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MINIREVIEW

Hyperinflation: Control of Functional Residual Lung Capacity

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Summary

Hyperinflation is the consequence of a dysbalance of static forces (determining the relaxation volume) and/or of the dynamic components. The relaxation volume is determined by an equilibrium between the elastic recoil of the lungs and of the chest walls. The dynamic components include the pattern of breathing, upper airway resistance and postinspiratory activity of inspiratory muscles. The respiratory and laryngeal muscles are under control and thus both static and dynamic hyperinflation can be secured. Our knowledge of the mechanism of increased FRC is based on clinical observations and on experiments. The most frequent stimuli leading to a dynamic increase of functional residual lung capacity (FRC) include hypoxia and vagus afferentation. Regulation of FRC is still and undetermined concept. The controlled increase of FRC, hyperinflation, participates in a number of lung diseases.

Key words

Functional residual activity • Hyperinflation • Control of breathing

Introduction

The mechanisms controlling functional residual lung capacity (FRC) have not yet been fully specified. This review will attempt to summarize the evidence concerning these mechanisms based both on clinical experience and animal experiments. The clinical aspects of hyperinflation were reviewed by Gibson 1996, Russi *et al.* 1997, Pellegrino and Brusasco 1997, De Troyer 1997 and Decramer 1997). The present review is intended to provide the physiological background of hyperinflation.

Definitions

Control of FRC comprises mechanisms that maintain the end-expiratory lung volume (EELV) at a certain level. Regulation of FRC involves the control of the volume with respect to other variables. The definitions of FRC, relaxation volume (V_{relax}), EELV, and their interrelationships have recently been well presented (Leith and Brown 1999). By convention, FRC is defined as the volume of gas in the lungs and airways at the end of spontaneous expiration (Agostoni and Mead 1964). In this review, the FRC will only be considered during quiet, resting ventilation. V_{relax} is defined as "the static equilibrium volume of the relaxed respiratory system, the volume at which the elastic recoil pressures of the lung and relaxed chest wall are equal and opposite in sign" (Leith and Brown 1999). Hyperinflation is defined as an acute increase of FRC (or residual volume – RV), or of total lung capacity (TLC). Chronic hyperinflation, however, has to be estimated by clinical examination and

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according to the reference values with all its disadvantages. In this text, references are made to FRC only and increased FRC and hyperinflation are used synonymously.

Hyperinflation has two components: static, based on V_{relax} that is partly under control and dynamic, which is fully under control (Paleček 1977, Feitová et al. 1987). Static means that hyperinflation is present irrespective of breathing movements. Dynamic hyperinflation is present only with breathing activity, is dependent on breathing frequency, and disappears during apnoea. Either one or both of these components participate in hyperinflation.

Control of FRC

Under physiological conditions, FRC is identical with V_{relax}. Therefore, changes of V_{relax} will also affect FRC. It is also stated that „during quiet breathing at rest people may be relaxed or nearly so during expiration“ (Leith and Brown 1999). It remains to be decided, at least under unphysiological conditions (such as lung disease), when true relaxation occurs. Reliable relaxation is obtained during muscular paralysis, which has occasionally been used as an argument to show that FRC exceeds V_{relax}. Complete relaxation of respiratory muscles at V_{relax} is not always present; during physical exercise, for instance, expiratory muscles contraction may drive FRC below V_{relax}. On the other hand, activity of inspiratory muscles continuing into expiration may elevate FRC above V_{relax}. FRC may also increase as the result of disproportion between the duration of expiration and the time constant of the respiratory system. Both types of respiratory muscle activity are under control; the former (activity of inspiratory muscles in expiration) is independent of the rate of breathing, therefore this type of hyperinflation is static (similarly as that due to increased V_{relax}). The latter is dynamic, dependent on the rate of breathing, and hyperinflation due to this mechanism will diminish or disappear at a slow rate of breathing. These various control systems will be discussed in detail later.

Regulation of FRC

Regulation of FRC, i.e. its control towards a known goal, is a matter of speculation. It makes use of the control mechanisms available (Fig. 1). A hypothesis can be based on the fact that hypoxia is a stimulus known to increase FRC. Hypoxia acts through peripheral chemoreceptors (see later). In addition, FRC approaching the closing capacity may stimulate dynamic mechanisms to maintain FRC at greater volumes. Thus, the closing capacity (CC) may play a key role in the regulation of FRC. CC is defined as such a volume in the lungs at which, during expiration, some airways begin to close. The primary measured variable is closing volume (CV), which is CC – RV. CC increases with the age and with obstructive lung diseases. Increased CC results in impaired distribution of ventilation, ventilation-perfusion inequality, and in hypoxemia. Hypoxemia and obstructive lung disease such as emphysema have been shown both clinically and experimentally to be combined with hyperinflation. In either case an adequate gas exchange would be the goal of FRC regulation. The signals of airway obstruction have not yet been identified. The likely receptors to increase FRC, when it approaches CC, are the rapidly adapting lung receptors (Vízek *et al.* 1983b, Meessen *et al.* 1995). Regulation of FRC may also provide a relative increase of bronchial diameter in bronchoconstriction by uncertain mechanism.

Acquisition of data - FRC in lung disease

Clinical data

Clinically, the most relevant cases of hyperinflation are observed in lung diseases. A review of the clinical aspects has already been presented (Gibson 1996). Here, only a few relevant observations are mentioned. Basically, there is a pronounced difference between acute and chronic hyperinflation, the latter providing a chance for adaptations both at the cellular and systemic levels.

Among the many instances of hyperinflation connected with lung disease the classical description relates to lung emphysema as a typical sign of hyperinflation (Briscoe *et al.* 1960).

Hyperinflation has been observed not only in emphysema but also in chronic obstructive pulmonary disease (COPD) in general (Gibson 1996). It was stated that in patients with COPD and hyperinflation of the lungs, dysfunction of the diaphragm may contribute to respiratory decompensation. Although their ability to generate pressure may be well preserved, the ability to increase lung volume is reduced (De Troyer 1997). However, functioning of the diaphragms in eight patients with stable COPD was as good as in normal subjects at the same lung volume (Similowski *et al.* 1991).

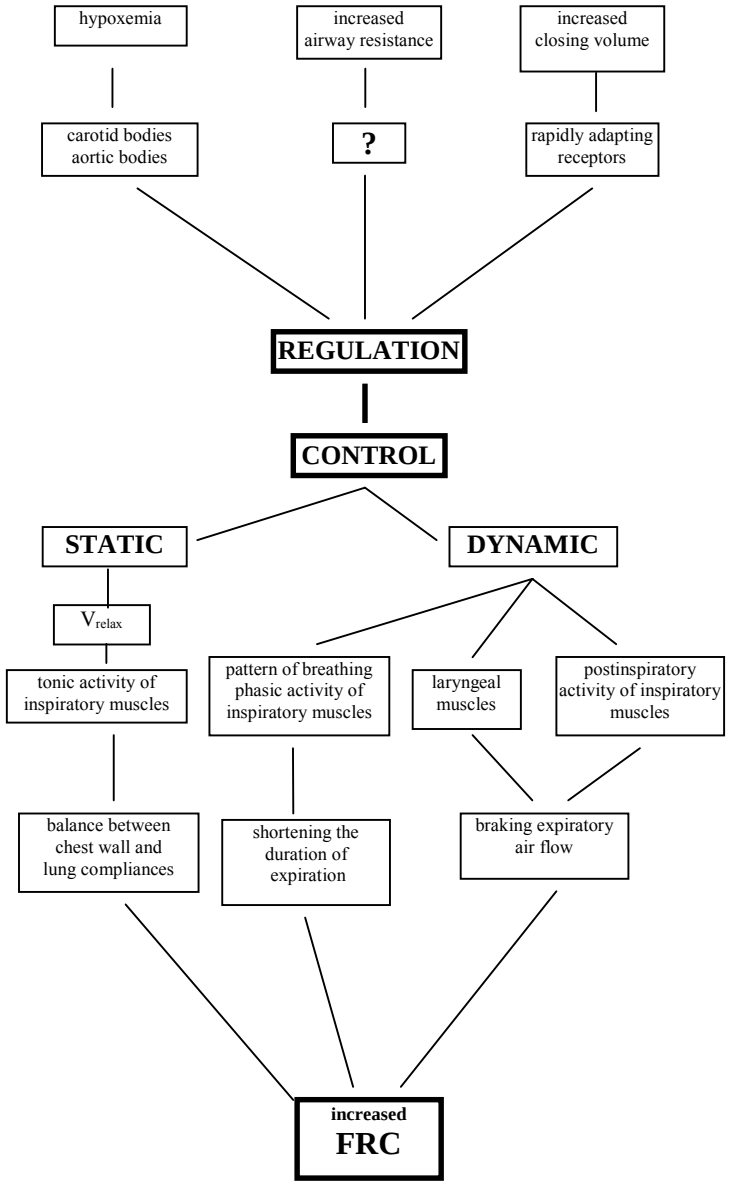

Fig 1. *A diagram indicating the relationship between regulation and control of FRC. Regulation may hypothetically serve to alleviate hypoxemia, bronchoconstriction or prematurely closing airways. The question mark relates to mechanisms not yet fully identified. Static control of FRC basically depends on the relaxation volume (V_{relax}). Chest wall compliance is affected by tonic contraction of inspiratory muscles. The dynamic control is mediated by the pattern of breathing which may influence FRC by shorter duration of expiration. The braking action of inspiratory muscles and/or of the glottis with respect to the duration of expiration are responsible for the other dynamic mechanisms of hyperinflation.*

Airway narrowing, as present in bronchial asthma, is also accompanied by hyperinflation. The increase of FRC and decrease of FEV_1 (forced expiratory volume in one second) in exercise-induced asthma may be due to different mechanisms (Kiers *et al.* 1981). Tonic activity of inspiratory muscles during expiration in exacerbation of asthma was regarded responsible, at least in part, for increased FRC (Muller *et al.* 1981). Hyperinflation during methacholine-induced broncho-constriction is triggered by dynamic compression of the airways and is associated with a moderate increase of electrical diaphragmatic activity during expiration (Pellegrino *et al.* 1993). Hyperinflation in asthmatics has also beneficial effects. It was shown that FRC was greater in asthmatic children with resulting higher diffusing lung capacity (measured by carbon monoxide) (Carel *et al.* 1973). Furthermore, lung distensibility may increase with hyperinflation in some healthy subjects (Hillman and Finucane 1983) similarly as in acute severe asthma.

An increase of FRC has also been observed with advanced age; in humans, the increase of FRC with age was greater in smokers than in non-smokers (Mándi *et al.* 1972).

Animal experiments

Animal models of lung diseases have been important in studying the control mechanisms of

hyperinflation. Lung emphysema belongs to many instances of hyperinflation connected with lung disease (Briscoe *et al.* 1960). Although attempts to produce emphysema experimentally were performed in several animal species, such as rats, hamsters, rabbits, and dogs (for reviews see Paleček 1969, Karlinsky and Snider 1978, Snider *et al.* 1986), only observations in rats and hamsters gave reproducible results, which also included *in vivo* measurements of FRC or intrathoracic gas volume (TGV). Increased FRC was observed in rats with emphysema after intratracheal papain administration and tracheal constriction (Paleček *et al.* 1967). High doses of elastase (1 IU/g b.w.) increased FRC in eight rats (Eidelman *et al.* 1990). In elastase-treated female rats, FRC and TLC increased compared with the controls; the effect was enhanced by exposure to cigarette smoke (Diamond and Lai 1987). Later, hamsters treated with intrapulmonary elastase became a standard of experimentally produced emphysema and increased FRC was observed as a rule (Snider *et al.* 1977, Snider and Sherter 1977, Sullivan *et al.* 1998).

Hyperinflation has also been observed in COPD. While patients with COPD represent a chronic situation, most of the animal experiments comprising inflammatory processes were performed acutely. Hyperinflation was observed in rats with pneumonia induced either with carragheenan or paraquat (Wachtlová *et al.* 1975, Vízek *et al.* 1975). In rats, FRC increased after Clara cell toxin (4-ipomeanol) together with tachypnoea and small tidal volume (VT) (Sabo *et al.* 1983). In rabbits, after an intravenous administration of 15 ml/kg Fluosol, a perfluorocarbon emulsion, an increase of FRC was observed together with decreased lung compliance (Eckmann *et al.* 1998). Experimental lung silicosis in rats was also accompanied by hyperinflation in spite of significantly lower lung compliance (Kuncová *et al.* 1971, 1972, Chválová *et al.* 1974). FRC/TLC was also increased in aging beagle dogs (Robinson and Gillespie 1973). It is not known whether there is a control component in old age hyperinflation.

Static hyperinflation

Basically, FRC during resting ventilation depends on an elastic equilibrium between the lungs and chest wall. Thus changes in either of these components increase or decrease the FRC. Although lung compliance may change acutely (e.g. in pulmonary edema), it is not considered to be under direct control. The chronic increase in lung compliance is considered typical for emphysema.

The function of respiratory muscles in hyperinflation has been analyzed in detail (Decramer 1993, 1997). Inspiratory muscles physiologically maintain their phasic activity into the first phase of expiration; this action of inspiratory neurons is called postinspiratory inspiratory activity (von Euler 1983). However, if their activity persists throughout expiration, it will decrease chest wall compliance, and thus increase both V_{relax} and FRC. In seven asthmatics, tonic inspiratory muscle activity correlated with hyperinflation (Muller *et al.* 1981).

As was mentioned above, should the tone of inspiratory muscles result in increased FRC, then its depression will decrease FRC. Therefore, the participation of tonic activity of inspiratory muscles in chest wall elasticity was assumed, when the authors observed a decrease in FRC in six volunteers after curarization (De Troyer and Bastenier-Geens 1979). Furthermore, decreased muscle tone after curarization, during anesthesia or in sleep also correlated with lung volumes in other experiments. FRC decreased in four curarized volunteers (De Troyer *et al.* 1980). However, FRC did not change in the course of curarization in other six volunteers (Gal and Arora 1982). After thiopental, FRC decreased within 30 s and it was not further affected by the administration of myorelaxing drugs (Bergman 1982).

It seems evident that subjects with a physiologically more compliant chest wall, such as neonates (Davis *et al.* 1988) rely more on inspiratory muscle tone to maintain an adequate volume of FRC; in six healthy new-born babies thoracic gas volume decreased by 31 % during REM sleep (Henderson-Smart and Read 1979). A similar observation was made in eight premature infants, underlining the importance of tonic activity of inspiratory muscles in maintaining FRC (Lopes *et al.* 1981). However, the situations of decreased muscular tone (such as sleep or general anesthesia) are usually combined with a slower rate of breathing. Thus a dynamic component may also participate (see further). In ten chronic quadriplegic patients, the pleural pressure at the level of FRC was half the normal value. One group of patients without EMG activity of intercostal muscles had decreased FRC; the other group with normal EMG activity had normal FRC (De Troyer and Heilporn 1980). Following deepened breathing, increased FRC was

consistently observed in cats, due to a change in end-expiratory muscle tone (Szereda-Przestaszewska *et al.* 1976).

Dynamic hyperinflation

Pattern of breathing

One way of maintaining FRC above V_{relax} is to begin inspiration before the decreasing lung volume reaches V_{relax}. This can be accomplished either by shortening the duration of expiration or by increasing airway resistance with slower emptying of the lungs. Essentially, the rate of expiration is based on the time constant of the respiratory system. The time constant (RC) can be expressed as the product of resistance (R) and compliance (C). Physiologically, RC would provide for an appreciably shorter duration of expiration and, therefore, expiration is braked by the resistance of larynx and also by contraction of inspiratory muscles overlapping into expiration. RC is shorter with lung volumes approaching TLC, because of the lower airway resistance and lower compliance of the respiratory system, and *vice versa* with small lung volumes. In newborns or animals with a compliant chest wall, FRC is actively maintained above V_{relax} mainly by a high rate of breathing (Vinegar *et al.* 1979, Paleček and Ježová 1988). However, this is not likely to be called hyperinflation.

Shortening the duration of expiration

Shorter duration of expiration may cause the following inspiration to begin at lung volume above V_{relax}. In such a condition, prolongation of the duration of expiration, typically as the result of slower frequency of breathing, will be followed by decreased FRC. Kosch and Stark (1984) report that the maintenance of FRC in full-term newborn infants depends on the time constant of the respiratory system and on the duration of expiration. Furthermore, the changes of FRC in premature newborns may correlate with changes of the breathing pattern rather than directly with the sleeping pattern (Takahashi *et al.* 1991). It was demonstrated in mice that their FRC is maintained above V_{relax} by an expiratory braking action of inspiratory muscles and the glottis, while their FRC tends to approach V_{relax} under anesthesia (Vinegar *et al.* 1979). Similar results were obtained in rats, when their pattern of breathing was compared under awake, unrestrained conditions and under anesthesia (Lamm *et al.* 1982). We may assume that general anesthesia exerts its effect on FRC not only by slowing the breathing frequency but also by decreasing inspiratory muscle tone (see the respective paragraph). For instance, the FRC decreased under Pentothal anesthesia in healthy human volunteers without being further affected by muscular paralysis (Westbrook *et al.* 1973). Hewlett *et al.* (1974) showed a standard decrease of FRC in patients during anesthesia compared with preanesthetic values. These authors reported similar results in five previous studies.

Increased airway resistance

Increased airway resistance, especially the braking action of the larynx, is one of the mechanisms controlling the breathing pattern physiologically (Gautier *et al.* 1973). In normal subjects, CO_2 rebreathing with higher expiratory flow resistance resulted in increased FRC (Garrard and Lane 1978). Hyperinflation during methacholine-induced bronchoconstriction is associated with a moderate increase of electrical diaphragmatic activity during expiration (Pellegrino *et al.* 1993). In another study in five adult subjects thoracic gas volume increased by 30 % after a histamine-induced increase of airway resistance. This increase correlated with increased EMG activity during expiration of both intercostal muscles and diaphragm indicating that increased airway resistance was not the sole cause of hyperinflation (Muller *et al.* 1980). The increase of FRC is considered a reflex response to airflow limitation during exercise (Babb *et al.* 1991).

There are pronounced interspecies differences with respect to maintaining FRC above V_{relax}. The braking mechanism seems especially important for maintaining higher FRC in subjects with a high compliance of the chest wall, such as mice, rats, and newborns in general. Thus, insufficient braking of expiration in anesthetized mice together with smaller VT, slower rate of breathing and longer duration of expiration resulted in decreased FRC, approaching relaxation volume (Vinegar *et al.* 1979). Differences in newborns of nine species were evaluated with respect to the time constant of the respiratory system, the breathing

frequency and the dynamic maintenance of FRC (Mortola *et al.* 1985).

It should be stressed that proving the existence of one controlling mechanism does not by itself exclude the possible participation of another one. Thus, the braking action of inspiratory muscles can be combined with shorter duration of expiration etc.

Sensors and/or stimuli affecting FRC control

Hypoxia and hypercapnia

Hypoxia is a well-established condition resulting in hyperinflation both in man and many species of experimental animals. The classical observation in man showed an increase of FRC during adaptation to high-altitude hypoxia (Tenney *et al.* 1953). This observation was not, however, confirmed by later studies on the effects of high altitude hypoxia lasting 6 days (Gautier *et al.* 1982). FRC also increased in healthy volunteers during isocapnic hypoxia (Saunders *et al.* 1977). In another study, 45 subjects exhibited a 12 % decrease in FRC during hyperoxia; 40 of 43 showed a 14 % increase in FRC during hypoxia and 42 of 43 showed a 15 % increase of FRC also during hypercapnia (Garfinkel and Fitzgerald 1978). The observation of the FRC increase in hypercapnia is rather exceptional, most other observations did not show any effect. Thus CO_2 rebreathing in normal subjects did not affect FRC (Garrard and Lane 1978). Hypoxia (5-8 % O_2 in inspired air) regularly increased lung volume in rabbits and cats, whereas hypercapnia (2-10 % CO_2 in inspired air) had no such effect (Peyser *et al.* 1950). Furthermore, lung volume in dogs is under the control of arterial chemoreceptors (Bouverot and Fitzgerald 1969). In anesthetized rats, acute and chronic hypoxia increased thoracic gas volume (Herget 1976, Barer *et al.* 1978). An increase of FRC was also demonstrated in rats after the carotid body stimulant (Almitrine). This effect was prevented by cervical vagotomy (Paleček and Chválová 1984). The mechanism of hyperinflation after hypoxia is complex. Postinspiratory activity of the diaphragm was demonstrated both in anesthetized and awake animals (Smith *et al.* 1989, Vízek and Bonora 1998). However, tachypnoea was also present and its possible participation in the dynamic hyperinflation is difficult to evaluate. Moreover, a small response to hypoxia remains in rats with denervated carotid bodies and this is abolished by vagotomy and may thus be due to aortic chemoreceptors or other vagally mediated effects. In other experiments, the increase of FRC in anesthetized rats during acute hypoxia was prevented by vagotomy (Vízek and Paleček 1982, Vízek *et al.* 1983a). Later experiments indicated that hypoxia still increased FRC after vagotomy, though significantly less than in intact animals (Vízek and Bonora 1998). With respect to the mechanism, other experiments indicated that the increase of diaphragmatic activity observed in hypoxic rats during expiration is independent of the conduction through vagal C fibres, but it may involve the thin myelinated vagal afferent fibres and also a non-vagal mechanism (Bonora and Vízek 1997).

Vagally mediated stimuli

Apart from the participation of vagus afferentation in hypoxia, its role was also demonstrated experimentally in other conditions. Bilateral cervical vagotomy decreased FRC in several experimental lung diseases in anesthetized rats (Wachtlová *et al.* 1975, Vízek *et al.* 1975). One mechanism of such a decrease may be the pronounced slowing of respiratory frequency, which occurred as a rule. This would correspond to a dynamic hyperinflation. However, the experiments performed in rats with paraquat pneumonia indicated that thin vagal fibers are involved in increasing FRC. Progressive cooling of the vagus nerves showed hyperinflation till the temperature of 8 °C. At this temperature, the Hering and Breuer inflation reflex is abolished and the rate of breathing is significantly slowed down. However, the FRC normalized only after vagotomy. Therefore, the importance of thin vagal fibers was assumed (Vízek *et al.* 1983b). Similar conclusions were made also by Meessen *et al.* (1995). These authors observed a dependence of end-tidal inspiratory activity on intact transmission along thin myelinated vagal fibers in anesthetized cats.

Conclusions

We may speculate on the basis of the above observations that the system of FRC control will be

activated: 1) in subjects with high chest wall compliance, which are threatened with an airway occlusion as the closing volume approaches FRC, 2) in airway obstruction, and 3) in hypoxia. Regulation of FRC should optimize the favorable and unfavorable consequences of hyperinflation in each individual subject according to the specific conditions.

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