine position using magnetometers to record ventilatory patterns. They found that 10 of their patients demonstrated asynchrony between ribcage and abdominal motion while 17 patients did not. In the asynchronous group the abdominal (ABD) and ribcage (RC) signal were out of phase. Most commonly the RC signal was synchronous with flow, the ABD signal showing inward abdominal motion at or near the end of inspiration and then outward abdominal movement in expiration. Mortality in patients demonstrating paradoxical motion was higher ($p < 0.02$) than in patients with more normal breathing patterns.

The major criticisms of using magnetometers are that they only look at movement in one direction and slight body movements result in loss of calibration. They have been effectively employed to investigate RC and ABD contributions to ventilation but have not proved to be satisfactory in longer term monitoring of breathing patterns.

Most recently, Milledge and Stott (1977) introduced respiratory inductive plethysmography (RIP) as a noninvasive method of measuring ventilation in man. They reported using an insulated wire coil applied around the thorax and abdomen from the upper chest to the pubis. The change in mean crossectional area of the coil during respiration resulted in a proportional change in the inductance of the coil. They stated that calibration of the transducer with a spirometer showed a linear

relationship within 2% over 75% of the vital capacity, and that calibration was accurate in supine or upright postures but was reduced by 20% in sitting. They found that movement produced large artifacts, and felt that this system could not be useful for ambulatory studies.

Watson (1980) described the technology of the RIP in more detail. He and coworkers (M.Sackner et al,1980) used 2 zig zag wire coils attached to an elastic bandage. One coil encircled the ribcage as close under the axilla as possible and the other coil was applied to the abdomen with the top of the coil situated at the level of the umbilicus. Both coils were connected to a small oscillator module which excited the coils at a frequency of 300 KHz and had an output frequency of $\pm$ 20 KHz. The frequencies of the oscillations in the coils were altered by changes in the inductance of the coils. The inductance of the coils was, in turn, altered by chest wall movements during respiration and the movement is a function of volume. One of the suggested advantages of the RIP over other methods is that it measures crossectional area, not circumference as do strain gauges, or anterio-posterior diameters as do magnetometers. Measurement of cross-sectional area was thought more likely to reflect volume in situations involving change of shape with volume change. This approach has been used by a number of groups.

It has been stated that the output of the RIP transducers is proportional to the volume within the coils, in that it measures an infinite number of cross sections over the height of the coil,(Watson,1980). It is assumed that the area within the coils positioned around the ribcage (RC) and abdomen (ABD) reflects proportionately all of the changes occurring in each region. Watson (1980) described the model by the following equation:

$$Vt = X(RC) + Y(ABD)$$

= total volume at the mouth as measured by a spirometer or an integrated pneumotachograph. RC = signal representing displacement of the ribcage. ABD = signal representing diplacement of the abdomen. X & Y = gain factors for the ribcage and abdomen (2 unknowns).

The gain factors can be solved by having the subject perform an isovolume maneuver (Konno & Mead,1967), or by solving 2 simultaneous equations involving the 2 unknowns (Watson 1980, M. Sackner et al,1980). With the latter method, volume, RC, and ABD signals are collected simultaneously in both the standing and supine positions to provide a wide variation in the contribution of both RC and ABD signals. The variation is necessary for the mathematical resolution of the equations. This approach assumes that the RC and ABD calibration factors do not change with changes in body position, and this may not always be true.

Watson (1980) stated that only one 'representative breath' had to be measured in each position for calibration of the gains. Only the middle 33-50% of the inspiratory and expiratory phases of each breath was used because Watson (1980) stated that recording points at the end of inspiration and expiration introduced large errors. In both positions small increments in spirometrically measured volume were compared to simultaneous RC and ABD signals, and the gains computed in the mid tidal volume range. The gains were meaned and their standard deviation (SD) and standard error of estimate (SEE) computed. Calibration was considered acceptable if the SD was between 10-15% and the SEE was $< 5\%$. Watson added that the RIP output accurately reflected the volume measured with a spirometer to within 5% in all positions in 90% of subjects.

J.D. Sackner et al (1980a) used the RIP to measure ventilation in subjects during exercise. They found that "90.9% of 535 RIP values for the bicycle and 86.9% of the 646 values for the treadmill deviated less than 20% from the spirometric values".

M. Sackner's group [Cohn et al (1982)] investigated the use of the RIP in smokers and nonsmokers in 7 different body positions. They stated that 88% of the means of the Vt measured by RIP in all positions fell within 10% of the values measured by spirometry.

Duffty et al (1981) investigated the accuracy of the RIP for measuring ventilation in infants. They were unable to calibrate the RIP using the 2 position technique described by Watson (1980). Therefore, they used the variation in breathing pattern between rapid eye movement (REM) sleep and quiet sleep to provide the difference required to solve for the RC and ABD scaling factors. They used 3 breaths from each sleep state in determining the gains. They found that the important aspect in calibration was to have a greater than 50% change in amplitude of the RIP signals between the 2 sleep states used to calculate the scaling factors. Using this criteria they were able to achieve acceptable calibration in infants 90% of the time. In 11 of the 14 infants during quiet sleep, the correlation coefficient (r) comparing Vt measured with RIP to Vt derived from a pneumotachygraph was > .83. Dolfin, Duffty et al (1982) further compared calibration methods using two sleep states in infants and found that turning the infant significantly changed the gain factors, and concluded that one must calibrate the system with the infant in the position in which the study is to be conducted.

Tabachnik and coworkers (1981) also used RIP to measure ventilation in 20 normal children. They calibrated the RIP using the 2 position

technique described by J.D.Sackner et al (1980a), and then used linear regression analysis to compare the RIP derived Vt to the pneumotachygraph derived Vt, finding a mean correlation coefficient of .962 in the seated position.

Chadha et al (1982) compared four methods of calibrating the RIP: the isovolume maneuver, the simultaneous equation method (2 position technique), the method Stagg et al (1978) used to calibrate magnetometers, and the least squares method, a modification of the 2 position technqiue. They tested the methods on 10 normal subjects. Based on their results, they suggested that the least squares method was the most accurate means of calibrating the RIP. This method requires the use of 2 positions in calibrating the RIP, but makes the computations of the scaling coefficients for the RC and ABD easier.

To date noninvasive techniques have accomplished little except to state that they can be employed with varying limitations to determine Vt. This is most likely due to the limitations imposed by the measuring devices themselves, as well as the limitations of the current methods of calibration. The RIP, although theoretically a better noninvasive method of measuring ventilation, also has not been adequately verified for use in determining the timing components of a breathing cycle in normals or in patients with respiratory disease.

IV METHODOLOGY

We used the RIP because it appeared to be the best non-invasive technique, and we developed a more stable calibration method which enabled us to measure breathing for a longer period of time. The methodology of the RIP employs the following assumptions:

1) that the respiratory system behaves as if it had 2 degrees of freedom, that is, when a subject breathes, the volume moved at the mouth must equal the sum of the volume displacements of the ribcage (RC) and abdomen (ABD), (Konno and Mead, 1967).

2) That the RC and ABD are independent variables.

The RIP consists of 2 independent wire coils, one placed around the ribcage (RC) and the other around the abdomen (ABD). Changes in lung volume produce changes in cross-sectional area beneath the coils which produces a change in the inductance of the wires (Watson,1980). Volume changes in the ribcage and abdominal compartments during breathing alter the RC and ABD outputs. These outputs represent independent indices of lung volume which when summed equal the volume of air moved at the mouth (Konno and Mead, 1967). The purpose of collecting the RC and ABD signals in this study was to generate a spirogram for their summed contributions from which the characteristics of the respiratory cycle could be analyzed.

Before being able to do this, it was necessary to develop a calibration method for the RIP that could be used in a single position, and to validate the calibration in young normals, old normals and CAO subjects. Therefore, the calibration and verification methodology and results in these three populations will be presented before discussing

the application of this method to the analysis of breathing patterns in CAO subjects.

A Description of the Data Collection System (Figure 1)

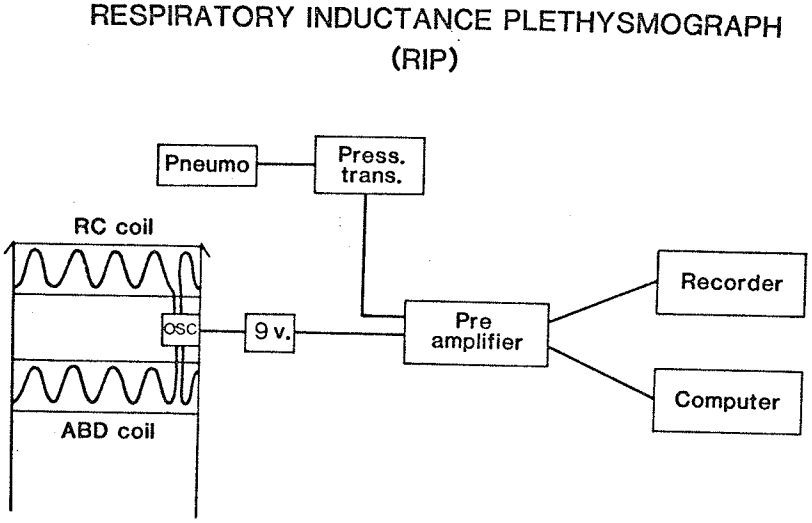


FIGURE 1: Data Collection System.Pneumo, Pneumotachygraph; Press. trans.,Pressure transducer; OSC., oscillator; RC coil,ribcage coil; ABD coil,abdominal coil.

The RC and ABD belts consist of coils of teflon coated 26 gauge multistranded wire sewn to six inch wide tensor bandages (Figure 2). The configuration of the wire as illustrated in Figure 2 enhances the signal from the belt. Preliminary trials with the RIP determined this configuration produced the best signal. The RC belt was positioned around the chest wall with the upper edge at the level of the axilla. The ABD belt was positioned around the abdomen with the lower level at the iliac crests. The leads from each coil were attached to an oscillator which was driven by a 9 volt battery and generated an electric current oscillating at 300 KHz (Respitrace, Ambulatory Monitorint Inc). The output signals from both belts were converted into a DC voltage

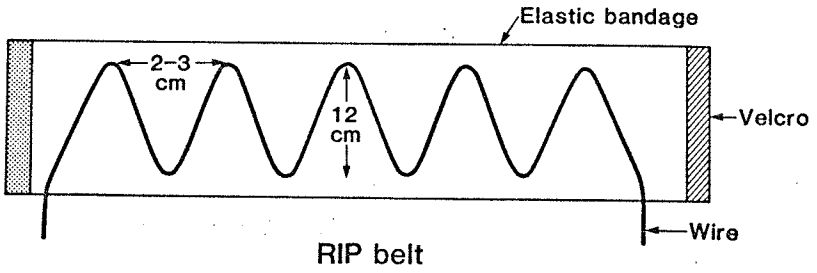


FIGURE 2: Respiratory inductance plethysmograph (RIP) coil.

and displayed on the console of a 32K digital microcomputer (Digital Equipment, MINC 11), and simultaneously on a polygraph (Grass Instruments, Inc., Model 78D).

The volume signals from the RC and ABD were calibrated against another validated volume source. In this study the integrated flow from a pneumotachygraph was employed. The computer integration of flow was verified and the method and results of verification are included in Appendix 1. The pneumotachygraph was calibrated prior to using it as a volume source for the RC and ABD signals. The method of calibration of the pneumotachygraph is outlined in Appendix 1. During calibration of the RC and ABD outputs, the flow signal was recorded in the same manner and at the same time as that described for the RC and ABD signals.

A computer processed the RC, ABD and flow signals simultaneously. It was interfaced with the monitoring devices via an analog to digital (A/D) converter. The computer featured an LSI 11.02 microprocessor, a video terminal with graphics capabilities (VT 105) and a mass storage medium (RX02, floppy disk) that provided 1 megabyte of storage. The computer sampled at a rate of 20 Hz in 10 second blocks. This high sample rate provided a large number of data points to be used in the analysis of the respiratory cycle. These points were first converted to digital values before being processed. Due to the large number of data points and the statistical computations required, blocks of greater than 10 seconds duration exceeded the storage and processing capabilities of the system. Therefore, consecutive 10 second blocks were sampled and analyzed throughout the calibration procedure.

B. Calibration and Verification of the RIP

1. IN YOUNG NORMAL SUBJECTS

1) Methods

We studied 8 normal subjects (Table 1) seated in a dental chair with back, arm and foot supports. The RIP was calibrated as described below. The stability of calibration (verification) was then determined at 20,40 and 60 minutes after the initial calibration.

i) Data Collection: The analogue signals from the RC and ABD (RIP) and from the pneumotachygraph were sampled at 20 Hz by the computer. During the calibration run and each verification run at 20,40 and 60 minutes post calibration, the subject wore noseclips and breathed through the pneumotachygraph. The data collection period for all runs was 1 minute. During calibration only inspiratory data was recorded.

TABLE I

CHARACTERISTICS OF YOUNG NORMAL SUBJECTS

SUBJECT	SEX	AGE	WEIGHT (kg)	HEIGHT (cm)	FVC (1.) % Pred.	$FEV_{1.0}$(1.) % Pred.
KL	M	40	68.0	180	94	96
ST	M	28	70.0	173	102	90
RC	M	25	70.5	178	99	107
CS	M	29	76.5	170	113	116
RN	M	35	71.0	178	105	107
ES	M	31	80.0	181	92	91
CD	F	21	57.0	169	92	97
VG	F	24	54.0	160	110	98

The computer identified the first positive point on the flow signal as the beginning of inspiration. Flow was digitally integrated to obtain volume (Appendix 1). The volume, RC and ABD signals were time synchronized. (Figure 3). The minimum and maximum points (peaks and troughs) on the RC and ABD signals were plotted on the console to identify baseline drift. If there was drift in any of the signals, calibration was repeated. For each point on the volume cycle, the corresponding points on the RC and ABD signals were obtained.

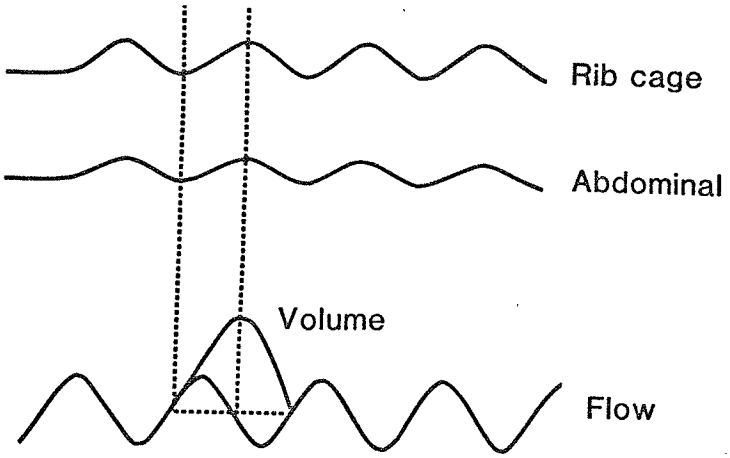


FIGURE 3: Time synchronization of signals. Flow is integrated to provide volume and for each point on theinspiratory limb of the volume signal, the corresponding point is selected on the ribcage and abdominal signals. The equation represents how volume is derived from the ribcage (RC) and abdominal (ABD) signals using multiple linear regression analysis. a is the intercept, b_1 the abdominal coefficient, b_2 the ribcage coefficient.

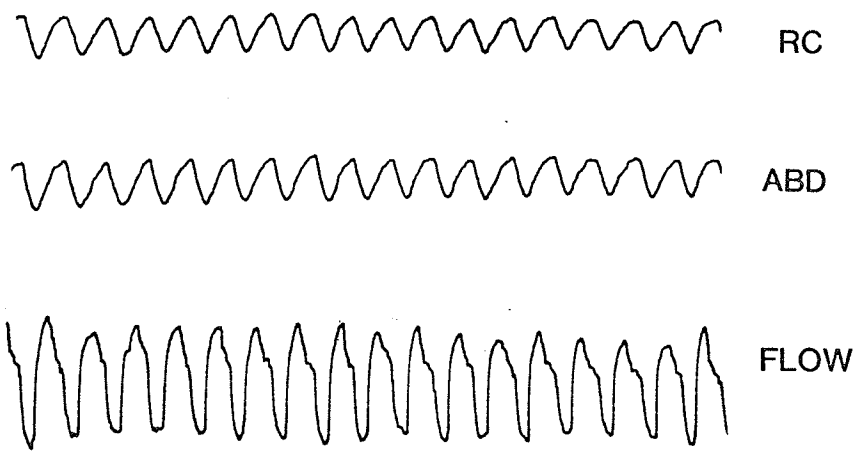
ii) Data Analysis: Multiple linear regression analysis was employed to predict the volume using the RC and ABD signals (Steele and Torrie, 1960). The equation for the relationship between volume, RC and ABD signals is as follows:

$$\text{Volume} = a + b_1 \text{RC} + b_2 \text{ABD}$$

a is the intercept

b_1 and b_2 are the regression coefficients for the RC and ABD, respectively.

The mean number of data points for a calibration or verification run was 266 ± 91 (SD). Because of the large sample size, data collection was divided into 10 second blocks for ease for statistical computation. The computer performed a multiple regression analysis on each 10 second block of inspiratory data to provide the intercept, regression coefficients, multiple correlation coefficient (r) and the standard error of the estimate (SEE) for that block. This was repeated cumulatively for six blocks of ten seconds during the data collection period. An example of the signals and the statistical analyses for a 1 minute calibration run is depicted in Figure 4. These computations allowed an inspiratory spirogram to be generated from the RIP data which was compared to that derived from the pneumotachygraph. To assist in this comparison, a graphics display on the console of the computer allowed a visual representation of the relationship between pneumotachygraph derived volume and the predicted RIP volume. Examples of the graphics display of this relationship are depicted in Figure 5 (CAO subject) and in Figure 6 (Control Subject). In these cases



MULTIPLE REGRESSION ANALYSIS

Intercept	RC Coefficient	ABD coefficient	r	SEE
0.01065	1.39651	1.12041	0.99891	0.00655
0.04193	1.26008	1.15607	0.99689	0.02443
0.04815	1.17147	1.23252	0.99610	0.02671
0.04753	0.94801	1.38882	0.99449	0.02542
0.04733	0.85121	1.46558	0.99464	0.02490
0.04670	1.12036	1.27531	0.99370	0.02455

FIGURE 4: RC(ribcage), ABD (abdominal) and flow signals for a 1 minute calibration. The computer calculated intercept, RC and ABD coefficients, r (correlation coefficient) and SEE (standard error of estimate) for each 10 second block are listed below the signals.

the relationships were fitted with a linear equation. As well, the computer provided a printout of the ABD, RC, RIP sum and pneumotachygraph derived volumes for each set of points sampled during all calibration and verification runs. The RIP was considered calibrated on the basis of the tightness of fit between the pneumotachygraph derived volume and the predicted volume from the RC and ABD signals using multiple regression analysis.

The slope, intercept, r and SEE were calculated for the relationship between the volumes derived from RIP and from the pneumotachygraph.

We also applied power, logarithmic and exponential transformations to the raw RIP data, to see if these non-linear models improved the goodness of fit.

If there was no significant drift in the RC, ABD and flow signals during calibration, it was possible to calibrate each subject on 1 run. If drift was present, it was usually in the pneumotachygraph signal, and the calibration run was repeated.

The same general procedure was repeated for each verification run. To determine the stability of the calibration with time, the verification data was analyzed using the statistics computed during the calibration run, that is, the equation used to define the relationship during the

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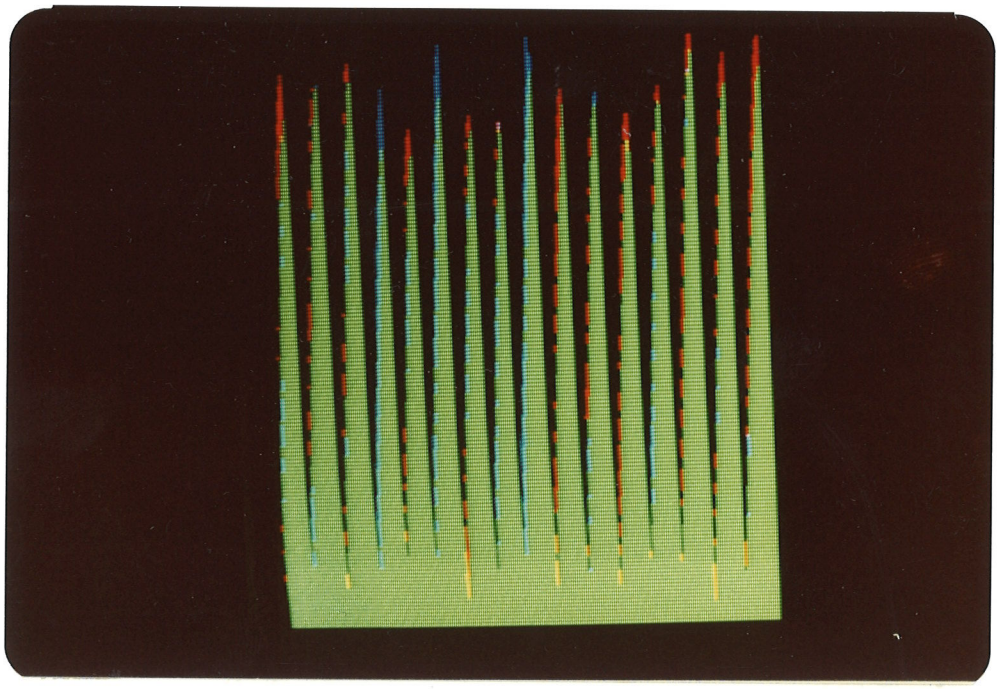

FIGURE 5: Graphics display of the relationship between instantaneous RIP volume and pneumotachygraph derived volume for 16 inspirations. Blue, pneumotachygraph derived volume; Red, RIP volume; Green, volume common to both pneumotachygraph and RIP volume for CAO subject.

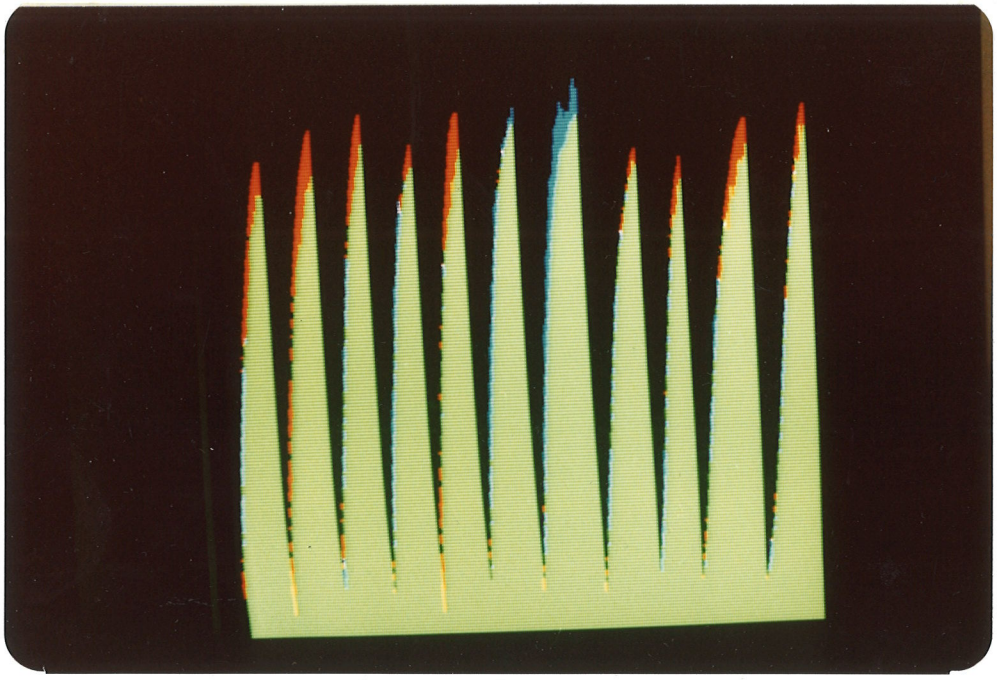

FIGURE: Graphics display of the relationship between RIP instantaneous volume and pneumotachygraph derived volume for 11 inspirations. Blue, pneumotachygraph derived volume; Red,RIP volume; Green, volume common to both pneumotachygraph and RIP volume for control subject.

initial calibration was used to analyze the data acquired during the verification runs 20,40 and 60 minutes after the calibration and compared to data acquired with the pneumotachygraph.

2) Results

When compared to the linear model, the power and logarithmic transformations only marginally improved the relationship of RIP and pneumotachygraph derived volume in two subjects. Therefore, the linear model was used in all data analyses. The results are summarized in Table 2, in terms of slope, intercept, correlation coefficient (r) and the standard error of the estimate (SEE). The SEE is a measure of the scatter in the data about the line of regression. 95% of all volume estimates will fall within 1.96 times the SEE (Steele and Torrie,1960). The SEE values listed in Table 2 represent volume in litres. As well, the slopes and intercepts determine how closely RIP predicted volume compares to the pneumotachygraph derived volume. The ideal relationship would have a slope of 1.00 and an intercept of 0.00. The values for the intercepts are in litres. There was no significant change with time in either the correlation coefficients, the SEE, the slopes or the intercepts. The verification data describing the relationship between RIP and pneumotachygraph derived volume was computed by applying the prediction equation achieved in RIP calibration to the data collected during the verification.

The mean tidal volumes measured with RIP and derived from the pneumotachygraph for the calibration and 60 minute verification run are included in Table 3. The RIP was able to measure Vt with < 10% error in all subjects during the one hour period except subject C.D. in whom the RIP volume overestimated the pneumotachygraph derived

TABLE 2

CALIBRATION AND VERIFICATION RESULTS IN YOUNG NORMALS

	CALIBRATION				VERIFICATION											
					20 min				40 min				60 min			
SUBJECT	r	SEE	SL	IN	r	SEE	SL	IN	r	SEE	SL	IN	r	SEE	SL	IN
KL	.994	.017	.995	.003	.996	.016	.942	-.013	.994	.016	.843	-.009	.995	.016	1.023	-.010
ST	.989	.024	1.008	.007	.993	.021	1.073	.031	.993	.025	1.050	-.024	.983	.023	1.039	.032
RC	.998	.026	.995	.002	.963	.023	1.004	-.011	.994	.022	1.076	.016	.982	:020	.962	.033
CS	.994	.023	.999	.001	.985	.022	1.018	.020	.987	.027	1.101	.006	.996	.028	1.088	.039
RN	.980	.020	1.040	-.001	.987	.016	1.065	.003	.988	.017	1.122	-.018	.989	.018	1.078	-.003
ES	.991	.022	1.002	-.000	.991	.020	.966	-.020	.981	.022	.960	.018	.995	.021	.893	.009
CD	.983	.015	1.009	-.008	.992	.015	.896	.012	.940	.018	.892	.036	.993	.015	.847	.015
VG	.993	.034	.987	.006	.991	.028	.918	-.026	.993	.030	1.069	-.010	.989	.029	.896	-.019
Mean	.990	.023	1.004	.001	.987	.020	.985	.001	.984	.022	1.014	.002	.990	.021	.978	.012

r is the correlation coefficient, SEE is the standard error of the estimate, SL is the slope,and IN is the intercept

TABLE 3

COMPARISON OF MEAN TIDAL VOLUMES MEASURED WITH RIP AND DERIVED FROM THE PNEUMOTACHYGRAPH RECORDINGS *

SUBJECT	CALIBRATION		VERIFICATION (60 Min)	
	PNEUMO	RIP	PNEUMO	RIP
KL	.939 ± .083	.915 ± .089	.888 ± .115	.857 ± .112
ST	1.265 ± .084	1.247 ± .131	1.168 ± .152	1.072 ± .110
RC	1.182 ± .144	1.200 ± .153	.993 ± .156	1.015 ± .171
CS	1.216 ± .172	1.182 ± .222	1.317 ± .094	1.186 ± .041
RN	.889 ± .117	.867 ± .126	.918 ± .067	.871 ± .076
ES	1.013 ± .068	.962 ± .080	.976 ± .041	1.044 ± .044
CD	.753 ± .077	.719 ± .061	.740 ± .056	.879 ± .064
VG	.834 ± .106	.826 ± .081	.681 ± .078	.600 ± .056

* Results are expressed in litres and are mean values ± S.D.

volume by 19%. There was no consistent change in any of the measurements with time.

Examples of the best and worst inspiratory spirograms for calibration and verification runs are depicted in Figures 7 and 8 respectively. Each inspiratory limb represents all the points from 3 randomly selected breaths from the calibration and the 60 minute verification in subject KL (Figure 7) and subject RN (Figure 8).

The largest error in estimation of volume occurred at the beginning of each breath. A regression line based on the data points for the breaths considered has been plotted. The r values and SEE for both subjects depicted in the spirograms are listed in Table 2. The differences between calibration and verification runs are small.

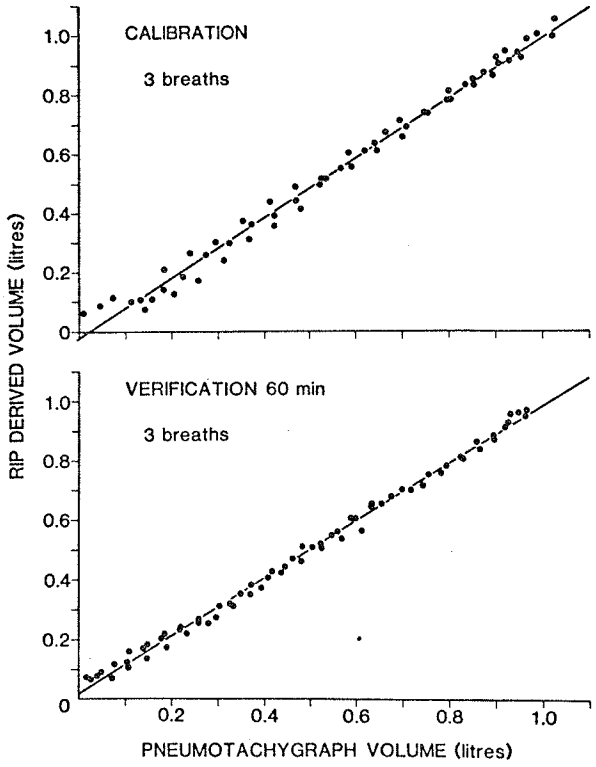

FIGURE 7: The relationship between RIP volume and pneumotachygraph derived volume for subject KL. Each plot represents all the points sampled in 3 randomly selected breaths from the calibration (above) and 60 minute verification (below). A regression line has been drawn through the data points.

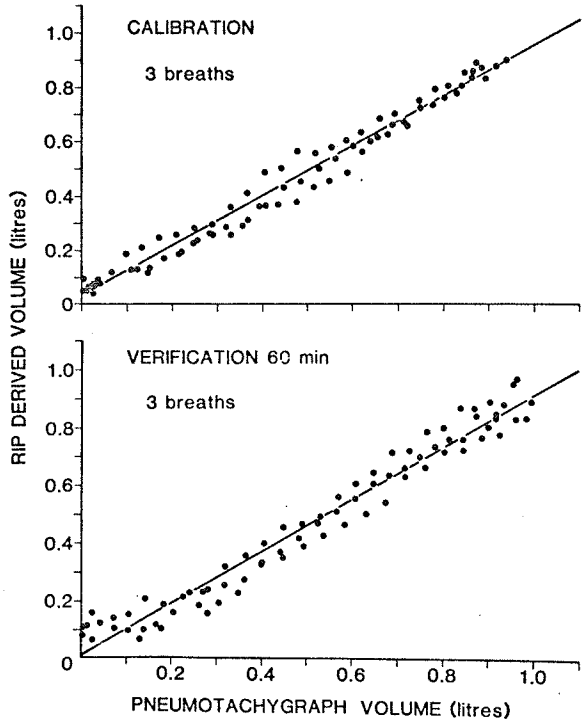

FIGURE 8: The relationship between RIP volume and pneumotachygraph derived volume for subject RN. Each plot represents all the points sampled in 3 randomly selected breaths from the calibration (above) and 60 minute verification (below). A regression line has been drawn through the data points.

2. IN PATIENTS WITH CAO AND IN AGE-MATCHED CONTROLS

Introduction

We intended to analyze breathing patterns using the RIP in patients with CAO and compare their results to an age and sex matched healthy control population. Therefore, it was necessary to ensure that the calibration procedure previously described for young normals was appropriate for patients with lung disease and for an older normal population.

1) Methods

We studied 12 patients with CAO and 8 age and sex matched controls. The characteristics of the 2 populations are depicted in Tables 4 and 5 respectively. The control subjects were in good general health with no history of cardiovascular, respiratory or any other medical condition. The CAO disease patients were selected randomly from patients previously involved in a multi-centre clinical trial (Division of Lung Diseases, National Heart, Lung and Blood Institute, 1978). All patients had resting PaO_2 > 55 mmHg and were not hypercapnic (Table 4). All subjects gave their informed consent, and the control subjects were paid for their participation.

i) Data Collection The study was the same as that described for the young normals, except that the verification of calibration was determined at 45 minutes after initial calibration.

ii) Data Analysis The data was analyzed as described for the young normals (page 29).

2) Results

The results for the CAO disease patients and controls are summarized in Tables 6 and 7 respectively. The best fit relationship

TABLE 4

CHARACTERISTICS OF CAO SUBJECTS

SUBJECT	AGE	WEIGHT kg	HEIGHT cm	FVC (1) % Pred.	$FEV_{1.0}$(1) % Pred.	PaO_2 mm Hg	$PaCO_2$ mm Hg
FP	63	71.0	173	93	48	80	28
EW	58	59.0	165	72	44	70	34
FdG	72	105.0	193	60	49	71	31
GP	57	46.0	173	67	45	70	38
JG	73	68.0	178	54	34	72	31
WL	67	72.0	183	59	27	66	37
EB	75	64.0	170	47	24	83	31
MS	67	74.0	175	49	22	62	37
EH	70	68.0	174	42	22	75	46
AB	66	65.0	197	19	15	74	39
AK	72	76.0	165	49	19	56	47
FT	58	80.0	169	33	18	60	42

TABLE 5

CHARACTERISTICS OF CONTROLS

SUBJECT	AGE	WEIGHT kg	HEIGHT cm	FVC (1) % Pred.	$FEV_{1.0}$(1) % Pred.
SH	72	72.0	176	94	105
JW	50	74.0	173	112	98
BS	58	96.0	186	98	95
JJ	65	64.0	158	97	91
JK	67	67.0	175	98	109
CW	61	73.0	179	117	112
EW	63	80.0	180	96	102
NT	63	87.0	183	99	101

was based on the equation that provided the best slope, intercept, r and SEE. The logarithmic transformation only marginally improved the relationship of RIP volume to pneumotachygraph derived volume in one control and two CAO subjects. This was consistent with the results in the young normal subjects. Therefore, all results were computed using the linear transformation of the data.

In most subjects the r,SEE, slope and intercept did not change appreciably with time. Subject FdG demonstrated the worst verification in the CAO group (Table 6) and subject BS was the worst in the age matched controls (Table 7). Subject BS had cardiogenic oscillations in his flow signal which introduced errors in volume calculations. This probably contributed to the discrepancy in slope between his calibration and verification runs.

C. ANALYSIS OF BREATHING PATTERNS IN PATIENTS WITH CAO AND CONTROLS

1) Methods

The same subjects described in Section B (Calibration and Verification of the RIP in patients with CAO and controls) were used for collecting data for the analysis of breathing.

i) Data Collection Following calibration of the RIP as described (page 27), the subjects remained seated in the dental chair for forty-five minutes of data collection. The RIP, RC and ABD signals were sampled at 20 Hz by the computer, and the signals were simultaneously recorded on the polygraph. Heart rate was monitored with three unipolar electrocardiogram (EKG) leads attached to the left anterior chest wall. Heart rate was used as an indication of steady state in the subjects, and as an indicator of movement. Body movements introduced artifacts in the EKG signals as well as baseline shifts of the RIP

TABLE 6

CALIBRATION AND VERIFICATION RESULTS IN CAO DISEASE PATIENTS

	CALIBRATION				VERIFICATION				TRANS-
SUBJECT	r	SEE	SLOPE	INTERCEPT	r	SEE	SLOPE	INTERCEPT	FORMATION
FP	.996	.024	1.012	.001	.979	.029	.925	.078	LINEAR
EW	.996	.023	.988	.010	.961	.024	.831	-.009	LINEAR
FdG	.989	.044	1.009	-.015	.931	.054	.860	.162	LINEAR
GP	.988	.013	.960	.030	.989	.014	.962	.058	LINEAR
JG	.994	.026	1.003	-.004	.989	.024	.941	.080	LINEAR
WL	.995	.026	.982	.013	.990	.023	.920	.040	LINEAR
EB	.984	.025	1.016	-.016	.973	.019	1.093	.163	LINEAR
MS	.997	.030	.997	.010	.993	.039	.983	-.021	LINEAR
EH	.984	.022	1.015	-.009	.982	.025	1.048	-.037	LINEAR
AB	.954	.024	1.061	-.059	.968	.047	1.059	-.080	LINEAR
AK	.987	.016	1.003	-.002	.993	.030	1.077	-.058	LINEAR
FT	.990	.016	1.000	.000	.991	.019	.998	.030	LINEAR
Means	.988	.024	1.004	.003	.978	.029	.975	.034	

TABLE 7

CALIBRATION AND VERIFICATION RESULTS IN AGE MATCHED CONTROLS

	CALIBRATION				VERIFICATION				TRANS-
SUBJECT	r	SEE	SLOPE	INTERCEPT	r	SEE	SLOPE	INTERCEPT	FORMATION
SH	.989	.015	1.001	-.008	.971	.011	1.001	.057	LINEAR
JW	.997	.030	.986	.022	.998	.032	1.080	.074	LINEAR
BS	.997	.034	.988	.016	.996	.029	.795	.014	LINEAR
JJ	.995	.025	.991	.009	.993	.022	1.109	-.044	LINEAR
JK	.995	.024	.992	.007	.988	.019	.865	.164	LINEAR
CW	.997	.026	1.007	.003	.996	.025	1.022	-.000	LINEAR
EW	.995	.028	.981	.015	.991	.041	1.005	.031	LINEAR
NT	.996	.053	1.010	-.009	.987	.026	.960	.059	LINEAR
Means	.995	.029	.995	.007	.990	.026	.980	.044	

signal. Segments in which there were EKG and corresponding RIP artifacts were deleted from the records prior to analysis.

Subjects were instructed to sit still and to avoid arm movements or crossing their legs, both of which were found to introduce artifacts in the RIP signals. Subjects watched a videotaped movie while their breathing was being monitored to distract them from the monitoring devices.

ii) Data Analysis The best fit multiple linear regression equation from calibration was used to reconstruct a spirogram from the RIP signals. The spirogram was processed by the computer to identify the peak and trough of each breath. The peak corresponded to the end of inspiration and the tough to the beginning of the next inspiration. Examples of the ability of the peak processing routine to accurately identify the required points on the spirogram are illustrated in Figure 9 (CAO subjects) and Figures 10 and 11 (control subjects).

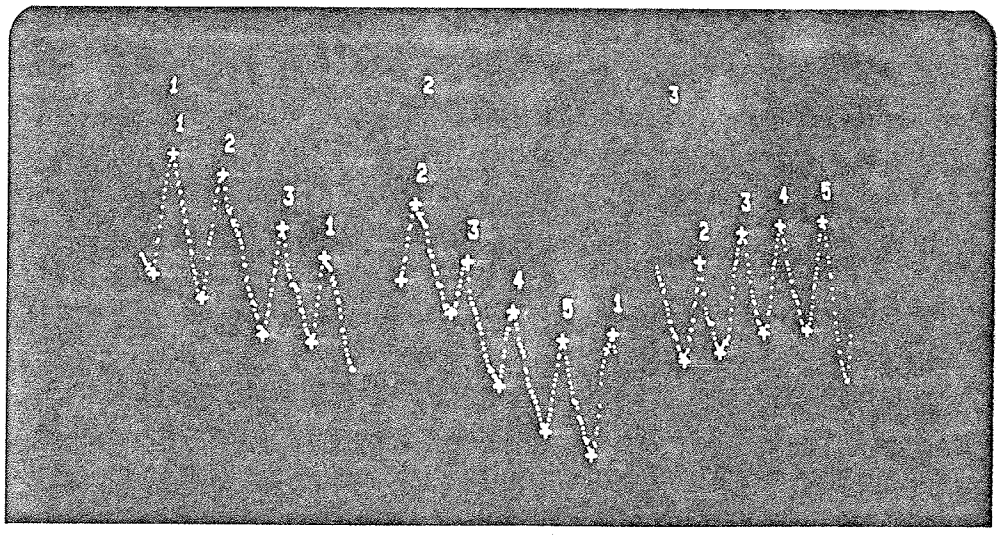

FIGURE 9 : Graphics display of peak processing in a CAO subject. All breaths from 3 consecutive 10 second blocks are displayed and each breath in each block is numbered. The x's mark the points that were identified as the peak of inspiration and the end of expiration.

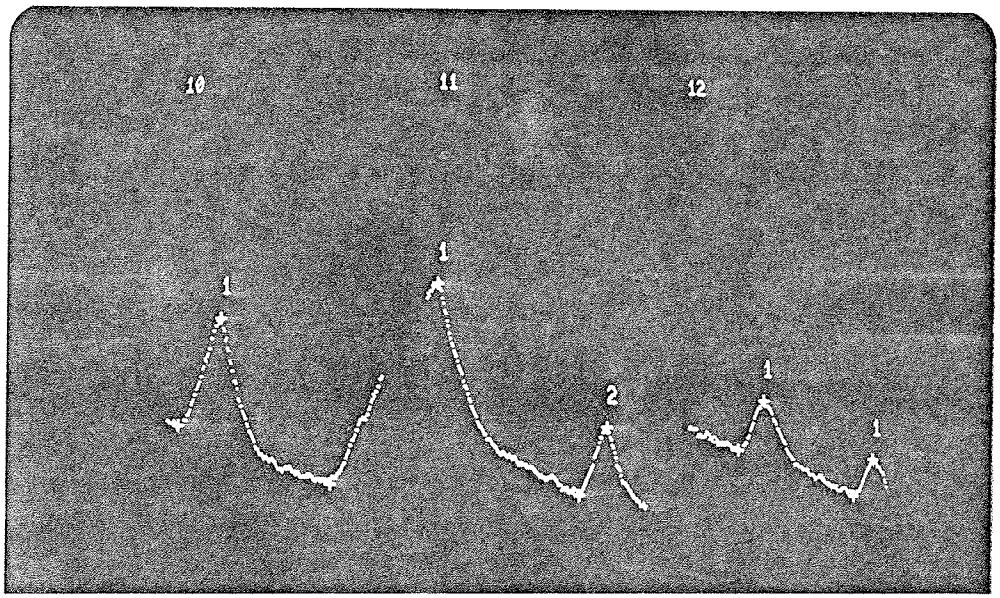

FIGURE 10: Graphics display of peak processing in a control subject. All breaths from 3 consecutive 10 second blocks are displayed and each breath in each block is numbered. The x's mark the points that were identified as the peak of inspiration and the end of expiration.

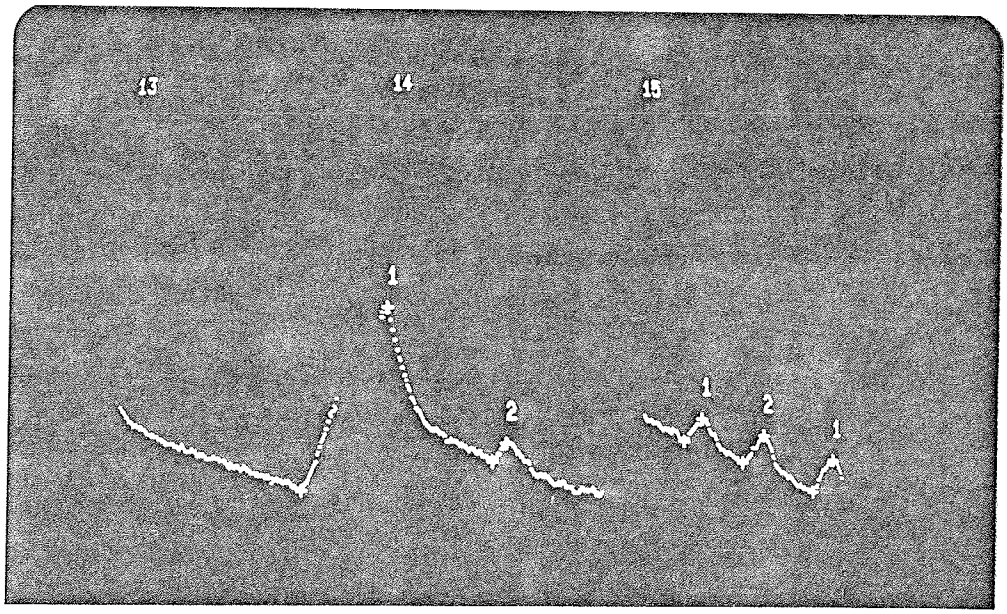

FIGURE 11: Graphics display of peak processing in a control subject. All breaths from 3 consecutive 10 second blocks are displayed and each breath in each block is numbered. The x's mark the points that were identified as the peak of inspiration and the end of expiration.

As demonstrated in these figures, the program was able to identify large and small breaths of varying frequencies, and was able to deal with apneic periods. The peak processing program allowed series of breaths to be observed on the console in consecutive 10 second blocks as the peaks and troughs were being plotted. The signal could be amplified to ensure accuracy. As well, the point to point differences for the establishment of a trend (positive or negative) could be altered. This feature allowed signals with a noisy baseline to be accurately processed. An important feature of the peak processing routine was the practice of setting the drift offset factor. This converted values around zero to continually decrementing numbers and allowed the accurate assessment of prolonged apneic periods, and accounts for the slope in the baseline as illustrated in Figures 9 to 11. The mean Ti, Te and Vt of 38 consecutive breaths were compared in a CAO subject with and without the drift factor to ensure that its use did not alter these variables. There was $< 3\%$ error in Ti, Te and Vt with the use of a drift factor. The computer was programmed to store the value for each peak (end of inspiration) and trough (end of expiration) and these values were then used to determine the timing components of the respiratory cycle as illustrated in Figure 12. Inspiratory time (Ti), expiratory time (Te) and tidal volume (Vt) were directly measured and the remaining components were derived from this information.

The number of breaths analyzed per subject is included in Table 8. The average number of breaths for all subjects was 702 ± 213 (SD). CAO subject AB had the smallest number of breaths for this group due to the deletion of numerous segments because of movement artifacts. From these breaths the following time components were computed:

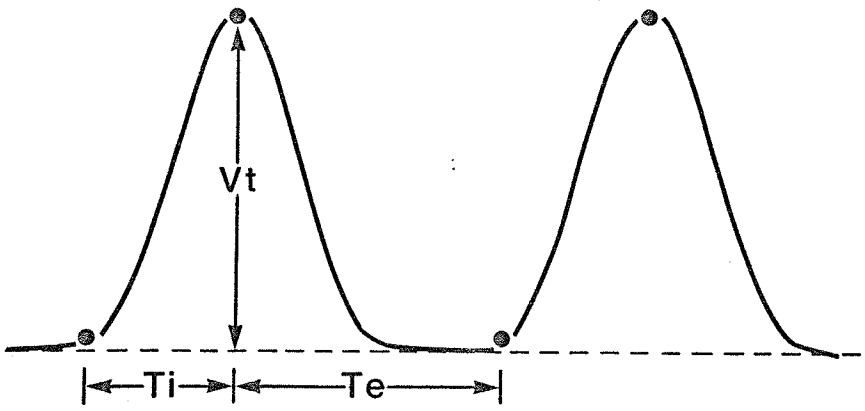

FIGURE 12: Timing components measured from the spirogram. Vt is tidal volume, Ti is inspiratory time, and Te is expiratory time.

Inspiratory time (Ti)

Expiratory time (Te)

Cycle duration (Ttot)

Tidal volume (Vt)

Breathing frequency (f)

Minute ventilation ($\dot{V}e$)

Mean inspiratory flow (Vt/Ti)

Inspiratory timing (Ti/Ttot)

For each component the mean, median, mode, standard deviation (SD) and coefficient of variation were calculated. Bartlett's T-test was used to determine if there was a significant difference in the variances of the data between the CAO and the control groups. No significant differences in variance were found for any component of

TABLE 8

NUMBER OF BREATHS ANALYZED

CAO SUBJECTS	NO. OF BREATHS	CONTROL SUBJECTS	NO. OF BREATHS
FP	813	SH	794
EW	721	JW	614
FdG	479	BS	620
GP	1085	JJ	368
JG	723	JK	631
WL	556	CW	621
EB	678	EW	643
MS	736	NT	600
EH	1181		$\bar{X}$ 611
AB	344		
AK	1034		
FT	779		
	$\bar{X}$ 761		

breathing measured. The mean values of all the timing components were compared between the two groups using both the Student-T-test and Welch's T-test for samples with unequal variances. As there were negligible differences in the levels of significance between the two tests, and Bartlett's T-test gave insignificant results, all results were expressed using the Student-T-test levels of significance.

The degree of variability of each component was assessed by comparing the coefficients of variation (C.V.) between the CAO and control groups. As well, histograms of Vt,Ti and Te were plotted for all subjects. The relationship between Vt and Ti, Vt and Ttot, Vt and f, Vt and $\dot{V}e$,f and $\dot{V}e$, Vt and Te, Ti and $\dot{V}e$, Ttot and $\dot{V}e$, and between Ti and Te were examined. The data was plotted for each of the above comparisons for each subject and the correlation coefficients, slope and intercepts of each was calculated. The correlation coefficients for the CAO group and for the control group were then compared.

The number of sighs in the 45 minute collection period was also compared between the 2 groups. A sigh was defined as a breath greater then 3 times the mean tidal volume for that subject (Bendixen et al,1964). Because the number of breaths analyzed varied between subjects, sighs were expressed as the number of sighs per one hundred breaths.

To determine if there was any correlation between the severity of disease and any of the respiratory parameters measured, the $FEV_{1.0}$ of all CAO subjects was correlated with each timing component and ratio.

The timing components were also measured from the polygraph during the one minute calibration when the subject was on the mouthpiece and wearing noseclips. The means of these parameters were then compared to the mean values recorded using the RIP for both the CAO and control

groups to allow a comparison between invasive (mouthpiece) breathing and non-invasive (RIP) measurements of respiration. Welch's T-test was used to test for significant differences.

2) Results

Tables 9a and 9b include the mean values of all components of breathing, and the coefficients of variation (C.V.) for both the subjects with CAO and the controls. The means of each component for the group, and the mean coefficient of variation for each variable are also included. $\dot{V}e$ in CAO patients was greater than in the controls. This was due to an increased breathing frequency (f).Both Ti and Te were shorter in CAO, while Vt was the same in both groups. Thus Vt/Ti was also greater in CAO. Because Ti and Te were shortened by similar amounts in CAO, Ti/Ttot did not differ from the controls. Several of the above measurements were less variable (as assessed by C.V.) in CAO: Ti, Vt, Ti/Ttot, and $\dot{V}e$. In both groups Ti/Ttot was the least variable. Vt was the most variable in controls, while in CAO, Vt was not as variable. In both groups Ti/Ttot was the least variable, while Te varied a great deal in both CAO and controls. The reduced variability in timing and Vt in CAO resulted in less variation in $\dot{V}e$.

The differences in mean Ti and Te are further demonstrated by the histograms of these two components for the CAO group (Figures 13 and 14) and for the controls (Figures 15 and 16). As a large number of breaths were analyzed in each subject, the frequency of breaths occurring in histogram cells around the mean was very high. Therefore, when a frequency distribution was plotted, cells with one

TABLE 9a

MEAN VALUES OF Ti, Te, Vt and Ttot

SUBJECTS	Ti (sec)		Te (sec)		Vt (Litres)		Ttot (sec)	
	$\bar{x}$	c.v.	$\bar{x}$	c.v.	$\bar{x}$	c.v.	$\bar{x}$	c.v.
CONTROLS								
SH	1.411	.148	1.879	.254	.402	.224	3.289	.164
JW	1.424	.172	2.793	.242	.630	.279	4.218	.170
BS	1.222	.194	2.402	.213	.682	.294	3.624	.148
JJ	1.757	.233	3.933	.236	.646	.247	5.690	.204
JK	1.014	.232	2.354	.297	.470	.438	3.368	.234
CW	1.276	.319	2.884	.457	.430	.489	4.159	.365
EW	1.249	.318	2.512	.519	.513	.454	3.761	.408
NT	1.398	.216	2.584	.332	.651	.269	3.982	.226
$\bar{x}$	1.344	.229	2.668	.319	.553	.337	4.011	.240
CAO								
FP	1.138	.156	1.902	.282	.584	.264	3.040	.191
EW	.945	.182	1.681	.408	.441	.331	2.626	.273
FdG	1.345	.239	2.676	.301	.928	.284	4.021	.237
GP	.784	.131	1.266	.386	.348	.233	2.050	.246
JG	1.230	.174	2.276	.361	.626	.294	3.506	.260
WL	1.712	.174	2.841	.382	.745	.273	4.552	.266
EB	1.042	.164	2.084	.185	.517	.232	3.126	.138
MS	.942	.247	1.669	.337	.439	.339	2.611	.257
EH	.784	.135	1.326	.368	.459	.182	2.110	.243
AB	.920	.209	2.118	.279	.643	.233	3.038	.210
AK	.839	.159	1.668	.331	.415	.186	2.507	.229
FT	.965	.162	1.967	.348	.501	.190	2.932	.254
$\bar{x}$	1.054	.178	1.956	.331	.554	.253	3.010	.234
$p <$	0.01	0.025	0.005	N.S.	N.S.	0.025	0.005	N.S.

TABLE 9b

MEAN VALUES OF Ti/Ttot, Vt/Ti, f, $\dot{V}e$

SUBJECTS	Ti/Ttot		Vt/Ti (L/Sec)		f (min)		$\dot{V}e$ (L/min)	
CONTROLS	$\bar{x}$	c.v.	$\bar{x}$	c.v.	$\bar{x}$	c.v.	$\bar{x}$	c.v.
SH	.433	.131	.287	.158	18.6	.12	7.392	.164
JW	.342	.175	.446	.266	14.5	.13	9.102	.315
BS	.340	.187	.568	.231	16.8	.12	11.432	.295
JJ	.315	.259	.371	.155	11.2	.36	6.965	.276
JK	.306	.202	.462	.249	18.5	.19	8.476	.333
CW	.318	.243	.328	.239	15.8	.27	6.207	.321
EW	.345	.209	.406	.205	17.6	.29	8.387	.286
NT	.360	.226	.478	.257	15.7	.26	10.043	.247
$\bar{x}$	.345	.204	.418	.220	16.1	.22	8.50	.280
CAO								
FP	.379	.139	.514	.214	20.2	.12	11.713	.255
EW	.368	.174	.469	.268	23.7	.16	10.186	.264
FdG	.342	.202	.697	.245	16.0	.40	14.102	.275
GP	.389	.130	.447	.186	30.0	.12	10.382	.203
JG	.357	.132	.508	.193	17.6	.13	10.810	.199
WL	.384	.166	.433	.164	13.7	.16	9.963	.235
EB	.335	.145	.501	.207	19.5	.14	9.936	.190
MS	.365	.166	.470	.228	24.1	.24	10.148	.239
EH	.376	.115	.589	.153	29.0	.10	13.262	.179
AB	.312	.242	.715	.250	20.6	.22	13.093	.272
AK	.339	.143	.501	.173	24.5	.12	10.073	.155
FT	.336	.155	.523	.162	21.2	.16	10.475	.191
$\bar{x}$	.357	.159	.531	.204	21.7	.17	11.20	.221
p <	N.S.	0.01	0.01	N.S.	0.005	N.S.	0.001	0.01

or two observations become obscured. To be able to see the cells with one or two breaths in them and to be able to compare histograms between subjects, the number of observations in each histogram cell was transformed by taking the square root of the observations in that cell and dividing it by the number of breaths. Taking the square root allowed better visualization of the histogram cells containing a small number of breaths and dividing by the total number of breaths allowed comparison of histograms between subjects. The lack of variability in Vt in spite of the same mean Vt was also apparent from comparing histograms of Vt between the CAO group (Figure 17) and the controls (Figure 18).

The correlation coefficients, slope and intercepts for the relationships between Vt and Ti, Vt and Ttot, Vt and f, Vt and $\dot{V}e$, f and $\dot{V}e$, Ti and Te, Ti and $\dot{V}e$, Ttot and $\dot{V}e$ and Vt and Te for all subjects are included in tables 10a,10b,10c,10d, and 10e. Because of the larger number of breaths analyzed, all correlation coefficients were significant, except those with the asterisks(Tables 10a,10b,10c,10d, and 10e). There were no significant differences in the correlation coefficients for any of the relationships between the 2 groups. Therefore, CAO subjects and normals vary their breathing by the same means. This suggests that the mechanisms of control of breathing may be the same. The strongest correlation was found between Vt and Ti, and Vt and Ti correlated better than Vt and Ttot for all subjects except one CAO subject EB in which the correlation between Vt and Ttot was slightly better than the correlation between Vt and Ti.

Vt and f were negatively correlated in all subjects.

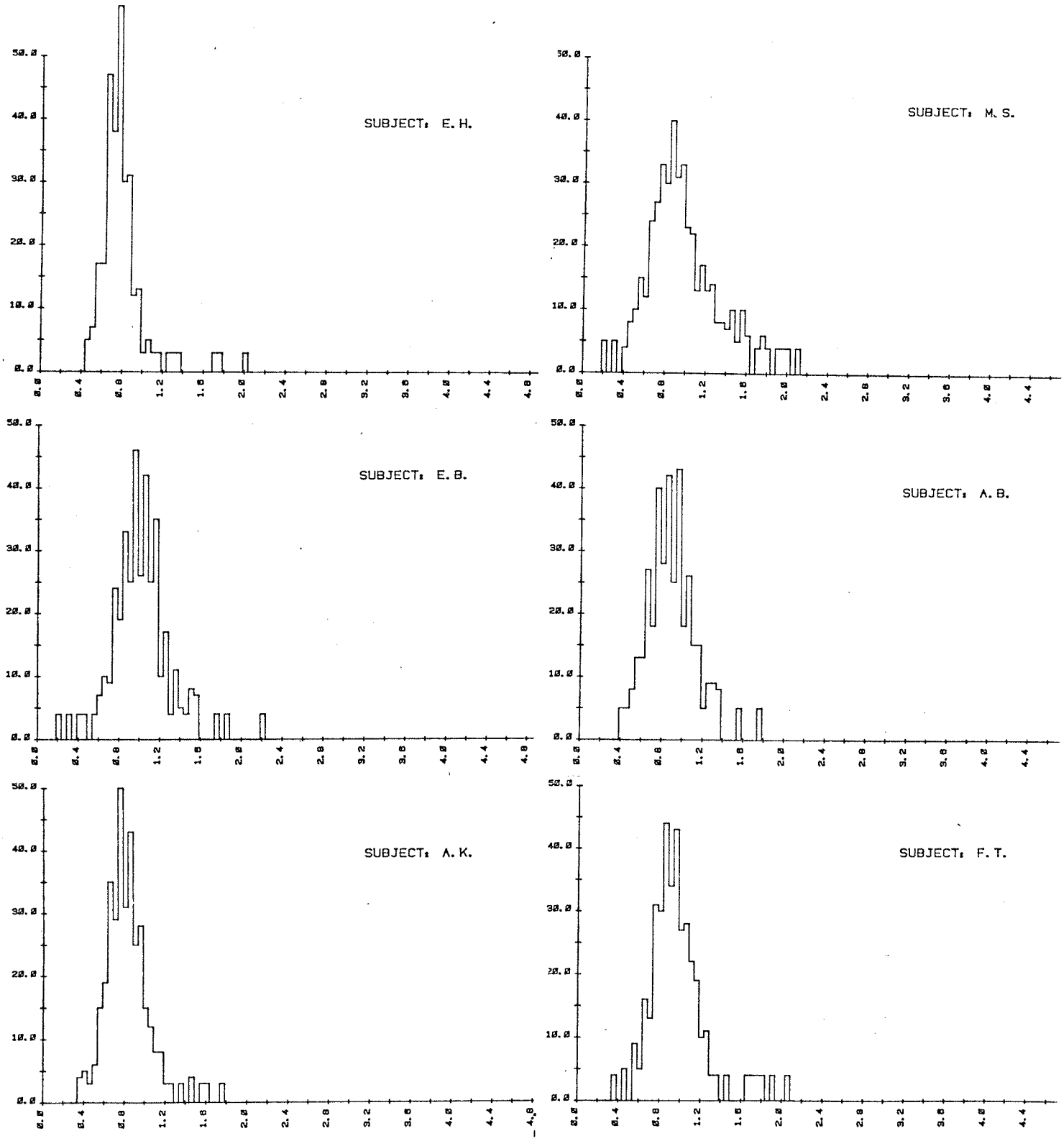

FIGURE 13a: Frequency distribution of inspiratory timing of breaths in CAO subjects. Number of observations is on the ordinate and is the square root of the number of observations divided by the total number of breaths. (see text for details)

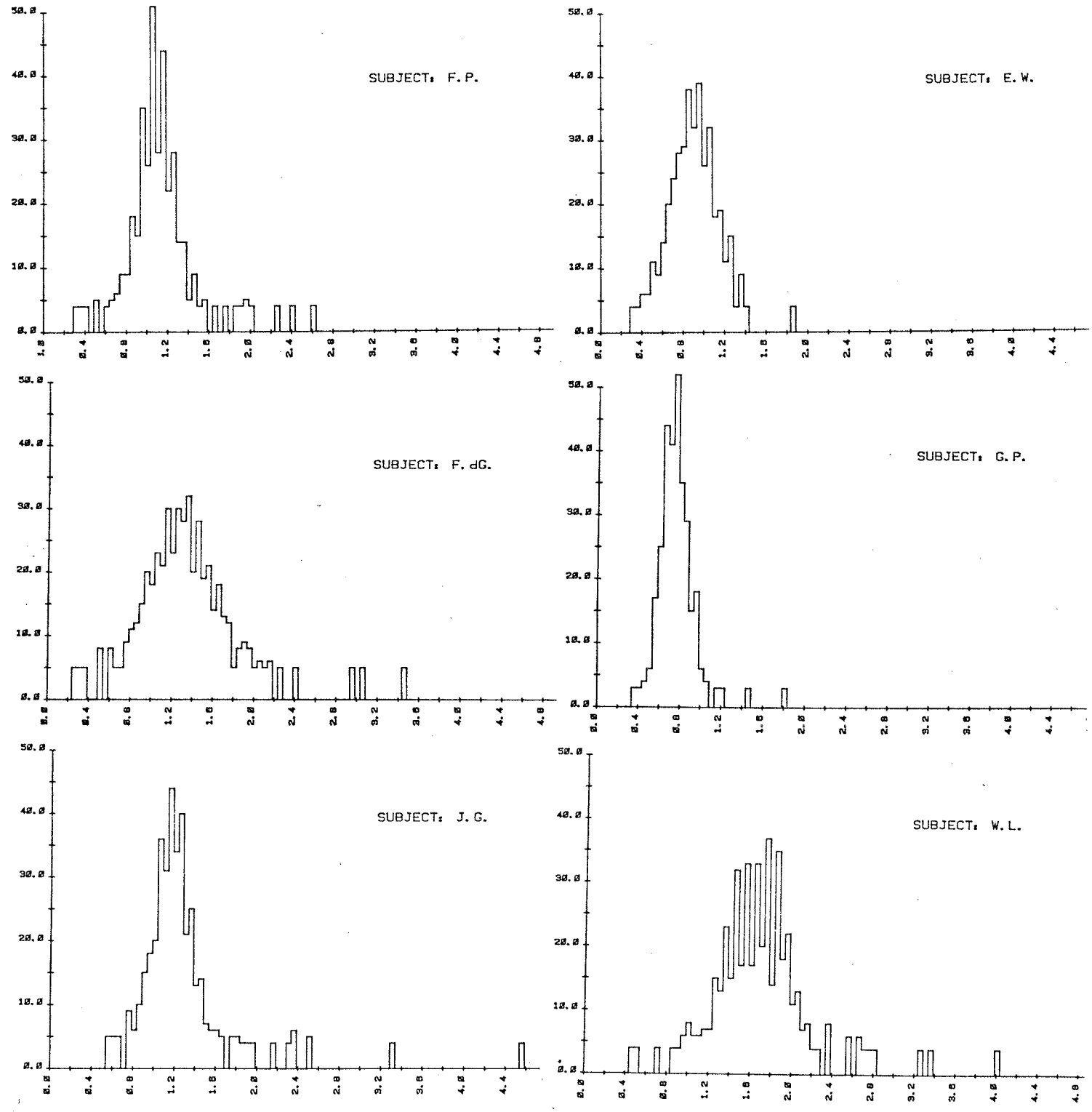

FIGURE 13b: Frequency distribution of inspiratory timing of breaths in CAO subjects continued.

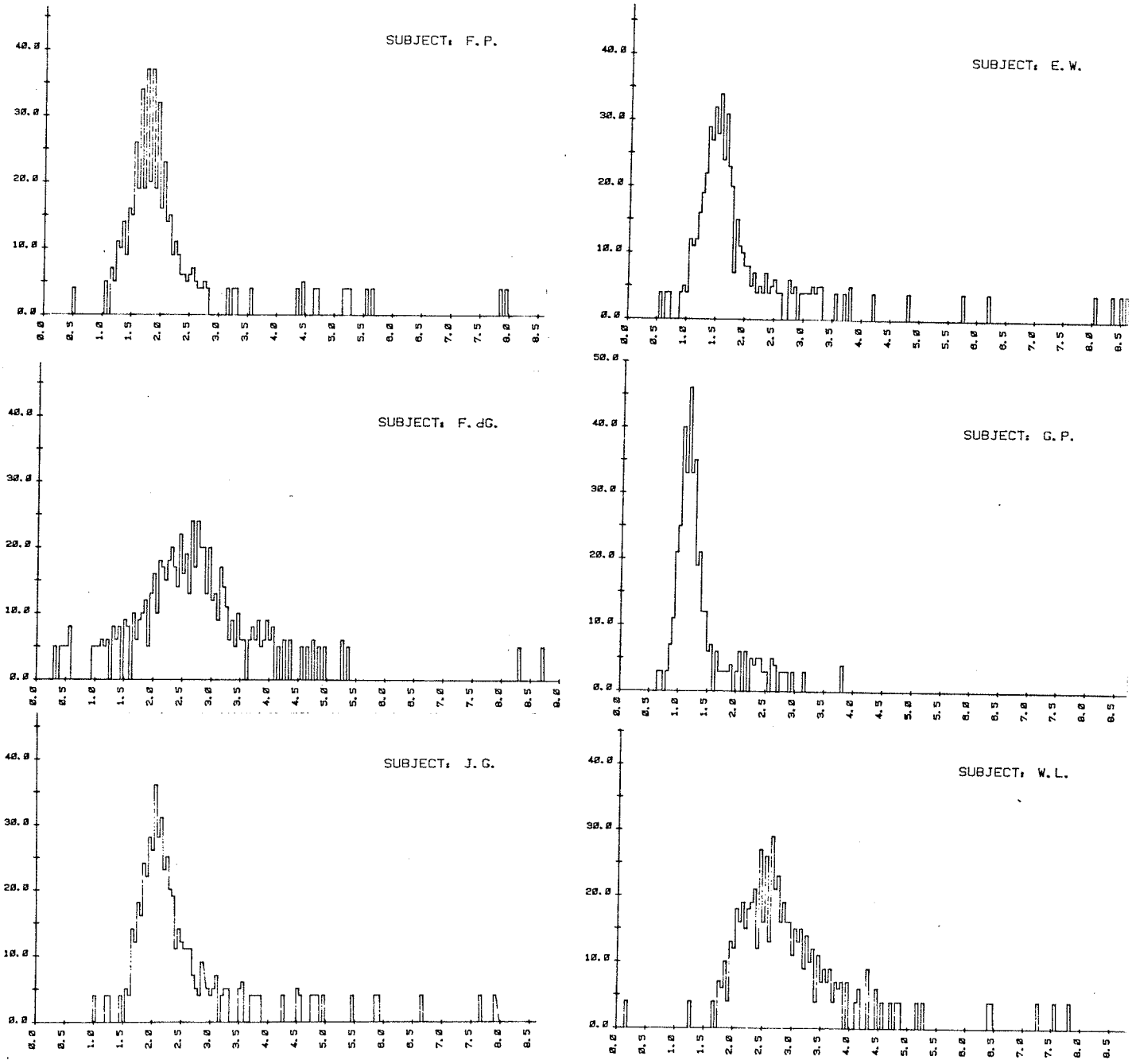

FIGURE 14a: Frequency distribution of expiratory timing of breaths in CAO subjects. Number of observations is on the ordinate and is the square root of the number of observations divided by the total number of breaths. (see text for details).

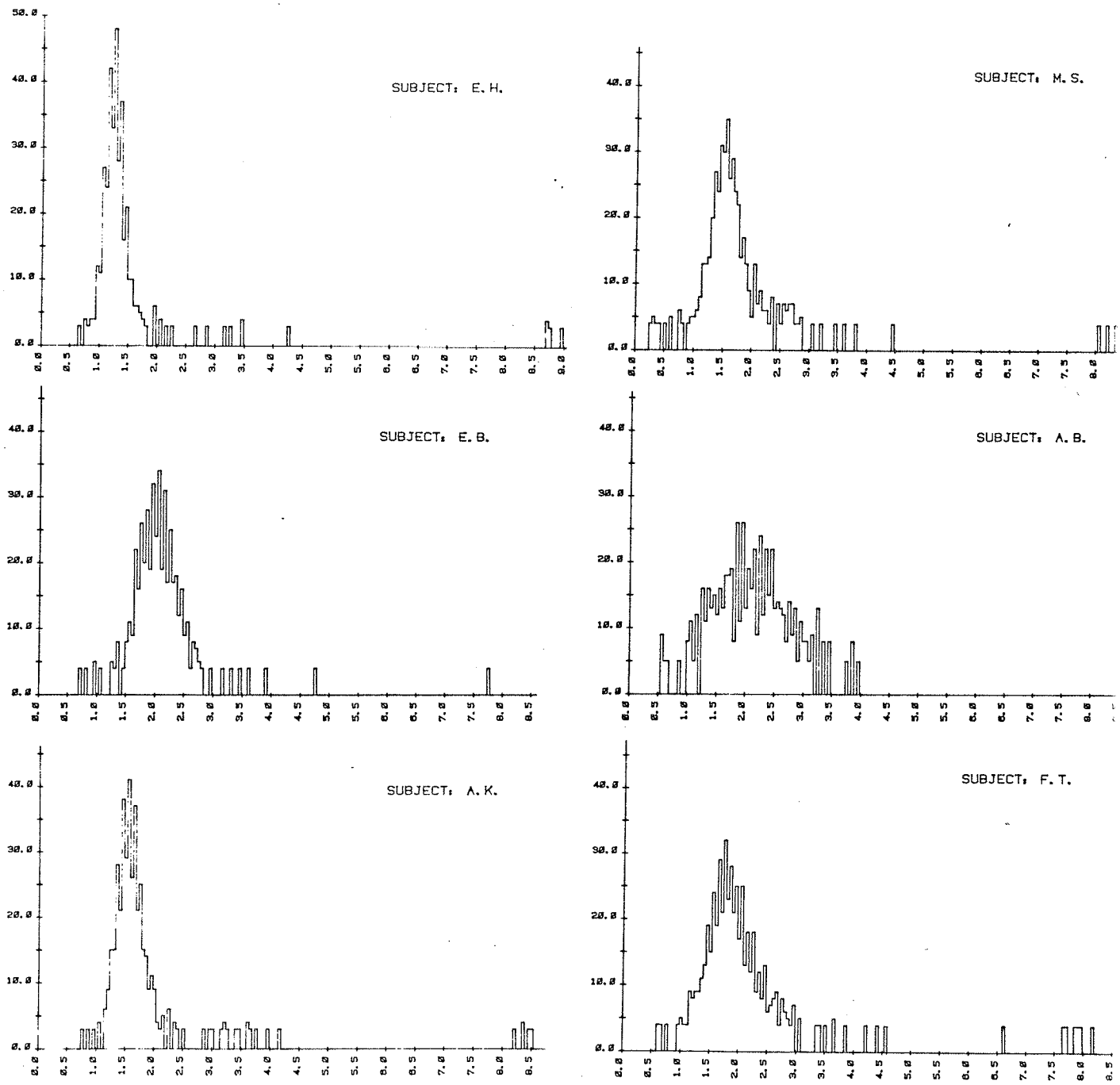

FIGURE 14b: Frequency distribution of expiratory timing of breaths in CAO subjects continued.

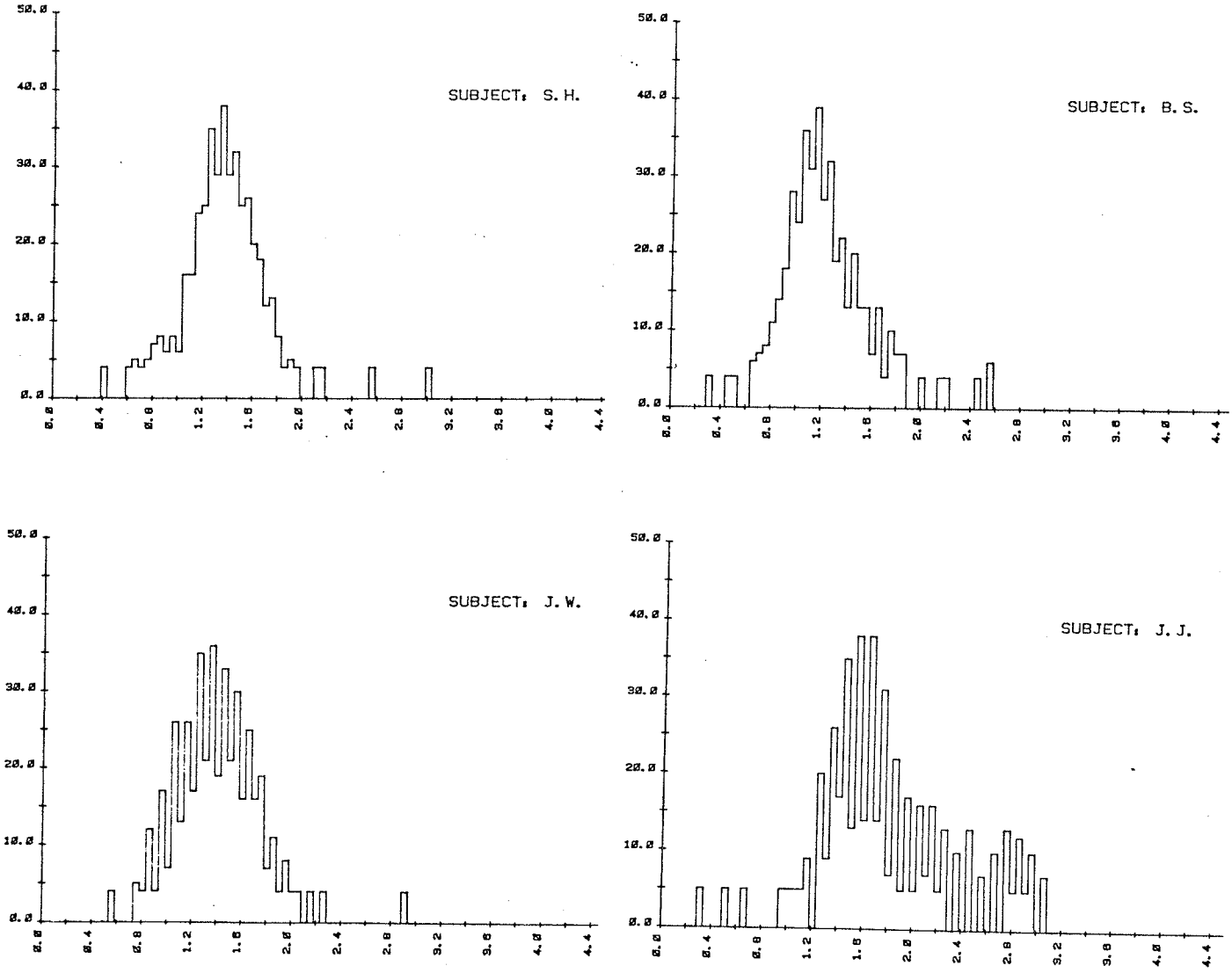

FIGURE 15a: Frequency distribution of inspiratory timing of breaths in controls. Number of observations is on the ordinate and is the square root of the number of observations divided by the total number of breaths. (See text for details).

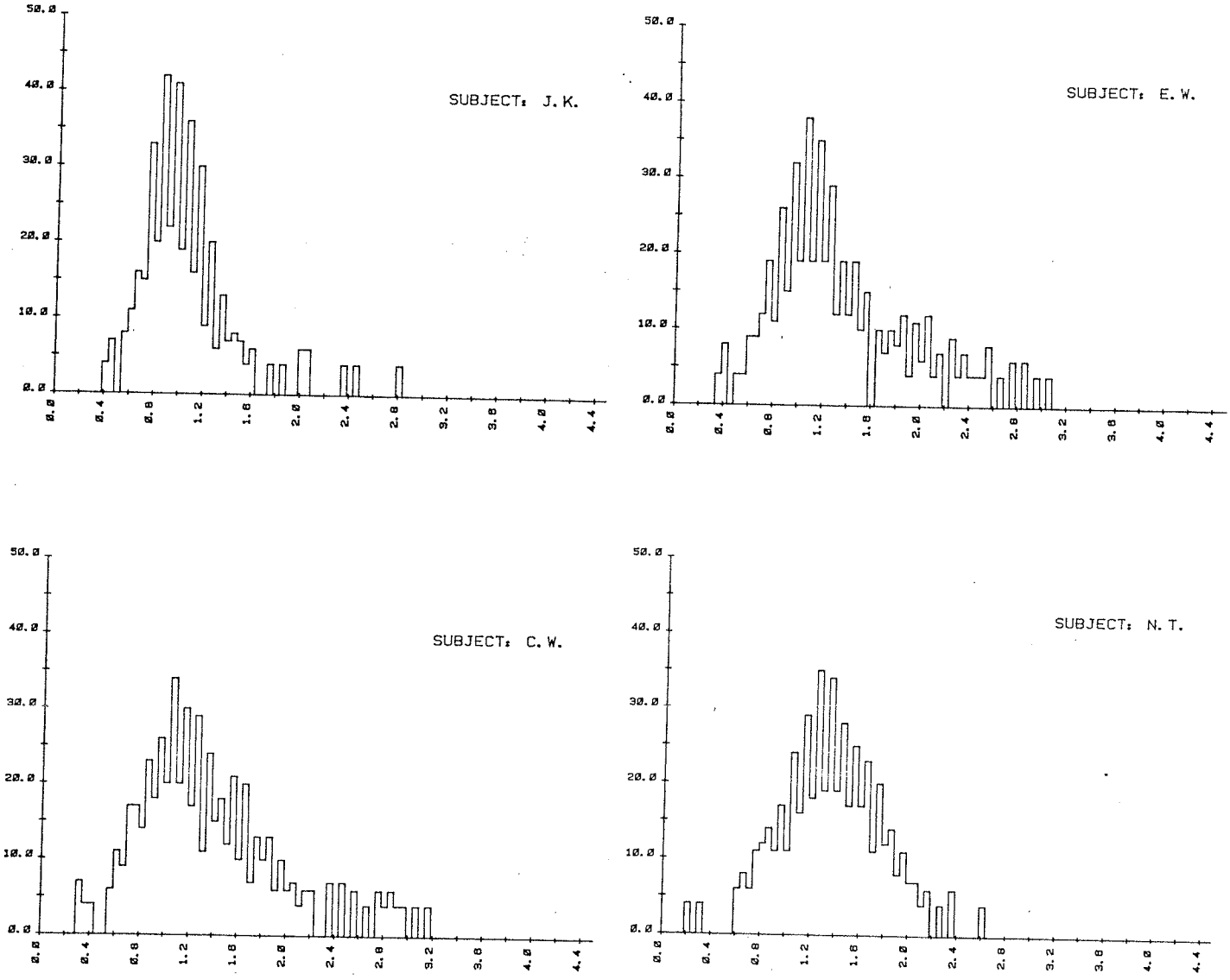

FIGURE 15b: Frequency distribution of inspiratory timing of breaths in controls continued.

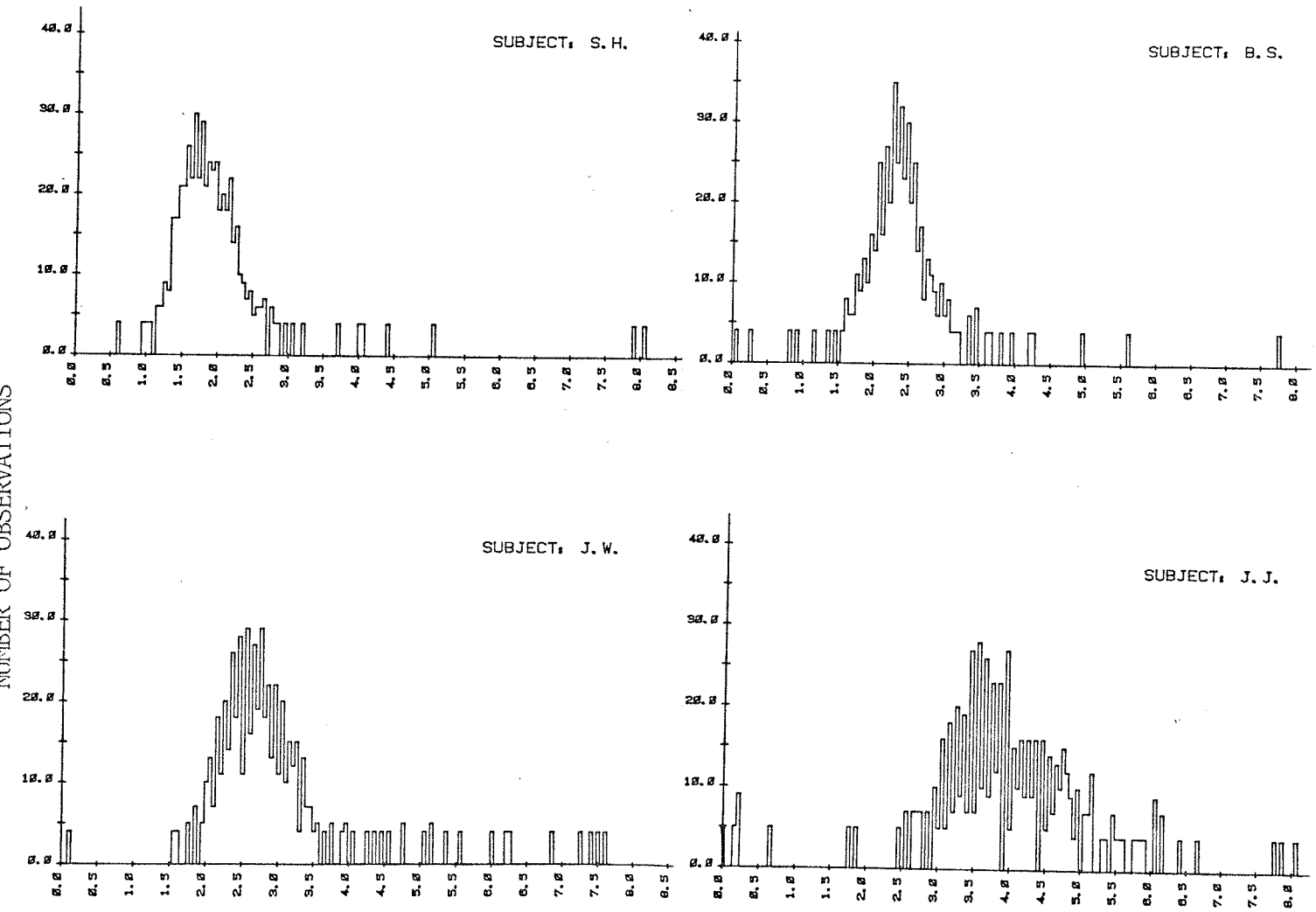

FIGURE 16a: Frequency distribution of expiratory timing of breaths in controls. Number of observations is on the ordinate and is the square root of the number of observations divided by the total number of breaths. (See text for details).

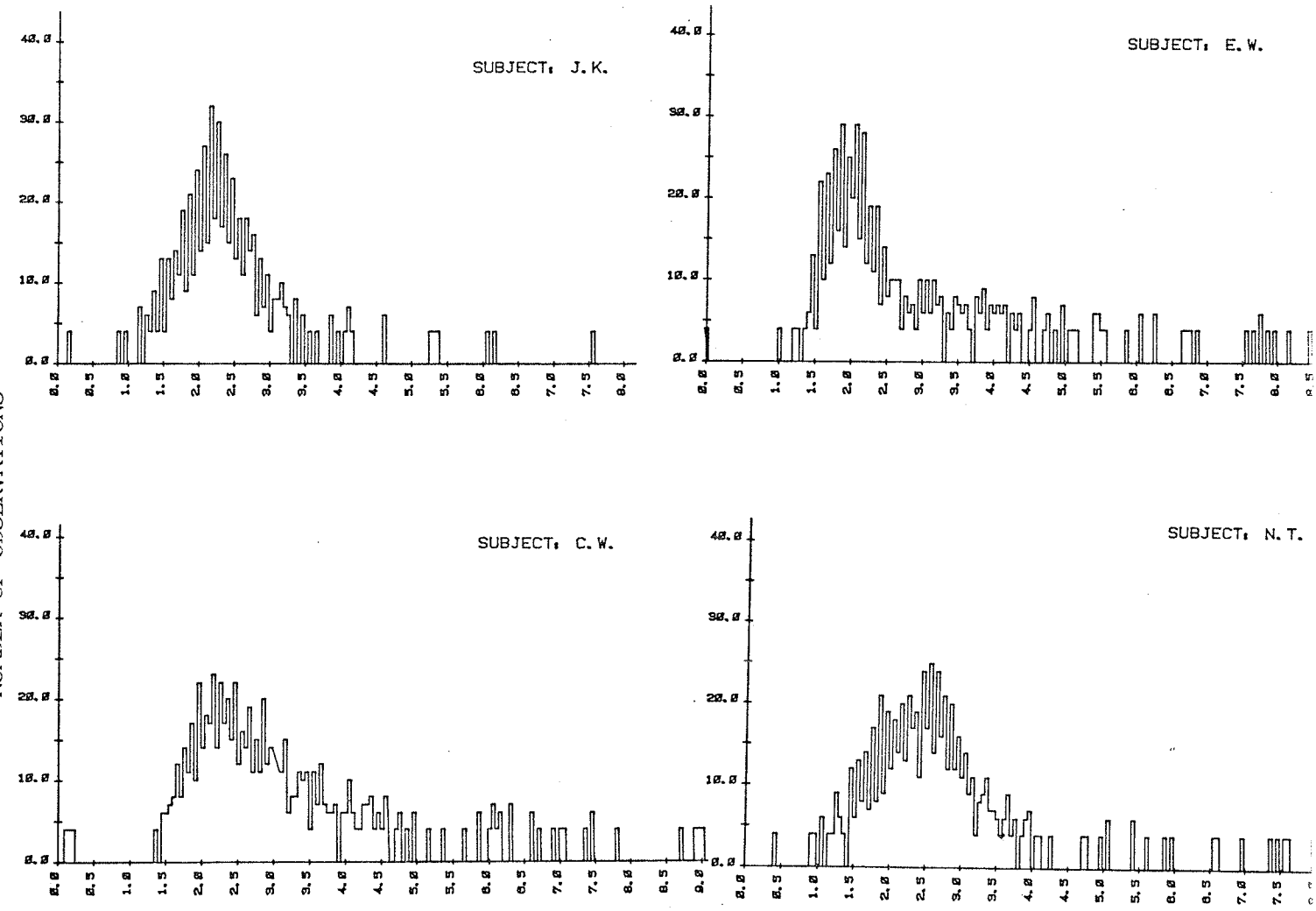

FIGURE 16b: Frequency distribution of expiratory timing of breaths in controls continued.

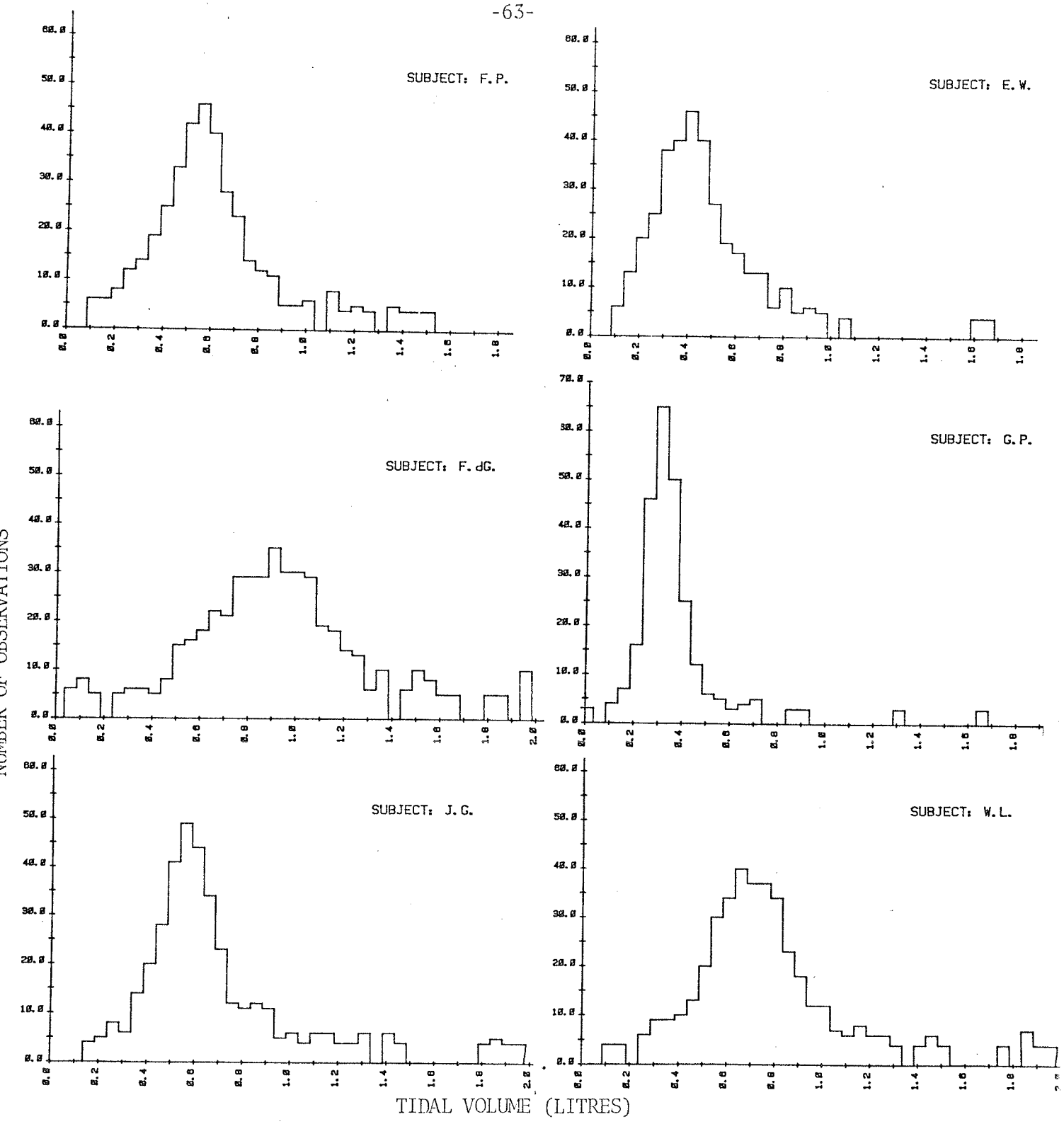

FIGURE 17a: Frequency distribution of tidal volume in CAO subjects. Number of observations is on the ordinate and is the square root of the number of observations divided by the total number of breaths. (see text for details).

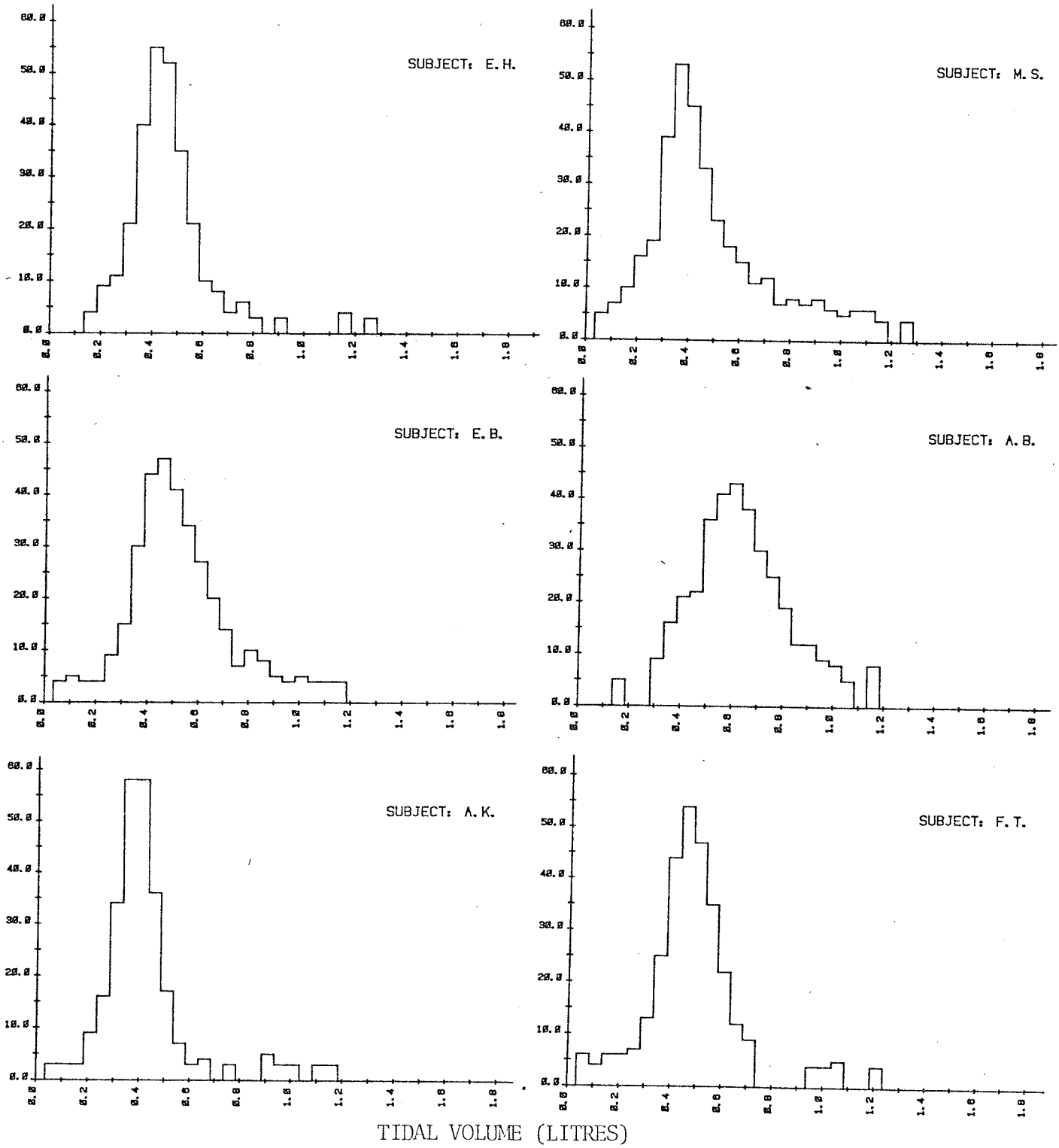

FIGURE 17b: Frequency distribution of tidal volume in CAO subjects continued.

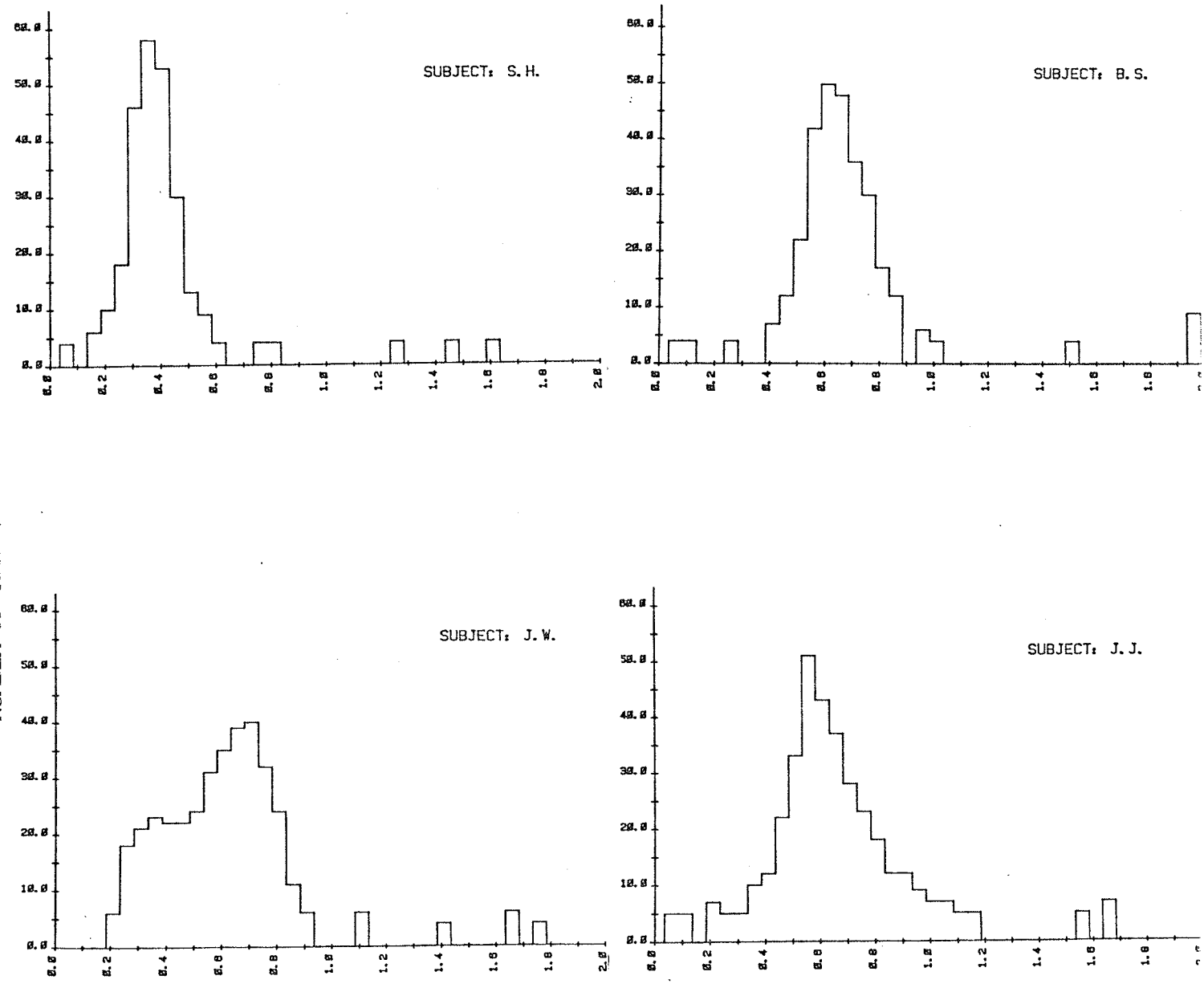

FIGURE 18a: Frequency distribution of tidal volume in controls. Number of observations is on the ordinate and is the square root of the number of observations divided by the total number of breaths. (see text for details).

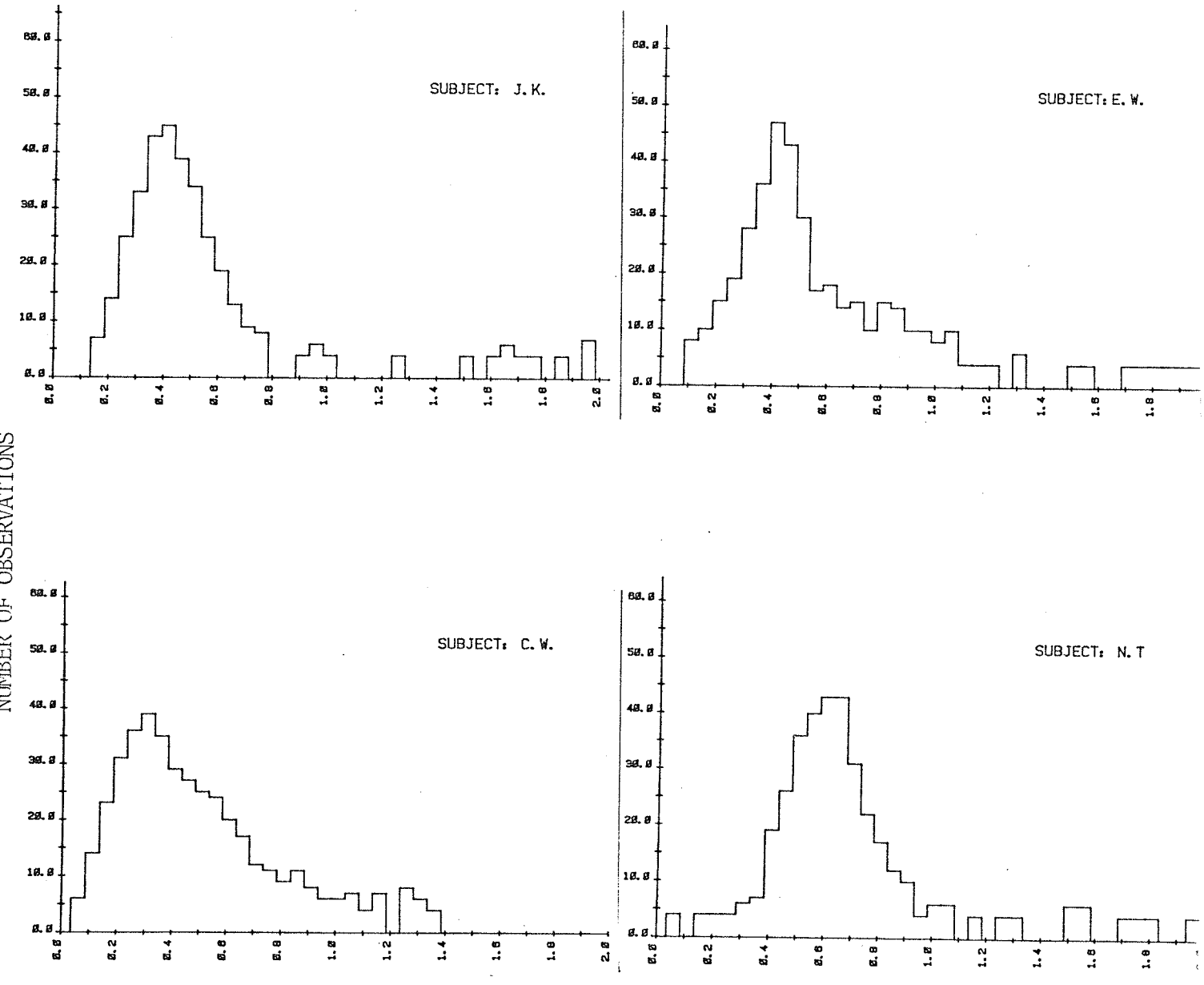

FIGURE 18b: Frequency distribution of tidal volume in controls continued.

TABLE 10a

RELATIONSHIP BETWEEN Vt AND Ti, AND BETWEEN Vt AND Ttot
IN CONTROL AND CAO SUBJECTS

	Vt - Ti			Vt - Ttot		
Subjects	r	slope	intercept	r	slope	intercept
CONTROL						
SH	.59	.257	.040	.46	.077	.149
JW	.43	.306	.193	.23	.056	.392
BS	.42	.318	.290	.21	.070	.423
JJ	.73	.286	.143	.58	.080	.188
JK	.71	.621	-.160	.46	.121	.064
CW	.89	.461	-.158	.64	.089	.061
EW	.85	.497	-.108	.59	.090	.175
NT	.43	.251	.300	.41	.080	.333
CAO						
FP	.58	.504	.010	.23	.062	.395
EW	.50	.427	.037	.38	.077	.239
FdG	.63	.520	.229	.50	.137	.375
GP	.44	.352	.073	.18	.029	.289
JG	.69	.591	-.101	.60	.140	.136
WL	.77	.529	-.161	.50	.106	.265
EB	.46	.324	.180	.50	.140	.080
MS	.67	.427	.037	.53	.118	.131
EH	.54	.429	.123	.26	.042	.371
AB	.36	.281	.384	.28	.067	.44-
AK	.46	.266	.192	.31	.041	.312
FT	.59	.356	.157	.43	.054	.342

TABLE 10b

RELATIONSHIP BETWEEN Vt AND f, AND BETWEEN Vt AND $\dot{V}e$
IN CONTROL AND CAO SUBJECTS

	Vt - f			Vt - $\dot{V}$		
Subjects	r	slope	intercept	r	slope	intercept
CONTROL						
SH	.40	-.016	.692	.67	.050	.036
JW	.14	-.013	.814	.82	.059	.095
BS	.09	-.008	.813	.75	.038	.245
JJ	.35	-.017	.833	.62	.081	.093
JK	.33	-.022	.883	.69	.046	.073
CW	.67	-.035	.977	.74	.085	-.095
EW	.61	-.033	1.090	.52	.051	.080
NT	.29	-.018	.930	.57	.041	.241
CAO						
FP	.17	-.010	.793	.78	.041	.105
EW	.49	-.019	.902	.72	.039	.038
FdG	.38	-.029	1.381	.63	.053	.184
GP	.18	-.004	.477	.72	.027	.064
JG	.53	-.042	1.360	.65	.057	.014
WL	.49	-.047	1.381	.60	.059	.161
EB	.51	-.027	1.040	.82	.052	-.002
MS	.56	-.022	.962	.74	.047	-.038
EH	.24	-.007	.665	.72	.026	.118
AB	.26	-.009	.824	.53	.024	.328
AK	.42	-.012	.700	.65	.032	.088
FT	.43	-.012	.755	.53	.025	.238

TABLE 10c

RELATIONSHIP BETWEEN f AND $\dot{V}e$, AND BETWEEN Ti AND Te
IN CONTROL AND CAO SUBJECTS

	f - $\dot{V}e$			Ti - Te		
Subjects	r	slope	intercept	r	slope	intercept
CONTROL						
SH	.32	.609	14.07	.10	.043	1.330
JW	.31	.242	12.32	.01*	-.004	1.437
BS	.58	.555	10.62	.12	-.057	1.359
JJ	.51	.849	5.06	.41	.179	1.054
JK	.32	.396	15.11	.27	.104	.772
CW	.12	-.255	17.28	.43	.149	.852
EW	.15	.295	15.06	.53	.187	.788
NT	.32	.396	15.11	.27	.104	.772
CAO						
FP	.42	.367	15.88	.10	.033	1.075
EW	.05*	.078	22.89	.05*	.012	.924
FdG	.23	.257	11.73	.30	.121	1.021
GP	.49	.833	21.32	.05*	.010	.772
JG	.20	.223	15.22	.34	.124	.949
WL	.22	.231	11.36	.13	.049	1.569
EB	.02*	.021	19.24	.06*	.026	.988
MS	.01*	.010	23.49	.30	.124	.735
EH	.43	.547	21.74	.13	.028	.747
AB	.54	.831	9.87	.08*	.027	.863
AK	.33	.602	18.41	.04*	.010	.821
FT	.48	.816	12.63	.30	.069	.829

TABLE 10d

RELATIONSHIP BETWEEN $\dot{T}i$ AND $\dot{V}e$ AND BETWEEN $\dot{T}tot$ AND $\dot{V}e$
IN CONTROL AND CAO SUBJECTS

	$\dot{T}i$ - $\dot{V}e$			$\dot{T}tot$ - $\dot{V}e$		
Subjects	r	slope	intercept	r	slope	intercept
CONTROL						
SH	.22	.038	1.132	.27	-.118	4.164
JW	.19	.019	1.249	.28	-.083	4.971
BS	.06	-.007	1.294	.46	-.124	5.011
JJ	.12	.026	1.577	.40	-.243	7.386
JK	.41	.037	.703	.14	-.043	3.735
CW	.56	.114	.565	.01	-.005	4.192
EW	.33	.059	.759	.21	-.143	4.955
NT	.13	.016	1.240	.41	-.147	5.458
CAO						
FP	.23	.014	.979	.32	-.063	3.772
EW	.27	.018	.767	.16	-.042	3.058
FdG	.21	.022	1.039	.22	-.067	4.971
GP	.12	.006	.725	.36	-.086	2.944
JG	.24	.024	.973	.13	-.049	4.016
WL	.36	.053	1.188	.21	-.096	5.461
EB	.22	.020	.848	.02	-.005	3.176
MS	.24	.024	.704	.08	-.022	2.835
EH	.13	.006	.703	.35	-.077	3.134
AB	.02	-.001	.930	.57	-.116	4.538
AK	.08	.007	.773	.38	-.139	3.905
FT	.002	.000	.963	.45	-.168	4.690

TABLE 10e

RELATIONSHIP BETWEEN Vt AND Te IN CONTROL AND CAO SUBJECTS

	Vt - Te		
Subjects	r	slope	intercept
CONTROL			
SH	.26	.050	.309
JW	.09	.023	.565
BS	.03*	.009	.657
JJ	.40	.069	.373
JK	.26	.088	.263
CW	.51	.092	.168
EW	.49	.100	.266
NT	.28	.057	.504
CAO			
FP	.06*	.018	.550
EW	.27	.057	.345
FdG	.34	.110	.634
GP	.09	.015	.329
JG	.45	.139	.312
WL	.22	.055	.586
EB	.36	.111	.286
MS	.36	.094	.282
EH	.15	.026	.425
AB	.19	.048	.541
AK	.21	.029	.367
FT	.33	.046	.410

The correlation between Vt and $\dot{V}e$ was stronger than the correlation between f and $\dot{V}e$ in all subjects except CAO subject A.B. in which they both correlated equally well. Ti and $\dot{V}e$ and Ttot and $\dot{V}e$ correlated less well than Vt and $\dot{V}e$. $\dot{V}e$ varied mainly by varying Vt in both groups.

The correlation between Ti and Te was insignificant in 2 controls and 5 CAO subjects and very low in many others. Ti and Te correlated least well of all variables examined. It appeared that Te in resting breathing in CAO subjects and normals was not associated with the preceeding Ti. Considerable variability was also present in the correlation of Vt and Te.

The number of sighs for each subject is listed in Table 11. Only 3 of 12 CAO subjects had breaths of volumes > 3 times mean Vt compared to 6 of 8 control subjects. The CAO group had significantly fewer sighs ($p < 0.01$).

The differences in variability of Ti, Vt, Ti.Ttot, and $\dot{V}e$ demonstrated in Tables 9a and 9b could be due to the fact that the CAO subjects took fewer large breaths than did the control subjects. Sighs contributed to variability and therefore, all breaths > 30% of the individual's predicted FVC were excluded and the data re-analyzed. 30% FVC for the controls meant removal of breaths with a mean volume > 1.34 litres and for the CAO group breaths > 1.31 litres were removed. The results are included in Table 12. All components in which there were significant differences when all the data were analyzed (Table 9a and 9b) remained significantly different when breaths < 30% FVC (predicted) were anlyzed except for the variability in Vt. Removing the large breaths in the normal subjects markedly decreased the variability in Vt.

TABLE 11

COMPARISON OF NUMBER OF SIGHS BETWEEN
CAO SUBJECTS AND CONTROLS

CONTROLS		CAO	
Subject	Sighs/100 breaths	Subject	sighs/100 breaths
SH	0.4	FP	0.0
JW	0.0	EW	0.3
BS	0.8	FdG	0.0
JJ	0.0	GP	0.2
JK	1.6	JG	0.3
CW	0.5	WL	0.0
EW	1.1	EB	0.0
NT	0.2	MS	0.0
		EH	0.0
	$\bar{x}$ 0.6	AB	0.0
		AK	0.0
		FT	0.0
		$\bar{x}$	0.07*

*$p < 0.01$

TABLE 12

COMPARISON OF TIMING COMPONENTS AFTER REMOVAL OF BREATHS WITH VOLUMES > 30% FVC PREDICTED

	CAO		CONTROL	
	$\bar{x}$	c.v.	$\bar{x}$	c.v.
Ti	1.048***	.167*	1.333	.213
Te	1.940***	.306	2.647	.306
Vt	0.548	.224	0.541	.255
Ttot	2.988****	.213	3.979	.225
Ti/Ttot	.357	.157**	.345	.200
f	21.723****	.167	16.153	.207
$\dot{V}e$	11.149****	.209**	8.416	.252
Vt/Ti	.529***	.200	.415	.205

* $p < 0.05$

** $p < 0.025$

*** $p < 0.01$

**** $p < 0.005$

There was no significant difference in the coefficients of variation for the mean tidal volume between the CAO and control groups when the big breaths were removed. In contrast, the variability in Ti,Ti/Ttot and $\dot{V}e$ remained significantly less in the CAO group. The big breaths had no effect on variability of these components. Therefore, the big Vt's were not regularly associated with large values of Vt/Ti, Ti, nor Ttot.

No correlation was found between severity of disease in the CAO group, assessed by $FEV_{1.0}$, and any variable measured. The results of measuring the timing components for mouthpiece breathing for the CAO group and for the controls are listed in Tables 13 and 14 respectively. Subject B.S. demonstrated the highest frequency 17.3/min on the mouthpiece. This subject was instructed to increase his frequency slightly during calibration due to the problem experienced by large cardiogenic oscillations in his flow signal. Therefore, his data were not included in the anlaysis of timing components between mouthpiece and RIP measured breathing in the control group. Table 15 demonstrates the comparison of the mean measurements between mouthpiece and RIP recorded variables for the CAO group and for the control group. Vt was significantly increased ($p < 0.025$ CAO group; $p < 0.005$ control group), and f was significantly decreased ($p < 0.025$) in both groups when breathing on the mouthpiece. Vt/Ti was also significantly increased on the mouthpiece in the CAO group ($p < 0.025$) and Te and Ttot were both close to being significantly increased. As well, Ti was significantly longer ($p < 0.05$) in the control group on a mouthpiece as compared to the control group when breathing was measured with RIP. It appears that the mechanism of the increased Vt induced by the mouthpiece was different between the 2

TABLE 13

COMPONENTS OF THE RESPIRATORY CYCLE FOR PATIENTS WITH CAO ON A MOUTHPIECE*

SUBJECT	No. of Breaths	f(min)	Vt(l.)	Ti(sec)	Te(sec)	Ttot(sec)	Vt/Ti	Ti/Ttot	$\dot{V}e$
FP	14	20.4	0.76	1.17	1.77	2.94	.659	.404	15.5
EW	13	15.7	0.93	1.54	2.29	3.83	.609	.404	14.6
FdG	5	10.9	1.19	1.77	3.75	5.52	.672	.325	13.0
GP	16	26.9	0.45	0.98	1.26	2.23	.486	.437	12.1
JG	9	11.8	1.05	2.15	2.95	5.10	.494	.425	12.4
WL	12	18.4	0.84	1.11	2.15	3.26	.750	.344	15.5
EB	11	14.3	0.79	1.22	2.97	4.19	.653	.292	11.3
MS	8	10.8	1.01	1.89	3.68	5.58	.539	.341	10.9
EH	11	21.3	0.49	0.64	2.17	2.82	.773	.236	10.4
AB	9	22.2	0.61	0.78	1.92	2.70	.796	.289	13.5
AK	14	18.3	0.40	0.78	2.50	3.28	.511	.239	7.3
FT	15	18.7	0.53	0.97	2.24	3.21	.539	.303	9.9

* Values are means

TABLE 14

COMPONENTS OF THE RESPIRATORY CYCLE FOR AGE MATCHED CONTROLS ON A MOUTHPIECE*

SUBJECT	No. of Breaths	f(min)	Vt(1.)	Ti(sec)	Te(sec)	Ttot(sec)	Vt/Ti	Ti/Ttot	$\dot{V}e$
SH	10	13.3	0.62	2.06	2.44	4.50	.305	.459	8.2
JW	10	12.4	1.13	2.05	2.80	4.85	.553	.423	14.0
BS	10	17.3	1.07	1.31	2.17	3.47	.820	.377	18.5
JJ	8	13.8	0.80	1.87	2.49	4.36	.432	.429	11.0
JK	6	12.2	0.73	1.70	3.22	4.92	.427	.348	8.9
CW	5	15.6	0.59	1.44	2.40	3.84	.412	.376	9.2
EW	9	12.2	1.05	2.22	2.69	4.91	.472	.453	12.8
NT	7	12.7	1.00	1.13	3.59	4.71	.883	.240	12.7

* Values are means

TABLE 15

COMPARISON OF TIMING COMPONENTS OF BREATHING BETWEEN RIP AND MOUTHPIECE

RECORDED VARIABLES FOR CAO AND CONTROL GROUPS

GROUP CAO	Ti		Te		Vt		Ttot		Ti/Ttot		Vt/Ti		f	
	$\bar{x}$	S.D.	$\bar{x}$	S.D.	$\bar{x}$	S.D.	$\bar{x}$	S.D.	$\bar{x}$	S.D.	$\bar{x}$	S.D.	$\bar{x}$	S.D.
Mouthpiece	1.25	.483	2.47	.75	.754	.260	3.72	1.14	.337	.069	.623	.111	17.5	5.0
RIP	1.05	.269	1.96	.48	.554	.163	3.01	0.74	.357	.024	.531	.091	21.7	4.9
	N.S.		N.S.		$p < 0.025$		N.S.		N.S.		$p < 0.05$		$p < 0.025$	
CONTROL														
Mouthpiece	1.72	.40	2.73	.47	.875	.213	4.45	.54	.337		.538	.206	13.2	1.23
RIP	1.34	.21	2.67	.60	.553	.112	4.01	.76	.345	.040	.418	.090	16.1	2.44
	$p < 0.05$		N.S.		$p < 0.005$		N.S.		N.S.		N.S.		$p < 0.025$	

groups. In the CAO group Vt/Ti increased on the mouthpiece but there was little change in Ti. In the controls, Ti was increased and although Vt/Ti was also increased the change was not significant.

V. DISCUSSION

The breathing patterns of patients with CAO are significantly different from age matched controls; the timing components are altered, and breathing is less variable. Particularly by altering inspiratory timing mechanisms, patients with CAO appear to lose the variability of breathing found in normal subjects.

Variations in the volume and timing components of breathing in man have been well documented in studies using a mouthpiece or facemask. Our results using RIP differ from those previously reported, and the use of this less invasive technique probably accounts for thses discrepancies.

Sorli et al (1978) studied 15 CAO patients, 7 with hypercapnia (mean age 56 years), and 8 without hypercapnia (mean age 63 years), and 7 young normal controls (mean age 26 years). They studied their subjects at rest in the supine position, and measured breathing with subjects on a mouthpiece. They found no difference in Ti between their stable CAO subjects and young normal controls. In contrast, we found Ti to be significantly shorter in our CAO group who were not hypercapnic as compared to age matched controls.

Bradley et al (1979) studied 20 hypoxemic CAO subjects and 17 control CAO subjects with PaO_2 > 60 mmHg in the seated position and breathing on a mouthpiece. They only found Ti to be significantly shorter in hypoxic CAO subjects as compared to normoxic CAO subjects. Similarly, Sorli et al reported a significantly shorter Ti in hypercapnic CAO subjects as compared to normocapnic CAO subjects. Both groups reported mean Ti's of ± 1.5 seconds and ± 1.3 seconds respectively in stable CAO subjects without respiratory failure. These

values are similar to the mean Ti values that we measured in our CAO subjects on a mouthpiece (± 1.25 seconds), but are significantly higher than the mean Ti's we recorded in CAO subjects during resting breathing with RIP. As both Bradley et al and Sorli et al recorded ventilation on a mouthpiece, that may explain the longer Ti's found in their CAO control groups. Furthermore,both authors reported higher mean Vt's and lower mean frequencies in their stable CAO subjects than we found. It has been demonstrated by many investigators (Gilbert et al, 1972; Askanazi et al, 1980; and Hirsch and Bishop,1982) and confirmed by us in this study that Vt is higher and f lower when ventilation is recorded on a mouthpiece. The discrepancy between their results and ours appears most likely due to this factor.

Sorli et al found that Vt was decreased in hypercapnic CAO subjects. They suggested that a shorter Ti resulted in a decreased Vt, and that this led to the rapid, shallow breathing observed in their patients. Our CAO subjects were neither hypercapnic nor hypoxic, and perhaps this is one of the reasons that in spite of a decreased Ti, Vt was the same as that of our normals. Frequency and, therefore, $\dot{V}e$ were also significantly higher in our CAO group. This is in contrast to Sorli et al who reported no difference in frequency between their stable CAO subjects and young normals.

Milic-Emili and Aubier (1980), and Sorli et al (1978) suggested that it would not be surprising to find a decrease in Ti, but not in Te in CAO subjects as expiration would be prolonged due to dynamic compression of airways. Therefore, they suggested that a decreased Ti/Ttot was to be expected. This may be true in hypercapnic CAO subjects, but based on Sorli's own results and the results of this study, this is not

the case in patients without respiratory failure. Sorli reported a mean Ti/Ttot in their stable CAO group of .39 and in their normals of .41 and found no significant difference between the two. Although we found Ti to be significantly shorter in the CAO group, Te was also significantly shorter, and therefore, Ti/Ttot did not differ between the CAO group and controls. Mean inspiratory flow was significantly higher in our CAO group both measured with RIP and on a mouthpiece. This is consistent with previous studies (Sorli et al,1978).

Both normals and CAO subjects increased Vt when breathing through a mouthpiece. CAO subjects achieved this in increasing inspiratory drive (Vt/Ti)with little change in Ti. In contrast, the normals on a mouthpiece increased Vt by increasing Ti with a much smaller increase in Vt/Ti. The response of the normal subjects is similar to the results of Daubenspeck (1981) in young normals breathing against increased resistive loading. They had a significantly increased Vt and Ti. The effects of mouthpiece breathing on normals might be due at least in part to the increased resistance to breathing imposed by this technique. It is not clear why the effects of the mouthpiece on breathing pattern should have differed between our groups, but the result does indicate that mouthpiece effects may not be non-specific.

When all breaths were included in the analysis, there was significantly less variability in Ti, Vt, Ti/Ttot and $\dot{V}e$ in our CAO group. The greater variability in Vt in the normals proved to be due to the larger number of big breaths in this group, for when breaths >30%

predicted FVC were removed from the analysis, variation in Vt in normals decreased to that shown by patients with CAO. The CAO group took significantly fewer large breaths (> 3 times mean Vt) than controls ($p < 0.01$). Most of the CAO subjects were able to take larger breaths as evidenced by the range of their FVC's (1.08 - 3.96 litres), but in CAO Vt is a larger fraction of $FEV_{1.0}$ and FVC . As well, big breaths must be more expensive in terms of energy expenditure in CAO patients due to the increased work of breathing on both inspiration and expiration in this group. Perhaps CAO subjects have learned that taking big breaths is too costly, and therefore, they do not sigh as frequently or with breaths of the same amplitude as normals.

Taking out the big Vt's did not change the variability of Ti, Ti/Ttot or $\dot{V}e$ in CAO subjects or normals. Therefore, in normals the big Vt's are not those with the long Ti's and Ti/Ttot's and variations in $\dot{V}e$ are at least in part not due to variations in Vt. The reduced variability in Ti, Ti/Ttot and $\dot{V}e$ in CAO subjects suggests that inspiratory timing and ventilation is more fixed in patients with CAO than in normals. Both the difference in breathing pattern and the lack of variability in breathing in CAO subjects could be the result of either mechanical limitation and/or neural readjustments as a result of their disease. In other words, decreased variability in breathing pattern could be due to changes in mechanics per se. This is unlikely given a certain variability of neural output. Mechanical loading does not decrease the variability of the mechanical results of this output, such as Vt and Ti (M. Younes, unpublished observations). It is also possible that mechanical loading results in decreased variability of neural output

for unspecified reasons. If this were the case, mechanical loading of normals should reduce the variability of their breathing pattern. A related hypothesis would be that the increased drive present in CAO reduced variability of breathing pattern. If this were so, variability should also be decreased in normals when their drive is increased. Finally, it is possible that the variability of breathing pattern in CAO is reduced for reasons other than those noted above.

Variability in the spirogram of normal subjects has been previously observed by many investigators (Bendixen et al, 1964; Gillam, 1972; Gardner, 1977; and Tabachnik et al,1981). Decreased variability in the timing components of the spirogram in young normals has been demonstrated both in chemostimulated breathing (Newsom-Davis & Stagg, 1975) and in resistive loaded breathing (Daubenspeck 1981). Newsom Davis and Stagg (1975) used the coefficients of variation to assess variability in the timing components of the spirogram in young normals during CO_2 stimulated breathing. They stated that the variability in Vt,Ti and Te tended to decrease during CO_2 administration. However, they found Ti remained unchanged, mean Vt increased and Te shortened in their group. The increased Vt in normals during CO_2 stimulated breathing appeared to be achieved by increasing mean inspiratory airflow with no change in inspiratory timing mechanisms. The shortened Te resulted in the increased frequency they observed. We also found a shorter Te in our CAO subjects which would account for the increased frequency observed in this group. However, in contrast to Davis & Stagg's CO_2 stimulated breathing experiments we did not find any difference in variability in Te between CAO subjects and normals, and did not find any difference in variability in Vt between CAO subjects and normals once the large breaths were removed.

Daubenspeck (1981) used the standard deviations (S.D.'s) of the timing components of the spirogram to analyze variability in breathing pattern during resistive loaded breathing in young normal subjects. He found significant decreases in the variability of f and Vt/Ti, and inconsistent, and insignificant decreases in the variability of other measurements. Daubenspeck included sighs in his initial analysis of variability and found that removal of breaths with volumes > 3 times the mean Vt did not change the variability of any parameter. In contrast, to our findings in CAO subjects, Daubenspeck found mean Vt and Ti were increased and mean frequency was decreased in young normals breathing against resistive loads. Although we found the variability in f and Vt/Ti was less in CAO subjects as compared to normals, the differences were not significant. Thus CAO patients breath differently from normals subjected to resistance.

In contrast to both resistive loaded and CO_2 stimulated breathing in young normals, we found that CAO subjects have a significantly decreased Ti and a significantly increased inspiratory airflow.

It is interesting to note that both increased drive (Davis & Stagg 1975) and increased load (Daubenspeck 1981) resulted in decreased variability in breathing in normal subjects. In our study, CAO subjects also demonstrated increased drive (Vt/Ti) and do breathe against large resistive loads, and we found that their breathing was less variable than normal. However, although these studies demonstrate some qualitative similarities, quantitatively breathing pattern changed differently in all three situations.Both Daubenspeck and Newsom-Davis and Stagg found Vt increased in response to loaded breathing in normals. In contrast, we found no difference in Vt between CAO subjects and age matched controls. In CO_2 stimulated breathing Vt increased by

increasing mean inspiratory airflow, with no change in Ti (Newsom-Davis & Stagg 1975). In resistive loaded breathing in normals, Vt increased by increasing Ti but Vt/Ti was significantly reduced, (Daubenspeck 1981). In contrast, CAO patients maintain the same Vt as normals,but achieve it with a shorter Ti and a higher Vt/Ti. Though the mechanical load imposed by CAO makes it difficult to compare Vt, in spite of their load, our patients both decreased Ti and increased Vt/Ti. This combination was not observed with either CO_2 breathing or resistance loading in normals, and indicates that neither increased drive nor increased resistance accounted for the breathing pattern in CAO. As well, Daubenspeck found f was significantly decreased during resistive loading and therefore, there was no change in $\dot{V}e$. In contrast, CAO subjects demonstrate an increased f and an increased $\dot{V}e$ compared to normals. Newsom-Davis and Stagg looked at only the variability of Vt, Ti and Te and found the variability of all these to be decreased with CO_2. Daubenspeck found significant decreases in variability in f and Vt/Ti and although there were similar decreases in other variables they were not significant. We found significant decreases in variability of Ti, Ti/Ttot and $\dot{V}e$ and insignificant decreases in variability of Vt, Vt/Ti, Te, and f in CAO subjects. This suggests that the decreases of variability we observed were like the mean breathing patterns, not entirely due to increase in drive or resistance.

Surprisingly, there were no significant differences in the correlation of any of the variables between the CAO group and age matched controls. The positive correlation found between Vt and Ti (Newsom-Davis and Stagg 1975) and between Vt and Ttot (Davis et al 1975, Dejours et al 1966, Hlastala et al 1973, and Lenfant 1967), and the negative correlation found between Vt and f (Priban 1963, and

Davis & Stagg 1975) were confirmed in both CAO and control subjects in this study. In most control and CAO subjects the Vt and Ti correlation was stronger than the correlation between Vt and Ttot. This also is consistent with the findings of Newsom Davis and Stagg (1975). The range of correlation coefficients for the Vt and Ti relationship that we found (.36 to .89) compare well with the range found in normal subjects by Davis et al (1975)(.44 to .89). Newsom-Davis and Stagg believed that the strong correlation between Vt and Ti allowed mean inspiratory flow to be kept relatively constant during breath to breath variations of Vt and Ti. They supported the model of Clark & Von Euler (1972) that ventilation was controlled largely by regulating mean inspiratory airflow.

In both controls and CAO subjects ventilation varied chiefly by varying Vt. The Vt and $\dot{V}e$ correlation was tighter than the $\dot{V}e$ and f correlation. Vt can be varied by varying Vt/Ti or by varying Ti at a relatively constant mean inspiratory flow. If tidal volume varied mainly by varying Ti, then Vt and Ti should correlate well, and this is indeed the case. Vt/Ti also should not vary much and it does not. Ti is less variable than Vt/Ti, but not by much in either group. However, Ti should correlate well with $\dot{V}e$, but it does not. If Vt varied by varying Vt/Ti at a relatively constant Ti, then Ti should vary less than Vt/Ti. This is the case, for CAO subjects, but not for age matched controls. The variability in Ti is slightly greater than the variability of Vt/Ti in controls but there is no significant difference in variability of Vt/Ti between controls and CAO subjects. As well, Vt/Ti should correlate well with $\dot{V}e$ and it does in both groups. Therefore, it appears that Vt is varied mainly by varying Vt/Ti at a

relatively constant Ti in both CAO and normal subjects.

Mechanical loading as occurs in CAO subjects should tighten the correlation between Vt and Ti. This has been demonstrated in resistive loaded breathing in young normals (M. Younes et al, unpublished observations, Daubenspeck 1981). However, the correlation between Vt and Ti is the same in both CAO subjects and normals. This suggests that the CAO group had a poorer correlation between neural Ti and the amplitude of neural output (Vt) than did normals. This might be construed as an increase in neural variability in CAO subjects, but this is not the case. Neural Vt and neural Ti do not have to be more variable, they simply do not correlate as well in CAO patients. Indeed, it has been demonstrated that neural variation is unchanged during mechanical loading of ventilation (M. Younes, unpublished observations). It appears as if neural output was less variable in the CAO subjects as Ti, Ti/Ttot and $\dot{V}e$ are significantly less variable in this group.

Davis et al (1975) reported a much more significant positive correlation between Ti and Te than we found. In fact, in seven of twenty subjects we found no correlation between Ti and Te and in five more subjects the correlation was < r 0.20. The strongest correlation between Ti and Te was found in the rebreathing experiments of Clark and Von Euler (1972). Davis et al (1975) suggested that the dependence of Te on Ti is not as evident in steady state breathing. Our results support this latter view.

We were unable to find any correlation between disease severity as assessed by $FEV_{1.0}$ and breathing pattern in the CAO subjects. In contrast Sorli et al (1978) found a significant correlation between $FEV_{1.0}$ and Ti/Ttot ($p < 0.05$). We did not examine patients with respiratory failure which may account for this difference.

It has been proposed that the Ti/Ttot ratio is a reflection of the neural timing mechanisms (Milic Emili and Grunstein 1976). However there is a problem in using Ti/Ttot to assess alterations in timing. Ttot is affected by alterations in Te which appears to be most important in regulating frequency (Gardner,1977) but which also affects the Ti/Ttot ratio. For example, in our study where Ti and Te are both significantly shortened in CAO subjects, Ti/Ttot is unchanged compared to Ti/Ttot in old normals, and yet significant alterations have occurred in inspiratory timing. The same Vt is achieved with a shorter Ti, and therefore, a higher mean inspiratory flow. The shorter and less variable Ti in CAO subjects suggests a resetting of the neural inspiratory timing mechanism such that inspiration is more fixed in this group. Although Ti/Ttot is also less variable in CAO subjects it appears to be a less sensitive index of timing mechanisms than is Ti. Such a decreased Ti has only been found in normals when Vt was increased beyond 2-3 times normal in chemostimulated breathing and it was suggested that this effect was due to increased vagal volume related feedback which was only believed to be effective at these high volumes, (Clark and Von Euler 1972). This might suggest that the increased lung volumes present in CAO subjects at rest may provide the same increased vagal volume feedback and result in a shortened Ti during resting breathing in these subjects. However, vagal influences on ventilation have been shown to be decreased in patients with CAO (Polacheck et al, 1980), so that this is an unlikely explanation for the shortened Ti.

The alterations in breathing pattern could also be due to hyperinflation of the lungs in patients with CAO. However, the findings of previous authors in hyperinflation experiments with normal subjects do not support this view. Grassino et al (1973) found no change in Vt or f

when end expiratory lung volumes were increased in normal subjects in a body plethysmograph. Bishop and Hirsch (1978) induced hyperventilation in young normals with positive pressure breathing and found that Te shortened, and that Vt, Vt/Ti and $\dot{V}e$ increased, but Ti remained unchanged from control. Therefore, although hyperinflation induces changes in breathing pattern the findings are not consistent with the pattern changes we observed in CAO subjects.

Another explanation for the shortening of Ti found in patients with CAO may be the fact that these patients do not expire to passive FRC . It has been shown (M.Younes et al, unpublished observations), that mechanical Ti is shortened when normal subjects begin inspiration at volumes as small as ± 200 cc above passive FRC. They maintain Vt by increasing Vt/Ti. CAO subjects in this study have shorter Ti's and increased Vt/Ti's compared to controls. It is possible that they do not explore to passive FRC during resting breathing and that this accounts for the shortening in mechanical Ti that we found. This explanation for decreased Ti in CAO subjects requires further investigation to determine its validity.

We have demonstrated that breathing pattern in CAO and in normals changes when subjects breathe on a mouthpiece, and that the mechanism of increased Vt observed appears to be different between the groups. Mouthpiece effects on breathing may not be as non-specific as was previously thought. The changes in breathing pattern in CAO subjects did not correlate with severity of disease assessed by $FEV_{1.0}$. Furthermore, breathing patterns are less variable in CAO subjects. The alterations in pattern probably are not explicable purely on the grounds of mechanical loading or increased drive in these subjects. As mechanical loading and the resulting increased inspiratory drive in CAO subjects does not entirely explain breathing pattern changes, it appears that neural adjustments in breathing control occur and that these adjustments appear to be in excess of the demands imposed by CAO.

VI REFERENCES

Abraham, W.M., Watson, H., Schneider, A., King, M., Yerger, L., and Sackner, M.A. (1981). Non-invasive ventilatory monitoring by respiratory inductive plethysmography in conscious sheep. J. Appl. Physiol: Respirat. Environ. Exercise Physiol. 51 (6): 1657-1661.

Agostoni, E., Mognoni, P., Torri, G., Saracino, F.(1965). Relation between changes in ribcage circumference and lung volume. J. Appl. Physiol. 20(6): 1179-1186.

Allison, R.D., Holmes, E.L., Nyboer, J. (1964). Volumetric dynamics of respiration as measured by electrical impedance plethysmography. J. Appl. Physiol. 19(1): 166-173.

Ashutosh, K., Gilbert, R.J., Auchincloss, .J.H., Erlebacher, J., and Peppi, D. (1974). Impedance pneumograph and magnetometer methods for monitoring tidal volume. J. Appl. Physiol. 37(6): 964-966.

Ashutosh, K., Gilbert, R., Auchincloss, J.H., and Peppi, D., (1975). Asynchronous breathing movements in patients with chronic obstructive pulmonary disease. Chest. 67(5): 553-556.

Askanazi, J., Silverberg, P.A., Foster, R.J., Hyman, A.I., and Milic-Emili, J., and Kinney, J.M. (1980). Effects of respiratory apparatus on breathing pattern. J. Appl. Physiol: Respirat. Environ. Exercise Physiol. 48(4): 577-580.

Aubier, M., Murciano, D., Milic-Emili, J., Touaty, E., Daghfous, J., Pariente, R., and Derenne, J.P. (1980). Effects of the administration of O_2 on ventilation and blood gases in patients with chronic obstructive pulmonary disease during acute respiratory failure. Am. Rev. Respir. Dis. 122: 747-754.

Bendixen, H.H., Smith, G.M. and Mead, J.(1964). Pattern of Ventilation in young adults. J. Appl. Physiol. 19(2): 195-198.

Bishop, B., Hirsch, J., and Thursby, M.(1978). Volume, flow and timing of each breath during positive-pressure breathing in man. J. Appl. Physiol. 45(4): 495-501.

Bradley, C.A., Fleetham, J.A., Anthonisen, N.R. (1979). Ventilatory control in patients with hypoxemia due to obstructive lung disease. Am. Rev., Respir. Dis. 120: 21-29.

Burki, N.K. (1979). Breathlessness and mouth occlusion presure in patients with chronic obstruction of the airways. Chest. 76(5): 527-531.

Chadha, T.A., Watson, H., Birch, S., Jenouri, G.A., Schneider, A.W., Chon, M.A., and Sackner, M.A.(1982). Validation of respiratory inductive plethysmography using different calibration procedures. Am. Rev. Respir. Dis. 125: 644-649

Clark, F.J., and Von Euler, C. (1972). On the regulation of depth and rate of breathing.J. Physiol. 222: 267-295.

Cohn, M.A., Rao, A.S.V., Broudy, M., Birch, S., Watson, H.,Atkins, N., Davis, B., Stott, F.D., and Sackner, M.A. (1982). The respiratory inductive plethysmograph: A new non-invasive monitor of respiration Bull. Europ. Physiopath. Resp. 18: 643-658.

Cherniack, R., Cherniack, L., and Naimark, A. (1972). Respiration in Health and Disease. W.B. Saunders Co., Toronto, Ont. 2nd edition.

Daubenspeck, J.A., (1981). Influence of small mechanical loads on variability of breathing pattern. J. Appl. Physiol: Respirat. Environ. Exercise Physiol. 50(2): 299-306.

Davis, J. Newsom, Stagg, D. (1975). Interrelationships of the volume and time components of individual breaths in resting man. J. Physiol. 245: 481-498.

Dejours, P., Puccinelli, R., Armand, J., and Dicharry, M.(1966). Breath-to-breath variations of pulmonary gas exchange in resting man. Respiration Physiology 1: 265-280.

Division for Lung Diseases, National Heart, Lung and Blood Institute. (1978). Protocol for intermittent positive pressure breathing collaborative program. Bethesda: National Institute of Health.

Dolfin, T.,Duffty, P., Wilkes, D.L., and Bryan, M.H.(1982). Calibration of respiratory induction plethysmography (Respitrace) in infants. Am. Rev. Respir. Dis. 126: 577-579.

Dornhorst, A.C., and Leathart, G.L. (1952). A method of assessing the mechanical properties of lungs and air passages. Lancet. July 19: 109-111.

Duffty, P., Spriet, L., Bryan, M.H., and Bryan, A.C. (1981). Respiratory induction plethysmography (Respitrace) An evaluation of its use in the infant. Am. Rev. Respir. Dis. 123: 542-546.

Gardner, W.N. (1977). The relation between tidal volume and inspiratory and expiratory times during steady state carbon dioxide inhalation in man. J. Physiol. 272: 591-611.

Gilbert, R., Auchincloss, J.H., Gerhard, B., Peppi, D., and Long, D. (1971). Breathing pattern during CO_2 inhalation obtained from motion of the chest and abdomen. Respir. Physiol. 13: 238-252.

Gilbert, R., Auchincloss, J.H., Brodsky, J. and Boden, W. (1972). Changes in tidal volume, frequency and ventilation induced by their measurement. J. Appl. Physiol. 33 (2): 252-254.

Gillam, P.M.S.(1972). Patterns of respiration in human beings at rest and during sleep. Bull. Physiopath. Resp. 8: 1059-1070.

Grassino, A.E., Lewinsohm, G.E., and Tyler, J.M. (1973). Effects of hyperinflation of the thorax on the mechanics of breathing. J. Appl. Physiol. 35(3): 336-342.

Grassino, A.E., Sorli, J., Lorange, G., and Milic-Emili, J. (1978). Respiratory drive and timing in chronic obstructive pulmonary disease. Chest. 73(2) Suppl: 290-293.

Hamilton, L.H., Beard, J.D., and Kroy, R.C. (1965). Impedance measurement of tidal volume and ventilation. J. Appl. Physiol. 20 (3): 565-568.

Hays, W.L. (1973). Statistics for the Social Sciences. 2nd edition. Holt, Rinehard and Winston, Inc., Toronto.

Hey, E.N., Lloyd, B.B., Cunningham, J.C., Jukes, M.G.M. and Bolton,D.P.G. (1966). Effects of various respiratory stimuli on the depth and frequency of breathing in man. Respirat. Physiol. 1: 193-205.

Hirsch, J.A. and Bishop, B.(1982). Human breathing patterns on mouthpiece or facemask during air, CO_2, or low O_2. J. Appl.Physiol. 1281.

Hlastala, M.P. Wranne, B., and Lenfant, C.J. (1973). Cyclic variations in FRC and other respiratory variables in resting man. J. Appl. Physiol. 34 (5); 670-676.

Konno, K., and Mead, J. (1967). Measurement of the separate volume changes of ribcage and abdomen during breathing. J. Appl. Physiol. 22(3): 407-422.

Kryger, M. (1981). Pathophysiology of Respiration. John Wiley & Sons. Toronto.

Kubicek, W.G., Kinnen, E., and Edin, A. (1964). Calibration of an Impedance Pneumograph. J. Appl. Physiol. 19(3): 557-560.

Lenfant, C. (1967). Time-dependent variations of pulmonary gas exchange in normal man at rest. J. Appl. Physiol. 22(4): 675-684.

Mead, J., Peterson, N., Grimby, G. (1967). Pulmonary ventilation measured from body surface movements. Science, 156: 1383-1384.

Milic-Emili, J., and Aubier, M.(1980). Some recent advances in the study of the control of breathing in patients with chronic obstructive lung disease. Anesthesia & Analgesia, 59(11): 865-873.

Milledge, J.A., and Stott, F.D. (1977). Inductive plethysmography- a new respiratory transducer. Proceedings of the Physiological Society. 4P-5P.

Milic-Emili, J., and Grunstein, M.M. (1976). Drive and Timing Components of ventilation. Chest, 70 (1) Suppl: 131-133.

Onal, E., Lopata, M., and Garrard, C.S. (1981). Diaphragmatic EMG in studies of inspiratory "off-switch" threshold in humans. Lung, 159: 265-273.

Pack, A.I., Delaney, R.G., and Fishman, A.P. (1981). Augmentation of phrenic neural activity by increased rates of lung inflation. J. Appl. Physiol: Respirat. Environ. Exercise Physiol. 50 (1): 149-161.

Parot, S., Saunier, C., Gauthier, H., Milic-Emili, J., and Sadoul, P. (1980). Breathing pattern and hypercapnia in patients with obstructive pulmonary disease. Am. Rev. Respir. Dis. 124: 985-991.

Polacheck, J., Strong, R., Arens, J., Davies, C., Metcalf, I., and Younes, M. (1980). Phasic vagal influence on inspiratory motor output in anesthetized human subjects. J. Appl. Physiol. 49(4): 609-619.

Priban, I.P. (1963). An analysis of some short-term patterns of breathing in man at rest. J. Physiol. 166: 425-434.

Remmers, J.E., and Marttila, I. (1975). Action of intercostal muscle afferents on the respiratory rhythm of anesthetized cats. Respiration Physiology. 23: 31-39.

Sackner, M. (1980). Monitoring of ventilation without physical connection to the airway; A review. In Stott,F.D.,Rafferty, E.B.,Goulding, L. Eds. Proceedings of the 3rd International Symposium on Ambulatory Monitoring. London. Academic Press. 299-319.

Sackner, J.D., Nixon, A.J., Davis, B., Atkins, N., and Sackner, M.A. (1980a). Non-invasive measurement of ventilation during exercise using a respiratory inductive plethysmograph. Am. Rev. Resp. Dis. 122: 867-871.

Sackner, J.D., Nixon, A.J., Davis, B., Atkins, N., and Sackner, M.A. (1980b). Effects of breathing through external dead space on ventilation at rest and during exercise. 11. Am. Rev. Resp. Dis. 122: 933-940.

Sackner, M.A., Rao, A.S.V., Birch, S.. Atkins, N., Gibbs, L., and Davis, B. (1982). Assessment of density dependent flow-volume parameters in non-smokers and smokers. Chest 82(2): 137-142.

Shapiro, A., and Cohen, H.D. (1965). The use of mercury capillary length gauges for the measurement of the volume of thoracic and diaphragmatic components of human respiration: A theoretical analysis and a practical method. Transactions New York Acad. Sci. Ser. II 27: 634-649.

Sorli, J., Grassino, A., Lorange, G., and Milic-Emili, J. (1978). Control of breathing in patients with chronic obstructive lung disease. Clin. Sci. Mol. Med. 54: 295-304.

Stagg, D., Goldman, M., and David, J.N. (1978). Computer-aided measurement of breath volume and time components using magnetometers. J. Appl. Physiol: Respirat. Environ. Exercise Physiol. 44 (4): 623-633.

Steele, R.G.D. and Torrie, J.H. (1960). Principles and Procedures of statistics. Toronto, McGraw-Hill Book Co., Inc.

Tabachnik, E., Muller, N., Toye, B., and Levison, H. (1981). Measurement of ventilation in children using the respiratory inductive plethysmograph. J. Peadiatrics. 99 (6): 985-899.

Von Euler, C., Herrero, F., and Wexler, I. (1970). Control mechanisms determining rate and depth of respiratory movements.Respiration Physiology 10: 93-108.

Wade, O.L. (1954). Movements of the thoracic cage and diaphragm in respiration. J. Physiol. 124: 192-212.

Wadhwani, R., and Longini, R.L. (1973). Analysisof quiet spontaneous breathing as measured by spirometer and electrical impedance plethysmograph. Computers and Biomedical Research. 6: 74-89.

Watson, H. (1980). The technology of respiratory inductive plethysmograph. In. Stott, F.D., Raferty, E.B., Goulding, L; eds. Proceedings of the 3rd international symposium on ambulatory monitoring London: Academic Press, 537-563.

West, S. (1909). Diseases of the organs of respiration. Vol. 1, 2nd edition. C. Griffin & Co., Ltd., London, England. pp 209.

Whitelaw, W.A., Derenne, J.P. and Milic-Emili, J. (1975). Occlusion pressure as a measure of respiratory center output in conscious man. Respiration Physiology. 23: 181-199.

APPENDIX I

Verification of Volume Measurements

As the volume used to calibrate the RC and ABD signals was derived from integrating a flow signal (Figure 1), it was necessary to verify the accuracy of the pneumotachygraph and the accuracy of the computer calculations.

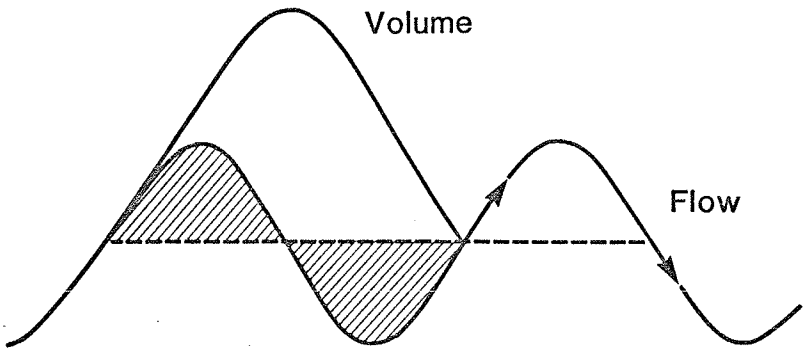

Figure 1: The pneumotachygraph measured flow. The dotted line represents the baseline (zero flow). The area under the flow curve (hatched area) is equal to volume. The hatched area above the baseline is inspiration and below the baseline is expiration. The volume signal is superimposed over the flow signal for one respiratory cycle.

1. Determination of Baseline

Baseline stability was important as drift in the flow signal would be integrated as volume. A digital voltmeter was used to measure the voltage at zero pressure recorded from the validyne pressure transducer.

A small amount of noise represented by a voltage (.01 - .02 mv) was present at zero flow. To prevent this noise from being integrated, the computer sampled the voltage recorded by the validyne pressure transducer during three 10 second periods when there was no flow through the pneumotachygraph. The maximum positive, maximum negative and average voltage seen during these periods was measured. The average "noise" voltage for these three blocks was stored and only signals greater than this background were subsequently integrated.

2. Since determination of volume required the measurement of area under a flow curve, we tested the computer system to ensure that it could measure area under conditions that we could verify manually. A function generator (Interstate Electronics Corp F33) was used to produce a square wave signal to simulate a fixed flow rate. The area under the square wave (volume), and the frequency were varied. The actual area under the flow curve as measured from the polygraph record, was compared to the computer calculated area. Frequency of the signal was determined from the polygraph. Five measurements were made at each frequency. The relationship was found to be linear over a wide range of volumes and frequencies, (Figure 2).

3. Once a calibration factor (computer units/unit flow) was obtained, the stability of this factor was tested.

The voltage/volume relationship for the pneumotachygraph output was calibrated against a volume delivered by a syringe (Hewlett Packard, model 14278B). This allowed calibration using a volume comparable to the subjects resting tidal volume. A series of these volumes were delivered through the pneumotachygraph at various flows and the computer calculated volumes were displayed on the console. The average of 3

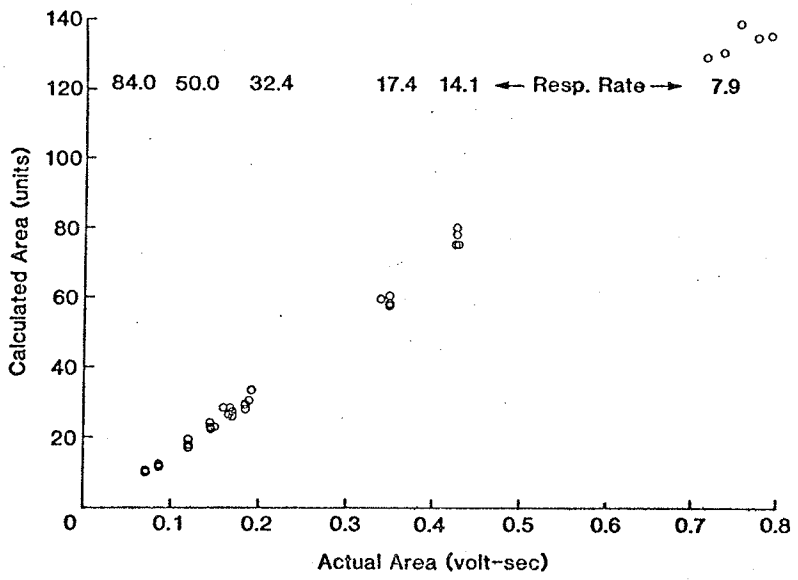

Figure 2: The computer calculated area is on the ordinate and the actual area calculated from the polygraph record is on the abscissa. Each group of points represents 5 measurements at frequencies (Resp.Rate) varying from 84/min to 7.9/min.

measurements was used as the calibration factor. It has been previously demonstrated that the computer accurately calculated volume over a wide range of frequencies and volumes. Using a syringe to deliver volume accurately, 5 measurements were made at 0.5, 1.0, 1.5 and 2.0 litre intervals at varying flow rates. The results are included in Figure 3.

4. Using this calibration factor, the computer was then tested to determine its accuracy in measuring volume. A calibrating syringe was used to deliver volumes between 0.1 L and 2.0 L at varying flow rates through the pneumotachygraph. Five measurements were made at each volume and compared to the computer calculated volume. The relationship was linear over the entire range which exceeds what would be expected in subjects during quiet respiration (Figure 4).

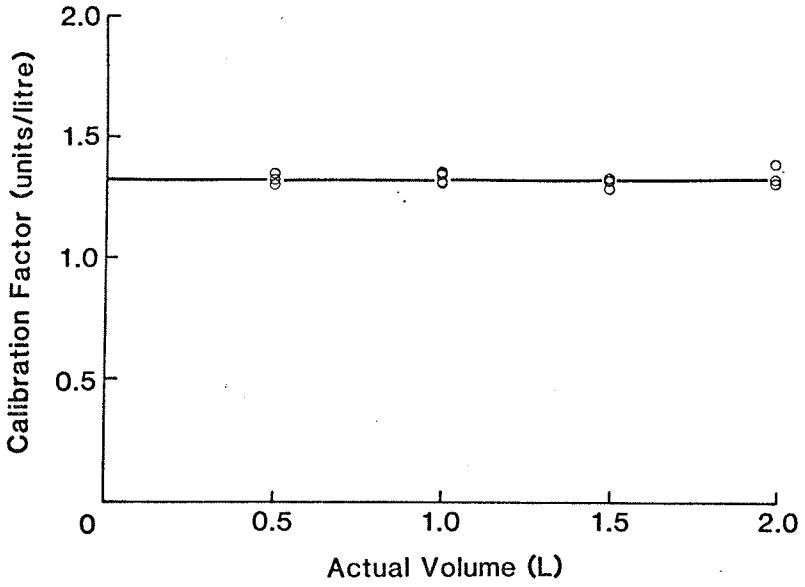

Figure 3: The computer calculated calibration factor (units/litre) is on the ordinate, and the actual volume delivered through the pneumotachygraph with a calibrating syringe in litres is on the abscissa. Each group of open circles represents five measurements. A regression line has been drawn through the points.

5. The measurements described in Figure 4 were made at ATPS and were subsequently converted to BPTS conditions.

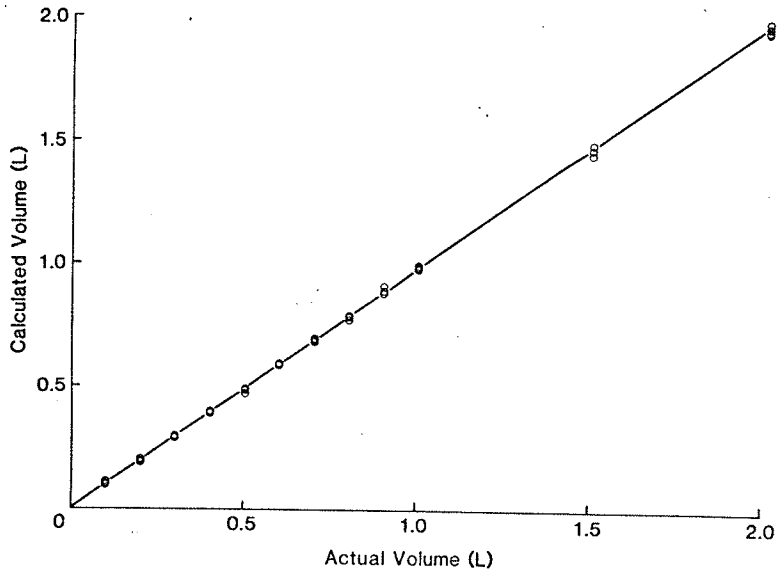

Figure 4: The computer calculated volume in litres (L) on the ordinate, and the actual volume in litres (L) delivered through the pneumotachygraph with a syringe is on the abscissa. A regression line has been drawn through the points.