STUDIES ON LUNGMECHANICS

P. G. DONLEBEN

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STELLINGEN

Behorende bij het proefschrift van

P. G. DONLEBEN

STUDIES ON LUNGMECHANICS

11 NOVEMBER 1959

STELLINGEN

1.

De beste behandeling van het coma hepaticum en aanverwante toestanden is de toediening van neomycine per os.

2.

Er bestaat een correlatie tussen de graad van lipaemie en de subjectieve en objectieve tekenen van angina pectoris en claudicatio intermittens.

3.

Het prophylactisch gebruik van nitroglycerine bij angina pectoris moet worden ontraden.

H. S. NANNINGA. Diss. Utrecht 1958.

4.

De leer van FREUD is in vele opzichten een pseudo-darwinistische beschouwingswijze, die als zodanig medisch en biologisch gezien niet is te handhaven.

5.

Uraemie par manque de sel ontstaat nog te vaak door de kortsluiting: hoge bloeddruk — zoutloos dieet.

6.

Het gebruik van magnesium sulfaat als laxans is niet zonder gevaar.

7.

De verticale diffusiemethode lijkt een eenvoudige en voldoend betrouwbare methode ter bepaling van het gehalte aan vrij isonicotinezuur hydrazide in het serum.

8.

Bij ongelijkmatige ventilatie is de compliance geen maat voor de long-elasticiteit.

9.

De frequentie afhankelijkheid van de compliance is geen bewijs voor het bestaan van ongelijkmatige ventilatie.

10.

De klachten van het „dumping syndrome" worden veroorzaakt door een afname van het bloedvolume.

11.

In bedrijven, inrichtingen en instellingen, waar een ruim raakvlak ligt tussen maatschappelijk werk en maatschappelijke gezondheidszorg, is het diploma A en/of B ziekenverpleging voor een daar aangestelde maatschappelijke werker(ster) noodzakelijk.

12.

Bij kunstmatige ventilatie in de anaesthesie ventilere men, indien men slechts één grootheid wil bepalen, op geleide van de pH.

J. G. DEFARES en L. A. BOERÉ
(wordt gepubliceerd)

13.

De retinitis diabetica is te genezen door een dieet met een zeer laag vetgehalte.

14.

De chemopraeventie bij tuberculose dient uitsluitend te worden toegepast in combinatie met B.C.G. toediening.

15.

Tijdens operatie voor een phaeochromocytoom is continue intra-arteriële bloeddruk registratie geïndiceerd.

Errata

	staat :	verander in :
blz. 65, regel 14 van onder	each each	each
blz. 65, regel 4 van onder	critisism	criticism
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blz. 110, regel 19 van boven	subjects	subject's
blz. 110, regel 9 van onder	biopsie	biopsy
blz. 111, regel 22 van onder	thit	that
blz. 111, regel 15 van onder	Neegaard	Neergaard
blz. 125, regel 16 van boven	stativ	static
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blz. 150, regel 12 van onder	available	the available

blz. 152, regel 4 van boven deel van de zin twee maal herhaald.

RIJKSUNIVERSITEIT TE GRONINGEN

STUDIES ON LUNGMECHANICS

(MET EEN SAMENVATTING IN HET NEDERLANDS)

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR
IN DE GENEESKUNDE AAN DE RIJKSUNIVERSITEIT
TE GRONINGEN OP GEZAG VAN DE RECTOR
MAGNIFICUS PROF. DR. P. J. BOUMAN,
HOOGLERAAR IN DE FACULTEIT
DER RECHTSGELEERDHEID,
IN HET OPENBAAR
TE VERDEDIGEN
OP WOENSDAG 11 NOVEMBER 1959
DES NAMIDDAGS OM 4 UUR

DOOR

PIETER GEORGE DONLEBEN

GEBOREN TE SEMARANG

1959

DRUKKERIJ ROMIJN - APELDOORN

PROMOTOR: Prof. Dr. N. G. M. ORIE

Met erkentelijkheid wordt melding gemaakt van de steun welke werd ontvangen van de Koninklijke Nederlandse Centrale Vereniging tot Bestrijding der tuberculose en van de gezondheidsorganisatie T.N.O. te 's-Gravenhage.

Aan de nagedachtenis van mijn Vader

The studies leading to this thesis were done in the division of pulmonary diseases (Prof. Dr. N. G. M. Orie) of the medical clinic of the University, Groningen.

τὰν κεφαλὰν καὶ μὴ τὰν γραμμάν
Archimedes

Een woord vooraf.

In mijn levenswandel is het verschijnen van dit proefschrift een rustpunt. dat mij de gelegenheid biedt gevoelens van dank en blijdschap tot uiting te brengen.

Dat mijn Moeder deze, voor mij zo belangrijke dag mag beleven, stemt mij tot dankbaarheid.

Met erkentelijkheid gedenk ik de Hoogleraren en Lectoren van de medische faculteit der Rijksuniversiteit te Leiden, die mij opgeleid hebben tot arts.

Degenen, van wie ik „geleerd" heb, zijn heengegaan.

Toen ik afstudeerde kon ik niet denken dat „turbulente stromingen" die tijden eigen, mij zo zouden aangrijpen, dat eerst ruim een kwart eeuw later die geestelijke en lichamelijke rust zouden terugkeren, die de bewerking van dit proefschrift mogelijk maakten, zodat ik nu mag zeggen de „turbulente stromingen" althans theoretisch te beheersen.

Hooggeleerde ORIE, Hooggeachte Promotor,

Dat Ge mijn promotor hebt willen zijn, was voor mij van zeer grote betekenis, waarvoor ik U veel dank verschuldigd ben.

Immers doordat Ge weet welk een (extra) inspanning het bewerken van een dissertatie nu eenmaal vraagt, hebt Ge me mijn vertrouwen in eigen physiek terug kunnen geven. Dat Ge mij, als „buitenstaander" dit onderwerp hebt willen toevertrouwen, stemt mij met verheugenis. Ik stel het op hoge prijs, dat ik van Uw waarlijk enorme belezenheid en grote ervaring heb mogen profiteren tijdens de vele uren die Ge aan de bespreking van de stof hebt willen wijden. Deze uren, die ik telkens weer met spanning tegemoet zag, en waaraan ik met een zekere weemoed terug denk, zijt Ge mij een leermeester geweest.

Zeer Geleerde DEFARES, beste JIM.

Zonder jouw leiding was dit proefschrift nimmer tot stand gekomen. Je originele vondsten en exacte denkwijze hebben in hoge mate bijgedragen tot het eindresultaat.

Ik heb getracht jouw wetenschappelijke paranoia: „vertrouw niemand, vooral niet je zelf" bij de bewerking van dit proefschrift tot leidraad te maken. Voor de lessen in hogere wiskunde en longphysiologie ben ik je zeer dankbaar. Ook ben ik je erkentelijk voor de Engelse vertaling van dit proefschrift.

Zeergeleerde Vos.

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Met waarlijk veel genoegen denk ik terug aan de tijd waarin je me de eerste schreden leerde zetten op het terrein van de röntgenfotografie. En aan de te nauwe deuropeningen!

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Hartelijk dank voor je terzake kundige uitleg van, voor mij als sociaal-hygienisch werkend longarts, niet alledaagse begrippen.

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Mijn oprechte dank voor de tijd die je me liet voor de bewerking van dit proefschrift en voor je hulp mijn dagelijks werk te verlichten!

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Loes, Marijke, komt de ware aard niet pas te voorschijn bij het schrijven van een proefschrift!? Gelukkig maar dat jullie geduld zo heel veel groter bleek dan het mijne!

CONTENTS

CHAPTER I.

GENERAL INTRODUCTION.

I *The meaning of elastance (compliance).*

Since the concepts elastance and compliance are derived from mechanics, it seems useful to illustrate their meaning with the aid of a simple mechanical model: a spring fixed at one end (see fig. 1).

In the simplest case, the force $\triangle F$ required to stretch the spring, will be proportional to the displacement, or

$$\triangle F = S \triangle L \qquad (1)$$

where $\triangle F$ = increment of force, S = constant of proportionality, and $\triangle L$ = displacement of the free end of the spring (increment of length), or $\triangle L = L - L_0$, where L_0 is the "resting" length of the spring and L its length under an arbitrary load.

Fig. 1

Mechanical model of a spring fixed at one end.

The constant of proportionality S is called the *elastance,* while its reciprocal value, i.e. 1/S is called the compliance C, so that

$$\text{compliance } C = \frac{1}{S}$$

The above relation may be applied to the lungs. Since however, the lung represents a three-dimensional body, we must replace length, by volume. It may be shown that then force must be replaced by pressure, which is force per unit area. The equivalent formula for the lung then becomes

$$\triangle P = S \triangle V \qquad (2)$$

where $\triangle P$ = increment of pressure in the pleural space measured under static conditions, i.e. during breathholding with open glottis and expressed in cm H_2O, $\triangle V$ = increment of lungvolume (i.e. tidal volume) expressed in liters.

Again S in (2) is called the elastance, while $1/S = C$ is called the compliance.

It should be stressed that formula (2) only applies when the relationship between volume and pressure (measured under static conditions) is linear, i.e. when this relationship may be represented by a straight line.

It follows from equation (2) that

$$S = \frac{\triangle P}{\triangle V} \text{ or dimensionally}$$

$$[S] = \left[\frac{\text{cm } H_2O}{\text{litre}}\right]$$

It is thus clearly seen that the elastance represents the ratio of the pressure change and the corresponding volume change, measured under static conditions.

We shall illustrate the above by giving an example:

Let it be assumed that the subject inspires 0.5 litre and that the pressure in the pleural space at the end of this inspiration (measured during apnea) is 6 cm H_2O more negative relative to its value at the end-expiratory level.

Then the elastance S is

$$S = \frac{6}{0.5} = 12 \text{ cm } H_2O/\text{litre}.$$

One might be inclined to think that a high elastance value (low compliance value) implies an increased "rigidity" of the lungs.

This conclusion does not necessarily follow; e.g. the lungs of babies possesses a very high elastance value, while it is known that the rigidity of the lungtissue of babies is certainly not "abnormally increased". (MC. ILROY e.a. 1955, SCHERRER e.a. 1957.) We shall now show that a high elastance value need not indicate an increased "stiffness" of lungtissue.

Let us consider the well-known HOOKE's law of elastic bodies which states

$$\triangle F = E \frac{\triangle L}{L_0} \qquad (3)$$

This equation (3) may be directly applied to our example of the (linear) spring. Again $\triangle L$ = displacement (increment of length). However, L_0 = initial (resting) length of the spring, i.e. the length of the spring when the spring it not subjected to the action of external forces.

$\triangle F$ = increment of force.

E = constant of proportionality, known as the modulus of elasticity.

Equation (3) simply states that increment of force is proportional to *relative* increase in length of the spring (here we consider stretch only; for compression an analogous statement could be made).

Let us consider two springs (one end attached) made of the same material. Let one spring have a resting length of 100 cm, while the initial length of the second spring is 1 cm.

Then, "intuitively", we know that it will require a much greater force to stretch the short spring over 1 cm (100 % stretch) than to stretch the long spring over 1 cm (1 % stretch).

But this is just what is quantitatively stated by equation (3). The modulus of elasticity E forms a direct measure of the "elastic" properties ("stiffness") of the material.

The greater E, the "stiffer" the material, since then the force required to establish a given relative increase of length ($\triangle L/L_0$) will be great.

Formula (3) only applies in the case of a linear spring, but even in the case of non-linear bodies, such as the lung, HOOKE'S law may be applied, when only a sufficiently small (i.e. linear) interval is considered.

It is evident that if we wish to apply equation (3) to a linearized lung-system, we must replace $\triangle K$ by $\triangle P$, $\triangle L$ by $\triangle V$ and L_0 by V_0 (where

V_0 is the volume of the lungs when the lungs are not under stress, i.e. (normally) when the interpleural pressure equals atmospheric pressure).

Hence we may write

$$\triangle P = E \frac{\triangle V}{V_0} \tag{4}$$

where E = modulus of elasticity.

Rearranging (4) yields

$$\frac{\triangle P}{\triangle V} = \frac{E}{V_0} \tag{5}$$

Or, since, per definition $\frac{\triangle P}{\triangle V}$ is the elastance S,

$$S = \frac{E}{V_0} \tag{6}$$

We thus see from (6) that the elastance is directly proportional to the modulus E, and inversely proportional to the "initial" volume V_0, i.e. the greater E (i.e. the "stiffer" the lung) the greater the elastance and similarly, the smaller the V_0, the greater the elastance. Since the value of V_0 is quite small in children, relation (6) explains why in babies etc. very high elastance values are found (high, of course, relative to the values found in normal adults).

The clinician primarily wishes to know whether the "elasticity" of the lung has changed, e.g. whether the lungs has become more "elastic", i.e. more rigid than normal. (SCHERRER e.a. 1957, ROSSIER e.a. 1958)

It should be noted that in technical language increased elasticity is expressed by a high value of E, which means that the lung has become "stiffer".

The value of E, when compared with normal E values, gives direct information as to the elastic condition of the lungtissue: as mentioned above, a high E value implies increased rigidity of the lungs, as may be encountered e.g. in fibrosis cases. E may be found experimentally from the equation (6), or

$$E = SV_0 \tag{7}$$

It is seen from (7) that E equals the product of the elastance S and the initial lungvolume V_0.

The experimental determination of V_0 requires further consideration.

We have defined V_0 as that lungvolume where the lung is not subjected to external forces (This condition would be obtained when the intrapleural pressure is zero.)

The essential requirement is, however, that the pressure across the lung is zero, i.e. (when breathing atmosferic air with open glottis) that the interpleural pressure equals the pressure inside the lung, i.e. equals atmospheric pressure.

From this observation it easily follows that in general V_0 does not equal F.R.C. or the residual volume (R.V.) but possesses a value lying between the F.R.C. and R.V. This follows from the observation that at end-expiratory level (F.R.C.) the intrapleural pressure is, in general, negative, while at the end of a maximal expiration, (R.V.), the intrapleural pressure is generally positive. Hence V_0, i.e. the lungvolume at zero pressure must in general possess a value lying somewhere between the F.R.C. and R.V. values.

The problem of obtaining a measure for the elastic properties of the lungtissue will be fully discussed in Chapter II.

II *Resistance to breathing and work of breathing.*

Let us return to our spring.

We will now take into account the influence of viscous damping (friction forces).

If we place the spring, e.g., in oil than we must exert a greater force to stretch the spring at a given velocity, than when the spring was placed in air.

Now when we keep all factors, except the velocity, constant, then we may say that the force required to overcome the viscous friction will be directly proportional to the velocity, in the simplest case, or

$$F_R = Rv \tag{8}$$

where, F_R = force component to overcome the (viscous) resistance, v = velocity, R = constant of proportionality and is called the damping coefficient, or coefficient of viscous resistance etc.

If we stretch the spring at a certain velocity v ($v \neq o$) then we must exert a force to overcome two contra forces, i.e.

1° the "elastic force" of the spring (F_e) and

2° the resistive force. (F_R).

The force required to overcome the elasticity of the spring is given by equation (1), while the force to overcome the resistance is expressed by equation (8). The total force F_T thus is

$$F_T = F_e + F_R = SL + Rv \tag{9}$$

In equation (9) we have replaced, for convenience, the symbols $\triangle$ F *and* $\triangle L$ *by the symbols* F *and* L.

This is merely a matter of notation and the symbol L used here should not be confused with the L used earlier to indicate the total length of the spring. In the remaining part of this chapter L and V will denote the displacement and volume change i.e. they will be used to indicate $\triangle L$ *and* $\triangle V$ *respectively.*

F_T = total force, F_e = force component to overcome the "elasticity", F_R = force component to overcome the resistance.

The equivalent of equation (9) for the lung obviously is

$$P_T = P_e + P_R = SV + R\dot{V} \tag{10}$$

where P = pressure across the lungs.

V = displaced gasvolume at any instant t, $\dot{V}$ = rate of volume flow, i.e.

the volume of gas passing a cross-section (of the common deadspace) per unit of time.

Since the compressibility of the gas may be ignored here, V also represents the volume change of the lung at any instant t.

Equations (9) and (10) are fundamental and express the fact that the total pressure (force) consists of 2 components, one component being required to overcome the "elasticity", and the other component being required to overcome the (viscous) resistance. In (10) the "elastic" pressure-component is directly proportional to the volume change, while the "resistive" pressure component is directly proportional to the rate of volume flow $\dot{V}$.

We shall now illustrate the meaning of (10) by giving a concrete example. At a first approximation we may consider the lungs as a balloon connected to a long narrow pipe. (See fig. 2, where the balloon represents the elastic lungtissue, and where the pipe stands for the airways.)

Fig. 2
Model of a balloon connected to a long narrow pipe.

If the pipe were absent, then we would, while blowing against the balloon, only require a force to overcome the "elasticity" of the balloon.* In the presence of a long narrow pipe, however, we must exert extra pressure to overcome the resistance in the pipe. and this extra pressure will be, according to the second term in the right-hand side of (10), directly proportional to the rate of flow $\dot{V}$.

The pressure-volume diagram.

In fig. 3 the tidal volume is plotted against the esophageal (pleural) pressure, (where the pressure is measured differentially against mouth-pressure).

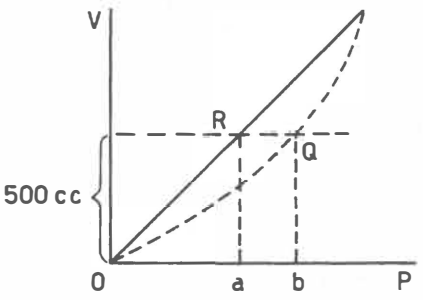


Fig. 3
For explanation see text.

The curved line is traced during a normal inspiration. The broken straight line results when the subject inspires very slowly, i.e. practically "statically" (implicitly we thus assume a linear relation between V and P, i.e. the validity of equation (1)). Let us consider the point Q on the curved line, i.e. the point at a volume change of 500 cc. The corresponding pressure apparently equals the distance O b, which represents 10 cm H_2O. In the static

* The relation betweet P_e and V is far from being linear in the case of a balloon, but this is immaterial here.

case (see straight broken line), the pressure required to maintain the lung at the inflated position of 500 cc above the end-expiratory level (see point R), would be given by the distance O a which is 4 cm H_2O.

We may thus think of the total pressure O b as being the sum of two components, the pressure O a, and the pressure a b (3 cm H_2O), where O a represents the static or elastic component and where a b represents the resistive (or dynamic) pressure component.

In fig. 4 the three different curves are obtained by inspiring on three different occasions with *different* flows. The broken straight line is again the "static" line obtained during breathholding at different degrees of lunginflation. The curved line 1 is obtained during slow inspiration, curve 2 is obtained during a moderately fast inspiration, while curve 3 is obtained during a fast inspiration. We thus see that the faster the inspiration the more the curve "bulges". It may also be seen that the "static" line is a limiting case which would be obtained when inspiration is "infinitely slow".

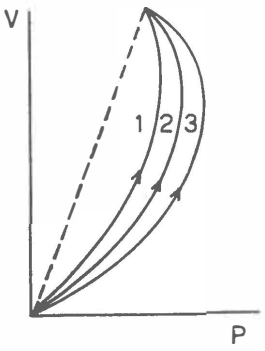


Fig. 4
For explanation see text.

In fig. 5 "bulging" occurs by a different cause. Curve 1 is obtained during quiet inspiration at a rate of flow of 100 cc/sec. say. Curve 2 is obtained at the same rate of flow, but with an added resistance (e.g. long narrow pipe) in the airways.

We thus see from the above examples that the curve during inspiration may become more curved ("bulging") as a result of 2 causes:

1° more rapid breathing
2° increased resistance.

This conclusion, moreover, can be directly derived from eq. (8) as applied to the lung which states.

$$P_R = R \dot{V} \qquad (11)$$

We see from this equation that the pressure to overcome the resistance, or the resistance pressure component, P_R, depends both on R (i.e. the resistance determined by the dimensions of the airways, etc.) and $\dot{V}$, the rate of volume flow.

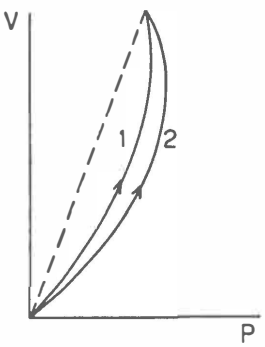


Fig. 5
For explanation see text.

It is obvious that these considerations also apply to the expiratory phase.

Combining both the inspiratory curve and the curve traced during expiration, a loop is obtained such as is shown in fig. 6.

From the above it further follows that the width of the loop is determined a) by the magnitude of the airway resistance, and b) by the rate of volume flow.

(The influence of hysteresis on the "fatness" of the loop will be considered later).

As will be shown later, the area enclosed by the loop represents the work required to overcome the resistance to breathing. Although not quite correct, we shall call this resistive work, following common usage, the viscous work.

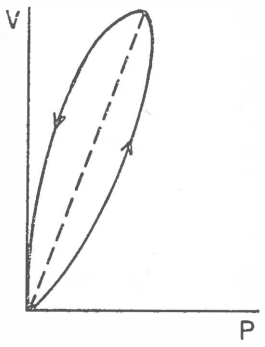


Fig. 6
For explanation see text.

If we desire to employ the viscous work (area of the loop expressed in proper units) as a measure of the resistance, then we must, as has been explained above, keep the rate of volume flow constant. The mean rate of flow during a single respiratory cycle may be held sufficiently constant by having the subject breathe at a fixed frequency and fixed tidal volume.

Only when the frequency and tidal volume are standardized it will be possible to obtain comparable values that may be used as an index for the magnitude of the resistance to breathing.

We have, more or less arbitrarily chosen the following standard frequencies and tidal volumes:

frequency cycle/min	tidal volume in litres	
15	1	0.6
40	1	0.6

The choice of these different standard conditions is based upon the following considerations. Some patients, e.g. fibrosis cases are unable to breathe at a frequency of 15 cycles/min over 1 liter These patient are able, however, to breathe over 600 cc at a f = 15 or/and f = 40.

Conversely some asthmatics are unable to respire at f = 15 over 600 cc without becoming "dyspneic". These patients breath spontaneously at large tidal volumes.

The frequency 40 has been chosen for a number of reasons (see chapter XII), one reason being that many patients have still greater resistances at high rates of flow as a result of a "checkvalve" effect.

Obviously, in order to know what values of viscous work under these standard conditions represent pathologically increased resistance to breathing we must possess "normal values" taken from healthy subject of the same age and sex distribution. The presentation of these "normal values" forms the subject of chapter XII.

CHAPTER II

THE DETERMINATION AND SIGNIFICANCE OF THE MODULUS OF ELASTICITY OF THE LUNGS

It will presently be shown that a decreased compliance does not necessarily imply an increased "stiffness" of the lung, since the value of the compliance depends on two variables, viz. the "stiffness' of the material, as numerically represented by the so-called modulus of elasticity and the initial lungvolume, i.e. the lungvolume available for gas, when no pressure difference exists across the lungsurface.

HOOKE's law, valid for all elastic bodies (in non linear elastic systems HOOKE's law may be applied when the range is chosen sufficently small to obtain a linear part of the curve) states:

$$\triangle P = E \frac{\triangle V}{V_0} \qquad (1)$$

In the case of the lung (for simplicity we assume that the static P—V curve is linear), $\triangle V$ = tidal volume = increase in lungvolume,
$\triangle P$ = corresponding change in pressure across the lungsurface and
V_0 = initial lungvolume, i.e. lungvolume when pressures inside and outside the lung are equal.

In order to avoid confusion, it should be stressed that $\triangle P$ and $\triangle V$, have the same meaning as symbols P and V in the second part of Chapter I, as may readily be checked.

The reason for employing the increment symbol $\triangle$ here, stems from the circumstance that here the "resting" volume V_0 is taken into account.

It must further be stressed that V_0 is by no means identical with the F.R.C., since at that volume the lung is still under tension, as manifested by the slightly negative intrapleural pressure. Only when, under static conditions, the intrapleural pressure is zero, the lungvolume may be identified with "equilibrium" volume V_0, as defined above.

HOOKE's law simply states that the pressure increment $\triangle P$, is proportional to the relative increase of volume $\frac{\triangle V}{V_0}$. The coefficient of proportionality E is a measure of the "stiffness" of the material.

The stiffer the material, the greater will, of course, be the pressure change required to effect a fixed relative volume increase. This requires that E should be large with stiff materials. From this, it follows that e.g. steel possesses a very high modulus of elasticity, while rubber possesses a very small E value.

Rearrangement, of (1), gives

$$\frac{\triangle P}{\triangle V} = \frac{E}{V_0}$$

But since $\frac{\triangle P}{\triangle V} = S =$ elastance, it follows

$$S = \frac{E}{V_0} \qquad (2)$$

Equation (2) is important, since it tells us that the elastance S, depends on two variables, namely E which depends on the stiffness of the material (lungtissue) and V_0, the equilibrium lungvolume.

It follows from (2) that a high value of the elastance does not necessarily mean an increased stiffness of the lungtissue, but may result from a smaller initial lungvolume V_0.

In smaller animals (in dogs weighing about 20 kg, the elastance is about 15 cm H_2O/litre, while in normal human adults the value is about 4 cm H_2O/litre) (VERSTRAETEN 1956, NISSELL e.a. 1954, LAWTON e.a. 1951) and children (COOK e.a. 1955, MC ILROY e.a. 1955,) the elastance is much greater than in normal adults, not as the result of greater rigidity of the lung, but because of smaller initial lungvolume V_0.

It would be of considerable importance to determine the modulus of elasticity E. This, from (2), requires a knowledge of S and V_0. The determination of V_0 is somewhat uncertain, however, since we require to know the lungvolume when the pressure across the lungsurface is zero, i.e. when the (static) pressure in the pleural space is zero. Now, two difficulties exist. First, it has not been unequivocally demonstrated that the absolute level of the pressure in the esophagus equals the absolute level of the pressure in the pleural space (DUOMARCO e.a. 1954) and second when the pressure is recorded with the esophagusballoon technique, the absolute level as recorded becomes a function of the filling of the balloon (MEAD e.a. 1954.)

However, assuming the "approximate" equality of absolute pressures in esophagus and pleural space it is possible to obtain an approximation of the initial volume V_0 in the following manner:

Let us study fig. 1.

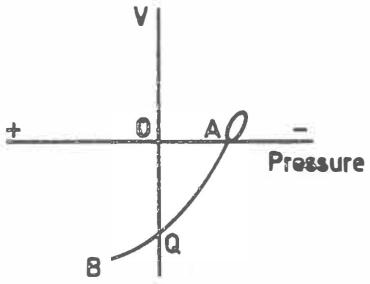


Fig. 1

For explanation see text.

Te origin of any coordinate system may be arbitrarily chosen. In fig. 1 the origin is chosen at zero (atmospheric) pressure and end-expiratory level.

The loop in the figure represents a normal respiratory cycle. If now, starting from the end-expiratory level (point A) the subject expires quite slowly and maximally, then the curve AQB will be described in the volume-pressure diagram. Since at the point Q the pleural pressure is zero, it follows that the lungvolume existing "at" the point Q represents V_0. Knowing the F.R.C. value, V_0 can now easily be found from the relation

$$V_0 = \text{F.R.C.} - T_0$$

where T_0 represents the "tidal volume" expired between the end-expiration level and the point Q, or better, T_0 in the figure is simply given by the distance OQ.

(Obviously the F.R.C. must be determined in the same position etc. as during the determination of T_0).

RESULTS.

The results of a small number of E determinations in normals are presented in table I.

TABLE I

Determination of the modulus of elasticity E in normal subjects

Subject	Age in years	Sex	S in cm H_2O/l	F.R.C. in ltr	T_0 in ltr	V_0 = F.R.C. — T_0 in ltr	E = SVO in cm H_2O
E	52	male	2.0	2.2	0.8	1.4	2.8
W	49	„	6.0	1.7	0.4	1.3	7.8
P	52	„	5.6	3.6	0.9	2.7	15.1
de V	65	„	2.0	5.7	0.8	4.9	9.8
Fibrosis pat.	27	„	2.5	1.6	0.3	1.3	32.5

DISCUSSION OF ERRORS.

The most important source of error lies in the determination of the initial volume V_0, which is taken as the difference of F.R.C. and T_0. With

standard methods F.R.C. may be determined with an accuracy of about 10 %.

The accuracy of T_0 depends upon the following factors:

a) The absolute level of the pressure recorded with the balloon technique
b) The constancy of end-expiratory level
c) The "hysteresis" effect

Since the static P—V curve is, in general, not linear the influence of the non-linearity on the validity of the equation E = SV must be studied.

ad a) It is well-known that the absolute pressure recorded with the balloon technique depends, within limits, on the degree of filling of the balloon (MEAD e.a. 1954)

It has further been shown that systematic differences exist between the absolute pressures recorded in the esophagus and in the pleural space. (DUOMARCO e.a. 1954.) However, it should be realized in this connection that systematic differences are also found with absolute pressures measured at different sites of the pleural space (See chapter on pressure recording). (COLERIDGE and LINDEN 1954, BROOKHART and BOYD 1947.)

The presence of a (constant) systematic error is however of little consequence in clinical studies, where values are to be compard with so-called "normal-values".

ad b) Clearly, with the technique described above it is important that the end-expiratory level during the determination of T_0 and F.R.C. should remain the same. However, the influence of end-expiratory level may be entirely eliminated by determining the total capacity (with the subject connected to the system at the end of a maximal inspiration).

If then, the static P—V curve is described over the vital capacity range, the initial volume V_0 is easily obtained in a manner which is independent of the end-expiratory level, since total capacity represents a fixed reference point.

ad c) Especially in certain pathological cases (e.g. emphysema) hysteresis effects intervene. This is illustrated in fig 2.

In such a hysteresis case the question arises whether the distance OA, OB or some intermediate value must be chosen to represent T_0.

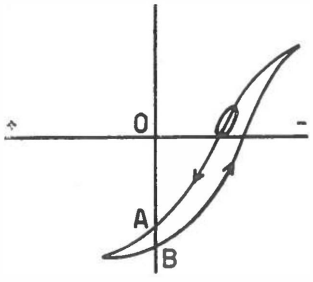


Fig. 2
For explanation see text.

In our opinion the choice depends on the theoretical interpretation of the hysteresis process. If RADFORD's theory of sequential opening of alveoli during inspiration is accepted, (MEAD e.a. 1957, RADFORD e.a. 1954) as we are inclined to do, then it seems to us that the distance OA should be taken as a measure of T_0, since during expiration the additional work to open up "collapsed" alveoli is absent. This problem however deserves further study.

The argument is sometimes raised that the lungvolume at zero pressure difference as seen at autopsy, or during thoraxoperations is very much smaller than the residual volume. It has been described that when the thorax at the position of extreme expiration is opened after death the lungs collapse still further (collapse volume).

It has been claimed that during thoraxoperation (when the thorax is opened and pressures around and in the lung are both atmospheric) the lung shrinks towards the hilus to form a small compact mass having a volume much below residual volume. These observations suggest that the initial volume V as determined by our technique, lying somewhere between F.R.C. and R.V. in most cases, cannot be the true „relaxed" volume since the latter is much smaller than the residual volume.

This argument, however, is invalid for a number of reasons. The observations after death are clearly of no significance whatsoever in this respect, since the „elastic" properties (surface-tension etc.) of the lungs may be profoundly modified after death. (HARTING 1957)

The observations during thorax-operations are also of little value since curare, anaesthetic gases etc. may strongly affect the mechanical properties of the lungs, as has been shown by various workers. (MASSION 1957; FOSTER 1957; NIMS e.a. 1955; VAN LIEW 1954)

When the pressuredifference across the lung, during operation in the opened thorax, is essentially zero (artificial respiration applied without negative phase) the lung may either be a small ‚contracted" ball like structure lying around the hilus, or may remain in a fairly well inflated state, its volume not being necessarily smaller than at residual volume. The volume depends on such factors as: resorbtion, partial closure of lungcompartsments, loss of elasticity. (Ritsema v. Eck.)

Perhaps the most significant argument in favour of our conception of relaxed volume is, that during pneumothorax tratment the lungs remain essentially in a well inflated position when the end-expiratory pressure in the pleural space is about zero. This is demonstrated in fig. 3, where the röntgenogram shown was taken at the moment when sufficient air was introduced into the pleuralspace to make the end-expiratory pleural pressure zero. (pleural, not esophageal pressure was measured!)

Whether the initial volume V_0 thus defined is applicable to emphysema is open to discussion. In emphysema the loss of elasticity is accompanied by a lungvolume (measured at pleural pressure zero) greater than normal. Is this increased lungvolume a consequence of increased distensibility or is this an independent phenomenon? In the latter case this lungvolume may not be taken to represent V_0.

Taking the spring analogy the problem is this:

If for some reason the spring loses some of its elasticity, i.e. if the spring becomes more distensible, does its initial length become greater?

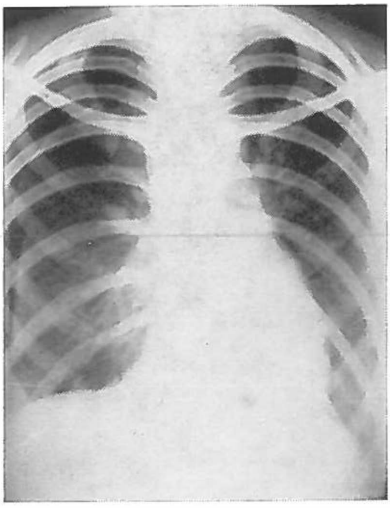


Fig 3
Pneumothorax after refilling.
End-expiratory pressure zero.

Experimentally the loss of elasticity of a metal spring is difficult to realize (this may be attained by bombardment with neutrons).

Theoretically however, it can be shown that increased distensibility is accompanied by increased initial length.

The proof of this is quite advanced and can not be given here (SOKOLNIKOFF, 1946).

It would thus appear that the concept of initial volume V_0 as defined above is equally applicable in the case of emphysema.

However, in emphysema the determination of the initial volume is impossible in most cases, owing to the large "hysteresis"-loops obtained during (quasi-) static breathing.

However, since in emphysema the end-expiratory pleura pressure is close to zero, the F.R.C. values obtained in emphysema cases are bound to be equal or nearly equal to the initial volume values.

In other words in emphysema cases the modulus of elasticity E may be approximated by using the equation

$$E = S \times (F.R.C.)$$

In fibrosis, however, where the pleural pressure at F.R.C. volume is usually greatly negative, the F.R.C. may not be taken to represent the "initial volume" V_0.

LIM e.a. (1959) recently introduced the concept "specific compliance", which is equivalent to the product of elastance and measured F.R.C.

We now come to an important problem which severely limits the applicability of this method to pathological and perhaps even to certain normal cases.

The S-shape of the "compliance line" (see fig. 4) may impose severe limitations.

The tendency of its slope to run more horizontally below the end-expiratory level may be due to the occlusion of lungcompartments. (SLAGTER and HEEMSTRA, 1955)

This would imply that the available lung-volume existing at zero pressure must be smaller thans the initial volume V_0 computed by the equation $V_0 = F.R.C. - T_0$.

This clearly means that E cannot be obtained from the relation $E = SV_0 = S\ (F.R.C. - T_0)$.

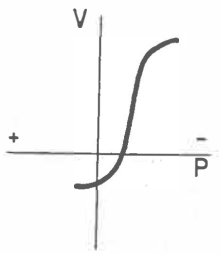


Fig. 4

This practical difficulty may be overcome in two different ways:

1) By extrapolating the "compliance-line" at end-expiratory level downwards until it intersects the vertical axis (zero pressure). The distance between the origin and this intersection must then be used as our T_0 value. This "corrected" T_0 may be denoted by the symbol $\overline{T}_0$.
2) Since, by hypothesis, the increased elastance at zero pressure is due to the occlusion of lungcompartments, i.e. the decrease of lungvolumes the change in elastance value indicates the change in lungvolume, i.e. when

the elastance at zero pressure is doubled, then the available volume at zero pressure, V_0, is halved as a result of occlusion of 50 % of the total lungvolume.

This means that the V_0 computed under 1) must be halved, and when this value is multiplied by the elastance value existing at zero pressure, the "true" value of E is obtained.

Both correction 1) and 2) will be illustrated by a numerical example. Consider fig. 5.

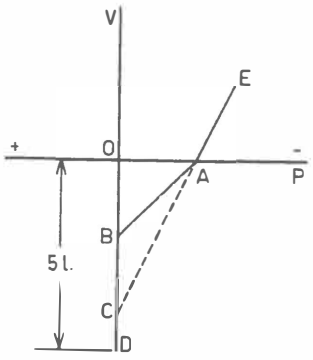


Fig. 5
For explanation see text.

The elastance at end-expiratory level is ½ cm H_2O/l. The elastance at zero pressure level is 1 cm H_2O/l (by assumption). We shall denote this elastance at zero pressure by S_0.

The F.R.C. is assumed to be 5 l, while the negative pleural pressure at end-expiratory level is assumed to be 2 cmH_2O. (All these figures are quite arbitrarily chosen).

Using method 1) the value of E is clearly $E = S\ (F.R.C. - \overline{T}_0) = ½\ (5 - 4) = ½$, where $\overline{T}_0$ is, as stated above, determined by the extrapolation of the "compliance line", i.e. OC in fig 5.

Using method 2) E is found from the relation

$$E = S_0 \left[\frac{S}{S_0} (F.R.C. - \overline{T}_0) \right], \text{ or}$$

$$E = 1 \cdot ½ \cdot 1 = ½.$$

As may readily be seen both methods yield the same value for E, viz ½, which is additional evidence of the soundness of both methods.

In view of the somewhat complicated corrections required we do not feel that this methode for obtaining E possesses much clinical value.

We believe that in practice the product of F.R.C. and S may be used to obtain a rough index of the elastic properties of the tissue.

However, the above discussion clearly demonstrates the inherent error associated with the choice of F.R.C., viz the variable stress applied to the lungs at end-expiratory level (variable pleura pressure).

If one wishes to answer the question: what is the best index of the elastic properties of the lungtissue, then our index E certainly constitutes the most logical answer.

Since $S = \frac{P_e}{T_0}$ where P_e is the pleura pressure existing at the end-expiratory

level, we may write (HEEMSTRA),

$$E = S\ (F.R.C. - T_0) = S\left(F.R.C. - \frac{P_e}{S}\right) = (F.R.C.)\ S - P_e.$$

This equation shows that the formula of LIM and LUFT (1959) $E = F.R.C. \times S$ should be corrected by the term P_e. More precisely, P_e should be subtracted from their result.

This clearly shows, that since P_e is a variable quentity, the uncorrected LIM formula leads to a variable error in the determination of E.

It should be realized that a normal E value does not imply that the "elastic" work of breathing must necessarily be normal. (ORIE)

This follows from the fact that the "elastic" work varies with the compliance, so that a normal lungelasticity (as assessed by a normal E value) associated with a decreased lungvolume still results in an increased "elastic" work component.

From this it may be seen that the term elastic work may be somewhat misleading and should perhaps be replaced by the term "compliance" work or "elastance" work.

CHAPTER III

On the choice between "Viscous Work" and the coefficient of "Viscous Resistance" as an Indicator of resistive forces.

The area of the loop represents the resistive work done during the cycle. (BÜHLMANN and BEHN 1957; SCHERRER e.a. 1957; NISELL e.a. 1956; OTIS 1954; MCILROY e.a. 1954; CHRISTIE 1953; NOELPP e.a. 1952; FENN 1951; OTIS e.a. 1950; RAHN e.a. 1946; DEAN e.a. 1941; BAYLISS and ROBERTSON 1939; CHRISTIE and MCINTOSH 1934; NEERGAARD, OTIS and PROCTOR 1948, VUILLEMIER 1944; NEERGAARD, v., and WIRZ 1927; WIRZ 1923.)

It is obvious that the area of the loop and hence the resistive work, varies with the tidal volume and the rates of flow (and hence, with frequency). Keeping e.g. the tidal volume constant (say, 1 l), then we may expect the "fatness" of the loop at a frequency of 30 cycles/minute, to be about twice as great as at f = 15 c/m.

Since, the area of the loop varies with tidal volume and frequency, the area of the loop tells us little about such factors as airway resistance, unless normal values have been established at fixed tidal volumes and frequencies.

Let us consider fig. 1.

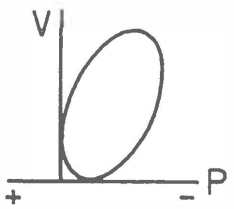


Fig. 1a
Pressure-flow diagram of a normal subject.

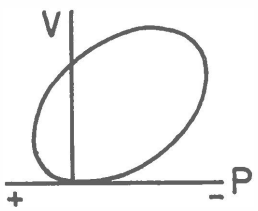


Fig. 1b
Pressure-flow diagram of an asthmatic case.

Let the loop in fig. 1a represent the "fattest" loop of a large series of "normals" taken at f = 15 and V_T = 1 l.

Then, the loop in fig. 1b, its area being about twice at "fat" as the area of the loop in fig. 1a, and taken at the same frequency and tidal volume, is certainly pathological, and its increased area indicates increased work against resistive forces.

However, there is a second, much advocated method to obtain a measure of the resistance to breathing.

This method is based upon the determination of the *coefficient of resistance* (viscous, turbulent, etc.) (NOELPP e.a. 1954; OTIS and PROCTOR 1948, VUILLEMIER 1944; NEERGAARD, v., and WIRZ 1927.)

By determining the rate of flow by means of a pneumotachograph and the "dynamic pressure component" of the total pressure across the lung-system, one may determine the coefficient R, simply from

$$R = \frac{\text{dynamic pressure component}}{\text{rate of flow}}$$

or dimensionally $[R] = \text{cm } H_2O/1/\text{sec.}$

It would, at first sight, appear that the last method gives us a direct measure of the degree of resistance to breathing, thus making the first method, based on the measurement of the area of the loop, superfluous.

However, because of the extreme variability of R in one and the same person, this variability depending, especially in certain pathological cases, on the phase of the cycle (inspiration or expiration), the rate of volume flow, the moment during a phase (e.g. initial or later part of expiration), the state of lunginflation and other factors, the determination of R gives a highly incomplete and unreliable index of the resistance to breathing. We shall now proceed to prove this statement.

Experimental evidence for the variability of R.

1) NEERGAARD and WIRZ were the first to demonstrate that even in normal subjects, the values of R measured during inspiration and expiration at the same volume flow, are different from each other. If we give the difference between total pressure and static pressure (during inspiration *or* expiration) the symbol P_R, than R is obviously given by $R = \frac{P_R}{\dot{V}}$,

where $\dot{V}$ = volume flow.

The curves in fig. 2a and b have been obtained from the expiratory

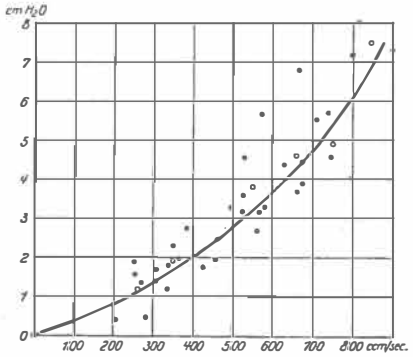


Fig. 2a
Flow-pressure diagram during expiration (normal resistances). (From Neergaard K. v., K. Wirz, Z. klin Med. 105.51.1927)

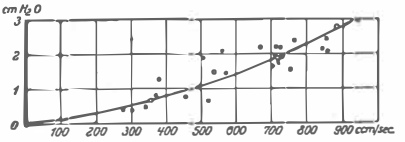


Fig. 2b
Flow-pressure curve during inspiration.

phase and inspiratory phase of the same cycle, respectively. It should be noted that at e.g. a volume flow of 300 cc/sec., P_R = 1.3 cm H_2O during expiration, while P_R = 0.5 cm H_2O during inspiration or, during expiration,

$$R = \frac{1.3}{0.3} = 4.3 \text{ cm } H_2O/l/\text{sec.}$$

and during inspiration,

$$R = \frac{0.5}{0.3} = 1.7 \text{ cm } H_2O/l/\text{sec.}$$

Or, R during expiration is 2.5 times greater than during inspiration. We have obtained similar results in pathological cases:

e.g. in an advanced emphysema case, the following values were found:

At a rate of flow of 250 cc/sec. the R value during inspiration was 3.8 cm $H_2O/l/sec.$, while during expiration the value of R was 49 cm $H_2O/l/sec.$, i.e. 13 times higher than during inspiration.

The original graph is shown in fig 3 (pneumotachogram obtained at 11 cycles/min.)

Case history

Male 42 years. Since 15 years chronic cough and attacks of dyspnoea.
Since 7 years respiratory tract infections.
Thorax: rigid, little chest motion.
Physical examination: expiratory wheezes.
Roentgenogram: no lesions except bullae in both lower lungfields.
The diaphragm is scarcely moving.
Lung function: V.C. 2965 cc (predicted 4130 cc)

T.V.C. 1 sec. 11 %
F.R.C. = 75 % T.C.
Residual volume: 50 % T.C.
Elastance S = 1.5 cm H_2O/l
Compliance C = 0.700 l/cm H_2O

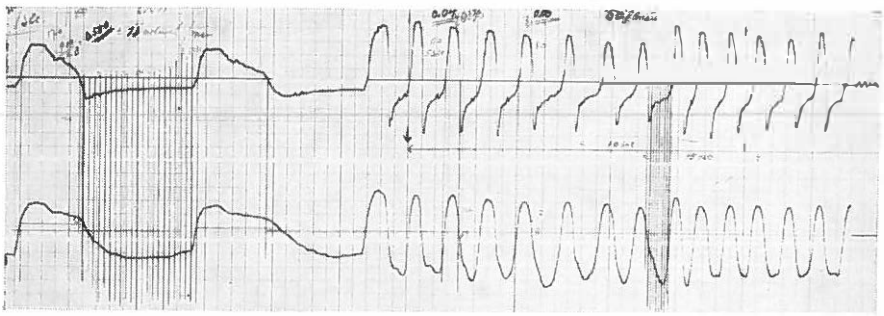


Fig. 3.

Pneumotachogram of emphysema case.

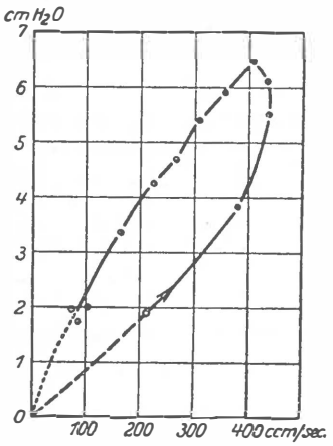


Fig. 4
Flow-pressure curve during expiration.
(From Neergaard K. v., K. Wirz. Z. klin. Med. 105.51.1927)

2) Even during a single phase the R's measured at the *same* volume flow at the beginning and later part of the phase may differ from each other. This is shown in fig. 4 taken from NEERGAARD and WIRZ where the P_R (the dynamic pressure component) is plotted against flow (cc/sec) during a single expiration.
The loop thus obtained clearly shows that (see direction of arrow) during the "ascending" (first) part of expiration the pressures are much lower than during the "descending (later) part of expiration, at corresponding volume flows.
For example, at a volume flow of 250 cc/sec. the pressure P_R on the ascending branch is 2.2 cm H_2O, while on the descending branch P_R is 4.5 cm H_2O. *Or the R-value during the latter part of expiration is twice as large as during the initial part of the same expiration!*
We have corroborated these findings as may be seen from the following results.

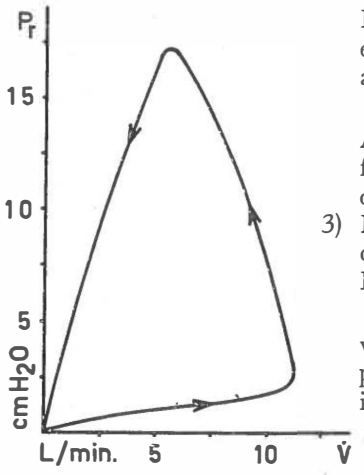


Fig. 5
Flow-pressure curve P_R-$\dot{V}$ during expiration in a case of advanced emphysema.

Fig. 5 represents the P_R—$\dot{V}$ curve during expiration in the above mentioned case of advanced emphysema.

Again here, the possible explanation of these findings, is immaterial for the present train of thought and will therefore be ignored.

3) NEERGAARD and WIRZ, have found that the constants k_1 and k_2 in the well-known ROHER *equation* *

$$P_R = k_1 \dot{V} + k_2 (\dot{V})^2$$

were different during inspiration and expiration. They obtained the following values in one subject.

* P is expressed in cm H_2O and $\dot{V}$ in l/sec.

	k_1 (cm H_2O/1/sec)	k_2 (cm H_2O/1/sec)
inspiration	1.16	2.1
expiration	2.35	6.5

OTIS and PROCTOR (1948) using the interruption-technique for obtaining alveolar pressure values, found no differences between *airway* resistance R-values measured during inspiration and expiration at the same rate of flow.

In this connection it should be realized that when the intrapleural or esophageal pressure is measured the R value represent the *sum of the deformation resistance* and the airway resistance proper.

Only when the alveolar pressure is measured differentially against mouth-pressure, the airway resistance may be (directly) obtained.

But even quite apart from these findings, the results discussed in the previous section, show conclusively that an equation of the form $y = ax + bx^2$ may be quite inadequate in pathological cases. Clearly, a loop such as shown in fig. 5, cannot possibly be fitted by a polynomial $y = ax + bx^2 + cx^3$, say.

Conclusion: in pathological (and even in normal) cases the k_1 and k_2 values in the ROHRER's equation, may differ during inspiration and expiration.

In pathological cases the ROHRER equation itself or an extension of it ($y = k_1 x + k_2 x^2 + k_3 x^3$) may be completely inadequate to describe the P_R—$\dot{V}$ curve during a single phase (e.g. expiration).

DISCUSSION.

The above evidence makes it abundantly clear that the use of a single R-value as an index of the degree of resistance to breathing, is entirely meaningless.

The R-value acquires some meaning when strict specifications are given: the phase (expiration of inspiration), the moment during a phase (e.g. initial or late stage of expiration) and the rate of flow.

But even then, the R-value only gives a very incomplete picture of the resistance pattern.

For example, in a patient with a normal R-value (1.5) measured during the initial stage of expiration at a flow of 250 cc/sec, the R-value became grossly abnormal (R = 26) when measured at the later stage of expiration at the same volume flow.

In this connection it is interesting to quote SCHERRER (1957) who states:

> „Atmet der Gesunde mit Strömungen über 0.6 1/sec. so treten regelmäszig Abweichungen des Flusz-Druck-Diagrammes von der Geraden auf, wobei sich die Meszpunkte niemals um eine Parabel gruppieren. Wir schlieszen daraus, das die Reibungskoeffizienten keine konstanten Gröszen sind:
>
> An verschiedenen Stellen der Luftwege herrscht ein dauernder Wechsel von turbulenter zu laminärer Strömung. Sinkt im Verlauf des

Atemzuges die Atemstromstärke unter 0.6 l/sec. so verschwindet die Turbulenz ganz. In pathologischen Fällen ist das Verhalten der viscösen Widerstände noch viel weniger gesetzmäszig: das Bronchialkaliber ist bei Emphysem und Asthma bedeutenden in — und exspiratorischen Schwankungen unterworfen, so dasz der visköse Widerstand während des Expiriums dauernd zunimmt. Der völlige Kollaps der feinsten Bronchien am Ende des Expiriums ist bei provozierten Bronchialspasmen nachweisbar, so dasz regionär mit unendlich groszen Reibungswiderständen zu rechnen ist. Ferner bestehen ungesetzmäszige Turbulenzen im Bronchialbaum, wenn Sekretverstopfungen oder andere Verlegungen der Luftwege vorliegen. *Auf Grund der bisherigen Erfahrungen sind wir der Auffassung, dasz in pathologischen Fällen der Reibungswiderstand R zahlenmäszig nicht zu erfassen ist.*

Um die viskösen Eigenschaften der Lungen trotzdem quantitativ auszudrücken, wird man mit Vorteil das Volumen—Druck-Diagramm zu Hilfe ziehen und als Masz die Atemarbeit an der Lungen gegen Reibung verwenden."

SCHERRER's statement thus clearly defines the severe limitations of the use of R as an index of the over all resistance to breathing.

CONCLUSION:

On the basis of experimental evidence it is shown that the friction coefficient R should not be used as an index of the resistance to breathing.

It is further explained that the viscous work determined at constant frequency and tidal volume, may be used as a reliable index of the resistance to breathing.

It should be clearly realised that although the standardized viscous work is an indicator of the resistance to breathing, the *standardized viscous work per se constitutes a significant clinical quantity.*

It is clearly of considerable clinical interest to know the amount of work required to overcome "viscous" resistance unaffected by variations in rate of flow.

In other words, from the clinical point of view the standardized viscous work possesses significance, not only as a measure of the resistance "R" but as a distinct quantity as well.

CHAPTER IV.

A graphical analysis of the work of breathing

In this chapter we shall answer the question what area in the pressure-volume diagram represents the work done during a complete cycle, and what area represents the work done during inspiration, when the forcing is an arbitrary (periodic) function of time. The distinction between "work done" and "work performed by the muscles" will be made clear.

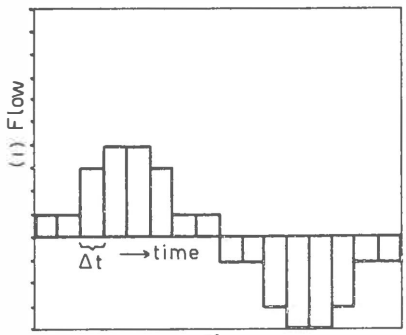


Fig. 1

Volume-flow curve as obtained by the pneumotachogram.

Consider fig. 1, which represents schematically a volume-flow curve, as obtained by the pneumotachogram.

Fig. 2 represents the pressure across the lungs, as a function of time, as may be obtained with a esophaguscatheter connected to a differential manometer.

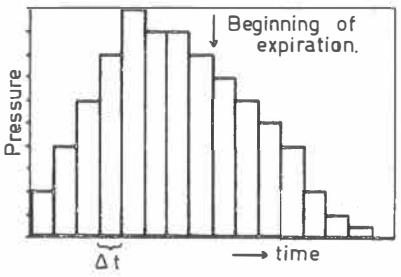


Fig. 2

Pressure across the lungs (obtained with an oesophagus catheter connected to a differential manometer) as a function of time.

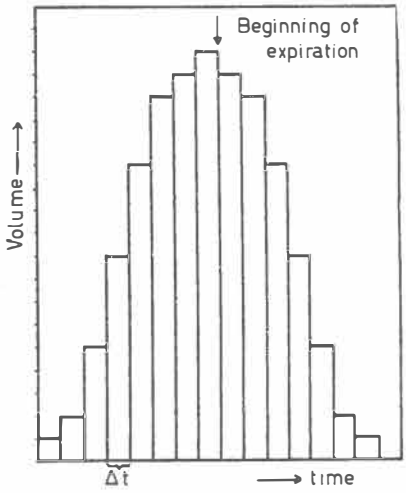


Fig. 3

Volume curve, obtained by integrating the volume-flow curve of fig. 1.

Fig. 3 represents the volume-curve, obtained by integrating the curve of fig. 1.

Fig. 4 represents the pressure-volume diagram, as obtained by combining the ordinates of fig. 2 and fig. 3, at corresponding times.

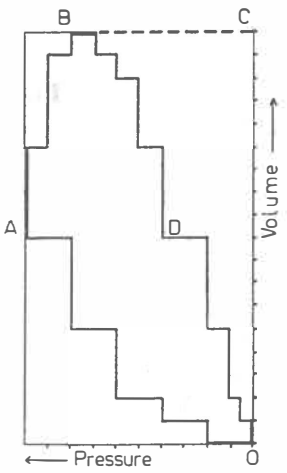


Fig. 4
Pressure-volume diagram.

The discontinuous curves were chosen for simplicity of calculation. It has the added advantage that the reader can easily check the numerical results. (In the original drawing one scale division is one centimeter).

From elementary mechanics we know that $dW = PdV$ (1)

where W = work, P = pressure, V = volume.

From (1) $$W = \int PdV \qquad (2)$$

Since volume flow i is $\frac{dV}{dt}$, $dV = idt$,

so that (2) may be written $W = \int P\, i\, dt$

Taking for dt, or $\triangle$ t, the width of a rectangle (fig. 1, fig. 2), the work is easily computed by graphical means.

The work during inspiration (expressed for simplicity in cm^2) is easily seen to be (from fig. 1 and fig. 2).

$2 \times 1 + 4 \times 1 + 6 \times 3 + 8 \times 4 + 10 \times 4 + 9 \times 3 + 9 \times 1 + 8 \times 1 = 140\ cm^2$. (e.g. the first rectangle of the pressure curve with a height of 2 cm, is multiplied with the first rectangle (height 1 cm) of the flow-curve).

Since in the pressure-volume diagram (fig. 4) the area OABCO is also 140 cm^2 (as can easily be checked by counting squares) it follows that the area OABCO represents the work done in *inspiration.*

The work done during expiration (its absolute value is 55.5 cm^2) is found in the same way to be numerically equal to the smaller area ODBCO.

But since flow during expiration has a direction contrary to inspiratory

flow, the work done during expiration must be deducted from the work done during inspiration, so that the total work done during a complete cycle is represented by the area OABDO, enclosed by the discontinous closed curve.

This may become clearer if we make a sign convention. Let the direction of flow toward the lungs (inspiratory) be negative, and let the pressure *lower* than the "static" pressure at end-expiratory level (equilibrium position) be called negative. Then, since work = pressure × volume, the inspiratory work is by our sign convention, *positive* * (—) × (—) = +.

During expiration flow is, by our sign convention, positive, and since, in our example, the pressure during expiration is always lower than the "static" end-expiratory pressure, the pressure carries the negativ sign during expiration.

Hence, the work during expiration carries the negative sign ((+) × (—) = (—)).

The total work, being the sum of inspiratory work and expiratory work consequently becomes (+ 140 cm²) + (— 55.5 cm²), which is the *area of the closed curve.*

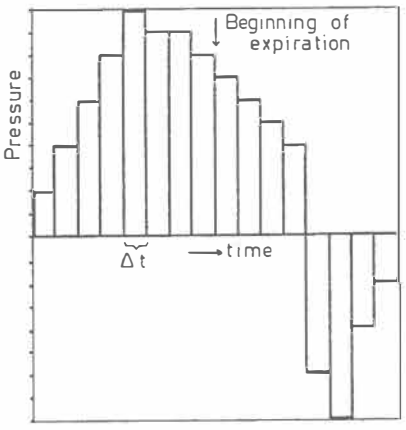


Fig. 5
Pressure as a function of time.

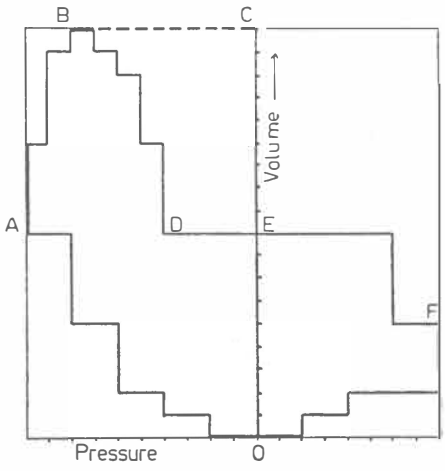


Fig. 6
Pressure-volume diagram constructed from fig. 1 and fig. 5.

Let us now consider a second, slightly more complicated example, using fig. 5, instead of fig 2, but retaining fig. 1 for the flow curve.

It follows that in this second example the pressure-volume diagram in fig. 6 is constructed from fig. 1 and fig. 5.

* This representation is in agreement with common practice: when the force and the movement have the same direction work is said to be positive, when their direction is opposite work is a negative quantity.

It will be found by computing $\int P\,i\,dt$ that the absolute value of the *expiratory* work is 98 cm^2, which is the numerical value of the area DBCED + EFOE.

Now, the work represented by area DBCED is negative (— 44 cm^2) since flow (expiratory) is positive and pressure negative ((—) × (+) = (—)).

The work represented by area EFOE (+ 54 cm^2) (to the right of ordinate axis) is positive, however, since flow and pressure are both positive here ((+) × (+) = (+)).

In this example total work during a complete cycle is the same as in the first example, (positive inspiratory work) + (negative expiratory work) + (positive expiratory work) or, area OABCO — area DBCED + area EFOE = area OABDEFO, or numerically, (+ 140 cm^2) + (— 44 cm^2) + (+ 54 cm^2) = + 150 cm^2, which is the value of the area of the (closed) loop, as may easily be checked.

We thus arrive at the important conclusion: *

The work done during a complete respiratory cycle is always represented by the area enclosed by the loop.

DISCUSSION.

The fact that the work done during a complete cycle is represented by area of the loop, does not mean that this area represents the "effort" expended by the respiratory muscles.

The energy expended by the muscles during a complete cycle, is represented by area OABCEFO in fig. 6.

This is sometimes called matabolic work.

This follows from the following considerations: during inspiration the inspiratory muscles spent an amount of energy equal to the area OABCO.

This spent energy can of course never be regained by the muscles and must be looked upon as a loss, whatever the subsequent events. During expiration the area EDBCE in fig. 6, or area ODBCO in fig. 4,** represents the work done by the elastic forces, i.e. expiratory muscles do not contribute to this work.

As stated above, this work done by the elastic force, does *not* "give back" to the inspiratory muscles, any of the energy spent by these muscles.***

---

* This conclusion could also be obtained, using the theory of plane curves, but the reasoning would have been rather lengthy and abstract.

** The exceptional case, when the elastic recoil is slowed down by the inspiratory muscles, is not considered here.

*** It might be supposed that the potential energy of the thorax may be contributary to the production of this area. We believe that this may only be so at extreme inspirations, beyond the equilibrium position of the thorax.

The area EFOE in fig. 6, represents work done by the expiratory muscles (unaided by elastic forces) and this work (EFOE) added to the work done by the inspiratory muscles (OABCO) gives the total work *performed by the respiratory muscles* (area OABCEFO).

If, e.g. one wishes to know the optimum frequency, i.e. the frequency of breathing at which the muscles spend a minimum amount of energy at a given alveolar ventilation, than area OABCEFO must be used when expiration is active, and area OABCO when expiration is passive.

SUMMARY

It is shown, by comparing the work as computed from the pneumotachogram and the pressure-time curve, with the numerical values of the area's of the pressure-volume diagram, as obtained with a planimeter, that the total work done during a complete cycle, is represented by the *area of the loop*.

CHAPTER V

General discussion of errors.

This chapter is devoted to a discussion of the possible sources of error associated with the measurements as used in this study. In this chapter these problems are discussed from the general point of view. For a description of the methods used in this study and for a specific discussion of errors the reader is referred to chapter VII.

The sources of error associated with a specific subject have been discussed in the chapter dealing with this subject. The discussion of errors is necessarily incomplete due to economy of space.

This chapter falls roughly into three parts, viz

I The determination of volume
II The meaning of esophageal pressure
III Sources of error in the measurement of esophageal pressure.

Part I *THE DETERMINATION OF VOLUME*

The determination of volume changes may be accomplished by 2 methods:

1) the spirometer method
2) the pneumotachograph method.

The proper choice of the method depends on the purpose of the investigation and other factors that will be discussed below.

In general it may be stated that the pneumotachograph is capable of yielding the most reliable results.

We shall start with a discussion of the advantages and disadvantages of the spirometer method.

I) *Advantages of use of spirometer.*

1° the resting expiratory level can be clearly observed.
2° the tidal volume can be directly seen.
3° the method is simple, cheap and/or time saving since integration is unneccessary.

ad 1) *The end-expiratory level can be observed and any shift of this level can be noted.*

This is important in many studies: e.g. the compliance depends on

the level of breathing; if breathing is shifted towards the inspiratory side, then the compliance will tend to decrease, since then the limit of the "extensibility" of the lung will be approached. Knowledge of the level of breathing is also of importance in the measurement of (airway) resistance, since it has been shown by MEAD and WHITTENBERGER (1953) that viscous resistance increases when breathing is shifted towards the expiratory side.

ad 2) *The tidal volume can be directly observed.*
In many studies the subject is required to breathe a predetermined tidal volume. Obviously the subject can only fulfill this requirement when he can "read" his tidal volume from the recorded excursions. If a pneumotachograph is used the fixed tidal volume can only be breathed when the signal is integrated electrically.

ad 3) The method is simple, since the time-consuming graphical integration or the relatively expensive electrical integration is avoided.
The disadvantages of the spirometer are:

1° amplitude distortion may occur at higher breathing frequencies;

2° phase shift between tidal volume and recorded excursions of the bell may occur;

3° increased work of breathing is induced due to inertia etc. Depending upon the construction of the spirometer (counterbalance, light bell etc.) this factor may be greatly reduced.

4° the external resistance of the spirometer induces hyperventilation, thus making e.g. the evaluation of work of breathing during "normal spontaneous" breathing impossible;

5° accumulation of CO_2 in the spirometer, with resulting hyperventilation. If e.g. soda-lime is used to absorb the CO_2 the resistance to breathing is considerably increased.

ad 1 and ad 2) Amplitude distortion and phase shift result from "resonance" of the spirometer system.
This problem is of great practical importance and knowledge of the responce characteristics of the spirometer used becomes essential when respiratory rates beyond, say, 25 cycles per minute are used. The concept of amplitude may be explained as follows:
Let a pump (or lungs) produce a fixed tidal volume of say 800 cc, at all frequencies. At a very low frequency (say 1 cycle/minute) the spirometer will certainly record the correct volume (after proper calibration), i.e. 800 cc.
Now, when the frequency of the pump is gradually increased the spirometer record will, at lower frequencies, still indicate 800 cc. Quite abruptly, however, say at a frequency of 50 cycles/minute, it may be found that the spirometer record indicates a tidal volume of only 400 cc, while actually the stroke volume is still 800 cc.
This sharp and abrupt reduction of the amplitude of the spirometer-record occurs near the so-called point of resonance. It is obvious that such a reduction of amplitude which results from artefacts of the

recording system constitutes a very serious source of error, since e.g. compliance and work of breathing determinations depend on the measurement of volume changes. Now, the graph relating the recorded amplitude and frequency at *constant* stroke volume may be called a "resonance curve".

The abruptness of depth and frequency at which resonance occurs (so-called resonance-frequency) varies among spirometers. Fig. 1 shows schematically various types of resonance curves that may be found in practice.

It may be noted in passing that the resonance frequency of a particular spirometer depends on the depth of immersion of the bell: the more the bell is immersed the lower the resonance frequency.

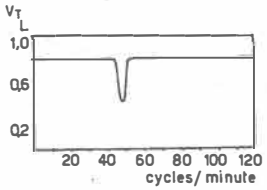


Fig. 1a

For explanation see text.

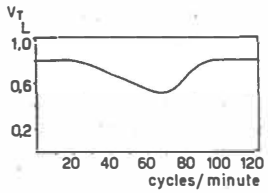


Fig. 1b

For explanation see text.

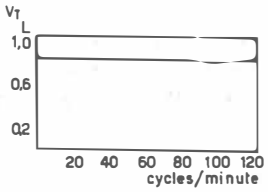


Fig. 1c

"resonance curves" of spirometers.
Excursions of bell versus frequency at fixed stroke volume of pump.

BERNSTEIN, D'SILVA and MENDEL (1952) have noted the influence of frequency on the recorded excursion (fig. 2).

Attention is called to the thin continuous line. It may be seen that up to 25 cycles/minute the recorded excursion is constant and equal to the stroke volume of the pump (100 %). Beyond 25 c.p.m. it rises and at 58 c.p.m. it reaches 120 % of the output. Above 58

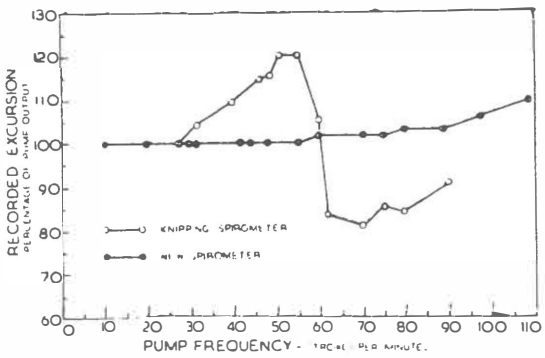


FIG 2 —Frequency response curves of Knipping spirometer (open circles) and new spirometer (black circles) determined with a piston pump delivering 2.800 ml per stroke

Fig. 2

Resonance curve of the knipping spirometer. (From Bernsten, L., J. L. O. Silva and D. Mendel-Thorax 7.255.1952).

c.p.m. it falls to reach only 80 % of the stroke volume at 70 c.p.m. In this example, where a ordinary Knipping spirometer was used, the volume recording was only accurate up to 25 c.p.m. Beyond this the spirometer is worthless.

Summarizing, we may state that the use of a spirometer without specifying its "resonance curve" is only permitted at low frequencies, say, up to 30 cycles per minute. At higher frequencies, the resonance curve must be known at specific depths of the bell to avoid gross errors.

For the construction of a spirometer with improved frequency response the papers of BERNSTEIN, D'SILVA and MENDEL and of VAN DEN BERG and DEFARES, WELLS; e.a., STEAD e.a., should be consulted.

The phase shift.

In most spirometers the phase shift between the spirometer tracing and the stroke of the pump is of minor importance. This phase shift should not be confused with the pronounced phase shifts between the movements of water and the clock of the spirometer.

ad 3) Work is expended to move the spirometer system. If a subject is connected to a spirometer and if the esophagus pressure is measured against atmospheric pressure, then the area of the loop (work diagram) not only represents the work done on the lungsystem, but also the work done on the spirometersystem.

The work done of the spirometersystem *alone* at the same tidal volume and frequency may be found by connecting the spirometer to a pump working at the same frequency and tidal volume and measuring the pressure at the mouthpiece against atmospheric pressure. The area of the loop obtained by recording this pressure variation against volume, is a direct measure of the work done on the spirometersystem. In most studies we only wish to know the work required for moving the lungsystem. This may be obtained without further correction, *if the differential pressure between a point in the esophagus and a point near the mouthpiece,* is recorded. Since with higher flows (higher frequencies, at constant tidal volume) the pressure at the mouthpiece of the spirometer may reach considerable values (up to 10 cm H_2O) *it is absolutely essential that differential pressure* is measured when a spirometer is used.

When normal subjects are studied during normal breathing, the pressure variation across the lungsystem is about 3 cm H_2O, while the pressure change at the mouthpiece relative to atmospheric pressure may be about 1.5 cm H_2O.

It follows that if esophagus pressure is not measured "differentially", but against the atmosphere, the apparent pressure across the lungsystem is not 3 cm H_2O, but 4½ cm H_2O an error of 50 %! If we are dealing with say a fibrotic with "stiff" lungs or a patient with increased airway resistance then the pressure swing in the esophagus (relative to mouth) during quiet breathing may be much greater, say 30 cm H_2O. The apparent pressure will then be 30 + 1.5 = 31.5 cm H_2O, giving an error of 5 %.

From this example it may be seen that especially with "normal lungs" the error may assume large values when the pressure is not measured "differentially".

Although to a lesser degree, this discussion also applies when a pneumotachograph is employed.

II *The use of the pneumotachograph.*

The main advantage of the pneumotachograph is:

The resistance may be quite small so that no hyperventilation is induced.

In a well-constructed pneumotachograph the pressure over the viscous resistance of the pneumotachograph should not exceed 20 mm H_2O at a volumeflow of 300 liter per minute.

During quiet breathing this pressure will not exceed 2 mm H_2O, a pressure which is not subjectively perceptible (HART 1946) and which does not appreciably influence the breathing pattern.

It follows that with a pneumotachograph breathing may remain little disturbed, so that the respiratory work during "spontaneous" breathing may be obtained by this method.

The disadvantages of the pneumotachograph are:

a) the necessity of integration. This process is either costly and difficult (electrical) or time consuming (graphical).
b) the level of breathing can not be observed. This statement has often been made, but is actually not correct. When a pneumotachogram is studied, it can be seen whether the end-expiratory level has shifted or not. (See fig. 3.)

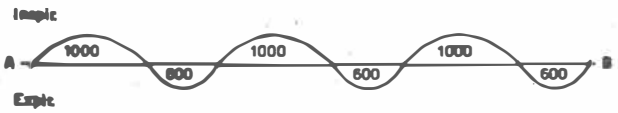


Fig. 3
Pneumotachogram.

In the schematic fig. 3, the inspired tidal volume is 1000 cc, while only 600 cc is expired during each expiration. It follows that at instant B the level of breathing has shifted to the inspiratory side, the shift being three times 400 cc = 1200 cc (relative to the level at instant A). Here the effect of R.Q. is ignored.

c) The subject can not "see" his tidal volume as on the spirogram, so that he can not breathe a fixed and imposed tidal volume. (This objection of course does not apply when electrical integration is used).
For many studies and clinical observations this represents indeed a serious drawback.

ad a) integration may be performed in three ways:
1) by electrical means;
2) by the use of a planimeter, integrimeter or integraph;
3) by graphical construction.

ad 1) electrical integration presents a difficult problem, the major difficulty being the zero drift of the output signal of the integrator.
This may be clarified as follows:
Let a voltage proportional to the esophagus pressure be impressed on the abscissa axis and the output voltage of the integrator (which is a measure of volume) be impressed on the ordinate axis of a cathode ray oscillograph.

During a single respiratory cycle a loop is then described. During a number of cycles a number of loops are described overlapping each other. But if the zero point shifts, then the loops will tend to "run away" in the manner shown in fig. 4.

The great disadvantage of this shift apart from its inconvenience lies in the fact that it becomes impossible to note a shift in the end-expiratory level.

It becomes important to analyse the cause of this zero drift. The concept "zero drift" is defined here in a somewhat unorthodox manner:

We shall speak of "zero drift" when at *constant level of breathing*, the lightspot does not return to its starting point at the end of a respiratory cycle (end-expiration). Here only non return in vertical direction (volume) is considered.

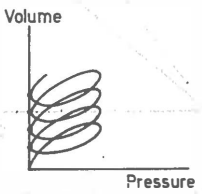


Fig. 4
Volumepressure diagram showing loops overlapping each other.

1) R.Q. < 1. Since the R.Q. is less than one, the volume expired is less than the volume inspired. Let the O_2 consumption be 240 cc per minute, the frequency be 12 breaths/minute and the R.Q. 0.85. The O_2 consumption pro breath is $\frac{1}{12} \times 240 = 20$ cc and the CO_2 output $\frac{85}{100} \times 20$ cc $= 17$ cc. Hence the difference pro breath is 3 cc. If the inspired tidal volume is 600 cc, then the difference (apparent zero shift) is 0.5 % of the tidal volume.
During twenty breaths the accumulated shift due to this cause will be 20×3 cc $= 60$ cc or 10 % of tidal volume in this example.
This is illustrated in fig. 5.
In fig. 5, loop B is a loop twenty breaths "later" than loop A, the shift being due only to the R.Q. < 1.
The "zero drift" due to the R.Q. can obviously be excluded in checking the apparatus, by replacing the lungs by a pump.

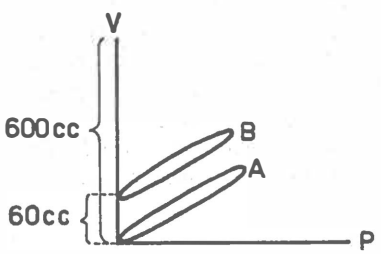


Fig. 5
Volumepressure diagram; loop B 20 breaths later than loop A.

2) The calibration line of the pneumotachograph during inspiration differs from the calibration line during expiration. (See fig. 6.)

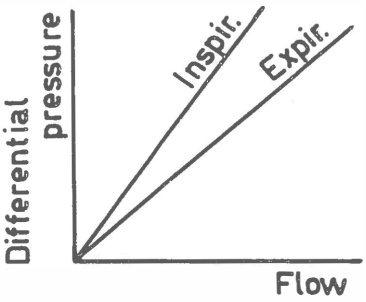


Fig. 6
Calibration lines during inspiration and expiration.

Before explaining why *non* coinciding expiratory and inspiratory calibration lines will cause a shift in zero position, we shall briefly discuss the various causes that may result in such non coincidence.

a) When the side tubes of the pneumotachograph leading to the differential manometer, are not absolutely perpendicular to the direction of flow, but sloping towards either direction as shown in fig. 7b in exaggerated form, then the calibration lines during inspiration and during expiration will be different.

In fig 7b, where the tubes are pointing towards the inspiratory flow, the differential pressure during expiration at the same volumeflow as during inspiration, will be the greater, since then "end-pressure" is added to the "lateral pressure".

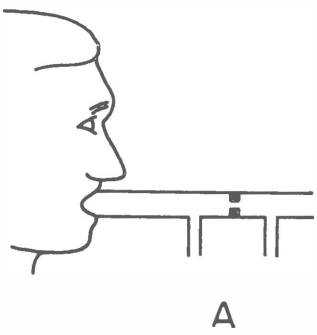


Fig. 7a
Pneumotachogram with side tubes perpendicular to the direction of flow.

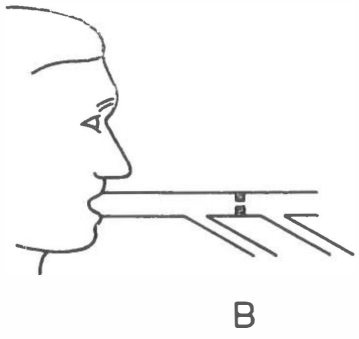


Fig. 7b
Pneumotachogram with side tubes at an oblique angle.

Obviously, it is only the latter that should be measured. It is clear that this will result in different calibration lines.

b) The different composition of inspired and expired air may constitute a second factor.

POISEUILLE's law for laminar flow, which applies to a well constructed pneumatochagraph, states

$$i = \frac{\pi r^4}{8 \eta l} \triangle p \qquad (1)$$

$$\triangle P = \frac{8 \eta l}{\pi r^4} i \qquad (2)$$

where $\triangle p$ = differential pressure, l = length of rube, r = radius, i = volume flow and η = coefficient of viscosity.
From (2) it may be seen that $\triangle p$ also depends on η and this implies that at constant volume flow $\triangle p$ will be different when η is different. Since η depends on the composition of the gasmixture, it is clear that η of the expired gas (saturated, body temperature, increased CO_2 content, decreased O_2 content) will differ from the η of the inspired air. It follows that the calibration lines during inspiration and expiration will be different.
This difference has not yet been studied quantitatively and has not been noted experimentally, since it is common practice to calibrate pneumotachographs (for both directions) by simply blowing room air through the tubes. (See BOUHUYS, 1956).
Remark: the non linearity of the calibration line, although a source of distortion, is not responsible for zero drift of the output signal of the integrator.
We shall now explain the effect of non-coinciding calibration lines on the zero-drift.
Let us assume, for concreteness, that "inspiratory" differential pressure is greater than "expiratory" differential pressure at equal volume flows. Let us further assume, for simplicity of presentation, that the volume flow curve is a sine wave. (See fig. 8).

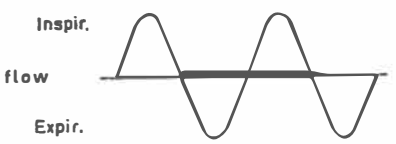


Fig. 8
Volume flow as a function of time (sine wave).

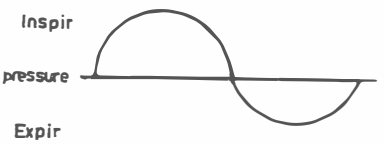


Fig. 9
Differential pressure across the pneumotachograph as a function of time.

Since, by assumption, differential pressure during inspiration is greater, it follows that the pressure amplitude during inspiration is greater than during expiration.
The resulting curve is shown schematically in fig. 9.
Since the outputsignal of the integrator is directly proportional to the area under the curve, it follows that at the end of inspiration, the "inspiratory tidal volume" as represented by the outputsignal of the integrator is proportional to the area under the inspiratory part of the curve.
The "expiratory tidal volume" will be proportional to the area under the expiratory part of the curve. Therefore in this example it will be smaller than the inspiratory tidal volume. It follows that the output signal of the integrator will not return to the original zeropoint at the end of expiration.
In this way the zerodrift of the integrator may be explained.

3) When the RC-time of the integrator in chosen "too small" zerodrift will result.

Lack of space does not permit us to discuss the reason why a too small timeconstant leads to "zerodrift" of the output signal.
Discussion of the characteristics of the various types of intergrators (MILLER integrator etc.) lies beyond the scope of this book. Electrical integration of the slow signals occuring during breathing is far from being a simple straightforward problem. The resulting volume curve should always be checked against the volume curve as obtained by graphical integration and a correspondance within 5 % should be obtained.

Part II *THE DETERMINATION OF PRESSURE.*

I) It has become commonplace to state that the pressure in the esophagus may be taken to represent the pressure in the pleuraspace.

We shall consider the validity of this assumption in detail. The problem has been studied experimentally by a number of workers. (HEEMSTRA 1957; FAHRI e.a. 1957; VERSTRAETEN 1956; CHERNIACK e.a. 1955; FRY e.a. 1954; COLERIDGE e.a. 1954; DUOMARCO e.a. 1954; DORNHORST and LEATHART 1952; BROOKHART and BOYD 1947; WIGGERS e.a. 1947.)

It was generally found that the *changes* in esophageal pressure during the breathing cycle corresponded to the *changes* in intrapleural pressure, whereas the intrapleural pressure was consistently more negative then the intra-esophageal pressure. However, deviations from this general trend were frequently noted. MEAD and WHITTENBERGER (1953) compared these pressures in the dog and in the cat. The results are shown in fig. 10 which was obtained under nearly static conditions.

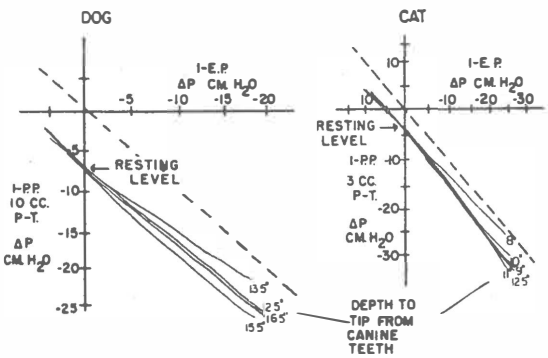


FIG. 3. Comparison of intraesophageal and intrapleural pressure variations in the cat and dog. The plots were obtained by means of the cathode-ray oscilloscope.

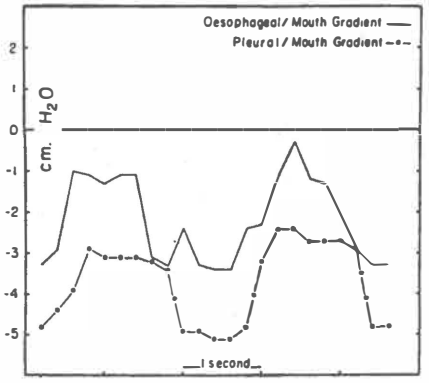
Fig.10
From Mead. J. and J. L. Whittenberger, J. Appl. Phys. 5.779.1953.

It may be seen that the intrapleural pressure is consistently more negative. If both pressures were always equal to each other, then the points would lie on the straight line passing through the origin and forming an angle with the abscissa of 45 degrees. Actually the points fall on a line running almost parallel to the one just mentioned. Obviously this means that the absolute pressures are different, but that they change to the same extent with changes of lungvolume.

The most extensive study of this problem was reported by CHERNIACK e.a. who made simultaneous records of intrapleural and intraesophageal pressures in 10 subjects during spontaneous and during controlled breathing.

In fig. 11a, the pressures during spontaneous quiet breathing are shown. It may be seen that the curves run parallel to each other and that the intrapleural pressure (i.p.p.) is more negative than the intra-esophageal pressure (i.e.p.).

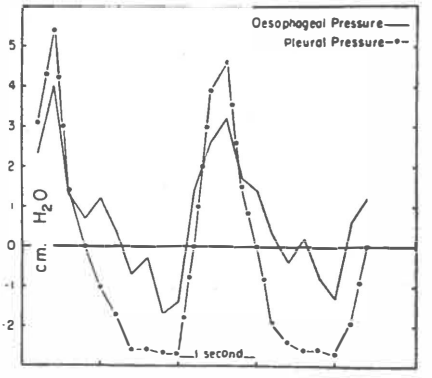
Obviously in this case the "esophageal record" may be used as a reliable substitute for *changes* in intra-pleural pressure. However in the same subject under controlled breathing (effected by squeezing an anesthesia bag) the changes in i.e.p. were less than the changes in i.p.p., as may be seen from fig. 11b.



Spontaneous Respirations

Fig. 11a

Comparison of intra-esophageal and intra-pleural pressure variations during spontaneous quick breathing.



Controlled Respirations

Fig. 11b

The same during controlled breathing. Records obtained during spontaneous breathing (fig. 11a) and during intermittent positive pressure breathing (fig. 11b) in a subject who was anesthetized with pentothal sodium. (From Cherniack R. M., L. E. Fahri, B. W. Armstrong and D. F. Proctor. J. Appl. Phys. 8.203.1955.)

These results were obtained on an anesthetized patient.

In conscious patients the relationship between i.e.p., and i.p.p. was studied by the following elegant method.

The i.p.p. was connected to one side of a differential manometer, while the i.e.p. was connected to the other side. It is clear that when both pressures are equal to each other during the recording the differential pressure would be zero and a straight line coinciding with the x-axis would be recorded when this differential pressure is recorded against time.

If these pressures are not identical, but change in parallel then a horizontal straight line paralled to the x-axis is recorded.

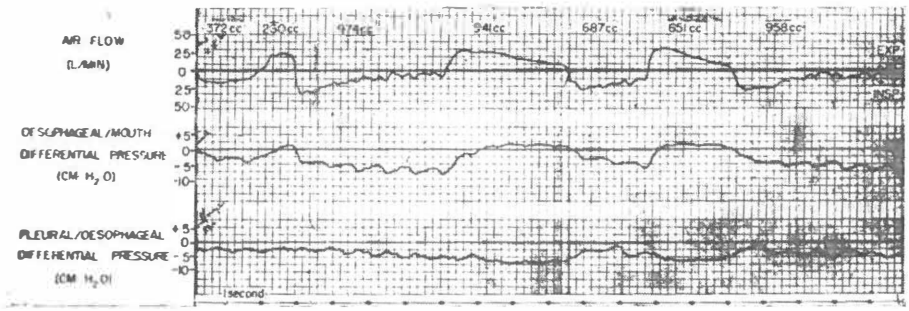


Fig. 12

Portion of record obtained in subject 11. The lowest tracing represents the difference between the intrapleural and esophageal pressures. The volume of each inspiration and expiration is indicated above the pneumotachographrecord. (From Cherniack R. M., L. E. Fahri, B. W. Armstrong and D. F. Proctor. J. Appl. Phys. 8.203.1955.)

In fig. 12 lower curve, this differential pressure (i.e.p. against i.p.p.) is recorded.The upper record is a pneumotachogram and the values of the tidal volumes are inscribed in this graph. It may thus be seen that at small tidal volumes (left part of curve) the differential pressure curve runs parallel to the x-axis (the tiny fluctuations are probably due to the cardiac action), thus indicating that under these circumstances the i.e.p. *changes* are a reliable index of i.p.p. *changes.*

At greater tidal volumes, however, this parallelism is occasionally disturbed and less constant. (right part of the curve).

This indicates that in this subject the i.e.p. changes do not faithfully reflect i.p.p. changes at greater tidal volumes.

FRY e.a. (1952) reported a comparison of intra-esophageal and intrapleural pressure variations recorded simultaneously in a patient recovering from a spontaneous pneumothorax.

They found the absolute level of intra-pleural pressure as measured in the residual rim of the pneumothorax to be slightly lower than the absolute

level of the intra-esophageal pressure ($\pm$ 1 cm H_2O). There was a general tendency for the two pressures to run parallel to each other.

The following experiment reported by CHERNIACK e.a. is also of interest.

The subjects inspired slowly after a maximum expiration. Periodically the flow was interrupted during $^1/_5$—$^3/_5$ second in the course of this inspiratory effort, so that static i.p.p. and i.e.p. could be measured.

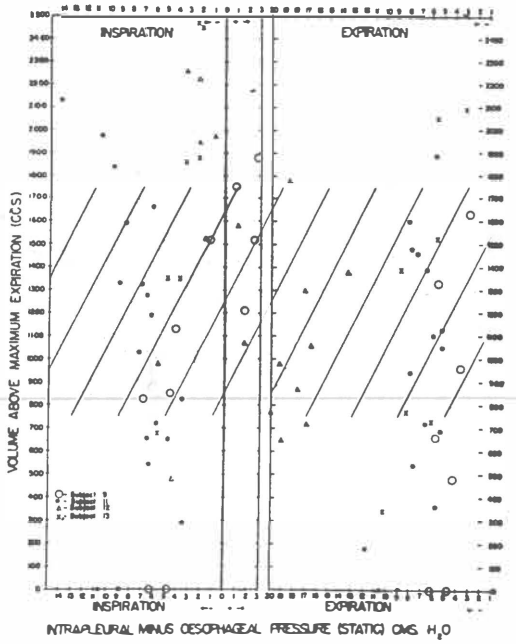


Fig. 13a; Fig. 13b

Relationship of the difference between static intrapleural and esophageal pressures (obtained during periods of interruption of air flow at the mouth for $^3/_5$—$^1/_0$ sec.) to state of lung-inflation in four subjects. The area covered by oblique lines represents approximately the lungvolumes illustrated in fig. 12. (From Cherniack R. M., L. E. Fahri, B. W. Armstrong and D. F. Proctor. J. Appl. Phys. 8.203.1955.)

The difference between i.p.p. and i.e.p. was plotted against volume (above the level at maximal expiration) as is shown in fig. 13a. In fig. 13b the same plot is obtained during slow interrupted expiration, starting from the maximal inspiratory position. It is clear that in the "ideal" case the points would fall on a straight line perpendicular to the abscissa and parallel to the "line of zero difference".

The large variation between static i.p.p. and i.e.p. at various degrees of lung inflation is clearly demonstrated in fig. 14.

In fig. 14 and 15 the static i.e.p. and i.p.p. obtained from different individuals are plotted against each other.

In fig. 14 the pressures are obtained during interrupted inspiration.

In fig. 15 these pressures are obtained during interrupted expiration.

There is clearly a tendency for the points to run parallel to (in some instances even to coincide with) the "45° line" passing through the origin. The considerable spread, however, should be noted.

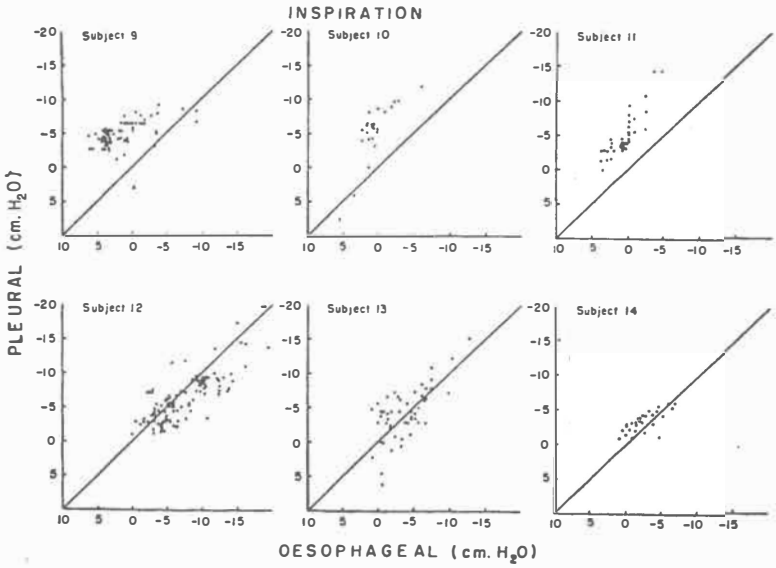


Fig. 14

Static intrapleural and esophageal pressures were obtained in inspiration during periods of interruption of airflow at the mouth for / — /0 sec. (From Cherniack R. M., L. E. Fahri, B. W. Armstrong and D. F. Proctor. J. Appl. Phys. 8.203.1955.)

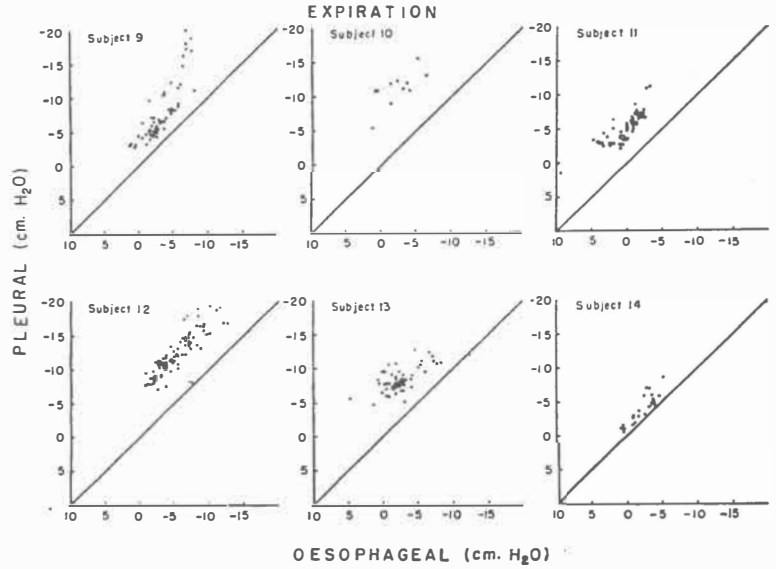


Fig. 15

Static intrapleural and esophageal pressures were obtained in expiration during periods of interruption of air flow at the mouth for / — /0 sec. (From Cherniack R. M., L. E. Fahri, B. W. Armstrong and D. F. Proctor. J. Appl. Phys. 8.203.1955.)

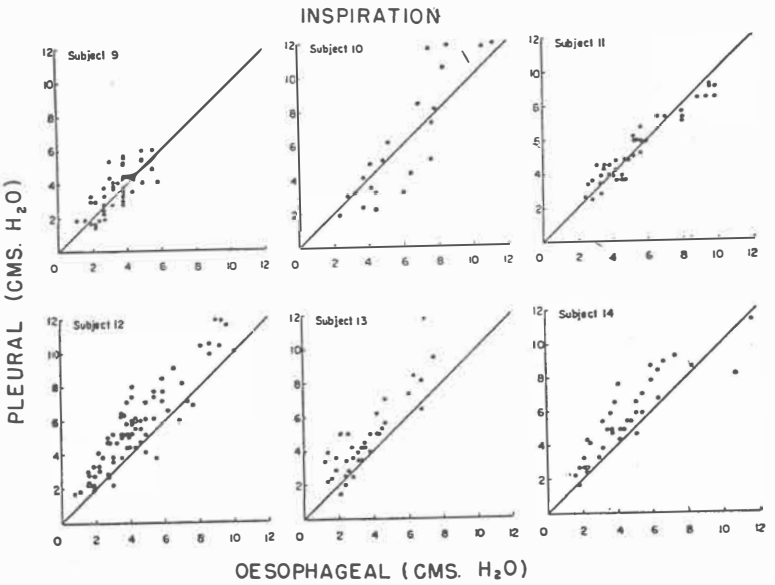


Fig. 16

Comparison of intrapleural and esophageal onelastic pressure during inspiration. (From Cherniack R. M., L. E. Fahri, B. W. Armstrong and D. F. Proctor. J. Appl. Phys. 8.203.1955.)

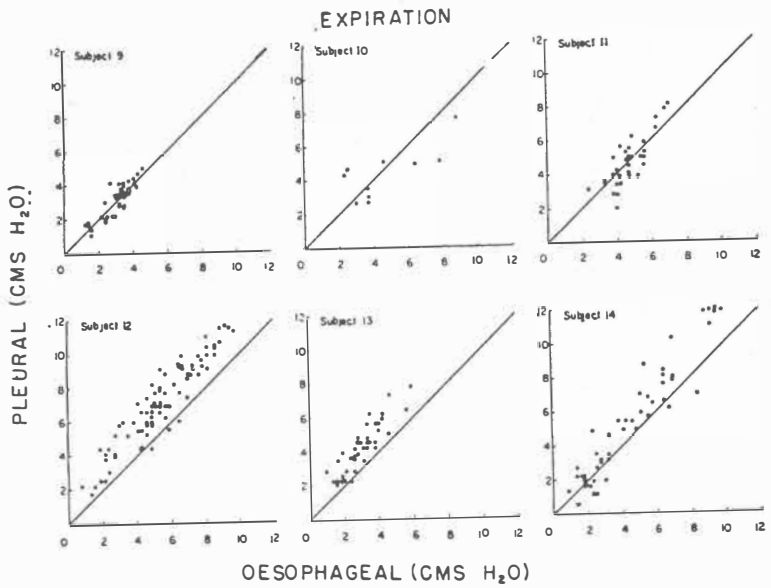


Fig. 17

Comparison of intrapleural and esophageal nonelastic pressures during expiration. (From Cherniack R. M., L. E. Fahri, B. W. Armstrong and D. F. Proctor. J. Appl. Phys. 8.203.1955.)

In fig. 16 and 17 the viscous pressures (i.e.p. and i.p.p.) during inspiration and expiration are plotted against each other. Here the difference between i.p.p. and i.e.p. is on the average, negligible, since the points tend to fall on the "45° line".

VERSTRAETEN compared esophageal pressures and pleural pressures (fronto-lateral) in healthy dogs.

The results are shown in table I.

TABLE I

pressure change between end-expiratory and end-inspiratory level

weight of dog in kg	pleura	oesophagus
21	1.8	1.7
19	6.6	6.6
27	2.5	2.6
22	4.9	4.8
25	5.7	6.0
17	8.3	8.5
24	10.5	9.6
16	10.8	11.6
28	5.5	5.3
27	9.3	8.7
16	21.0	20.8

No figures were given concerning the absolute values. Only the differences between end-expiratory and end-inspiratory pressures, were compared. It can be seen that on the whole, the correspondance between pleural pressure changes and esophagus pressure changes is fairly good, the discrepancy, as a rule, not exceeding 5 %. Hence it may be concluded that in healthy dogs pressure *changes* measured with the esophagus catheter are a fairly accurate index of pressure changes occuring in the (fronto-lateral) pleural space.

For further experimental evidence see FAHN e.a. (1957), WIGGERS e.a. (1947).

DISCUSSION.

From the evidence given above the following conclusions may be drawn:

1° static i.p.p. tends to be more negative than static i.e.p.;

2° the difference between i.e.p. and i.p.p. is not constant, but varies with the state of inflation and during the cycle;

3° The *general trend* of the two pressures is to run parallel as assessed by meaurements in man and dog.

The measurements were made on patients with thoracic diseases undergoing operation, most of these patients suffering from lungtuberculosis, emphysema, Morbus Besnier Boeck and other pulmonary affections.

On a priori grounds it might be possible that the pleura pressures in these patients are regionally different, i.e. it is conceivable that pleura pressures

measured at different sites may give different values; e.g. if pleura pressure is measured over a large bulla in emphysema, with pleura adhesions isolating this site from the rest of the pleura space, than the pressure thus measured may not be an adequate measure for the "over-all" pressure across the lungs.

In such a case, the esophagus pressure might even be a better measure, since the esophagus pressure results from the influence of a larger lung-field.

This hypothesis, recognized by CHERNIACK e.a. is supported by experimental evidence.

Experiments have shown that even in healthy individuals, marked differences may exist between pressures measured at different locations in the pleural space. (HEEMSTRA 1957, BROOKHART e.a. 1947, WIGGERS e.a. 1947).

It was shown by COLERIDGE and LINDEN (1954), that pressures measured in very small air pockets in the lateral and medial pleural space in the dog, differ by about 5 cm H_2O during quiet breathing the difference increasing to about 9 cm H_2O at the end of maximal inspiration.

Fig. (18) shows an experimental record.

It can be seen that during the pre-inspiratory phase the lateral pleural space pressure is 5 cm H_2O more negative than the medial pleural space pressure. During inspiration, this *difference* becomes greater, assuming values of 6.5 cm H_2O and even 8 cm H_2O (at end of maximal inspiration).

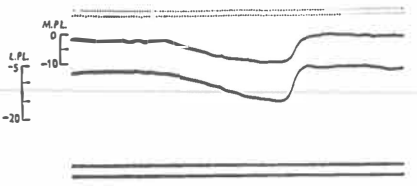


Fig. 18

Normal respiration. Records from above downwards: time $^1/_{50}$ sec., medial pleural pressure lateral pressure, zero reference lines. Calibrations in cM H_2O. (From Coleridge J. C. G. and R. J. Linden. J. Phys. London 126.304.1954.)

It should be mentioned that these authors also compared pressures recorded in the mediastinum and in the medial pleural space. A typical record is shown in fig. 19, where it can be seen that during the pre-inspiratory

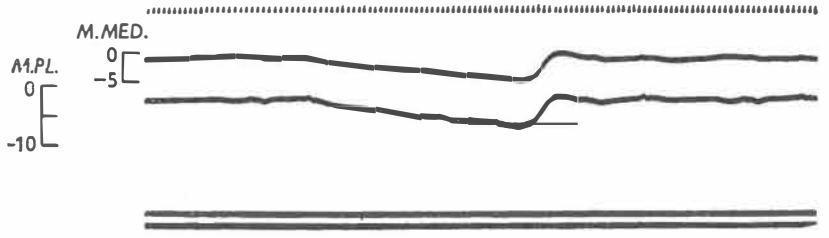


Fig. 19

Normal respiration. Records from above downwards: time $^1/_{50}$ sec., mid-posterior mediastinal pressure, medial pleural pressure, zero reference lines. Calibrations in CM H_2O. (From Coleridge J. C. G. and R. J. Linden. J. Phys. London 126.304.1954.)

phase the medial pleural pressure was 1.5 cm H_2O more negative than the pressure in the mediastinum. During inspiration this difference became 2 cm H_2O. It is thus seen that the pressure in the mediastinum closely approximates the pressures in the medial pleural space. The differences between these pressures are smaller than the differences between the pressures in the lateral and medial pleural spaces. Since the esophagus pressure is apparently most directly influenced by the pressures in the mediastinal tissues surrounding it, this result suggests that esophagus pressure more closely approximates medial pleural pressure than lateral pleural pressure.

BROOKHART and BOYD (1947) and WIGGERS e.a. (1947) also found the lateral pleural pressure to be more negative than the medial pleural pressure.

WIRZ, however, failed to find systematic topographical variations in the rabbit. Recently FARHI e.a. (1957) report only minor pressure differences at different locations. Pressures measured at points between the third and eighth interspaces varied one from another by less than 1.0 cm H_2O.

In the light of the finding that marked differences may exist between pressure-changes (and absolute pressures) occuring at different locations in the pleural space, the basic concept "pressure change across the lung-system" (see later) becomes devoid of meaning, unless the location is specified, e.g. mouth-medial pleural pressure, etc.

An extremist might even argue, in the light of these findings that the mouth-esophagus pressure changes, may, with equal justification (or lack of it) be taken as a measure of the pressure change across the lungs, as the mouth-lateral or medial pleural pressure changes.

"Pressure change across the lungs" should be redifined as the *average* value of the pressure changes occuring at all the different points of the lungsurface (surface-integral). Apparently this value can not be measured experimentally.

Conclusion: esophagus pressure changes run roughly parallel with pressure changes in the pleural space.

Pressure changes in the pleura space show marked local differences so that measurement at a single pleural location can not be taken as a yard-stick for assessing the reliability of the esophagus method. The value of the esophagus method depends on the accuracy required in a particular study, and its limitations as a measure for the "pressure change across the lungs" should be constantly kept in mind. The same applies to the pleura-method.

The direct measurement of pleural pressure may introduce an error due to local muscular contractions in the lungs at the site of the small pneumothorax. As a result of the local contraction of lungtissue, local tracion may be exerted.

As a result of this the pressure may be measured too low. (BRONKHORST and DIJKSTRA 1940, DIJKSTRA 1939).

Part III *SOURCES OF ERROR IN THE PRESSURE MEASUREMENT WITH THE ESOPHAGEAL TECHNIQUE.*

1) The occurrence of esophagus contractions may seriously distort the pressure record. In fig. 20, typical contractions are recorded. The upper curve represents the pressure curve. A downward swing represents a pressure change in the positive direction. In A the contractions (random positive pressure pulses) are numerous, while in B, C and D only isolated contractions are seen. The contraction in D resulted from a sound stimulus. The esophagus contractions, resulting in positive pressure waves, may either occur "spontaneously" or result from swallowing, mental distress, bodily exercise, excessive respiratory gymnastics etc.

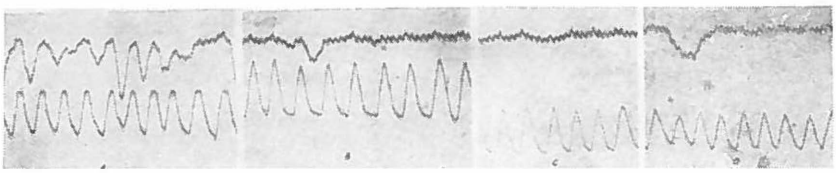


Fig. 20

Oesophagogram and spirogram
A. Initially many contractions are present.
B. After 10 minutes only a few contractions are present.
C. After 20 minutes all contractions have disappeared.
D. A contraction following an auditory stimulus.
(From Buytendijk H. J., thesis Groningen 1949.)

2) Heart pulsations or artery pulsations may result in tiny pressure pulses synchronous with the heart beat. They are easily recognized and their occurrence in the pressure record depends, among other things on the location of the tip of the catheter and the physical characteristics of the pressure recording system. They are usually of little consequence, although MEAD and WHITTENBERGER state that the influence of the heartbeat, which is maximal in the lower third of the esophagus, may be so great as to make "interpretation" of the record impossible.
3) Stiffness of the esophagus and/or its surrounding tissue. Consider the extreme case, when the esophagus is like a metal tube. Then, of course, no pressure changes will be recorded in the esophagus during the respiratory cycle. On the other extreme i.e. when the esophagus (including "mediastinum") is a completely flaccid "bag", the para esophageal pressure changes across the lungsystem may be faithfully recorded from within the esophagus.
A rigid tube represents a body with "infinite" elasticity, while a flaccid bag posesses no elasticity. It thus follows that the greater the elasticity of the esophaguswall (its "stiffness") the smaller will be the pressure variation in the esophagus relative to the pressure variation across the

lungsystem. Only when the esophagus behaves like a flaccid bag (no elasticity of its own) will it be possible to record the pressure changes across the lungsystem by the esophagus method * faithfully. In certain pathological cases (e.g. inflammation and fibrotic changes of the mediastinum, collagen diseases etc.) it is conceivable that the esophagus or its surroundings tissues, behaves like a body with strong elastic properties of its own.

4) Method of recording esophageal pressure

a) filling volume of the balloon.

However, it is probable that even in normals "elastic" properties of the esophagus come into play. (At this stage we shall use the term "elasticity" in a loose way, including tonic contractions of the muscles of the esophagus).

Certain experimental findings substantiate this view. It was found by MEAD, WHITTENBERGER (1953), that when the volume of air in the balloon placed in the esophagus, was increased in 0.1 cc steps, (within the volume range that did not affect the pressure in the esophagus-balloon when the balloon was placed in the atmosphere), then a) the absolute level of the esophagus pressure increased with increasing air volume in the balloon and b) the pressure variations decreased with increasing airvolume in the balloon. This is shown in fig. 21.

FIG. 4. Pressure recorded within the esophageal balloon as a function of balloon volume. The *dotted line* was obtained with the free balloon before passage into the esophagus. The *vertical lines* indicate the level and amplitude of the pressure variation during respiration with the balloon in the esophagus of a dog at different balloon volumes.

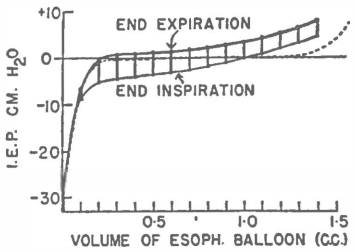


Fig. 21

From Mead. J. J. and J. L. Whittenberger. J. Appl. Phys. 5.779.1953.

These facts may be explained as follows:

The esophagus is a closed cavity (closed below by the cardia, above by a sphincter and a muscus plug around the catheter). The introduction of air in the flaccid balloon has the same effect as the introduction of air *directly* into the esophagus cavity.

The more air is introduced into the esophagus, the more the walls of the esophagus are "stretched" (either directly or reflexly resulting in increased tonus of its muscles) and hence, the more the "elastic" properties of the esophagus wall become operative.

As we have seen, this will result in decreased pressure variations. It is easy to see that this will also result in a rise of the absolute level of the pressure in the esophagus (e.g. end-expiratory).

Here we have explained the findings by this theory.

* The question of topografical differences in pleura-pressures is ignored here.

However, these findings could scarcely be explained in a different way, and it may safely be stated that these findings actually prove that the esophaguswall (and/or surroundings) possesses marked "elastic" properties, in normals, even under non-extreme conditions.
The practical consequence of these findings is that the volume of air in the balloon should be kept as small as possible. From this consideration it might be thought that the smaller the balloon dimensions the better. However, this is not true, since a small balloon makes it difficult to adjust the volume of air in such a way as not to bring the elastic properties of the balloon into play.
This may be seen from fig. 22.

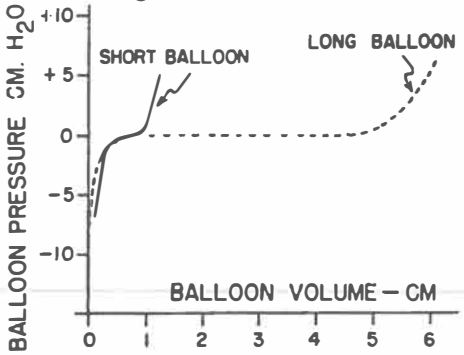


FIG. 6. Graph of balloon pressure plotted against balloon volume for short and long esophageal balloons

Fig. 22

From Mead. J. J., M. B. Mc. Ilroy, N. J. Selverstone and B. C. Kriete. J. Appl. Phys. 7.491.1955.

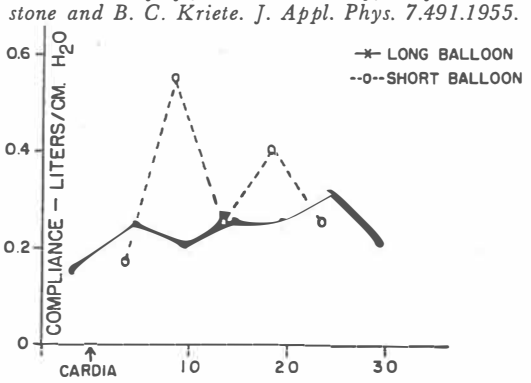


FIG. 2. Lung compliance in a normal subject recorded at different levels in the esophagus with the long and short balloon methods.

Fig. 23.

From Mead. J.J., M. B. Mc. Ilroy, N. J. Selverstone, and B. C. Kriete. J. Appl. Phys. 7.491.1955.

b) choice of balloon and filling medium.

The pressure may be recorded either with an air-filled system, or with a water-filled system as described by DORNHORST and LEATHART (1952). MEAD e.a. (1955) have compared the efficiency of the short balloon (3 cm long 1 cm in diameter) and that of the long balloon (16 cm long and 0.8 cm in diameter). The balloons were filled with air. In fig. 23 the compliance values measured at various sites in the esophagus are plotted for the long and short balloon (open circles). It will be seen that the compliance values using a short balloon vary in a haphazard manner with the site of the balloon. With the long balloon the variation with position is much reduced. This finding clearly favours the use of a long balloon.

MEAD and WITTENBERGER attribute these variations to compression of the balloon by external structures.

The short balloon is more strongly affected by the heartbeat.

MEAD has arbitrarily divided the esophagus into 5 levels (in 9 individuals).

He found the scatter least in the lower $^2/_5$ and the upper $^1/_5$.

The high values for compliance obtained in the midesophagus could result from local compression of the esophagus by external structures such as the trachea and great vessels, which lie immediately anteriorly to the esophagus in this region and which may be pulled against the esophagus as the lungs increase in volume.

By making simultaneous records with the long balloon air-filled system, and the water-filled open system it was found that both methods gave about the same results, as may be seen from fig. 24. It is seen from

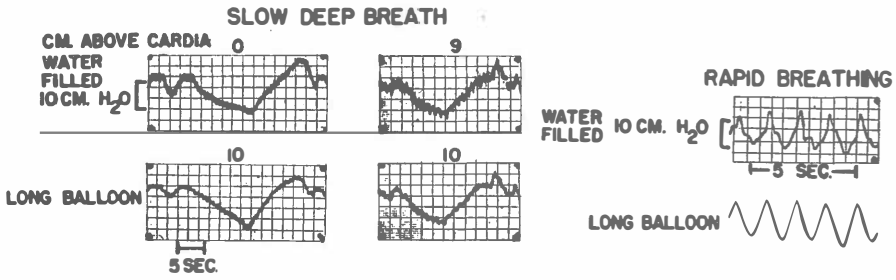


Fig. 24

Simultaneous tracings of intraesophageal pressure recorded by the long-balloon and water-filled methods during a slow deep breath and during rapid breathing. (From Mead J. J., M. M. Mc. Ilroy, N. J. Selverstone and B. C. Kriete. J. Appl. Phys. 7.491.1955.)

fig. 24, that during rapid breathing pressure swings recorded with the water-filled system are rather irregular. This was ascribed to motion artefact.

It should be realized that in the water-filled system the pressure (relative

to atmospheric), also depends on the height of the water column, which means that for "absolute" values a correction must be made, using the position of the catheter tip relative to the manometer.. The measurement of this is at times rather uncertain.

The use of helium, has been advocated by FRY e.a. (1952) but its use appears to be a superfluous complication in most studies. With the balloon-method the use of a water manometer, even for "static" measurements is unsound practice. This follows from the fact that the water manometer requires a large volume displacement.

Let the initial balloon volume be 5 cc, then a positive pressure of 10 cm H_2O would force 5 cc from the balloon into the water manometer, so that the balloon would be empty. A further pressure rise could then not be recorded, or, with the balloon containing 5 cc air. the maximum (positive) pressure that can be recorded with the average water manometer, is about 10 cm H_2O. It was shown by QUIGLEY (1955) that with a balloon in a bottle (pressure chamber) but closed off from its water manometer, the introduction of 5.5 cc of air in the bottle produced a pressure of 10 cm of water. On restoring connection between the balloon and its water manometer the pressure of the chamber fell to 5.2 cm of water.

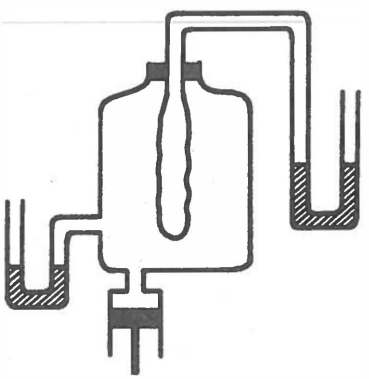


Fig. 25
Watermanometer in conjunction with the balloon.

The complete inadequacy of the water manometer used in conjunction with the balloon, is easily demonstrated by using the arrangement shown in fig. 25 and comparing the pressures recorded with the water manometer connected to the bottle and the water manometer connected to the balloon. It will be found that beyond a certain range, the water manometer connected to the balloon will be unresponsive. When negative pressure is applied, the balloon must accomodate large extra amounts of air coming from the water manometer, so that the balloon will be stretched up to the point where proportionality between pressure change and volume change is lost. It is thus clear that with negative pressures too, a point is reached where the water manometer will become quite unresponsive. In summary we state, that the use of a water manometer in conjunction with the (air-filled) balloon constitutes a serious abuse and results obtained with this method are next to worthless, unless dimensions, volume-pressure coefficient and useful range of pressure readings are explicitly stated. However, no one aware of the necessity of specifying these points, would bother to use such a hopelessly inadequate instrument as the balloon-water manometer system.

A physiological argument against the use of a water manometer-balloon system is that the large volume changes in the balloon may cause further irritation of the excitable esophagus.

The air-filled open tube method has been tried by some workers, including the author. QUIGLEY obtained satisfactory results in dogs, using a tip 2 cm long with an internal diameter of 4 mm. The tip was merely used to retard the process of obstruction by mucus. The author has tried this method on humans, but the problem of mucus obstruction remained unsolved.

The volume of air introduced into the balloon should be kept as small as possible. Quite often, it is stated that this volume should not exceed 1 cc.

A better requirement seems to be that so much air is introduced into the balloon (initially made "vacuum") suspended in the atmosphere, until the pressure equals atmospheric pressure. The balloon is than in its natural collapsed state.

5) Pertinent theoretical considerations relating to the dynamic characteristics of the catheter manometer system.

In general it may be stated that optimal damping is obtained with $\alpha = 0.7$, where

$$\alpha = \frac{p}{2\sqrt{D.\Theta}} \qquad (1)$$

P = coefficient of viscous resistant D = spring constant, Θ = mass. The natural frequency of the recording system should be about 2.5 times the highest significant FOURIER term.

It has recently been shown (FRY e.a. 1957) that say the fifth harmonic constitutes the highest significant term. If then, we wish to record up to a respiratory frequency of 120 cycles/minute, i.e. 2 herz, then the highest harmonic will have a frequency of $4 \times 2 = 8$ Hz. Hence the natural frequency of the recording system should be at least $2.5 \times 8\ \text{Hz} = 20\ \text{Hz}$.

The natural frequency f_0 of the recording system is defined by

$$f_0 = \frac{1}{2\pi}\sqrt{\frac{D.}{\Theta}} \qquad (2)$$

Especially when air is used the balloon catheter is rarely, if ever, a limiting factor whatever the dimensions of the catheter. The adequacy of the catheter manometer system is easily tested by determining the natural frequency of the over-all system. The use of an ordinary ink-recorder having a natural frequency of about 10 Hz is adequate only up to a frequency of 60 cycles/minute.

A thorough discussion of this problem lies beyond the scope of this study.

CHAPTER VI

A criticism of Christie's method of experimental verification of Rohrer's theory of mechanical economy.

INTRODUCTION

Theoretically it can be shown that the curve relating the total respiratory work per minute and the frequency of breathing at constant alveolar ventilation possesses a minimal value.

ROHRER (1916), OTIS e.a. (1950) advanced the hypothesis that the frequency during normal breathing coincides with this minimum value, i.e. that during spontaneous breathing work done by the respiratory muscles is "most economical".

CHRISTIE e.a. (1953), MCILROY e.a. (1954), devised a method to verify this hypothesis on normal subjects and patients.

It will be shown, however, that CHRISTIE's method suffers from a number of false assumptions which make the method and its results unacceptable.

An alveolar ventilation of $\dot{V}_A = 5$ l/min, assuming a constant dead-space $V_D = 200$ cc, may be obtained in various ways as shown in Table I.
$\dot{V}_A = 5$ l/min, $V_D = 200$ cc, $\dot{V}_A = f\ (V_T - V_D)$

TABLE I.

f cycles/min	V_T cc	$\dot{V}$ (minute volume) cc/min
10	700	7000
15	533	8000
20	450	9000
30	366	11000
40	325	13000

From this example it may be seen, that at constant alveolar ventilation, the tidal volume decreases with increasing frequencies.

At high frequencies, the tidal volumes are small, while the minute volumes are large.

As the result of small tidal volumes the work done against elastic forces is lessened, while the large minute volumes imply increased work against friction forces. At low frequencies, tidal volumes must be large to effect the same $\dot{V}_A$. Large tidal volumes involve increased work against elastic forces. (ATTINGER and SEGAL 1957, BUTLER 1955, OTIS 1954, CHRISTIE e.a. 1954, MEAD and WHITTENBERGER 1953, STEAD e.a. 1952, ROHRER 1916.)

It can easily be shown, that the elastic work increases with the square of the tidal volume, which implies that elastic work rises steeply with decreasing frequencies.

The demonstration runs as follows:
P = SV (i.e. pressure = elastance × total volume).
For a small increment of work we may write
dW = PdV, where W = work
or

$$W = \int PdV = \int SVdV = \tfrac{1}{2} SV^2.$$

As may be seen from table I, minute volumes are low at low frequencies, so that at low frequencies work against friction forces is relatively small.

From the above introduction the following qualitative assertion may become plausible:
at high frequencies the total work per minute (consisting of elastic work + friction work) becomes "very high" (due to the great amount of friction work required), while at low frequencies the total work per minute again becomes "very high" (due to the increase in elastic work).

This suggests that the curve relating total work per minute and frequency will posses a minimum value at some moderate frequency, i.e. will be of the following type:

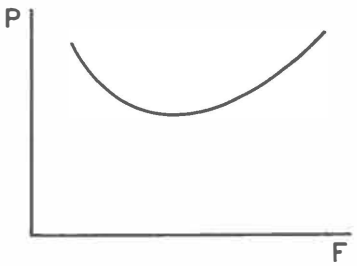


Fig. 1
Curve relating total work per minute and frequency.

ROHRER derived an equation which expresses total respiratory work per minute as a function of frequency, at constant alveolar ventilation. This expression is given by

$$W = \left(\frac{S}{2} \cdot \frac{1}{f} + \frac{R}{30} \right) \left(\dot{V}_A + f.D \right)^2 \qquad (1)$$

where W = total respiratory work per minute, S = elastance, f = frequency, R = coefficient of viscous resistance, $\dot{V}_A$ = alveolar ventilation, D = deadspace.

By differentiating equation (1) with respect to f and setting $\frac{dW}{df} = O$, the value of f may be found at which the total work per minute is least, at a constant alveolar ventilation.

Using normal values for the parameters, ROHRER calculated that this minimum was obtained at f = 17.

In other words, a given alveolar ventilation (4.7 l/m is this example) could be obtained with a *minimum* expenditure of energy at a frequency of 17 cycles/minute.

Since the frequency during spontaneous breathing is of the same magnitude (about 15 cycles/minute) ROHRER quite naturally advanced the hypothesis that during spontaneous breathing that frequency is selected that yields a minimal amount of work (per minute) to effect a given alveolar ventilation.

OTIS, FENN and RAHN essentially arrived at the same conclusion.

As a starting-point they used the equation

$$P = kV + k^{I}\left(\frac{dV}{dt}\right) + k^{II}\left(\frac{dV}{dt}\right)^{2} \qquad (1)$$

where P = total pressure across lungsystem, k, k^{I}, k^{II} are constants, and V = volume. The assumption is made that the D.S. remains constant and that the volume flow curve is a harmonic function of time.

The numerical values of k, k^{I} and k^{II} were obtained experimentally by applying artificial respiration to a trained relaxed subject placed in a DRINKER respirator.

From

$$\frac{dV}{dt} = a \sin bt, \text{ where } a = \text{amplitude of volume flow}$$

$b = 2\pi f$ = circular frequency,

it follows that the tidal volume V_T is given by

$$V_T = \int_0^{\pi/b} a \sin bt \, dt = -\frac{a}{b} \cos bt \Big|_0^{\pi/b} = \frac{2a}{b} = \frac{a}{\pi f} \qquad (2)$$

Since Work = pressure times volume, we may write

$$dW = P\,dV \qquad (3)$$

Substituting (1) in (3) yields

$$dW = kVdV + k^{I} a^{2} \sin^{2} bt \, dt + k^{II} a^{3} \sin^{3} bt \, dt \qquad (4)$$

The total work during an inspiratory tidal volume V_T of duration π/b is obtained by integrating (4),

$$W = \int_0^{V_T} kVdV + \int_0^{\pi/b} (k^{I}a^{2} \sin^{2} bt + k^{II} a^{3} \sin^{3} bt)\, dt$$

$$= \tfrac{1}{2} k V_T^2 + \tfrac{1}{4} k^{I} \pi^{2} f V_T^2 + \tfrac{2}{3} k^{II} \pi^{2} f^{2} V_T^3 \qquad (5)$$

Multiplying by the frequency f yields the inspiratory work per minute, or *

* Due to an unfortunate choice of notation the symbol P, which was used earlier for pressure, is used to denote power in remainder of this chapter.

$$P = \tfrac{1}{2}\, k\, f\, V_T^2 + \tfrac{1}{4}\, k^I\, \pi^2\, (fV_T)^2 + \tfrac{2}{3}\, k^{II}\, \pi^2\, (fV_T)^3 \qquad (6)$$

where P = work per minute (abbreviated from "Power").

When we assume that expiration is entirely passive, the above equation represents the total work per minute done on the lungsystem.

By splitting up the tidal volume into its alveolar portion and its deadspace portion,* equation (6) may be written

$$P = \tfrac{1}{2}\, kf \left(\frac{\dot{V}_A}{f} + V_D \right)^2 + \tfrac{1}{4} k^I\, \pi^2\, (\dot{V}_A + fV_D)^2 + \tfrac{2}{3} k^{II}\, \pi^2\, (\dot{V}_A + fV_D)^3 \qquad (7)$$

where $V_A f = \dot{V}_A$ = alveolar ventilation

V_D = deadspace portion of tidal volume.

By substituting numerical values for, k^I, k^{II}, a particular case yields

$$P = 5000\, f \left(\frac{\dot{V}_A}{f} + 0.2 \right)^2 + 150\, (\dot{V}_A + 0.2f)^2 + 3\, (\dot{V}_A + 0.2f)^3 \qquad (8)$$

Keeping $\dot{V}_A$ constant, the respiratory work per minute (P = power) may be plotted against the frequency f, to yield a curve such as shown in fig. 2 for a $\dot{V}_A$ = 6 l/min.

It can be seen from fig. 2 that the curve possesses a minimum value at f = 15.

This means that at f = 15, the respiratory work per minute, P, required to effect a given alveolar ventilation (6 l/m) is least.

Hence, when the organism chooses, in this example f = 15, its breathingmechanism would operate most "economically".

We wish to point out, however, that the concept "economical" here refers to the external work done by the respiratory muscles and not to the oxygen consumption of these muscles.

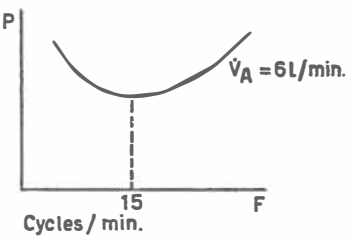


Fig. 2
Curve relating total work per minute and frequency for a $\dot{V}_A$ = 6 l/min.

It would seem to us, that at least in normals the oxygen consumption might, with at least equal justification, be taken as a yardstick for economy. When e.g. in he above example the efficiency of the muscles, at f = 15, is much lower than at some other frequencies, then the oxygen consumption at f = 15, might be higher than at some other frequency, in spite of the fact that the P—f curve possesses a minimum at f = 15. Only when the efficiency of the muscles remains constant at all possible frequencies (and tidal volumes) does a least value of the P—f curve imply that the energy *consumption* of the muscles is least at the same frequency.

* $\dot{V}_A = f(V_T - V_D)$ $\qquad \frac{\dot{V}_A}{f} = V_T - V_D$ $\qquad V_T = \frac{\dot{V}_A}{f} + V_D$

In this connection, it should be emphasized that OTIS e.a. have not attempted to verify their theoretical considerations expetimentally. The numerical values for k, k^I and k^{II} which they obtained with the use of a DRINKER respirator, of course did not contribute towards the experimental verification of their theory.

CHRISTIE e.a. (1954) have attempted to offer experimental evidence in favour of the hypothesis that during spontaneous breathing the "most economical" frequency (in the sense explained above) is selected.

Since CHRISTIE's results have excited wide clinical interest and are of acute theoretical importance, it becomes of interest to inquire into the validity of their method and assumptions.

SECTION 2

A brief description of CHRISTIE's *method of testing the "economy" hypothesis.*

CHRISTIE, MCILROY and MARSHALL employed the following procedure: subjects at rest and during work (on an bicycle ergometer) breathed at various predetermined frequencies with such tidal volumes that the alveolar ventilation was kept constant.

The enforced tidal volumes were calculated under the assumption that the deadspace remains constant and a normal value of 200 cc was assumed for the latter.

The esophageal pressure and the tidal volume were measured simultaneously. A spirometer (and pneumotachograph) were employed.

From the constructed pressure volume curve the total work per minute done on the "lungsystem" is obtained in the usual way. (It should be noted, that when expiration is passive, inspiratory work coincides with total work done during the cycle).

By computing the work per minute, as experimentally determined, at different frequencies, the empirical P—f curve (P = power = "work per minute") could be determined for each each individual, for a given constant alveolar ventilation. In fig. 3 (see page 66) one such curve taken from MCILROY e.a. (1954) is shown (lowest curve). It will be noticed that the curve possesses a minimal value at f = 15.

It so happens that in this particular case the frequency during spontaneous breathing is 15 cycles/min. This finding apparently confirms the economy hypothesis.

For a more detailed discussion of their methods, assumptions and results the reader is referred to the original papers.

SECTION 3

Critisism of CHRISTIE's *method.*

Our criticism is mainly levelled against the following items:

1) the assumption that deadspace remains constant at all tidal volumes;
2) the estimate of a "normal" deadspace value (of 200 cc);

3) the assumption that the work done on the lungs is a reliable guide for evaluating the "economy" of the respiratory muscles.

ad 1) *The assumption that deadspace remains constant at all tidal volumes is, at least, highly controversial.*

It is obvious that in the problem of keeping $\dot{V}_A$ constant at all frequencies, the *physiological* deadspace with reference to CO_2 should be considered. In view of the complexity of the controversy concerning the constancy of D.S., lack of space forbids us to discuss this item analytically.

We wish however to make the following pertinent remarks.

ROSSIER and BÜHLLMAN (1955), using their CO_2 method based on the determination of arterial P_{CO_2}, have found that the deadspace varies linearly with tidal volume.

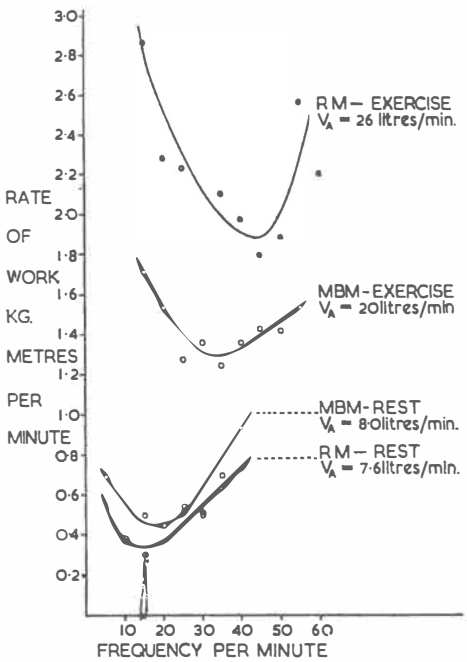


Fig. 3

Curves relating total work per minute and frequency during exercise and at rest. (From Mc. Ilroy M. D., Marshall R. and Christie R. V. Clin. Sce 13.127.1954.)

Fig. 4 shows one of their findings.

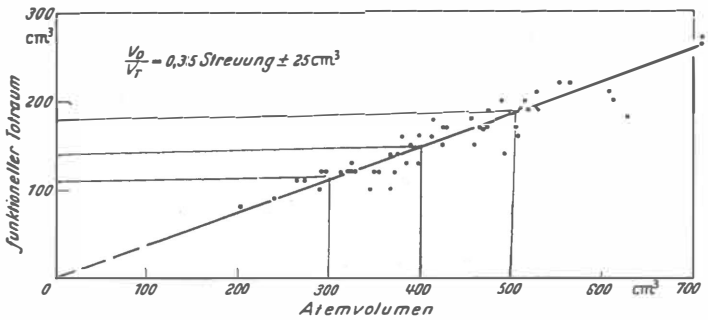


Abb. 9. Verhältnis von funktionellem Totraum zu Atemvolumen bei 50 gesunden Exploranden in Ruhe liegend, Volumen BTPS (ROSSIER u. BÜHLMANN 1957)

Fig. 4

Relationship between functional deadspace and tidal volume in 50 normals (supine position). (From Rossier P. H., A. Bühlmann. Phys. Rev. 35.860.1955.)

The results obtained with foreign "inert" gases (BATEMAN 1950, FOWLER 1948, MUNDT e.a. 1941, KROGH and LINDHARD 1931, SIEBECK 1911) have no bearing upon this problem which requires the use of the *physiological deadspace* for CO_2.*

(RILEY and COURNAND 1949, GROSSE-BROCKHOFF 1937, HENDERSON e.a. 1915, HALDANE 1915, DOUGLAS and HALDANE 1912).

PAPPENHEIMER's results (1952) based on the iso-saturation method have recently (WILLIAMS and RAYFORD 1956, FISHMAN 1954) been shown to be incorrect.

WILLAMS e.a. (1956) found that the deadspace varies linearly with tidal volume. They compared the iso-saturation method with a technique based on the BOHR equation and established the fact that the "alveolar" CO_2 tension measured with the PAPPENHEIMER technique was consistently lower than the arterial CO_2 tension. This experimental finding invalidates PAPPENHEIMER's claim that deadspace is independent of tidal volume.

Recently GRAY e.a. (1956) in a thorough theoretical and experimental analysis of the deadspace problem, have shown that the deadspace increase linearly with tidal volume.**

Although the above discussion is not offered as a proof that deadspace is not constant, but varies with tidal volume (a "proof" would require a detailed analysis of *all* the evidence, such as attempted by ROSSIER e.a. and GRAY e.a.), it does indicate that the evidence against a constant deadspace is very strong indeed. Any unprejudiced reader viewing the literature,

* Deadspace for O_2 is not required, since P_{CO2} and not P_{O2} is primarily regulated.

** In their study they introduce the term virtual deadspace. For its definition the reader is referred to the original paper.

should admit that th existence of a constant (physiological) deadspace, is, at *least,* highly controversial.

Only when the evidence in favour of constancy were overwhelming and shown to be so would this assumption have been justified: such, however, is far from being the case.

ad 2) *The assumption of a numerical value for the deadspace (200 cc) may lead to large variations in the true alveolar ventilation at different frequencies.*

The assumption of a numerical value for the deadspace (CHRISTIE e.a. assumed a value of 200 cc) based on data found in the literature, need not, of course, be valid in the individual case. Although the assumption of 200 cc represents a sound *average* value, there is good experimental evidence that the deadspace values (at rest) vary between say 120 and 220 cc among individuals. Let us study, by means of a numerical example, what effect the assumption of D.S. = 200 cc will have on the $\dot{V}_A$ value at various frequencies, when the *true* D.S. is e.g. 150 cc. It is perfectly obvious that such an error of 50 cc may easily be made in practice.

Now, let us trace the steps very carefully. First of all, the alveolar ventilation during spontaneous breathing must be established. The $\dot{V}_A$ value thus obtained, must be kept constant at all frequencies of breathing. Let us assume, e.g. that during *spontaneous* breathing, a tidal volume of 600 cc and a frequency of 15 cycles/minute are recorded. With the assumption of D.S. = 200 cc, the alveolar ventilation during spontaneous breathing will be 15 (600 — 200) = 6000 cc/min. or 6.0 litres/min.

During the actual experiment this $\dot{V}_A$ = litres/minute must be retained.

From table II it may be seen what tidal volume must be selected at a particular frequency, under the condition of $\dot{V}_A$ = 6.0 ltr/min.

TABLE II

$\dot{V}_A$ = 6 l/min D.S. = 200 cc

f	V_T
5	1400
15	600
30	400
60	300

Having calculated the values of V_T shown in table II, the subject is instructed to breathe at a particular frequency with a corresponding tidal volume (indicated by a spirometer) e.g. at f = 30, the subject must breathe with a tidal volume of 400 cc. But suppose the actual deadspace is 150 cc instead of 200 cc. Then with the frequencies and tidal volumes selected and computed in table II and actually carried out by the subject, the *actual* alveolar ventilations at the various frequencies would no longer be constant as may be seen from table III.

TABLE III

f	V_T	actual $\dot{V}_A$
5	1400	6250 cc/min; from 5 (1400—150)
15	600	6750 cc/min; from 15 (600—150)
30	400	7500 cc/min; from 30 (400—150)
60	300	9000 cc/min; from 60 (300—150)

From table III it is seen that in this example the *actual* alveolar ventilation is 6250 cc/min at f = 5 and 9000 cc/min at f = 60, an increase of 50 % of the value at f = 5.

It is thus demonstrated that an error in the estimation of the deadspace of only 50 cc may result in the alveolar ventilation changing by as much as 50 % (of the lowest value) in the course of the experiment.

It follows that the condition of constancy of alveolar ventilation may not be fulfilled at all, when the value of D.S. is merely assumed, instead of accurately measured.

Ergo, the assumption of a numerical value of the D.S. is unvalid.

ad 3) *The assumption that the work done on the lungsystem alone, may be used to evaluate "muscle economy" is unvalid.*

This assumption clearly implies that the work to move the thoracic cage etc. is negligible.

However, BÜHLMANN and BEHN (1957) determined the *total* respiratory work and the work done on the lungs in human subjects.

They found that the "thoracic" work constitutes 40 % *of the total respiratory work.*

In fig. 5, one of their results is shown graphically.

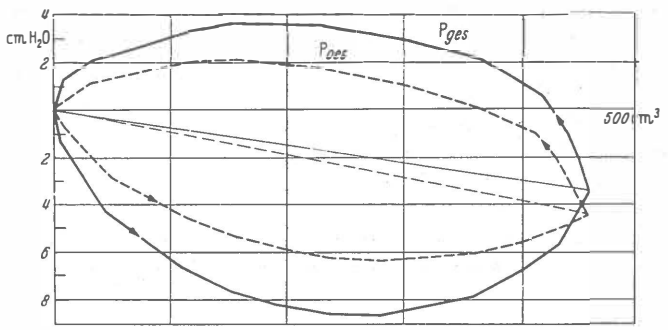


Abb. 55. Atemschleife bei Tankbeatmung. Ausgezogene Linie = Gesamtdruck, unterbrochene Linie = Oesophagusdruck. Die Differenz entspricht der an Thorax und Zwerchfell zu leistenden Atemarbeit

Fig. 5

Loop during induced ventilation in a tank respirator. Contiuous line: total pressure. Broken line: esophagus pressure. The difference constitutes the work required to move thorax + diaphragm. (From Bühlmann A. und H. Behn. Schweiz Med. W.schr. 49.1500.1957.)

From these findings it would appear that the "thoracic" work can hardly be looked upon as a negligible fraction of total work.

This certainly applies to normal cases. When, however, the viscous and/or elastic work on the lungs is greatly increased (asthma, fibrosis), then the work on the thorax will only constitute a small fraction of the total work (assuming that the thorax itself is normal).

In emphysema however, (rigid thorax) both the work on the lungs and the work on the thorax is increased, so that the work on the thorax constitutes a considerable fraction of the total work.

We shall next show that the correspondance between the spontaneous frequency, and the optimum frequency of the so-called "lungcurve" (i.e. the P—f-curve, relating work per minute done on the lungs and frequency) does *not* give us information about the "muscle economy".

This follows from the fact that the respiratory muscles must perform work on the lung + spirometer + thorax etc. Consequently, the system only works most economically when the spontaneous frequency coincides with the optimal frequency of the "total work" curve (lung + thorax + spirometer etc.)

This may be clarified graphically as follows.

In fig. 6 the form of the curves are arbitrarily chosen. (The "spirometer"-curve has been left out for simplicity.*

In fig. 6, the optimal frequency of the "lung" curve is 10 cycles/min, while the optimal frequency of the "thorax"-curve is assumed to be 50 cycles/min.

The 'total" curve is obtained by algebraic addition of the lung-curve and thorax-curve. As we explained above, the "total" curve should be considered in the evaluation of work economy.

If, and only if, the spontaneous frequency coincided with the optimal frequency of the "total" curve, (in this example 40 cycles/min.) can we conclude that the system functions most economically.

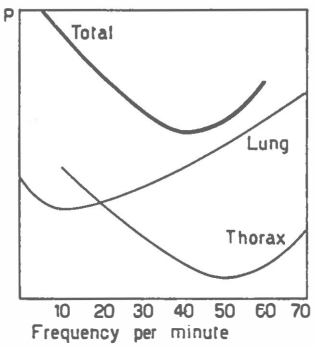


Fig. 6
Curves relating total work per minute and frequency. „Lung"-curve; „thorax"curve and „total"curve.

Let, in this example, the "spontaneous frequency" be 10 cycles/min. If we compare the spontaneous frequency with the optimum frequency of

* From the paper of McIlroy e.a. the impression is gained that they did not measure the pressure differentially and that they subtracted the work to move the spirometer from the total work (here defined as lung + spirometer work.)

The use of the spirometer correction is, however, unjustified, since the work to move the spirometersystem should be included. This follows from the fact that work economy refers to total work done by the muscles, in casu work done on the lungs, thorax and spirometer.

the lung-curve (10 cycles/min.) then we would with CHRISTIE erroneously conclude that the system functions most economically.

CONCLUSION

On the basis of the above analysis it is concluded that CHRISTIE's technique of measuring the economy of the respiratory muscles, is based on assumptions that may lead to gross errors of unknown extent.

From this it follows that the good correspondance found by MC ILROY e.a. between the spontaneous frequency and the optimumfrequency of the "lung-curve" both in normals and patients at rest and during work, gives no reliable information concerning the "economy' of the respiratory muscles.

It thus follows that ROHRER's theory of work economy still awaits experimental verification.

APPENDIX:

On the form of the "lungcurve"

One trained subject was used in an experiment with the same technique described by CHRISTIE e.a. The esophageal pressure was measured against atmospheric pressure and not against "mouth"-pressure and no (unjustified!) correction was made for the work to move the spirometer.

Since the *calculated* alveolar ventilation during spontaneous breathing while connected to the spirometer was 5.0 liters per minute, the alveolar ventilation was held constant at 5.0 l/m in subsequent calculations. The frequencies range from 5—40 cycles/min, with intervals of 5 cycles/min.

The resulting P—f curve is shown in fig. 7.

This curve shows, in contrast to CHRISTIE's curves, a flat range of minimal values (plateau): between f = 10 and f = 20, the curve runs horizontal at minimal values.

Since we used intervals of 5 cycles/min. it is clear that the real "plateau" might extend between say, f = 8, and f = 22. Because of the width of this minimal range in this subject, the finding of this minimal range (even if the technique used were correct) means little, since a spontaneous frequency of f = 8 and of f = 22 (nearly 3 times as high) would both fall within this minimum plateau.

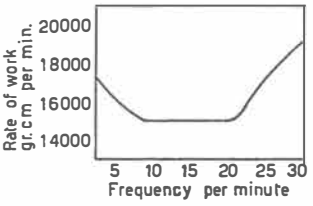


Fig. 7

Curve relating total work per minute and frequency of a normal trained subject for $\dot{V}_A = 5$ *l/min.*

It should be stressed that this experiment was merely used to obtain familiarity with the CHRISTIE method.

CHAPTER VII

Standard viscous work : Methods and discussion of errors.

In this chapter we shall mainly discuss the method of obtaining standardized viscous work values, with the Lode-P/V-Recorder SH-57.

As has been explained in chapter I and chapter XI, this method gives an index of the resistance to breathing.

A justification of the use of this index in preference to the friction coefficient R, has been given in chapter III.

It should be realized that the area of the loop consists of a "dynamic part", "viscous" work, and a "static part" due to hysteresis as defined by RADFORD e.a.

By using a planimeter the area of the loop may be determined. Using proper units, e.g. gram-cm, this area represents the "viscous" work done by the lungsystem.

The term "viscous" work is really a misnomer since the term viscous implies the existence of forces which are directly proportional with flow.

Due to tubulence and other factors this direct proportionality is lost.

At high rates of flow ($f > 40$) no narrowing of the vocal cords occurs, as has been verified by direct laryngoscopic observation. (HUIZINGA).

Since within the 1 liter range near the normal end-expiratory level the hysteresis factor is negligible in normals, (MEAD, RADFORD, DONLEBEN, DEFARES), our *normal* "viscous" work values represent dynamic effects only.

In order to evaluate the resistance to breathing in patients it is necessary to subtract the hysteresis area (obtained during very slow breathing) from the total area.

The difference, expressed in gr-cm should then be compared with the normal values.

However, there is considerable merit in including this hysteresis comeponent, i.e. in taking the total area of the loop, since hysteresis work represents non-reversible work in the same sence as "viscous" work (in contradistinction to elastic work).

However, it should be fully realized that when the total loop area is

taken the "hysteresis" work may account for a considerable portion of the total. In other words, the loop area expressed in work units) is no longer a measure of viscous work. In most clinical cases, including asthmatics, hysteresis at the normal range and level of breathing is negligible. However, the possible existence of hysteresis should always be kept in mind and appropriate correction should be applied when only a measure of resistance to breathing is desired.

The methods and sources of errors associated with the determination of the modulus of elasticity E, the static compliance and the frequency dependent compliance, have been discussed in the appropriate chapters and will not be mentioned here. However, some of the items discussed here, e.g. the properties of the balloon, the arrangement of the spirometer-circuit etc., also refer to the above mentioned measurements.

The method of obtaining the P—V diagram is conventional and conforms to the principles outlined in the chapter on general principles (chapter I).

Tidal volume is measured with a LODE spirometer.

The dynamic characteristics of the spirometer were tested by connecting the spirometer to a STARLING-pump delivering a constant stroke volume of 1 litre. The motion of the piston was approximately harmonic and the frequency of the pump could be continuously varied between zero and 150 cycles/minute.

The excursions of the spirometer bell were recorded by an inkwriter while the vertical excursions of the lightspot of the pressure-volume apparatus were simultaneously recorded.

It was found that no amplitude distortion or phase shift occurred up to about 75 cycles/min. The resonance peak occurred at about 85 cycles/minute, the excursions of the bell at peak resonance being only 60 % of the constant excursions below f = 75 cycles/minute.

The influence of the degree of immersion of the bell was taken into account. Obviously phase shift here applies to the excursions of the bell relative to those of the pump and not to those of the water. It is concluded that volume recording is adequate up to frequencies of about 70 cycles/minute.

The spirometer contains low resistance valves and a soda-lime cannister is used to absorb CO_2. In this manner the subject may remain connected to the spirometer over long periods, since CO_2 accummulation has been obviated.

The rise of the spirometer tracing resulting from the absorption of CO_2 is compensated by adding oxygen continuously to the spirometer, the volume flow of oxygen being equal to the oxygen consumption of the subject. Although the presence of the soda-lime cannister greatly increases the resistance of the spirometer pathway, this is of *no* consequence for our purpose, since

1° the pressure is measured differentially, and

2° frequency and tidal volume are standardized, i.e. mentally controlled.

As has been stated in chapters I and XIV, breathing is standardized at f = 15 and f = 40, over 1 liter and 0.6 liter. It has been shown (BRISCOE and DUBOIS, 1956, FRY e.a. 1954, MEAD and WHITTENBERGER, 1953) that levelshifts may influence the resistance to breathing.

The possible end-expiratory levelshifts resulting from breathing at high frequencies, or from the presence of the soda-line cannister could easily be detected, even in the presence of O_2 consumption changes as may occur at freq. = 40 c/min.

The differentiation between increased oxygen consumption not exactly balanced by the O_2-flow to the spirometer and increased mid-position is made by having the subject produce a maximal inspiratory effort (inspiratory reserve volume). If this inspiratory reserve volume is smaller than the inspiratory capacity an increase of mid position has occurred.

Following common practice volume is measured at A.T.P.S. Although B.T.P.S. would theoretically be more desirable, this complication has been omitted, since only relative values are required, and since the room temperature was kept fairly constant (20—22°) so that variations in the systematic error fall well within the range of experimental error due the other causes.

The pressure recording

Due to the properties of the differential manometer the sensitivity for negative pressures (below atmospheric) differs from the sensitivity for positive pressures (above atmospheric). Moreover, the relationship between applied pressure and displacement of the lightspot on the screen, is non-linear for positive pressures.

These are undesirable properties, but at the time of the experiments we have not succeeded in having these technical dificiencies eliminated.

In our present apparatus this non-linearity is eliminated. These disturbing factors may be corrected for in the following manner.

With the lightspot adjusted to the zero position when both sides of the differential manometer are exposed to atmospheric pressure, negative pressures are applied to check the sensitivity and linearity of the "negative" range: e.g. at a chosen sensitivity of 10 mm deflection/8 cm H_2O (1.25 mm/cm H_2O) it is found that:

— 8 cm H_2O produces a deflection of —10 mm
—16 cm H_2O „ „ „ of —20 mm
—24 cm H_2O „ „ „ of —30 mm
—32 cm H_2O „ „ „ of —40 mm

In this way the sensitivity on the negative side is established (1.25 mm/cm H_2O) and the linearity on the negative side checked.

With the sensitivity knob of the instrument remaining in the same position (corresponding to 1.25 mm/cm H_2O on the negative side) the positive range is explored.

The results are shown in the table below

TABLE I

sensitivity 1.25/cm H_2O as established on the negative side

applied positive pressures in cm H_2O	deviations of light-spot to positive side in mm	positive pressures in cm H_2O calculated from values in column II under the assumption that sensitivity is unchanged	error resulting from the assumption of constant overall sensitivity in cm H_2O
4	4.5	3.6	—0.4
8	9.0	7.2	—0.8
12	13.5	10.8	—1.2
16	17.5	14.0	—2.0
20	22.0	17.6	—2.4
24	26.25	21.2	—2.8
28	31.25	25.0	—3.0

It is obvious that knowing the pressure-displacement curve on the positive side, the true pressure-volume diagram may be constructed from the recorded loops, when the point of zero position is marked on the photograph.

Since this is a rather laborious procedure it is of interest to inquire into the magnitude and range of variation of the systematic error when *constant* over-all sensitivity is assumed.

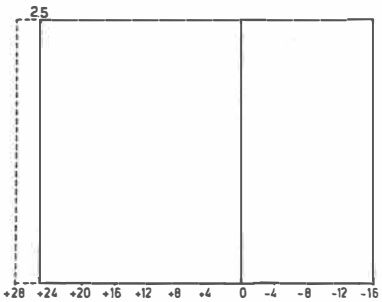


Fig. 1

For explanation see text.

Let us assume, for simplicity, a rectangular loop such as shown in fig. 1. The ratio of positive portion — negative portion is about 70 %: 30 %, which is typical for the loop of pronounced emphysema or asthmatic cases. It will be seen that on the positive side (left side) the (maximal) pressure is 25 cm H_2O, *when no proper correction is made.*

Applying the correction from table I, it is seen that the true positive pressure is 28 cm H_2O.

Thus without correction the total pressure range is 25 + 16 = 41 cm H_2O, while the true pressure range is 28 + 16 = 44 cm H_2O, or without correction the pressure range is measured 7 % too low.

This means that the viscous work (area of loop) computed without correction is 7 % too low in this example. It is easy to see that the systematic error resulting from not applying the correction varies between 0 % and 10 %; this depends on whether the loop falls entirely on the negative side (as in normals) or whether 95 % of the loop is on the positive side (as in the most extreme forms of emphysema).

In the above example we have neglected the slight non-linearity, but this is immaterial for estimating the *magnitude* of the systematic error.

The loops of normal subjects used for the construction of normal values, all fall within the negative range, so that no corrections are required in this group.

Detailed corrections, taking the non-linearity into account, were applied in those cases where the specific problem demanded accurate absolute values.

In fig. 2, the schematic set-up is shown.

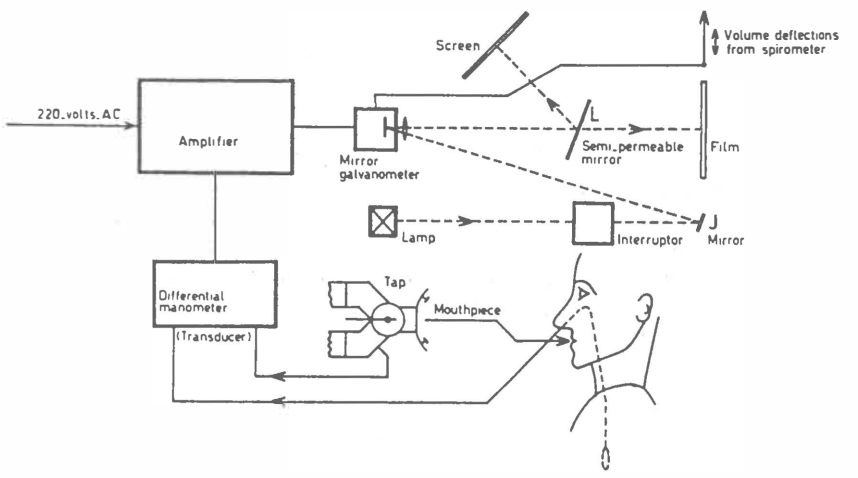


Fig. 2B

In fig. 2B the schematic set-up is shown.

Principle of the Lode-P/V-Recorder SH-57:

Both the pressures active in the oral cavity and the esophagus are communicated simultaneously to a receiver, a differential pressure transducer which converts pressure fluctuations into electrical signals.

These impulses are amplified by an electronic amplifier giving its output to a mirror-galvanometric system.

The galvanometer changes the direction of a light-beam, the latter being projected in two ways, viz. a) on the photographic material and b) on the screen of the viewer, thus enabling the operator to keep a continuous visible control on the deflections of the manometric system.

In the above-mentioned way the positive and negative swings of the esophagus-pressure-variations are recorded. horizontal axis).

The volume-variations (vertical axis) are recorded and projected by inclining the galvanometer itself. This is realized by a mechanical system consisting of a lever to which, by means of a special coupling mechanism, the spirometer is connected.

Both the vertical movements of the spirometer bell (vertical axis) and the esophagus-pressure-variations (horizontal axis) are recorded simultaneously.

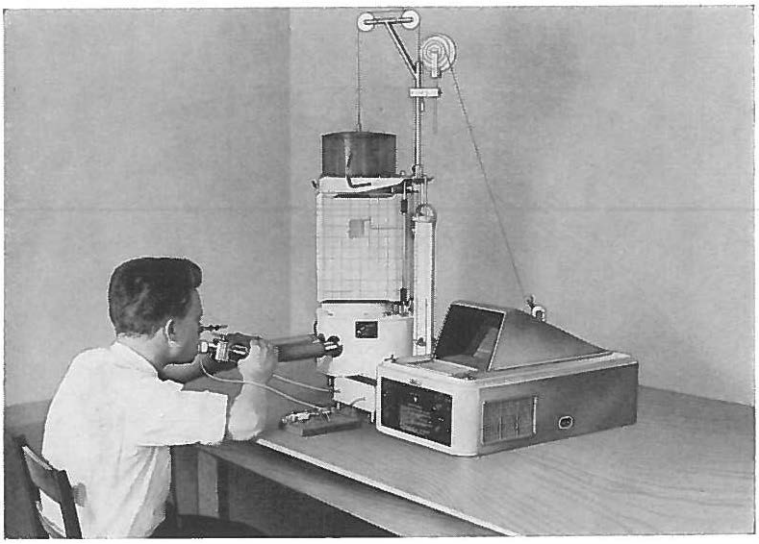


Fig. 2A
The Lode-P/V-Recorder SH-57.

The catheter and balloon.

The choice of the balloon was determined by the considerations expressed in chapter I (General methods). The length of balloon is 15 cm and its diameter 1 cm.

The pressure volume diagram of the balloon, freely suspended in the atmosphere is shown in fig. 3.

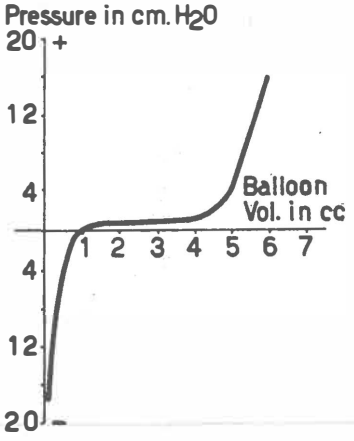


Fig. 3

The pressure volume curve of the balloon used in our experiments. The balloon is freely suspended in the atmosphere.

The technique is standard: after local anaesthesia (¼% tetracaine), the evacuated balloon (—4 cm H_2O) is introduced.

The length between the end of the catheter and the nostril is about 38 cm in men and 34 cm in women. This standard distance had previously been verified by fluoroscopic examination. Two additional criteria for correct placing of the balloon were employed:

1° the position where minimal heart pulsations are encountered,

2° the introduction of the balloon into the stomach (positive pressures during inspiration) and slow retraction until clearcut negative pressures during inspiration are obtained.

During the actual recording, the subject breathed at fixed frequency and tidal volume.

By visual observation of the spirogram the subject could keep his tidal volume close to the desired value. The fixed frequency was induced in the following manner:

Under the guidance of a metronome the experimenter "coached" the subject by calling out during the whole inspiration "i-i-i-i-i-n", and similarly for the expiration.

Prior to the actual recording some trials were made in this manner. It should be emphasized that with most subjects the use of the metronome alone leads to highly irregular results. In our technique however, the breathing pattern was monitored *by the voice and gestures of the experimenter* and not by the metronome.

It is obvious that complete correspondance between the desired values and the actual values could not be obtained in all cases. For this reason a certain spread was tolerated.

However, in those instances where the precise emulation of standard values is very critical (see e.g. chapter on Allergens in asthmatics), only those experimental values which agreed with the standard values within the error of observation, were accepted.

The frequency distribution at f = 15 and f = 40 are shown in fig. 4 for a tidal volume of 1 litre and 0.6 litre respectively. (The distributions

at the other tidal volume values are essentially the same).

It will be seen that at f = 15 the mean viscous work value tends to be somewhat too high, while at f = 40.

The mean viscous work value tends to be slightly too low for 40/0.6 litre, and definitely too low for 40/1 litre since a large proportion of the subjects breathes at freq. 36 c/min.

In view of the relatively low-sensitivity of viscous work values for frequency changes of this magnitude, in normal subjects, it was found unnecessary to reject those aberrant cases (aberrant relative to frequency) shown in fig. 4.

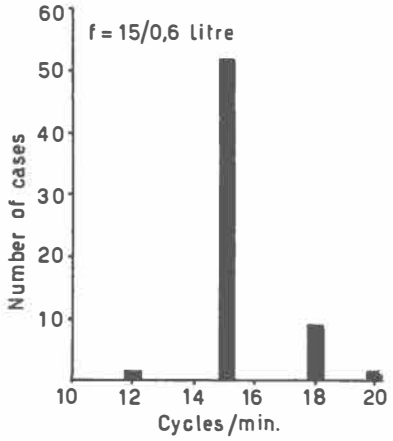


Fig. 4 A

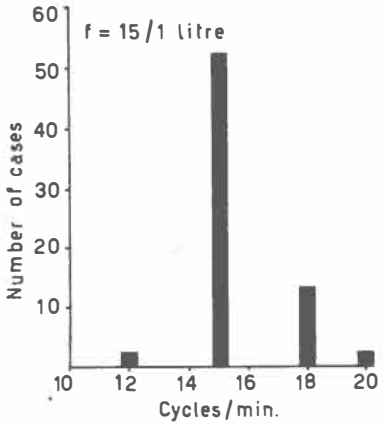


Fig. 4 B

Frequency distribution; for explanation see text.

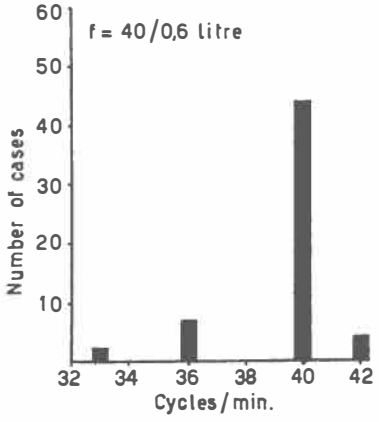


Fig. 4 C

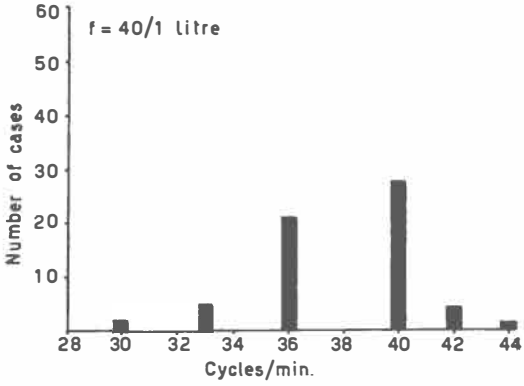


Fig. 4 D

Frequency distribution; for explanation see text.

Mean viscous work values calculated after elimination of these "aberrant" cases would differ by less than 1 % from the normal values given in table III (chapter XII).

The inclusion of these cases accounts for the inevitable spread of frequency that is also bound to occur in routine determinations.

In nearly all cases tidal volumes were well within 10 % of the desired values.

At a tidal volume of 1.0 L *all* values were within 10 % of the desired value.

At a tidal volume of 0.6 litre, 10 % of the cases yielded values which differed 15 % from the desired value, while 90 % of the cases gave values differing less than 10 % from the desired value. Now it should be clearly understood that the above mentioned deviations from the wanted values do not constitute a deficiency when the existence of the range of variation of tidal volumes and frequencies of breathing is recognized.

Since the normal values of viscous work are intended as a standard of normality under routine conditions, i.e. where it would be impossible (even more so than in our group of normals) to emulate the desired values with absolute precision, it would have been unrealistic to select only those cases in which no deviations from the desired values occur.

Variations within a single individual.

Variations of viscous work values and compliance values in the course of a single experiment (duration up to one hour) were slight and were caused, in the case of viscous work, by minor variations in frequency and tidal volume.

Disturbances due to oesophageal contractions, heart-beat etc. are easily recognized. This item has been fully discussed by BUYTENDIJK and MEAD e.a.

It turned out to be extremely difficult to obtain volunteers for the study of day-to-day variations in a single individual. Only three normal subjects were found willing to swallow the balloon on three different occasions (within a fortnight).

Here then, statistics once again has suffered from the limitations linked up with the study of human material.

The results obtained in these three individuals are shown in table II.

TABLE II

Age initial sex	S	C	Freq/T.V. 15/600	Freq/T.V. 40/600	Vit. Cap. measured	Vit. Cap Predicted	T.V.C 1 sec	Freq./T.V. 15/1L	Freq /T.V. 40/1L
B ♂	4.8	0.2	1400		4160	3880	80 %	3000	
50 jr	4.8	0.2	1600		4135	3880	80 %	3200	
H.W. ♀	8	0.125	2300		3720	3150	80 %	4200	
				3000				4000	9900
18 yrs	8	1.125	2000	3300	3850	3150		4300	8300
H ♀	8	0.125	1200	3000	3100	2900	76 %	3100	7500
44 yrs	8	0.125	1300	3300	3300	2900		2900	8300

It may be seen that individual variations at f = 15 are of the order of 10 %, and that a greater degree of constancy is obtained at a tidal volume of one litre. This is due to the fact that, in general, it is easier to keep a large tidal volume constant than a small one.

At f = 40 the variations are exaggerated as a result of variations in tidal volume and frequency. In the table only those values have been retained whose associated frequencies and tidal volumes were within 10 % of the desired values. These findings again stress the limitations at f = 40.

Gross failure to emulate the wanted values (e.g. f = 40/1 litre) will, of course, result in large errors in the desired viscous work values.

Since, many subjects are unable to perform satisfactorily at f = 40, measurements at f = 40 have, on the whole, less usefullness than determinations at f = 15. As has been explained elsewhere in this book, determinations at f = 40 derive their main usefullness from the fact that check-valve effects, not detectable at f = 15, may become manifest at high rates of flow.

Remarks:

Hysteresis of manometer is less than 1 %.

Some "normals" having aberrant values will now be discussed.*

Nr. 5 (female)

The following values were obtained:

T.V.C. 1 sec. = 80 %.

Freq. c/min.	T.V.	value
18	700	2300 gr cM
42	650	5300 gr cM
18	1100	4200 gr cM
42	1100	14000 gr cM

Tests with thiazinamidum (multergan) 25 mgr i.m.:

	V.C. measured	V.C. predicted	T.V.C. 1 sec.
before th.	3720 cc	3150 cc	80 %
after th.	3980 cc		82 %

It may be seen that instead of freq. 15 c/min., freq. 18 c/min. is produced, and instead of freq. 40 c/min., freq. 42 c/min.

More over the tidal volumes tend to be too high.

Tests with thiazinamidum (multergan) failed to reveal a reversible bronchodilation, from which the abscence of an asthmatic component is concluded.

Nr. 13 (male). The following values were obtained:

T.V.C. 1 sec. = 81 %.

Freq. c/min.	T.V.	value
15	625	1500 gr cM
42	650	4300 gr cM
15	1000	3200 gr cM
42	1100	12000 gr cM

* The figures refer to table I and II in chapter XII.

Tests with thiazinamidum (multergan)

	V.C. measured	V.C. predicted	T.V.C. 1 sec
before th.	4735 cc	4600 cc	81 %
after th.	4435 cc		88 %

In this case too, the high viscous work values are due to the fact that instead of freq. 40 c/min., freq. 42 c/min. is produced, with tidal volumes too high.

The tests with thiazinamidum (multergan) failed to reveal an asthmatic component.

Nr. 24 (male).

The following values were obtained:

T.V.C. 1 sec. = 68 %.

Freq. c/min.	T.V.	value
18	650	2800 gr cM
40	650	3800 gr cM
18	1100	4200 gr cM
40	1100	12000 gr cM

Tests with thiazinamidum (multergan):

	V.C. measured	V.C. predicted	T.V.C. 1 sec
before th.	3380 cc	3850 cc	68 %
after th.	3430 cc		74 %

Although both the frequencies and tidal volumes tend to be too high, this factor cannot explain the high viscous work values obtained in this subject.

Tests with thiazinamidum failed to reveal an asthmatic component. His T.V.C. 1 sec. is too low. This subject while classified as "healthy" from the "pulmonary point of view" suffers from ulcus duodeni.

Nr. 38 (males).

In this subject the following values were obtained:

T.V.C. 1 sec. = 60 %.

Freq. c/min.	T.V.	value
18	600	2700 gr cM
18	1000	5300 gr cM
36	1100	11400 gr cM

The low T.V.C. 1 sec. and the high viscous work values obtained in this subject may be due to a check valve phenomenon, which may operate in some "normals" in the older age groups. (DAYMAN)

Nr. 42 (male).
The following values were found:
T.V.C. 1 sec. = 73 %.

Freq. c/min.	T.V.	value
15	600	1800 gr cM
15	1000	4700 gr cM
40	1100	12000 gr cM

In this subject too, the high viscous work values may be due to a check valve phenomenon, which may operate in the older age groups. (DAYMAN)

CHAPTER VIII

A critical evaluation of the significance of the frequency dependent compliance in relation to unequal ventilation.*

Since the notable paper of OTIS e.a. (1956) there has been widespread clinical interest in the possible relationship existing between frequency-dependent compliance resulting from unequal time-constants of the various path-ways and the problem of unequal ventilation. It has been claimed or implied by various authors that the presence of compliance values decreasing with increasing frequencies of breathing, involves the presence of unequal ventilation. (RAU e.a. 1957, SCHERRER e.a. 1957, BÜHLMANN and BEHN 1957, OTIS e.a. 1956.)

In this connection it is of interest to quote from "Clinical Cardiopulmonary Physiology": (ATTINGER 1957, page 120)

"As a third method (of measuring unequal ventilation), one could measure compliance at different respiratory rates and conclude from a drop in compliance that unequal ventilation exists".

It will be of considerable interest to subject this hypothesis to closer scrutiny.

Let us study the electrical model with 2 parallel pathways. The analogous quantities in mechanical and electrical systems are for the sake of convenience shown in table I.

TABLE I

Mechanical			Electrical		
quantity	symbol	units	quantity	symbol	units
volume	V	l	charge	Q	coulomb
flow	$\dot{V}$	l/sec	current	i	ampère
pressure	P	cm H_2O	voltage	E	volt
resistance	R	cm H_2O/l/sec	resistance	R	ohm
compliance	C	l/cm H_2O	capacitance	C	farad

The product of compliance and resistance has the dimension of time and is called the time constant.

* This study will appear in the November issue of the Jour of Applied Physiology (1959).

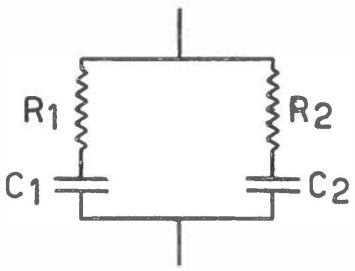


Fig. 1
Electrical equivalent of a two path-way lungmodel.

Let us assume that $R_1C_1 \neq R_2C_2$. Then, in the general case, we will obviously have, since the impedance

$$Z_{RC} = \sqrt{R^2 + \frac{1}{\omega^2 C^2}},$$

$$Z_1 \neq Z_2$$

Since $I = \frac{E}{Z}$ and since the voltage drop is the same across both branches, it follows that the currents (volume flows) in both branches differ from each other in the general case.

From the familiar relationship* $V_T = \frac{\hat{\imath}}{\pi f}$ where V_T = tidal volume, $\hat{\imath}$ = amplitude of flow, f = frequency, it further follows that when $R_1C_1 = R_2C_2$,

$$V_{T1} \neq V_{T2} \tag{1}$$

This is what happens *generally* when $R_1C_1 \neq R_2C_2$. Of course even with the time-constants being equal V_{T1} may be made unequal to V_{T2} with proper choice of values for R, C, and ω but this exceptional case is not relevant to our present discussion, which aims to study what happens in the *general* case.

The unequality expressed by (1) is not, of course, equivalent to unequal ventilation. Before proceeding, let us define the term "unequal ventilation".

For a simple 2 chamber system (the definition may easily be extended to a n chamber system) unequal ventilation is said to be present when

$$\frac{V_{T1}}{F_1} \neq \frac{V_{T2}}{F_2} \tag{2}$$

where V_T = tidal volume, F = end-expiratory lung-volume.

Actually, for a 2 chamber-system with 2 separate and a common dead-space, this definition is not strictly true, the condition for the existence of unequal ventilation being

$$\frac{F_1 + V_{T1}}{V_{T1} - d_1 - \lambda_1 d_3} \neq \frac{F_2 + V_{T2}}{V_{T2} - d_2 - \lambda_2 d_3} \tag{3}$$

where d_1, d_2 are separate deadspaces and d_3 = common deadspace, $\lambda_1 = \frac{V_{T1}}{V_{T1} + V_{T2}}$ and similarly for λ_2.

* $V_T = \int_0^{\pi/\omega} \hat{\imath} \sin \omega t \, dt = -\frac{\hat{\imath}}{\omega} \cos \omega t \Big|_0^{\pi/\omega} = \frac{2\hat{\imath}}{\omega} = \frac{\hat{\imath}}{\pi f}$

Condition (3) is derived and proved in a theoretical paper of WISE and DEFARES.

We shall, however, for simplicity of presentation make use of (2) in our subsequent discussion, since although not quite true, (2) is a "sufficiently good" index of unequal ventilation for our present purpose.

Now with the simple electrical circuit and the assumption of unequal time-constants we have got as far as (1).

But unequal ventilation demands (2).

Let us see if we can advance further than (1) with the aid of the parallel-circuit concept.

Since $V_{T1} \neq V_{T2}$ and $R_1C_1 \neq R_2C_2$ it follows that again in the *general* case,

$$\frac{V_{T1}}{R_1C_1} \neq \frac{V_{T2}}{R_2C_2} \tag{4}$$

By a simple rearrangement of Hooke's law which may be used here as a first approximation, we have, since HOOKE's law states $\triangle P = E \frac{\triangle V}{V}$ and $\frac{\triangle V}{\triangle P} = C$ = compliance * ($\triangle P$ = pressure increment, $\triangle V$ is volume increment, equivalent to tidal volume V_T, V = initial volume of lung-chamber, i.e. volume when the pressure across the lungchamber is zero, E = modulus of elasticity),

$$C = \frac{V}{E} \tag{5}$$

It should be carefully noted that V defined as the volume of the lung-chamber when the lung is not under stress, differs from the end-expiratory volume F.

Again to simplify our formulae, let us replace the approximate index for unequal ventilation by another approximate index, simply by replacing F by V, or, the condition for unequal ventilation is

$$\frac{V_{T1}}{V_1} \neq \frac{V_{T2}}{V_2} \tag{6}$$

insted of (2). We wish to emphasize that the simplifications (2) and (6) are by no means necessary for the analysis but that they merely serve to simplify the presentation.

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* The use of the same symbol C for capacitance in the electrical case and for compliance in the mechanical case is justified since both concepts are strictly equivalent mathematically.

Since the compliance C is the mechanical aequivalent of the capacitance, we may substitute (5) in (4), yielding,

$$\frac{V_{T1}}{R_1 \frac{V_1}{E_1}} \neq \frac{V_{T2}}{R_2 \frac{V_2}{E_2}} \quad \text{or} \quad \frac{E_1 V_{T1}}{R_1 V_1} \neq \frac{E_2 V_{T2}}{R_2 V_2} \tag{7}$$

We may summarize as follows:
when the timeconstants are unequal, inequality will hold in general and by substitution of (5) based on HOOKE's law for elastic bodies, may be written as (7) in the general case.

Now when $\frac{E_1}{R_1} = \frac{E_2}{R_2}$, then it follows from (7)

that

$$\frac{V_{T1}}{V_1} \neq \frac{V_{T2}}{V_{T2}}$$ i.e. that unequal ventilation exists.

In other words, when the compliance is found to depend upon frequency (decreasing with increasing f) i.e. in the presence of unequal timeconstants, we may conclude that unequal ventilation exists, when and only when

$$\frac{E_1}{R_1} = \frac{E_2}{R_2} \text{ or } E_1 R_2 = E_2 R_1 \tag{8}$$

or, for a n chamber system

$$\frac{E_1}{R_1} = \frac{E_2}{R_2} = \frac{E_3}{R_3} = \ldots\ldots = \frac{E_n}{R_n} \tag{9}$$

Since, of course, it is impossible to check whether (8) or (9) is satisfied in a given clinical case, the only conclusion we derive from the finding of unequal time constants is that

$$\frac{E_1 V_{T1}}{R_1 V_1} \neq \frac{E_2 V_{T2}}{R_2 V_2} \neq \ldots\ldots \neq \frac{E_n V_{Tn}}{R_n V_n}$$

a conclusion which gives no information about the existence of unequal ventilation.

The possible presence of "Pendelluft" in the sense described by OTIS e.a. (1956) also does not give information about the presence of unequal ventilation. Lack of space prohibits the demonstration of this statement which runs along similar lines as given above.

The above theoretical consideration lead us to the hypothesis that no "obligatory" connection exists between the finding of frequency dependent compliance and unequal ventilation, or that frequency dependent compliance tells us nothing about the uniformity of ventilation. To prove our hypothesis it suffices to demonstrate a case of frequency dependent compliance in the presence of equal ventilation.

Experimental findings

In order to study the hypothetical relationship between frequency dependent compliance and unequal ventilation nitrogen wash-out curves were obtained in a number of cases having pronounced changes of their compliance values with frequency. In order to prove the hypothesis that frequency dependent compliance does not necessarily imply the existence of unequal ventilation, it suffices to demonstrate a case where frequency dependent compliance values and *linear* semi-log washout curves are obtained simultaneously. Or, a single such case suffices to prove our point.

We have actually studied four cases. These cases were selected as follows:

A group of 100 healthy subjects was used to study the changes of compliance values with frequency of breathing. In a small number of subjects the compliance was found to decrease uniformly with frequency. In four subjects who had the most pronounced compliance changes nitrogen washout curves were made to evaluate the uniformity of ventilation.

In each case frequency dependent compliance was associated with equal ventilation as assessed by the linearity of the semi-log plots.

Methods

Three factors require special attention in the measurement of frequency dependent compliance, viz a) the dynamic characteristics of the recording system, b) the influence of the end-expiratory level, and c) the determination of the reversal points.

Two different methods were employed:

1) the spirometer method with optical recording. The Lode Pressure/Volume Recorder SH 57 in combination with the Lode D51 spirograph was used and

2) the pneumotachograph method with a specially designed ink recorder having a high natural frequency (120 Hz); The Godart pneumotachograph-manometer apparatus was employed. (fig. 2).

a) *Dynamic response.*

In the spirometer method pressure was recorded on the abscissa and volume on the ordinate axis. In this way a pressure-volume loop was optically recorded and photographed. The pressure was measured differentially (mouth pressure against esophageal pressure). The differential pressure was changed into an electrical signal by a moving-anode transducer and the amplified signal was then recorded optically by means of a mirror galvanometer.

The dynamic characteristics of the spirometer were tested by connecting the spirometer to a Starling-pump delivering a constant stroke volume of 1 litre. The motion of the piston was approximately harmonic and the frequency of the pump could be continuously varied between zero and 150 cycles/minute.

The excursions of the spirometer bell were recorded by an inkwriter while the vertical excursions of the lightspot of the pressure-volume apparatus were simultaneously recorded.

It was found that no amplitude distortion or phase shift occurred up to about 75 cycles/min. The resonance peak occurred at about 85 cycles/minute, the excursions of the bell at peak resonance being only 60 % of the constant excursions below f = 75 cycles/minute.

The influence of the degree of immersion of the bell was taken into account. Obviously phase shift here applies to the excursions of the bell relative to those of the pump and not to those of the water.

It is concluded that volume recording is adequate up to frequencies of about 70 cycles/minute. Pressure recording presented no problem here, since the natural frequency of the manometer system (including tubes and catheter etc.) far exceeded 3 times the value of the fifth harmonic of frequencies up to 1 Hz., being in fact about 100 Hz. The manometer system was rather heavily damped (D = 2) but this results in negligible phase shift, since only the first three or four harmonics are of interest here.

The Godart pneumotachograph-manometer apparatus fig. 2 possesses dynamic characteristics far in excess of the demands posed by the present problem. The natural frequency of the inkrecorder has the unusually high natural frequency of 120 Hz. For the measurement of volume both electronic integration (error less than 2 %) and graphical integration were employed. Here too, of course, esophageal pressure was measured differentially against mouth pressure.

Technical data: the two channel recorder (speeds up to 100 mm/sec. has a frequency response flat between 0—100 c.p.s. for recording up to 30 mm, the pneumotachograph head has a dead space of 45 ml and is linear over 0—600 liters/min flow, the resistance is 3 mm H_2O at 100 l/min, gauze: 35 μ wire, 385 mesh/39 inch, integrator data: chopper stabilised D.C. amplifier, stability 0.004 %, bandwith 1000 c.p.s., RC = 50.

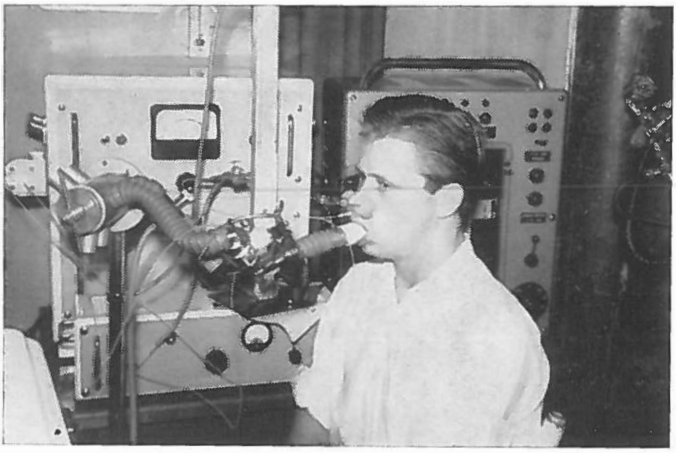


Fig. 2

The pneumotachograph-manometer apparatus.

Nitrogen washout curves were obtained with the GODART-LILLY nitrogen meter, previously described by LUNDIN (1953). Lundin's methode (1953) which is a modification of the method of FOWLER, CORNISH and KETY (1952) was used. The tidal volume was kept constant at 500 cc and 1000 cc in different washouts on the same subject. The subject could read his own tidal volume on the spirogram.

b) *Control of end-expiratory level.*

With the spirometer method end-expiratory level shifts could be directly observed from the spirogram. The spirometer contained soda-lime and a continuous flow of oxygen equal to the O_2-consumption was added to the spirometer. In this way the subject could remain connected to the spirometer during the whole experiment and any shift in end-expiratory level could be directly observed.

The dynamic characteristics, of course, were tested with the soda-lime cannister in place and the pressure recording was unaffected by this added resistance since pressure was measured differentially against mouthpressure. When the pneumotachograph method was used end-expiratory level shifts could easily be observed by comparing the area's under the inspiratory portions of the curve with the area's under the expiratory portions of the curve.

In the schematic fig. 3, the inspired tidal volume is 1000 cc, while only

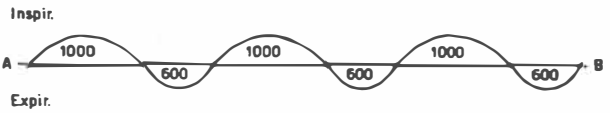


Fig. 3
Pneumotachogram.

600 cc is expired during each expiration. It follows that at instant B the level of breathing has shifted to the inspiratory side, the shift being three times 400 cc = 1200 cc (relative to the level at instant A).

Here the effect of R.Q. may be ignored since the time interval is small.

c) Determination of the reversal points when the spirometer method was used, presented no problem, since in these normal subjects studied no "fat" loops were obtained. When using the pneumotachograph method reversal points can always be accurately determined from the points of zeroflow obtained with the paper run at high speed.

TABLE II

subject	sex	age	history	family history (asthma)	cough dyspenea expecto-ration	physical examina-tion	roentgeno-gram	V.C.	theoretical value of V.C.	1-second timed V.C.
J.K.	m	15		—	—		—	3200 cc	3600 cc	89%
H.H.	f	27		—	—		—	3300 cc	3200 cc	88%
R.P.	m	22	in clinic for suspected myasthenia	—	—		—	3950 cc	4290 cc	95%
A.S.	m	25	in clinic for observation for transient attackss of dyspnea	father has asthma	—	systolic murmur at ictus	—	5225 cc	4700 cc	71%

RESULTS

We shall first present the clinical data of the four subjects studied. They are given in table II.

Subject A.S. who was suspected of asthma of minor degree was found to have negative instracutaneous allergy tests and negative histamine effects (on V.C. and timed V.C.). At the time of the examination the subject was objectively and subjectively symptom free. In table III, the results of the compliance measurements are shown. The compliance values of subject A.S. (fifth column) were obtained with the pneumotachograph method.

TABLE III

Effective compliance ($1/CMH_2O$) of normal subjects.

frequence	J.K. 1 sec. timed V.C. = 89 %	H.H. 1 sec. timed V.C. = 88 %	R.P. 1 sec. timed V.C. = 95 %	A.S. 1 sec. timed V.C. = 71 %
0	0.13	0.14	0.18	0.40
15	0.11	0.13	0.13	0.28
45	0.08	0.07	0.07	0.22
60	0.05	0.05	0.07	0.07
130				0.05
500				0,05

The C-value of f = 500 was obtained during very superficial breathing. Since the natural frequency of the recording system lies above 100 Hz, (i.e. 6000 cycles/minute) the C-value at f = 500 is probably correct. All the other measurements were obtained with the spirometer method and were therefore not extended byond 1 Hz.

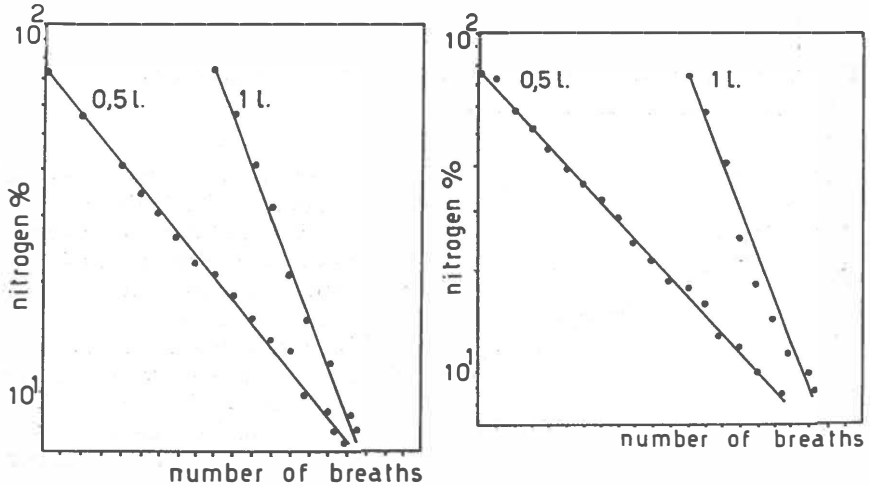


Fig. 4

Nitrogen washout curves of normal subjects.

In fig. 4 the washout curves of these subjects are shown. For each subject

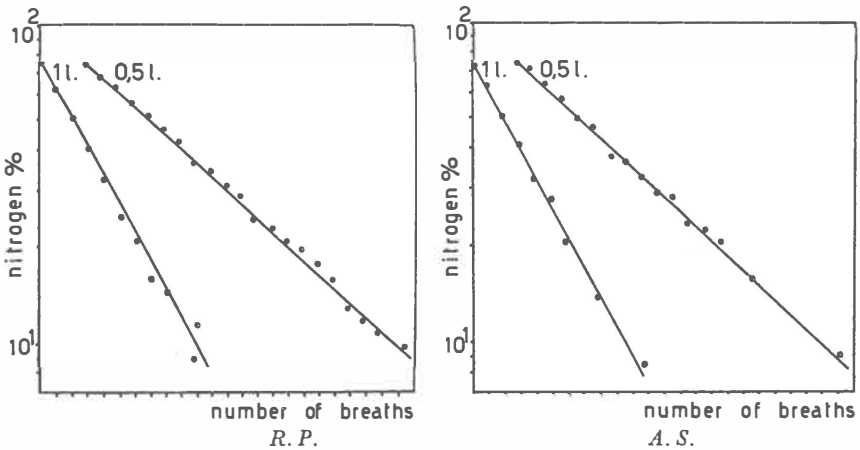


Fig. 4
Nitrogen washout curves of normal subjects.

the washout curves at a tidal volume of 500 cc and 1000 cc are given. It will be seen that in all the curves obtained from the four subjects the semi log plots are linear, i.e. the ventilation is uniform. These curves have essentially the same form as those obtained in a random sample of healthy subjects.

The washout curve, shown in fig. 5 is taken from an emphysema case. (Clinical findings: V.C. 2165 cc (theor. value: 3780 cc). V.C. after adrenaline 2635 cc (+ 12 %) 1 second timed V.C. 29 %, residual volume 2485 cc = 53 % of T.C. F.R.C. = 67 % of T.C., 0_2 saturation = 86 %.

Allergy tests: negative i.c.

Roentgenogram: no lesions.

Fluoroscopy diaphragm in a lowered position, moves but little.

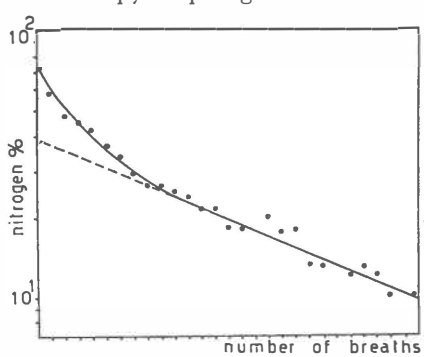


Fig. 5
Nitrogen washout curve of pat. H. with emphysema.

In contrast with the washout curves shown at fig. 4, the washout curve of this emphysema case deviates grossly from linearity and this demonstrates a pronounced degree of uneven ventilation.

This emphysema case, randomly selected, is given merely to illustrate how well the washout method as used by us, differentiates between "normality" and "disease" or better, between equal and unequal ventilation.

DISCUSSION

In our experiments the minor changes in end-expiratory level remained well within the linear part of the static compliancecurve. It should be understood that whatever the numerical values of these shifts as long as they remain within the linear part of the static P—V curve, these level shifts can not explain changes of the (effective) compliance.

The experimental findings reported above demonstrate that frequency dependent compliance can not be used as an index of unequal ventilation.

These findings lend support to the theoretical considerations given above.

The argument might be raised that the wash-out method is not "sufficiently sensitive" and that frequency dependent compliance may indicate unequal ventilation of slight degree not detectable with the less sensitive wash-out methods. Logically this argument is a valid one, but this contention has little practical value since

a) this statement has no theoretical justification, as has been shown above;
b) no experimental way exists to validate this supposed super sensitive method since only the washout methods are available to demonstrate the existence of unequal ventilation *;
c) degrees of unequal ventilation not detectable with the wash-out methods fall well within the normal range and are of no clinical interest;
d) above we have shown that the method is non-selective being influenced by the E/R ratio.

It is concluded from the theoretical analysis and the experimental evidence that the finding of frequency dependent compliance tells us nothing about the possible existence or degree of unequal ventilation.

SUMMARY

It is shown theoretically that frequency dependent compliance may be used as an index of unequal ventilation when, and only when $E_1/R_1 = E_2/R_2 = \ldots = E_n/R_n$, where E is modulus of elasticity, R = resistance and the indices refer to the parallel pathways. Since it is of course impossible to verify whether these equalities obtain in a particular case, it is concluded that the finding of frequency dependent compliance gives no information on the existence of unequal ventilation.

The theoretical conclusions have been substantiated experimentally. Four subjects from a group of 100 normal subjects studied were found to have pronounced frequency dependency of their effective compliance values. In all four subjects no evidence of unequal ventilation, as assessed by nitrogen wash-out curves, was found. It is concluded that theoretical and experimental evidence refutes the hypothesis that the phenomenon of frequency dependent compliance may be used as an index of unequal ventilation.

* Historically, the wash-out method did not require validation against some other method, since the wash-out method was based on a sound theoretical basis.

CHAPTER IX

The influence of Mediastinum-Compliance on the tidal volume ratio and esophageal pressure recording in the lateral position.

From simple considerations it would appear that the ratio of tidal volumes as obtained during bronchospirometry, equals the ratio of the compliances of both lungs. This may be seen as follows.

Since both lungs are situated in the common thoracic cage, the pressures across both lungs, are equal to each other at any instant.

The compliance of the right lung may be written as

$$C_r = \frac{T_r}{P} \text{ and similarly}$$

on the left $C_l = \frac{T_l}{P}$

where C = compliance, T = tidal volume, P = pressure change and indices r and l denote right and left lung respectively. Since the pressure change P on the right and on the left must be the same, P is written without index.

The ratio C_r/C_l is obviously given by

$$\frac{C_r}{C_l} = \frac{T_r}{P} \times \frac{P}{T_l} = \frac{T_r}{T_l} \qquad (1)$$

or, the ratio of the compliances equals the ratio of the (simultaneous) tidal volumes. This result follows from the conception that the lungsystem may be represented by the model shown in fig. 1.

The essential thing of this model with reference to equation (1), is that both lungs are enclosed in a common chamber, so that, whatever the values of their compliances, the pressures across both lungs are always equal to each other.

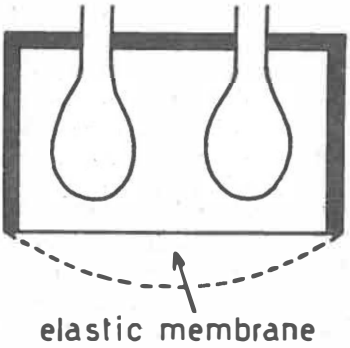


Fig. 1
Model of both lungs enclosed in a common chamber.

Although some studies (HEEMSTRA 1957, FAHRI e.a. 1957, CHERNIACK e.a. 1955, COLERIDGE e.a. 1954) indicate that regional pressure differences exist in the thoracic space, it is assumed here that free pressure equalization occurs in the pleural space surrounding a single lung.

The influence of posture on ventilation and circulation has been extensively studied by various workers (WADE and GILSON 1951). The data obtained by SVANBERG will be used here to study these effects from the mechanical point of view.

TABLE I

	O_2 — uptake right as % of total			tidal volume right as % of total		
	supine	right lateral	left lateral	supine	right lateral	left lateral
H. H.	50	56	46	56	59	48
K. T.	50	55	51	50	61	43
K. G. F.	52	51	47	53	58	45
C. T.	49	58	42	49	63	40
A. G.	54	65	53	53	62	51
Y. E.	56	60	51	59	67	43
G. F.	59	65	47	55	71	48
L. C.	56	64	49	57	67	49
C. C.	54	65	49	56	61	45
Ax. J.	54	58	46	51	51	50
S. R.	52	61	50	57	70	50
Ar. J.	53	63	44	53	63	49
Go. N.	59	57	50	59	48	55
G. N.	51	74	42	48	63	43
mean	54	61	48	54	62	47

(from SVANBERG, thesis)

The subjects are all normal young males. From table I, it can be seen that when the subject shifts from the supine position (subject lying on his back) to the right lateral position the O_2 % uptake on the right increases, accompanied by an increase of the tidal volume % on the right. On the average, in his group the right O_2 % uptake changes from 54 % to 61 % and the right tidal volume % increases from 54 % to 62 % when the subject shifts from the supine position to the right lateral position.

Now, the change in O_2 % uptake on the right may be taken to indicate a change in bloodflow % on the right; in other words, it may be concluded that when the subject changes from the supine to the right lateral position a greater percentage of blood will flow through the right (lowermost) lung. On the average this shift in differential bloodflow will be from 54 % in the supine position to 61 % in the right lateral position. Now, from (1) it may be seen that the ratio of the right and left tidal volumes equals the ratio of the respective compliances.

Applying (1) to the present situation, the ratio of the compliances in the supine position is given by

$$\frac{C_r}{C_l} = \frac{54}{46}$$

Similarly, during the right lateral position

$$\frac{C_r}{C_l} = \frac{62}{38}$$

Since the bloodflow % on the right shifts from 54 % to 61 %, one would expect to find a decrease of the C_r/C_l ratio when the subject changes from supine to right lateral. (We may also say that we would expect a decrease of the procentual compliance on the right).

Instead, an increased C_r/C_l ratio is found in the right lateral position, and this, at first sight, paradoxical increase, forms the central theme of this discussion.

Although increased bloodflow does not necessarily involve the presence of increased bloodvolume, we may assume, on the basis of the physical characteristics of the pulmonary vessels, that in the lateral position the bloodvolume of the lower lung is increased.

On a priori grounds, and on certain experimental evidence (VERSTRAETEN 1956, MACK e.a. 1947) it would seem that the increased bloodflow on the right in the right lateral position would result in increased "stiffness" of this lung (increased modulus of elasticity) and in a decrease of the alveolar space (capillaries "bulging" into alveoli) available for gas exchange, both factors contributing to a decrease of the compliance of the right lung.

(In the left lung, the decreased bloodflow would result in an increased compliance).

MACK e.a. (1947) have perfused isolated doglungs suspended in a closed chamber with known amounts of blood, so that the volume of blood in

the lungs could be regulated. It was found that compliance decreased with increasing amount of blood in the lungs.

Whether this influence of bloodflow and bloodvolume is large or small is immaterial for the present discussion.

The essential point is, that it is highly unlikely that the increased relative bloodflow on the right could result in an increased compliance.

From this it follows that the increased compliance of the right (lowermost) lung in the right lateral position cannot be explained by the increased (procentual) bloodflow passing through this lung.

THEORY

It seems difficult to explain this apparently paradoxical phenomenon. The asymmetrical changes in the activity of the respiratory muscles cannot (without additional assumptions) account for this finding.

The tidal diaphragmatic movement on the lowermost side (right side in this example) will be more marked than on the upper side, while the thoracic excursions are greatest on the upper side (WADE, O. D. and GIBSON, I. C. 1951, MANN 1957).

The latter effect is however, not a constant finding. Theoretically, the presence of regional pressure differences may also lead to the ratio "unbalance".

Especially in the lateral position, where the regional differences are increased, the factor may assume some importance.

It is obvious that when the thoracic space is considered as a single chamber in which pressures are freely transmitted, then these asymmetrical excursions cannot explain the above findings. This is illustrated by the model in fig. 2.

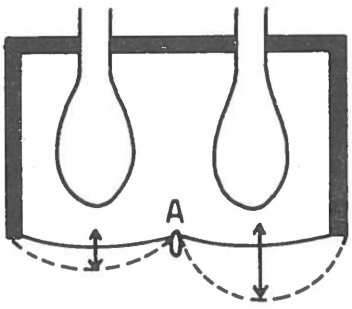


Fig. 2

Model of both lungs enclosed in a common chamber. The bottom of the chamber consists of 2 rubber membranes separated by a metal "dam" A.

The bottom of the chamber consists of 2 rubber membranes seperated by a metal "dam" A. The lengths of the arrows indicates the magnitude of the synchronous excursions. Unilaterally increased excursions affect the tidal volumes of both lungs, i.e. do not affect the tidal volume ratio.

When however the thoracic cage is seperated into a right and left compartment by a rigid mediastinum, then unilaterally increased (diaphragma) excursions could explain the

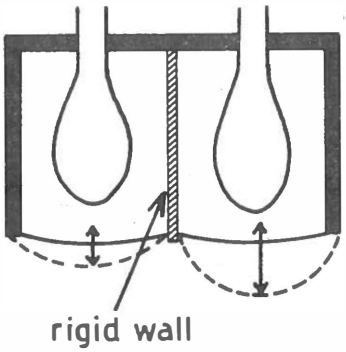


Fig. 3
The chamber subdivided by a rigid wall.

changed tidal volume ratio. This situation is schematically illustrated in fig. 3. The chamber is subdivided by a rigid wall. In this condition the unilaterally increased excursions only increase the tidal volume on the homolateral side, thus causing an increased tidal volume ratio.

However, such a concept must be rejected since it would imply that esophageal pressure changes can not reflect even approximately correct pressure changes across the lungs. Such a conclusion which follows from the fact that the esophagus is situated in the mediastinum, would be contrary to experimental evidence.

Clinical observations strongly support the view that the mediastinum is a "compliant" structure.

It would appear that the findings may be explained by the unlaterally increased excursions when the elastic properties of the mediastinum are taken into account.

Consider fig. 4.

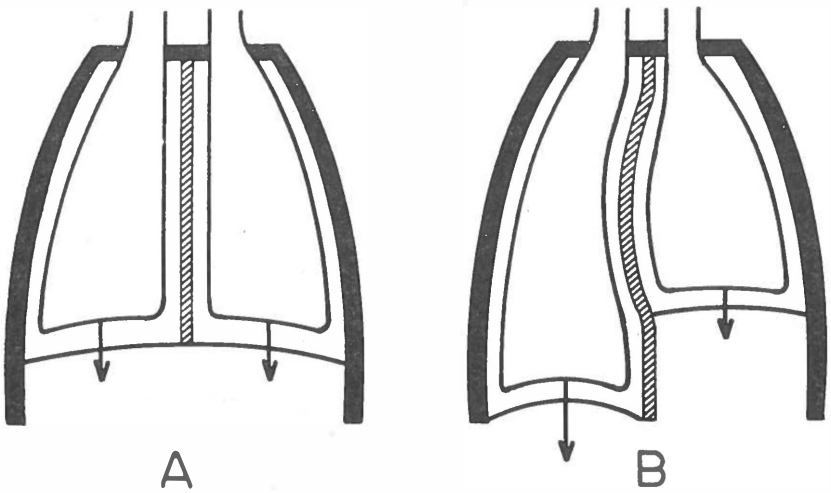


Fig. 4
Model of thoracic cage with lungs and diaphragm.
a. right and left diaphragmatic excursions are of equal magnitude.
b. Diaphragmatic excursions on the right are greatly increased.

Let it, for simplicity of presentation be assumed that the thoracic cage remains rigid (i.e. no thoracic excursions) so that only diaphragmatic breathing is present.

Fig. 4A represents the case where right and left diaphragmatic excursions

are of equal magnitude. In fig. 4b, the diaphragmatic excursions on the right are greatly increased.

As a result of the increased contraction of the right diaphragm during inspiration, more space is available to accommodate the right lung, so that the right tidal volume will increase correspondingly.

The mediastinum is "sucked" to the right, thus permitting some expansion of the left lung, i.e. some increase of the left tidal volume.*

The essential features of this conception may be grasped more clearly by using the electrical aequivalent of the mechanical model. See fig. 5.

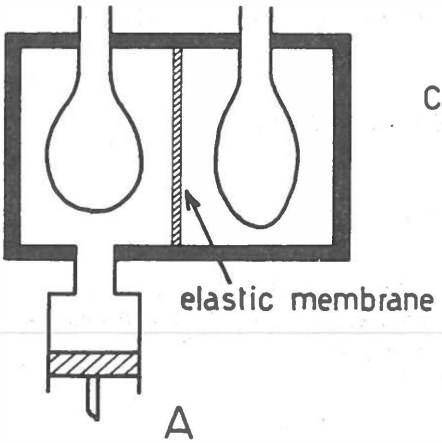


Fig. 5a
Mechanical model of thoracic cage with lungs and diaphragm, with greatly increased diaphragmatic excursions on the right.

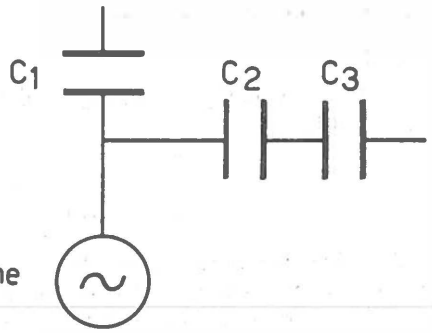


Fig. 5b
Electrical aequivalent of the mechanical model.

The analogous quantities in mechanical and electrical systems are for the sake of convenience shown in table II.

TABLE II

Mechanical			Electrical		
quantity	symbol	units	quantity	symbol	units
volume	V		charge	Q	coulomb
flow	$\dot{V}$	l/sec	current	i	ampère
pressure	P	cm H_2O	voltage	E	volt
resistance	R	cm H_2O/l/sec	resistance	R	ohm
compliance	C	l/cm H_2O	capacitance	C	farad

In fig. 5b, C_1 represents the compliance of the right lung, while C_3 represents the compliance of the left lung, C_2 represents the compliance due to the presence of the mediastinum.

* The magnitude of this passive expansion depends on the magnitude of the mediastinum compliance and "saturation" effects may be entirely ignored.

We have $E_1 = E_2 + E_3$

or

$$\frac{q_1}{C_1} = \frac{q_2}{C_2} + \frac{q_3}{C_3} \quad (1), \text{ or, } q_1 = \frac{C_1 C_3 q_2 + C_1 C_2 q_3}{C_2 C_3} \qquad (2)$$

where E = voltagedrop across condensor, q = charge.

We further have $q_2 = q_3$ (3)

(In the mechanical case this means that the volume change due to the bulging of the mediastinum equals the left tidal volume).

Using numerical values we can easily compute q_3 (left tidal volume) when the value of q_1 is given.

Case 1.

Let $C_1 = 0.1$, $C_2 = \infty$, $C_3 = 0.1$, $q_1 = 0.5$ litre.

From (1)

$$\frac{0.5}{0.1} = \frac{q_3}{0.1} \quad \text{or } q_3 = 0.5$$

Or, when the mediastinum behaves like a plastic loose curtain or what amounts to the same, is absent, the tidal volumes will be equal when the compliances of right and left lungs are equal.

This result is, of course, quite obvious.

Case 2.

Let $C_2 = 0$, hence from $q_2 = C_2 E_2$ it follows that $q_2 = 0$ for all values of E_2. Let again, $C_1 = C_3 = 0.1$, $q_1 = 0.5$ litre.

Since $q_2 = 0$, it follows from (3) that $q_3 = 0$.

Or, when the mediastinum is very rigid the tidal volume on the left is essentially zero. This result too is intuitively obvious.

Case 3.

Let the mediastinum be less "stiff" than the lungs,* i.e. let us assume e.g. $C_2 = 1.0$. Then, with the other values remaining the same, from (2),

$$0.5 = \frac{0.1 \times 0.1 \times q_2 + 0.1 \times 1.0 \times q_3}{1 \times 0.1}$$

or $0.5 = \frac{1}{10} q_2 + q_3$.

Since $q_3 = q_2$, we may write $0.5 = \frac{q_3}{10} + q_3 = \frac{11}{10} q_3$

or $q_3 = 0.4545 = 0.45$.

* This is only loosely speaking.

Or, in this case, the left tidal volume is 0.45 litre i.e. close to the right tidal volume.

Case 4.

Let the compliance C_2 be 0.1 i.e. equal to C_1 and C_3. Then q_3 is easily found to be 0.25.

Or, when $C_1 = C_2 = C_3$, then the left tidal volume equals half the right tidal volume.

Case 5.

Let $C_2 = 0.01$, i.e. let the mediastinum be less "compliant" than the lungs.

Then from (2)

$$0.5 = \frac{0.1 \times 0.1 \times q_2 + 0.1 \times 0.01 \times q_3}{0.01 \times 0.1}$$

With (3), we find $q_3 = 0.045$ litre.

Or, the left tidal volume is only 45 cc, while the right tidal volume is 500 cc.

Now in our model, we have for simplicity assumed that on the left no generator (pump) was present. This implies the abscence of muscular activity on the left. Now, this assumption is by no means necessary and the above model applies equally well to the case where (effective) muscular action on the right is greater than on the left.

The essential thing is that an unbalance exists between pump action on both sides. In the special case where both right and left pumps exert equal pressures then, apparently, the tidal volume ratio will only be determined by the ratio C_1/C_3.

This observation implies that the above discussion equally applies to the following model, that approximates the real situation more closely.

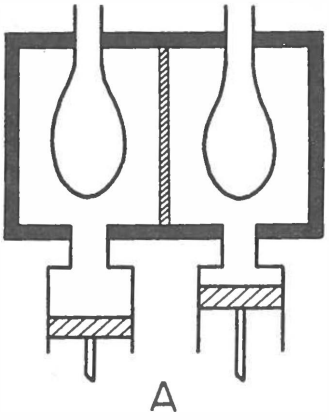


Fig. 6A
For explanation see text.

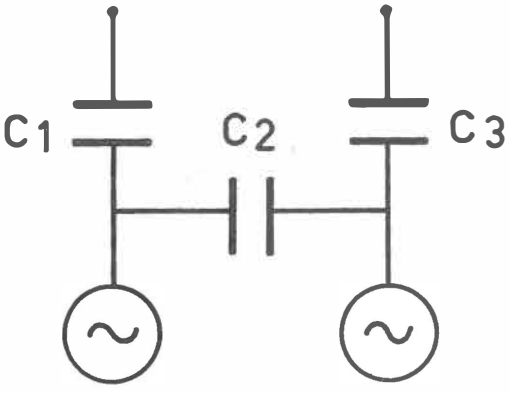


Fig. 6B
For explanation see text.

The electrical linearized model is, of course, only an approximation. However, the essential features are retained in the case where the relationship between pressure and volume is non-linear.

Owing to anatomical complications and to the lack of certain numerical data, quantitative analysis of the problem would be very difficult indeed.

RESULTS

The theory presented above requires that a) in the lateral position the over-all excursions (diaphragm and intercostal muscles) of the lowermost side exceed those of the upper side and b) that during inspiration in the lateral position the mediastinum does not shift towards the upper side.

It is clearly implied in the theory that the mediastinum should shift towards the side where the diaphragmatic excursions are greatest (lower side). In the case where the excursions on the lower side only slightly exceed those on the upper side or where the mediastinum is very rigid, this shift of the mediastinum may not be noticable.

A shift towards the upper side, however, would contradict the theory.

These requirements have been checked experimentally both by direct fluoroscopic observations and röntgenograms.

Fig. 7a was taken at the end of a normal expiration, while fig. 7b was taken at the end of a deep inspiration. The well-known excessive diaphragmatic excursion on the lowermost side is clearly seen. The most important finding is the slight shift of the mediastinum towards the lowermost side, during inspiration. On the original films (30/40 cm) this shift is about 1 cm. This shift was measured by placing one picture on top of the other and aligning the spinae vertebrae.

DISCUSSION

The shift of the mediastinum towards the lowermost side has very recently (May 1958) been reported by MANN. He states: "A marked shift of the mediastinum toward the recumbent * side could be seen, especially on the plate of the young woman whose mediastinal structures are still elastic".

This finding which is in perfect accord with our observations, refutes the unsupported statement of SVANBERG (1957) that during inspiration the mediastinum is shifted towards the upper lung.

The exaggerated excursions of the lowermost diaphragma have been fully described by MANN (1959), SVANBERG (1958), WADE and GILBON (1951).

The above theory explaining the change in the tidal volume ratio in the lateral position is thus supported by experimental evidence, viz the increased unilateral diaphragmatic movements and the tendency of the mediastinum to shift towards the lowermost side.

It is recognized that further semi-quantitative information is required:

* I.e. lowermost.

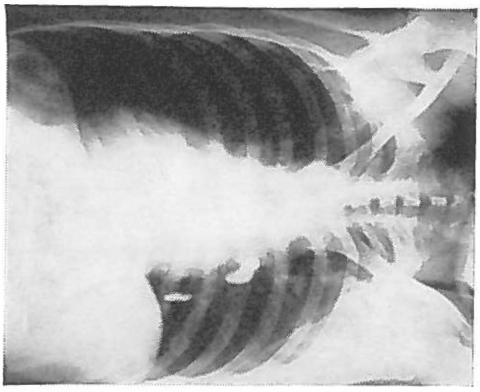


Fig. 7a

Roentgenogram of the same subject in the right lateral position at the end of a normal expiration.

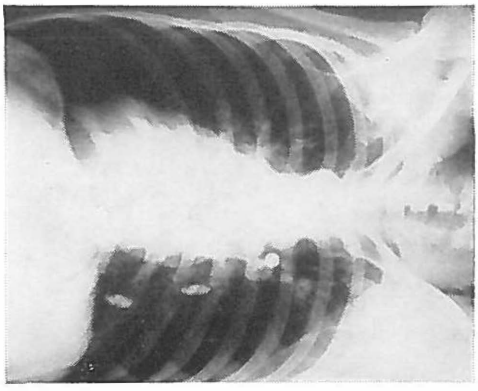


Fig. 7b

Roentgenogram of a subject in the right lateral position at the end of a deep inspiration.

e.g. in cases where the tidal volume ratio remains unchanged in spite of increased diaphragmatic movements on the lower side, the mediastinum in terms of theory, must be greatly displaced towards the lower side, during inspiration (compare with the electrical cases discussed above).

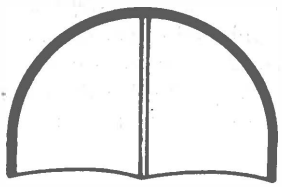
Since no alternative simple theory can be advanced to explain the change in tidal volume ratio and since observations lend support to our hypothesis, we regard this hypothesis as an adequate explanation of the facts.

An important consequence of the theory is that in the lateral position and in any other condition where an unbalance of the diaphragmatic movements exists, the pressure change recorded with the esophageal technique is no longer valid, since then during inspiration the pressure in the esophagus represents a sort of mean value of the pressures across the left and right lungs which differ from each other.

This may be clarified by a simplified example:
let us, for simplicity of presentation, ignore the action of the intercostal muscles. Let the left diaphragm be paralysed and let the mediastinum be fairly "elastic". Let again for simplicity, both lungs possess the same compliance. In our simplified case, we assume that at the end of expiration the mediastinum is in its equilibrium position.

See fig. 8A.

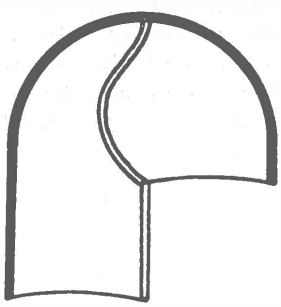
The costal excursions are, for simplicity, ignored here.



end-expiratory position

A

Fig. 8A
Model of thoracic cage with mediastinum in its equilibrium position and diaphragm at end expiratory level.



end-inspiratory position

B

Fig. 8B
Model of thoracic cage with mediastinum and diaphragm at end inspiratory level, when diaphragm on the left side is paralysed (mediastinum sucked towards the non paralysed side).

During inspiration the mediastinum is sucked towards the non paralysed side until its "elastic limit" is reached. In spite of further inspiratory movement of the active half of the diaphragm the mediastinum then remains stationary in a position illustrated in fig. 8B.

We shall consider the events beyond this "elastic limit". It is clear that during further inspiration the homolateral lung further expands, while the lungvolume on the paralysed side remains constant.

Since both lungs have the same compliance and since pressure across the lung (in the static case) depends upon tidal volume, it follows that at the end of inspiration, the pressure across the homolateral lung is greater than the pressure across the lung on the paralysed side.

Let e.g. the pressure change across the "paralyzed" lung be 5 cm H_2O and on the other side be 12 cm H_2O. The pressure change recorded in the esophagus will then be some intermediate value and it is clear that this recorded pressure will be next to worthless for studies on lung mechanics.

The precise intermediate value of the esophageal pressure depends upon many variables (compliance of mediastinum etc.) and will not be considered here.

Although our discussion is based on an unbalance of the diaphragm, essentially the same conclusion applies when an unbalance of the thorax halves exists (e.g. caused by fibrosis of the pleura after pleurisy).

SUMMARY

The changed tidal volume ratio that may occur during lateral position is not due to bloodshift, but results from the combined effect of unbalance of excursions on both sides and low compliance of the mediastinum.

Whenever unbalance between overall excursions on both sides exists the esophageal pressure may not be a correct measure for the pressures across the lungs.

CHAPTER X

On the significance of the visco elastic properties of the lungs in relation to the timed vital capacity.

Introduction

When a subject, connected to a closed spirometersystem, expires maximally fast and deeply following a maximal inspiration, a characteristic curve is obtained.

The expiratory part of the curve consists of an approximately linear initial part followed by a curved portion. This is illustrated in fig. 1.

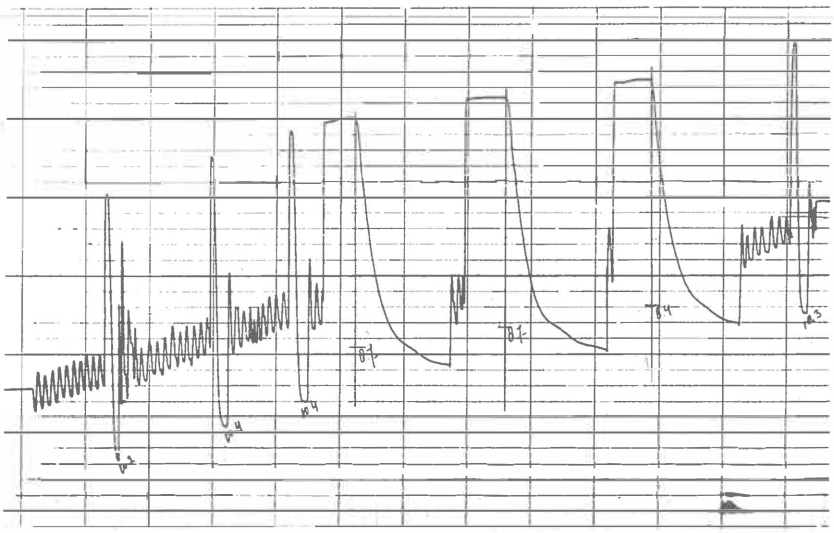


Fig. 1
Normal spirogram.

Obviously, during the linear part of the curve the volume of air expelled per unit of time remains constant. In the course of the curved portion of the curve the volume of air expelled per unit of time decreases with time.

OLIVIER (1949) makes the erroneous assumption that the linear part may

be clearly distinguished from the curved part in both normals and pathological cases.

TIFFENEAU (1948) on the other hand, stresses the indeterminateness of this transition in many cases. This point is fully discussed by HIRDES and VAN VEEN (1952). OLIVIER and DRUTEL (1949) call the linear part of a maximal forced expiration the "capacité utilisable maximum".

But just because of the difficulty of determining this linear part, TIFFENEAU (1948) introduced the concept "capacité utilisable par seconde", (C.U.S.).

The C.U.S. is defined as the volume of air expired in the first second during a forced maximal expiration.

It has become customary since the work of GAENSLER to express this volume expired during the first second as a percentage of the vital capacity (1-second timed vital capacity).

It has become a clinical tradition to regard a timed vital capacity value lower than 70 % as abnormal and conversely.

This tradition appears to have been set up by the studies of GAENSLER, who in a younger age group of 35 healthy subjects found a mean value of 82.7 % for the 1-second timed vital capacity, with no value lower than 72 %.

In recent years some objections have been raised against the method of timed vital capacity. We shall briefly state the following two aspects:

1) *The time factor*

ORIE studied 2 groups of patients who had undergone pneumonectomy. One group consisted of bronchiectasis cases (13 cases) while the second group consisted of 10 tuberculosis cases.

The 1 second timed vital capacity and the volume of air expelled during the first ½ second, expressed as a % of the 1 second timed vital capacity, were determined.

In the bronchiectasis group the mean value of the T.V.C. was 66 % while 68 % of the T.V.C. was expelled during the first ½ second (mean value).

In the tuberculosis group the mean value of the T.V.C. was found to be 68 %, while on the average 79 % of the T.V.C. was expelled during the first ½ second.

The expiratory disturbance present in the first group, not shown by the 1 sec. timed vital capacity, is thus clearly demonstrated by the ½ second volume expressed as % of 1 second T.V.C.

SCHEME

loss of tissue (pneumonectomy)

bronchiectasis	tuberculosis
expiratory disturbance present 1 sec.	expiratory disturbance absent
T.V.C. 66 %	1 sec. T.V.C. 68 %
½ sec. volume as % of T.V.C. 68 %	½ sec. volume as % of T.V.C. 79 %

2) *Volume*

LAROS (1956) has found that in pneumonectomy cases having a relatively large residual capacity as a result of stretching, the qualitative changes of lungfunction are more adequately expressed by the 1 sec. T.V.C. expressed as a percentage of *total* capacity (1 sec. T.V.C. % T.C.).

A comparison of the 1 sec. T.V.C. values, expressed as % of V.C., obtained before and after the operation yields no information concerning the ventilatory capacity after the operation.

It would appear from his study (see table 41) that in such cases the 1-sec. T.V.C. expressed as a % of *total* capacity constitutes a better index of ventilatory change than the 1 sec. T.V.C. as % of V.C.

TABLE 41 thesis LAROS

	time	RV % TC	VC % TC	TVC 1 sec % VC	TVC 1 sec % TC
group I	before oper.	25 %	75 %	66 %	51 %
group I	after oper.	34 %	66 %	66 %	44 %
group II	before oper.	30 %	70 %	60 %	42 %
group II	after oper.	40 %	60 %	61 %	37 %

One second timed vital capacity as a percentage of the total capacity before the pneumonectomy and at the follow up, for the group I (without thoracoplasty) and II (after thoracoplasty).

Remarks:

WINDEMULLER (1951) has shown that the curve obtained during maximal expiration may, in many cases, be approximated by a hyperbola.

CARA (1957) on the basis of theoretical considerations derived the following equation for this curve,

$$V_t = a_1 \, e^{-t/T_1} + a_2 \, e^{-t/T_2}$$

which, in this case, represents the solution of a second order differential equation.

By comparing timed vital capacity values with "viscous work" values, it was found that in some pathological cases a pronounced discrepancy was found between results obtained with the two methods

On the basis of case histories we shall discuss the limitations of the timed vital capacity method. It should be emphasized that this discussion is not a criticism of this extremely useful and simple method.

We merely wish to analyze the pathophysiological interpretation of the C.U.S. results on the basis of mechanical findings and considerations.

Case I) *A "normal" subject with a low one second value* (61 %) *and normal "viscous work" values.*

A male healthy subject, age 56. Since the subjects was an intelligent volunteer, motivation for malingering (expressed by expiring below

capacity) was naturally absent. No history of pneumonia, tuberculosis, bronchitis, asthma, or other chest diseases. There was no asthma in this family history. The subject was free from dyspnoea, cough, expectoration or other chest complaints, physical examination and fluoroscopy of his lungs and diaphragm revealed no abnormalities.

His vital capacity was 4100 cc (predicted V.C. 3700 cc).

The one-second value was 61 %.

Mechanical data:elastance S = 7.2 cm H_2O/l (C = 0.140 l/cm H_2O). The kinetic volume-pressure diagrams gave normal loops, at the frequencies 15, 40 and 60 cycles/min, at tidal volumes of 600 and 1000 cc. This values for viscous work are shown in table 1.

TABLE I

Viscous work in gram cm.

Freq. c/min	V_T = 600 cc work/cycle	work/minute	V_T = 1000 cc work/cycle	work/minute
f = 15	1200	18000	2000	31000
f = 40	2400	94000	6700	270000

From the results in table 1, and the normal values reported in chapter XII, it is clear that in this case the viscous work, and hence the resistance to breathing is completely within the normal range at all frequencies and tidal volumes studied.

Since the T.V.C. method gives an abnormal value while the pressure-volume loop gives normal values, the question arises which of the two methods gives the right answer in this particular case.

Now, although low one-second values are usually interpreted in terms of increased resistance to breathing, it should be recognized that low C.U.S. values may be due to weakness of the respiratory muscles, incoordination of these muscles, and other extra pulmonary factors.

Since, on the basis of this discrepancy, we suspected muscles incoordination as a cause of the low 1 sec. T.V.C. value, motion pictures were made of the patients' chest during maximal forced breathing as performed during the 1 sec. T.V.C. determination.

The most remarkable finding, however, is that during expiration these accessory (inspiratory) muscles are held in a contracted state (fig. 3). This results in a fixation of the apex of the lung and the upper thorax aperture, so that the subject expires by using only the lower part of his thorax and his abdominal muscles. (As CAMPBELL has stressed the diaphragm is only active during inspiration).

The fixation of the lung apex is physiological during the initial stage of coughing (CAMPBELL 1958). Our subject, although simulating the coughing mechanism, produces a forced expiration while keeping his mm

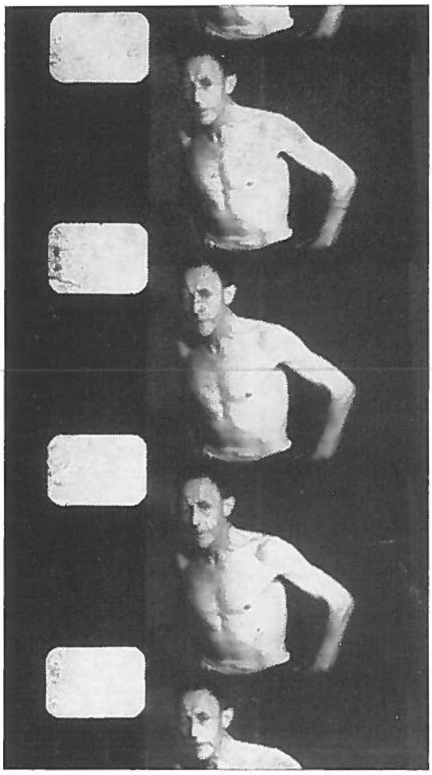


Fig. 3.

Pictures during performance of 1 sec T.V.C

scaleni and sterno-cleidomastoidii rigidly fixed. He clearly demonstrates a wrong expiration technique. The pictures shown of course do not actually *prove* our point, but merely serve to support our tentative explanation.

From these observations, it is concluded that the low one second value (61 %) may be due to muscle-incoordination during forced expiration. The low one second value cannot be explained, in this case, by increased resistance to breathing, since the viscous work was well within the normal range at all "levels" studied.

Case II *A normal subject with a low one second value and normal viscous work at* $f = 15$.

A healthy volunteer, age 51, with no history of pulmonary disease (no history of tuberculosis pulmonum, asthma, pneumonia, chronic cough, dyspnoea, etc. No family history of asthma). The subject is completely symptomless. Physical examination and x-ray revealed no abnormalities.

Fluoroscopy: no impairment of diaphragmatic excursion.

The measured V.C. was 3700 cc (predicted V.C. 4175 cc).

The one-second timed vital capacity was 64 %.

The elastance value was normal: S = 5.2 cm/H_2O/l. C = 0.194 l/cm H_2O.

The striking finding was that while his loops were quite normal at f = 15 over 1 ltr. and 0.6 ltr., the loops became definitely "abnormal" at f = 40.

The viscous work values are shown in table 2.

TABLE 2

	V_T = 1 litre		V_T = 600 cc	
f	work/cycle	work/minute	work/cycle	work/minute
	viscous	viscous	viscous	viscous
15	3900	58400	1400	21500
40	19300	770000	12500	500000

Naturally, it would be incorrect to say that his loops at high frequencies ($\geqslant 40$) are abnormal. We use the term "abnormal" (with quotation marks) in this context to emphasize that the viscous work at high frequencies, in this case is much greater than the mean value of the population of normals.

It might be argued that the low 1 sec T.V.C. value (64 %) indicates that this symptom-free subject was actually pathological, since a one second-value of 64 % is generally looked upon as pathological. However, as will presently be discussed, PEMBERTON and FLANAGAN (1956) in a recent study of timed vital capacity in 428 normal men over forty, have

found in this group a mean value of 79.1 % with a standard deviation of 7.2 %, which indicates that not until values fall below 65 % should a pathological condition be suspected on the basis of this test alone.

From this it follows that the 1 sec. T.V.C. of 64 % in this case, (since within experimental error, and day-to-day variations it does not differ significantly from 65 %) does not suggest a pathological condition. (DISSMAN (1950), RAHN e.a. (1949), MILLS (1949)).

However, the low one-second value of 64 % does suggest an increased resistance to breathing as compared with that found in most normals of the same age group.

This suggestion "emanating" from the 1 sec. T.V.C.-value is confirmed by the disproportionately high viscous work values at high frequencies.

However, whereas the timed vital capacity method does not differentiate between resistance to breathing at normal flowrates and at high rates of flow, the viscous work method clearly shows that while the resistance is increased at high rates of flow, resistance to breathing is perfectly normal at moderate rates of flow.

It is thus demonstrated with the "mechanical" method that during spontaneous breathing the subjects resistance is normal, an important fact not detectable with the 1 sec. T.V.C. method which can, by its very nature "measure" R at maximal rates of flow only.

The causes of this increase of resistance at high flow rates does not concern us here. Suffice it to say that this may be due to the following factors: a) check-valve effects resulting from decreased strength of the bronchial walls, (DAYMAN 1957, 1951, FRY e.a. 1954, MCILROY and CHRISTIE (1952) KING and LAWTON 1950.) WIRZ 1927, ROHRER 1915), b) increased turbulence at high rate of flows (MEAD and WHITTENBERGER 1953, NEERGAARD v., and WIRZ 1927).

Case III

We shall now discuss a severe fibrosis case. The patient is a young man, 27 years old, who until four years ago, could perform any amount of heavy work. The patient is very dyspneic, especially during effort. The chest roentgenogram exhibits a diffuse generalized haziness with a granular pattern.

DANIELS biopsie showed no abnormalities. His V.C. is 1700 cc (predicted value 4600 cc).

The timed vital capacity is 68 %.

The elastance is 25 cm H_2O/l. C = 0.04 l/cm H_2O.

Diagnosis: fibrosis e causa ignota.

The remarkable finding here was the discrepancy between the (almost) normal one-second-value and the definitely abnormal viscous work value at f = 15/600 cc. Because of extreme limitation of vital capacity it was not possible to measure over 1 litre.

The viscous work values are shown in table 3.

TABLE 3
$V_T = 600$ cc

f	viscous work/cycle	viscous work/min.
15	5000	75200
40	6300	254000

It will be seen that whereas the viscous work at f = 15, is much greater than normal (highest normal value 2500 gr cm, hence this value is 2 times "too high"), the viscous work at high frequencies and the timed vital capacity (68 %) are only abnormal to a mild degree.

We may formulate these findings thus: the timed vital capacity value in this case, does not reveal the pronounced increase in resistance present during breathing in the "normal" frequency range.

Another interesting point is, that the spontaneous frequency here is about 30 cycles/minute. From this it would appear that the organism in this case, chooses a higher frequency range where the airway resistance is lower than at the usual range (f = 10—f = 15).

This teleological explanation is, however, not very likely, and it would appear, since his elastance value is very high (S = 25) thit it is this high elastance that modifies his mode of ventilation in a manner predicted by the ROHRER—OTIS hypothesis. (OTIS e.a. 1950, ROHRER 1925). This apparent decrease of airway resistance at higher frequencies requires, at least, a *possible* explanation.

One possible explanation is the following: It has been shown that even in normals the airway resistance changes with the rate of airflow (OGILVIE e.a. 1950, OTIS e.a. 1950, NEEGAARD v., and WIRZ 1927, ROHRER 1915). the expiratory resistance being greater at high rates of flow. This is, for a large part, due to a check-valve mechanism operating at higher rates of flow.

Since the pressure drop is inversely proportional to the fourth power of the radius, it follows that even minor degrees of narrowing (of say, the order of 0.1 mm) may greatly increase airway resistance (ARNOTT 1955, STUTZ 1952).

The bronchogram studies of HUIZINGA (1940, 1938, 1937) during breathing in adults are particularly suggestive in this respect.

If, by hypothesis, we assume that due to the fibrotic process the bronchial walls have become more rigid, adherent and unyielding than normal, then at higher rates of flow the "check-valve" physiological diminution of diameter would not occur. In other words, then the increase of R at higher flows, present even in normals, would not occur.

This then would explain, why, although the resistance is much elevated at f = 15, the resistance at f = 40, and during 1 sec. T.V.C. is only slightly above normal.

In the fibrotic case, at higher frequencies, the rigid bronchial walls lacking check-valve behaviour, compensate for elevated resistance values present at lower frequencies.

Case IV)

Brief case history (see also chapter XI, case III): male, age 37.

Since his second year he has been suffering from chronic cough with paroxysms of asthma.

Allergy tests:
with grasspollens positive skin test and positive inhalation test.

Roentgenogram:
some linear strands in the left apex.
Clear lungfields.
V.C.: 4200 cc (predicted 4250 cc).
T.V.C. 1 sec.: 49 %.

The viscous work and the timed vital capacity values have been determined before, "during", and after the inhalation of allergen (grasspollens). In the 1st period preceding the inhalation of allergen, the patient has been inhaling a "placebo" (coca see chapter XIV) for about 10 minutes. After this, viscous work, vital capacity and timed vital capacity were determined (three times each). The determination of spirometry values fell between the determinations of viscous work.

In this way the "time-factor" was eliminated.

This phase was followed by a 10 minutes period of allergen-inhalation. Immediately after these 10 minutes determinations were made as described above. In the third phase, isopropyl noradrenaline inhalation 1 % was given to relieve the bronchoconstriction induced by the allergen. Again, after isopropylnoradrenaline, determinations were made.

The results are shown in the table below.

TABLE 4

	after placebo (coca) inhalation for 10 min.	after allergen (grasspollens) inhalation for 10 min.	isopropyl noradrenaline after aleudrine inhalation for 10 min.
V.C.	4200	2000	3700
1-second volume	2600	800	2050
1 sec. timed V.C.	62 %	40 %	55 %
viscous work/cycle freq. 15/11 in gr. cm	9600	53300	27700

It will be seen that in the allergen period the timed vital capacity drops from 62 % to 40 %, while the viscous work increases from 9600 to 53300 gram cm, i.e. the viscous work after allergen inhalation is 5½ times its previous value!

After isopropylnoradrenaline inhalation, although the timed vital capacity has risen to 55 %, the viscous work (27700 gram cm) is still nearly 3 times greater than in the placebo phase.

Especially in this last phase it is very clearly demonstrated that viscous work is a much more sensitive index of the severity of the bronchial obstruction than the 1 sec. timed vital capacity.

An even more striking example of the superior sensitivity of the viscous work method relative to the timed vital capacity method is given below.

Case 5)

In the next asthma case (female, age 22; for case history, see chapter XII, case VII) the mechanics of breathing were first determined prior to inhalation of Coca and allergens. After this, Coca inhalation during 10 minutes was given followed by determinations etc. in the manner described in case 4.

The results are shown in table 5.

TABLE 5

C.W. 22, years	control period without inhalation	10 min. Coca-inhal.	10 min. cathairs extr. allergen inhal.
V.C.	3400	3400	3400
1 sec. volume	2200	2350	2200
1 sec. T.V.C.	65 %	69 %	65 %
viscouw work (f = 15/1 ltr.) in gr. cm	6100	5700	9700
viscous work as % of control value	100 %	93 %	162 %

It will be seen from table 5, that while the timed vital capacity after 10 minutes allergen inhalation remains the same as during the control period without inhalation (65 %), the viscous work in the allergen period rises to 162 % of the control value.

Clearly this example very strikingly illustrates the much greater sensitivity of the viscous work method.

APPENDIX

It has been an established clinical practice to regard a timed vital capacity value below 70 % as pathological. This value of 70 % is largely based on Gaensler study of young adults.

PEMBERTON and FLANAGAN have collected normal values for timed vital capacity in normal men over forty. Their sample contained 428 subjects with ages ranging between 40 and 88 years.

The age distribution was far from being homogeneous, however, as may be seen from the figures below.

age	40	45	50	55	60	65	70	75	80	85
number	116	79	77	59	43	29	14	5	3	3

However, treating the sample as a whole, a mean value of 79.1 % was found with a standard deviation of 7.2. Taking, following statistical usage, the mean minus twice S.D. as the lower limit of normality, it follows that a timed vital capacity of 65 % must still be looked upon as *normal,* at least in subjects over forty.

The limitations of the timed vital capacity method as an indicator of airway resistance have been adequately discussed by ATTINGER and SEGAL (1957), JOHNSON and MC. NEELY (1957), PEMBERTON and FLANAGAN (1956), MEAD e.a. (1955, 1953), OGILVIE e.a. (1955), DAYMAN (1951). who showed that the one second T.V.C. value is influenced by such "external factors as position of mechanical advantage of the ventilatory mechanism, pulmonary compliance, muscular force etc." (MEAD e.a.)

CHAPTER XI

Normal values of Compliance in relation to age and sex.

This chapter requires an apology in view of the fact that so many reports have already been published on normal values for lungcompliance.

However, although FRANK's study (1956) on 70 normal young adults is probably the largest series studied, a series of similar magnitude which takes the possible influence of age and sex into account has not been presented so far.

Our group of 77 normals forms a stratified sample in relation to age and sex, the ages ranging between 15 and 65 years, while 33 subjects were women.

For a discussion of the various techniques of measuring compliance the reader is referred to chapter V (General methods).

The considerable spread in the normal values reported in the literature results, at least in part, from the different techniques employed (water-balloon, air-filled balloon, determination of true static compliance, or dynamic compliance from the reversal points during normal breathing etc.)

Method

Starting from the normal end-expiratory level the subject was instructed to inspire as slowly as possible with a tidal volume of 1 litre. At the end of the inspiration the subject started to expire very slowly until the resting end-expiration level was reached.

The P—V curve thus obtained was recorded.

The subject could "read" his tidal volume from the spirometer tracing.

By very slow breathing we mean rates of flow below 0.2 l/sec.

According to MEAD e.a. (1954) dynamic factors due to resistance and inertia are eliminated in normals when volume flow is below 0.2 l/sec. It is easy to verify this theoretically. In other words, when the compliance is determined from a P—V curve obtained at a volume flow < 0.2 l/sec. the compliance is determined under essentially *static* conditions.

This statement applies to normal subjects.

In patients having very high resistance values this limit will be lower.

We may thus state that with our technique the *static compliance* is measured.

This statement is contrary to the view of VERSTRAETEN (1956) who claims that true static compliance values can only be obtained when the volume flow is zero.

A simple calculation based on known normal values of resistance and inertia shows us that such a view is erroneous.

We shall not carry out this computation here since the matter has been fully discussed by MEAD e.a. (1954).

Results

The elastance S was determined in 44 healthy males and 33 healthy females. Both groups were stratified in relation to age as may be seen from tables I and II in chapter XII.

For the criteria of normality the reader is referred to chapter XII. In all these subjects studied the P—V curve determined during "slow" breathing over 1 liter, was essentially linear over the tidal-volume range of 1 liter, while hysteresis over this 1 liter range was negligible.

1) In both groups (males and females) no significant differences in elastance values were found, as assessed by the Student-t test, between the older and younger age group.
2) It was found that the elastance values constitute a logarithmic normal distribution.
3) The mean elastance of the male population differs from the mean elastance value of the female population.
4) The estimates of the mean and the standard deviation are

sex	Mean value of elastance S cm H_2O/l	Standard deviation	Number of subjects used
males	4.8	1.77	44
females	6.3	1.62	33

Now, for males, the value of the mean, 4.8, refers to the mean value of the sample (44 males). We wish to know, however, for comparing our findings with values reported in the literature, the mean value of the whole "population" of males.

The mean of the sample (4.8) is also the best estimate of the mean of the population, but represents no more than an estimate.

On the basis of our sample, we estimate (5 % basis) that the mean of the population lies somewhere between 4.3 and 5.4, or

$$\text{for males} \quad 4.3 \leqslant S_{mean} \leqslant 5.4$$

$$\text{similarly for females} \quad 5.8 \leqslant S_{mean} \leqslant 6.9$$

The difference between the mean values of males and females is thus clearly significant.

It should be clearly understood that e.g. $4.3 \leqslant S_{mean} \leqslant 5.4$ does not indicate the limits of normality; it merely defines the interval in which the "true" mean value of the population is likely (95 %) to lie.

In very much the same way we find that the best estimate of the mean value of the compliance is 0.21 *for males and* 0.16 *for females and that*

$$\text{for males } 0.19 \leqslant C_{mean} \leqslant 0.23$$

$$\text{for females } 0.14 \leqslant C_{mean} \leqslant 0.017$$

Compliance as a function of body length.

In our material no correlation can be found between compliance and body length.

Compliance as a function of measured Vital Capacity.

In our female sample no correlation can be found between actual Vital Capacity and compliance.

Our male sample suggests the possibility of a negative correlation, a faint indication, which however is unprobable on physiological grounds.

It seems safe to assume from our figures that no (useful) correlation exists between V.C. and compliance.

Discussion.

Our best estimates of the mean of the compliance (0.21 for males, 0.16 for females) may be compared with the values found in the literature as compiled in table I.

FRANK found a difference of 0.05 between the mean compliance values in males and females.

He further states that when males and females of the same length are compared no significant differences in compliance values are found.

We have failed to obtain a significant correlation between compliance and body length.

In contradistinction to our observations FRANK obtained a correlation between compliance and body length which may be represented by the equation $C = bl + a$, where l = length, a and b are regression coefficients. The scatter in his diagram was very large, however.

Our results indicate that no significant correlation between age and compiled in table I.

PIERCE (1958), however, obtained a higher mean compliance value in eldery persons.

In contradistinction to these findings FRANK, MEAD and FERRIS (1957) obtained lower compliance value in subjects above 50 years than in the younger age group.

NISELL and DUBOIS (1954) observed a linear relationship between F.R.C. and compliance in cats, and stress the importance of simultaneous measurements of F.R.C. and compliance in the assessment of pathologic changes. This item has been fully discussed in the chapter on the modulus of elasticity (chapter II).

TABLE I

Author	Number	Compliance	
MURALT	1	0.22	pn. th.
BUYTENDIJK	32	0.25	
STEAD	10	0.23	
SCHERRER	1	0.22	
MEAD	10	0.22	
PIERCE	8	0.25	
CHERNIACK	7	0.20	
FRANK	38 ♂	0.19	0.05
	32 ♀	0.14	
VERSTRAETEN	9 ♂	0.20	0.04
	6 ♀	0.16	
own material	44 ♂	0.21	0.05
	33 ♀	0.16	

In fig. 1 are shown the scatterdiagrams of compliance vs age for females and males.

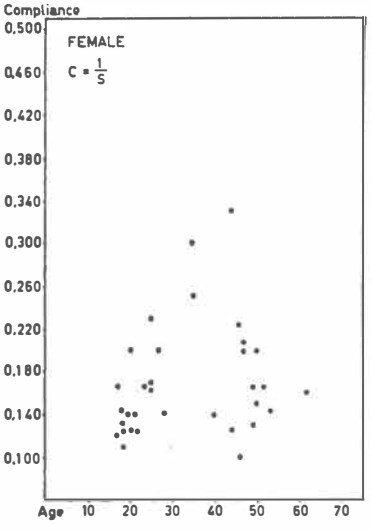


Fig. 1a
Scatterdiagram of compliance vs age for females.

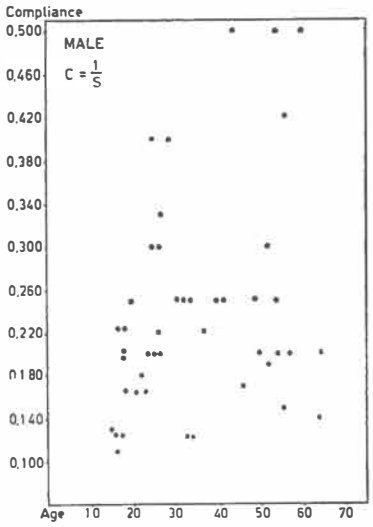


Fig. 1b
Scatterdiagram of compliance vs age for males.

CHAPTER XII

Normal values of "Viscous Work" in relation to sex and age at fixed frequency and tidal volume

The "viscous work" at fixed frequency and tidal volume was determined in 77 normal subjects. The sample consisted of 44 males and 33 females.

The determinations were made at a frequency of 15 and 40 cycles per minute, over a tidal volume of 0.6 and 1.0 litre.

The choice of these values is, although arbitrary within limits, dictated by practical considerations.

At high rates of flow (f = 40) the resistance to breathing may differ greatly from that found during "quiet" breathing (f = 15) e.g. due to the presence of check-valve mechanisms.

Since e.g. fibrosis-cases cannot produce tidal volumes of 1 litre and since certain asthmatics cannot breathe at a tidal volume of 0.6 litre (at f = 15) without becoming dyspneic, both the values of 1.0 and 0.6 litre have been selected.

The subjects were selected in relation to sex and age.

In other respects the subjects may be considered as a non-selected sample from a population of "healthy" subjects (healthy, of course, in relation to lungmechanics).

The subjects, who were all volunteers, may be divided in the following categories:

1) nurses, technicians, office personnel, friends, sport-club members, etc.
2) patients from the Medical Clinic
3) ambulatory patients from the department of surgery
4) young individuals undergoing routine x-ray control.

In order to obtain "normal values" of standardized viscous work and elastance 77 healthy subjects were employed. The concept of normality (with regard to the pulmonary system) forms the subject of this discussion.

A subject is labelled "normal" when he is free from subjective (pulmonary) symptoms, and when no objective (pulmonary) symptoms are detectable on examination.

Characteristics of normal individuals:

1) The case history should be free from:
   pleurisy, asthma, tuberculosis, periodic periods of cough (LOEWENBERG has shown that 50 % of the patients consulting their physician for cough excluding influenza epidemics are chronic coughers, and showing abnormalities in their lungfunction as a consequence of their asthmatic constitution.
   Subjects with "smokers-cough" were also excluded. This measure especially affected the group of males beyond the age of 45.

2) Physical and x-ray examination revealed no pulmonary abnormalities in the selected cases.

3) Since tracheitis may increase the resistance to breathing without being detectable on physical examination, we have laid special stress on the abscence of coughing in the case history. (Hyperventilation during the test (f = 40) never caused cough in these 77 selected cases).
The concepts "normal" or "healthy" are, of course, subject to controversy. ORIE points out that many chronic coughers are quite unaware of their symptom and that persons with so-called "smokerscough" really belong to the formentioned group of chronic coughers. (e.a. chronic bronchitis).

Four levels of "normality" (with respect to the pulmonary system) may be roughly distinguished, depending on the severity of our criteria. (ORIE)

1) A person may be called normal in the absence of cough, expectoration, dyspnea and other symptoms or complaints "referable" to the pulmonary system.

2) A better selection of normality is obtained when we demand the realization of the criteria mentioned in (1) plus the absence of pulmonary disease (t.b.c., asthma etc.) in the history and in addition to the demands mentioned in (1) and (2), it is required that objective examination (i.e. physical and x-ray examination) reveals no pulmonary abnormalities.

3) A still better selection is obtained when, in addition to the demands in (1) and (2) it is required that lungfunction studies should reveal no abnormalities.

4) The most severe selection is obtained when, in addition to the demands in (1) (2) and (3) it is required that lungfunction studies should reveal no abnormalities on testing with bronchoconstricting and bronchodilatting drugs.

Of course the concept "lungfunction studies" is quite vague since these may range from simple V.C. and C.U.S. to diffusion capacity and wash-out studies. It may be demanded that the timed vital capacity and V.C. are unaffected. In the 4th category it is required that the normal functions remain unaltered by the administration of histamine, acetylcholine, adrenaline, isopropyl-nor-adrenaline, atropine, oxythenoiibromidum and thiazinamidum.

However such a demand seems premature since the bronchial effects of these drugs in "normals" (here the whole population is meant) have not yet been established in a statistically satisfactory manner.

Moreover, it should be realized that it we make our demands too severe in a false attempt to be scientifically rigorous, we may find ourselves left with a small group of "normals" (read "supernormals") constituting only

a fraction (say 10 %) of the population as a whole. Such a definition of normality would be devoid of meaning.

The choice of normals should probably be made in such a way that the 6 % of the population which in our country is affected with pulmonary signs and symptoms of clinical significance is rejected (ZUIDERWEG, 1959).

Our group of normals was selected according to the criteria stated in (2). In nearly all selected cases V.C. and timed vital capacity were made.

The group consists of 44 males and 33 females and forms a stratified sample in relation to age and sex (see tables I and II) the ages ranging from 16 to 65 years.

RESULTS

The data are collected in table I and II.

Statistical analysis:

I *Viscous work as a function of age and sex.*

In order to take the possible influence of age and sex into account the sample is stratified in relation to these factors.

The logarithms of the viscous work values yielded a normal distribution. (See graphs fig. 1). For this reason, the calculations have been based on the logarithm of the viscous work.

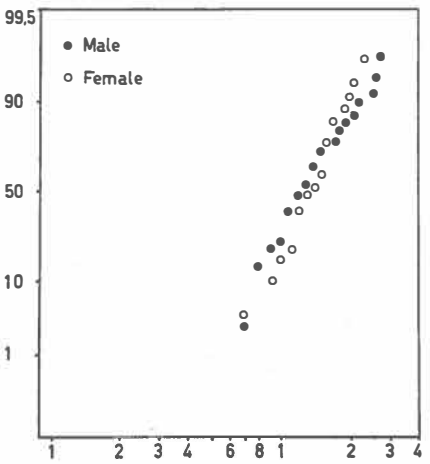


Fig. 1a
Cumulative log-normal distribution of standard viscous work (for 15/1 l).

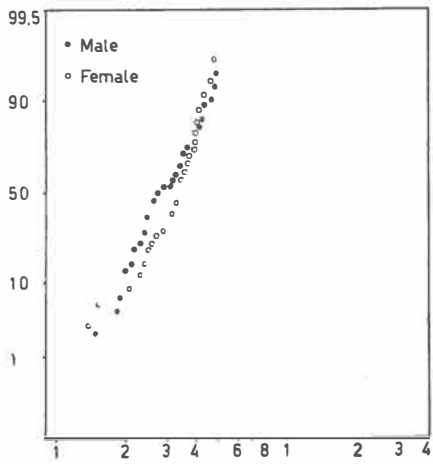


Fig. 1b
Cumulative log-normal distribution of standard viscous work (for 15/0.6 l).

No significant difference exists between the viscous work values of the older age groups (45 *years and older*), and those of the younger age groups. The same applies in relation to sex. These conclusions are based

on the Student-t test and apply to viscous work at all levels studied (15/600, 40/600, 15/1 L, 40/1 L).

II *Normal values.*

Once it was shown that no significant age and sex differences exist, the 77 values for each work level, were pooled to obtain the "normal" values shown in table III.

The mean values were simply obtained by taking the arithmetic mean of the observed values.

It is obvious that although e.g. at 15/600 the mean value is 1400 gram cm, the upper limit of normality may lie considerably higher (See columns under "limits").

The meaning of the last three columns under the heading "limits" will now be explained:
the chance that (at fixed frequency and tidal volume) the viscous work exeeds the value of g_1, g_2 or g_3, is 10, 5 or 1 % respectively.

These limits are thus obtained by taking the mean value plus 1.28, 1.64 or 2.33 times the standard deviation in logarithmic scale. The eight standard deviations (15/600 etc. and both sexes) show no significant differences. The best estimate of their value is 0.139 in logarithmic scale.

In normal scale the standard deviation is 38 % of the mean.

The limits of normality as shown in table III should be interpreted as follows.

TABLE III

Normal values of standard viscous work

frequency and tidal volume	mean value of viscous work in gr.cm.	(10 % level) g_1	(5 % level) g_2	(1 % level) g_3
15/600	1400	2100	2400	3000
40/600	2900	4400	4900	6100
15/1 L	3100	4600	5100	6300
40/1 L	7300	10900	12200	15100

a) viscous work $\leqslant g_1$: normal
b) $g_1 <$ viscous work $\leqslant g_2$: upper limit of normal
c) $g_2 <$ viscous work $\leqslant g_3$: dubious
d) $g_3 <$ viscous work : pathological

In case c) further examination is required before the subject should be excepted as normal.

In case d) the viscous work is in all probability pathological.

FEMALES

Table I

Age yrs.	S.	C = 1/S	Freq./T.V. 15/600 gr.cm.	Freq./T.V. 40/600 gr.cm.	V.C. Measured	V.C. Predicted	T.V.C. 1 sec.	Freq./T.V. 15/1000 gr.cm.	Freq./T.V. 40/1000 gr.cm.	Nr.	Tests with thiazinamidum 25 mg i.m. (multigram)	V.C. measured	V.C. predicted	T.V.C. 1 sec.
17	8.4	0.12	1.600	3.800	2.900	2.700	84 %	4.000	9.000	1				
17	6	0.16	1.700	3 800	3.400	3.100	80 %	4.200	9.500	2				
18	7	0.14	1.200	3.600	4.100	3.000	70 %	2.400	6.500	3				
18	7.5	0.13	900	1.900	2.900	2.800	91 %	2.100	4.000	4				
18	8	0.12	2.300	5.300	3 700	3.150	80 %	4.200	14.000	5	before th.	4.735	4.600	81 %
											after th.	4.435		88 %
18	9	0.11	1.600	3.300	3.100	2.700	91 %	3.400	14.000	6				
19	7	0.14	1.000	3.100	3.400	2.800	80 %	2.600	10.000	7	before th.	3.380	2.800	80 %
											after th.	3.430		85 %
20	8	0.12	1.700	3.800	3.400	3.000	86 %	3.400	8.700	8				
20	5	0.20	700	1.700	4.000	3.300	83 %	1.400	9.200	9				
21	7	0.14	1.500	3.000	3 300	3.100	76 %	3.800	7.700	10				
22	8	0.12	1.300	3.100	3.400	3.100	82 %	3.100	5.200	11				
24	6	0.16	1.600	3.000	3.900	3.100	77 %	3.700	8.100	12				
25	6	0.16	1.100	2.800	3.900	3.100	81 %	2.500	7.800	13				
25	4.4	0.23	2.100	3.700	3.600	3.000	91 %	3.700	7.700	14				
25	6	0.16	1.600	3.600	2.900	3.100	72 %	3.600	7.300	15				
27	4.8	0.2	2 000	3.200	—	—	—	4.300	9.700	16				
28	7	0.14	1.600	3.200	3.300	3.200	88 %	4.100	8.100	17				
35	4	0.25	1.000	2.500	3.000	3.200	75 %	2.300	4.700	18				
35	3	0.3	—	—	3.000	3.000	81 %	1.500	—	19				
40	7	0.14	1.200	2.700	2.600	3.000	76 %	3.400	5.300	20				
44	8	0.12	1.200	3.000	3.100	2.900	76 %	3.100	7.500	21				
44	3	0.3	1.200	2.400	3.000	2.700	85 %	2.700	6.800	22				
46	10	0.1	2.800	4.600	2.400	2.600	77 %	5.000	13.000	23				
46	4.5	0 22	1.300	4.400	3.700	2.800	—	3.500	12.500	24				
47	5	0.2	1.700	2.500	2.500	2.600	82 %	4.800	6.700	25				
47	5	0.2	1.900	2.700	3.500	2.900	70 %	3.300	6.300	26				
49	7.6	0.13	900	2.000	4.300	3.100	76 %	2.900	4.400	27				
49	6	0.16	1.200	2.300	2.600	2.900	80 %	3.400	5.700	28				
50	6.6	0.15	—	—	—	—	—	4.700	7.200	29				
50	5	0.2	1.500	3.000	3.400	2 700	69 %	3.500	8.300	30				
52	6	0.16	1.200	2.500	2.900	2.700	72 %	2 500	6.900	31				
57	7	0.14	1.300	3.300	2.900	2.800	61 %	3.900	6.200	32				
64	7	0.16	1.400	3.600	2.000	2.600	75 %	3.300	5.900	33				

MALES

Table II

Age yrs.	S.	C = 1/S	Freq./T.V. 15/600 gr.cm.	Freq./T.V. 40/600 gr.cm.	V.C. Measured	V.C. Predicted	T.V.C. 1 sec.	Freq./T.V. 15/1000 gr.cm.	Freq./T.V. 40/1000 gr.cm.	Nr.	Tests with thiazinamidum 25 mg i.m. (multigram)	V.C. measured	V.C. predicted	T.V.C. 1 sec.
15	7.6	0.13	1.400	4.000	3.200	3.600	89 %	3.600	6.700	1				
16	9	0.11	—	—	4.400	4.700	93 %	2.400	—	2				
16	8	0.12	2.600	3.700	3.900	3.900	79 %	5.300	7.000	3				
17	4.4	0.22	—	—	—	—	—	2.800	6.600	4				
17	7.6	0.13	—	—	4.500	4.300	65 %	2.000	4.900	5				
18	5	0.20	1.300	—	5.000	4.700	90 %	2.400	7.000	6	before th.	5.020	4.725	90 %
											after th.	4.965		91 %
18	5	0.20	900	—	4.800	4.500	82 %	2.700	8.100	7				
18	6	0.16	800	3.700	5.400	4.900	68 %	2.700	6.100	8				
18	4.5	0.2	700	1.600	6.000	5.100	81 %	2.000	4.200	9				
20	4	0.25	—	—	—	—	—	4.000	—	10				
21	6	0.16	1.400	2.600	3.900	3.800	89 %	4.000	7.700	11				
22	5.6	0.18	800	1.300	4.000	4.300	94 %	1.800	5.700	12				
23	6	0.16	1.500	4.300	4.700	4.600	81 %	3.200	12.000	13	before th.	4.735	4.600	81 %
											after th.	4.435		88 %
24	5	0.2	1.900	4.800	4.900	4.800	—	1.900	9.700	14				
25	3.2	0 3	2.500	4.000	5.600	4.600	70 %	4.300	8.500	15				
25	2.5	0.40	1.300	3.500	5.900	4.800	74 %	2.700	7.000	16				
25	5	0.20	800	2.500	5.400	4.700	71 %	2.700	5.500	17				
26	3.5	0.3	2.100	4.100	5.200	4.200	67 %	3.500	6.200	18				
26	4.5	0.22	1.500	4.000	4.600	4.800	69 %	3.100	10.000	19				
26	5	0.2	1.500	—	4.600	4.600	76 %	2.800	9.200	20				
27	3	0.3	1.400	2.900	4.600	4 300	70 %	3.300	8.000	21	before th.	4.575	4.325	70 %
											after th.	4.575		69 %
29	2.5	0.40	2.200	3.200	5.500	4.300	71 %	4.900	9.000	22				
31	4	0.25	800	1.600	—	—	—	2.500	3.700	23				
33	8	0.12	2.800	3.800	3.400	3.900	68 %	4.200	12 000	24	before th.	3.380	3.850	68 %
											after th.	3.430		74 %
33	4	0.25	1.200	—	4.800	4.200	74 %	2.500	4.200	25	before th.	4.810	4.160	74 %
											after th.	4.835		78 %
34	8	0.12	—	—	3.600	4.100	76 %	3 600	—	26				
37	4.5	0.22	—	—	5 900	4.300	82 %	3.600	—	27				
40	4	0.25	900	1.800	4.400	4.000	75 %	2.300	4.200	28				
41	4	0.25	—	—	5.400	4.400	61 %	2.200	—	29				
44	2	0.5	1.100	2.300	5.200	4.400	77 %	2.200	5.600	30	before th.	5.200	4.400	77 %
											after th.	5.150		80 %
46	6	0 17	1.100	—	4.300	3.500	70 %	3.500	—	31				
49	4	0.25	1.100	2.800	4.800	4.300	71 %	4.000	6.200	32				
50	5	0.20	1.400	2.400	4.200	3.900	80 %	3.000	4 700	33	before th.	4.135	3.880	80 %
											after th.	4.210		84 %
52	3	0.3	1.200	1.700	4.100	4.100	74 %	2.100	5.400	34				
52	5.6	0.18	1.800	3.000	4.300	3.500	70 %	4.100	6.000	35				
54	4	0.25	1.000	2.000	5.100	4.000	76 %	4 800	10 000	36				
54	5	0.20	—	—	3.600	3.700	65 %	2.500	8.300	37				
54	2	0.50	2.700	—	3.100	3.400	60 %	5.300	11.400	38				
56	6.4	0.15	1.200	2.400	4.100	3.700	61 %	2.000	6.700	39	before th.	4.420	3.730	59 %
											after th.	4.760 (+ 9 %)		59 %
											before adrenaline 0.3 cc., s.c. after adrenaline	4.265 / 4.600 (+ 8 %)	3.730	57 % / 59 %
56	2.3	0.42	—	—	3.800	3.700	71 %	1.500	—	40				
57	4.4	0.2	1.700	2.300	—	—	—	3.700	7.700	41				
63	7	0.14	1.800	—	4.100	3.900	73 %	4.700	12 000	42				
64	5	0.20	1.100	3.800	3.500	3.600	62 %	4.300	6.900	43				
65	2	0.5	1.100	2.000	4.100	3.700	60 %	2.500	9.300	44				

To simplify we may take the mean value plus twice the standard deviation as the highest limit of normality e.g. at 15/1 L this would be

$$\text{(since standard deviation is 40 \%) } 3100 + \left(\frac{8}{10} \times 3100\right) = 5600 \text{ gr . cm.}$$

i.e. value lying between g_2 and g_3.

We may thus consider the range g_2 — g_3 as the borderland between normality and pathology, and values close to g_3 should be viewed with suspicion.

For the discussion of variations within a single individuals and other sources of error, the reader is referred to chapter III.

CHAPTER XIII

Influence of pulmonary and extra-pulmonary factors on the shape of the static volume pressure diagram.

At the end of maximal expiration the pressures may reach high positive values, while volume changes may be very small. In this respect the lung may be compared with a sponge that is being squeezed empty. When the sponge is greatly compressed, pressures may become very high while very little volume reduction occurs. Finally, a point is reached where pressures are 'infinitely" great, while the volume reduction is vanishingly small, i.e. the elastance "infinite". Theoretically, such an infinite elastance can always be obtained in any lung, when the expiratory muscles could develop infinitely high pressures and when the thoracic cage, would not impede further reduction.

It would appear that this observation offers a means of differentiating between reduced thoracic mobility (as in ankylosing spondilitis) and lung "stiffness" as a factor limiting expiratory reserve volume and thus vital capacity (since a similar condition occurs during maximal inspiration we may generalize to vital capacity).

When the static pressure volume curve obtained during a slow vital capacity effort is of the form shown in fig. 1a, then the lung is probably the factor limiting the vital capacity.

When, however a curve as shown in fig. 1b is obtained, then the thoracic cage (which may be quite normal) impedes further volume change.

Relative weakness of the respiratory muscles could also account for the form of the curve shown in fig. 1 b.

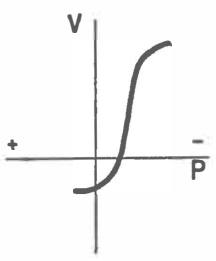


Fig. 1a
Static volume pressure diagram when the lung is the factor limiting the V.C.

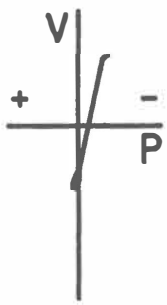


Fig. 1b
Static volume pressure diagram when the thoracic cage is the factor limiting the V.C.

The following case reports will serve to illustrate the above considerations.

Case report I.

Patient P, age 27, male, since about a year suffering from increasing dyspnoea, cough after exertion.

Fluoroscopy: diaphragm moves freely.

X-ray exhibits a diffuse generalized haziness with a granular pattern. DANIELS biopsy showed no abnormalities.

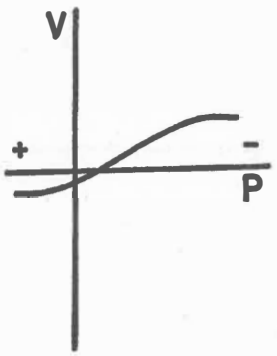


Fig. 2.
Static volume pressure diagram of a patient with fibrosus pulmonum.

Diagnosis: fibrosis pulmonum of unknown origin.

V.C. = 17775 cc (predicted value 4590 cc).

T.V.C. one sec. = 68 %.

F.R.C. = 1600 cc. Elastance S = 25 cm H_2O/l, compliance = 0.04 L/cm H_2O.

The compliance curve over the vital capacity range is shown in fig. 2.

In fig. 3, the stativ P—V curve over the vital capacity range of a normal subject is shown for comparison.

The short volume range of the curve in the fibrosis case is of course a manifestation of the greatly reduced vital capacity.

The flat course of the curve is expressed by the high elastance value. It may be seen from the horizontal extremes of the curve that the factor limiting vital capacity is primarily situated in the lungs (stiffness of the lungs). In the normal case vital capacity is also limited by the lungs (very high elastance values at the extremes) the difference between the fibrosis case and the normal case being that in the fibrosis case the extreme elastance values are reached earlier.

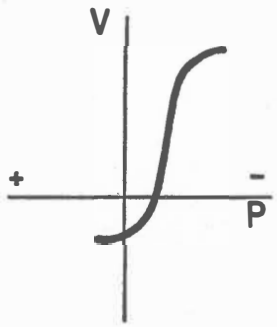


Fig. 3
Static volume pressure diagram of a normal subject.

Case report II.

The above examples may be contrasted with a case ankylosing spondylitis.

Patient M, age 31, male; he has been suffering from ankylosing spondylitis for years. Rigid spine, thorax rigid and barrel shaped, reduced thoracic mobility.

Circumference of the thorax at maximal expiration 86 cm, at maximal inspiration 88 cm.

No cough, no expectoration, no history or symptoms of asthma, pneumonia or other lungdisease.

Fluoroscopy: no abnormalities in the lungs.

The most striking finding is the greatly increased diaphragmatic excursion.

The activity of the abdominal muscles is greatly increased during the expiratory phase, as may be observed by simple inspection.

V.C. = 2260 cc (predicted value = 3630 cc).

T.V.C. one second = 91 %.

Elastance S = 8 cm H_2O/L.

Compliance C = 0.125 L/cm H_2O.

The greatly increased motion of the diaphragm is demonstrated in fig. 4.

The compliance line over the vital capacity range is shown in fig. 5.

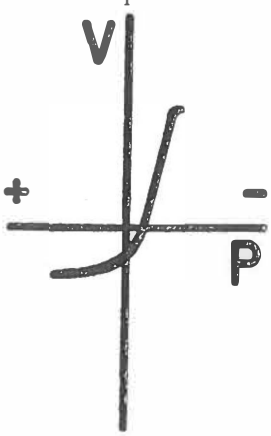


Fig. 5

Static volume pressure diagram of a patient with ankylosing spondylitis.

The "shortness" of the curve corresponds to the reduced V.C. At the end of a maximal inspiration the curve breaks off abruptly, while at the end of a maximal expiration the curve runs horizontally, showing the development of fairly high (positive) pressure across the lungsystem. Surely these positive pressures are not high relative to those found in normals, but in view of the greatly reduced mobility of the thoracic cage such high expiratory pressures are scarcely to be expected.

The unexpectedly large positive pressures could not be ascribed to the active action of the diaphragm during expiration, since the diaphragm does not contribute actively to the expiratory effort, as has been shown by CAMPBELL and others.

It would thus appear from the finding of reduced thoracic mobility associated with increased (expiratory) activity of the abdominal muscles that the high positive pressures at the end of maximally deep expiration result from the action of the abdominal muscles. The large diaphragmatic excursions observed during fluoroscopy result, in part, from the strong contractions of the abdominal muscles during expiration, pushing the diaphragm beyond (above) its position of equilibrium.

Case report III.

Patient, age 33, female, two years ago she fell victum to poliomyelitis of severe degree. At the time of the examination paresis of the back musculature and abdominal muscles was found. The neck-musculature (scaleni etc.) was unaffected.

Fluoroscopy: lungs no abnormalities.

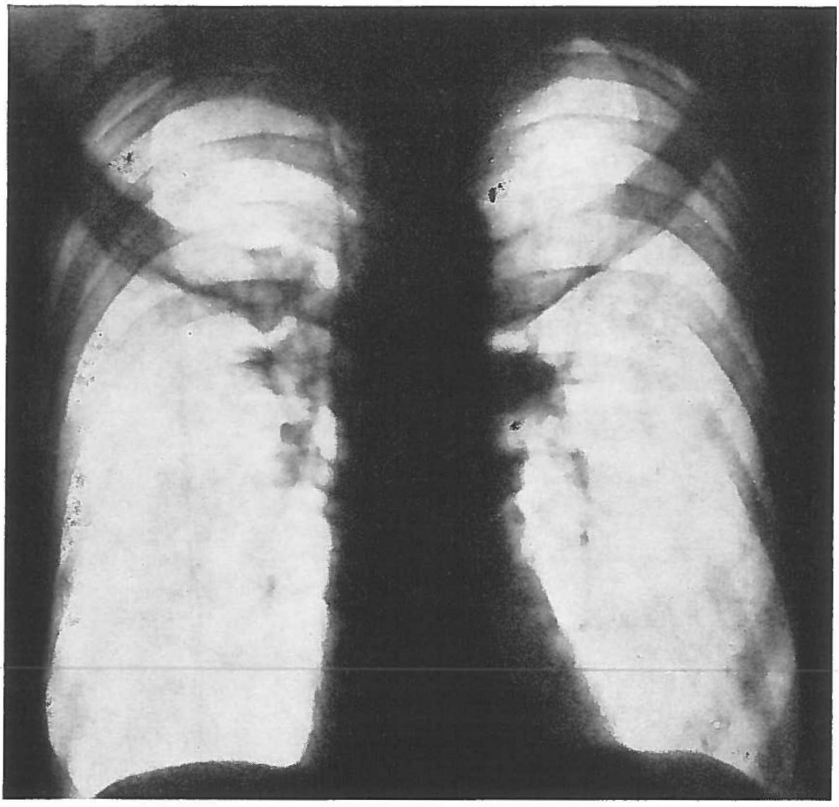


Fig. 4A
Diaphragma at maximal inspiration.

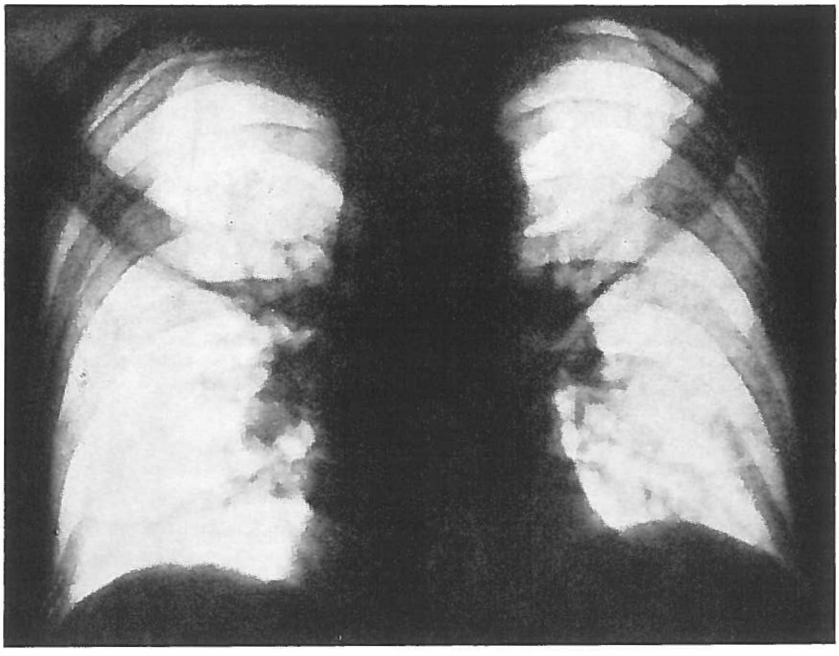


Fig. 4B
Diaphragma at maximal expiration.

Diaphragm immobile. Circumference of the thorax at maximal expiration: 84½ cm.

At maximal inspiration: 86 cm.

V.C. = 1500 cc (predicted value 3160 cc).

T.V.C. one second = 88 %.

The compliance line over the vital capacity range is shown in fig. 6.

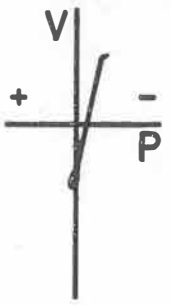


Fig. 6
Static volume pressure diagram of patient with poliomyelitis.

It should be noted that no high negative and positive pressures are developed at the end of inspiration and expiration respectively.

The abrupt break-off at both ends in this polio case is probably not due to rigidity of the thoracic cage but to weakness of the respiratory muscles.

Case report IV.

Patient, J. L. age 38, male.

In September 1956 he underwent operation for echinococcus of the liver. In December of the same year the presence of a fistula necessitated the removal of the gall-bladder. In October 1958 he again entered the hospital for stenosis of the duodenum. No coughing, no expectoration, no history of lungdisease or pleurisy. Physical examination: greatly reduced movement of the lower border of the right lung.

X-ray: no abnormalities in the lungs.

The right diaphragm is adherent.

Fluoroscopy: the right portion of the diaphragm is paralysed laterally and shows greatly reduced motion medially.

The left portion of the diaphragm moves freely.

V.C. 3200 cc (calculated 4160 cc).

C.U.S. 91 %, elastance 5 cm H_2O/L.

On 3 November 1958 gastro-jejenostomy was performed. On 18 November 1958 thoracotomy was performed to establish vagotomy. When the thorax was opened an thorax absces communicating with the liver was found. The empyema was drained and the healing process was uneventful.

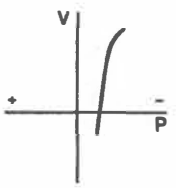


Fig. 7
Static volume pressure diagram of a patient with empyema thoracis.

The compliance curve determined prior to the removal of the absces is shown in fig. 7.

The abrupt ending of the curve at the end of a "maximal" expiration may be explained by the presence of the capsulated empyema which apparently inhibits further compression (reflexly?) at the end of expiration during the vital capacity effort.

Note on the SLAGTER method for the determination of the compliance of the thorax.

The following proccdure, suggested by SLAGTER, may be used to determine the elasticity of the thoracic wall:

In this test it is essential that the quiet expiration slows down towards the equilibrium position, i.e. the position at which the respiratory muscles are relaxed. When breathing against atmospheric pressure this equilibrium position is associated with lungvolume V_r, i.e. (by definition) the volume at which the lungelasticity (force of retraction) balances the elasticity of the thoracic wall (force of expansion). When breathing against pressure higher than atmospheric the lungvolume at equilibrium is increased, being determined by the equilibrium between lungelasticity + excess pressure in the alveoli on the one hand and the elasticity of the thoracic wall on the other hand. Of course an analogous situation is found when breathing against pressure lower than atmospheric. The subject is connected to a spirometer (closed circuit) and breathes quietly against various pressures including atmospheric pressure. When the pressure volume loops thus obtained are plotted in the same diagram a graph such as shown in fig. 8 is produced. The curve connecting the end-expiratory reversal points of the loops constitutes the "compliance curve" of the thoracic wall.

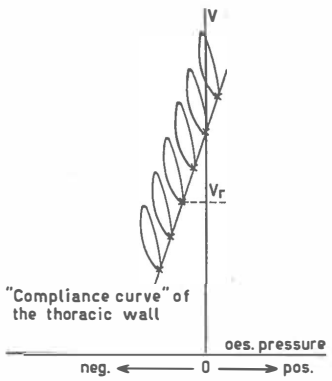


Fig. 8
For explanation see text.

When the angle between this curve and the horizontal axis is denoted by α, then α represents the compliance of the thorax.

CHAPTER XIV

Viscous work as an indicator of the effect of allergen and drug therapy in asthmatics.

In this chapter the applicability of the viscous work method to the study of the effect of allergens and drugs on the resistance to breathing of asthmatics will be discussed.

BOOY-NOORD, ORIE, TEN CATE (1957) studied the influence of various drugs on the V.C. of asthmatics. They found that thiazinamidum had both a favorable effect on the V.C. and a good protective activity in the asthma attack produced by means of allergens.

These investigators and others (HERSCHFUS et al 1951) also studied the degree of protection offered by various drugs in protection tests in asthma attacks induced by the inhalation of allergen extracts.

HERXHEIMIER (1951) TEN CATE (1954) COLLDAHL (1952) studied the hypersensitivity towards allergen extracts in asthmatic patients.

SCHERRER (1957) MC. ILROY & MARSHALL (1956) FRIEBEL (1954) NOELPP (1954) have studied the pressure-volume diagram during spontaneous and induced attacks of asthma.

Although these studies are of practical value, they do not give quantitative information with regard to changes of the resistance to breathing, since tidal volume and frequency of breathing have not been kept constant in these studies.

In order to study the effect of drugs on the airway resistance with the aid of the loop area method it is essential to keep the tidal volume and frequency of breathing constant. This has been fully explained in chapter one and three.

We are fully aware of the possibility that the breathing at fixed frequency and tidal volume, being non-physiological, may alter the airway resistance and possibly other mechanical parameters, to an unknown extent. However it should be realized that no adequate clinical method exists today which measures the airway resistance without altering the breathing pattern. The timed vital capacity method requires a highly unphysiological pattern of breathing.

We believe, but cannot prove, that the changes in resistance to breathing caused by the fixed breathing pattern are of negligible extent.

It is not the purpose of this chapter to give new quantitative data on the effect of various drugs and allergens, but merely to demonstrate the sensitivity of this method relative to the spirographic method (vital capacity and timed vital capacity).

Before proceeding we shall give a description of the concept asthma as defined by the Groninger school.

To quote ORIE:

"Both bronchial asthma and eosinophilie bronchitis (asthmatic bronchitis) are considered as an expression of the asthmatic constitution.

Bronchial asthma is a disturbance of the expiration, appearing in attacks, usually accompanied by some inspiratory impairment. The attacks — the character of which is not fully clear — are considered to be caused by a narrowing of the bronchial tubes. This can be effected by swelling of the mucous membranes, by a spasm of the smooth musculature or by alterations in bronchial secretions. The attacks occur in persons who easily react with narrowing of the bronchi after application of acetylcholine or histamine (CURRY 1947 and TIFFENEAU) in doses usually without effect in normal persons. They especially are seen in young adults. As a rule allergic skin and inhalation reactions can be provoked. Some slight physical symptoms and/or lungfunction disturbances can mostly be found between attacks and the patients often expectorate small amounts of mucus during the interval.

In this way there is a gradual transition to:

chronic eosinophilic "bronchitis" or chronic asthmatic bronchitis, which appears predominantly during childhood and early youth as well as in persons of advanced age. Here variations in dyspnoea are present but as a rule no violent attacks are seen. The shortage of breath is of longer duration: during the interval the patient is not completely free from complaints and physical symptoms persist.

Although bronchial infections may repeatedly complicate this state in the same way as they may complicate paroxysmal asthma, they are by no means obligatory or essential."

Infected asthma occurs at all ages especially in combination with asthmatic bronchitis. When dilatations of the airways occur in the course of asthmatic bronchitis the picture of bronchiectasis arises when secundary infection is superposed.

METHODS

The asthmatic patient was placed in a sitting position. After the introduction of the catheter the subject was allowed a few minutes rest. For the determination of the elastance the subject then breathed very slowly over one liter (see chapter on methods).

After this slow effort he inhaled a placebo (coca solution) during ten minutes. After this period, vital capacity, timed vital capacity and viscous work determinations were done; each determination was done two or three times.

The spirometric measurements fell between the viscous work measurements. In this way the "time factor" was eliminated.

The viscous work was determined at a frequency of 15 cycles per minute and a tidal volume of one liter.

"The placebo-measurements" were followed by a period during which the patient inhaled the particular allergen, or drug (histamine-aerosol). After this period N-isopropyl-nor-adrenaline sulfate aerosol was given to some patients.

The patient did not know what substance he was inhaling.

Further details of the method used are given in the chapter on "Methods".

We shall now discuss a few case reports just to illustrate the usefullness of our method in the study of the effect of drugs and allergens in asthmatic cases.

Prior to the actual experiment (but not on the same day) the effect of drugs on the spirometric values was tested. The following drugs and doses were used:

Adrenaline	0.3	cc s.c.
Histamine	0.02	mg i.v.
Acetylcholine	10	mg i.v.
Thiazinamidum	25	mg i.m.

Case I.

J. de V., male, 22.

History: Since early infancy the patient has been suffering from infantile eczema and coughing.

Family: a cousin has asthma while an uncle has a chronic cough.

Physical examination: wheezing over both lungfields with prolonged expiration.

Sputum: predominantly pus (frothy) 100 eo's.

X-ray thorax: heart and lungs show no abnormalities, ribs in elevated position.

Fluoroscopy: diaphragm shows reduced mobility.

Lungfunction: V.C. 2940 cc (calculated V.C. 4650 cc)
V.C. after thiazinamidum 3430 cc (+ 17 %)
TVC 1 sec. 34 %; after thiazinamidum 65 %.

Allergy tests: intracutaneous reactions positive for housedust, moulds, treepollens, grasspollens, hair, feathers, cheese, milk, egg, fish.

Inhalation: positive with house-dust, moulds-, fish-extracts.
Blood esonophilia: 36 × 11.

Results: (table I) Elevated control values.

Inhalation of a 3 % histamine aerosol during one minute causes a doubling of the "standardized" viscous work.

Six minutes after the cessation of histamine inhalation the viscous work is still much above the control value (50 % increase).

Inhalation of N-isopropyl-noradrenaline aerosol during one minute causes the familiar dramatic fall of resistance to breathing as manifested by the reduction of viscous work to about 50 % of the control value.

It is further of interest to note that the dynamic compliance (f = 15,1 liter) which is 0.08 l/cm H_2O after histamine rises to 0.17 l/cm H_2O after N-isopropyl-noradrenaline.

After histamine the timed vital capacity only falls from 37 % to 36 % while the viscous work is doubled. This clearly demonstrates that the TVC 1 sec. may be very misleading and that when spirography is used, the absolute values of both the V.C. and the 1-sec. volume must be considered separately.

TABLE I.

J. de V. 22 yrs	"normal" value	rest	Inhalation coca 10 min.	Inhalation histamine aerosol 3 % 1 min.	6 min. after cessation histamine inhalation	Inhalation isopropyl nor adrenaline aerosol, 1 min. E %
V.C.	4650	3200	3250	2250		3300
1 sec. vol.		1100	1200	825		1625
T.V.C. 1 sec.		34 %	37 %	36 %		49 %
Work 15/1 L in gr. cm	3100	11000	10.500	21.500	17.400	6000
Work % "resting" state		100	95	195	158	54
cm H_2O/l S	4.8	8		12		6
l/cm H_2O C	0.21	0.125		0.08		0.166

Case II.

A.V., male, 43.

History: since 1937 the subject has been suffering from bronchitis. In 1940 he had attacks of dyspnoea of great intensity which lasted a few hours. Since 1956 increasing shortness of breath. In childhood he had been suffering from infantile eczema.

Family: no manisfestation of asthmatic constitution.
cough: on rising, with yellowish, mucoid sputum.
physical exam.: diffuse wheezing.
sputum: pus, gram-negative rods.
X-ray thorax: heart and lungs no abnormalities.
fluoroscopy: reduced diaphragmatic excursions.
lungfunction tests: V.C. 3700 cc (calculated 4550 cc),

Adrenaline effect: + 13 %
Histamine effect: — 29 %
Acetylcholineeffect: — 15 %

TVC 1 sec. 40 %, after thiazinamidum: 61 %.
Allergy tests: intracutaneous reactions positive for flour, moulds, grass-pollens, hair, feathers.
inhalation positive with various forms of flour.
Blood eosinophilia: 58 × 11.

TABLE II

A.V. 43 yrs	"normal" value	"resting" value	coca inhalation 10 min.	Allergen inhalation flour extracts 10 min.	flour extracts allergen inhalation 18 min.	10 min. *after* allergen inhalation
V.C.	4550	4300	4450	3350	3000	2450
1 sec. vol.		1750	1700	1250	950	700
T.V.C. 1 sec.		40 %	38 %	37 %	32 %	29 %
Work 15/1 L in gr. cm	3100	3820	4600	10.800	16.600	58400
Work % of "resting" state		100	121	280	434	1528

Results: (table II). After 10 minutes inhalation of allergen (flour) the viscous work has risen to 280 % of its control value. The TVC 1 sec has only changed from 38 % to 37 %. Here, too, it is seen that the timed vital capacity 1 sec is quite insensitive and that when spirography is used, the absolute values of V.C. and 1-sec. volume must be considered.

It is of interest to note the further rise 10 minutes after cessation of the allergen inhalation.

The viscous work is then 15 times its control value and 3 *times its value directly following cessation of allergen inhalation.*

Case III.

A.K.: male, 37.

History: since infancy he has been suffering from cough and attacks of dyspnoea.

family: brother with asthmatic bronchitis.

X-ray thorax: a few linear strands in left apex, clear lung fields.

fluoroscopy: somewhat reduced diaphragmatic mobility.

sputum: mucoid.

lungfunction: V.C. 4200 cc (calculated 4250 cc), TVC 1 sec. 49 %.*

Allergen tests: positive for inhalation of grasspollen extract.

Results: (table III).

The control value of the viscous work is grossly abnormal. The slightly reduced TVC 1 sec. (60 %) is out of proportion with the greatly increased resistance to breathing as assessed by the viscous work value.

TABLE III

A.K. 37 yrs.	"normal" value	"resting" value	coca inhalation 10 min.	Allergen inhalation grasspollens extracts 10 min.	Inhalation isopropyl nor adrenaline 4 min.
V.C.	4250	4000	4200	2000	3700
1 sec. vol.		2400	2600	800	2050
TVC 1 sec.		60 %	62 %	40 %	55 %
Work 15/1 L in gr cm	3100	15000	9700	42600 over 800 c	27700
Work % of "resting" state		100	64	280	185

* These values were, in general, determined on a different occasion and were obtained during routine examination.

Furthermore, the absolute values of V.C. and 1-sec. volume, 4000 cc and 2400 cc respectively give little more information than the timed vital capacity in this particular example. This stems from the fact that we are now considering deviations from the normal and not relative changes resulting e.g. from the effect of drugs. These relative changes will now be considered.

After a 10-minutes' period of coca inhalation (coca is generally assumed to be inert) the viscous work falls considerably (9700 gr cm) while the TVC 1 sec. improves to 62 % (the improvement is not shown fully by the TVC 1 sec. value since both the V.C. and 1-sec. volume increase).

This improvement demonstrates, by the way, that coca solution is not as inert as is generally assumed.

After a 10-minutes' period of allergen inhalation the viscous work rises dramatically. Since the subject could only breathe over 800 cc the actual value is at least 20 % greater than the 42600 gr cm found.

(In situations of extreme suffocation the subject of course, may not be able to breathe in "standard form". In our series this situation arose but rarely).

Although inhalation of N-isopropyl-noradrenaline during 4 minutes reduces the viscous work to 185 % of the "resting" value, this reduction is much less impressive than the fall after 1 minute N-isopropyl-noradrenaline inhalation seen in the first patient where the viscous work value fell much below the resting value. (table I).

Case IV.

J.P.: male, 48.

History: since 1½ year he has been suffering from nocturnal attacks of dyspnoea.

family: no manifestation of asthmatic constitution.

physical exam.: no abnormalities.

X-ray thorax: heart and lungs are normal.

fluoroscopy: diaphragmatic movements are normal.

sputum: mucoid.

lungfunction: V.C. 3535 cc (calculated 3700 cc), after acetylcholine — 9 %. TVC 1 sec. 69 %.

Allergy tests: intracutaneous positive for pollens, after inhalation of grass-pollensextract, housedust and moulds gradual diminution of the V.C.: the effect, however, was slight and not convincing.

Bloodeosinophilia: 19 × 11.

Results: (table IV)

The "resting"-value is normal.

Coca-inhalation causes a 50 % increase of the viscous work.

After the inhalation of grasspollensextract the viscous work rises to pathologic values, attaining a value 7 times the resting value after a 17 minutes' inhalation period.

The dynamic elastance (at f = 15,1 ltr) rises from 5.5 cm H_2O/liter, to 8.0 cm H_2O/ltr after inhalation of the allergen. This change probably resulted from a diminution of "available" lungvolume caused by local blocking of bronchioles.

TABLE IV

J.P. 43 yrs	"normal" value	"resting" value	coca inhalation 10 min.	Allergen inhalation grasspollens extract 2 min.	Allergen inhalation grasspollens extract 17 min.
V.C.					
1 sec. vol.					
TVC 1 sec.					
Work 15/1 L in gr. cm.	3100	1200	1800	5600	8100
Work % of "resting" state		100	150	466	676
cm H_2O/l S		5.5 d			8 d
l/cm H_2O C		0.181			0.125

Case V:

de B: female, 53.

History: since about a year she has been suffering from nocturnal attacks of dyspnoea.

During the winter months she suffers from cough and expectoration, especially after contact with house dust.

Since the age of 16 she has been suffering from hayfever.

family: no manifestation of asthmatic constitution.

Physical examination: a few sibilant râles.

X-ray thorax: no abnormalities.

Fluoroscopy: no abnormalities.

Sputum: pus, 100 % eo's.

Lungfunction: V.C. 1900 cc (calculated 2825 cc), after adrenaline + 13 %, after histamine (— 31 %), T.V.C. 1 sec. 51 %, after adrenaline 59 %.

Allergy tests: intracutaneous positive for housedust, hair and feathers, slightly positive for moulds.
special hypersensitivity towards: pigshairs and cathairs;
slightly pos. dogshairs
pos.: feathers.
Bloodeosinophilia: 44 × 11.

Results: (table V)

Greatly elevated "resting" value. The effect of allergen inhalation is slight but noticeable in both the viscous work and the spirometry values.

N-isopropyl-noradrenaline inhalation reduces the viscous work to 30 % of the "resting" value.

TABLE V

B. S. de B. 53 yrs	"normal" value	"resting" value	coca inhalation	Allergen inhalation housedust and hair extracts 10 min.	Isopropyl nor adrenaline 2 min.
V.C.	2825	2150	2200	2100	2250
1 sec. vol.		1200	1200	1175	1600
TVC 1 sec.		56 %	54 %	56 %	72 %
Work 15/1 L in gr. cm.	3100	13000	14400	15600	4100
Work % of "resting" state		100	110	120	31

Case VI.

J.L.: male, 15.

History: he has been suffering from dyspnoea since early childhood. During infancy he suffered from infantile eczema.

Since about 6 mounths he has been suffering from attacks of dyspnoea lasting several hours and occurring 2—4 times a month.

family: father is a chronic "cougher", sister suffers from attacks of dyspnoea.

Physical exam.: prolonged expiration.

X-ray thorax: heart and lungs no abnormalities.

Sputum: absent.

fluoroscopy: no abnormalities.

Lungfunction: V.C. 3250 cc (calculated value 3050 cc), after adrenaline

+ 4 %, after histamine — 35 %, after acetylcholine — 22 %.
TVC 1 sec. 36 %, after adrenaline 57 %.

Allergy tests: intracutaneous reactions positive for housedust, grasspollens, hair and feathers.

inhalationtest: positive with grasspollenextract.
Bloodeosinophilia: 167 × 11.

Results: (table VI)

"resting" value definitely abnormal. The allergen effect is moderate (40 % increase of viscous work), while the N-isopropyl-noradrenaline inhalation gives a striking decrease of the resistance to breathing.

The fall of the (dynamic) elastance (at f = 15/1 ltr) after N-isopropyl-noradrenaline is worth noting and is probably fully explained by the opening of "trapped-air areas".

TABLE VI

J. L. 15 yrs	"normal" value	"resting" value	coca inhalation 10 min.	Allergen inhalation grasspollens extracts 10 min.	Inhalation isopropyl nor adrenaline 1 min.
V.C.	3050	3200		3500	3600
1 sec. vol.				1400	1800
TVC 1 sec.				40 %	50 %
Work 15/1 L in gr. cm.	3100	6200	6300	8600	2300
Work % of "resting" state		100	101	140	37
cm H_2O/l S		11 d			7 d
l/cm H_2O C		0.09			0.14

Case VII.

C.W.: female, 22.

History: since the age of four she has been suffering from attacks of dyspnoea and recurrent bronchitis.

The dyspnoea occurs in the morning after rising and is heralded by sneezing, shortness of breath on exertion.

family: father and grand-father chronic "coughers".

Physical exam.: no abnormalities.

X-ray thorax: heart and lungs no abnormalities.
Fluoroscopy: heart and lungs no abnormalities.
Sputum: mucoid and pus, 100 % eo's.
Lungfunction: V.C. 3170 cc (calculated value 3240 cc) after histamine — 12 %, after acetylcholine — 5 %, after adrenaline + 5 %.
TVC 1 sec. 67 %, after adrenaline 72 %.
Allergy tests: intracutaneous positive for housedust, hair, feathers, moulds, pollens.
*inhalation*tests: positive for cathairsextract
negative for housedust and moulds.
Bloodeosinophilia: 66 × 11.

Results:

The "resting" value of the viscous work (and TVC 1 sec.) is moderately abnormal). After inhalation of cathairsextract during 8 minutes the V.C. and TVC 1 sec. remain unchanged while the viscous work has increased by 60 % of its resting value.

Since the changes here are minor it should be mentioned that the tidal volume and frequency have remained strictly the same during the test, so that the 60 % increase must be attributed to an increase in the resistance to breathing.

It is of interest to compare the ½-second vital capacity values as suggested by ORIE (see Chapter X) with the viscous work values. Before allergen inhalation the ½ sec. T.V.C. value (expressed as a percentage of the T.V.C. 1 sec.) is 70 %, while after allergen inhalation the ½ sec. T.V.C. value is 63 %, a change which agrees with the change of the viscous work values.

This finding suggests that the ½ sec. T.V.C. is capable of yielding information masked by the use of the T.V.C. 1 sec.

TABLE VII

C. W. 22 yrs	"normal" value	"resting"	coca inhalation 10 min.	Allergen inhalation cathair extract 2 min.	Allergen inhalation cathair extract 8 min.
V.C.	3240	3400	3400	3400	3400
1 sec. vol.		2200	2350	2300	2200
TVC 1 sec.		65 %	69 %	67 %	65 %
Work 15/1 L in gr. cm	3100	6100	5700	9400	9700
Work % of "resting" state		100	93	154	162

The above examples, randomly chosen, merely served, as stated above, to demonstrate the application of the viscous work method to the study of allergen and drug effects on the resistance to breathing.

Stress was laid on the parallelism between the spirographic and viscous work findings, while the greater sensitivity of the last method has been demonstrated.

Advantages of viscous work method:

1) no (uncontrollable) cooperation required
2) no special exertion required (at f = 15 c/min.)
3) the test can easily be repeated in quick succession without producing fatique.
4) "greater" sensitivity.

We feel that for most routine work the spirographic method is adequate. For more refined studies of this sort the viscous work method is to be preferred.

It goes without saying that the method does not allow us to separate the actual airway component from the over-all resistance which includes the deformation resistance.

The discussion that follows is given to highlight some interesting aspects of the problem studied above.

Discussion.

On the first case studied (table I) the effect of histamine is demonstrated. Although its action is known to be evanescent the viscous work 6 minutes after cessation of histamine inhalation is still 60 % above the "resting" value.

The evanescence of its action on the bronchial tree of asthmatics has been described by SCHERRER e.a. (1956 and 1957), MCILROY and MARSHALL (1956). HALPERN (1950), LOPEZ-BOBET, WYSS, WILBRANDT (1952), PASTEUR e.a. (1950), studied histamine induced "asthma" in guinea-pigs. They conclude on the basis of the rapid reversibility after cessation of histamine inhalation and of the pathological anatomical picture that histamine aerosol does not induce oedema of the bronchial wall.

LOPEZ-BOBET e.a. (1952) found no weight differences between the lungs of normal animals and those of his histamine-treated guinea-pigs. Nor could they, by a more direct method, observe an increase in blood-volume of the histamine-treated lungs.

HALPERN (1950) and SCHERRER e.a. (1957) found that inhalation of adrenaline, N-isopropyl-noradrenaline etc. causes a prompt relieve of histamine "asthma".

These observations speak strongly against the production of oedema during histamine inhalation.

In contradistinction to the fugitive action of histamine, the effect of allergen inhalation has a prolonged and tenacious character. In ovalbumine-sensitized guinea-pigs the relieving action of anti-histamine and adrenaline was found to be slow and incomplete. (HALPERN 1950). These results are probably also applicable to our cases. Once the allergic attack had reached full development, death was certain to follow in spite of stopping the allergen inhalation and administration of adrenaline. At autopsy oedema was found in the bronchial walls.

FRIEBELL, working on guinea-pigs, observes that the dyspnoea may grow worse *after the cessation of allergen inhalation.*

This phenomenon is clearly demonstrated in our second patient. (Table II).

After cessation of the allergen inhalation the viscous work continues to rise, to attain, after ten minutes, a value 3½ times greater than that existing at the moment the allergen inhalation was stopped. (58400 gr. cm against 16600 gr. cm).

The incomplete relieving effect of N-isopropyl-noradrenaline in our third patient (table 3) may (by hypothesis) be attributed to the formation of oedema in the bronchial wall.

This incomplete action may be contrasted with the "overcomplete" action of N-isopropyl-noradrenaline in the histamine treated case (table I), where the viscous work is reduced to below the initial "resting" value.

The prompt and intense effect of N-isopropyl-noradrenaline inhalation in the fifth patient (table 5) throws doubt on the allergic nature of the reaction of the patient towards housedust and hairs extracts. In this case the slight increase of viscous work (accompanied by slight lowering of V.C. and 1-sec. volume) after allergen inhalation may possibly be due to an a-specific reaction, similar to that occasionally observed after coca-inhalation (see second, fourth and fifth patient).

Let us now briefly discuss an interesting question of some importance from the pharmacological standpoint: *is the initial ("resting") value of the resistance of importance in the evaluation of the action of drugs and allergens?*

It would appear that this question should be answered in the affirmative.

Let us take an example.

In our third patient (table 3) the viscous work rises, as a result of allergen inhalation, from 15000 gr cm to 42600 gr cm (over 800 cc: corrected for 1 liter the value is much higher but this is immaterial here).

The greatly elevated resting value (15000 gr cm) indicates the presence of a high resistance to breathing, i.e. pronounced narrowing of the bronchial tree, prior to the administration of allergen (here we ignore, for the sake of argument, the deformation component. The hysteresis component as defined by RADFORD e.a. is negligible in this case). Now, a given decrease of the radius (say, 1 mm) would cause a much greater (relative) increase of the resistance when the radius is small than when the radius is great.

Ignoring turbulence, this easily follows from the relation

$$R = \frac{128.\eta.l}{\pi\, d^4}, \text{ or simply } R = \frac{A}{d^4},$$

where R is the resistance coefficient, A a constant, d = diameter.

Choosing simple figures,* let A = 100, and let the fixed decrease be 1 (cm).

Let in the first case d = 2. The initial resistance is then

$$R = \frac{100}{2^4} = 6{,}25$$

After the decrease of diameter caused, say, by the allergen,

$$R = \frac{100}{1^4} = 100$$

In this case R increases 16 times.

Let in the second case d = 4. The initial resistance is then

$$R = \frac{100}{4^4} = 0{,}25$$

After the decrease of diameter, $R = \frac{100}{3^4} = 1.25$,

so that here R increases only 5 times.

Could we conclude from this example that an allergic reaction (or drug effect) of the *same degree* would cause a much greater change of the resistance when the initial value of the resistance is high than when it is small?

In other words, would an allergen or drug *appear* to be more effective when tested on a narrowed bronchial tree than when tested on a bronchial tree of normal dimensions?

We certainly can not draw such a conclusion from this theoretical example, for the simple reason that we have omitted to *define* such expressions as "effectiveness of a drug or allergen effect", "reaction of the *same* degree" etc.

The crux of the problem is this: how are we to define the strength or intensity of the allergen effect (drugeffect).

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* These figures have no physiological meaning.

If by definition, we state that two reactions are of the *same* degree when the (absolute) change in diameter has the same value, e.g. 1 mm, then the above conclusion is justified.

But such a definition is quite arbitrary and with better justification we might take *relative* change of diameter, or even the relative change of resistance as a measure of reaction equality. In the latter case the problem obviously becomes a tautology.

Choosing relative change of diameter as a measure of equality, we find, using as above, d = 2 and d = 4 as initial diameters and assuming a 50 % decrease of diameter and A = 100 in both cases:

in the first case R changes from $R = \frac{100}{2^4} = 6.25$ to $R = \frac{100}{1^4} = 100$ (16 times).

In the second case R changes from $R = \frac{100}{4^4} = 0.25$ to $R = \frac{100}{2^4} = 6.25$ (25 times).

It is seen that with these premises the resistance changes to a greater extent in the case of the *larger* diameter, i.e. the conclusion is reversed.

The response depends upon the following factors (ORIE, DEFARES);

1° the intensity of the stimulus;

2° the sensitivity of the "tissue" (this term is, following common usage, defined as the slope of the dose-response curve, obtained under *constant* conditions).

3° the physical nature of the stimulus (e.g. smoke, histamine, cold);

4° the nature of the "irritability", e.g. muscular contraction, oedema formation (vascular reaction) etc.;

5° the initial condition; (e.g. presence of broncho-constriction prior to drug inhalation).

The *degree* of initial narrowing is of considerable importance. This may be illustrated by histamine which may shorten the length of the bronchial muscles. When prior to the administration the muscle is already maximally contracted, histamine will, by definition be unable to cause further shortening of the muscle.

The initial narrowing may be caused by a) spasm, b) oedema, or c) a combination of both.

When a spasm-inducing agent acts on oedema-narrowed bronchi it will, in general, be "easier" to induce further narrowing then when this agent acts on spasm-narrowed bronchi.
No semi-quantitative discussion of this item will be attempted.

We have shown that the problem depends on how we define the intensity of the drug effect. *In practice the most reliable way to compare the action of two or more drugs would be to test the drugs on the same subject or subjects.*

It is perhaps pertinent to add that viscous work is not directly proportional to resistance R so that under the same conditions, a doubling of the viscous work does not imply a doubling of the resistance R, even when the frequency and tidal volume are held constant.

For a correct evaluation of the effect of bronchodilators the underlying *cause* of the initial bronchial narrowing is of importance, e.g. it should be known whether the high initial resistance is caused by muscular contraction or by oedema.

E.g. a greatly increased viscous work resulting from histamine inhalation may be dramatically reduced by the administration of adrenaline-like drugs, while high initial viscous work caused by allergens may, due to the presence of oedema, show little reduction after the administration of such substances.

This is illustrated by comparing table I and table III. The effect of N-isopropyl-noardrenaline in a histamine treated case is compared with its effect in an allergen treated case.

It should be noted that the effect in the histamine case is the greater by far. (The profound effect of N-isopropyl-noradrenaline in table V does not contradict the above since the allergens have produced very little effect here, i.e. this case can not be regarded as "allergen treated" in the sense meant above).

Obviously this example is not given to *prove* our statement which is physiologically to obvious to require experimental proof.

A distinction should be made between the preventive use of a drug and its therapeutic use.

In a number of cases the elastance S was determined by letting the patient breathe "slowly", i.e. with a volume flow less than 200 cc/sec over the range of 1 liter (this implies a frequency of 6 cycles/minute, at the highest).

However, most of the subjects were, especially during the induced attack unable to breathe at this slow rate. In the tables I—VII the "static" elastance thus obtained is denoted by the minor letter while the "dynamic" elastance (here measured exclusively at f = 15/1 ltr) is denoted by the letter d.

The changes in elastance observed in some of the cases studied are probably attributable to alterations in "free" lungvolume resulting from obstruction (or opening) of bronchi.

The sensitivity of the viscous work method (when constancy of tidal volume, frequency and "pattern" of breathing are strictly maintained) is shown in table VII, where after 8 minutes allergen inhalation the spirometer values have remained unaltered, while the viscous work has increased by 60 % of its "resting" value.

SUMMARY

The applicability of the "standardized" viscous work as an indicator of the resistance changes in asthmatics induced by allergens and drugs, is demonstrated.

The superior sensitivity of this method, as compared with spirography, is shown.

A further advantage of this method is, that no maximal efforts are required.

CHAPTER XV

Standard viscous work in emphysema.

In this chapter the application of our method to emphysema cases is demonstrated.

According to ORIE emphysema is easy to recognise in clear-cut clinical cases. Exertional expiratory dyspnea in a patient with a permanently distended chest is the most important feature in the clinical picture. The diagnosis must be supplemented by radiological evidence and lungfunction data reflecting the irreversible component.

According to TAMMELING (1958) the enlarged TC constitutes the most significant change of the lung compartment system. According to the same author this enlarged total capacity is specific for emphysema.

Recently a patho-physiological definition has been given by EBERT e.a. (1959) in a special committee report.

In table 1, the clinical data of five emphysema cases are shown. These patients conform to the following criteria (SLUITER, TAMMELING):

1) the thorax excursions are greatly diminished;
2) the thorax is barrel-shaped;
3) the lower lungborders are almost immobile;
4) the diaphragm is low and its motion is greatly reduced;
5) the ribs are horizontal;
6) the air-capacity of the lungs is greatly increased;
7) the subdivisions of the lungs are grossly abnormal;
8) the total capacity is increased.

All our patients studied have histories of asthma, a finding which agrees with literature reports (SEGAL, SLUITER). ORIE stresses the fact that personal and family history, hypersensitivity to acetylcholine and histamine and (partial) improvement after application of drugs all point to a close

association with asthmatic disease. Spontaneous changes in the condition — although less pronounced than in bronchial asthma — point to the same direction.

In chapter XII it was shown that the *normal* viscous work values at $f = 15$ and $V_T = 600$ cc and $V_T = 1.0$ litre are 1400 gr cm and 3100 gr cm respectively.

At $f = 40$, 1 ltr the normal viscous work was found to be 7300 gr cm. The upper limits of normality have been established in chapter XII.

In the cases collected in table I the viscous work values are many times greater than the corresponding normal values.

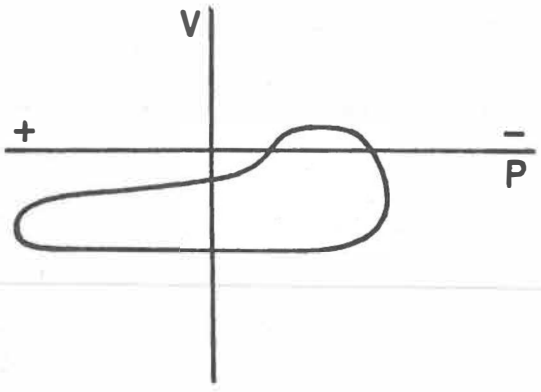

Fig. 1
„Compliance line" in emphysema.

E.g. in patient F.R. the viscous work at 15/600 is 22000 gr cm, which is about 16 times the normal value.

It is of interest to observe that in the last patient the viscous work at 15/600 (4700 gr cm) is "only" 3 times greater than the mean normal value, whereas the timed vital capacity is as low as 20 %.

This apparent discrepancy is explained by the check-valve mechanism that operates in emphysema cases.

Due to the inability of the emphysema patient to produce "sufficiently low" rates of flow combined with the high resistance to breathing, the determination of the compliance value could be made in two cases only (F.R. and J.N.).

In case F.R. the compliance was obtained at a volume flow of about 200 cc/sec. The high compliance value (0.7 1/cm H_2O) suggest the "loss of elasticity". However, as has been explained before, such a conclusion is only warranted when the lungvolume is taken into account.

The rather typical form of the compliance line obtained in emphysema cases under (almost) static conditions deserves brief mention (fig. 1).

This "boot-shaped" loop may probably result from hysteresis (as defined

by RADFORD and MEAD) and dynamic effects. In view of the high resistance to breathing found in emphysema cases, the rate of flow required to reduce the dynamic effects to negligible magnitude drops to values below 100 cc/sec.

Our emphysema patients were unable to produce these low rates of flow. Consequently we have not succeeded in studying the pure hysteresis loops in emphysema cases. Possibly slow breathing may be obtained by having the patient breathe pure oxygen.

TABLE I

Age	Init.	Freq. T.V. 15/600	Freq. T.V. 15/1000	Maximal effort	V.C. measured	V.C. predicted	T.V.C. 1 sec.	S	C	F.R.C. at rest	R.V. % T.C.	T.C.
„normal" value		1400	3100									
42	F.R.	22000		27/500 = 40000	2300	4100	11%	1.5	0.700	75%	50%	5200
56	J.L.	10200		32/600 = 26000	2300	3700	32%			67%	44%	4900
51	J.N.	18500		15/750 = 29000	2000	3700	21%	2.8	0.36	76%	61%	5500
54	G.H.	12300			2200	3800	29%			67%	53%	4700
51	B.	4700	15000		2500	3700	20%			67%	36%	5900

SUMMARY AND CONCLUSIONS

Chapter I: Some of the fundamental principles of lung mechanics are explained. The central concept of this thesis, viz the use of standardized "viscous" work as a measure of pulmonary resistance to breathing is briefly expounded.

Chapter II: When it is desired to obtain a measure of the elastic properties of the lungtissue per se, then the elastance (compliance) does not yield adequate information. This follows from the fact that the compliance depends on both the "elasticity" of the lungtissue and the volume of the lung.

It is shown that an approximate measure of the elastic properties of the tissue of the lungs is obtained by using the equation, $E = SV_0$ where E is the "modulus of elasticity", S is the elastance and V_0 is the lungvolume at zero pleural pressure. It should be stressed that this measure E is approximate only since it is based on a linearization of non-linear system.

It is suggested, however, that this measure of tissue elasticity is theoretically better founded than attempts to use the product or ratio of S or C and measured functional residual capacity ("specific compliance"). The application of the concept E and the sources of error are discussed.

It is shown that in emphysema, where the precise measurement of E is impossible, the value of F.R.C. may be substituted for the initial value V_0 without introducing a significant error, since in emphysema the end-expiratory pleural pressure is close to zero.

In fibrosis and other conditions where the end-expiratory pleural pressure is greatly negative the use of F.R.C. may lead to gross errors. The practical applicability of the concept of E is only briefly explored here and deserves further study.

It should be stressed that a normal E value may be associated with abnormal "elastic" work. This follows from the fact that the "elastic" work varies with the compliance, so that a normal lungelasticity (as assessed by a normal E value) associated with a decreased lungvolume still results in an increased "elastic" work component.

Chapter III: It is shown that at direct single measurement of the "viscous" damping coefficient R is of little value in the evaluation of the resistance to breathing because of the extreme variability of R in one and the same subject.

However, when R is determined under strictly specified conditions, R

may be used as a valid, though incomplete, measure of the overall resistance to breathing (airway + tissue resistance).

An integrated measure of the resistance to breathing is obtained from the pressure volume diagram by keeping the rate of flow constant. This may be effected by having the subject breathe at fixed frequency and tidal volume. The area of th loop thus obtained forms (after subtraction of RADFORD's hysteresis) an unequivocal measure of the resistance to breathing.

In contradistinction to the use of R, the method of standardized viscous work constitutes an overall measure of "viscous" resistance and does not require the use of a pneumotachograph.

It is shown that from the clinical point of view the standardized viscous work possesses significance, not only as a measure of the resistance „R" but as a distinct quantity as well.

Chapter IV: It is shown by comparing the work as computed from the pneumotachogram and the pressure-time curve with the numerical values of the areas of the pressure-volume diagram as obtained with a planimeter, that the total work done during a complete cycle is represented by the area of the loop.

It is further shown that the fact that the work done during a complete cycle is represented by the area of the loop, does not mean that this area (expressed in work units) constitutes the "effort" expended by the respiratory muscles.

The fundamental distinction between "metabolic" work and total work is analysed.

The main purpose of this chapter is to analyse the various components of the work of breathing.

Chapter V: The validity of the esophageal pressure recording as a measure of the pressure across the lungsystem is critically discussed in the light of available literature.

The limitations of the various experimental techniques employed in lungmechanics are discussed.

It is shown that the direct measurement of pleural pressure does not necessarily yield a better measure of transpulmonary pressure than the use of esophageal pressure.

Chapter VI The ROHRER-OTIS theory of mechanical economy has been verified experimentally by CHRISTIE e.a.

It is demonstrated that the method used by CHISTIE e.a. may be inaccurate for the following reasons:

1 the assumption of a constant dead space at all tidal volumes, is unjustified.

2 the assumption of a numerical value for the dead-space (200 cc) may lead to large variations in the true alveolar ventilation at different frequencies.

3 the assumption that the work done on the lungsystem alone, may be used to evaluate "muscle economy" is unvalid.

From this it follows that the ROHRER-OTIS theory of work-economy still awaits experimental verification.

Chapter VII: This chapter contains the discussion of the experimental method and the discussion of errors.

Chapter VIII: It is shown theoretically that frequency dependent compliance may be used as an index of unequal ventilation when, and only when, $E_1/R_1 = E_2/R_2 = \ldots = E_n/R_n$, where E is modulus of elasticity, R = resistance and the indices refer to the parallel pathways. Since it is of course impossible to verify whether these equalities exist in a particular case, it is concluded that the finding of frequency dependent compliance gives no information on the actual occurrence of unequal ventilation.

The theoretical conclusions have been substantiated experimentally.

Four subjects from a group of 100 normal subjects studied were found to have pronounced frequency dependency of their effective compliance values. In all four subjects no evidence of unequal ventilation, as assessed by nitrogen wash-out curves, was found.

It is concluded that theoretical and experimental evidence refutes the hypothesis that the phenomenon of frequency dependent compliance may be used as an index of unequal ventilation.

The results discussed in this chapter appear as an "official" publication in the November issue (1959) of the Journal of Applied Physiology.

Chapter IX: The changed tidal volume ratio that may occur during lateral position is not due to bloodshift, but results from the combined effect of unbalance of excursions on both sides and low compliance of the mediastinum.

Whenever unbalance between overall excursions on both sides exists, the esophageal pressure may not be a correct measure of the pressures across the lungs.

From this it follows that the esophageal pressure measurement should not be used in the lateral lying position.

Chapter X: By comparing "standard viscous work" values, with one second timed vital capacity values, it was found that in some pathological cases a pronounced discrepancy exists between results obtained with the two methods. On the basis of case histories the limitations of the timed vital capacity method are discussed.

It is stressed that in contradistinction with the "standard viscous work" method, the timed vital capacity method does not differentiate between resistance to breathing at normal flow rates and at high flow rates, the T.V.C.-method measuring resistance at high flow rates, the T.V.C.-method measuring resistance at maximal flows only.

Chapter XI: The compliance C (elastance S) was determined in 44 healthy males and 33 healthy females, the ages ranging between 15 and 65 years.

It was found that the best estimate of the mean value of the compliance is 0.21 l/cm H_2O for males and 0.16 l/cm H_2O for females, and the mean value of the elastance S is 4.8 cm H_2O/l for males and 6.3 cm H_2O/l for females.

Our main finding is that the compliance is unaffected by age (15 years and older) in both males and females.

Chapter XII The "viscous work" at fixed frequency and tidal volume was determined in 77 normal subjects. The sample consisted of 44 males and 33 females, the ages ranging between 15 and 65 years.

The determinations were made at a frequency of 15 and 40 cycles/minute, over a tidal volume of 0.6 and 1.0 litre.

The normal values of standard viscous work are given. Obviously knowledge of these normal values is essential for the clinical applicability of the "standardized viscous work" method.

The difficulties of establishing normality are discussed.

Chapter XIII: The influence of pulmonary and extra-pulmonary factors on the shape of the static volume-pressure diagram is discussed.

It is shown that the shape of the "compliance line" offers a means of differentiating between reduced thoracic mobility (as in ankylosing spondylitis, poliomyelitis) and lung "stiffness" as a factor limiting expiratory reserve volume and thus vital capacity.

The clinical significance of the shape of the "compliance line" is discussed.

Chapter XIV: The applicability of the "standardized viscous work method" as a measure of the resistance changes in asthmatics induced by allergens and drugs, is demonstrated.

The suggested superior sensitivity of this method, as compared with spirography, is shown. A further advantage of this method is that no maximal efforts are required, while the test can easily be repeated in quick succession without producing fatigue.

Chapter XV: In this chapter the results are given of the values of standardized viscous work in five emphysema patients.

SAMENVATTING

Dit proefschrift behandelt bepaalde pathophysiologische aspecten van de longmechanica zowel uit theoretisch als uit klinisch oogpunt.

Hoofdstuk I: In dit hoofdstuk worden enkele grondbeginselen van de longmechanica uiteengezet.

Het grondthema van dit proefschrift, n.l. het gebruik van de *gestandariseerde* visceuze ademarbeid als maat van de ademweerstand wordt in het kort besproken.

Hoofdstuk II: Omdat de elastance (compliance) afhankelijk is, zowel van de elasticiteit van het longweefsel als van het longvolume, kan deze grootheid niet als maat gebruikt worden voor de elastische eigenschappen van het longweefsel als zodanig.

Langs theoretische weg wordt afgeleid dat de meest nauwkeurige maat voor de elastische eigenschappen van het longweefsel verkregen wordt door toepassing van de vergelijking $E = S\ (F.R.C.) - P_e$, waarin E = elasticiteitsmodulus, S = elastance, F.R.C. = gemeten functionele residu en P_e = de pleuradruk die bestaat op het einde van een normale uitademing.

Een normale E houdt echter niet in dat de elastische ademarbeid noodzakelijk normaal moet zijn. Immers de elastische arbeid is afhankelijk van de compliance, zodat een normale longelasticiteit (normale E) bij verkleind longvolume (b.v. na resectie) door rekking een verhoogde elastische arbeid tot gevolg heeft.

Hoofdstuk III: Aangetoond wordt dat een enkele bepaling van de coëfficient R van de visceuze ademweerstand van weinig waarde is voor een juiste beoordeling van de grootte van deze ademweerstand door de grote variabiliteit van R in één en dezelfde persoon.

Indien echter bij de bepaling van R aan bijzondere voorwaarden wordt voldaan, kan R gebruikt worden als een goede, zij het onvolledige, maat van de gehele visceuze ademweerstand (luchtwegweerstand + weefseldeformatie weerstand).

Het druk-volume diagram, verkregen bij een constant gehouden stroomsterkte, kan cen zuivere maat voor de visceuze ademweerstand verschaffen.

Een dergelijk druk-volume diagram kan verkregen worden door de proefpersoon te laten ademen met vastgestelde ademfrequentie en bepaald ademvolume. De oppervlakte van de aldus verkregen lus (na aftrek van RADFORD's hysteresiscomponent) blijkt een verantwoorde maat te zijn voor de ademweerstand, in tegenstelling tot de coëfficient R, terwijl bovendien dan geen gebruik behoeft te worden gemaakt van een pneumotachograaf.

Hoofdstuk IV: Door de grootte van de ademarbeid, berekend uit het pneumotachogram en de druk-tijd curve, te vergelijken met de numerieke waarden verkregen door planimetrie van de oppervlakken van bet druk-volume diagram, blijkt dat de totale ademarbeid van 1 ademhalingscyclus voorgesteld kan worden door de oppervlakte van de "ademlus". Dit feit houdt echter niet in dat deze oppervlakte (uitgedrukt in arbeidseenheden) tevens de totale energie voorstelt, die door de ademhalingsspieren opgebracht moest worden.

Het fundamentele verschil tussen "metabole" arbeid en totale arbeid wordt uiteengezet.

Dit hoofdstuk heeft hoofdzakelijk tot doel een analyse tc geven van de verschillende componenten van de ademarbeid.

Hoofdstuk V: Aan de hand van literatuurgegevens wordt aangetoond dat de esophagusdruk een juiste maat is voor dc transpulmonaire druk. Er wordt echter op gewezen dat de directe meting van de pleuradruk geen betere maat oplevert voor de transpulmonaire druk dan de oesophagus druk.

De beperkte mogelijkheden van de verschillende in de longmechanica toegepaste onderzoekingsmethoden worden besproken.

Hoofdstuk VI: De theorie van ROHRER-OTIS betreffende de mechanische economie werd experimenteel geverifieerd door CHRISTIE e.a.

De methode door CHRISTIE e.a. gebruikt, is echter om de volgende redenen onnauwkeurig:

1 het aannemen van een constante dode ruimte bij een wisselende grootte van het ademvolume is niet gerechtvaardigd.

2 het aannemen van een bepaalde numerieke waarde voor de dode ruimte (200 cc) kan leiden tot grote afwijkingen van de ware alveolaire ventilatie bij verschillende ademfrequenties.

3 het is niet juist dat de arbeid verricht aan het longsysteem gebruikt mag worden als maatstaf voor de "spier-economie".

Aangetoond wordt dat resultaten gebaseerd op bovenstaande veronderstellingen niet als bewijs kunnen worden gebruikt voor de theorie van ROHRER-OTIS. Met andere woorden, de theorie van ROHRER-OTIS betreffende arbeidseconomie moet alsnog experimenteel geverifieerd worden.

Hoofdstuk VII: Dit hoofdstuk behandelt de toegepaste methodiek, de apparatuur en de fouten discussie.

Hoofdstuk VII: Langs theoretische weg wordt afgeleid dat de frequentie-afhankelijkheid van de compliance alleen dan een bewijs is voor het bestaan van een ongelijkmatige ventilatie indien voldaan wordt aan de betrekking $\frac{E_1}{R_1} = \frac{E_2}{R_2} = \ldots \frac{E_n}{R_n}$, waarin E de elasticiteitmodulus en R de weerstand voorstelt.

Omdat het uiteraard onmogelijk is na te gaan of aan deze voorwaarde in een bepaald geval wordt voldaan, wordt de conclusie getrokken dat het vinden van een frequentie afhankelijke compliance niet behoeft te betekenen dat er tevens een ongelijkmatige ventilatie bestaat.

Deze conclusie wordt experimenteel bewezen. Vier personen uit een groep van 100 gezonde proefpersonen bleken een uitgesproken frequentie afhankelijke compliance te hebben. In geen van deze 4 proefpersonen echter, kon met behulp van stikstof uitwas curves het bestaan van ongelijkmatige ventilatie worden aangetoond.

Op grond van theoretische beschouwingen en experimentele bevindingen wordt dan ook de hypothese weerlegd dat een frequentie afhankelijke compliance bewijzend is voor het bestaan van ongelijkmatige ventilatie.

Hoofdstuk IX: De verandering in de verhouding van de ademvolumina, zoals deze kan optreden in zijligging, wordt niet veroorzaakt door een verandering van de verdeling van het bloedvolume van de longen, maar is het gevolg van de combinatie van de bij zijligging optredende ongelijke diafragma excursie rechts en links en de geringe compliance (soepelheid) van het mediastinum.

Bij het voorkomen van een aan beide zijden ongelijke diafragma excursie is de oesophagusdruk geen juiste maat voor de transpulmonaire druk. De oesophagusdruk moet dus nimmer in zijligging gemeten worden.

Hoofdstuk X: Bij vergelijking van de resultaten verkregen met het onderzoek, waarbij gebruik gemaakt wordt van de gestandariseerde visceuze ademarbeid, en de spirografische methode (1 sec. waarde volgens TIFFENEAU) werd in enkele normale en pathologische "gevallen" een uitgesproken discrepantie gevonden.

Aan de hand van ziektegeschiedenissen wordt de beperktheid van de spirografische methode besproken. De nadruk wordt gelegd op het feit dat in tegenstelling tot de eerste methode, de spirografische methode niet differentieert tussen ademweerstand bij normale stroomsterkte en bij hoge stroomsterkte, daar de weerstand alleen gemeten word bij maximale stroomsterkten.

Hoofdstuk XI: De elastance S (compliance C) werd bepaald bij 44 gezonde mannen en 33 gezonde vrouwen, waarvan de leeftijden lagen tussen 15 en 65 jaar.

Zowel bij vrouwen als bij mannen bleek met behulp van de t-toets, dat geen significant verschil tussen ouderen (45 jaar en ouder) en jongeren bestaat t.a.v. de elastance. De elastance bij mannen is significant verschillend van die bij vrouwen.

De beste schattingen voor gemiddelde S zijn:
bij mannen gemiddeld 4.8 cm H_2O/l,
bij vrouwen gemiddeld 6.3 cm H_2O/l,
en voor de compliance C:
bij mannen gemiddeld 0.21 l/cm H_2O,
bij vrouwen gemiddeld 0.16 l/cm H_2O.

Hoofdstuk XII: Bij 77 "gezonde" proefpersonen werd de visceuze ademarbeid telkens bepaald bij een ademhalingsfrequentie van 15 en 40 ademhalingen per minuut met ademvolume van 0.6 l en 1 l.

De groep proefpersonen bestond uit 44 mannen en 33 vrouwen, wier leeftijden varieerden van 15 tot 65 jaar.

Besproken worden de moeilijkheden bij het vaststellen van wat onder "gezond" moet worden verstaan en de soms tamelijk arbitraire criteria, hierbij gebruikt.

De normale- en grenswaarden van de visceuze ademarbeid worden gegeven.

Hoofdstuk XIII: In dit hoofdstuk wordt de invloed van "long" en extrapulmonaire factoren besproken op de vorm van het statische druk volume diagram.

Aangetoond wordt dat de vorm van het statische druk volume diagram, de z.g. "compliance lijn", een mogelijkheid biedt om bij verkleining van de V.C. te kunnen differentieren tussen een verminderde thorax beweeglijkheid (zoals bij M. BECHTEREW en poliomyelitis) en "stugheid" van de long als oorzakelijke factoren.

Hoofdstuk XIV: De gestandariseerde visceuze ademarbeid blijkt een duidelijke maat te verschaffen voor de wisseling in grootte van de ademweerstand bij asthma-patiënten na toediening van allergenen en pharmaca. De grotere gevoeligheid van de methode waarbij gewerkt wordt met gestandariseerde visceuze ademarbeid in vergelijking met de spirografische methode wordt aangetoond. Bovendien heeft de methode het voordeel dat van de patiënt geen maximale krachtsinspanning wordt gevraagd terwijl het onderzoek gemakkelijk in snelle opeenvolging herhaald kan worden zonder vermoeidheid te veroorzaken.

Hoofdstuk XV: In dit hoofdstuk worden de resultaten besproken die verkregen zijn met de gestandariseerde visceuze ademarbeid methode bij 5 emphyseempatiënten.

Literature

ARNOTT, W. M.: Order and disorder in pulmonary function. Brit. med. J. 279:7 1955.

ATTINGER, E. O. and SEGAL, M.: The mechanics of breathing in: Clinical Cardiopulmonary Physiology. Grune and Stratton, London 1957.

BAYLISS, L. E. and ROBERTSON, G. W.: The visco-elastic properties of the lungs. Quart. J. exper. Physiol. 29: 27, 1939.

BATEMAN, J. B.: Alveolar air, respiratory dead space, and the "ventilation index." Proc. Soc. exper. Biol. N.Y. 73: 683, 1950.

BERG, J. W. VAN DEN, and DEFARES, J. G.: in preparation.

BERNSTEIN, L., D'SILVA, J. L. and MENDEL, D.: The effect of the rate of breathing and the maximum breathing capacity determined with a new spirometer. Thorax 7: 255, 1952.

BOOY-NOORD, H., ORIE, N. G. M., TEN CATE, H. J., SLOOTS, S. and BOLT: The influence of various drugs on the vital capacity of asthmatics. Int. Arch. Allergy, Basel 10: 321, 1957.

BOUHUYS, A.: Pneumotachografie. Med. Thesis, Amsterdam 1956.

BRISCOE, W. A. and DUBOIS, A. B.: The relationship between airway conductance and lungvolume. XXe Congrès International de Physiologie, p. 256. Bruxelles, 1956.

BRONKHORST, W. and DIJKSTRA, C.: Das neuromuskuläre System der Lunge. Anatomische und physiologische Untersuchungen über die Lungenmuskulatur und ihre Bedeutung für die klinik der Tuberkulose. Beitr. Klin. Tuberk. 94: 445, 1940.

BROOKHART, J. M. and BOYD, T. E.: Local differences in intrathoracic pressure and their relation to cardiac filling pressure in the dog. Amer. J. Physiol. 148: 434, 1947.

BÜHLMANN, A. und BEEN, H.: Klinische Ergebnisse atemmechanischer Untersuchungen. Schweiz. med. Wschr. 87: 1500, 1957.

BUTLER, J. and ARNOTT, W. M.: The work of pulmonary ventilation at different respiratory levels. Clin. Sci 14: 703, 1955.

BUYTENDIJK, H. J.: Oesophagusdruk en longelasticiteit. Med. Thesis, Groningen, 1949.

CARA, M.: Etudes sur la fonction respiratoire. Le Poumon, 1958.

CATE, H. J. TEN: Onderzoek bij asthmapatienten naar overgevoeligheid voor verstoven allergeenextracten. Med. Thesis, Groningen, 1954.

CHERNIACK, R. M., FAHRI, L. E., ARMSTRONG, B. W. en PROCTOR: A comparison of esophageal and intrapleural pressure in man. J. appl. Physiol. 8: 203, 1955.

CHRISTIE, R. V. and MCINTOSH, C. A.: The measurement of the intrapleural pressure in man and its significance. J. clin. Invest. 13: 279, 1934.

—— Dyspnoea in relation to the visco-elastic properties of the lung. Proc. roy Soc. Med. 46: 381, 1953.

OTIS, A. B.: The work of breathing. Physiol. Rev. 34: 449, 1954.

COLERIDGE, J. C. G. en LINDEN, R. J.: The measurement of effective atrial pressure. J. Physiol., Lond. 126: 304, 1954.

COLLDAHL, H.: A study of provocation tests on patients with bronchial asthma.
1) the reliability of provocation-tests performed under different conditions. Acta allerg. 5: 133, 1952.
2) the outcome of provocation-tests with different antigens. Ibid. 5: 143, 1952.
3) the interpretation of the provocation-tests and the value of the tests for allergy diagnosis and treatment. Ibid. 5: 154, 1952.

COMROE, J. H., JR., FORSTER, R. E., DUBOIS, A. B., BRISCOE, W. A. en CARLSEN, E.: The lung. Clinical physiology and pulmonary function tests. Chicago: The Year Book Publishers, Inc., 1955.

COOK, CHARLES, D., CHERRY, R. B., O'BRIEN, D., KARLBERG, P. and SMITH, C. A., Studies of respiratory physiology in the newborn infant. I. observation on normal premature and fullterm infants. J. clin. Invest. 34: 975, 1955.

COURNAND, A., BROCK, H. J., RAPPAPORT, I., RICHARDS, D. W.: Disturbance of action of respiratory muscles as a contributing cause of dyspnoea. Arch. intern. Med. 57: 1008, 1936.

CURRY, J. J.: Comparative action of acetyl-beta-methyl choline and histamine on the respiratory tract in normals, patients with hay fever and subjects with bronchial asthma.
J. clin. Invest. 26: 430, 1947.

DAYMAN, H.: Mechanics of airflow in health and in emphysema. J. clin. Invest. 30: 1175, 1951.

DEAN, R. B. en VISSCHER, M. B.: The kinetics of lung ventilation. An evaluation of the viscous and elastic resistance to lung ventilation with particular reference to the effects of turbulence and the therapeutic use of helium.
Am. J. Physiol. 134: 450, 1941.

DEFARES, J. G. and VAN DEN BERG, J. W.: to be published.

—— and WISE, M. E.: A mathematical analysis of unequal ventilation of the lungs based on a model containing two seperate and a common dead space. Bulletin of Mathematical Biophysics (in press).

DISSMAN, E.: Zur Frage von Eigenrhytmus und Grundrhytmus in der Tagesschwankungen der Vitalkapazität. Acta med. scand. 137: 441, 1950.

DOUGLAS, C. G. and HALDANE, J. S.: The capacity of the air passages under varying physiological conditions. J. Physiol. Lond. 45: 235, 1912.

DORNHORST, A. C. and LEATHORST, G. L.: A method of assessing the mechanical properties of lungs and air-passages. Lancet 263: 109, 1952.

D'SILVA, J. L. and MENDEL, D.: The maximum breathing capacity test. Thorax 5: 325, 1950.

DUOMARCO, J. L., RIMINI, R. and MIGLIARO, J. P.: Intraesophageal pressure and the local differences in pleural pressure. Acta Physiol. lat. amer. 4: 133, 1954.

DIJKSTRA, C.: Ueber die innervation der Lungen. Beitr: Klin. Tuberk. 92: 445, 1939.

EBERT, RICHARD V., BATES, D., FISHMAN, ALFRED P., FOWLER, WARD S., PRATT, PHILIP C.: Report of committee on definition of emphysema. Amer. Rev. Resp. Dis. 80: 114, 1959.

FARHI, L., OTIS, A. B. en PROCTOR, D. F.: Measurement of intrapleural pressure at different points in the chest of the dog. J. appl. Physiol. 10: 15, 1957.

FENN, W. C.: Mechanics of respiration. Am. J. Med. 10: 77, 1951.

FISHMAN, A. P.: Respiratory dead space and alveolar gascomposition. J. Clin. Invest. 33: 469, 1954.

FOSTER, C. A., HEAF, P. J. D. and SIMPLE, S. J. G.: Compliance of the lung in anaesthetized paralyzed subjects. J. appl. Physiol. 11: 383, 1957.

FOWLER, W. S., CORNISH, E. R. and KETY, S. S.: lungfunction studies VIII. analysis of alveolar ventilation by pulmonary N_2 clearance curves. J. clin. Invest. 31: 40, 1952.

FRANK, N. R., MEAD, J., SIEBENS, A. A. en STOREY, C. F.: Measurements of pulmonary compliance in seventy healthy young adults. J. appl. Physiol. 9: 38, 1956.

FRANK, N. R., MEAD, J. en FERRIS, JR. B. G.: The mechanical behaviour of the lungs in healthy elderly persons. J. clin. Invest. 36: 1680, 1957.

FRIEBEL, H.: Ueber das experimentelle allergische asthma der Meerschweinchen und seine Beziehungen zum.Asthma des Menschen. Int. Arch. Allergy 5: 401, 1954.

FRY, D. L., STEAD, W. W., EBERT, R. V., LUBIN, R. I. en WELLS, H. S.: The measurement of intraesophagic pressure and its relationship to intrathoracic pressure. J. Laborat. clin. Med. 40: 664, 1952.

—— HYATH, R. E. MCCALL, CH and MALLOS, A. J.: Evaluation of three types of respiratory flowmeters. J. appl. Physiol. 10: 210, 1957.

GAENSLER, E. A.: Analysis of the ventilatory defect by timed capacity measurements. Amer. Rev. Tuberc. 64: 256, 1951.

GRAY, J. S., GRODIUS, F. S. and CARTER, E. T.: Alveolar and total ventilation and the dead space problem. J. appl. Physiol. 305: 9, 1956.

GROSSE-BROCKHOFF, F. und SCHOEDEL, W.: Der effektive schädliche Raum. Pflügers Arch. ges. Physiol. 238: 213, 1937.

HALDANE, J. S.: The variations in the effective dead space in breathing. Amer. J. Physiol. 38: 20, 1915.

HALPERN, D. N.: L'asthma experimental. Rapports du 2e congrès international de l'asthma. Le Mont-Dore, Juin 1950.

HART, J. S.: Resistance to breathing, in symposion on Physiology of respiration as applied to aviation equipment. mem. Rep. A.A.F.A.T.S.C., Aero Med. Lab. T.S.E.E.A.-660-83-E, 1946.

HARTING, W.: Ueber die Bestimmung der Lungelastizität an der isolierten Leichenlunge. Beitr. path. Anat. 117: 1, 1957.

HEEMSTRA, H. and SLAGTER, B.: Interpretation of esophageal pressure and of „alveolar" pressure obtained by the interruption method. Acta physiol. pharmacol. neerl. 4, 1955.

—— Lecture delivered during the Philips international conference on pulmonary function. Nijmegen, Holland. May 1957.

—— Mechanische eigenschappen van de gezonde en zieke long. Ned. tschr. geneesk. 101: 736, 1957.

HENDERSON, Y., CHILLINGWORTH, F. P. and WHITNEY, J. L.: The respiratory dead space. Americ. J. Physiol. 38: 1, 1915.

HERSCHFUS, J. A., RUBILSKY, H. J., BEAKY, J. F., BRESNICK, E., LEVINSON, L. and SEGAL, H. S.: Evaluation of therapeutic substances employed for the relief of bronchial asthma. Int. Arch. Allergy. 2: 97, 1951.

HERXHEIMER, H.: Bronchial obstruction induced by allergens, histamine and acetyl-

—— Induced asthma in man; Lancet 1: 1337, 1951.

HERXHEIMER, H.: Induced asthma in man; Lancet 1: 1337, 1951.

HIRDES, J. J. and VEEN, G. VAN: Spirometric Lungfunction Investigations. The form of the expiration curve under normal and pathological conditions. Acta tuberc. scand. 26: 264, 1952.

HUIZINGA, E.: Ueber die Physiologie des Bronchial Baumes. Pflügers Arch. ges. Physiol. 238: 766, 1937.

—— Over de physiologie van den bronchialen boom. Ned. T. Geneesk. 81: 3829, 1937.

—— De l'anatomie et de la physiologie de l'arbre bronchique. Acta otolar, Stockh. 26: 182, 1948.

—— Ueber die Entstehung der Bronchiectasie. Acta radiol. Stockh. 29, 1940.

—— personal comm. 1959.

JOHNSON, H. E., MCNEELY, G. R.: Constrictive chest conditions, in clinical Cardiopulmonary Physiology. Grune & Stratton, London 1957.

KING, A. L. and LAWTON, R. W.: Elasticity of body tissues, in O. Glaser: Ed. med. Phys. vol. 2. Yearbook Publishers Chicago 1950.

KROGH, A. and LINDHARD, J.: The volume of dead space in breathing. J. Physiol. Lond. 47: 30, 1913.

LAROS, C. D.: De prognose van de pneumonectomiepatient. med. Thesis Groningen 1956.

LAWTON, R. W. and JOSLIN, D.: measurements on the elasticity of the isolated rat lung. Am. J. Physiol. 167: 111, 1951.

LIM, THOMAS P. K., LUFT, ULRICH and GRODIUS, FRED. S.: Effects of cervical vagotomy on pulmonary ventilation and mechanics. J. appl. Physiol. 13: 317, 1958.

—— THOMAS P. K. and LUFT, ULRICH: Alternations in lungcompliance and functional residual capacity with posture. J. appl. Physiol. 2: 164, 1995.

LOPEZ-BOTET, E., WYSS, F. und WILBRANDT, H.: Untersuchungen über das experimentelle Histamine asthma beim Meerschweinchen. Helv. med. Acta. 19: 218, 1952.

LÖWËNBERG, A.: Causes of coughing in a Groningen general practice. med. Thesis Groningen 1959.

LUNDIN, G.: Nitrogen elimination during oxygen breathing. Acta physiol. scand. 130: 111, 1953.

MACK, I., GRASSMANN, M. I. and KATZ, L. N.: Pulmonary congestion and distensibility of lungs. Amer. J. Physiol. 150: 654, 1947.

MANN, Z.: Effect of lateral recumbency on pulmonary function. Diseases of the Chest 550: 5, 1958.

MASSION, W. H.: Effects of curare on elastic properties of chest and lungs of the dog. J. appl. Physiol. 11: 309, 1957.

MC ILROY, M. B. and CHRISTIE, R. V.: A post mortem study of the visco-elastic properties of normal lungs. Thorax 7: 29ij, 1952.

—,—, MARIHALL, R. en CHRISTIE, R. V.: The work of breathing in normal subjects. Clin. Sci 13: 127, 1954.

—— en TOMLINSON, E. S.: The mechanics of breathing in newly born babies. Thorax 10: 58, 1955.

—— en MARSHALL, R.: The mechanical properties of the lungs in asthma. Clin. Sci 15: 345, 1956.

MILLS, J. N.: Variability of the vital capacity of the normal human subject. J. Physiol. Lond. 110: 76, 1949.

MUNDT, E., SCHOEDEL, W. und SCHWARZ, N.: Ueber den effektiven schädlichen Raum der Atmung. Pflügers Arch. ges. Physiol. 244: 107, 1941.

MEAD, J. en WHITTENBERGER, J. L.: Physical properties of human lungs measured during spontaneous respiration. J. appl. Physiol. 5: 779, 1952/53.

—— en WHITTENBERGER, J. L.: Evaluation of airway interruption technique as a method for measuring pulmonary air-flow resistance. J. appl. Physiol. 6: 408, 1953/54.

—— MC ILROY, M. B. SELVERSTONE, N. J. en KRIETE, B. C.: Measurement of intraesophageal pressure. J. appl. Physiol. 7: 491, 1954/55.

—— Measurement of inertia of the lungs at increased ambient pressure. J. appl. Physiol. 9: 208, 1956.
—— WHITTENBERGER, J. L. en RADFORD, E. P.: Surface tension as a factor in pulmonary volume-pressure hysteresis. J. appl. Physiol. 10: 191, 1957.

NEERGAARD, K. v. en WIRZ, K.: Die messung der Strömungswiderstände in den Atemwegen des Menschen, insbesondere bei Asthma und Emphysem. Z. klin. Med. 105: 51, 1927.

NISELL, O. I. and DUBOIS, A. B.: Relationship between compliance and F.R.C. of the lungs in cats, and measurement of resistance to breathing. Am. J. Physiol. 178: 111, 1951.
—— en EHRNER, L. S. G.: A simple apparatus for the measurement of pressure volume relationship in respiration. J. appl. Physiol. 8: 565, 1956.

NIMS, R. G., CONNER, E. H. and COMROE JR., J. H.: The compliance of the human thorax in anaesthetized patients. J. clin. Invest. 34: 744, 1955.

NOELPP, B. and NOELPP-ESHAREN, I.: Das experimentelle Asthma bronchiale des meerschweinchens. Int. Arch. Allergy 3: 302, 1952.
—— and NOELPP-ESCHENHAGEN, I. and LOTTENBACH, K.: Das Verhalten der experimentellen asthmatiformen Dyspnoe. Int Arch. Allergy. 5: 245, 1954.

OGILVIE, C. M., STONE, R. W. and MARSHALL, R.: The mechanics of breathing during the maximum breathing capacity test. Clin. Sci 14: 101, 1955.

OLIVIER, H. R. and DRUTEL, P.: Etude spirographique d'une expiration forcée. Ann. Biol. clin. 7: 343, 1949.

ORIE, N. G. M.: personal comm.
—— unpublished data.
—— Pulmonary tuberculosis and asthmatic bronchitis. Proc. Tuberc. Research Council. 44, 1957.

OTIS, A. B. en PROCTOR, D. F.: Measurement of alveolar pressure in human subjects. Amer. J. Physiol. 152: 106, 1948.
—— FENN, W. O. en RAHN, H.: Mechanics of breathing in man. J. appl. Physiol. 2: 592, 1949/50.
—— MCKERROW, C. B., BARTLETT, R. A., MEAD, J., MCILROY, M. B., SELVERSTONE, N. J. en RADFORD, E. P.: Mechanical factors in distribution of pulmonary ventilation. J. appl. Physiol. 8: 427, 1956.
PETERS, J. P. and SLIJKE, DONALD D. VAN: Quantitative clinical chemistry. Bailliere, Tindall and Cox, London 1955.

PAPPENHEIMER, J. R., FISHMAN, A. P. and BORRERO, L. M.: New experimental methods for determination of effective alveolar gas composition and respiratory dead space, in the anaesthetized dog and in man. J. appl. Physiol. 4: 855, 1952.

PASTEUR VALLERY-RADOT, HALPERN, B. N., DUBOIS DE MONTREYNAUD, J. M. en PÉAN, V.: Les bronches au cours de la crise d'asthma. Etude expérimentale, bronchoscopique et anatomopathologique. Presse méd. 58: 601, 1950.

PEMBERTON, J. and FLANAGAN, ELISABETH G.: Vital capacity and timed vital capacity in normal men over forty. J. appl. Physiol. 9: 291, 1;56.

PIERCE, J. A. en EBERT, R. V.: The elastic properties of the lungs in the aged. J. Lab. clin. Med. 51: 63, 1958.

QUIGLEY, J. P.: Medical Physics. ed. by O. Glaser. 310, 1955. Yearbook Publishers Chicago.

RADFORD, E. P., LEFCOE, N. en MEAD, J.: Factors governing longterm (static) pressure-volume characteristics of the lungs. Fed. Proc. 13: 114, 1954.

RAHN, H., OTIS, A. B., CHADWICK, L. E. en FENN, W. O.: The pressurevolume diagram of the thorax and lung. Amer. J. Physiol. 146: 161, 1946.

—— FENN, W. O. and OTIS, A. B.: Daily variations of vital capacity, residual air and expiratory reserve including a study of the residual air method. J. appl. Physiol. 1: 725, 1949.

RAU, G., BEHN, H., GERHART, W., ROSSIER, P. H. en BÜHLMANN, A.: Atemmechanische Untersuchungen am Lungenmodell, bei Lungengesunden und bei Patienten mit obstruktivem Emphysem. Schweiz, med. Wschr. 87: 374, 1957.

RILEY, R. L. and COURNAND, A.: „Ideal" alveolar air and the analysis of ventilation-perfusion relationships in the lungs. J. appl. Phys. 1: 825, 1949.

RITSEMA VAN ECK, C. R.: Personal comm.

SOKOLNIKOFF, I. S.: Mathematical theory of elasticy. Mc. Graw. Hill Book Cy. N.Y. 1946.

ROHRER, F.: Der strömungswiderstand in den menschlichen Atemwegen und der Einfluss der unregelmässigen Verzweigung des Bronchialsystems auf den Atmungsverlauf in verschiedenen Lungenbezirken. Pflügers Arch. ges. Physiol. 162: 225, 1;15.

—— Der Zusammenhang der Atemkräfte und ihre Abhängigkeit vom Dehnungszustand der Atmungsorgane. Pflügers Arch. ges. Physiol. 165: 421, 1916.

—— NAKASONE, K. en WIRZ, K.: Physiologie der Atmung, in: BETHE, A., BERGMANN, G. v., EMBDEN, G. en ELLINGER, A.: Handbuch der normalen und pathologischen Physiologie, II, p. 70. Berlin: Springer Verlag, 1925.

ROSSIER, P. H. et BLICKENSTORFER, E.: Espace mort et hyperventilation. Helvet. med. Acta 13: 328, 1946.

ROSSIER, P. H., BÜHLMANN, A. et MÜLLER, H. E.: Espace mort respiratoire et clearance alveolaire. Schweiz, med. Wschr. 557, 1953.

ROSSIER, P. H. and BÜHLMANN, A.: The respiratory dead space. Physiol. Rev. 35: 860, 1955.

—— BÜHLMANN, A. en WIESINGER, K.: Physiologie und pathophysiologie der Atmung. Berlin: Springer Verlag, 1956.

SCHERRER, M., KOSTYAL, A., WIERZEJEWSKI, H., SCHMIDT, F. en GUENS, H. A. VAN: Zur pathophysiologie des provozierten bronchialasthmatischen Anfalls. Int. Arch. Allergy, Basel 9: 65, 1956.

—— BUCHER, U. en KOSTYAL, A.: Zur Technik atemmechanischer Untersuchungen. Schweiz, med. Wschr. 87: 1493, 1957.

SEGAL, M. S., DULFANO, M. J.: Chronic pulmonary emphysema. 1953 N.Y.

SIEBECK, R.: Ueber die Bedeutung und Bestimmung des „schädlichen Raumes" bei der Atmung. Skand. Arch. Physiol. 25: 81, 1911.

SLAGTER, B.: unpublished data 1957.

SLAGTER, B. and HEEMSTRA, H.: Limiting factors of expiration in normal subjects. Acta physiol. pharm. neerl. 4: 419, 1955.

SVANBERG, L.: Influence of posture on the lungvolumes, ventilation and circulation in normals. med. Thesis Lund 1957, Sweden.

SLUITER, H. J.: Cor pulmonale. med. Thesis, Groningen, 1955.

STEAD, W. W., FRY, D. L. en EBERT, R. V.: The elastic properties of the lung in normal men and in patients with chronic pulmonary emphysema. J. Lab. clin. Med. 40: 674, 1952.

—— WELLS, H. S., GAULT, OGNANOVICH, J.: Inaccuracy of the conventional waterfilled spirometer for recording rapid breathing. J. appl. physiol. 14: 448, 1959.

STUTZ, E.: Beitrag zur pathologischen Physiologie des Asthma bronchiale. Z. klin Med. 149: 405, 1952.

TAMMELING, G. J.: The residual volume and the functional residual capacity. med. Thesis Groningen, 1958.

TIFFENEAU, R. and PINELLI, A.: Régulation bronchique de la ventilation alveolaire. J. franc. Med. Chir. thor. 2: 221, 1948.

TOMASKEFSFI, J. F. and ATWELL, R. J.: Ventilation und Lungvolumes, in Clinical Cardiopulmonary Physiology. Grune & Stratton, London, 1957.

LIEW, H. D. VAN: Contribution of vagusnerves to pressurevolume characteristics of chest and lungs in dogs. Am. J. Physiol. 147: 161, 1954.

VERSTRAETEN, J. M.: Klinische en experimentele onderzoekingen over de „elastance" van de longen. med. Thesis. Gent, 1956.

VUILLEUMIER, P.: Ueber eine Methode zur Messung des intraalveolären Druckes und der Strömungswiderstände in den Atemwegen des Menschen. Z. klin Med. 143: 698, 1944.

WADE, O. L. and GILSON, J. C.: The effect of posture on diaphragmatic movement and vital capacity in normal subjects with a note on spirometry as an aid in determining radiological chest volumes. Thorax. 6: 103, 1951.

WELLS, H. S., STEAD, W. W., ROSSING, T. D., OGNANOVICH, J.: Accuracy of an improved spirometer for recording of fast breathing. J. appl. Physiol. 14: 451, 1959.

WIGGERS, C. J., LEVY, M. N. and GRAHAM, G.: Regional intrathoracic pressures and their bearing on calculation of effective venous pressures. Amer. J. Physiol. 151: 1, 1947.

WILLIAMS, M. H. JR. and RAYFOLD, CLAUDIA: Effect of variation of tidal volume on size of physiological dead space in dogs. J. appl. Physiol. 30: 9, 1956.

WIRZ, K.: Das Verhalten des Druckes im Pleuraraum bei der Atmung und die Ursachen seiner Veränderlichkeit. Pflügers Arch. ges. Physiol. 199: 1, 1923.

ZUIDERWEG, A.: med. Thesis, Groningen 1951. To be published.