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CHANGES IN ABSOLUTE LUNG VOLUMES IN ASTHMA

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The progress of severe attacks of asthma is now assessed routinely in hospital by measurements of blood gases and by simple bedside tests of airway function, such as spirometry or peak expiratory flow. Ever since Woolcock and Read [1] drew attention to the accompanying changes in lung volumes, clinicians have been worried that their routine assessment may ignore an important component of the asthmatic attack but unfortunately it still is not easy to measure absolute lung volumes. In this talk I will discuss what we know about these changes in lung volumes in asthma and try to assess their importance to the patient's symptoms and clinical course to the physician's assessment.

Paradoxically the most easily measured volume, the vital capacity (VC), is the only volume that decreases as asthma becomes more severe; residual volume (RV) and functional residual capacity (FRC) invariably increase and, more surprisingly, total lung capacity (TLC) itself may increase in the asthmatic attack. I will consider first what determines the limits of the change in lung volume (RV and TLC) and then discuss changes in FRC which are probably more relevant to the patient's symptoms.

Increase in RV

RV consistently rises in asthma; this is probably due to enhanced airway closure or at least to very severe airway narrowing. Though closing volume cannot be defined in severe asthma, it is increased above normal in remission (McCarthy and Milic-Emili [2]. Maximum expiratory flows are so low close to RV that it semms likely that many airways are completely closed and that alveolar gas is being expired only through a few, severely narrowed airways. Analysis of static pressure-volume curves suggests that RV is achieved at higher lung recoil pressure during attacks os asthma than during remission, implying that airways close at more positive recoil pressures (see Fig. 10 in Freedman, Tattersfield and Pride [3]). This does not necessarily indicate an increase in bronchial tone as reduction of the airway lumen by mucus plugs or mucosal oedema would have the same effect.

In fatal asthma mucus plugs are present which appear to completely occlude medium-sized bronchi even in the inflated lung (Dunnill [4]) but the lung served by the obstructed airway does not usually develop absorption atelectasis. (Some areas of collapse may develop but this is not the dominant change because RV is so consistently increased). Probably the parts of lung served by obstructed airways are kept expanded by collateral pathways which are largest when the lung is well inflated (Wagner et al, 1978).

Increase in TLC

When large changes in TLC in the asthmatic attack were first described by Woolcock and Read in 1966 [1], there was some doubt as to whether the measurements could be correct and even more uncertainty as to the physiological mechanism that could allow such an increase to take place. Thirteen years later the same problems remain. The original observations were made with the difficult technique of prolonged helium dilution (over 20 minutes) and the changes in TLC were observed over several days as asthma improved. Subsequently similar observations were made using the Boyle's law technique in the body plethysmograph to measure volumes, and increases in TLC were sometimes observed acutely after challenge with drugs or histamine (see summary in Fig. 9, Freedman, Tattersfield and Pride [3]. The change is not seen in all patients and is usually less than 1 litre, but occasionally considerably greater.

A recent contribution to this problem has been a re-examination of two possible sources of errors in the Boyle's law method the contribution of abdominal gas and inaccuracies due to the presence of lung regions with closed airways.

DuBois and his colleagues [5] examined the role of abdominal gas in contributing to the gas volume measured by the plethysmographic technique in their original sequence of papers in 1956. They concluded that abdominal gas was of little importance for two reasons: *1)* its volume was usually small (average 116 ml) (Bedell et al. [6]); *2)* the

usual panting technique produced only small changes in abdominal pressure, compared to the large swings in alveolar pressure (DuBois et al, [5]). Recent work in Boston (Brown et al. [7]), and Montreal (Habib and Engel [8]) has produced slightly higher values for the vovolume of abdominal gas (average 360 ml) and confirmed DuBois' second conclusion while clarifying the role of using different muscles in the panting manoeuvre. In the usual manoeuvre, at FRC, the change in gastric pressure is in phase with, but smaller than, the change in alveolar pressure (Fig. 1). Hence, there is some rarefaction of abdominal gas in phase with rarefaction of alveolar gas, which leads to an overestimate of true thoracic gas volume (Vtg). At worst this could be equal to the abdominal gas volume but on average the overestimate is about one-third of abdominal gas volume (Habib and Engel [8]). Converseley, subjects can be taught to pant using mainly the diaphragm, so that changes in gastric and alveolar pressure are out of phase, which leads to an underestimate of TGV due to the rarefaction of alveolar gas being offset by simultaneous compression of abdominal gas. In normal subjects there is a greater tendency to use the diaphragm during panting at volumes towards TLC than at FRC and this probably accounts for estimates of TLC being up to 300-400 ml smaller if based on panting at large lung volume rather than at FRC. In asthmatic subjects, pressure changes during the usual panting manoeuvre resemble those in normal subjects at FRC, so that although Vtg may be slightly overestimated by simultaneous rarefaction (or compression) of alveolar and abdominal gas, the overestimate should be similar in remission and exacerbation of asthma in a given individual.

A more important criticism has been advanced in a further paper by Brown and colleagues [9] - that the plethysmographic techniques gives erratic results when there are areas of lung with closed airways, as is probable in exacerbation of asthma. It is not clear yet how important these errors are, or whether they result in a systematic overestimate of TLC. We have re-examined this problem using both body plethysmography and a modification of the radiological technique, originally described by Barnhard et al [10], to estimate TLC. Surprisingly there have been few previous systematic attempts to use the radiological technique in asthma. We used the modified technique described by Lloyd, String and DuBois [11] and recently further developed by Pierce and colleagues [12] (in press) at the Brompton Hospital in London. Our preliminary analysis suggests that plethysmography may slightly overestimate TLC as indicated by radiology, but the differences do not appear great and we did not confirm earlier observations (Brown et al [9]), that estimates of TLC increased markedly if asthmatic subjects panted below FRC (Table I). I believe Pierce and colleagues have also noted good agreement between radiological and plethysmographic (panting at FRC) estimates of TLC in asthmatic subjects.

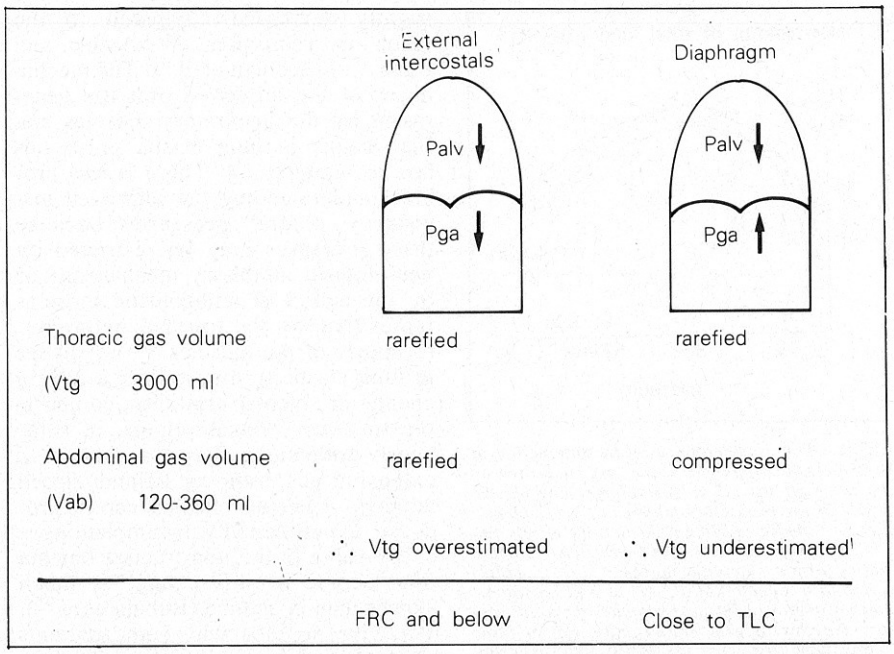

Fig. 1. Influence of different panting manoeuvres on measured thoracic gas volume (Vtg). If panting is performed by the external intercostals changes in alveolar pressure (Palv) and gastric pressure (Pga) are in phase on inspiration and Vtg will be slightly overestimated. If panting is performed by the diaphragm, changes in Palv and Pga are of opposite sign and Vtg will be underestimated. Estimates of abdominal gas volume (Vab) vary from a mean of 120 to 360 ml, but in the usual panting manoeuvre at FRC, Vtg is only overestimated by about 0.33 Vab. (See text for further discussion).

I conclude that although we still have some doubts about the accuracy of the plethysmographic measurements, the balance of evidence remains that a true increase in TLC can occur in the asthmatic attack.

How can such an increase be achieved? The volume at full inflation depends on the extent to which the pleural pressure can be lowered by the inspiratory muscles and on the distensibility of the lung (fig. 2). TLC in normal subjects is not quite the maximum potential volume (V_{max}) but the exponential analysis suggests only a small increase in volume could be achieved by applying a greater distending force to the lung (Gibson et al [13]). Towards TLC in a normal subject, the capacity of inspiratory muscles to reduce pleural pressure declines, so that the muscles would be expected to be severely compromised at volumes greater than the normal TLC. In our own studies of asthma we found that when TLC increased, the lungs were distended to a greater volume by a given static transpulmonary pressure (Freedman, Tattersfield and Pride [3]). This implies also that the inspiratory muscles become more effective at lowering pleural pressure at large volume and this prediction has been confirmed

TABLA I

Estimates of TLC (litres)

	BODY PLETHYSMOGRAPH			X)RAY (SEATED)
panting volume	towards RV	at FRC	towards TLC	
Normal	5.69	5.52	5.37	
Asthma				
series 1	7.45	7.33	7.08	
series 2	8.17	7.89	7.65	7.52

Body plethysmography: TLC was calculated from the thoracic gas volume during panting plus the subsequent inspiratory capacity. The subjects were instructed to pant at FRC and subsequently towards RV and towards TLC.
X-Ray: Postero-antero and lateral radiographs were taken at full inflation with the subject in the seated position. The two series of patients with asthma each comprised 7 subjects with moderate airflow obstruction.

(Data of Petrik Pereira, Hunter and Pride, in preparation).

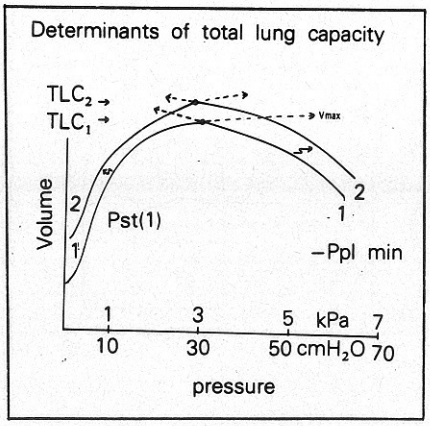

Fig. 2. TLC is determined by the interaction of (1) the elastic properties of the lung (indicated by the curve of Pst (1) versus volume) and (2) the ability of the inspiratory muscles to lower pleural pressure during maximum inspiratory efforts (indicated by the curve of -Ppl min versus volume). During asthma increase in TLC (TLC1 TLC2) is due to a reduction in Pst (1) at a given volume and an improvement in the ability of the inspiratory muscles to generate negative Ppl at large lung volume. Pst (1) at TLC2 is usually similar to, or slightly less than, Pst (1) at TLC1. Vmax = = theoretical maximum volume at infinite Pst (1) obtained from exponential analysis. Note: Ppl min is a negative pressure; the mirror image of its relationship to volume is plotted to illustrate the intersection of Pst (1) and -Ppl min at TLC.

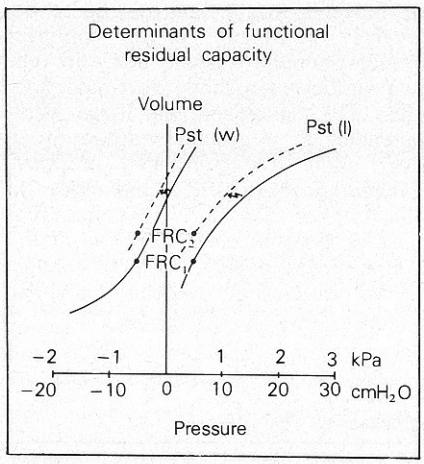

Fig. 3. Determinants of FRC in asthma. In the normal subject (or in remission of asthma) FRC is the neutral position of the respiratory system, where the inward-acting recoil pressure of the lung [Pst(l)] is exactly balanced by the outward-acting recoil pressure of the relaxed chest wall [Pst(w)]. In asthma some of the increase in FRC (FRC1 FRC2) may be due to loss of Pst(1) at a given volume and possibly also due to decreases in Pst(w). But FRC may also be increased because expiration is terminated before the neutral position is reached (see text).

in one asthmatic subject by Peress, Sybrecht and Macklem [14]. The maximum transpulmonary pressure at the increased TLC is either the same or slightly decreased compared to the value in remission (Woolcock and Read [15]; Freedman et al [3]). The mechanisms of the improved pressure generation by the inspiratory muscles and the change in lung elastic properties are not understood. There is less problem understanding the improved inspiratory pleural pressures because these pressures may be restricted by neurological inhibitory mechanisms or by the action of antagonistic muscles rather than by the true maximum performance of the muscles. The change in lung elasticity may reflect a diffuse change in alveolar elasticity (comparable to stress relaxation), or, in some poorly-understood way, be related to extensive gas trapping behind closed airways. Analogus changes can be produced experimentally by implanting a check-valve in the dog trachea but the time course of this change is much slower than in asthma (Buhain et al [16]). We have no idea why some patients show this change and others do not.

Effects of hyperinflation on tidal breathing

These changes in TLC and RV are instructive to the investigator but the effects onf FRC and the breathing pattern are of more relevance to the patient and to the assessment of the asthmatic attack. FRC (when measured by plethysmography) consistently rises in exacerbation of asthma. In normal subjects FRC is the neutral volume of the respiratory system where inward recoil of the lungs is exactly counterbalanced by outward recoil of the chest wall. During a passive expiration, expiration, expiratory flow ceases at this volume. Some of the increase in FRC in asthma may be due to a reduction in lung recoil pressure at a given volume; in addition, recoil pressure of the relaxed chest wall may be reduced as found in the patient of Peress, Sybrecht and Macklem [14] (fig. 3). But in very severe asthma tidal flow volume curves suggest that FRC does not correşpond to the initiation of the following inspiration rather than by the cessation of passive expiratory flow (fig. 4).

Therefore the patient with severe asthma probably breathes tidally with an end-expired volume even above the increased neutral volume of the respiratory system. What are the advantages and disadvantages of this breathing pattern? The primary mechanical problem in severe asthma is the inability to empty the lung rapidly, even although tidal expiratory flows may coincide with the maximum expiratory flow that can be achieved at that lung volume (fig. 4). Although airway narrowing is also present on inspiration, the absence of unfavourable dynamic

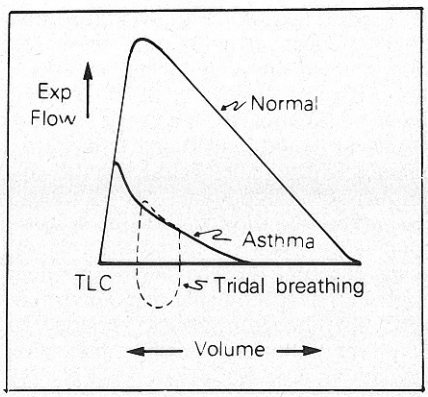

Fig. 4. Schematic representation of relation between maximum expiratory flow-volume (MEFV) curve (solid line) and flow-volume curve during tidal breathing (dashed loop) during asthma. During asthma MEFV curve changes from the normal shape so that flow is reduced at all volumes and RV increases greatly. As a result adequate expiratory flows for tidal breathing can only be achieved towards TLC. In remission similar tidal flows can be achieved over almost all the VC.

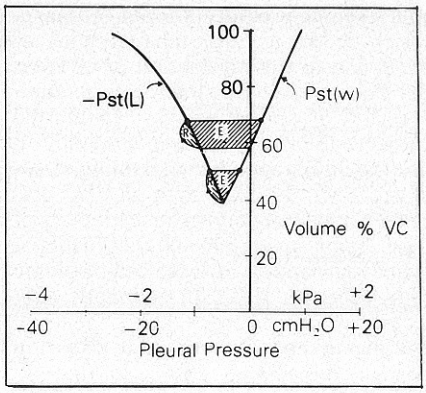

Fig. 5. Analysis of the mechanical work (muscle pressure × volume displacement = Pmus · dV) done by the inspiratory muscles during a tidal breath. When respiratory muscles are relaxed, pleural pressure (Ppl) at any lung volume equals Pst(w) (right hand heavy line). The curve of -Pst(1) versus volume (left hand heavy line) plots the pleural pressure required to overcome the static lung recoil pressure at any volume and so is the mirror image of the Pst(1) versus volume curve. At any instant on inspiration the horizontal distance between the Pst(w) and the -Pst(1) lines represents the muscle pressure required to overcome the elastic (E) properties of the lungs and chest wall (the two lines meet at the neutral position of the respiratory system, FRC). Muscle pressures to the left of the -Pst(1) line are required to overcome the flow resistance (R). The work of a single inspiration is represented by the total hatched area for resistive and elastic work. If tidal breathing takes place at an increased lung volume there is a large increase in work performed by the inspiratory muscles due to increase in elastic work (E) which far aoutweighs any reduction in flow resistive work (R) due to enlargement of the airways.

factors in this phase of breathing, allows larger maximum inspiratory flows to be developed. A small improvement in ventilation can be obtained by speeding up inspiration and allocating a greater proportion of the respiratory cycle to expiration. Tidal expiration can be speeded up by breathing at a large lung volume, distending the airways and increasing maximum expiratory flow capacity. Because of the marked volume dependence of maximum expiratory flow tidal breathing has to take place at increasing volumes as asthma becomes more severe if expiration is to be completed in a reasonable time.

The disadvantage is the increased work placed on the inspiratory muscles and the restriction placed on the tidal volume. The inspiratory pressures that have to be generated can be visualized on the Campbell diagram which shows that to achieve the same inspiratory flow a normal subject requires a much greater muscle pressure at large than at small lung volume (fig. 5). Furthermore, the capacity to generate inspiratory pressures declines with increasing lung volumes due to the unfavourable effects on the length-tension characteristics of the inspiratory muscles (fig. 6). As muscle fatigue can develop when the tidal requirement for muscle pressure exceeds 40 % of the maximum capacity to develop muscle pressure (Roussos and Macklem [17]), breathing at large lung volume may predispose to the development of muscle fatigue.

The same principles will apply in the asthmatic attack. While it is true that any reductions in lung and chest wall recoil pressures and improvements in the ability to lower pleural pressure at large volume will offset some of the disadvantages of breathing at large volume, lower (more negative) tidal pleural pressures will be required to overcome the increased inspiratory airways resistance and the reduced dynamic compliance. The major component of the increased oesophageal (pleural) pressure swings during asthmatic attacks results from the lower (more negative) inspiratory pressures required to overcome the elasticity of the lung and chest wall at large volumes (fig. 7) (Hedstrand, 1971 [18]; Freedman, Tattersfield and Pride, 1975 [3]; Stalcup and Mellins [19]. Because plateaux of maximum expiratory flow are reached at lower alveolar pressures during asthma than in remission (Pride et al [20]; McFadden and Lyons [21], only slightly positive pleural pressures are required to generate maximum expiratory flows and excessive expiratory pressures appear to be unusual, at least until the patient becomes very distressed. Paradoxically therefore although the primary mechanical problem with asthma is limitation of maximum expiratory flow, the stress falss on the inspiratory muscles. This may account for the difficulty many as-

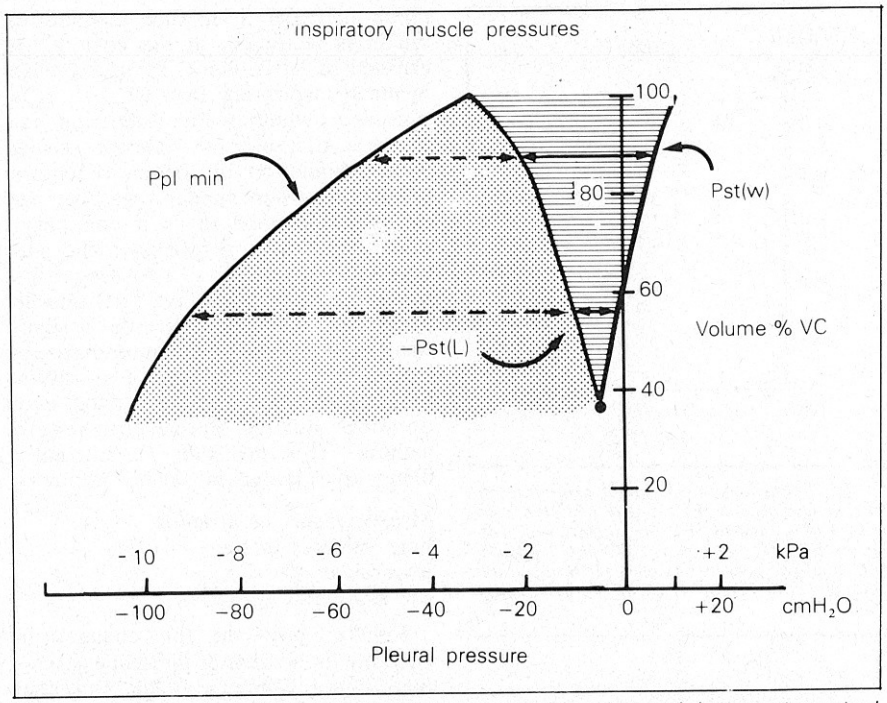

Fig. 6. Relation between pleural pressures (Ppl) during tidal breathing and during static maximal inspiratory efforts. The lowest (most negative) Ppl the inspiratory muscles can generate are shown by the curve of Ppl min versus volume (left hand solid line). In tidal breathing Ppl has to be lowered to the values indicated by the curve of -Pst(l) versus volume (middle solid line) to statically inflate the lung and in addition flow resistance has to be overcome (compare Fig. 5). The horizontal distance between the -Pst(l) and Pst(w) lines (horizontal hatching) therefore indicates the smallest muscle pressure required during quiet inspiration at any given volume, while the horizontal distance between the Ppl min and -Pst(l) lines (dotted area) indicates the available reserve of inspiratory muscle pressure. When breathing at large lung volume the inspiratory muscle pressure required for distending the lung and chest wall progressively increases while the capacity of the muscles to reduce pleural pressure steadily deteriorates.

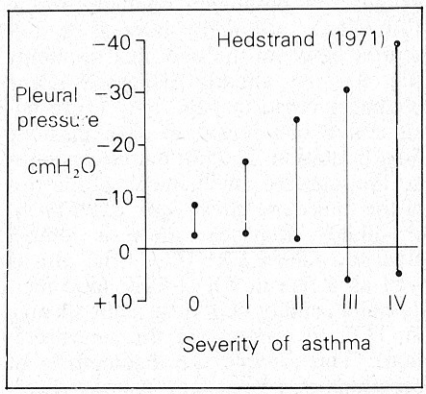

Fig. 7. Pleural pressures developed during tidal breathing with increasingly severe asthma (O = no symptoms, increasing to IV = intense symptoms). Upper closed circles = end inspiratory pressure, lower closed circles = en expiratory pressure. Drawn from data of Hedstrand (1971).

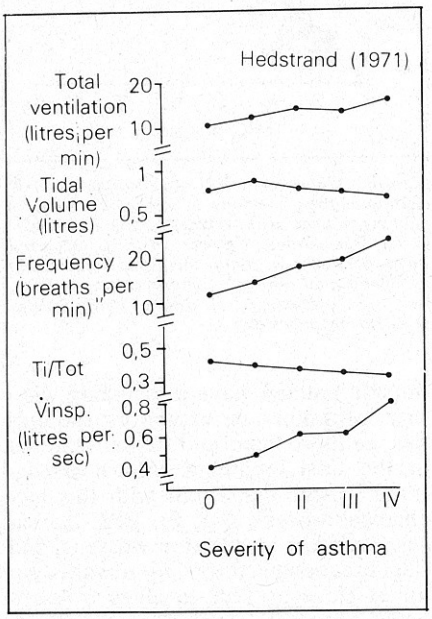

Fig. 8. Changes in breathing pattern as asthma becomes more severe (O = no symptoms, IV = intense symptoms). Ttot = time to inspire and expire a tidal breath. Ti = time to inspire a tidal breath. Vinsp = mean inspiratory flow = tidal volume/Ti. Calculated from data of Hedstrand (1971).

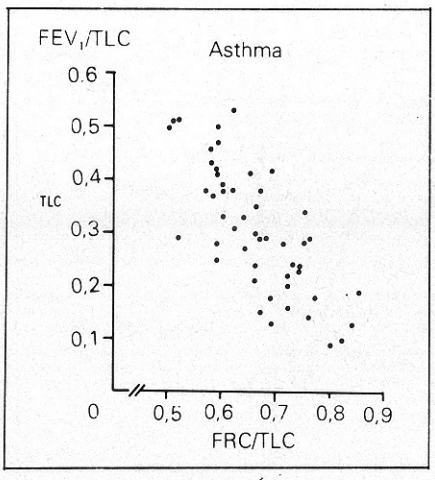

Fig. 9. Relation between forced expiratory volume in one second (FEV_1) and FRC (both expressed as a ratio of TLC) in patients with asthma. As FEV_1/TLC declines, FRC/TLC increases. FRC and TLC measured by body plethysmograph. Data of Petrik Pereira et al (to be published).

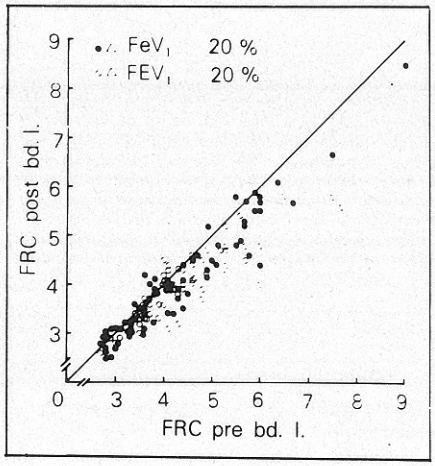

Fig. 10. Changes in FRC (measured by body plethysmograph method) in asthmatic subjects after treatment with inhaled bronchodilatador (b.d.). The largest changes in FRC occurred when volumes were greatly increased before bronchodilator and when the improvement in FEV_1 was > 20 % (open circles). Data of Petrik Pereira et al (to be published).

thmatic patients have in deciding whether inspiratory or expiratory difficulties are more important. Other features of the tidal breathing pattern (Hedstrand [18]), are consistent with this mechanical analysis (fig. 8). FRC increases as airflow obstruction worsens, and tidal breathing is forced up towards volumes close to TLC to allow a reasonable expiratory flow. Therefore there is little scope for increase in tidal volume and total ventilation is increased by an increase in respiratory frequency. A small reduction in the proportion of the respiratory cycle allocated to inspiration (T_i/T_{tot}) is insufficient to allow much increase in minute ventilation, which is achieved, at the cost of increased resistive work, by an increase in mean inspiratory flow ($\dot{V}_{insp}$). It is not clear whether this breathing pattern is dictated by reflexes arising from stimulation of irritant receptors 95hich results in similar breathing patterns in animals) or is a voluntary, possibly learned, response to the mechanical problems. Adopting this breathing pattern requires tidal muscle pressures which will represent a significant proportion of the pressuregenerating capacity of the inspiratory muscles, so that muscle fatigue may develop during persistent severe asthma. This possibility is currently being investigated in several centres.

Measurements of absolute lung volumes in the assessment of the asthmatic attack

Finally, how do the changes in absolute lung volumes influence assessment of the asthmatic attack? In recent years it has often been suggested that a change in FRC may account for a change in clinical state or symptoms which is not accompanied by an appropriate change in spirometry or peak expiratory flow, but there have been few supporting measurements. We have found that reductions in forced expiratory volume in one second (FEV_1) usually are paralleled by increases in FRC/TLC, although there is a fair scatter between the two measurements (fig. 9). As already discussed, some of the increase in FRC may represent an active compensation to expiratory flow limitation, and not merely changes in the passive mechanical properties of the lungs and chest wall. After bronchodilator treatment there is almost always a fall in FRC/TLC (fig. 10) as well as a rise in FEV_1/TLC (and incidentally usually very little acute change in TLC to complicate the interpretation). Thus, while the discomforts of breathing at a large lung volume represent a important component of the patient's problems and may contribute to the eventual development of exhaustion and respiratory failure, in general such changes can be assumed to be present whenever simple tests of airway function are severely abnormal. Changes in breathing pattern, minute ventilation, tidal pressure swings, or inspiratory muscle function, none of which are routinely measured, could equally well be the mechanical cause for a change in clinical state unaccompanied by alteration in FEV_1 or peak expiratory flow. While we must continue to investigate other aspects of respiratory mechanics in the asthmatic attack, I suspect routine sequential measurements of absolute lung volumes are unlikely to add much to the assessment of severe asthma in the vast majority of patients. Certainly they should not be allowed to detract from the frequent and simple application at the bedside of spirometry or peak flow, supplemented as necessary by blood gases.

Summary

1. Increase in residual volume is probably caused by enhanced airway closure due to increased bronchomotor tone and/or occlusion by mucus plugs.
2. In some patients total lung capacity increases. To allow this change recoil pressures of lung and chest wall at a standard volume are reduced and inspiratory muscle strength at large volume is increased. The mechanisms of those changes are unknown.
3. Increase in functional residual capacity compensates for airway narrowing and expiratory flow limitation but the requirement for more negative inspiratory pressures may lead to inspiratory muscle fatigue in prolonged asthmatic attacks.
4. Falls in functional residual capacity usually parallel increases in spirometry (FEV_1). Isolated changes in functional residual capacity without change in airway function are probably unusual.

Resumen

CAMBIOS EN LOS VOLUMENES PULMONARES ABSOLUTOS EN EL ASMA.

1. El incremento del volumen residual está causado probablemente por un mayor cierre de las vías aéreas, debido al tono broncomotor aumentado y/o a la oclusión por tapones de moco.
2. En algunos pacientes aumenta la capacidad pulmonar total. Para permitir este cambio se reducen las presiones del retroceso de los pulmones y de la pared torácica con un volumen standard y aumenta la fuerza de los músculos inspiradores con un volumen grande. Se desconocen los mecanismos de estos cambios.
3. El incremento en la capacidad residual funcional compensa el estrechamiento de las vías aéreas y la limitación del flujo espiratorio, pero la necesidad de mayores presiones inspiratorias negativas puede conducir a una fatiga de los músculos inspiradores en las crisis asmáticas prolongadas.
4. La disminución de la capacidad

residual funcional generalmente va paralela a los aumentos en la espirometría (FeV_1). Los cambios aislados en la capacidad residual funcional sin cambios en la función de las vías aéreas seguramente son raros.

Discusión

Dr. Castillo: En una de sus primeras diapositivas ha señalado la mejoría del volumen de cierre, tras la administración del broncodilatador. Pienso que el volumen de cierre, al realizarse partiendo de capacidad pulmonar total, puede verse afectado el tono bronquial a este volumen pulmonar, disminuyendo este tono. Si observamos la altura de la fase cuatro, ¿no sería un método mejor y con menos errores? Me refiero a la crítica de la medida del volumen de cierre cuando partimos de capacidad pulmonar total, debido a la influencia del volumen en el tono bronquial.

Dr. Pride: La influencia de una maniobra de pleno llenado, sobre el tono broncomotor, es cierto que reduce el tono bronquial en el sujeto normal; sin embargo, no estoy muy seguro que esto suceda en el asma.

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