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REVIEW

Bronchial hyperresponsiveness: The need for a distinction between hypersensitivity and excessive airway narrowing

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ABSTRACT: Bronchial hyperresponsiveness is currently defined as an increase in sensitivity to a wide variety of airway narrowing stimuli. Most patients with asthma and chronic obstructive pulmonary disease (COPD) exhibit such an enhanced sensitivity. In asthma, in particular, this hypersensitivity is accompanied by excessive degrees of airway narrowing. This raises the question as to whether measures of sensitivity, *e.g.* the provocative concentration or dose producing 20% fall in FEV_1 (PC_{20} or PD_{20}), comprise all the relevant information in bronchial hyperresponsiveness. In adjunct to model studies, there is experimental evidence in man that the potential mechanisms of bronchial hyperresponsiveness can be divided into those causing hypersensitivity and those responsible for the increase in the maximal attainable degree of airway narrowing. The recognition and distinction of these components of hyperresponsiveness have clinical implications in the diagnosis and therapy of asthma and COPD. Bronchial hyperresponsiveness is a composite functional disorder, which requires treatment of each of its components.

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Bronchial responsiveness is usually defined as the sensitivity of the airways to a wide variety of nonsensitizing bronchoconstricting stimuli of chemical or physical origin [1, 2]. This refers to the ease with which inhaled irritants can cause airway narrowing. In humans, *in vivo*, the sensitivity is currently measured by the use of various bronchial challenge tests, that have all been standardized to a reasonable extent [3, 4]. Preferably, sensitivity is determined in a dose-response way: *e.g.* a measure of airway narrowing against increasing doses of the stimulus [5]. Hypersensitivity is then reflected by a leftward shift of the dose-response curve, and has almost universally been labelled as bronchial hyperresponsiveness *e.g.* expressed as the provocation concentration or dose producing a 20% fall in FEV_1, (PC_{20} or PD_{20}).

By definition bronchial hyperresponsiveness is merely a functional disorder. It is associated with several clinical diagnoses, such as bronchial asthma [6], chronic obstructive pulmonary disease (COPD) [7], and cardiac asthma [8]. In many patients with one of these clinical entities the dose-response curve to inhaled histamine or methacholine is shifted to the left. It is likely that very divergent pathology contributes to a similar functional abnormality among these patients [9, 10]. Indeed there are many mechanisms that could theoretically produce hypersensitivity to airway narrowing stimuli, either alone or in combination with each other [11]. It is, therefore, conceivable that the measures of sensitivity are of limited value in elaborating the complex pathophysiology of bronchial responsiveness [12].

The question is, whether measurement of the sensitivity comprises all the relevant information that can be obtained from dose response curves *in vivo*. Apart from its position, other indices of the sigmoid-shaped curve might be important to characterize the response to inhaled airway narrowing stimuli. The meaning of the term bronchial responsiveness then needs to be extended, including both position and shape of the curve. The present review is an attempt to propagate the usage of the shape of the dose-response curve, along with sensitivity, in clinical and basic studies on bronchial responsiveness. This will considerably extend the potential of these physiological measurements in being an intermediate between the pathology and clinical expression of bronchial asthma and COPD.

Shape of dose-response curves

At present there is increasing evidence that bronchial hyperresponsiveness implies more than just hypersensitivity. In 1984, Woolcock *et al.* [13] were the first to recognize the importance of recording the whole dose-response curve to inhaled histamine. Their curves were expressed as the change in a measure of airway calibre, the forced expiratory volume in one second (FEV_1), in percentage fall from baseline value over the

log dose. This method of normalizing the response provided the advantage of eliminating the effects of baseline airway calibre on the shape of the dose-response curve [14]. It was found that the curves from asthmatics could be differentiated from those of normals by their position, slope, and maximal response. Apart from a shift to the left, the dose-response curves in asthma had a steeper slope and a higher maximal response at high doses as compared to normals [13].

Measurement of the slope of the dose-response curve has been advocated by OREHEK *et al.* [15]. In order to avoid confusion, we support their recommendation to reserve the term bronchial "reactivity" to designate the slope of the curve, as opposed to bronchial "sensitivity" indicating the position. It was felt that relevant information could be extracted from slope measurements [15], but subsequent studies showed a poor relationship between reactivity and sensitivity of log dose-response curves among normal and asthmatic subjects [13, 16, 17]. However, this does not exclude the slope from being of any importance in pathophysiological research, as illustrated by the observed differences in slope between stimuli with distinct pharmacodynamic properties [18]. So far, this aspect has not been addressed systematically.

The maximal response plateau on the dose-response curve seems to add relevant information to sensitivity measurements. It reflects the extent to which the airways can narrow, when being exposed to high doses of inhaled stimuli. Normal subjects reach a reproducible maximal response plateau to both histamine [13] and methacholine [19] at similar, relatively mild, degrees of airway narrowing [18]. In contrast, asthmatic patients are capable of reaching more severe obstruction with higher or immeasurable plateau levels [13]. This indicates that bronchial hyperresponsiveness in asthma is characterized by at least two abnormalities: a shift of the dose-response curve and a lift of the maximal response.

The theoretical aspects of the position and maximal response of dose-response curves have been elegantly worked out by MORENO *et al.* [20] in 1986. They applied knowledge of the pharmacology of dose-response curves *in vitro* [21] to the curves of airway narrowing observed *in vivo*. A leftward shift of the curve can be regarded as being the result of any augmentation of the airway narrowing stimuli ("prejunctional" mechanisms) [20, 21]. On the other hand, upward movement of the maximal response plateau is theoretically the result of any increase in the response of the effector organ ("postjunctional" mechanisms) [20, 21]. In the following, we have compiled recent experimental evidence in favour and against a separate role of "pre- and postjunctional" mechanisms in human bronchial hyperresponsiveness *in vivo*.

Hypersensitivity: shift of the dose-response curve

Examples of "prejunctional" mechanisms potentially causing an increase of the stimuli and thereby a leftward shift of the dose-response curve are shown in figure 1 and table 1.

Table 1: Examples of "prejunctional" and "postjunctional" mechanisms that are potentially involved in bronchial hyperresponsivness*

"Prejunctional"	"Postjunctional"
a) epithelial damage or malfunction	g) smooth muscle contractility
b) neural control	h) viscous and elastic loads
c) inflammatory cell number	i) swelling of the airway wall
d) inflammatory cell activity	j) intraluminal exudate and secretions
e) interaction	
f) metabolism or absorption	

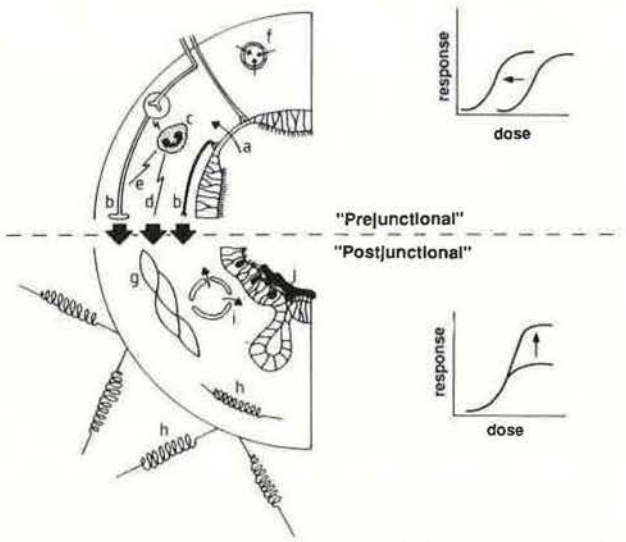

Fig. 1. – Schematic display of a cross-section of the airway wall with examples of potential "prejunctional" (upper part) and "postjunctional" (lower part) mechanisms determining a leftward shift and an increase in maximal response, respectively, of dose-response curves to inhaled airway narrowing stimuli *in vivo*. The potential "prejunctional" (a–f) and "postjunctional" (g–j) mechanisms are listed in table 1.

Epithelial damage or malfunction is the first possible mechanism, which could increase the accessibility of stimuli to their receptor sites. Profound epithelial destruction, at all levels of the bronchial tree, has been observed in a morphological study in patients with asthma [9]. However, these observations could not be confirmed in a recent report [22]. The degree of epithelial damage does not seem to be related to the sensitivity (*e.g.* PC_{20}) of the airways [9], although the number of epithelial cells in bronchoalveolar lavage fluid does [23]. In addition to damage, epithelial metabolic dysfunction may be involved [24]. This could be due to decreased production of "epithelium derived relaxing factor" [25], or to impaired breakdown of tachykinins by reduced activity of airway neutral endopeptidase [26]. Therefore, at present, the relationship between bronchial sensitivity and epithelial integrity is still unclear.

Abnormal autonomic neural control of the airways is a second possibility for increased "prejunctional" stimuli, which has recently been reviewed in great detail

[27, 28]. Remarkably, primary autonomic dysfunction does not seem to be a cause of bronchial hypersensitivity in asthma or COPD [27, 28]. This holds for the cholinergic [29], alpha-adrenergic [27] and noncholinergic excitation [30], as well as for the beta-adrenergic [31] and even nonadrenergic [32] inhibition. However, several of these components seem to function abnormally, secondary to other mechanisms such as epithelial damage and/or the presence of inflammatory mediators [27, 28] (see below). It is not unlikely that this secondary autonomic malfunction is one of the major causes of a leftward shift of the dose-response curve in bronchial hyperresponsiveness. In addition, it can not be excluded that there is a defect in autonomic feedback mechanisms in bronchial hypersensitivity, *e.g* in prejunctional inhibitory autoreceptors on cholinergic efferents [33]. Recent *in vitro* experiments with isolated human airways have indicated that there might also be differences in autonomic neural control between patients with asthma and COPD [34].

An increased number of inflammatory cells in the airway wall could also account for an enhanced stimulus to airway narrowing. There are recent morphological reports on increased numbers of mast cells and eosinophils [22, 23], lymphocytes and macrophages [23], and neutrophils [35] in the airway mucosa of asthmatics. The presence of at least some of these cells seems to be associated with bronchial hypersensitivity, because of the positive correlation between the number of eosinophils, metachromic cells [36] or neutrophils [37] in lavage fluid and the PC_{20} to methacholine in asthma. This has not been addressed systematically in COPD, although there is a correlation between histological inflammation in membranous bronchioles and the PC_{20} in these patients [10].

The activity of inflammatory cells is obviously more important than their number. There are numerous reports of enhanced spontaneous mediator release from blood leucocytes [38], lavage mast cells [39–41] and eosinophils [40] in atopic asthma. The histamine [38, 40, 41] and major basic protein [40] release, and macrophage chemiluminescence [37] appear to be inversely related to the PC_{20} in these patients. In COPD a similar relationship has been observed between superoxide generation by polymorphonuclear leucocytes in peripheral blood and the PC_{20} [42]. This confirms an association between inflammatory cell activity and bronchial sensitivity in various clinical entities in man.

Interaction between inflammatory cells, mediators, neural control and smooth muscle in the airways may play an essential role in shifting the dose-response curve to the left. The evidence for this comes from both ultrastructural [43] and pharmacological [44] studies. In man *in vivo* for instance, prostaglandin D_2 potentiates histamine and methacholine induced bronchoconstriction [45], which is likely to be caused by ganglionic or postganglionic prejunctional [46] enhancement of cholinergic tone [47]. Similar potentiation of the efferent vagal activity has been reported from *e.g.* serotonin, adenosine, prostaglandin $F_{2\alpha}$, thromboxane A_2 and substance P [27, 44]. Add to this the other potential effects of inflammatory mediators, such as epithelial damage or malfunction [48], or secondary neuropeptide release in response to C-fibre ending stimulation [30], and it will be obvious that these various interactions are a likely source of augmentation of airway narrowing stimuli.

The above examples illustrate multiple associations between an increase in "prejunctional" stimuli of airway narrowing and bronchial hypersensitivity, which is in support of theoretical analyses [20, 21]. It is obvious that removal of the mediators and neurotransmitters, by enzymatic breakdown or absorption into the circulation, is an important determinant of the effect of these stimuli. Finally, it should be emphasized that the leftward shift of the dose-response curve under all these circumstances is not necessarily "nonspecific" with regard to the various bronchoconstrictor stimuli [1]. Indeed the sensitivities to the numerous physical and chemical stimuli often appear not to be interrelated [12], thereby suggesting that the leftward shift of the dose-response curve is not caused by one simple mechanism.

Excessive airway narrowing: lift of the maximal response

When interpreting the maximal response, it first needs to be confirmed that (supra)maximal stimulation really occurs at the plateau levels. We addressed this question by combining plateau doses of two pharmacodynamically distinct stimuli, histamine and methacholine, in normal subjects [49]. It was found that there is no additive effect of these two agonists on the maximal response, thereby indirectly indicating that the plateau on the dose-response curve *in vivo* indeed represents (supra)maximal stimulation of airway narrowing.

Examples of "postjunctional" mechanisms that might be responsible for an increase in maximal response on the dose-response curve are listed in figure 1 and table 1.

Smooth muscle contractility is a potential determinant of the maximal response [50]. It could be altered by receptor regulation [51], propagation of excitation (through gap junctions) [43], smooth muscle mass, *(e.g.* hypertrophy and hyperplasia) [50], resting membrane potential [21, 50], calcium handling [21, 50], cross-bridges cycling [50] or length-tension characteristics [20, 50]. Most of these factors have not been addressed systematically with regard to the *in vivo* maximal response in man. In animals it has been observed that sensitized smooth muscle *in vitro* shows increased isotonic shortening due to a reduction in so-called internal resistance, associated with enhanced velocity of shortening [52]. In man it is known that patients with asthma or COPD often show airway smooth muscle hypertrophy and hyperplasia, which has been reported in a number of studies to be associated with increased maximal contractility *in vitro* [53]. In non-asthmatics there is also a positive relationship between the amount of smooth muscle and the maximal isometric tension *in vitro* [54]. However, in non-asthmatics who were

scheduled for thoracotomy, DE JONGSTE *et al.* [55] recently showed that the level of the maximal response plateau *in vivo* was not related to the maximal degree of isotonic shortening of bronchiolar strips *in vitro* nor to the amount of smooth muscle hypertrophy. This suggests that smooth muscle contractility is not a major determinant of the level of the plateau in inhalation challenge tests, even though this has not been investigated in (mild) cases of asthma. In addition, it should be emphasized that some aspects of muscle function, such as cell-to-cell coupling, cannot be investigated in the organ bath [43].

Viscous and elastic loads on airway smooth muscle shortening, contributed by structural elements in the airway wall and lung parenchyma, are likely to play a major role in causing the plateau on the dose-response curves *in vivo* [20]. So far, however, there is only indirect evidence in favour of this hypothesis. Airway smooth muscle is capable of shortening isotonically to about 20% of its optimal length (where maximal isometric tension can be generated) [50]. A plateau can only be achieved if *in vivo* bronchoconstriction does not occur (quasi)isotonically in the presence of adequate counterbalancing forces [56]. From animal models it appears that this is the case. Cartilage exerts a considerable load on smooth muscle shortening in tracheal rings *in vitro* [57] and in rabbit airways *in vivo* [20]. In addition, elastase heightens the maximal response plateau in rats *in vivo* [58], presumably due to a reduction in elastic load by the parenchyma on muscle shortening [59]. In man the level of the plateau is lung volume dependent [60], which also indirectly supports the role of parenchymal elastic recoil in limiting airway narrowing, as opposed to neural or humoral regulatory factors [61]. Even though these observations underline the effects of mechanical loads on the maximal response, it still remains to be established whether the increased maximal response in asthma results from a reduction in those loads. One of the possibilities could be degradation of elastin and collagen in the submucosa by migrating inflammatory cells [62], which may lead to breakdown of the interdependence between parenchyma and the airway wall [56].

Swelling of the airway wall and intraluminal exudate or secretions are theoretically important contributors to the maximal degree of airflow obstruction [20]. Without substantially changing baseline airway calibre, inflammatory changes in the airways (hyperaemia, oedema, plasma exudation or mucus hypersecretion) can profoundly increase the maximal degree of obstruction in series to smooth muscle shortening in model studies [20]. Several inflammatory mediators have the potential of inducing mucosal swelling or plasma exudation by microvascular dilatation and increased postcapillary venular permeability [63, 64]. In atopic asthmatics *in vivo* hyperaemia, oedema [65], and increased vascular permeability [66] have been observed following allergen challenge. However, the effect of these changes in the airway wall on maximal airway narrowing has not yet been documented. We have recently addressed this question by comparing the levels of the maximal responses to high doses of a muscarinic agonist (methacholine) and a pro-inflammatory agent (leukotriene D_4) in normal subjects *in vivo* [67]. Inhaled leukotriene D_4 not only led to a higher maximal response plateau than methacholine, but also increased the maximal response to methacholine for at least 72 h. This prolonged heightening effect of leukotriene D_4 on the methacholine plateau was not accompanied by a change in methacholine sensitivity, which is indicative of a partial independence of position and maximal response of dose-response curves *in vivo* [67]. In a subsequent study, it was shown that inhaled corticosteroids can prevent the leukotriene D_4 induced increase of the maximal response plateau [68]. This strongly suggests that the pro-inflammatory actions of leukotriene D_4, such as increased vascular permeability and mucus hypersecretion [69], selectively account for excessive airway narrowing. This agrees with the predictions obtained from model studies [20], indirectly favouring an important role of airway wall thickness in determining the maximal response to bronchoconstrictor stimuli.

Limitations of interpreting in vivo *dose-response curves*

Based on the experimental evidence given above, "postjunctional" mechanisms indeed seem to be responsible for the severity of airway narrowing in man *in vivo*. This has pathophysiological and clinical implications. The potential of distinguishing "pre- and postjunctional" mechanisms by physiological measurements would offer great prospects in research on bronchial hyperresponsiveness. However, it should be emphasized that it remains questionable whether such simplification of mechanisms is allowed when studying *in vivo* dose response curves. Firstly, extrapolation of *in vitro* pharmacology to the response of the branching bronchial tree might be inappropriate, because of parallel and/or in series heterogeneity of airway narrowing [20].

Secondly, "pre-and postjunctional" mechanisms are likely to be interrelated. For instance, as shown in figure 1, inflammatory reactions in the airway wall not only increase the stimulus, but also augment the response by (sub)mucosal swelling. Smooth muscle characteristics such as agonist-receptor interaction and cell-to-cell coupling could also affect sensitivity as well as contractility [51, 62]. In addition, a well known potential determinant of hyperresponsiveness, namely a reduction in baseline airway calibre, can theoretically arise from both enhanced levels of baseline stimuli and altered airway wall geometry. It is tempting to suggest that this divergence of mechanisms might explain some of the controversy about the role of initial lung function on bronchial responsiveness: reduced baseline airway calibre does not explain the shift of the dose-response curve in asthma [6], whereas it may in COPD [7]. The influence of baseline function on the maximal response in asthma and COPD still needs to be examined. This may further elaborate the role of "pre- and postjunctional" mechanisms in these clinical entities.

Clinical implications

Patients with variable airways obstruction usually present themselves with a history of chest tightness, dyspnoea, wheezing on the chest, or a cough. Besides regular spirometry, challenge tests with histamine or methacholine have been advocated in clinical practice, in order to provide additional information in these patients regarding the sensitivity of their airways to inhaled irritants [70]. The question is whether these measures of sensitivity, such as the PC_{20} or PD_{20}, are the most relevant indices of inhalation challenge tests in the diagnosis and treatment of diseases characterized by bronchial hyperresponsiveness. It could be argued that the severity of airways obstruction is not solely dependent on the sensitivity to airway narrowing stimuli but also, and more directly, on the maximal degree of obstruction that potentially can be attained [71]. Maximal response measurements could therefore be useful, the more so as there is recent evidence that the maximal response may differ between patients with asthma and COPD [72].

Bronchial asthma is characterized by abnormalities in both features of the dose-response curve: a leftward shift usually coincides with an increase in maximal response [13]. In normal and mildly asthmatic subjects there is an association between the sensitivity and the level of the maximal response plateau [18]. The greater the sensitivity, the higher the plateau. At PC_{20} levels of around 1 $mg \cdot ml^{-1}$ or below, the maximal response in asthma is usually too severe to measure, the decrease in FEV_1 being >60% fall from baseline [18]. This is suggestive of an interrelationship of "pre- and postjunctional" mechanisms in asthma. On the other hand, Du Torr *et al.* [72] reported that a number of patients with COPD are hypersensitive without a distinct rise in maximal response. Even at PC_{20} values in the asthmatic range these COPD patients still feature a maximal response plateau, which could be indicative of a predominance of "prejunctional" mechanisms in COPD. However, it should be borne in mid that it may not be appropriate to express the response in percentage fall from baseline value when baselines are reduced in COPD.

These observations fit in with the following three postulates on the clinical relevance of the distinction between sensitivity and maximal response in bronchial hyperresponsiveness. The first two points have already been put forward by Macklem [71] in 1986.

1. Bronchial hyperresponsiveness in asthma is potentially dangerous, because of the excessive airway narrowing as opposed to hypersensitivity *per se* [71]. This distinguishes asthmatics from COPD patients, who do not seem to be able to severely aggravate their degree of obstruction in response to acute stimuli [72].

2. Therapy in asthma should be directed not only towards diminishing airway sensitivity but, more importantly, also towards diminishing or preventing excessive airway narrowing [71]. The objective of either short- or long-term reduction in sensitivity in patients with bronchial hyperresponsiveness has been widely accepted [73]. Bronchodilators such as β_2-adrenoreceptor agonists induce a short-term rightward shift of the dose-response curve to histamine [74], which acutely protects the patient to some extent from newly encountered airway narrowing stimuli. Moreover, anti-inflammatory drugs can produce a long-term attenuation of airway sensitivity, at least in atopic asthmatics [75]. However, the need for a reduction in the high maximal response in asthma has not yet been recognized. It may be hypothesized that bronchodilators do not affect the maximal attainable level of airway narrowing, which leaves the risk of severe obstruction in response to high irritant doses. On the other hand, recent evidence of a selective diminishing effect of glucocorticosteroids on the maximal response [68] indicates that anti-inflammatory treatment might be successful in preventing severe degrees of airways obstruction.

3. There is no reason to expect a clear association between measures of bronchial sensitivity and the severity of asthma symptoms. Many research workers have tried to calculate the predictive value of *e.g.* PC_{20} measurements for the diagnosis of bronchial asthma based on clinical symptomatology [76–78]. Their disappointing results are not at all surprising when considering the concept of airways obstruction shown in figure 2.

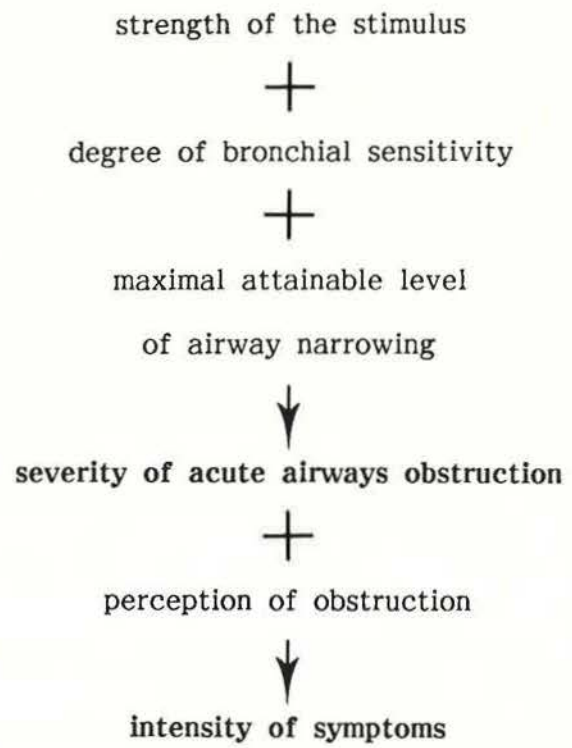

Fig. 2. – Schematic representation of the determinants of the intensity of clinical symptoms of acute airways obstruction.

The severity of symptoms is related to the degree of obstruction, even though the perception of airway narrowing varies considerably among patients [79, 80]. In turn, the degree of obstruction is determined by three factors: the strength of the stimulus, the sensitivity of

the airways, and the maximal attainable degree of airway narrowing. The stronger the stimulus, the lower the sensitivity that is required to induce bronchoconstriction, and *vice versa* [81]. Moreover, at relatively high stimulus levels the maximal attainable degree of airway narrowing determines the ultimate degree of obstruction and thereby presumably the severity of symptoms. It is evident, therefore, that bronchial sensitivity (*e.g.* the PC_{20}) can only be one of the determinants of clinical symptomatology. In our view the level of the maximal response is likely to be a stronger predictor of the severity of symptoms, particularly in patients with asthma.

Conclusion

As for any other physiological measurement, bronchial responsiveness by definition implies a functional characteristic. It appears that bronchial hyperresponsiveness *in vivo* is a composite functional disorder, the main components being bronchial hypersensitivity and excessive airways obstruction. These two abnormalities need to be carefully distinguished, because in adjunct to model studies there is experimental evidence in man of distinct underlying mechanisms. This provides a useful concept of thinking on bronchial hyperresponsiveness in pathophysiological as well as clinical studies. Strict terminology of each component of bronchial hyperresponsiveness is mandatory. The distinction between hypersensitivity and excessive airway narrowing may be included in future definitions of asthma and COPD, in view of appropriate diagnosis and, more importantly, rational therapy. The limitations of this approach are those that apply for any functional characteristic. Bronchial hypersensitivity and excessive airway narrowing are each multicausally determined, indicating that neither bronchial hyperresponsiveness nor each of its components can be a diagnosis in itself.They just form an intermediate between the pathology in the airways and the associated clinical entities. This link is essential as long as asthma and COPD are mainly functionally defined [82].

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Hyperréactivité bronchique. Nécessité d'une distinction entre l'hypersensibilité et un rétrécissement excessif de la voie aérienne. P.J. Sterk, E.H. Bel.

RÉSUMÉ: L'hyperréactivité bronchique est généralement définie comme une augmentation de la sensibilité à une grande variété de stimuli bronchoconstricteurs non sensibilisants, d'origine chimique ou physique. Les patients atteints d'asthme et de BPCO sont caractérisés par une augmentation de cette sensibilité avec en plus, particulièrement dans l'asthme, un rétrécissement excessif de la voie aérienne. Les mécanismes potentiels de l'hyperréactivité bronchique peuvent âtre divisés en ceux qui entraînent une augmentation de la sensibilité (glissement à gauche de la courbe dose-réponse) et ceux responsables d'un degré excessif de rétrécissement de la voie aérienne (augmentation de la réponse maximale). Premièrement, le glissement à gauche est causé théoriquement par une augmentation préjonctionnelle de l'activation des récepteurs des muscles lisses. Des preuves expérimentales en faveur de ce mécanisme apparaissent dans les observations récentes qui suivent: 1) libération accélérée de l'acétylcholine due à des médiateurs inflammatoires, 2) altération des barrières d'accès due à des lésions épithéliales dans l'asthme; 3) augmentation de l'apparition de cellules inflammatoires. En second lieu, l'augmentation de la réponse maximale est due théoriquement à dees phénomènes post-jonctionnels, comme la force et la charge des muscles lisses et l'épaississement de la paroi de la voie aérienne. Les observations en faveur de ces mécanismes sont: 1) la dépendance de la réponse maximale à l'égard du volume pulmonaire; 2) l'altération de la réponse maximale après administration de leukotriène D_4 ou de corticostéroïdes; 3) l'augmentation de la perméabilité vasculaire et le gonflement muqueux après médiateurs inflammatoires; (4) l'hypertrophie et l'hyperplasie des muscles lisses des voies aériennes. En conclusion, des données récentes confirment que l'hyperréactivité bronchique est une anomalie fonctionnelle multifactorielle. A côté des études sur modèles, il y a des preuves expérimentales chez l'homme que l'hypersensibilité et le rétrécissement excessif de la voie aérienne sont des aspects distincts de l'hyperréactivité bronchique. Ceci est en accord avec son expression différente dans les diagnostics cliniques associés d'asthme et de BPCO. La distinction de ces deux composantes de l'hyperréactivité bronchique a des implications cliniques pour le diagnostic et le traitement de ces entités cliniques.
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