Bronchial mechanics in healthy subjects and patients with long-lasting asthma

Luchtweg mechanica bij gezonde personen en bij patiënten met langdurig astma

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Frontpage

Balloons are related to youth and to festivities.

The elastic recoil pressure of an inflated balloon is the driving pressure for its 'expiratory' flow. This flow is limited by the elastic properties of the neck (the 'airway') of the balloon. In this way the balloon represents flow limitation during forced expiration in humans.

The Perspex model on the right shows the intrathoracic airway compression during forced expiration. The left one shows the static situation.

Dit boek en het werk is voor
Marianne, Caroline, Annemieke en Bart

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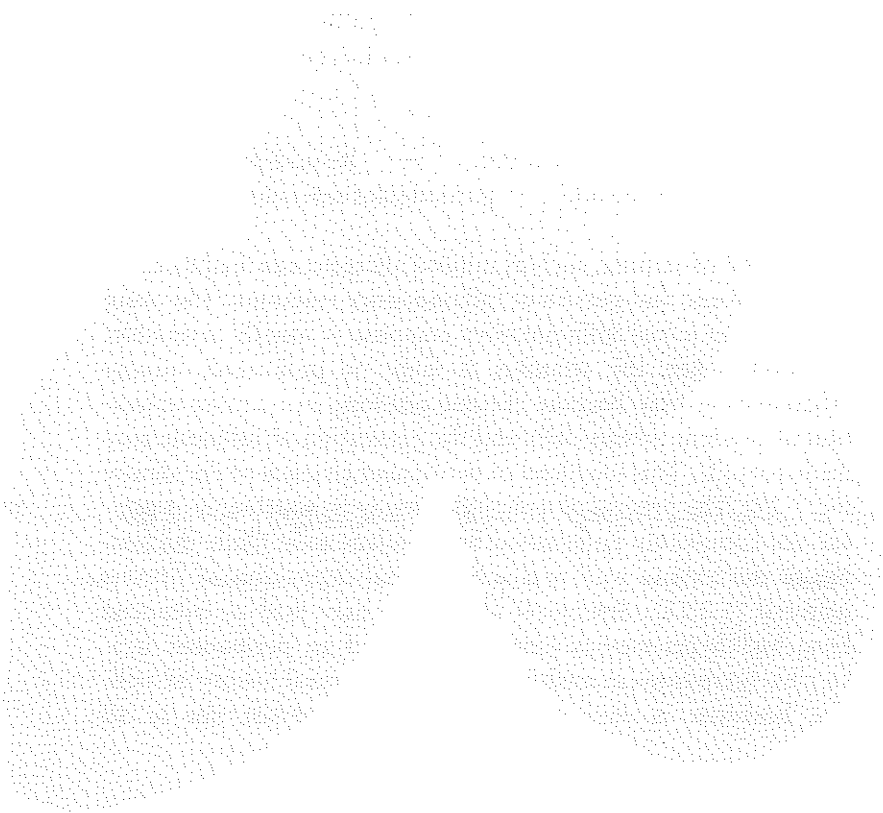
General introduction



ASTHMA

Asthma is one of the most common chronic diseases in children and adults in the Netherlands and in other countries with a 'Western Lifestyle'. It is characterized by recurrent excessive, mostly reversible, narrowing of airway caliber, in response to a variety of endogenous and exogenous stimuli. Increased bronchial responsiveness to the inhalation of non specific irritants is a hallmark of asthma (33) and includes an increase in reactivity as well as in sensitivity of the airway (34;39). Asthma is considered to be a life long disease: it starts at a very young age (17;40) and persists in approximately 40% - 60% of the children into adulthood (9;30). More than 50% of the adult patients with asthma still have symptoms after 25 years (18).
Decreased airway patency in asthma is mainly caused by bronchoconstriction caused by an increased bronchial smooth muscle tone, hypersecretion and edema of the airway wall. These are the result of (chronic) inflammation of the airway wall, nowadays considered to be the major factor in the pathogenesis of asthma in association with bronchial hyperresponsiveness and the level of severity of the disease (3;6).

Acute ↔ Chronic → Remodeling
reversible (partially/not reversible)

'Provokers' of asthma, such as inhaled allergens can lead to acute and/or chronic and persistent inflammatory reactions. The acute phase of the initial inflammatory response is usually reversible. However, when the stimulus is large or prolonged, airway inflammation may become chronic resulting in ongoing activation of resident airway cells and the generation of inflammatory mediators (3). This may lead to permanent changes of the airway (6;27-29). The process of asthmatic airway remodeling is at present not completely understood but involves most likely thickening of the airway wall and subepithelial deposition of fibrous material (1;2;12). Structural alterations may lead to enhanced bronchial hyperresponsiveness (4;12) and to permanent irreversible limitations in airflow (8;37). The natural history of asthma, however, is very variable: symptoms persist not in all

patients, nor does a progressive obstructive lung function disorder develop in all subjects with asthma (9;18;30). The long term evolution of the airway inflammation and lung function in asthma need to be established and their relationship with structural remodeling need to be investigated.

FLOW LIMITATION

The flow volume curve of a forced expiration (the maximal expiratory flow volume (MEFV) curve) is based on the principle that expiratory flow at a given volume is (almost) independent of pressure (and therefore of expiratory effort) and markedly dependent on volume: the lower the volume, the lower is expiratory flow. In other words: expiratory flow is affected by a flow limiting process during forced expiration. The explanation of this process is as follows: coupling of elastic properties of the airways with pressure distribution leads to the formation of a choke point in the intrathoracic airways during forced expiration (chapter 3). The shape of the MEFV curve can thus be considered as a blueprint of the mechanical properties of the lung and airways. The fact that the MEFV curve is highly reproducible within one subject, explains why it could develop into the most widely used pulmonary function test, especially in subjects with airway obstruction.

The shape of the MEFV curve enables us to obtain instantaneous and reliable information about the condition of the lungs and the patency of the airways. However, to give a detailed pathophysiological interpretation of the shape of the MEFV curve is another matter. We understand how the elastic properties of the lung, the resistance of the peripheral airways and the elastic properties of more central airways in general contribute to maximum flows (Chapter 3). However, we are e.g. not informed to what extent the elastic properties of the airways vary in healthy individuals and in patients with obstructive airway disease. This can be explained by the great difficulty in obtaining information, particularly from *in vivo* experiments. We also have to cope with this problem when we want to establish whether peak expiratory flow (PEF) reflects the resistance of the airways from alveoli to

mouth, what the contribution of rapid air compression is to PEF, or whether PEF reflects 'choke flow' plus some compression.

Usually the MEFV curve can be characterized by reproducible configurational details, such as concavities, convexities, and sudden decreases in expiratory flow ('knees') at a given lung volume (35). A number of mechanisms are believed to contribute to the MEFV shape. One is a change in the site of flow limitation within the airways. Studies in a mechanical model and in dogs indicated that a plateau knee configuration occurs when a rather narrow and stiff central airway limits the flow during the initial part of expiration and that at the knee the flow limiting site (FLS) moves (jumps) towards more peripheral airways. Although studies by Smaldone and Smith (32) indicated that the FLS went not much farther than beyond the segmental bronchi in human subjects, it is unknown to what site into the periphery the FLS moves.

By applying the 'waterfall concept' of Pride et al. (26), Smaldone and Bergofski (31) described that the FLS is the most downstream point in the airway, where the transmural pressure is uninfluenced by changes in expiratory effort. FLS may also be defined as the most upstream point where actual airway flow equals the wave speed flow, being the maximum flow permitted through the airway due to the elastic properties of the airway. The latter can be determined from the tube law of the airways. Jones et al. (11) obtained tube laws under static conditions from the relationship between measured transmural pressure and cross sectional area determined optically. An almost similar method was used by Hyatt et al. (10) in excised human lungs.

The wave speed concept of flow limitation (5) has provided insight into the mechanisms determining maximal expiratory flow from the lungs by establishing the relationship between airway elastic properties, lung elastic recoil pressure and frictional pressure losses peripheral to the flow limiting sites. These relationships have been tested in experiments with mechanical models (19-22), in dogs (23), and in excised human lungs (10). However, no data have been obtained in living humans.

In addition to the above mentioned mechanisms, also viscous flow limitation is important, especially at low lung volume (38). Elaborate computer models have been developed to predict the

behavior of the human lung (7;13) but their predictability depends very much on the validity of the data used for the calculations. Reliable and appropriate experimental data are not available on airway elastic properties (tube laws, i.e. airway compliance curves establishing the relationship between the distending airway pressure and the cross sectional area), and/or their variation with airway generation (7). To interpret the configurational details of the MEFV curve, knowledge of supercritical velocity is important. Therefore, the occurrence of flow with supercritical velocity needs to be studied.

Although wave speed flows, predicted from static tube laws, may agree fairly well with the overall maximal flows determined from the MEFV curve, such tube laws are not ideal because they possibly do not reflect the dynamic condition during forced expiration. Firstly, tube laws are volume dependent (15;23) and secondly, they may change during expiration probably due to pressure distribution within the airway (23).

Tube laws may be determined dynamically from intrabronchial pressures, esophageal pressure taken as a measure of pleural pressure (Ppl), and expiratory flow (15;23). Intrabronchial pressures can be measured using a intrabronchially positioned Pitot static probe. This is a device with an endhole for measurement of local impaction pressure and with several sideholes for measurement of lateral airway pressure. In principle, air velocity is determined by use of the Bernoulli equation, stating that the difference (i.e. Pca) between impaction pressure and lateral pressure at a certain point in the airway is proportional to air velocity (v) squared: ($Pca = \frac{1}{2} \bullet \rho \bullet v^2$, ρ = density of air). Next, airway cross sectional area (A) is determined by dividing airflow (V') by velocity ($A = V'/v$), and finally A is related to transmural pressure (Ptm), obtained as the difference between airway lateral pressure and esophageal pressure.

Frictional pressure loss (Pfr), from the alveoli down to the Pitot static probe, can be determined as the pressure difference between lung elastic recoil pressure (Pel), (assumed to be identical during static and dynamic conditions (36)) and the pressure head (J) at the Pitot static probe (i.e. the impaction pressure relative to pleural pressure) (23).

In frictionless flow where Pfr is zero, there is a unique relationship between the maximum flow static recoil (MFSR) curve,

describing maximal expiratory flow (V'max) as a function of Pel, and curves describing A as a function of Ptm at the flow limiting site. If one of the two is known the other can be calculated (20-22). Therefore the MFSR curve, that can easily be obtained in humans, can be transformed into a compliance curve (i.e. a tube law or A/Ptm curve) for the flow limiting segment of the airway. However, if the FLS moves between airways with different tube laws this curve will have a composite appearance reflecting the elastic behavior of the different flow limiting segments. It has also to be taken into account that the validity of this curve depends on the assumptions that peripheral friction loss is negligible and that well defined tube laws exist. Two findings, however, support that frictional losses under certain circumstances may not be very important in this context. Firstly, calculation of A/Ptm curves from MFSR curves in dogs provided curves that were comparable to A/Ptm curves for the bronchial system that could experimentally be obtained by use of the Pitot static probe method mentioned above (23). Secondly, a change in gas physical properties that diminishes viscous frictional losses in the peripheral airways, did not change the compliance curve calculated from the MFSR curve in normal subjects to a great extent (22).

Large epidemiological studies of the configuration of the MEFV curve (14;24;25) showed that a plateau knee configuration is most common in young non-smokers. Age, smoking and disease lead to disappearance of the knee, most likely due to peripheral displacement of the FLS. This indicates that changes in the airway mechanical properties do occur as the result of a chronic stimulus as e.g. chronic asthmatic inflammation. The configuration of the MEFV curve is certainly modified by environmental factors, possibly as early as in childhood (16).
We do know that childhood asthma continues into adulthood (9). The questions arise whether in some or maybe in all young patients with asthma (e.g. puberty or adolescence) a change in airway elastic properties does exist, whether this change is reversible by (a change in) therapy or whether it can be used as a prognostic feature of asthma.

PURPOSE OF THE STUDIES

In the studies in this thesis (patho-) physiology of expiratory flow limitation in man *in vivo* was investigated. The main goal was to study both 'directly in vivo measured' and 'indirectly calculated' airway mechanics during forced expiration in non-smoking young adults, and, furthermore, to extend our physiological knowledge of the end result of asthmatic inflammation. Therefore, both healthy controls and patients with long-lasting mild to moderate asthma were studied in order to test the hypothesis that structural remodeling caused by chronic inflammation of the airway wall, results in altered mechanical properties of the airway.
We applied simultaneously an intrabronchially placed Pitot static probe and an esophageal balloon in order to measure local airway compliance, and to determine the occurrence of flow limitation. Airway parameters calculated from Maximal Flow Static Recoil curves were compared with the *in vivo* Pitot static probe results.

According to this approach we tried to answer the following questions:

- Does airway compliance, as a measure of (remodeled) airway structure, differ between healthy controls and patients with asthma?
  (Chapter 4)
- Where does flow limitation, based on the wave speed concept, occur *in vivo* in human airways?
  (Chapter 5)
- Does chronic airway inflammation (and possible airway wall remodeling) lead to a change in the site of flow limitation in patients with asthma?
  (Chapter 5)
- Can airway elastic behavior be meaningfully described by airway compliance curves derived from MFSR curves?
  (Chapter 6)
- Is Peak Expiratory Flow only determined by effort or by flow limitation as well?
  (Chapter 7).

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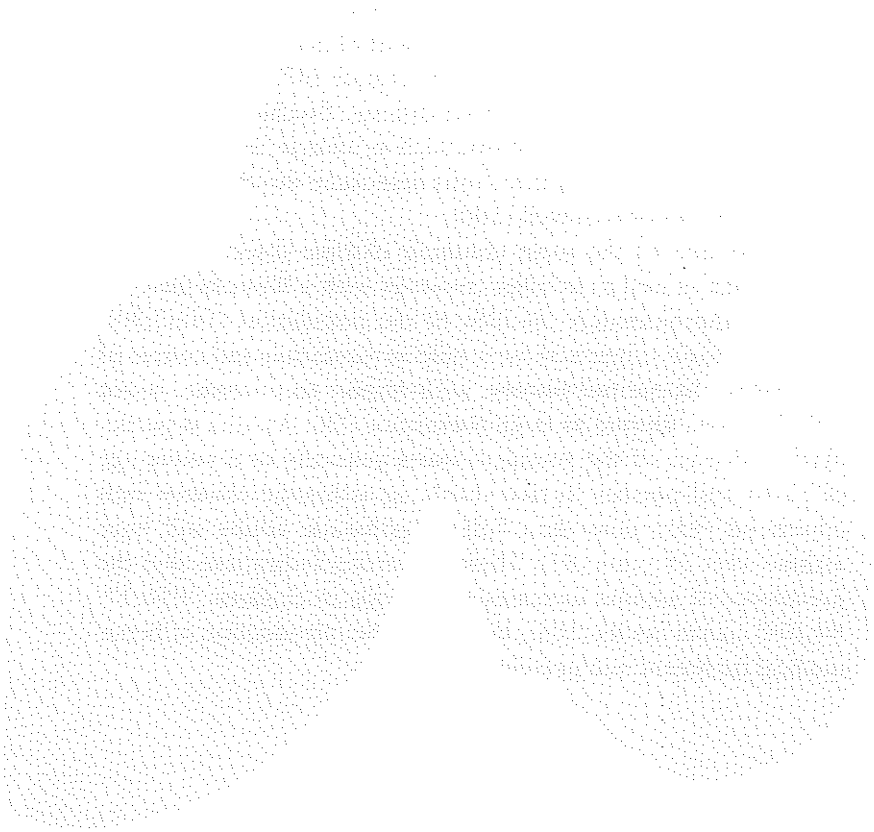
ASTHMA, INFLAMMATION AND REMODELING



GENERAL DESCRIPTION

Asthma has been discussed in medical literature for over 2000 years by its Greek term 'αστμα', meaning panting, as a special, clinical discriminative disorder occurring in people with difficult breathing. The most common symptoms are episodic wheezing, dyspnoe, chest tightness and cough. Bronchial hyperresponsiveness to non specific triggers and irritants like cold air, exercise, cigarette smoke and fog is generally present and is regarded as a hallmark of asthma. Early morning and nocturnal symptoms are characteristic and are related to bronchial hyperresponsiveness (4;76). Most patients with asthma are allergic to airborne allergens and show an early bronchial reaction caused by the direct effects of mediators and a late allergic reaction related to an inflammation of the bronchial mucosa. In most patients with asthma the family history for atopy is positive. The genetic prevalence for non specific bronchial responsiveness and allergy seems to increase with the number of parents or siblings with an atopic disorder (54). Although a genetic predisposition for atopy and possibly for asthma, with assignment of gene loci for allergy to different chromosomes, becomes clearer (87;98), asthma is still considered as a multifactorial disease. Psychological (emotional) and environmental factors, such as allergic, aspecific stimuli and (viral) respiratory infections determine the character and severity of symptoms as well (100).

Asthma is one of the most common chronic disorders in the Netherlands as well as in other countries with a Western lifestyle, affecting approximately 10-20% of the population (54;62;90). Most asthmatic subjects show a mild presentation and course of the disease. Its natural history, with respect to outcome, is not well described despite its large prevalence (18). Asthma is particularly a disease of the young; it starts generally at a young age (67;116) and persists in two thirds of asthmatic children into adulthood (95); more than half of asthmatic adults still have asthma after 25 years (81). There are strong indications that the prevalence of asthma increases worldwide in children (5;16;17; 84;109) and in adults (106), in spite of the introduction of better medical treatment and preventive measures.

In spite of real progress in understanding the nature of asthma and its possible causes in the second half of the last century, the exact pathogenesis remains unclear. This also explains why we still lack a precise, universally accepted definition of asthma, although every experienced clinician immediately recognizes the clinical presentation in childhood as well as in adulthood.

ASTHMA, BRONCHIAL OBSTRUCTION AND BRONCHIAL HYPERRESPONSIVENESS

For many decades, asthma was mainly considered as a disease with varying and reversible bronchial obstruction due to episodic bronchospasm. Therefore the therapeutic approach was focused on symptomatic relief and control and consisted of a bronchodilator, even as maintenance treatment, to regulate smooth muscle contraction. The inaccessibility of airway tissue for further study explains the long lasting lack of understanding the basic mechanism of asthma, and the emphasis on physiological methods to assess airway obstruction in asthma (43). Spirometry and flow volume measurements (65) in the clinical setting and, later, peak flow measurements in the clinic and at home, however, taught physicians to regard asthma more as a chronic disorder with often a disagreement between clinical symptoms and objective measures of airway obstruction (97).

The introduction of pulmonary function tests provided also a tool to assess bronchial hyperresponsiveness objectively. The concept of specific and/or non specific bronchial hyperresponsiveness explained plausibly the paroxysmal symptoms of asthma and gave a link to exogenous triggers, causing exacerbation of bronchial obstruction. Activators of asthma can be divided into two general classes: 'inducers' (cause) and 'provokers' (exacerbation) (75). 'Inducers' are not only considered to increase the intensity of asthma or its severity but also the underlying bronchial inflammation. As such, allergens (14;22), viral respiratory infections (19;20;26;64) and occupational agents (66) increase the severity of asthma and their effects persist long after initial exposure (21). 'Provokers' such as exercise (6;49), exposure to irritants such as fog or cold dry air (78), and emotional

factors induce bronchoconstriction and influence airway obstruction in an acute manner but do not necessarily cause or enhance existing bronchial inflammation.
Bronchial hyperresponsiveness, measured with triggers as histamine or methacholine acting directly on the airway, broadly indicates the severity of the underlying asthma (52). However, repeated measurements over longer periods fail to do so (51). Indirectly acting agonists, such as exercise, cold air, hypotonic or hypertonic saline, adenosine or sodium metabisulphite indicate involvement of nerves and inflammation in bronchial hyperresponsiveness in asthma but correlate only marginally with histamine or methacholine tests. Although tests on bronchial hyperresponsiveness increased insight into the mechanisms of episodic bronchial obstruction, they did not explain why asthmatic airways show an exaggerated response to many different stimuli, occurring in normal life as well. However, they lead to redirection of aims in asthma therapy, nowadays described in 'global guidelines' (77), with elimination of known and/or suspected triggers and the use of 'reactivity modifying' drugs as (inhaled) corticosteroids.

IRREVERSIBILITY OF AIRWAY OBSTRUCTION

Smooth muscle contraction, hypersecretion of mucus and airway wall edema are the main pathophysiologic alterations in asthma responsible for airway obstruction and are potentially reversible. However, all clinicians are familiar with asthmatic patients with a significant degree of airway obstruction persisting in spite of aggressive anti-asthma treatment. Furthermore, some degree of airway hyperresponsiveness persists in most patients with asthma despite prolonged treatment with an (inhaled) corticosteroid. That an irreversible component of bronchial obstruction develops during long existing asthma was confirmed in earlier studies (15;85). More recent studies, that looked into the decline of lung function (63) and into preventive effects of anti-inflammatory asthma therapy (3;40;41;55;80;99), reconfirmed this finding. Lange and coworkers reported that patients with asthma experience a greater decline in FEV1 when compared to control sub-

jects (38 versus 22 ml/yr) (63). Haahtela et al. (40) reported in a longitudinal study comparing an inhaled corticosteroid (budesonide) and a short acting β-2-agonist (terbutaline), that the potential to restore airway obstruction and to decrease bronchial hyperresponsiveness is impaired in patients in whom anti-inflammatory treatment has been postponed. Agertoft and Pedersen (3) found that the annual increase in FEV1 was greatest in children with the shortest duration of asthma at the start of steroid treatment. These findings indicate that postponing the start of anti-inflammatory treatment may cause loss of functional reversibility. This may be explained by the fact that structural changes, which occur in chronic asthma, may be prevented by the use of inhaled corticosteroids. Probably, it is more difficult to reverse these structural changes once they have occurred, than it is to prevent with anti-inflammatory treatment (88). This was also shown by two related Dutch studies by respectively Kerstjens and coworkers and Overbeek and colleagues (55;80). The pathogenesis of these clinical findings is poorly understood but is increasingly related to airway remodeling in the asthmatic airway (31). On the other hand, the clinician can witness that not all patients with long-lasting asthma show a marked loss in reversibility of airway obstruction. Additionally, Merkus et al. showed that growth of airways relative to volume was not significantly different in symptomatic (i.e. respiratory symptoms) and asymptomatic subjects, in spite of persisting lower expiratory flows for a given lung volume in the symptomatic subjects (71). It may therefore be concluded that the intensity and prognosis of 'scar formation' and remodeling in the airways is unpredictable and varies greatly between patients (39). We do not know the risk factors that are responsible for the occurrence of airway remodeling and/or the resulting deterioration of lung function (39).

INFLAMMATION AS THE BASIS OF ASTHMA

The first reports of the pathophysiological features of asthma were based on autopsy findings in patients who had died from asthma. Osler (79) was the first who referred to asthma as 'a special form of inflammation of the smaller bronchi: bronchiolitis exudative', in his first edition of the Principles and Practice of Medicine (1892). In this way he differentiated airway inflammation from 'spasm of the bronchial muscles'. Several other authors described the pathology of asthma from autopsy studies as well (32;35). It took, however, till the 1960's before Dunnill described extensively the cellular components of the airways in asthma deaths compared to other airway disorders (29;30). Gradually a better explanation of the process resulting in asthma death became clear. One recognized increasingly the presence of excess luminal secretion, hypertrophy and hyperplasia of submucosal glands and goblet cells, edema, epithelial damage, thickening of the epithelial basement membrane region, and infiltration of the airway wall with mononuclear cells and granulocytes (mainly eosinophils) in asthma (7;48). Although the presence of airway inflammation was interpreted as characteristic of severe, fatal asthma, the occurrence and recognition of these findings during asthma excacerbations and the association of asthma with other atopic diseases indicated that asthma was more than only airway smooth muscle dysfunction.

The development and use of fiberoptic bronchoscopy with bronchial alveolar lavage and biopsy was the breakthrough in the study of the pathogenesis of asthma (1). Histologic evaluation of the airways of asthmatics showed that chronic inflammation of the airway wall (28) is a common feature of asthma, present in severe asthma in a varying degree (7;60), as well as in moderate or even in mild asthma (8;34;48). Asthma inflammation appeared to be multicellular in nature (28;48), with mast cells (53;108), neutrophils, eosinophils (107), macrophages, basophils, lymphocytes, and epithelial cells all present as active participants. Each different cell type showed its own characteristic and important contribution to the development and presentation of airway inflammation. Mast cells and granulocytes are capable of releasing different mediators and proteins which may

affect (the regulation of) airway caliber and lead to changes in bronchial responsiveness.
Ultimately, above findings led to a more extensive definition of asthma (76) as 'a chronic inflammatory disorder of the airways' in which many cells play a role, including mast cells and eosinophils. In susceptible individuals this inflammation causes symptoms that are usually associated with widespread but variable airway obstruction that is often reversible either spontaneously or following bronchodilator treatment, and causes an associated increase in airway responsiveness to a variety of stimuli' (76). As such, two characteristic features define asthma: intermittent reversible airway obstruction and airway hyperresponsiveness due to airway inflammation.
The main focus of much recent asthma research has been on establishing a direct link on the one hand between pulmonary function as measure of airway obstruction and (hyper-)responsiveness and on the other hand the profusion and activation state of inflammatory cells. If this link is present, than functional changes could be used as a surrogate for airway inflammation and therefore as an effect marker of anti-inflammatory treatment. However, it is unlikely that this will be possible because inflammatory cells modify airway responses in at least two different ways (42). Firstly, cell released chemical mediators as histamine, leukotrienes, platelet activating factor and various proteases (mediators with a very short half-life) can mediate direct changes in airway patency and airway responsiveness. These factors could explain reasonably well a correlation between airway inflammation and functional changes. However, a second way in which inflammatory cells can modify airway patency and responsiveness is through release of cytokines and chemokines, molecules with intense and long-lasting biologic effects as well in the direct environment of their release as at distant sites (50;94). Cytokines and chemokines cause recruitment of additional inflammatory cells, modification of epithelial cells, mast cells and smooth muscle cells and result in changes in the non cellular components of the airway wall (42). An example is eosinophilic cationic protein that can stimulate fibroblasts, causing among other things, modifications in the proteoglycan metabolism (104) which may result in thickening of the airway wall (92). At the time the effects of cytokines are apparent, it is quite possible that

the original inciting cells may no longer be present, as described in a study by Crimi et al. (24). They found no correlation between methacholine hyperresponsiveness and the number of inflammatory cells. If one assumes that airway hyperresponsiveness is an expression of the pathobiologic process in asthma, then it may be accompanied by cellular infiltration, like e.g. a late phase asthmatic reaction (2;27;47;96). However, bronchial hyperresponsiveness may also be solely associated with chronic thickening of the airway wall (46;110).

In other words: asthma can be regarded as an inflammatory disorder, but the relationship between the number of inflammatory cells in the airway wall and measures of airway function is not very strong and may vary. This indicates that other factors, e.g. airway remodeling, are related to airway patency as well (42).

REMODELING

The concept of asthma as a chronic inflammatory disorder was widely accepted in the last decade. At the same time, however, careful histologic and morphometric studies showed structural changes to be present throughout the airway wall (56) even in patients with mild, intermittent asthma (105). These structural changes are grouped under the heading 'airway remodeling' and include airway wall thickening, subepithelial fibrosis, mucous metaplasia, myofibroblast hyperplasia, myocyte hyperplasia and hypertrophy, and vascular abnormalities as its most important features (31).
Many elements, including an increase in airway smooth muscle, edema, infiltration with inflammatory cells, glandular hypertrophy, and connective tissue deposition, contribute to thickening of all components of the airway wall. Models of airway behavior showed that thickening of the airway wall reduces the smooth muscle shortening required for airway closure. These models showed also that the magnitude of airway wall thickening is sufficiently great to explain part of the airway hyperresponsiveness in asthma (46;111). Others suggest that wall thickening hampers the control of airway caliber, causing airway collapse (36).

Electron microscopic studies demonstrated that, in contrast with earlier conclusions from postmortem studies (45), the basement membrane itself was probably not thickened in asthmatic airways. However, an enhanced deposition of collagen I, III and V, fibronectin and tenascin in the reticular layer beneath the true basement membrane (48;58;59;69;92;93;102;113) was found. The significance of subepithelial fibrosis ('scarring') and other aspects of airway remodeling remain unknown (88). Although the number of myofibroblasts seems to correlate with the duration of asthma (13), there is no clear correlation between the thickness of the subepithelial layer, measured in the large bronchi, and clinical or physiological indicators of asthma severity (92). An injury repair process driven by inflammation is thought to be responsible for the structural changes in the airway wall as seen in airway wall remodeling. These changes are supposed to result not only in partially irreversible airway obstruction but also to contribute to the development and/or persistance of bronchial hyperresponsiveness (33).

PATHOPHYSIOLOGIC CONSEQUENCES OF INFLAMMATION AND REMODELING OF THE AIRWAY IN RELATION TO FLOW LIMITATION IN ASTHMA

Enhanced tone of bronchial smooth muscle, inflammation and edema of the airway wall, increased endothelial and epithelial permeability and hypersecretion are the main characteristics of asthmatic airway obstruction. They may all affect the three main, interrelated determinants of maximal attainable airflow: lung elastic recoil pressure, upstream pressure loss, and airway tube law determined by the relationship between airway distending pressure and airway cross sectional area. As such, these factors contribute directly or indirectly to a decrease in expiratory flow in asthma.

Lung elastic recoil: Several studies have focussed on the elastic properties of the lung parenchyma and reported a reduction of lung elastic recoil pressure in asthma (38;70;115). Mauad and coworkers suggest that disrupture of fiber attachments at the basement membrane in the superficial layer could impair the

mechanism of airway recoil in asthmatic patients (68). Although, a case control study by Merkus et al. (72) showed larger lungs after childhood asthma, it did not support a mechanism with progressive loss of elastic recoil of the lung (72). Artifacts may partly explain a reduced lung elastic recoil pressure in asthma: in case of airway obstruction or even airway closure alveolar pressure is not reflected by mouth pressure. Lung elastic recoil pressure may then be underestimated (57;86). Maximal bronchodilation relieves airway constriction but relaxes contractile elements that contribute to the overall elasticity of the lung, as well (44). This may reduce lung elastic recoil pressure as well.

If indeed lung elastic recoil is decreased in long lasting asthma, this will directly result in a reduced expiratory flow because lung elastic recoil is the main driving pressure for maximal expiratory flow. This may explain partly the apparent irreversibility of airflow in some patients with asthma (11;15;89).

Cross sectional area: An increased airway wall thickness reduces airway cross sectional area and may effect baseline airway resistance (37). Elaborate computer models show that airway wall thickening dramatically affects changes in airway caliber and provide a potential explanation for bronchial hyperresponsiveness (46;74;112). A decrease in local cross sectional area reduces directly the local wave speed and therefore the local maximal attainable expiratory flow (chapter 3). Furthermore, it causes an increase in pressure loss due to friction and therefore an upstream shift of the flow limiting segment which usually leads to a decrease in maximal flow as well.

Airway compliance: Asthmatic airway inflammation is associated with airway wall thickening and subepithelial fibrosis with possible thickening of the basement membrane (13;25;92). The mechanical consequences of subepithelial fibrosis as part of the remodeling process will depend on the chemistry of the different collagen types involved and on the architecture of the collagen deposits. Therefore, it is unclear what the effect will be on e.g. airway compliance.

One can imagine that thickening of all components of the airway wall, as the result of 'scarring' (91) with increased subepithelial deposition of densely packed collagen, will increase the tensile stiffness of the airway wall and resistance to airway deformation (82;83;91). Wilson and coworkers (114) and Colebatch and

associates (23) support this hypothesis. They concluded that the distensibility of asthmatic airways was decreased *in vivo*. Furthermore, Mitchell and colleagues concluded that lung inflammation increased airway wall stiffness from a model of sensitized pig bronchi (73). On the other hand, the process of chronic destruction, healing and repair in asthmatic airways will involve degradation of matrix components, as described by Bousquet and coworkers (9;10). They demonstrated that an abnormal, fragmented, superficial network of elastic fibers as well as patchy, tangled and thickened elastic fibers in the deeper layers, were present in the airways of most asthmatic patients. Electron microscopy studies suggested severe elastolysis with fragmented elastin fibers in the larger airways of asthmatic subjects. This indicates elastic fiber degradation and may explain an increased compressibility of the larger airways, coinciding with a decreased elastic retraction in the lung. Consequently, elastic fiber degradation could lead to an increase in compressibility of the airways coinciding with a decrease in elastic recoil of the lung. Both effects may result in more narrow airways and, possibly, to earlier airway closure during forced expiration in asthmatic subjects. This hypothesis was supported by an *in vitro* study by Bramley and coworkers. They showed that a single asthmatic airway preparation showed less passive tension and a threefold greater shortening than six non asthmatic airway preparations (12). Tiddens and coworkers studied *in vitro* isolated peripheral airways from smokers with different degrees of COPD. They concluded that smooth muscle area and smooth muscle tone, but not total airway wall area are the main determinants for compliance, hysteresis, and collapsibility. Reduction in smooth muscle tone made these peripheral isolated airways more compliant and collapsible (103). An increased local airway compliance will decrease the local wave speed and therefore maximal expiratory flow (chapter 3). This decrease in flow will be augmented by a decrease in elastic recoil as driving expiratory force.

On the other hand, increased collagen fibril density and thickened subepithelial matrix may also increase the tensile stiffness and resistance to deformation of the airway wall (82;83;91). This may have a protective effect because it imposes a greater load on bronchial smooth muscle during bronchoconstriction and possibly prevents excessive airway narrowing (61). However, thicken-

ing of the airway wall may contribute to excessive airway narrowing (46).
Whether and to what extent possible changes in airway compliance, related to asthmatic remodeling, will affect expiratory flow limitation is subject of study in this thesis (chapter 5).

CONCLUSION

The main focus of current research is on the understanding of the cellular and molecular abnormalities in asthmatic inflammation. Eventually this may lead to clarification of its pathogenesis and to preventive strategies. The concept of airway remodeling as the result of chronic airway inflammation and its role in irreversible airway obstruction is widely accepted. However it is still a concept. Attempts to unravel the physiological consequences of the numerous specific histopathologic abnormalities related to airway remodeling are at an early stage of development (33). To learn more about and to be able to influence the prognosis of asthma, knowledge of the mechanisms determining the severity of airway obstruction is necessary (101). Studies, combining physiology, morphology and the molecular basis of asthma are needed to help identify who is at risk of the physiologic consequences of remodeling and to develop new rational therapeutic intervention (101).

The studies in this thesis try to reveal a piece of the puzzle of asthma. They focus on the functional consequences of long lasting asthma with regard to airway mechanics that may not be detected by conventional pulmonary function techniques.

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3

Flow limitation during forced expiration

Physiological background in historical perspective.
Determinants and derived indices.

INTRODUCTION

Maximal Expiratory Flow Volume measurement (MEFV) is the cornerstone of modern lung function assessment. Because, above a certain expiratory effort, the expiratory flow is independent of the pleural pressure, MEFV curves are highly reproducible within one person. The pleural pressure is the result of the expiratory effort and is transferred through the chest wall to the lungs. The effort independence of the maximal expiratory flow together with its volume dependency strongly suggests a flow limiting mechanism within the lung and the airways (4). In this chapter the evolution of our understanding of expiratory flow limitation is described, with special emphasis on the aspects forming the theoretical basis for the experiments described in the chapters 4-7.

It was already recognized in the 19th century that increased expiratory airway resistance could be very disabling to patients with severe obstructive airway disease, since increased effort in breathing resulted in a limited increase in ventilation. Hutchinson (15) was in 1846 the first to report that airway obstruction could be derived from forced expiration, but he did not understand the mechanism.

DESCRIPTIVE APPROACH TO FLOW LIMITATION

In 1892, Einthoven (6) hypothesized intuitively, based on lung function experiments with dogs, that during forced expiration compression of intrathoracic airways results in expiratory flow limitation. He related the peribronchial pressure (Ppb) over the airways with the different segments of the bronchial tree: from the alveoli via small, medium and large bronchi to the trachea (Fig.1). During breathholding, when alveolar pressure equals the pressure in the airways, pressure in the pleural space , and hence in the peribronchial space, is lower ('negative') than pressure in the alveoli by an amount equal to Pel, the elastic recoil pressure of the lung. Einthoven was aware of the fact that this pressure

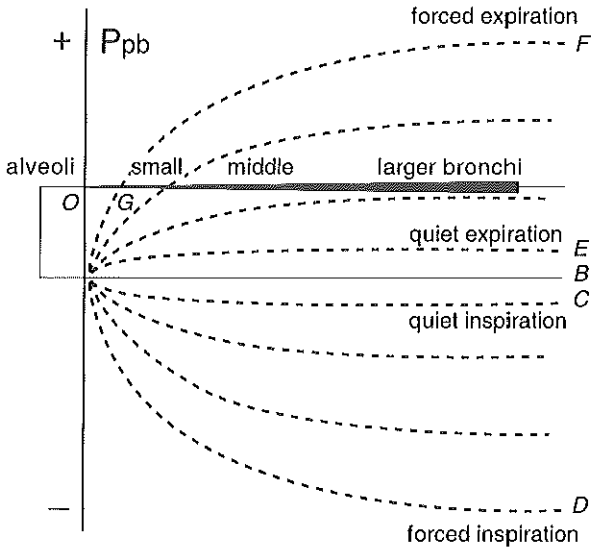


Figure 1

Einthoven's theoretical model of dynamic airway compression (from reference 6). Ppb = peribronchial pressure relative to mouth pressure.
(further explanation: see text).

gradient distends the airways, and that this distending pressure increased during inspiration both because Pel increases with lung volume and drops more than bronchial pressure (curves C and D). During expiration alveolar pressure rises; so does intrabronchial pressure, being highest near the alveoli, and dropping gradually towards the mouth. During quiet expiration the transbronchial pressure gradient still distends the airway (curve E). During a forced expiration, however, the distending pressure may drop to zero at some point in the intrathoracic airways (G)(this was later called the Equal Pressure Point (EPP)). Einthoven hypothesized that, downstream from this point, the airways will be compressed and narrowed. This will result in a hampered, and prolonged expiration, and in increased work of breathing and hyperinflation; i.e. the symptoms of obstructive airway disease. Einthoven found proof of his hypothesis of airway compression and/or collapse in the recruitment of accessory respiratory muscles during an asthma exacerbation and in the closing valve sound his dogs produced when coughing or barking. He suggested that quiet expiration to be of benefit for asthma patients. Nowadays pursed lip breathing is supposed to decrease the expiratory effort patients with chronic airway obstruction. Einthoven's pioneer work was purely descriptive. His suggestions were con-

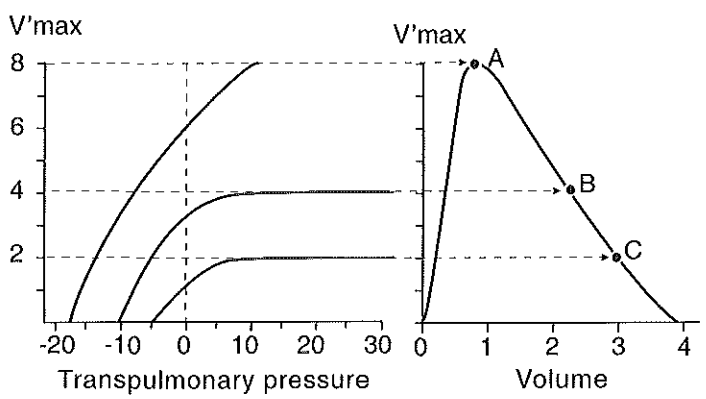
firmed by Dayman (5) who described that the intrathoracic airways behaved as check valves and stressed the importance of the elastic recoil of the lung for the occurrence of maximal expiratory flow.

ISOVOLUME PRESSURE FLOW ANALYSIS (IVPF)

In 1954, Fry and Hyatt showed and quantified actual expiratory flow limitation with their crucial observations (11;12). They obtained inspiratory and expiratory flows at the same lung volume (isovolume) during maneuvers carried out with varying respiratory effort. The effort was estimated from transpulmonary pressure, i.e. the pressure difference between pressure in the pleura (obtained with an esophageal balloon catheter) and pressure in the mouth. Using the flow results at different isovolumes and at different intrathoracic (pleural) pressures, they constructed iso volume pressure flow curves (IVPF curves). Using these curves,

Figure 2

Right: flow - volume plot for a normal subject. Expiratory flow (V'max, l/s) values are plotted against their corresponding volume at A, B, and C and define the MEFV curve (solid line). *Left*: three isovolume pressure flow curves from same object. Curves A, B, and C were measured at volumes of 0.8, 2.3 and 3.0 liters from total lung capacity (TLC), respectively. Transpulmonary pressure (cm H_2O) is the difference between pleural (estimated by an esophageal balloon) and mouth pressures. (figure modified from reference 17)



Fry and coworkers were able to show that the expiratory flow reached a maximum at moderately positive transpulmonary pressures (12). From a family of multiple isovolume pressure maximal flow relations a maximal expiratory flow volume (MEFV) curve could be constructed (9;12). This demonstrated that maximal expiratory flow (V'max) is limited over a large range of the forced vital capacity. This method allowed the analysis of a forced expiratory maneuver in terms of volume, pressure and flow. Fig. 2 shows the IVPF results from measurements in a body plethysmograph recording breathing maneuvers while increasing effort. Flow and transpulmonary pressure values were obtained at specific lung volumes and used to construct the IVPF curves (18;20) and thereby indirectly a MEFV curve. Two important aspects could be deducted from these IVPF curves: 1) at a high level of lung inflation (±TLC) flow increased with increasing positive pressure without a clear limit. This indicated that the effort by subjects, i.e. the force velocity behavior of respiratory muscles, is the limiting factor for maximum expiratory flow (V'max) at high lung volume (curve A). 2) After exhaling ±20% of the forced vital capacity (FVC) the IVPF curves exhibited flow plateaus, indicating that the expiratory flow became effort independent and a flow limiting mechanism occurred in the airways. When lung volume decreased the V'max decreased (curve B and C). Based on experimental data from a rubber model of a bronchial segment, Fry presented evidence that the elastic properties of the intrathoracic pulmonary system and the physical characteristics of the exhaled gas determined the flow at the plateau on the IVPF curves (9;12).

During forced expiration V'max values were highly reproducible when the expiratory pressures exceeded the pressure value at which maximum expiratory flow was reached (12;16;18). Therefore MEFV curves could be constructed from V'max and volume measured simultaneously, without measuring transpulmonary pressure as was demonstrated by Hyatt, Schilder and Fry (20). Because V'max depends on lung volume, it is essential to specify the volume at which V'max is reached. Close to residual volume V'max was considered to become effort dependent because the outward acting elastic recoil of the chest wall antagonizes the driving pressure generated by respiratory muscles contracting at a

disadvantageous length tension relationship at low lung volume.
The above described analysis of pressure and flow in relation to volume was the breakthrough in the concept of expiratory flow limitation in the lung during (forced) expiration, 62 years after the first description by Einthoven. Although such flow limitation had previously been noticed in various vascular beds, an explanation of the underlying mechanisms had never been available and the analysis had only been descriptive.

Fry (9;12) extended his theories by using a mathematical model of flow along an elastic (bronchial) segment, in which the caliber of a compliant tube segment varied with the transmural pressure. By relating the pressure gradient at a certain locus in the tube to the density and viscosity of the gas, the flow and the local area, Fry was able to show that expiratory flow limitation could occur at this particular point. He also predicted that a change in resistance downstream from this point (e.g *in vivo*: upper airway resistance) would only have a slight effect or no effect at all on the local maximal flow. Only after many years some investigators were able to prove the rightness of his predictions. Further elaboration of the work by Fry et al. was hampered because detailed data on the anatomy, geometry and dimensions of the airways, the mechanical properties of the airways and/or the flow regimes in the (human) lung were missing (17). In 1958, Martin and Proctor (31) first described in detail the elastic behavior of dog bronchi. In his classic work from 1963, Weibel gave eventually data that were suitable for modeling the geometry of the human lung (53).
That it was important to correct for gas compression in the evaluation of maximal expiratory flow was recognized by Mead (32) and documented by Ingram and Schilder (22) after the introduction of the volume displacement body box by Mead in 1960 (33). Macklem and coworkers (28;29) measured directly the intrabronchial pressure during forced expiration. They provided as such the first estimates of the dimensions of the airways during forced expiration and of the location of flow limiting points in the airways.

EQUAL PRESSURE POINT (EPP)

In 1967 Mead et al. (35) introduced the descriptive approach to flow limitation during forced expiration in terms of the 'Equal Pressure Point' (EPP) concept. By stating that the alveolar pressure (Palv) is the driving pressure causing gas to flow from alveoli to the mouth, Palv can be regarded as the sum of pleural pressure (Ppl) and the elastic recoil pressure of the lungs (Pel):

$$Palv = Ppl + Pel$$

During rapid and forced expiration Ppl is positive in sign in relation to the mouth pressure (atmospheric pressure). During slow expiration and during inspiration Ppl is negative. There is a drop in pleural pressure to perialveolar and peribronchial pressures during forced expiration, caused by tissue friction. However, this drop in pleural pressure is minimal when compared to the pres-

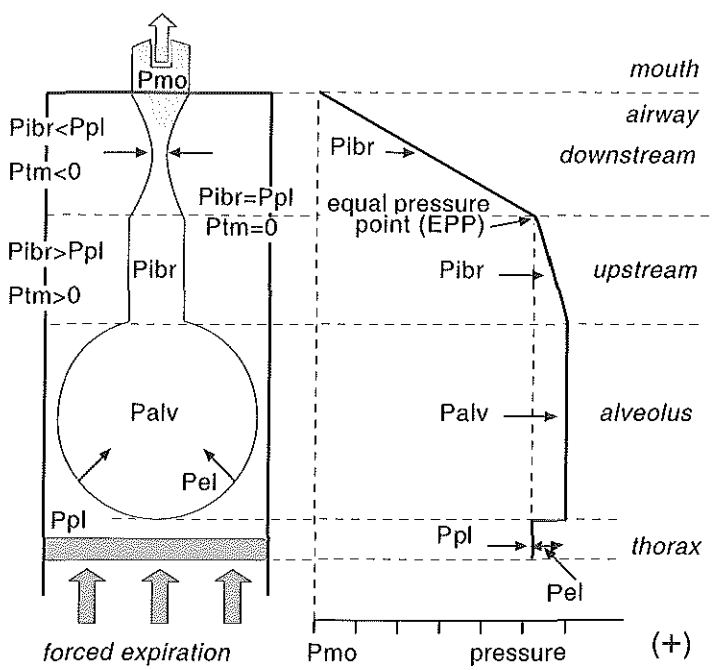


Figure 3

Pressure relationships during forced expiration in a one-compartment model of the lung (with permission from Ph.H.Quanjer). Tammeling GJ, Quanjer PhH. Contours of Breathing. Boehringer Ingelheim s.a., 1978.
(Pmo: mouth pressure, Pibr: intrabronchial pressure, Ppl: pleural pressure, Ptm: transmural pressure, Palv: alveolar pressure, Pel: lung elastic recoil pressure)

sure drop caused by frictional resistance to gas flow in the airway (30). Mead showed indeed that tissue resistance could be neglected (32).
During expiration the intrabronchial pressure falls due to frictional resistance (Pfr) and due to the energy needed to accelerate the air in the convergent bronchial system, i.e. the pressure drop due to convective acceleration (Pca) (35). As Palv represents the total fall in pressure between alveoli and mouth, then at some point in the conducting airways this fall in pressure equals Pel. At this particular point the intrabronchial pressure (Pbr) equals the peribronchial intrathoracic pressure which can be regarded to be similar to Ppl (at least in the extrapulmonary intrathoracic airways). The point where Pbr equals Ppl is called the EPP (Fig. 3). Crucial in the analysis by Mead is that Pel is considered to be the driving pressure in the airways upstream from EPP (alveoli -> EPP) and that Ppl is the remaining driving pressure from EPP to the mouth. A positive transmural pressure Ptm distends the airways upstream from EPP:

$$Ptm = Pbr - Ppl$$

The airways downstream from EPP will be compressed increasingly as the intrabronchial pressure decreases towards the mouth (Ptm becomes more negative). Indirect measurements via neighboring blood vessels suggest that the pressure outside the intrapulmonary airways are negative with respect to Ppl (14;46). Therefore, actual Ptm will remain positive immediately downstream from EPP until a point is reached where the ongoing intrabronchial pressure drop overcomes the difference between Ppl and the peribronchial pressure.

Compression of airways during forced expiration can only take place downstream from the point where Ptm is zero. However, airway narrowing is not a binary phenomenon. The change in airway cross sectional area with changing Ptm is a continuous one and takes place over a wide range of positive as well as negative transmural pressures. The EPP approach divides the bronchial system into two differently behaving parts. When expiratory flow (V') is limited (V' equals maximal flow (V'max)) the bronchial system can be considered as an elastic element empty-

ing through a fixed upstream resistance (Rus) at a given volume:

$$Rus = Pel / V'max$$

in series with a variable resistance in the downstream airways (Rds).

THE LOCATION OF EPP

In the intrathoracic airways, no EPP can exist with a subatmospheric Ppl. With gradually increasing Ppl, the EPP will firstly occur at the thorax aperture when Ppl equals the intratracheal pressure at that site. The EPP will proceed upstream with a further increase in Ppl. In isovolume circumstances the elastic recoil pressure, as driving force, is unchanged. Therefore flow can only increase by a decrease in resistance upstream from EPP (Rus), which is possible by a shortening of the upstream segment (i.e. upstream movement of EPP). The IVPF curves by Fry (5;6;11) demonstrate a plateau indicating a maximal attainable flow (V'max). With both flow and volume (and therefore Pel) fixed, Rus must be fixed at a given volume and thus the geometry of the lung upstream from the fixed location of EPP. Mead explained the phenomenon of reaching a V'max by the lengthening of the downstream segment during this process, causing a greater degree of compression and an increase in resistance downstream of EPP (35) thereby preventing a further increase in expiratory flow and fixation of EPP. According to Mead, the increase in downstream resistance counterbalanced the increase in Ppl with regard to the effect on flow. This phenomenon was observed and proven in experiments with living dogs by Martin (31).

Experiments with *in vivo* intrabronchial measurements of total and lateral airway pressures during forced expiration in man and in dogs by Macklem et al. (28;29) showed that at high lung volumes EPP indeed existed and was located in the large extrapulmonary airways. Airway compression occurred between the segmental bronchi and the glottis at lung volumes between 75% and 25% vital capacity (VC) and was the main factor in limiting expiratory flow. Tracheal resistance varied little with lung vol-

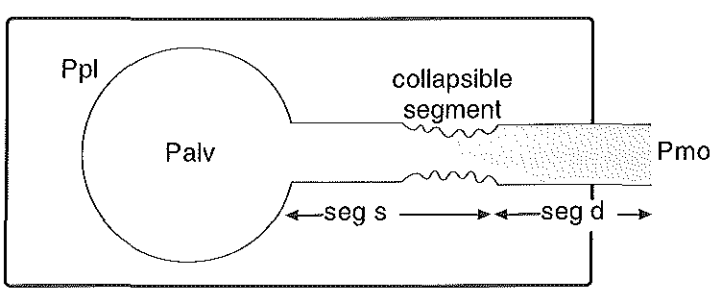
ume but considerably with pleural pressure in contrast with the upstream resistance between alveoli and segmental bronchi, that was largely influenced by lung volume but far less by pleural pressure. At low lung volumes EPP moved beyond the reach of the intrabronchial catheters with a marked decrease in pressure (Pca) required to accelerate air from alveoli to EPP and an increase in pressure loss due to friction (Pfr). Macklem concluded that in normal lungs: "the cross sectional area (A) at EPP (to which Pca is inversely related) and lung elastic recoil are the most important determinants of V'max at high lung volume. At low lung volume V'max is determined mainly by lung elastic recoil and the frictional resistance of airways upstream from EPP" (29).

THE CRITICAL TRANSMURAL PRESSURE (Ptm')

The concept by Mead, which divided the airways in two segments separated by the EPP, was extended by Pride et al. (47) using another descriptive approach to flow limitation. Pride introduced the mechanical elastic properties of the airway wall as determinants of flow limitation and stated that the bronchial collapsibility of the airways downstream from EPP determines at which critical Ptm value (Ptm') instability, compression or collapse of an airway segment occurs. According to the so called 'waterfall' or 'Starling resistor' model by Pride et al., all events downstream from the dynamically compressed airway segment

Figure 4

Waterfall model of the lung by Pride and coworkers (from reference 47). (Palv: alveolar pressure, Ppl: pleural pressure, Pmo: mouth pressure, seg s: upstream segment, seg d: downstream segment)



(with elastic properties characterized by Ptm') are irrelevant with regard to flow limitation (Fig. 4). Pride's model separates therefore the location of EPP and Ptm'. According to Pride et al., the Ptm' locus is the waterfall locus, where actual flow limitation takes place. They concluded from the work by Macklem and Wilson (29) that this waterfall locus had to be located between the segmental bronchi and the trachea in normal subjects and therefore downstream from EPP (47). In this model, both the peripheral and central airways are thought to be a system of collapsible tubes surrounded by pleural pressure and divided in two parts by a collapsible segment with an abrupt narrowing caused by an exceeded Ptm'. Rs (i.e. Rus + something more if Ptm' < 0) and Rd represent subsequently the airway resistance upstream and downstream from those airways where a 'waterfall' with regard to pressure drop occurs during forced expiration. Ptm' quantifies the collapsibility of the airways at the locus of the 'waterfall'. In extra pulmonary airways, Ptm' is determined by the airway wall characteristics: elasticity, smooth muscle tone and surface forces; in the intrapulmonary airways effects of surrounding lung tissue as radial traction and/or compression are added as determinants of Ptm'. The compressed locus in the airways with the waterfall was called the Flow Limiting Segment (FLS). *In vitro* experiments with tracheobronchial trees of dogs (40) supported the theoretical separation of EPP and FLS as assumed from the model. A decrease in lung volume resulted in a shift of EPP towards the periphery whereas the FLS stayed in the central airways over a large volume range. Work by Macklem and Wilson showed that with a fixed volume and expiratory flow the EPP remained fixed somewhere between segmental and lobar bronchi and did not shift with increasing expiratory effort (29). An FLS at the EPP would mean that Ptm', by definition, is zero. According to the Pride model this can only occur in very thin walled airways as is not the case *in vivo*. Therefore a 'waterfall locus' (FLS) occurring at the EPP is unlikely. Macklem and Wilson (29) showed that in normal subjects at the isovolume plateau flow, with increasing expiratory effort, the transmural pressure of the intrathoracic trachea became more negative. This implies that the trachea is downstream from the "waterfall". Therefore the "waterfall locus" had to be located between the segmental bronchi and the trachea in normal subjects.

In summary Based on the above findings the basic mechanism of flow limitation was the coupling of airway compression and a flow dependent drop in intrabronchial pressure (54). On the one hand, the fall in pressure along the airways is essential for the generation of flow and the acceleration of air in a converging bronchial system with a decreasing total airway cross sectional area (Pca). On the other hand, the pressure drop along the airways is the result of laminar and turbulent energy dissipation in the airflow (Pfr). The transmural bronchial pressure (Ptm) in peripheral airways is positive and therefore distending during expiration. Ptm decreases downstream and becomes negative or compressive in more centrally located airways. An increased driving pressure for flow is in balance with a decrease in airway area caused by the decrease in transmural pressure when flow limitation is present.

MODELING FLOW LIMITATION; THE PHYSIOLOGICAL APPROACH

The coincidence that an increase in Ppl as driving force for flow was in balance with a decrease in Ptm and airway area and therefore resulted in flow limitation was remarkable and thus far amazing. The fact that it occurred over a large range of lung volumes in health as well as in disease indicated that local explaining flowlimiting mechanisms had to exist. The qualitative approaches by Mead, Pride, Macklem and others gave some insight into the site of flow limitation and its behavior in various disease states. However, they did not really explain the mechanism of flow limitation itself. Mead et al. and Pride et al. showed the importance of the elastic recoil pressure (Pel) and the transmural pressure to be crucial determinants of maximal flow. Their approaches were, however, mainly based on pressure distribution in the airways and were very limited with regard to the orientation of flow limitation in the bronchial tree. Limitations of their approach were that Ptm' and the upstream and downstream resistance were regarded as relatively 'static', i.e. independent of lung volume. The influences of the properties of the airflow itself (speed, density, and viscosity) and their relation with airway wall properties were only partly taken into account.

The conducting airways in the human lung form a complex system, composed of 23 generations of dichotomic branched elastic tubes, converging from alveoli to the trachea (53). The bronchial system can thus be regarded as a 'trumpet' or even as a 'thumbtack' model: a broad base of ±300 cm^2, representing the total of the area of the respiratory bronchioles, connected with the mouth with a conical shaped airway with a minimum cross sectional area of ± 2 cm^2 at lobar bronchi (53). The total cross sectional area of the conducting human airways decreases thus ± 150 fold from the alveoli to the mouth. The velocity of air at a given flow is negligible at the smallest conducting peripheral airways but accelerates by a factor of more than 100 because of the decrease in total cross sectional area (A) of the conducting airways.
The pressure drop between the alveoli and the mouth results in an expiratory flow, provides the energy for the accelerating velocity of air and compensates for dissipative energy losses associated with laminar and/or turbulent flow (friction).
This intrabronchial pressure drop results in a drop in total pressure (Ptot) by frictional losses as well as in a drop in laterally directed airway pressure (Plat). Focussing on convective acceleration and neglecting unsteady and compressible effects on the exhaled gas, the Bernoulli equation can be used to relate the lateral pressure Plat to the flow speed (v):

$$Plat + \tfrac{1}{2} \bullet \rho \bullet v^2 = C$$

The Bernoulli constant C is the stagnation pressure which is equal to the intrabronchial pressure at any point in the flow when airspeed is zero and dissipative energy losses due to friction are neglected. In the most peripheral bronchioli at alveolar level airspeed is negligible and therefore the Bernoulli constant C equals the alveolar pressure (Palv). If flow has a blunt profile, v is uniform over a cross section (A) of the airways and can be defined as

$$v = V'/A$$

with V' identical to flow at the mouth. Gas compressibility, unsteady changes of volume of airways and frictional pressure losses are neglected in this approach.

The Bernoulli equation can, in this case, be written as (21):

$$Plat = Palv - \tfrac{1}{2} \bullet \rho \bullet V'^2/A^2$$

In other words: the laterally directed pressure (Plat) at a point in the airways is entirely determined by the local flow and the local cross sectional area (A) if the intrabronchial pressure drop is entirely due to convective acceleration. A local mechanism then determines V'max because V'max is totally independent from the variations in A upstream from that point. (The effects of dissipation of energy due to friction and the intrinsic mechanical properties of airways will be discussed elsewhere).

Fry (9;11) in 1968 restudied the problem of flow limitation by a formal mathematical operational approach. He combined one equation describing the mechanics of airway deformation: the cross sectional area (A) of an airway as a function (g) of transpulmonary pressure P and the position (x) along the bronchial tree (A = g(P,x)), with another equation describing the pressure gradient (dP/dx) in the airways as a function of area, position and flow: (dP/dx = g(A,x,V')). Fry pointed out that the coupled set of equations would have to be solved simultaneously, going stepwise from the periphery to the central airways, in order to obtain a solution of local airway properties that could explain a local maximal flow. In other words: for some airway pressure area curves, there is a maximum value of expiratory flow for which a solution for both equations is present.

A graphic example of the mathematical approach by Fry is given in Fig.5 that can be explained as follows:

The following conditions are assumed: a) the bronchial tree is a symmetric binary branching network with a known cross sectional area (A) for each generation, b) the elastic properties ($dA/dPtm$) of the airways of all generations are known (A as function of Ptm is represented as the partial curves labeled with a generation number in Fig. 5, with the generation 3 curve shown as the minimum are a) and c) the only pressure drop in the system is due to convective acceleration: $Pca = \tfrac{1}{2} \bullet \rho \bullet V'^2/A^2$.

At a given static lung volume with a static recoil pressure Pel shown on the abscissa, all intrathoracic airway generations have an A given by the intersection of the A/Ptm curves with the vertical Pel line in the absence of flow. For a given flow V'1 or V'2

(V'1 < V'2) the transmural (distending) airway lumen pressure Ptm is reduced by Pca = ½•ρ•V'^{2}/A^2 (Ptm = Pel - Pca). Theoretical curves of A of a local airway segment as a function of Ptm for a given V'1 or V'2 (V'1 < V'2) are given by the two dashed lines. The actual area and distending pressure Ptm of an airway generation for a given flow are given by the intersections of the generations A/Ptm curves (solid) and the theoretical A/Ptm curves (dashed). Point 'a' gives the minimal actual airway area for a given flow V'1 which happens in generation 3, whereas the actual area's of generation 1 and 2 are given by the vertical line above 'a'. Because at flow V'1 two intersections ('a' and ' a' ') occur with e.g. the generation 3 compliance curve, no stable solution resulting in one unique flow value originates.
With increasing flow (V'1->V'2) the pressure drop between alveoli and generation 3 is large enough that the curve of A versus Ptm is tangent to one of the airway area curves. In Fig. 5 this happens at the tangency point 'b' in generation 3, the corresponding curve is the one shown for flow V'2. Flows larger than V'2 are not possible because the flow pressure area will then not intersect the airway area curve of generation 3: no simultaneous solution would exist for the flow and the airway mechanics at that point in the bronchial tree. In other words airway generation 3 allows no larger flow than flow V'2 and can be regarded as the

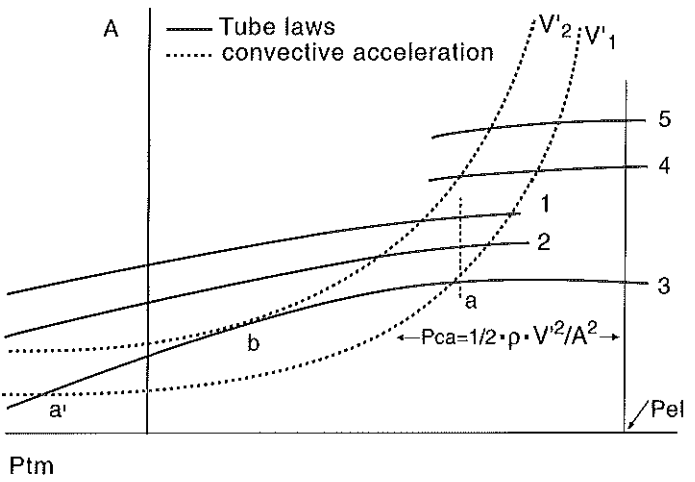


Figure 5

Graphic solution to the limitation of expiratory flow. (explanation: see text)
Curves 1-5: Cross sectional area (A) – distending (transmural) airway pressure (Ptm) curves of 5 different airway generations. V': expiratory flow, Pel: lung elastic recoil pressure, Pca: pressure drop due to convective acceleration.

flowlimiting segment for a flow with a V'2 value. At high lung volumes (at large Pel) and at large flows flow limitation will start in the first generation (e.g. the intrathoracic part of the trachea). With decreasing Pel, decreasing maximal flows and/or increasing upstream pressure drops, the tangency points will occur in the A/Ptm curves of more peripheral airway generations with a higher number and minimal A. At the points of tangency at common values of A and pressure Ptm, a simultaneous solution (the common curve slope) exists for the two equations describing the two curves.

Solving equation Ptm $= Palv - \frac{1}{2} \bullet \rho \bullet V'^2/A^2$ for V', gives:

$$V'max = A \bullet [A/(\rho \bullet dA/dPtm)]^{0.5} \quad (19)$$

(This is the same equation, Dawson and Elliott described later for flow limitation at wave speed (4;7;8)).

This theoretical graphical analysis predicts a maximal flow (V'max) for pressures greater than necessary to obtain V'max. At maximal flow, curves of area against pressures are tangent to curves of actual airway area versus pressure. Maximal flow is entirely determined by the properties of the airway generation with minimal area. The value of maximal flow and the pressure difference required to achieve maximal flow both depend on Pel and therefore on lung volume.

Although this graphical approach was a major simplification, it proved to be successful in Penrose tubing (25) and in the larger extra parenchymal airways in excised dog lungs as a method of predicting flow (23). The simplification being that pressure losses because of friction and turbulence and effects of surrounding lung tissue and disease were not taken into account. However, Fry extended the understanding of flow limitation and made it likely that local airway characteristics play a major role in determining the maximal flow for the total bronchial system. Unfortunately no sufficiently precise data existed about actual flow or airway elastic properties to apply Fry's approach with trustworthy results. The occurrence of flow plateaus on the iso volume pressure flow curves was not explained either.

Subsequently, simplified models were proposed for localized mechanisms that could explain flow limitation. Pardaens et al. (41), Lambert and Wilson (26) and Pedersen et al. (45) all stated

that pressure drop due to convective acceleration (Pca) takes place mainly in the central airways and that frictional pressure is lost mainly in peripheral airways. These qualitative mechanisms can be expressed by a common equation:

$$Plat = Palv - Pfr - Pca = Palv - Pfr - \tfrac{1}{2} \bullet \rho \bullet V'^2/A^2$$

Experiments by Hyatt et al. (21) showed indeed that combining actual measures of Pfr with central airway pressure area plots from excised human lungs resulted in a graphical solution of V'max that agreed with measured maximal flows at high and middle lung volumes. However, at low lung volume this agreement was poor, suggesting that other flowlimiting mechanisms were dominant.

In summary

It was likely that two basic mechanisms were responsible for flow limitation:

1) The coupling of airway compliance with pressure drop due to convective acceleration, occurring at high and middle lung volumes and mostly in central airways (later called the 'wave speed mechanism') and
2) A mechanism related to viscosity dependent pressure loss playing its role mainly at low lung volumes and in the more peripheral airways.

Both mechanisms are summarized in the equation:

$$Plat = Pel - Pfr - \tfrac{1}{2} \bullet \rho \bullet V'^2/A^2$$

WAVE SPEED FLOW LIMITATION

Airways of the lung are compliant meaning that their caliber, i.e. cross sectional area (A), depends on the transmural pressure Ptm. Ptm is the difference between the pressure inside the airways and the peribronchial pressure which approximates the pleural pressure. In case of flow the intrabronchial pressure distribution is determined by lung volume, gas properties, flow and airway caliber. Therefore airway and flowmechanics are coupled by the concept of airway compression. Fry (9-12) and Hyatt (16) under-

stood in a qualitative way that this coupling could lead to flow limitation. Dawson and Elliott (4;5;7;8) provided, however, the most important breakthrough in the understanding of flow limitation and its quantitative modeling. They understood that gas filled airways in the lung behave identical to fluid filled compliant tubes with regard to flow limitation. The wave speed theory of flow limitation states: elastic tubes can not carry fluid at a mean velocity greater than the speed at which a pressure disturbance propagates along the tube. The speed at which a pressure disturbance travels through a fluid filled compliant tube was called wave speed. Not in lung mechanics but during micturation in males, Griffiths et al. (13) explained steady flow by the wave speed mechanism. In the arteries the propagation speed of the pulse is equal to the wave speed. Mathematics in fluid and gas mechanics are the same, only the physical entities differ.
Dawson and Elliott applied the wave speed concept to the bronchial tree and stated that the maximal possible airflow through (compliant) airways is reached when the local air velocity becomes equal to or exceeds the local wave speed at any point in the tube. This point is called the choke point (CP).
Given a compliant tube with a cross sectional area A, a transmural pressure Ptm, a tube wall compliance $dPtm/dA$ and filled with a fluid (or gas) with a density ρ, the wave speed (c) is given by:

$$c = [(A/\rho)\bullet(dPtm/dA)]^{0.5}$$

Because maximal flow V'max is equal to: $A\bullet c$, it follows that

$$V'max = A\bullet[(A/\rho)\bullet(dPtm/dA)]^{0.5}$$

As previously described, the same equations can be derived mathematically from the simultaneous solution of the Ptm/A curve and the V'2 curve at their point of tangency at point 'b' in Fig. 5 in the graphical approach of flow limitation.
It is important to realize that every elastic tube can always be characterized by a wave speed, even if the flow is zero. Wave speed should not be confused with the velocity of the gas. The less dense the fluid or gas is, the stiffer the tube (airway) is, and/or the larger its cross section (the area) is, the higher the

wave speed will be (4;43). Using the wave speed approach, Jones et al. (23) were able to calculate V'max from the A-Ptm-relationship of the flow limiting segments in dog lungs. Hyatt (21) and Mink (39;40) demonstrated graphically the maximal flows in dogs and in man are consistent with wave speed flow at middle and high lung volumes.

In isovolume conditions the wave speed is high when there is no flow or only a low flow. The explanation is that the airways area is large in absence of relevant compression and that the airways are stiff because they are on the upper part of their sigmoid pressure area characteristic, so their $dA/dPtm$ is low. In case of low expiratory flow, the downstream directed gas velocity will only slightly diminish the upstream transmission of a pressure change at the outlet (e.g. the mouth). However, the upstream transmission speed of a downstream located pressure change will fall when expiratory flow increases. This is the result of an increase in opposing airflow velocity and a decrease in wave speed.

The drop in wave speed c is the result of a decrease in transmural pressure Ptm causing a decrease in area A and possibly in airway wall compliance as well. Airway compliance (Caw) may both increase or decrease with decreasing Ptm, according to the shape of A/Ptm curves (Fig. 9). When the upstream velocity of pressure disruption (the wave speed predicted by the wave speed equation) no longer exceeds the actual downstream flow velocity, downstream pressure changes can not move upstream nor affect the flow anymore. Flow has then become independent of downstream events. When this phenomenon happens, flow limitation is a fact and the point in the airways at which it occurs is called the choke point. In this situation the speed index (SI = v/c), as indicator for the occurrence of flow limitation, is equal or larger than one.

The airway area A diminishes during expiration because the tethering force of the lung parenchyma diminishes with decreasing volume and Plat decreases with increasing flow because of the Bernoulli effect, causing more compressive force on the compliant airway walls. At high lung volume the total cross sectional area of the peripheral airways is very large compared to the narrow central airways, explaining the inevitable acceleration of the gas in the converging bronchial system. The large increase in gas velocity due to acceleration when reaching the relative narrow

central airways, leads to further airway narrowing, and therefore to further acceleration up to the point where gas velocity becomes equal to a local wave speed. This also explains that a choke point will occur first where the wave speed flow is minimal, i.e. where airway area cubed divided by airway compliance is minimal. As A is the stronger determinant of the two, the choke point is likely to occur at the narrowest airway segment, being the outlet of the system as was shown by Macklem (28). When lung volume and therefore lung static recoil decrease during expiration, the peripheral total airway area A decreases dramatically, resulting in a net drop in peripheral wave speed. If peripheral wave speed is less than central wave speed, this will result in an upstream movement of the choke point. This can be compared with a shift of the point of tangency in Fig. 5 to area pressure curves of more peripheral airways.

The wave speed concept represents the theoretical approach of the assumption described by Pride (47) that a "waterfall" (or Starling resistor) could occur in any collapsible tube at a critical transmural pressure Ptm'. When the velocity of gas at a (choke) point in the airway is equal to or exceeds the speed of upstream pressure propagation, events (e.g. an outflow pressure drop) downstream from this choke point can no longer influence what will happen at or upstream from this point. This is also the case in a real waterfall: the flow of the waterfall itself is determined by upstream events and independent of changes in the downstream water level up to a certain level. Translated to the lung: an increase in effort (i.e. in pleural pressure) results in a decrease in transmural pressure Ptm. Ptm is the analog of the downstream water level: when Ptm becomes equal to or more negative than a critical Ptm value (Ptm'), Ptm itself can no longer determine the local flow and flow limitation will occur. One can compute V'max for each airway segment from airway wall compliance at all Ptm values. Hyatt et al. (21) predicted accurate maximal expiratory flows in excised human lungs using this quantitative theoretical approach. Mink (38) was able to show that the characteristics of forced expiratory flows at high and middle lung volume in dog lungs agreed with the wave speed model using the same principle.

DETERMINANTS OF Ptm, THE PRESSURE WALK

The wave speed concept explains that the maximal flow through a collapsible tube can be deducted from the product of the wave speed and the cross sectional area of the tube (4). Flow at wave speed (V'ws) is:

$$V'ws = (1/\rho)^{0.5} \bullet (dPtm/dA)^{0.5} \bullet A^{3/2} \qquad (34).$$

Tube compliance ($dA/dPtm$) and gas density as intrinsic factors and local transmural pressure (Ptm) as an extrinsic one, determine the local wave speed flow. $dPtm/dA$ and A can be derived from the pressure area characteristic of the collapsible tube (Fig. 6). The tube characteristics in Fig.6 show stiffening of the tube at the two extremes, a phenomenon that corresponds to real *in vivo* airway characteristics (31). $dPtm/dA$ and V'ws diminish over a wide range with decreasing A. However, with further decreasing of A, at a certain A the stiffness of the tube starts to increase again with an increase of V'ws at the end. Mead pointed out that the tube stiffness $dPtm/dA$ is a local intrinsic factor, mostly determined and/or influenced by local and neighboring conditions (e.g. its directly surrounding tissues) (34). However,

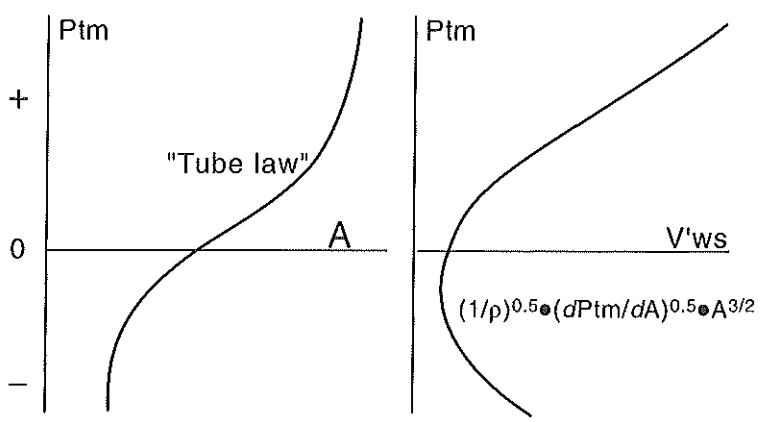
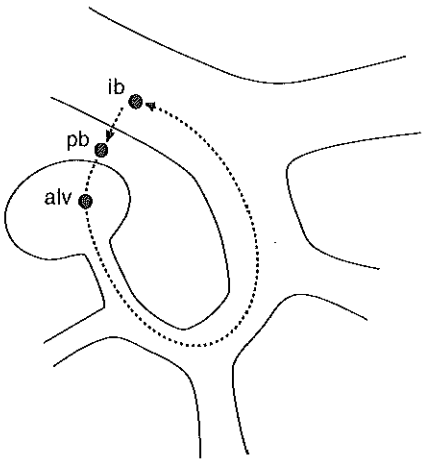


Figure 6

Left: a typical transmural pressure (Ptm) - area (A) characteristic for an elastic tube: the 'tube law'. Right: corresponding wave speed flow (V'ws), based on the equation given in the figure; ρ is the fluid density, and $dPtm/dA$ is the slope of the 'tube law' characteristic at a point. (from reference 34)

Figure 7

A 'map' of the 'pressure walk' by J. Mead. (explanation: see text) (ib: intrabronchial starting point, pb: peribronchial point, alv: alveolus) (from: reference 34)



Ptm is a complicated extrinsic factor determined by factors some of which originate far from this local airway. These extrinsic factors can be illustrated by the "pressure walk" through the lung as pointed out by Mead (34) (Fig. 7). We start in the bronchus (point 'ib') and cross the airway wall into the peribronchial tissue ('pb') further progressing into the alveolus ('alv'). From the alveolus we proceed towards the mouth through the bronchi to our original bronchus ('ib'). Along this walk we encounter several pressures. The first is Ptm (Ptm = Pib - Ppb), the second is the pressure difference between Pb and the alveolus (Ppb - Palv) and the third is the intrabronchial pressure difference between the alveolus and our starting point (Palv-Pib).
The sum (Pib-Ppb)+(Ppb-Palv)+(Palv-Pib) ends up in zero (2nd Kirchoff's law). This 'walk' indicates that Ptm is determined by two (extrinsic) factors:

$$Ptm = (Palv-Ppb) - (Palv-Pib)$$

The first term (Palv-Ppb) equals the lung elastic recoil pressure (Pel) in a homogeneously expanded lung under static conditions (and probably during forced expiration as well (52)) because in such a lung the perialveolar and/or peribronchial pressure is regarded to be similar to the pleural pressure (Ppl)

$$Pel = Palv-Ppl$$

The greater the Pel is, the greater Ptm will be. The second term (Palv-Pib) is zero under static conditions resulting in Ptm equal to Pel and it explains a decrease in Ptm during expiration when Palv is greater than the bronchial pressure (Pib).
During MEFV maneuvers, V'ws decreases over the larger range of the Ptm/A relation with decreasing Ptm (Fig. 6). This may result in V'ws becoming equal to expiratory flow, resulting in local flow imitation.
Palv-Pib has dynamic characteristics during expiration and contains the two components Pca and Pfr. Pca is the pressure drop due to convective acceleration solely determined by the local cross sectional area A at our specific point in the bronchi. Pfr is the pressure drop due to any friction of gas in the conducting airways and is a more complicated term. Pfr depends on: 1) the geometry, length, branching and area of the airways between the alveoli and the starting point of our pressure walk; 2) the density (ρ), 3) the viscosity (μ) and 4) the flow characteristics. For pure laminar flow (expected in peripheral airways) Pfr depends on viscosity. In full turbulent flow, Pfr depends on the density. Between these extremes Pfr depends on both factors and the character of the flow.

In summary

The transmural pressure Ptm at a chosen point in the airways is determined by two main factors. 1) Lung elastic recoil (Pel) is a positively contributing *static* component and is positively correlated to lung volume. Pel can be considered to be independent of flow, contributes to all intrathoracic airways to the same extent and results in positive transmural pressures, which increase with increasing lung volume. 2) The intrabronchial pressure drop is a negatively contributing *dynamic* component. It correlates with flow (Ptm becomes less with expiratory flow), increases with increasing distance between alveoli and the position in the bronchial tree and increases with decreasing cross sectional area A. This dynamic component changes therefore over the bronchial tree.
With increasing expiratory flow, the transmural pressure Ptm decreases from static elastic recoil level progressively along the bronchial tree from alveoli to the thoracic outlet (34).

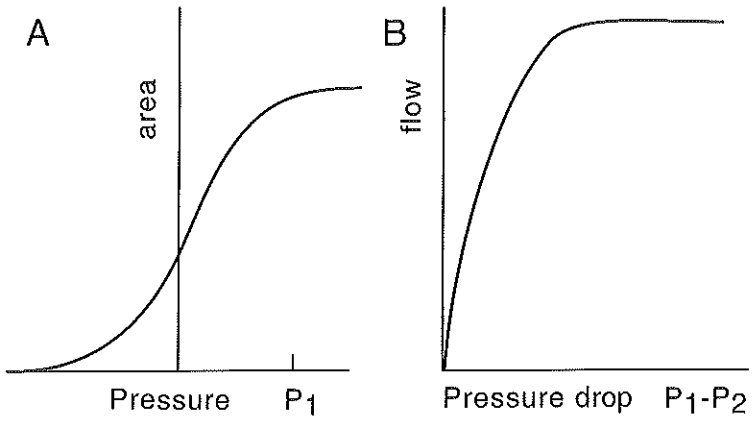


Figure 8

Viscous flow limitation. A: pressure- area curve of a smaller airway. B: if the Poiseuille equation describes the pressure gradient in the flow, then for a fixed pressure at the upstream end of a tube (P_1), flow will depend on the pressure at the downstream end of the tube (P_2). (From Wilson and coworkers, reference 54).

VISCOUS FLOW LIMITATION

The wave speed equation ($c = [(A/\rho)\bullet(dPtm/dA)]^{0.5}$) makes wave speed (c), airway area (A) and airway compliance ($dA/dPtm$) functions of transmural pressure (Ptm). In other words: the laterally directed intrabronchial pressure Plat determines wave speed and therefore maximal flow. However, the intrabronchial pressure will be, apart from the pressure drop due to convective volume acceleration, also be determined by intrabronchial frictional or dissipative pressure losses.

This is illustrated by the poor predictive capability of the wave speed theory at low lung volumes, where (apart from the relatively larger influence of non homogeneity and airway closure) the density dependence of maximum flow is small and the viscosity dependence is large. The frictional loss is dependent on the flow regime being laminar or turbulent. Reynolds and Lee (48;49) described frictional pressure losses in studies of expiratory flow in models and bronchial casts. Pfr, the dissipative gradient along an airway, was expressed by an equation comparable to the Rohrer's equation (50):

$$Pfr = (a+b\bullet Re)\bullet 8\bullet\pi\bullet\mu\bullet V'/A^2$$

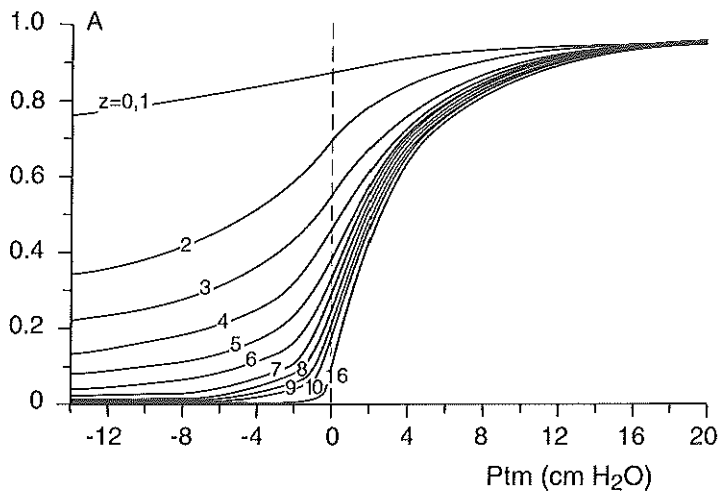
(a and b are experimentally determined parameters, μ being vis-

cosity; the coefficient $8\pi\mu V'/A^2$ is the pressure loss per unit length in Poiseuille flow; Re is the local value of the Reynolds number ($Re = 2 \bullet \rho \bullet V'/\mu \bullet [(\pi \bullet A)^{0.5}]$).
Shapiro (51) used a compliant tube with a pressure area characteristic as shown in Fig. 8 and described purely viscous flow limitation in a compliant tube based on the coupling between the viscous losses and the tube compliance. A viscous flow limit can be reached dependent on diameter and elastic properties of the tube wall, as indicated in Fig. 8b.
The important result of the analysis, described in detail in the paper by Wilson et al. (55) is that in larger central airways wave speed limitation dominates. In smaller peripheral airways the viscous mechanism has already established effectively a limiting flow before the wave speed limit is reached.
Flow passes many parallel paths in the periphery of the lung. The area and the flow through an individual airway in a generation with 'n' parallel airways are respectively A/n and V'/n. According to Weibel the A/n is minimal for the 8th through 12th generations (53). At high lung volume, the wave speed limit on flow in the central airways is less than the viscous limit in the peripheral airways, causing flow limitation to be located in the central airways. At low lung volumes, the viscous limit to expiratory flow in the peripheral airways is lower than the wave speed limit in the central airways (54). Viscous flow limitation has thus become a fact.

WHERE DOES FLOW LIMITATION OCCUR?

The maximal possible flow through an elastic tube can be derived from the tubelaw, an intrinsic purely local feature of a tube, and the Ptm (an extrinsic determinant) according to the wave speed theory. Air is expired through thousands of elastic airways in the human lung. Each airway or airway segment has its own characteristic tubelaw and therefore wave speed flow. Mead (34) gave a 'physiologists view' on the localization of flow limitation in this maze of airways: starting at the alveoli and after passing a number of branches we arrive in parallel airways of similar size and presumably similar tube law. If the tube law of

Figure 9



Airway cross sectional area A (expressed as fraction of maximal A) versus transmural pressure (Ptm (cm H_2O)) for each airway generation from trachea (z=0) through 10th generation. Generations 11-15 lie between z=10 and z=16. The pressure-area curves are according a computational model for expiratory flow by Lambert and coworkers (see text) (from reference 27)

these comparable, parallel operating airways can be expected to be the same, the total tube wave speed flow for the sum of these airways at a specific Ptm is the product of the local wave speed and the total sum of cross sectional areas. Different levels (generations) in the lung are thus characterized by their individual airway size and total wave speed flows. Lambert et al. (24;27) composed pressure area curves ('tube laws') for the generations 0 (trachea) till 16 (Fig. 9). They applied these tube laws in a computer model in order to predict the pressure distribution in the airways, IVPF curves and, above all, maximal flow volume curves. Lambert's choice for basic measured data on human pressure area curves was constrained to pressure area data obtained from central airways by Hyatt (21) and the data by Weibel on the maximal area for all generations (53). However, Lambert's computer model was able to predict sufficiently accurately the average MEFV curves of five human lungs when introducing high compliance values for the peripheral airways.

The wave speed flows of the different generations are highest under static conditions, i.e. no flow. Three features (a, b and c) result in a progressive downstream decrease in wave speed flows and one (d) works opposite in the upstream direction during expiration. All these features are influenced by lung volume.

a) Ptm decreases progressively along the airways during expiration. Therefore wave speed flows can be expected to be the lowest near the farthest point: the thoracic outlet. b) Cross sectional area decreases from alveoli towards the mouth; thereby favoring low wave speed flow near the thoracic outlet. c) The intrapulmonary airways may behave relatively more stiffly compared to the more centrally located extrapulmonary airways as a result of mechanical interdependence between intrapulmonary airways and the surrounding pulmonary parenchyma. This results in relatively lower wave speed flows centrally. d) Airway compliance data from excised dog lungs by Martin (31) showed that excised trachea's have a substantially larger intrinsic stiffness than excised 5 mm airways which, in turn, are stiffer than 2 mm airways. This factor alone would result in a decreasing gradient of tube wave speeds running opposite (upstream) to the gradient of the cross sectional areas.

The localization of developing choke points depends on the (lung volume dependent) contribution of each of these factors. In healthy subjects, at high lung volumes the first three are expected to locate the FLS in the neighborhood of the main carina. Indirect evidence for this claim can be found in the experience that, at high lung volume, only the configuration of the upper part of the MEFV curve will be influenced by stretching and thereby increasing the stiffness of the trachea and carina by neck extension (36). At lower lung volumes, neck extension has no effect indicating that the choke point(s) has (have) moved to more peripheral generations. This was confirmed by intrabronchial pressure measurements in a model and in dogs by Pedersen et al. (2;3;42;44;45). In many subjects the shape of the MEFV curve is irregular with reproducible abrupt changes in MEFV configuration. This can be explained by sudden shifts of flow limitation to other airway levels during expiration. *In vivo*, the proposed lumping of the airways with a comparable size is probably not justified with regard to the prediction of the localization of wave speed flow. Apart from possible intrinsic differences between airways, systematic extrinsic differences can be expected (34). An example is the gravity induced expansion of the upper lobes, resulting in higher local wave speed flows than in comparable airways in the lower lobes. Following this reasoning, it may be expected that multiple choke points may exist

simultaneously. This remains undetected as long as for instance a central choke point still limits the total flow. When the rest of the peripheral airways parallel to one or more already "choking" airways choke as well, the overall flow limitation moves to that level with a different V'max and subsequently a more or less abrupt change in MEFV shape results. In general: the airway level with the lowest V'ws will determine the V'max for the whole lung.

In summary

Intrinsic airway characteristics (e.g. A and tubelaw, modified by mechanical interaction with surrounding lung tissue) and extrinsic factors (e.g. Pel and Ptm, influenced by complicated features of airway flow resistance) are distributed along the bronchial tree and change differently with lung volume. These factors collaborate and/or compete with regard to the process and the localization of expiratory flow imitation in the complex bronchial branching system. To predict where flow limitation will occur is therefore difficult.

CONCLUSION

Many different individual and interdependent factors contribute to the determination of expiratory flow. The wave speed concept of flow limitation explains that the coupling between geometry, size and compliance of the airways, in combination with pressure distribution and flow results in flow limitation (Fig. 10). Although it is an all embracing concept, the phenomenon of expiratory flow limitation has still not been solved completely. As described by Hyatt: 'We are still confused but at a much higher level'(17).

In the studies as described in this thesis, we applied the wave speed concept in combination with intrabronchial measurements in order to obtain more insight in the qualitative and quantitative effects of abnormalities of airway mechanics present in asthma. These abnormalities may be the result of airway remodeling caused by chronic inflammation.

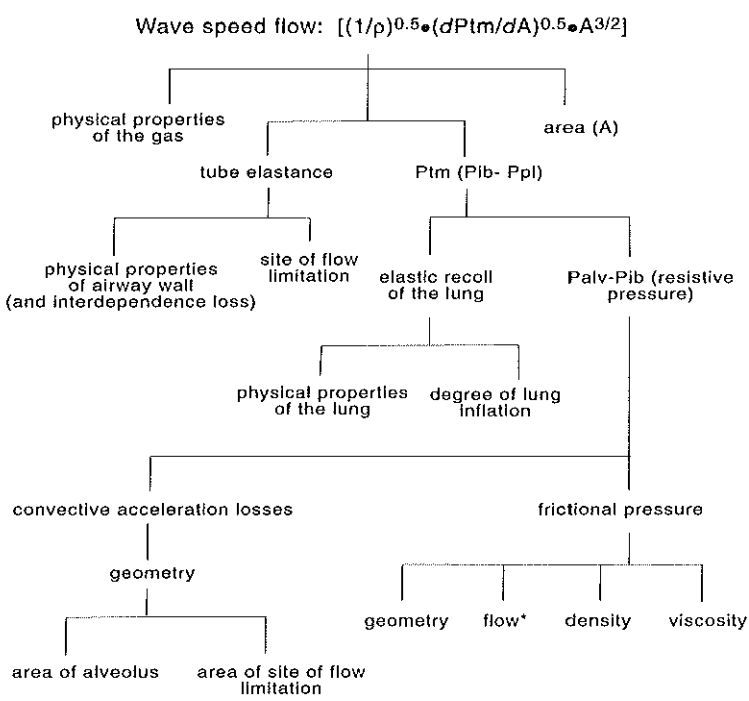


Figure 10

Factors determining wave speed flow limitation
Ppl: pleural pressure, Pib: intrabrochial pressure, Ptm transmural pressure. Palv: alveolar pressure. *: Flow: laminar to fully developed turbulent flow.
(Modified from Beck Wohl (1), with permission from PJFM Merkus (37)).

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4

Central airways behave more stiffly during forced expiration in patients with asthma

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ABSTRACT

Chronic inflammation and extracellular remodeling of the airway wall characterize asthma. The purpose of this study was to examine whether these features cause a change in airway mechanical properties.

We examined 14 healthy and 10 young adults with long-lasting asthma, the latter treated with inhaled bronchodilators and corticosteroids. To obtain area-versus-transmural pressure (A-Ptm) curves during forced expiration (Pedersen O.F. et al. J.Appl. Physiol. 1982; 52: 357-369), we used an esophageal balloon and a Pitot static probe positioned at five locations between the right lower lobe and midtrachea. Cross sectional area (A), airway compliance (Caw = $dA/dPtm$) and specific airway compliance (sCaw = Caw/A) were obtained from the A-Ptm curves.

Results showed that: 1) A was larger in males than in females, 2) Caw and sCaw decreased with a more downstream position and 3) Caw and sCaw were significantly lower in the patients with asthma, with the differences between the asthmatic patients and the healthy subjects becoming smaller toward the trachea.

The lower Caw and sCaw in the patients with long-lasting asthma support the concept that chronic inflammation and remodeling of the airway wall may result in stiffer dynamic elastic properties of the asthmatic airway

INTRODUCTION

Chronic airway inflammation plays a central role in the pathophysiology of asthma. Mucosal biopsies show that in adult patients with different grades of asthma (2;10), even after 10 yr of treatment with inhaled corticosteroids (20), inflammatory changes are present in the airways. Studies of asthmatic children indicate that airway inflammation is present in childhood as well (9;16).

Simultaneously with these effects, extracellular remodeling associated with fibrosis and elastolysis takes place in the airway wall (3), probably as a result of a repair process following acute allergic inflammation and driven by mediator release after chronic allergic inflammation (31). Extensive thickening of the basement membrane, due to subepithelial fibrosis, is commonly observed even in stable asthma (9;15;17) at an early stage (7;17), as well as in childhood asthma (9). The deposition of collagen in the subepithelial matrix is increased (36), and the lamina propria is thickened as a result of increased microvascular permeability and plasma exudation in combination with an increase in the number of blood vessels (19). The entire airway wall is thickened (28), and the percentage cross sectional area (A) of the airway occupied by airway wall tissue is increased by 1.5- to 2- fold (14).

One may expect that these extracellular structural changes within the airway wall alter the mechanical properties of the airways in asthma through geometric effects (31), by changes in tissue biomechanics (36), and a change in the interaction between airways and the surrounding lung parenchyma (30). However, the net airway mechanical effect of these changes remains unclear. Both increased thickening of the airway wall and increased collagen fibril density are important determinants of airway collapsibility, and may stiffen the subepithelial matrix (36) and increase the ability of the airways to withstand bronchoconstriction (18). On the other hand, reorganization and degradation of elastin and cartilage could result in a decrease in airway wall stiffness (4), thereby decreasing the load on airway smooth muscle (31).

The present study was done to test the hypothesis that structural remodeling, together with chronic inflammation of the airway wall, results in altered mechanical airway properties in long-last-

ing asthma. It is the first *in vivo* study comparing differences in airway compliance in asthmatic patients and healthy controls.

METHODS

Subjects

The study was done with 24 non-smoking young adults, consisting of eight healthy female and six healthy male subjects and three female and seven male patients with asthma meeting American Thoracic Society (ATS) criteria (1). The subjects' mean ages and anthropometric data are given in Table 1.

The patients had a history of moderate to severe asthma (27) beginning in early childhood, and had used maintenance treatment with inhaled corticosteroids for at least 3 yr. They exhibited bronchial hyperresponsiveness (BHR) and were atopic, as defined by total IgE > 100 IU/ml and a positive radioallergosorbent test for at least one inhaled allergen. All of the asthma patients were in stable clinical condition. If an exacerbation or a respiratory tract infection had occurred within 1 mo before scheduled measurements, the measurements were postponed until at least 2 wk after recovery. In an attempt to minimize bronchial obstruction caused by edema or hypersecretion at the time of measurements, all of the asthma patients were pretreated with a 10-d tapering course of prednisolone in addition to their regular treatment (45 mg on day 1, 25 mg on study day 7). Within 1.5 h before the Pitot static probe (PS) experiment, all of

Table 1.

Anthropometric data and spirometry results for healthy and asthmatic subjects.

	N	Age	Height	TLC	RV / TLC	FVC	FEV1	FEV1/FVC	PEF
		Yr	Cm	%pred**		%pred**	%pred**		%pred**
Healthy	14	26.1 ± 5.1	179 ± 9	104 ± 9	0.26 ± 0.05	111 ± 8	107 ± 11	0.83 ± 0.07	114 ± 13
Asthma*	10	22.2 ± 3.9	177 ± 10	101 ± 16	0.27 ± 0.05	97 ± 16	85 ± 7	0.76 ± 0.09	90 ± 14
p-value		0.06	0.56	0.50	0.89	0.01	<0.001	0.05	<0.001

PEF = peak expiratory flow.

* Asthmatics: values after bronchodilatation and antiinflammatory treatment. **Means ± sd expressed as percent predicted according to the European Community for Coal and Steel standard (21)

the asthmatic subjects inhaled the dose of terbutaline (generally 1 mg) that had resulted in maximal bronchodilation during recording of a dose-response curve 1 wk before the prednisolone course. The healthy subjects obtained no pretreatment with a β–2-agonist, since they showed no significant change from baseline after inhalation of 1 mg terbutaline.
The medical ethics committee of the University Hospital Rotterdam approved the study. Informed written consent was obtained from all subjects.

Lung Function

Baseline lung function tests consisted of maximal expiratory flow volume (MEFV) maneuvers, whole body plethysmography, and quasistatic pressure-volume (PV) measurements (Table 1). MEFV curves were generated with a pneumotachometer (Jaeger, Würzburg, Germany) with a heated Lilly head. Both the pneumotachometer and the volume constant plethysmograph were part of a Jaeger Masterlab system.
Maximal bronchodilatation was determined during generation of a dose response curve with terbutaline, the need of which was considered if an extra dose of 500 μg of terbutaline resulted in less than a 5% increase in FEV1, expressed as a percent of baseline.
PV measurements were made according to the method of Zapletal and colleagues (43) and the European Community for Coal and Steel Standard (34). A latex balloon 8.5 cm long and with a 2-cm perimeter (International Medical Products bv., Zutphen, the Netherlands) was introduced into the esophagus in such a way that the length of the catheter from the nares to the balloon tip was one-fifth of the subject's body height (in cm) plus 9 cm (43). At the corresponding esophageal location, the pressure proved to be most negative during maximal inspiration. The balloon was filled with 1.5 ml of air, remained *in situ* throughout the subsequent PS probe experiment, and was subsequently checked for leakage.

Equipment

For a detailed description of the equipment used to measure airway pressures, we refer to the studies by Pedersen and colleagues based on similar PS probe experiments (32;33). The PS probe was a device comparable to the one used by Macklem and Mead (21) (Figure 1). The tubes connected to the PS probe for measure-

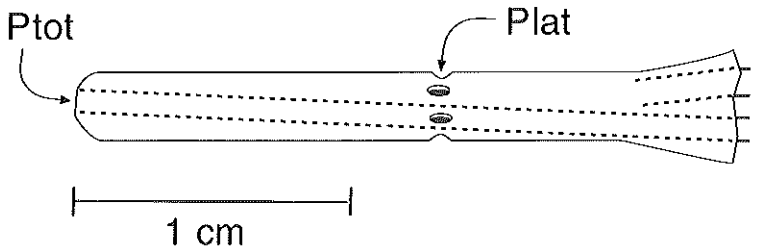

Figure 1

Pitot static probe O.D. = 3mm; hole at tip to record Ptot; 1.3 cm from tip: six lateral holes with 0.5 mm diameter to record Plat. (from reference 22, with permission)

ment of end hole pressure (Ptot) and lateral pressure (Plat), and the tube attached to the esophageal balloon for indirect measurement of pleural pressure (Ppl), were connected to three identical pressure transducers (EMT34; Elema Schönander, Stockholm, Sweden) and via EMT 311 amplifiers to an electronic subtractor. Thus, both the pressure loss due to convective acceleration (Pca) (= Ptot - Plat) and the transmural pressure (Ptm) (= Plat - Ppl) were calculated on line.

Mouth flow (V'm) was measured with a non heated Fleisch no. 3.5 pneumotachograph (Fleisch, Lausanne, Switzerland). Mouth flow and the pressure signals for Pca, Ptm, and Ppl were visible on line. The electronic subtractor, flow amplifier, and PS probe were fabricated for this purpose at the University of Aarhus. The method used for tuning of the catheters among themselves and in combination with the pneumotachometer, and for testing of the PS probe, is described elsewhere (32). During *in vitro* tests, the accuracy of measurement of the A of different rigid tubes was in the range of ± 10% with Pca > 0.5 kPa, except for values of A > 2 cm^2 (32).

Experimental procedure

All subjects were premedicated with 0.5 mg atropine intramuscularly at 0.5 hour before introduction of the PS probe. The mouth, pharynx, vocal cords, and bronchial tree were anesthetized with topical anesthetic. A cuffless endotracheal tube (ETT) was passed between the vocal cords into the trachea after introduction of the bronchoscope. The bronchoscope was pulled back, and, after placing the PS probe with its two catheters into the trachea through the ETT, the tube was removed. Through use of the reintroduced bronchoscope, the tip of the PS probe was positioned just above the entrance of the right lower lobe (in one subject the left lower lobe). This was the most peripheral position (Position

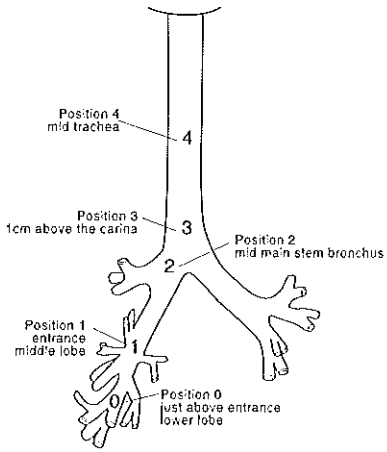

Figure 2

Positions of the Pitot static probe in the bronchial tree.

0) used for measurements. The PS probe was then pulled back under bronchoscopic view until the four other intended locations were reached. These were, respectively, the entrance to the middle lobe (Position 1), the middle of the main stem bronchus (Position 2), 1 cm above the main carina (Position 3) and midtrachea (Position 4) (Figure 2). In the following text, the term 'position' indicates the intrabronchial position of the PS probe unless used in another context. The distance between two intended intrabronchial locations was determined individually by measuring at the subject's mouth the distance across which the catheter was pulled back between these locations. Next, the PS probe was repositioned at Position 0, the bronchoscope was carefully withdrawn, and the two catheters were pushed through and secured in two tightly fitting sideholes in a specially designed mouthpiece. The free ends of the PS probe catheters and the esophageal balloon catheter were then connected to the pressure transducers, and the mouthpiece was connected to the pneumotachograph. For all measurements subjects were in the sitting position in a chair, and were wearing a nose clip. Before each individual forced expiratory maneuver, the Ptot and Plat catheters were flushed forcefully with air to remove secretions from the end and side holes in the PS probe. If the on line visible pressure signals indicated plugging or blockage of the endhole or sideholes, flushing was repeated and/or the PS probe was carefully turned or moved upstream and downstream for a maximum of 1 cm. All subjects were asked to perform several MEFV maneuvers with the PS

probe at each position, starting at Position 0. In addition, most of the subjects were asked to produce sigh and huff maneuvers, for the purpose of another study (21). At each position the procedure was repeated until acceptable results were obtained or four or five maneuvers had been performed. A total up to 30 MEFV maneuvers was performed. A complete PS probe experiment took about 1 to 1.5 h.

Data selection and analysis

Initial assessment of the quality of the experimental maneuvers was done by eye, using the on line visible curves on the computer screen. The V'm, Pca, Ptm and Ppl signals from accepted maneuvers were saved digitally for subsequent calculations. Curves with obvious errors (non maximal effort or blockage of the end-hole or lateral sideholes in the PS probe) were discarded. Asyst software (Asyst Software Technologies Inc., Rochester, N.Y.) and the Statistical Package for Social Sciences (SPSS Inc. Chicago, IL) were applied for data acquisition and calculation of additional variables. Initially, the results of V'm, Ppl, Pca, and Ptm, and their derived variables at 13 different 'levels' of each MEFV maneuver with the PS probe, were selected for further analysis. Each level was characterized by a lung volume equal to 80, 70, 60, 50, 40% TLC, or 75, 50, 25% FVC, or by a V'm equal to 100, 80, 60, 40, or 20% of peak expiratory flow (PEF). Each of these volume or flow levels counted as one 'case' in the subsequent analysis. Ideally, a complete data set from a single PS probe MEFV maneuver therefore consisted of 13 'cases'. Subsequently, cases with a lung volume within 20% to 0% of FVC and cases with Ppl, Pca, airway compliance (Caw) or upstream pressure loss (Pfr) values of zero or less were discarded.
In order to reduce problems of differences in the number of measurements and/or missing values among subjects and/or between positions, all data per variable per position from a single subject were later pooled within the following four lung volume ranges: 100% to 80% , 79% to 60%, 59% to 40% and 39% to 20% of FVC.

Calculations

During each individual MEFV maneuver, with the PS probe *in situ*, data on V'm, Ppl, Pca and Ptm were collected simultaneously. The curves for these variables served as the basis for the calculation of additional parameters. Figure 3 gives an overview of the

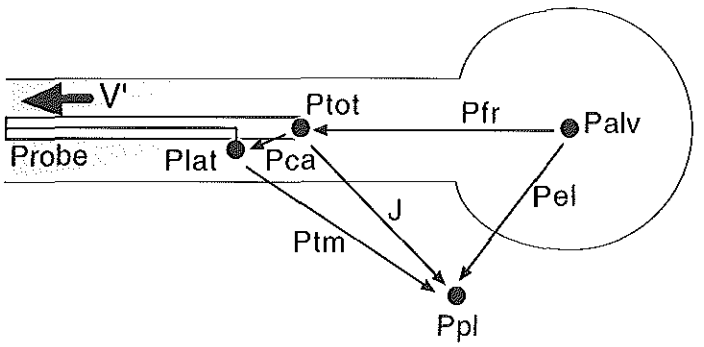

Figure 3

Pressures and pressure differences measured in an airway during expiration.
V' = expiratory flow, Palv = alveolar pressure, Ppl = pleural pressure, Ptot = impaction pressure, Plat = lateral pressure, Pel = lung elastic recoil pressure, Ptm = transmural pressure, Pfr = upstream pressure loss, Pca = pressure loss due to convective acceleration, J = pressure head. (from reference 23, with permission)

different intra- and peribronchial pressures during forced expiration in terms of a 'pressure walk' along the airway, as suggested by Mead (24).
Using the Bernoulli equation, and assuming a blunt velocity profile and an incompressible medium gives:

$$Pca = Ptot - Plat = 100 \bullet \rho \bullet V'^2 / (2 \bullet A^2)$$

where ρ is the density in g/cm^3, A is cross sectional area in cm^2, P is pressure in kPa, and V' is flow in l/s.
A at the PS probe can be calculated if Pca and V' at the PS probe (V'ps) are known. The change in A with change in Ptm is a measure of Caw at the PS probe ($Caw = dA/dPtm$).
For the calculations of V'ps and of other parameters used in the study and for the correction of exhaled volume for intrathoracic pressure (V_{Ppl}) we refer to the article by Pedersen and coworkers (32). A values calculated from Pca values below 0.5 kPa were disregarded in the subsequent analysis, since they proved to be less reliable during testing of the PS probe in rigid tubes (32). V'm was not corrected to body temperature- pressure-saturation conditions, and no attempt was made to correct for the difference in composition of air and alveolar gas. This will introduce a

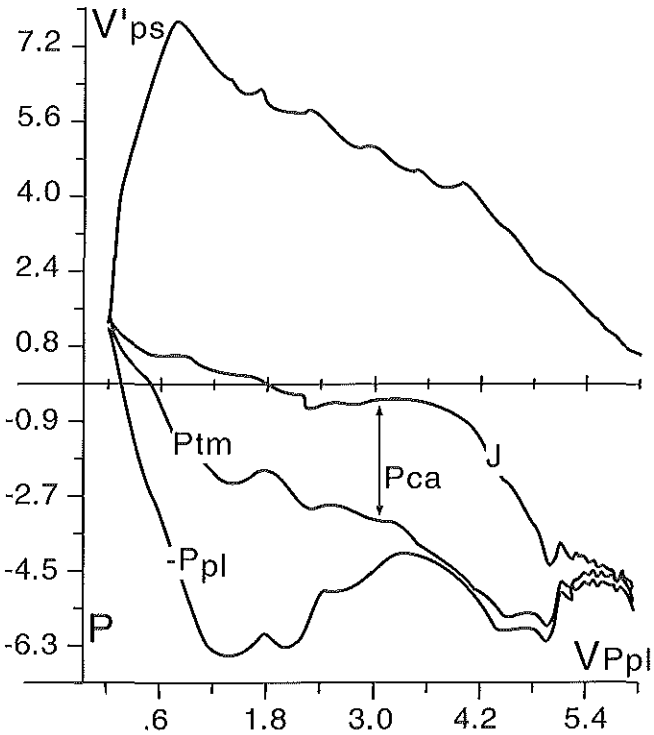

Figure 4a

MEFV maneuver in a healthy subject; local flows and pressures with the Pitot static probe at the lower end of the trachea. V'ps = local flow (l/s), V_{Ppl} = exhaled volume (l), Ptm = transmural pressure, Pca = pressuredrop due to convective acceleration, J = pressure head at tip of the probe, Ppl = pleural pressure (pressures in kPa).

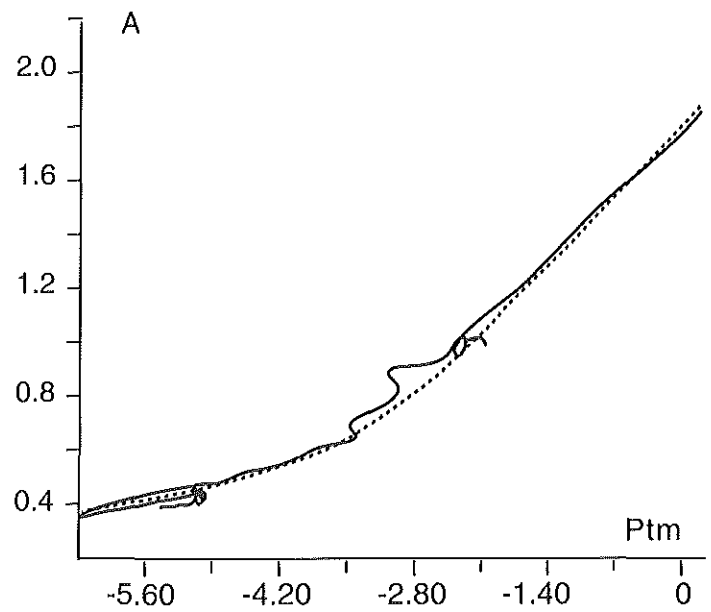

Figure 4b

On line calculated curve of cross sectional area A (cm^2) versus Ptm (kPa) (solid line) and fitted polynomial (dashed line)

small but systematic error in both the asthmatic and the healthy subjects, which we considered to be of no significance in the present study (35).
Figure 4A shows an example of an MEFV maneuver by a healthy subject with the PS probe at the lower end of the trachea (Position 3). V'ps and different pressures at the PS probe was plotted against the change in V_{Ppl}. For each individual PS probe experiment, A at the PS probe was plotted against local Ptm. This generally resulted in a curve with a regular and irregular region (Figure 4B). A 2nd- to 5th-degree polynomial was fitted through the regular part of the A-versus-Ptm curve, and its agreement with the actual curve was assessed visually. The polynomial was saved for subsequent calculation of Caw values (provided by the first order differentiation of the polynomial), together with the lower and upper Ptm values of the fitted part of the A-Ptm curve. For further analysis, A and Caw derived from the polynomial were used. Specific airway compliance (sCaw) was calculated as Caw/A.

Statistics

Lung function results for asthmatic and healthy subjects were compared through a two sample *t*-test. All initial values for A, Ptm, Caw and sCaw were logarithmically transformed.
When two or more values for a variable from a particular subject and specific position within a single volume range were available, the values were averaged. The aim was to ensure that for each subject, all 20 combinations of the five PS probe positions and four volume ranges used in the study contained a single mean logarithmic value of Caw, A, sCaw and Ptm. Nevertheless, values for some positions and/or volume ranges were still missing for some subjects.
The outcome variables A, Caw, sCaw and Ptm were then analyzed, using release 7 of the BMDP software system, module 5V (BMDP Statistical Software Inc., Los Angeles, CA), by applying analysis of variance (rmANOVA).
In this analysis, the following independent factors were used: 1) two intersubject factors, each with two levels: sex (male/female) and asthma (yes/no); and 2) two intrasubject factors: volume (four ordinal levels) and position (five ordinal levels [pos]).
The assumed variance or covariance structure of the residuals was compound symmetry. The analysis began with a full model

containing the four explanatory factors just described (volume and position as categorical factors) and all of their first order interactions.

The initially used full model was as follows: predicted variable = dis + sex + pos + volume + dis•sex + dis•pos + dis•volume + sex•pos + sex•volume + pos•volume, with dis = disease and pos = airway position.

A backward elimination method was then applied, using likelihood ratio tests (embedding tests), in which in each step the factor with the highest p value above 0.05 was eliminated, in hierarchical fashion starting with the first order interaction (i.e., main effects were not eliminated as long as they had a significant interaction with one of the other factors). If the restricted model thus selected still contained at least one of the categorical (ordinal) factors of volume and/or position, then these categorical factors were replaced (one at a time) by their continuous (numeric) versions in order to test whether an embedded model with a linear trend gave a better goodness of fit, considering the lesser number of degrees of freedom required for the further restricted model.

As a consequence of the logarithmic transformation, model predictions were back transformed to geometric means, and effects must be interpreted in a multiplicative way.

When in the following text A, Ptm, Caw or sCaw are discussed, their predicted values according to the final model are meant. Otherwise the suffix 'measured' is used. A two sided level of significance of $p < 0.05$ was used.

RESULTS

Data

Because of the invasive nature of the measurements, no complete 13-case data set from each MEVF maneuver with the PS probe could be obtained for each subject at each airway position. For the healthy subjects, an average of 2.9 volume ranges and for the asthmatic subjects an average of three volume ranges with data from each position per subject could be obtained. A data set with 1,477 cases from a total of 218 accepted MEFV maneuvers with the PS probe was used for final analysis of A, Ptm, Caw and sCaw.

Table 2.

Healthy subjects, measured values of cross sectional area of the airway, transmural pressure, airway compliance, and specific airway compliance

Healthy		100-80% FVC	79-60% FVC	59-40% FVC	39-20% FVC
Pos 0	A	1.31 (0.69 / 2.27)	1.17 (0.80 / 1.88)	0.72 (0.44 / 1.02)	0.65 (0.37 / 1.17)
	Ptm	-0.67 (-0.18 / -2.10)	-1.04 (-0.15 / -2.66)	-1.80 (-0.43 / -7.16)	-2.72 (-0.96 / -8.05)
	Caw	0.71 (0.20 / 1.82)	0.60 (0.21 / 1.41)	0.40 (0.11 / 0.88)	0.26 (0.10 / 0.51)
	sCaw	0.54 (0.21 / 1.34)	0.51 (0.19 / 1.32)	0.55 (0.21 / 1.19)	0.41 (0.13 / 1.07
	n	9	10	9	7
Pos 1	A	1.42 (0.87 / 2.27)	1.18 (0.66 / 1.75)	0.87 (0.47 / 1.44)	0.64 (0.08 / 1.40)
	Ptm	-0.87 (-0.41 / -1.51)*	-0.95 (-0.08/ -3.90)	-1.83 (-0.36 / -5.71)	-2.35 (-0.93 / -8.08)
	Caw	0.47 (0.18 / 3.84)	0.39 (0.17 / 2.28)	0.31 (0.08 / 1.49)	0.23 (0.04 / 0.84)
	sCaw	0.33 (0.16 / 1.02)	0.33 (0.16 / 1.36)	0.35 (0.08 / 1.49)	0.36 (0.07 / 1.26)
	n	10	12	13	11
Pos 2	A	1.22 (0.59 / 2.41)	1.07 (0.58 / 1.69)	0.85 (0.52 / 1.37)	0.85 (0.53 / 1.32)
	Ptm	-1.37 (-0.82 / -4.41)	-1.61 (-0.40 / -3.40)	-2.63 (-0.94 / -5.28)	-2.83 (-1.67 / -4.80)
	Caw	0.22 (0.03 / 1.14)	0.27 (0.09 / 0.82)	0.19 (0.04 / 0.59)	0.23 (0.06 / 0.44)
	sCaw	0.18 (0.05 / 0.64)	0.25 (0.08 / 0.57)	0.22 (0.07 / 0.43)	0.27 (0.11 / 0.50)
	n	7	10	8	8
Pos 3	A	1.05 (0.61 / 1.77)	0.84 (0.40 / 2.04)	0.72 (0.33 / 1.29)	0.80 (0.34 / 1.40)
	Ptm	-2.15 (-0.51 / -5.60)	-2.82 (-0.55 / -11.53)	-3.26 (-1.04 / -11.17)	-2.58 (-1.17 / -7.35)
	Caw	0.24 (0.08 / 0.64)	0.12 (0.02 / 0.40)	0.12 (0.03 / 0.81)	0.11 (0.02 / 0.34)
	sCaw	0.23 (0.12 / 0.59)	0.15 (0.03 / 0.45)	0.16 (0.05 / 0.60)	0.14 (0.05 / 0.38)
	n	9	13	12	11
Pos 4	A	0.98 (0.41 / 1.79)	0.90 (0.30 / 1.58)	0.86 (0.42 / 1.67)	1.02 (0.53 / 1.78)
	Ptm	-2.69 (-0.90 / -5.77)	-3.62 (-1.01 / -10.18)	-4.34 (-1.68 / -10.10)	-2.43 (-1.03 / -3.96)
	Caw	0.14 (0.04 / 0.68)	0.12 (0.01 / 1.41)	0.15 (0.04 / 1.36)	0.15 (0.06 / 0.49)
	sCaw	0.14 (0.04 / 0.69	0.13 (0.02 / 0.89)	0.17 (0.07 / 0.81)	0.15 (0.04 / 0.55)
	n	10	13	10	10

A = cross sectional area of airway (cm^2) ; Caw = airway compliance (cm^2/kPa); Ptm = transmural pressure (kPa); sCaw = specific airway compliance (1/kPa); Pos = Pitot static probe position: 0 = at lower lobe, 1 = at middle lobe, 2 = middle of main stem bronchus, 3 = end trachea, 4 = mid trachea; * = calculated in eight subjects. Values are expressed as group geometric means (minimum/ maximum value) of measured values in n subjects.

Table 3

Asthmatic subjects, measured values of cross sectional area of the airway, transmural pressure, airway compliance, and specific airway compliance

Asthma		100-80% FVC	79-60% FVC	59-40% FVC	39-20% FVC
Pos 0	A	0.78 (0.21 / 1.49)	0.63 (0.20 / 1.44)	0.82 (0.57 / 1.32)	0.97 (0.50 / 1.84)
	Ptm	-2.08 (-1.22 / -2.62)	-3.33 (-0.56 / -8.77)	-2.14 (-0.22 / -7.18)*	-2.53 (-1.17 / -4.38)
	Caw	0.11 (0.04 / 0.22)	0.17 (0.07 / 0.85)	0.21 (0.11 / 0.33)	0.16 (0.04 / 0.28)
	sCaw	0.15 (0.04 / 0.43)	0.27 (0.09 / 1.48)	0.25 (0.11 / 0.41)	0.16 (0.04 / 0.35)
	n	6	8	8	7
Pos 1	A	1.38 (0.67 / 2.84)	1.04 (0.54 / 2.41)	1.06 (0.46 / 2.62)	1.14 (0.69 / 2.42)
	Ptm	-1.36 (-0.11 / -5.23)	-2.68 (-0.51 / -6.96)	-2.96 (-1.12 / -8.40)	-2.09 (-0.85 / -5.25)
	Caw	0.19 (0.11 / 0.28)	0.22 (0.07 / 0.57)	0.27 (0.15 / 0.77)	0.21 (0.07 / 0.43)
	sCaw	0.14 (0.04 / 0.33)	0.21 (0.06 / 0.66)	0.26 (0.08 / 0.74)	0.19 (0.08 / 0.39)
	n	7	9	8	6
Pos 2	A	1.41 (0.88 / 2.45)	1.22 (0.62 / 2.58)	1.22 (0.74 / 2.32)	1.37 (0.83 / 3.26)
	Ptm	-1.51 (-0.47 / -2.94)	-2.05 (-0.43 / -4.77)	-2.21 (-0.47 / -5.79)	-2.48 (-0.73 / -7.23)
	Caw	0.20 (0.04 / 1.03)	0.15 (0.06 / 0.24)	0.12 (0.05 / 0.27)	0.14 (0.02 / 0.43)
	sCaw	0.14 (0.03 / 0.42)	0.13 (0.09 / 0.31)	0.10 (0.03 / 0.15)	0.10 (0.01 / 0.17)
	n	7	9	8	7
Pos 3	A	1.02 (0.86 / 1.41)	1.01 (0.63 / 2.13)	0.98 (0.67 / 1.89)	0.97 (0.67 / 1.87)
	Ptm	-1.89 (-0.53 / -4.65)	-3.14 (-1.43 / -7.38)	-3.39 (-1.39 / -7.99)	-3.11 (-1.29 / -7.43)
	Caw	0.15 (0.10 / 0.30)	0.14 (0.07 / 0.24)	0.10 (0.07 / 0.17)	0.12 (0.07 / 0.18)
	sCaw	0.14 (0.09 / 0.35	)0.14 (0.08 / 0.22)	0.11 (0.06 / 0.21)	0.13 (0.07 / 0.20)
	n	6	8	8	7
Pos 4	A	1.13 (0.83 / 1.34)	0.91 (0.43 / 1.35)	0.93 (0.70 / 1.52)	1.10 (0.86 / 1.57)
	Ptm	-3.52 (-1.41 / -7.03)	-4.35 (-0.75 / -12.86)	-4.17 (-0.72 / -12.36)	-3.41 (-0.89 / -9.54)
	Caw	0.17 (0.08 / 0.72	0.10 (0.04 / 0.26)	0.10 (0.05 / 0.22)	0.12 (0.07 / 0.34)
	sCaw	0.15 (0.07 / 0.60)	0.11 (0.05 / 0.19)	0.11 (0.07 / 0.20)	0.11 (0.06 / 0.22)
	n	7	8	8	8

A = cross sectional area of airway (cm^2); Caw = airway compliance (cm^2/kPa); Ptm = transmural pressure (kPa); sCaw = specific airway compliance (1/kPa); Pos = Pitot static probe position: 0 = at lower lobe, 1 = at middle lobe, 2 = middle of main stem bronchus, 3 = end trachea, 4 = mid trachea; * = calculated in seven subjects. Values are expressed as group geometric means (minimum/ maximum value) of measured values in n subjects.

Table 4

Factors explaining the logarithmic values of cross sectional area of the airway, transmural pressure, airway compliance, and specific airway compliance according to the final statistical model

p values	lnA	ln -Ptm	ln Caw	ln sCaw
Disease	0.793	0.654	< 0.001	< 0.001
Sex	0.002	0.003	-	0.018
Position (categorical)	< 0.001	< 0.001	-	-
Position (continuous)	-	-	< 0.001	< 0.001
Volume (categorical)	< 0.001	< 0.001	-	-
Volume (continuous)	-	-	< 0.001	-
Dis · Position	0.002	0.025	< 0.001	0.003
Dis · Volume	< 0.001	< 0.001	-	-
Sex · Position	-	0.039	-	0.013
Sex · Volume	0.019	0.017	-	-

Dis = disease; ln A = logarithm of airway cross sectional area; ln Caw = logarithm of airway compliance; ln -Ptm = logarithm of negative transmural pressure; ln sCaw = logarithm of specific airway compliance; Position = Pitot static probe position; Volume = lung volume range. p-values according to Wald tests of significance of fixed effects and covariates.

Tables 2 and 3 give the geometric means of the values of measured A, Ptm, Caw and sCaw for the healthy and the asthmatic subjects, respectively.

Results for A

A was significantly determined by sex, airway position, volume, the interactions of disease with airway position, and volume level, and of sex with volume (Table 4). In general, A became smaller with decreasing volume, with the greatest decline in A occurring between the volume ranges of 100% to 80% and 79% to 60% FVC. A was smaller in the female subjects at all volume ranges: at 100% to 80% FVC, A_{female} was 65% of A_{male} ($p<0.001$); at 79% to 60% FVC it was 63% of A_{male} ($p<0.001$); at 59% to 40% FVC it was 77% of A_{male} ($p<0.05$); and at 39% to 20% FVC it was 83% of A_{male} ($p>0.1$). The difference in A between males and females did not depend on the healthy or asthmatic status of the subjects or on the position of the PS probe.

Results for Ptm

Ptm became more negative with decreasing volume during forced expiration in the individual subjects. Overall, disease status did not contribute significantly to Ptm. However, there was a significant interaction between disease status and airway position and volume range that contributes in a non-log-linear way to Ptm. In the asthmatic subjects, Ptm was on average more negative in the upstream positions at comparable high lung volumes.

Results for Caw

Caw was log-linearly related to disease status, airway position, and volume level, and to the interaction of disease and airway position. Caw at the entrance of the lower lobe (Position 0) in the asthmatic subjects was 0.52 of local compliance in the healthy subjects. This difference decreased toward the trachea and became minimal at the trachea. In both the asthmatic and the healthy subjects, Caw was lower at a more central position of the PS probe (from Position 0 to Position 4). With each downstream step in position, Caw decreased in the healthy subjects by 29.5 % and in the asthmatic subjects by 10.5 %. In the healthy subjects, Caw at the lower lobe (Position 0) was 4.04 times larger than at the midtrachea (Position 4), whereas in the asthmatic subjects this factor was 1.56.

Results for sCaw

Disease status, sex, airway position, and the interaction of airway position with sex and disease contributed to sCaw in a log-linear way. sCaw was significantly lower in the asthmatic than in the normal subjects (Figure 5: measured sCaw). In contrast to Caw, sCaw was not significantly determined by volume. As could be expected from the dependence of A on sex, sCaw was also determined by sex and was smaller in the male subjects for a given disease status (Table 5). The difference in sCaw between males and females became smaller with a more downstream position. There was no interaction between sex and disease status. With each subsequent downstream position, sCaw decreased by 33% in the healthy females, 24% in the healthy males, 23% in the asthmatic females and 13% in the asthmatic males.

In summary the foregoing results show that: *1*) Central airways of asthmatic subjects behave more stiffly during forced expiration than those of healthy subjects. The difference between healthy and asthmatic subjects became smaller at the level of the trachea. 2) Caw and sCaw decrease with a more downstream

Table 5

Ratio of specific airway compliance in asthmatic versus healthy subjects and in males versus females.

	sCaw asthmatic: Healthy subjects	sCaw male : female
At lower lobe	0.55	0.70
At middle lobe	0.62	0.78
Mid-mainstem bronchus	0.72	0.88
End trachea	0.84	0.99
Midtrachea	0.96	1.12

Definition of abbreviation: sCaw = specific airway compliance

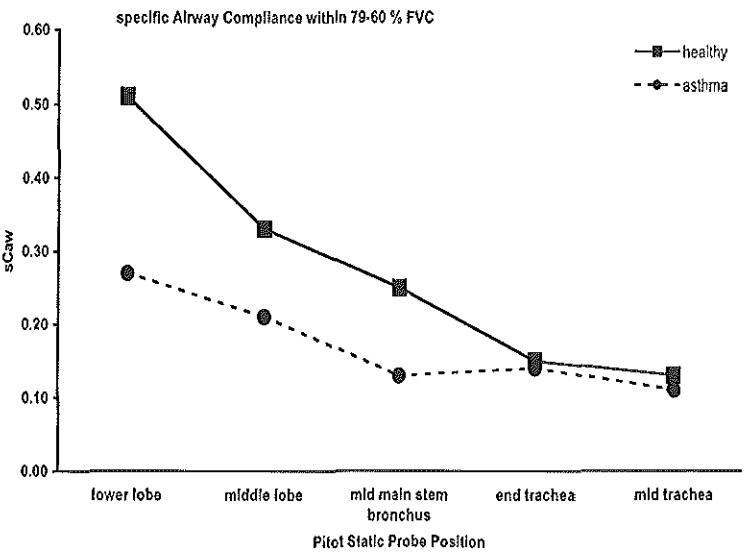

Figure 5

Geometric mean values of measured specific airway compliance (sCaw, 1/kPa) versus Pitot Static Probe position for lung volume range of 79% to 60% FVC in healthy and asthmatic subjects.

position in the tracheobronchial tree. *3*) A in the central airways is larger in males than in females. The difference between the sexes became smaller with decreasing lung volume. *4*) sCaw is volume independent.

DISCUSSION

This is the first *in vivo* study in long-lasting asthma of functional airway change as a possible result of chronic inflammation and structural remodeling of the airway wall. The main purpose of the study was to examine the compliance of central airways during forced expiration in young adult subjects with long-lasting asthma. The results indicate that central airways behave more stiffly in asthma patients than in healthy subjects.

Technical aspects, subjects, spirometry, and data collection and analysis

With regard to the technical aspects of the study and their limitations, we refer to related studies by Pedersen and colleagues (32;33) done with the same method and calculations.

The invasive nature and the time consuming complexity of the experiments conducted in the study limited the inclusion of more volunteers. A complete matching of the two groups could therefore not be obtained (Table 1). However, because we found no significant differences in TLC or measures of airway patency, we assumed that differences between the two groups in lung volume changes caused by air compression could be neglected.

For ethical reasons, only the asthmatic subjects were pretreated with systemic corticosteroids and a β-2-agonist. The β-2-agonist may have reduced bronchial tone and therefore increased Caw in the asthmatics as compared with the healthy subjects (29). The difference found in sCaw may therefore have been even larger before bronchodilatator treatment.

Despite instructions and encouragement, not all subjects could repeatedly exhale across the full range of FVC with the PS probe *in situ*. Typical problems were fits of coughing during the experiment, increased mucus production with a need to swallow, and a premature cessation of local anesthetic effect. At some PS probe positions in some subjects, no reliable data could be obtained because of wedging of the probe, especially at low lung volumes, or because of temporary mucus obstruction of one or more holes in the probe.

Accepted maneuvers could still have contained artifacts over certain volume ranges. These ranges were omitted in the final analysis. Although FVC was lower in the asthmatic subjects, FVC was chosen as the basis for distribution of data over volume ranges

because both FVC and PS probe data were obtained during comparable forced expiratory maneuvers. It was expected that the mechanism(s) responsible for a reduced FVC in the asthmatic subjects also occurred during MEVF maneuvers with the PS probe in these subjects.
For each individual PS probe measurement, only the volume range corresponding specifically to the Ptm range for which the polynomial through the A-Ptm curve was fitted, could be used for analysis. Because this volume range was generally smaller than FVC, this often resulted in less than the intended total of 13 cases per measurement.
These factors explain why almost all subjects had volume ranges with missing data for A, Ptm, Caw and sCaw. However, no clear pattern was noticeable in the distribution of these 'empty' volume ranges among the 10 asthmatic and 14 healthy subjects that could have significantly influenced the results of the multiple regression modeling.
With regard to the differences in A, ln A, Ptm, ln Ptm, Caw, ln Caw, sCaw and ln sCaw between the healthy and the asthmatic subjects, there were no statistically significant differences between the data set used for final analysis and the data set containing the finally excluded cases. This was analyzed for the pooled data of all five PS probe positions and all four volume ranges. Therefore, no bias with regard to the differences found for asthmatic versus healthy subjects and caused by the exclusion of these cases is likely to have occurred. Because data from only 24 subjects were analyzed, we assumed a compound symmetry structure for the variance and covariance matrices of the residuals in the statistical model used in the study, in order to reduce the number of estimated parameters.
The choice for the logarithmic transformation was based on the theory that the physically defined relationships between the various outcome measures (A, Ptm, Caw, and sCaw) imply that values for these variables are generated by multiplicative rather than by additive processes.

Results for A

The values of A found in our study are comparable to those described by Macklem and Wilson (22), who used the same method that we used. Brooks using the acoustic reflection technique, found a mean tracheal area of 1.87 ± 0.1 cm^2 in 11 ado-

lescent subjects (6). This is somewhat larger than our results at midtrachea. However, our findings were obtained during forced expiration with a compressive negative transmural pressure. The value of A throughout the central airways was significantly smaller in the females in our study at all volume ranges, independent of whether they had asthma or not. This is consistent with the difference in A between sexes as found by Martin and colleagues with the acoustic reflection technique during tidal breathing (23).

The decrease in A during forced expiration can be explained by dynamic compression causing a decrease in the dilating effect of Ptm. As shown in our study, Ptm decreases with volume. A may also decrease in direct relation to volume because of a reduction in axial tension and possibly because of a decrease in tethering by surrounding tissue. This is in agreement with findings by others. Hoffstein and associates found that the area of tracheal and bronchial segments increases with an increase in lung volume and transpulmonary pressure (11). Hughes and coworkers found decreasing airway diameters with a history of volume deflation (12).

Results for Ptm

At all positions we found that on average, measured Ptm (= Plat - Ppl) became more negative during forced expiration with decreasing lung volume. This can predominantly be explained as follows: Ppl and therefore peribronchial pressure are maintained during an MEFV maneuver. In contrast, elastic recoil pressure and therefore outward acting intrabronchial pressure (Plat) decrease progressively when lung volume becomes smaller. The end result is a negative Ptm, compressing the airway.

Narrowing of the airways may increase the pressure loss caused by friction and (possibly) by convective acceleration during forced expiration. This leads to a further reduction of intrabronchial pressure and therefore of A. Extra narrowing of the airways stretches the airway-parenchyma attachments and increases parenchymal support. This may lead to a decrease in dynamic airway compliance (Cdyn) (13;38;40).

At comparable (high) lung volumes, Ptm was on average, more negative at the more peripheral positions in the asthmatic subjects. A more leftward (negative) position on the A-Ptm curve of an airway will coincide with a lower A and with a less steep

slope. A more negative Ptm at comparable lung volume may therefore (partly) explain lower Caw values in our study, and may hamper comparison of data on compliance for the asthmatic as compared with the healthy subjects for evaluation of differences in the two groups' airway structures.

Results for Caw and sCaw

The (non-linear) A-Ptm relationship was volume dependent, mainly at high lung volumes, with Ptm becoming more negative and A and Caw decreasing with decreasing lung volume. This was also concluded from similar PS probe experiments in humans during repetitive huff maneuvers by Pedersen and associates (32). This means that the volume at which Caw is measured has to be taken into account when comparing compliance data.
The decrease in Caw with decreasing volume may be caused by cartilage rings moving toward each other when length tension is reduced during exhalation, resulting in stiffer central airways, as reported for calves' tracheas by Suki and coworkers(39). This is in agreement with findings by Olsen and colleagues (29). They observe that muscular constriction of central airways may lead to a decrease in compressibility by covering the soft parts of the airways with sleeves of fibrocartilage (29).
The larger Caw at more upstream airways in both groups of subjects in our study is in agreement with findings in dogs (26) and humans (11).
The dependency of Caw on volume and Ptm complicates the interpretation of differences in Caw in healthy and asthmatic subjects. When Caw was corrected for A (Caw/A = sCaw), the volume dependency of Caw disappeared. This indicates that the decrease in Caw with decreasing lung volume is mainly related to a decrease in A. We also made this finding during maximal effort huff maneuvers in our study of the speed index at peak flow (32).
When correlated with the dependence of A on sex, sCaw was sex dependent: a lower sCaw was found in the central bronchi for male subjects. The difference between males and females in sCaw did not depend on disease status, and became smaller toward the trachea.
Sasaki and colleagues (38), Takishima and coworkers (40) and Nakamura and coworkers (26) deducted from experiments with excised dog lungs that sCaw is independent of Ptm (see appendix). The use of sCaw as a measure of airway elastic properties

therefore circumvents the problem of differences in Ptm between asthmatic and healthy subjects at comparable lung volumes. In the studies just cited, the slope of the change in bronchial volume plotted against the change in the bronchial pressure ($d$logVbr /dPbr) became steeper with a lower distending pressure at a lower elastic recoil. These findings indicate that comparison of elastic behavior of bronchi should preferably be made with sCaw as the most relevant parameter, and at fixed elastic recoil values. This latter condition was met in our study because sCaw was determined over equal ranges of lung volume with comparable elastic recoil values.

In our study, sCaw was significantly lower in the asthmatic than in the healthy subjects, especially at the more peripheral positions in the airway. This strengthens the conclusion that in asthmatic individuals the airway wall behaves more stiffly during forced expiration.

Pathophysiologic interpretation of results

The decrease in sCaw found in our asthmatic subjects may be due to structural remodeling in a chronically inflamed airway wall. However, the net effect on airway mechanics of each of the many different structural changes that occur in the asthmatic airway wall is unclear.

A number of arguments favor the hypothesis that inflammatory remodeling results in a decrease in Caw. Thus, all layers of the airway wall have been found to thicken as a result of extensive formation of granulation tissue (36). The end result may be scar-like tissue with an increased deposition of densely packed subepithelial collagen below an essentially normal epithelial basal lamina (37), with fragments of elastic fibers and with inactive appearing fibroblasts. The mechanical consequences of this probably depend on the chemistry of the different collagen types involved and on the architecture of the collagen deposits. It can be imagined that an increased collagen fibril density and thickened subepithelial matrix will increase the tensile stiffness and resistance to deformation of the airway wall (30;31;36). Indeed, Wilson and colleagues found a reduced increase of airway dead space volume during inspiration in asthmatic as compared with control subjects (42). They suggested that the addition of scar type collagen to the airway wall contributes to a reduction in airway distensibility without reducing airway lumen. Work by

Colebatch and associates supports the notion that airways of asthmatic individuals are less distensible than those of normals (8). However, one may question whether distensibility can be compared with compressibility of airways as a measure of Caw. Mitchell and coworkers conclude, on the basis of a recent model study of sensitized pig bronchi, that lung inflammation increases airway stiffness and, by implication, airway wall load on the smooth muscle (25).

Despite factors that may decrease Caw, airway remodeling in chronic asthma will involve degradation of matrix components as a result of the chronic destruction, healing, and repair that occur in the disease. Bousquet and colleagues reported that an abnormal, fragmented, superficial network of elastic fibers was present in most asthmatic subjects, together with patchy, tangled and thickened elastic fibers of the deeper layers of the airway wall (3;4). Electron microscopy studies suggested a severe elastolysis with fragmented elastin fibers in the asthmatic subjects' large airways, possibly as a consequence of chronic inflammation, and/or mechanical stretching caused by hyperinflation or airway edema in asthma or both (3;4). An intact network of elastic fibers is crucial for the maintenance of structure and mechanical properties of the lung. A consequence of elastic fiber degradation could be an increased compressibility of central airways in long-lasting asthma, coinciding with decreased elastic retraction in the lung. This was supported by the finding of Bramley and associates that a single asthmatic airway preparation showed less passive tension and a threefold greater shortening than did six nonasthmatic lobar airway preparations, without any difference in the amount of smooth muscle in the two types of preparation (5). Bramley and associates suggested that the release of protease enzymes (such as elastases and/or collagenases) from inflammatory or resident cells degrades elements of the extracellular matrix and reduces airway tissue elastance.

It remains unclear whether these pathophysiologic findings *in vitro* may be extrapolated to the *in vivo* situation, in which many other different factors interact and determine the final mechanical behavior of the airways. Paré and coworkers reported cartilage proteoglycan degradation and cartilage remodeling in each of six fatal cases of asthma, changes that may decrease the force needed to deform the airways (31;36). Recent computational

modeling by Lambert and associates (18) predicted that the Ptm resulting in airway narrowing or collapse depends on the number of folds in the airway mucosa. The degree of mucosal buckling is, according to the computational model studies by Wiggs and colleagues, mainly determined by the compressive stiffness of the airway wall (41). The sum of the elastic moduli of the different layers in the airway wall is therefore an important determinant of airway compressibility.

Main conclusion and implications

We found stiffer airway behavior during forced expiration in stable asthmatic patients than in healthy subjects. This supports the hypothesis that chronic airway inflammation and/or remodeling in asthmatic individuals may lead to a decreased Cdyn of the airways. Since our observations were limited to the central airways, we can not predict whether a decreased compliance can also be found in the more peripheral, intrapulmonary airways. It is unclear how chronic inflammation with subsequent remodeling of the airway wall changes the mechanical properties of the airways. The only way to obtain more insight into this process seems to be by means of *in vivo* measurements. However, the exact role of airway inflammation as a factor contributing to decreased airway compliance can only be assessed when subepithelial structural changes (e.g. collagen) deposition and airway mechanical properties are studied simultaneously.

Increased stiffness of the airway wall will impose a greater load on bronchial smooth muscle during bronchoconstriction, and therefore has, to a certain degree, a protective effect. However, it does not rule out the appearance of excessive bronchoconstriction related to BHR, because many factors causing thickened airways also contribute to excessive airway narrowing (14).

The finding in relatively young asthmatic subjects of functional abnormalities of the airways as a possible result of long lasting inflammation stresses the importance of preventing and treating the airway inflammation in asthma as early and optimally as possible. It has to be kept in mind, however, that the possible long-term effects of these functional abnormalities remain unknown.

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APPENDIX

Sasaki and colleagues (38), Takishima and coworkers (40) and Nakamura and coworkers (26) describe a linear relationship between the logarithm of bronchial volume (Vbr), expressed as a percent of Vbr at zero bronchial pressure (Pbr), and bronchial pressure Pbr at fixed elastic recoil values. This was true except for the range of 100 to 80% of initial Vbr.

The following equation can be applied to the linear relationship between log Vbr and Pbr: slope = $d\log Vbr/dPbr$.

Using Ptm instead of Pbr produces a shift only along the abscissa, and Vbr can be expressed by: Lbr•A, where Lbr= length of the bronchus. Therefore:

$$
\begin{aligned}
d\log Vbr/dPbr &= d\log Vbr/dPtm \\
&= [d\log Vbr/dA] \bullet [dA/dPtm] \\
&= \text{constant} \bullet [d\log A/dA] \bullet [dA/dPtm] \\
&= \text{constant} \bullet 1/A \bullet dA/dPtm \\
&= \text{constant} \bullet Caw/A \\
&= \text{constant} \bullet sCaw
\end{aligned}
$$

As the slope is linear, sCaw is a measure of airway elastic properties independent of Ptm.

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5

Flow limitation during forced expiration in healthy and asthmatic subjects

submitted

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ABSTRACT

The occurrence and behavior of flow limitation during forced expiration was studied *in vivo* in 14 healthy and 10 asthmatic subjects. Using an esophageal balloon and a Pitot static probe at 5 positions between right lower lobe and mid trachea, we obtained dynamic cross sectional area transmural pressure (A/Ptm) curves (Pedersen O.F. et al. J. Appl. Physiol. 52: 357-369, 1982). From the A/Ptm curves we obtained airway compliance (Caw=dA/dPtm), flow at wave speed (V'ws = A•[10A/(Caw•ρ)]$^{0.5}$ (ρ is density) and the speed index (SI = V'/V'ws) within 80-40% FVC. SI values ≈ 1, indicative for a local chokepoint (CP), were found at all 5 positions in the healthy subjects and only at the two most upstream positions in the asthmatics. Conclusion: wave speed is reached throughout all central airways in the healthy subjects and only around the lower lobe in the asthmatics. The difference in CP distribution may be explained by changed local airway wall properties related to asthmatic remodeling. It can not be excluded that wave speed is also reached in more peripheral airways and that the most upstream points with flow limitation are located more peripherally.

INTRODUCTION

The various aspects of flow limitation during forced expiration have been subject of study for many years. Fry et al. were the first to point out that, above a certain expiratory effort, expiratory flow is independent of the pleural pressure (6). The effort independence of maximal expiratory flow, together with volume dependency, strongly suggested a flow limiting mechanism within the conducting airways (3) and indicated that Maximal Expiratory Flow Volume measurements (MEFV) could be regarded as the blue print of the mechanical properties of the lung parenchyma and airways. This was supported by the high reproducibility within one subject of concavities, convexities and sudden decreases in flows ('knee's') in the MEFV curve (22,35).

Several mechanisms are believed to determine the shape of the MEFV curve. One of these is the change in site of flow limitation within the airways during forced expiration, as demonstrated e.g. in studies in a mechanical model (24) and in dogs (28). Studies by Mink et al., Smaldone et al. and others indicated that the site of flow limitation during forced expiration is located in the central airways of living dogs (20,33) as well as in excised dog and human lungs (7,19,32). Macklem and coworkers showed during *in vivo* studies in humans that the lobar and segmental bronchi were flow limiting in both normal and obstructed subjects over large ranges of volume (13,16). Smaldone and Smith showed that even near residual volume the dynamic airway compression, as defined by the flow limiting site, occurs in the central airways and did not move beyond subsegmental bronchi (34).

The explanation of flow limitation can be based on the 'wave speed' concept by Dawson and Elliott (3-5). They described that flow is limited at that point in the airway where the velocity of expired air reaches the local speed of wave propagation ('wave speed'). This point is called the choke point (CP) in mechanical terms. The wave speed is a characteristic of an airway (segment) and is determined by its local cross sectional area (A), its compliance and the density (ρ) of the expired gas. Airflow can normally not exceed the local maximal flow, called 'wave speed flow' (V'ws). The airway with the lowest maximal flow determines the maximal flow for the whole lung (3,26) (the weakest link concept) and is called the flow limiting segment (FLS). This is, in general, the most upstream site where local flow equals wave speed flow. The wave speed concept explains that maximal attainable flow during forced expiration is basically determined by the interaction between elastic recoil pressure (Pel), intrabronchial pressure loss upstream to CP (Pfr) and the tube law at CP. The latter is the relationship between the distending transmural pressure (Ptm) and the cross sectional area (A). The slope of this curve represents the airway compliance (Caw).

No *in vivo* results with regard to the location of flow limitation, based on the wave speed concept, have been published for living humans, except at peak expiratory flow (23). Furthermore the effects of (possible) remodeling of the airway wall, due to chronic asthmatic inflammation, on the mechanism of flow limitation and therefore on the shape of the MEFV curve are unknown.

We applied an *in vivo* method, using an intrabronchial Pitot static probe (PS probe), to measure intrabronchial pressure, transmural pressure, airway compliance and the velocity of flow in relation to calculated local wave speed in order to study *in vivo* the occurrence and behavior of choke points and flow limiting segments in central airways during forced expiration. Both healthy subjects and patients with long lasting asthma were studied.

SUBJECTS AND METHODS

Subjects

The mean age and anthropometric data of the participating 14 healthy and 10 asthmatic non-smoking young adults are given in Table 1. The patients had a history of moderate to severe asthma (21), according to ATS criteria (1), since early childhood and used maintenance treatment with inhaled corticosteroids for at

Table 1.

Anthropometric and spirometry data of healthy and asthmatic subjects.

	age yr	height cm	TLC %pred	RV / TLC	FVC %pred	FEV1 %pred	FEV1 / FVC	PEF %pred
8 healthy f	25.8±3.9	173±4	104±9	0.28±0.05	108±9	106±14	0.85±0.06	109±13
6 healthy m	26.5±6.9	187±8	105±11	0.22±0.03	114±7	108±7	0.79±0.08	121±10
healthy f+m	26.1±5.1	179±9	104±9	0.26±0.05	111±8	107±11	0.83±0.07	114±13
3 asthma f	24.9±4.3	166±4	112±25	0.31±0.03	104±30	86±9	0.75±0.16	87±7
7 asthma m	21.1±3.4	182±8	96±10	0.25±0.05	94.3±8	85±7	0.76±0.04	91±17
asthma f+m	22.2±3.9	177±10	101±16	0.27±0.05	97±16	85±7	0.76±0.09	90±14
p (f+m)	0.06	0.56	0.50	0.89	0.01	<0.001	0.05	<0.001

f=female,m=male. asthmatics: values after bronchodilation and anti-inflammatory treatment, values: means ± sd, p: p-value according to a two sample T-test comparing healthy and asthmatic subjects

least the last three years. They were atopic for at least one inhaled allergen and demonstrated bronchial hyperresponsiveness. Although they were in a clinical stable condition, all asthmatics were pretreated with a tapering course of prednisolone (45 mg on day 1, 25 mg on study day 7) in addition to their regular maintenance treatment, in order to minimize possible persistent airway wall edema and hypersecretion due to chronic bronchial inflammation. Measurements were postponed for at least two weeks after recovery in case of a respiratory infection or an exacerbation within one month before scheduled measurements.
One week prior to the prednisolone course all subjects performed a dose response curve with an inhaled bronchodilator. The dose of the β-2-agonist terbutaline that resulted in maximal bronchodilatation (mostly 1 mg) was inhaled by all asthmatics within 1.5 h before the Pitot static probe (PS probe) experiment. Because the healthy subjects showed no significant change from baseline lung function after inhalation of 1 mg terbutaline, they obtained no β-2-agonist prior to the PS probe experiments.
The medical ethics committee of the University Hospital Rotterdam approved the study. It was conducted in conformity with the principles embodied in the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Pulmonary function

Baseline pulmonary function tests (Table 1) consisted of: maximal expiratory flow volume (MEFV) maneuvres with measurement of FVC, FEV1 and peak expiratory flow (PEF); body plethysmography with determination of total lung capacity (TLC) and residual volume (RV) and quasi static pressure-volume (PV) measurements. A 'Jaeger Masterlab' system (Jaeger, Würzburg, Germany) provided the used volume constant plethysmograph and the pneumotachometer with a heated Lilly head. Calibration of lung function equipment was based on standardized procedures (29). Lung function results are expressed as percentage of the predicted values according to the summary equations of the European Coal and Steel Community (ECCS) (29).
Maximal bronchodilation was considered to be reached if less than 5% increase in FEV1, expressed as % baseline, was obtained by an extra dose of 500 microgram inhaled terbutaline.

Quasi static Pressure Volume (PV) measurements were performed according to the ECCS (29) and Zapletal et al. (37). A latex balloon (8.5 cm long, 2 cm perimeter, International Medical Products) was introduced, via one nostril into the esophagus, in such a way that the length of the catheter from the nares to the balloon tip was one-fifth of body height (in cm) plus 9 cm (37). At the corresponding esophageal location the pressure proved to be most negative during maximal inspiration. The balloon stayed *in situ* throughout the subsequent PS probe experiment and the filling with 1.5 ml air was checked afterwards. Because of the large positive esophageal pressures, occurring during the forced expiratory maneuvers a somewhat larger volume of air in the balloon was chosen than is customary (29)

The PV data were obtained prior to the forced maneuvres. After maximal inspiration till TLC level a slow expiration followed till RV level, the expiratory flow being such that alveolar pressure was negligible. Three technically satisfactory PV curves were matched at TLC and pressures were averaged at 2% TLC levels. Volume dependent esophageal pressures were considered to be elastic recoil pressures (Pel) and used as such in the subsequent analyses. During the experimental forced expirations the esophageal pressure was considered to be the representative of pleural pressure.

Equipment

For a detailed description we refer to the related studies by Pedersen et al. and by Brackel et al., based on similar experiments (23,28,2). A PS probe (Fig. 1) was used to measure impaction pressure (Ptot) and lateral airway pressure (Plat). It was comparable to the one used by Macklem and Mead (15). The Ptot and Plat tube of the PS probe and the tube attached to

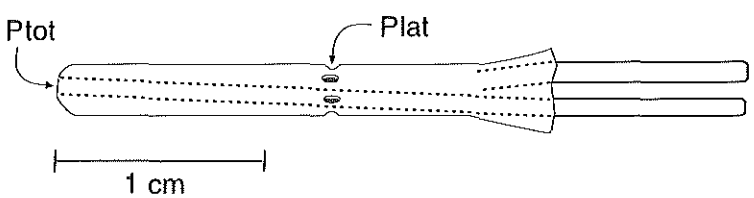


Figure 1

Pitot static probe outer diameter: 3mm, hole at the tip to record Ptot. 1.3 cm from tip: 6 lateral holes with 0.5 mm diameter to record Plat.

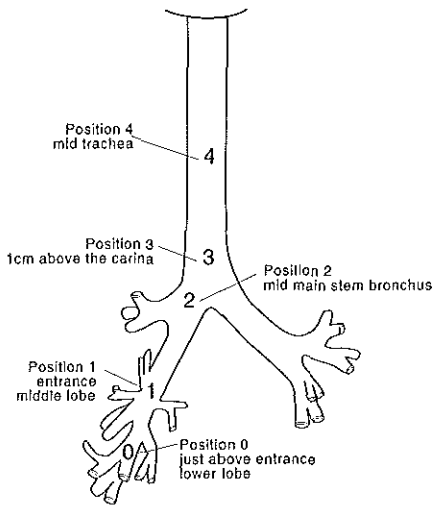
the esophageal balloon for indirect measurement of pleural pressure (Ppl), were connected to three identical pressure transducers (EMT34, Elema Schönander, Stockholm) and via EM311 amplifiers to an electronic subtractor. The transmural pressure Ptm (= Plat - Ppl) and the pressure drop due to convective acceleration Pca (= Ptot - Plat) were calculated on line in this way. A non heated Fleisch no. 3.5 pneumotachograph was used to measure mouth flow (V'm). The pressure signals Pca, Ptm, Ppl and V'm were visible on line.
Calibration of the equipment, tuning of the catheters among themselves and in combination with the pneumotachometer, and testing of the PS probe is described by Pedersen (23). The accuracy of measurement of the cross sectional area of rigid Plexiglas's tubes was in the range of ± 10% with Pca > 0.5 kPa, except for cross sectional areas > 2 cm^2 (23).

Experimental procedure

In order to minimize mucus production and prevent a vasovagal reaction, all subjects were premedicated with 0.5 mg atropine intramuscularly 0.5 hour before the introduction of the PS probe. The oropharynx, larynx were anaesthesized topically with xylocaine 10% puffs or lidocaine spray 4%. Further local anesthesia was given to the vocal cords and bronchial tree with maximally 20 ml novesine 0.5% or lidocaine 1% solution. A cuffless endotracheal (ET) tube was passed into the trachea over an introduced flexible bronchoscope. The bronchoscope was pulled back and, after placing the PS probe with its two Polystan catheters into the trachea through the ET tube, the ET tube was removed. The tip of the PS probe was positioned just above the entrance of the right lower lobe (pos.0) (in one subject the left lower lobe) under visual control by the re-introduced bronchoscope. Pos.0 was the most peripheral position that could be reached in all subjects without visible plugging of the airway by the PS probe. Subsequently the PS probe was carefully pulled back under bronchoscopic view and the distance between the subsequent intended intrabronchial positions was measured at the mouth by the catheter length (pos.1: above the entrance of the middle lobe (truncus intermedius), pos.2: mid main stem bronchus, pos.3: 1 cm above the main carina and pos.4: mid trachea (Fig. 2). In the following text, 'position' means the intrabronchial position of the PS probe if not used in another context. Subsequently the PS

Figure 2

Positions of the Pitot static probe in the bronchial tree.



probe was repositioned at pos.0 and its two catheters were pushed through and secured in two tightly fitting side holes in a specially designed mouthpiece. The free ends of the PS probe catheters and the esophageal balloon catheter were connected to the pressure transducers and the mouthpiece was connected to the pneumotachograph. The Ptot and Plat catheter were flushed forcefully with at least 2 x 50 ml of air before each individual forced expiratory maneuver to remove secretions from the end and side holes in the PS probe.

Flushing was repeated and/or the PS probe was carefully turned or moved upstream and downstream for maximally 1 cm if the pressure signals indicated (persistent) blockage of the end or side-holes.

Subjects wore a nose clip and were sitting straight up in a chair during the measurements. All subjects were asked to perform several MEFV maneuvres with the PS probe at each position. In addition the healthy subjects were asked to produce sigh and huff maneuvers as well for another study purpose (23). Each procedure was repeated at each position until acceptable results were obtained or a maximum of about 5 maneuvres was reached. A complete PS probe experiment took 1 to 1,5 hours with on average 30 MEFV maneuvres. In some subjects the measurements had to be stopped prematurely due to no longer effective local anesthesia resulting in uncontrollable coughing and/or hypersecretion.

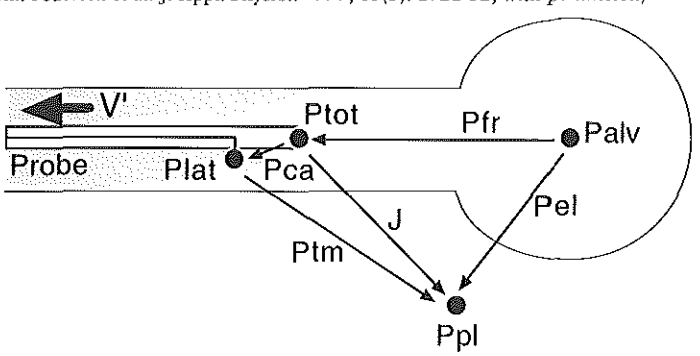
DATA SELECTION AND ANALYSIS

Data selection

Initial assessment of the quality of the on line visible V'm, Ppl, Pca and Ptm curves was done by eye. Curves with obvious errors (non maximal effort or non maximal in or exhalation, blockage of holes in the PS probe) were discarded. Asyst software (Asyst Software Technologies Inc., Rochester, N.Y.) and SPSS (Statistical Package for Social Sciences, SPSS Inc. Chicago, Illinois) were applied for saving the accepted maneuvers and calculation of additional variables. Thirteen different 'levels' of each MEFV maneuvre with the PS probe (characterized by a lung volume equal to: 80, 70, 60, 50, 40% TLC or 75, 50, 25% FVC or by V'm = 100, 80, 60, 40, 20% PEF) were used for further analysis. Ideally a complete dataset of one single PS probe MEFV maneuvre consisted thus of 13 'cases', each with the values of V'm, Ppl, Pca, Ptm and their derived variables. Since only a few of the subjects were able to reach an exhaled volume larger than 80% FVC with the PS probe in situ these 'cases' (n=72) were excluded. Also 'cases' with values less or equal to zero for Ppl (n=11), Pca (n=30), Caw (n=24) or Pfr (Pfr = Ppl + Pel - Ptot, n=24) were discarded for further analysis as these were considered to be not in agreement with forced expiration or physiologically unlikely to occur.

Figure 3

Pressures and pressure differences 'measured' in an airway during forced expiration. V': expiratory flow, Palv: alveolar -, Ppl: pleural -, Ptot: impaction -, Plat: lateral -, Pel: elastic recoil -, Ptm: transmural pressure, Pfr: upstream pressureloss, Pca: pressureloss due to convective acceleration, J: pressure head.
(from: Pedersen et al. J. Appl. Physiol. 1997; 83(5): 1721-32, with permission)



Calculations

In accordance with the 'pressure walk' by Mead (17), Fig. 3 shows a schematic bronchoalveolar unit with different intra- and peribronchial pressures along with flow (V'). Pca (= Ptot - Plat) is the pressure drop due to convective acceleration of air molecules when passing the bronchial cross sectional area (A) and is related to the kinetic energy of the passing air. Using the Bernoulli equation, assuming a blunt velocity profile and incompressible medium gives: $Pca = 50 \bullet \rho \bullet V'^2/A^2$ (ρ:density in g/cm^3, A: cm^2, P: kPa, V': flow l/s). A at the PS probe can be calculated if Pca and V' at the PS probe (V'ps) are known.

Table 2 gives an overview of the variable definitions and their equations used in the present study. Gas density ρ was calculated, using the weighted density at 37°C of expired gas from data presented by Radford (31) and Boyle's law, to be 0.00113 g/cm^3. Bronchial flow at the PS probe level (V'ps) was similarly calculated by use of Boyle's law. In order to correct for the effect of gas compression (8) the expired volume from TLC level was corrected for the compressive influence of pleural pressure Ppl. This rep-

Table 2 Variable definitions and equations

	Definition	Equation	Unit
Pca	Pressure for convective acceleration	Ptot - Plat	kPa
Ptm	Transmural pressure	Plat - Ppl	kPa
Palv	Alveolar pressure	Ppl + Pel	kPa
Pfr	Upstream pressure loss	Palv - Ptot	kPa
J	Pressure head	Ptot - Ppl = Pca + Ptm = Pel - Pfr	kPa
Caw	Airway compliance	$dA / dPtm$	cm^2/kPa
ρ_{Plat}	Gas density at the probe	$\rho_{Pb}(Pb+Plat)/Pb$	g/cm^3
V'ps	Flow at the PS probe	V'm•Pb/(Pb+Plat)	l/s
V_{Ppl}	Thoracic gasvolume change from TLC	(Pb∫Vm•dt+TLC•Ppl)/(Pb + Ppl)	l
A	Airway cross sectional area	$V'ps \bullet (50 \bullet \rho_{Plat}/Pca)^{0.5}$	cm^2
V'ws	Wave speed flow	$A[10 \bullet A/(\rho_{Plat} \bullet Caw)]^{0.5}$	l/s
SI	Speed index	$V'ps/V'ws = (2 \bullet Pca \bullet Caw/A)^{0.5}$	

Ptot: impaction pressure, Plat: lateral airway pressure, Ppl: pleural pressure, ρPb: weighted density of expired gas at 37°C by use of Boyle's law, Pb: barometric pressure, Pm: pressure at the mouth, V'm: flow at the mouth.

resented the largest part of Palv that ideally should have been used in the correction. A values calculated from Pca values less than 0.5 kPa were disregarded as these proved to be less reliable during testing of the PS probe in rigid tubes (23). Mouth flow (V'm) was not corrected to BTPS conditions and no attempt was made to correct for the difference in composition of air and alveolar gas. This will introduce a small, but systematic error in both the asthmatic and the healthy subjects, considered to be of no significance in the present study (30).

We assumed that the pressure surrounding the airway is equal to the pleural pressure (Ppl). The upstream intrabronchial pressure loss (Pfr) from the alveoli to the endhole of the PS probe can be expressed by: Pfr = Palv - Ptot = Pel - Ptm + Pca. The term Ptm + Pca is, in fluid mechanical terms, the pressure head J at the tip of the PS probe relative to Ppl (3). Rfr is calculated as Pfr/V'ps. Bronchial cross sectional area (A) plotted versus Ptm resulted mostly in a curve with a regular and irregular part. The agreement of a 2^{nd} to 5^{th} polynomial fitted through the regular part was assessed by eye. For further analysis only Caw values (calculated as first order differentiation of the polynomial) and A values from the part of the polynomial corresponding to the regular part of the actual A/Ptm curve were used.

In accordance with Dawson and Elliott (3), local maximal flow (V'ws°) at a certain point in the airways with a given tubelaw Caw° and cross sectional area A°, can be calculated as: $V'ws^{\circ} = A^{\circ} \bullet [(10 \bullet A^{\circ} \bullet d\mathrm{Ptm}^{\circ})/(\rho \bullet dA^{\circ})]^{0.5}$ (the notation '°' indicates values at a local maximum) (25,28). When V' equals V'ws, air speed (v) is supposed to be the speed of wave propagation (i.e. wave speed c = V'ws/A) through the local airway (3) and the speed index (SI = v/c = V'/V'ws) will be equal to one.

Fig. 4a illustrates the relation of expiratory flow (V') and speed index (SI) with volume (V) during an MEFV maneuver with the PS probe at one central and a more peripheral position. Fig. 4b the A/Ptm curves obtained at these two different PS probe positions.

Figure 4a

MEFV curves and their related speed index curves (SI) with the Pitot static probe in the truncus intermedius (1 = pos.1) and at mid-trachea (4 = pos.4) in one healthy female subject. V': expiratory flow (l/s), V: volume (l), SI: Speed Index

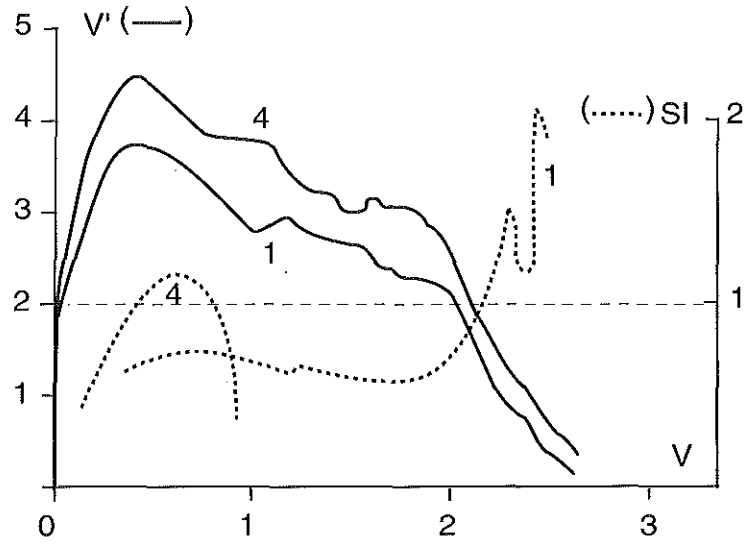
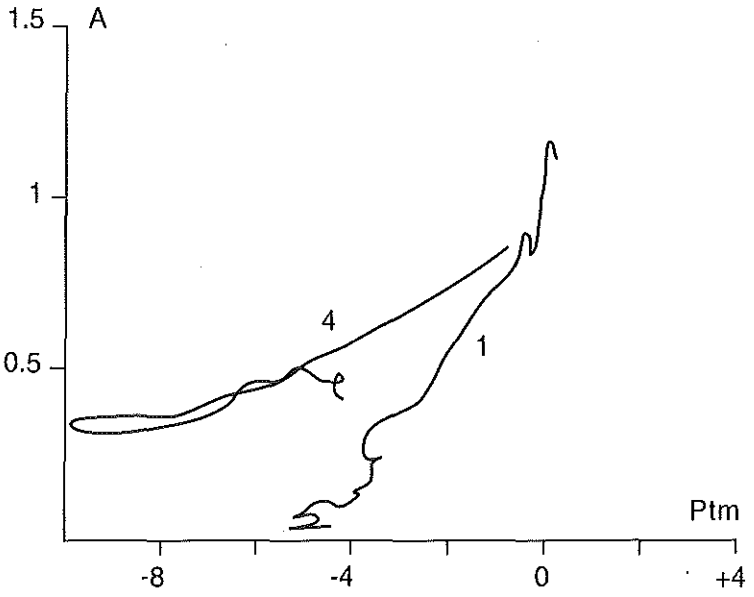


Figure 4b

Corresponding A/Ptm curves at the truncus intermedius (1 = pos.1) and at mid-trachea (4 = pos.4). A: cross sectional area (cm^2), Ptm: transmural pressure (kPa). Note: the steeper slope of A/Ptm curve 1, indicating a more compliant airway at the truncus intermedius compared to mid trachea.



STATISTICS

A two sample T-test was used for comparison of lung function results between asthmatics and normals.
All initial values for Caw, A, Pfr, Rfr, SI and Ptm were logarithmically transformed.
Within one subject all data per variable per position were pooled according to their V_{Ppl} within the following 4 volume ranges: V_{Ppl} = 100-80%, 79-60%, 59-40% and 39-20% FVC. The aim was to reduce the problems in analysis due to differences in the number of measurements and/or missing values between subjects and/or between positions. Two or more values for a variable from one subject per position within one volume range were averaged. The aim was that for each subject, all 20 combinations of the 5 positions and 4 volume ranges contained a single mean logarithmic value of Caw, A, Pfr, Rfr, SI and Ptm. Nevertheless missing values at some positions and/or volume ranges were still present in some subjects.
Therefore we applied rmANOVA using BMDP module 5V (BMDP Statistical Software Inc., release 7, 1992, Los Angeles) to analyze the geometric mean values of the outcome variables Caw, A, Pfr, Rfr, SI and Ptm per combination of position and volume range for each subject, in order to compensate for missing values. As only 24 subjects were analyzed, the assumed (co-)variance structure of the residuals was compound symmetry in order to reduce the number of estimated parameters.
In this analysis the following independent factors were used:

- two between subject factors with two levels: sex (male/female) and disease (healthy or asthma),
- two within subject factors: volume ('20%-FVC' ranges: 2 or 4 ordinal levels) and position (5 ordinal levels).

A full model with the above described four explanatory factors (volume and position as categorical factors) and all their first order interactions formed the basis of the analysis. This initially used full model was as follows:
'Predicted' variable =

disease + sex + position + volume + disease•sex + disease•position + disease•volume + sex•position + sex•volume + position•volume.

Subsequently a backward elimination method was applied using likelihood ratio tests (embedding tests), where in each step the factor with the highest p-value larger than 0.05 was eliminated, starting with the first order interaction in hierarchical fashion (i.e. main effects were not eliminated as long as they had a significant interaction with one of the other factors). If the restricted model thus selected still contained at least one of the categorical (ordinal) factors volume and/or position, then these categorical factors were replaced (one at a time) by their continuous (numeric) versions in order to test if an embedded model with a linear trend gave a better goodness of fit considering the lesser number of degrees of freedom required for the further restricted model.
Model predictions were back transformed to geometric means. Effects need to be interpreted in a multiplicative way because of logarithmic transformation.
When discussing the different variables in the following text, we discuss the predicted values according to the final model. Otherwise the suffix 'measured' is used. A level of significance of $p < 0.05$ two sided was used.

RESULTS

Data collection, selection and analysis

The average number of replicate MEFV measurements per subject for each PS probe position was 1.35 (range 0-3) for the healthy subjects and 2.46 (range 0-5) for the asthmatics. From each individual PS probe measurement only the volume range, corresponding to the Ptm range for which the polynomial through the A/Ptm curve was fitted, could be used for analysis. As this volume range was mostly less than the FVC range, this often resulted in less than the aimed 13 'cases' per measurement. A small number of 'cases' with negative Pca, Ppl, Pfr, and Caw values was excluded for reasons stated earlier. Volume ranges with missing data occurred therefore in almost all subjects. There was no clear pattern noticeable in the distribution of these 'empty' volume ranges within the 10 + 14 subjects that could have influenced the results of the multiple regression modelling significantly. Between the healthy and the asthmatic subjects there were no statistical differences for the pooled data of all 5 positions and

4 volume ranges between the dataset used for final analysis and the dataset containing the excluded 'cases'. Therefore a bias with regard to the found differences between asthmatic and healthy subjects due to exclusion of these 'cases' is unlikely.
A dataset with 1477 'cases' from in total 218 accepted PS probe MEFV maneuvers, resulting in 352 position - volume - range combinations with data, was used for final analysis. Tables 3a and 3b give the geometric means of the values of 'measured' Pfr, Rfr, SI, A and Caw values for the healthy and the asthmatic subjects.
The main factors and their interaction terms, contributing to the multivariate regression models finally fitted by the maximum likelihood method for ln(Pfr), ln(Rfr) and ln(SI) are given with p-values in Table 4. For these three variables no linear trend could be found with regard to volume and/or position.

Speed index (SI)

Disease, position, volume and the interactions: disease with position, disease with volume and sex with volume contributed all significantly to SI (Table 4). Due to these interactions it was not possible to express differences in SI between healthy or asthmatics independent of the factors volume, position or sex. Within the healthy subjects SI values were near one at all 5 positions within the volume ranges 79-60% and 59-40% FVC. In the asthmatics this was only true at pos.0 and pos.1 within 79-60% and at pos.0 within 59-40% FVC whereas low SI values (SI < 0.8) were found at the other PS probe positions (Fig. 5a and 5b).
A position - volume - range combination with an individual geometric mean 'measured' SI value > 1.2 (indicating supercritical flow) was found at pos.0: 11, at pos.1: 9, at pos.2: 1, at pos.3: 4 and at pos.4: 5 times in 10 healthy subjects and 12 times (at pos.0: 8 and at pos.1: 4 times) in 9 asthmatics.

Pressure loss upstream from PS probe (Pfr)

Pfr was predicted by disease, sex, position, volume and the interaction of disease with position and sex with position (Table 4). At the most peripheral position (pos.0) Pfr was higher in the healthy subjects compared to the asthmatics within a given sex. At the more downstream positions, Pfr in the healthy subjects was lower compared to the asthmatics. At pos.4 the difference disappeared (Table 5). Pfr increased significantly with decreasing volume and with a more downstream position of the PS probe in

Table 3a **Healthy subjects, 'measured' values of Pfr, Rfr, SI, A and Caw.**

Healthy		100-80% FVC	79-60% FVC	59-40% FVC	39-20% FVC
Pos.0	Pfr	0.57 (0.17 / 1.65)	0.71 (0.07 / 2.42)	0.76 (0.05 / 3.43)	1.03 (0.24 / 5.63)
	Rfr	0.10 (0.02 / 0.35)	0.15 (0.02 / 1.01)	0.24 (0.02 / 0.78)	0.72 (0.16 / 3.31)
	SI	1.04 (0.63 / 1.61)	0.95 (0.58 / 1.61)	1.13 (0.67 / 1.72)	0.92 (0.34 / 1.55)
	A	1.31 (0.69 / 2.27)	1.17 (0.80 / 1.88)	0.72 (0.44 / 1.02)	0.65 (0.37 / 1.17)
	Caw	0.71 (0.20 / 1.82)	0.60 (0.21 / 1.41)	0.40 (0.11 / 0.88)	0.26 (0.10 / 0.51)
	n	9	10	9	7
Pos.1	Pfr	0.33 (0.03 / 1.04)	0.44 (0.05 / 1.11)	0.86 (0.11 / 3.05)	1.21 (0.23 / 6.15)
	Rfr	0.05 (0.01 / 0.14)	0.08 (0.02 / 0.22)	0.24 (0.02 / 1.03)	0.72 (0.09 / 11.48)
	SI	0.83 (0.56 / 1.32)	0.89 (0.62 / 1.56)	0.84 (0.38 / 1.93)	0.74 (0.31 / 1.87)
	A	1.42 (0.87 / 2.27)	1.18 (0.66 / 1.75)	0.87 (0.47 / 1.44)	0.64 (0.08 / 1.40)
	Caw	0.47 (0.18 / 3.84)	0.39 (0.17 / 2.28)	0.31 (0.08 / 1.49)	0.23 (0.04 / 0.84)
	n	10	12	13	11
Pos.2	Pfr	0.65 (0.20 / 1.02)	0.68 (0.03 / 1.69)	1.23 (0.41 / 2.62)	1.71 (1.00 / 3.81)
	Rfr	0.10 (0.05 / 0.15)	0.13 (0.01 / 0.29)	0.32 (0.10 / 0.62)	0.84 (0.39 / 1.74)
	SI	0.73 (0.35 / 1.19)	0.82 (0.31 / 1.12)	0.78 (0.54 / 1.37)	0.60 (0.36 / 0.97)
	A	1.22 (0.59 / 2.41)	1.07 (0.58 / 1.69)	0.85 (0.52 / 1.37)	0.85 (0.53 / 1.32)
	Caw	0.22 (0.03 / 1.14)	0.27 (0.09 / 0.82)	0.19 (0.04 / 0.59)	0.23 (0.06 / 0.44)
	n	7	10	8	8
Pos.3	Pfr	0.79 (0.09 / 1.60)	0.78 (0.09 / 2.29)	0.83 (0.01 / 3.86)	1.47 (0.30 / 5.04)
	Rfr	0.12 (0.02 / 0.25)	0.14 (0.02 / 0.41)	0.22 (0.00 / 0.79)	0.80 (0.20 / 2.88)#
	SI	0.99 (0.88 / 1.12)	0.86 (0.36 / 1.41)	0.85 (0.39 / 1.44)	0.43 (0.22 / 0.68)
	A	1.05 (0.61 / 1.77)	0.84 (0.40 / 2.04)	0.72 (0.33 / 1.29)	0.80 (0.34 / 1.40)
	Caw	0.24 (0.08 / 0.64)	0.12 (0.02 / 0.40)	0.12 (0.03 / 0.81)	0.11 (0.02 / 0.34)
	n	9	13	12	11
Pos.4	Pfr	1.28 (0.30 / 2.82)	1.60 (0.34 / 6.80)	2.59 (0.46 / 7.30)	1.70 (0.30 / 3.84)
	Rfr	0.21 (0.06 / 0.44)	0.29 (0.08 / 0.87)	0.65 (0.17 / 1.21)	1.13 (0.24 / 4.03)#
	SI	0.79 (0.40 / 1.26)	0.81 (0.38 / 1.82)	0.73 (0.36 / 1.67)	0.34 (0.16 / 0.70)
	A	0.98 (0.41 / 1.79)	0.90 (0.30 / 1.58)	0.86 (0.42 / 1.67)	1.02 (0.53 / 1.78)
	Caw	0.14 (0.04 / 0.68)	0.12 (0.01 / 1.41)	0.15 (0.04 / 1.36)	0.15 (0.06 / 0.49)
	n	10	13	10	10

Values as group geometric means (min / max. value). Pfr: pressure loss upstream from PS probe (kPa), Rfr: resistance upstream from PS probe (kPa/l/s)(#: calculated in 9 subjects), SI: speed index (see text), A: cross sectional area (cm^2), Caw: airway compliance (cm^2/kPa), n: no. subjects. Pos: PS probe position: 0=at lower lobe, 1=at middle lobe, 2=mid main stem bronchus, 3=end trachea, 4= mid trachea.

Table 3b **Asthmatic subjects, 'measured' values of Pfr, Rfr, SI, A and Caw.**

Asthma		100-80% FVC	79-60% FVC	59-40% FVC	39-20% FVC
Pos.0	Pfr	0.54 (0.09 / 1.65)	0.46 (0.02 / 2.94)	0.32 (0.01 / 2.20)	1.24 (0.32 / 3.23)
	Rfr	0.10 (0.01 / 0.60)	0.12 (0.01 / 1.01)	0.14 (0.01 / 1.23)	1.01 (0.17 / 5.13)$
	SI	0.74 (0.45 / 1.59)	1.23 (0.62 / 1.83)	0.85 (0.45 / 1.71)	0.55 (0.39 / 0.88)
	A	0.78 (0.21 / 1.49)	0.63 (0.20 / 1.44)	0.82 (0.57 / 1.32)	0.97 (0.50 / 1.84)
	Caw	0.11 (0.04 / 0.22)	0.17 (0.07 / 0.85)	0.21 (0.11 / 0.33)	0.16 (0.04 / 0.28)
	n	6	8	8	7
Pos.1	Pfr	1.02 (0.10 / 5.31)	1.22 (0.10 / 5.29)	0.99 (0.06 / 5.42)	1.23 (0.24 / 4.77)
	Rfr	0.19 (0.01 / 1.44)	0.27 (0.01 / 2.44)	0.36 (0.03 / 1.77)	1.14 (0.12 / 4.25)
	SI	0.51 (0.20 / 1.08)	0.81 (0.27 / 1.71)	0.78 (0.25 / 1.71)	0.43 (0.22 / 0.82)
	A	1.38 (0.67 / 2.84)	1.04 (0.54 / 2.41)	1.06 (0.46 / 2.62)	1.14 (0.69 / 2.42)
	Caw	0.19 (0.11 / 0.28)	0.22 (0.07 / 0.57)	0.27 (0.15 / 0.77)	0.21 (0.07 / 0.43)
	n	7	9	8	6
Pos.2	Pfr	1.31 (0.76 / 2.86)	1.63 (0.38 / 4.44)	1.73 (0.14 / 4.98)	1.91 (0.60 / 7.10)
	Rfr	0.22 (0.13 / 0.38)	0.32 (0.10 / 0.77)	0.59 (0.08 / 2.63)	1.16 (0.41 / 3.64)
	SI	0.55 (0.22 / 0.81)	0.51 (0.33 / 0.74)	0.32 (0.17 / 0.61)	0.23 (0.04 / 0.82)
	A	1.41 (0.88 / 2.45)	1.22 (0.62 / 2.58)	1.22 (0.74 / 2.32)	1.37 (0.83 / 3.26)
	Caw	0.20 (0.04 / 1.03)	0.15 (0.06 / 0.24)	0.12 (0.05 / 0.27)	0.14 (0.02 / 0.43)
	n	7	9	8	7
Pos.3	Pfr	1.04 (0.23 / 2.56)	1.99 (0.55 / 5.16)	2.26 (0.50 / 7.78)	2.51 (0.97 / 5.12)
	Rfr	0.18 (0.06 / 0.33)	0.41 (0.15 / 0.90)	0.93 (0.22 / 2.68)	1.53 (0.65 / 3.67)
	SI	0.71 (0.43 / 0.89)	0.65 (0.37 / 0.93)	0.42 (0.23 / 1.17)	0.32 (0.12 / 0.96)
	A	1.02 (0.86 / 1.41)	1.01 (0.63 / 2.13)	0.98 (0.67 / 1.89)	0.97 (0.67 / 1.87)
	Caw	0.15 (0.10 / 0.30)	0.14 (0.07 / 0.24)	0.10 (0.07 / 1.17)	0.12 (0.07 / 0.18)
	n	6	8	8	7
Pos.4	Pfr	2.13 (1.33 / 4.42)	2.53 (0.41 / 6.96)	3.00 (0.42 / 9.91)	2.74 (0.68 / 8.66)
	Rfr	0.32 (0.24 / 0.45)	0.44 (0.11 / 1.11)	0.85 (0.23 / 2.43)	1.59 (0.85 / 4.73)
	SI	0.78 (0.56 / 1.01)	0.75 (0.52 / 1.08)	0.55 (0.37 / 0.68)	0.33 (0.23 / 0.44)
	A	1.13 (0.83 / 1.34)	0.91 (0.43 / 1.35)	0.93 (0.70 / 1.52)	1.10 (0.86 / 1.57)
	Caw	0.17 (0.08 / 0.72)	0.10 (0.04 / 0.26)	0.10 (0.05 / 0.22)	0.12 (0.07 / 0.34)
	n	7	8	8	8

Values as group geometric means (min / max. value). Pfr: pressure loss upstream from PS probe (kPa), Rfr: resistance upstream from PS probe (kPa/l/s)($: calculated in 6 subjects), SI: speed index (see text), A: cross sectional area (cm^2), Caw: airway compliance (cm^2/kPa), n: no. subjects. Pos: PS probe position: 0=at lower lobe, 1=at middle lobe, 2=mid main stem bronchus, 3=end trachea, 4= mid trachea.

Table 4 Factors explaining the logarithmic value of Pfr, Rfr and SI according to the final statistical model based on the data in the volume ranges 79-60% and 59-40% FVC.

p values	ln(Pfr)	ln(Rfr)	ln(SI)
Disease	0.781	0.188	<0.001
Sex	0.001	0.062	0.313
position (cat)	<0.001	<0.001	<0.001
volume (cat)	0.02	<0.001	<0.001
dis · pos	<0.001	<0.001	0.001
dis · vol	-	-	0.002
sex · pos	0.006	0.005	-
sex · vol	-	-	0.026

Figures represent the p values according to Wald-tests of significance of fixed effects and covariates. (cat: categorical, dis: disease, pos: position, vol: volume range)

Table 5 Pfr and Rfr: ratio healthy : asthma within a given sex and volume range

PS probe position		Pfr healthy / Pfr asthma	Rfr healthy / Rfr asthma
at lower lobe	(pos.0)	3.54	2.54
at middle lobe	(pos.1)	0.57	0.39
mid main stem bronchus	(pos.2)	0.59	0.43
end trachea	(pos.3)	0.53	0.15
mid trachea	(pos.4)	1.00	0.86

Pfr: pressure loss upstream from the PS probe
Rfr: airway resistance upstream from PS probe

both groups (Table 3a, 3b and 4). Pfr was significantly lower in the females compared to the males within equal disease status and volume range (Table 4).

Resistance upstream from PS probe (Rfr)

Rfr depended significantly on position, volume range and the interaction between disease and position and sex and position (Table 4). Rfr increased, on average, with decreasing volume and with a more downstream PS probe position in all asthmatic and healthy subjects. Within equal volume range and sex, Rfr was higher in the healthy subjects at the most peripheral position (pos.0). At the more downstream positions 1, 2 and 3, Rfr was

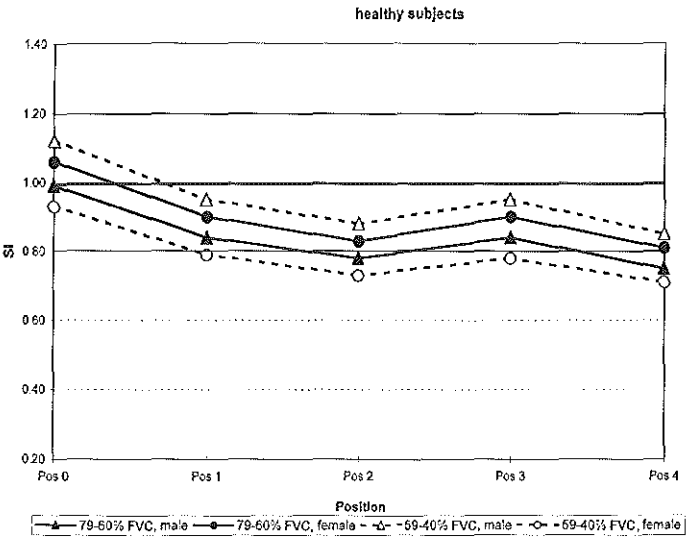


Figure 5a

Statistical predicted Speed index values (SI) at different PS probe positions at volume range 79-60% and 59-40% FVC for male and female healthy subjects.
Pos 0: entrance right lower lobe, 1: entrance middle lobe, 2: mid main stem bronchus, 3: end trachea, 4: mid trachea.

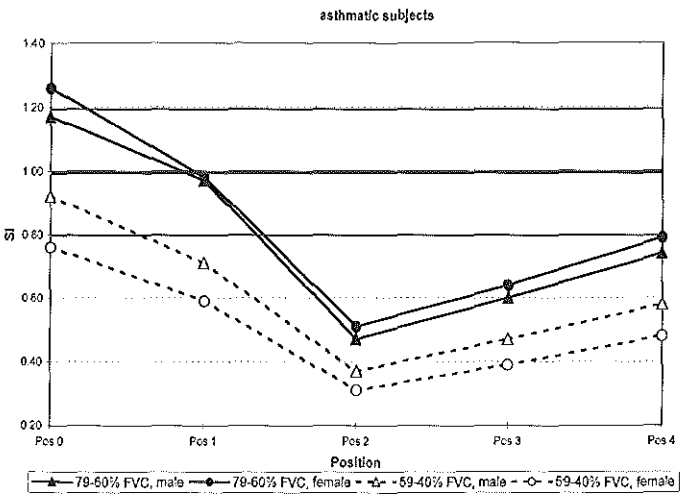


Figure 5b

Statistical predicted Speed index values (SI) at different PS probe positions at volume range 79-60% and 59-40% FVC for male and female asthmatic subjects.
Pos 0: entrance right lower lobe, 1: entrance middle lobe, 2: mid main stem bronchus, 3: end trachea, 4: mid trachea.

significantly higher in the asthmatics and at mid tracheal level comparable between both groups (Table 5). Rfr was significantly lower in the females compared to the males within equal disease status and volume range (Table 4).

Airway characteristics at positions with the condition 0.8 ≤ 'measured' SI ≤ 1.2

At the most peripheral PS probe position (pos.0) 'measured' cross sectional area A and airway compliance Caw were significantly smaller, Ptm significantly more negative and local Pca significantly larger in the asthmatics compared to the healthy subjects. In contrast, local 'measured' V'ws was comparable between both groups (Table 6). At the more downstream PS probe positions 1, 2, 3 and 4 no significant differences for these 'measured' variables were found between asthmatic and healthy subjects.

TABLE 6 **Variables at lower lobe with condition 0.8< 'measured' SI <1.2**

	Healthy	Asthma	p
Pos.0	n = 19	n = 5	
A	1.20 (0.46)	0.88 (0.18)	0.02
Caw	0.71 (0.37)	0.23 (0.08)	<0.001
V'ws	5.07 (2.31)	5.61 (2.69)	0.66
Pca	1.03 (0.57)	2.01 (0.71)	0.004
Ptm	-1.33 (0.96)	-2.45 (1.08)	0.034

T-test comparison between healthy and asthmatic subjects of the geometric mean values per subject at lower lobe (Pos.0) of 'measured' A (cross-sectional area, cm^2), Caw (airway compliance, cm^2/kPa), V'ws (calculated wavespeed flow, l/s), Pca (pressure loss due to convective acceleration, kPa) and Ptm (transmural pressure, kPa). Only 'cases' with a 'measured' SI (speed index) between 0.8 and 1.2 were selected, all 4 volume ranges were pooled.

DISCUSSION

The purpose of the present study was to examine, *in vivo*, the occurrence and behavior of choke points in central airways of healthy and asthmatic human subjects. Measurements and calculations were based on the wave speed concept and the method was previously applied in dogs (28) using a Pitot static probe as originally used by Macklem and Wilson in 1965 (16).

In this study we defined a choke point (CP) as an intrabronchial position where flow (V') reaches wave speed flow (V'ws). As such, we characterized an CP by an SI value (SI = V'/ V'ws) between 0.8 and 1.2. The SI results, based on the statistical model, describe the overall distribution of chokepoints within the two groups of subjects. These model SI results indicate that, in humans during forced expiration, chokepoints do occur central airways and that the distribution and volume dependent behavior of the chokepoints (CP) differ between healthy subjects and patients with asthma. In the healthy subjects CP's were distributed over all central airways and in the asthmatics limited to the most upstream intrabronchial position. The difference can possibly be explained by differences in local airway properties as described in another paper (2), based on the same subjects and set of measurements, where we concluded that airway compliance (Caw) and specific airway compliance (sCaw = Caw/A) were significantly lower in patients with asthma than in the normal controls.

Technical and analytical difficulties

Using a Pitot static probe for this purpose is technically difficult as mentioned by Macklem and Wilson (16). Related papers by Pedersen et al. (23) and Brackel et al. (2) using the same method discuss most of the technical problems encountered. Crucial for the calculation of A and therefore of Caw, V'ws and SI are the measurements of Pca (Ptot - Plat) with the PS probe and of Ptm (Plat - Ppl) by further use of an esophageal balloon. Measurement of A was reasonably accurate even for small Pca values for A values up to 2 cm^2 (23). In the present study only 3.6% of the original 1477 'measured' A values was > 2 cm^2. These A results may have been overestimated by ± 10-15% (23). Obstruction of 1-4 sideholes of the PS probe did not change the results of the *in vitro* control experiments significantly. However, the conditions during the *in vivo* measurements were far more complicated. Mucus could temporarily plug the endhole and one or more sideholes of the PS probe. This was checked by eye using the on line signals of V'm, Ptm, Pca and Ppl, as much as possible. Measurements were rejected and repeated if not reliable. A non axial position of the PS probe may have altered the A results, although in a previous study an angle up to 20° changed 'measured' A less than 10% (28). Diverging airways in the flow direc-

tion may lead to underestimation or overestimation of A depending of the position of the PS probe in relation to the wall (23,28). In the present study, however, tracheal A decreased, on average, with a more downstream PS probe position.

The smaller number of MEFV measurements per subject in the healthy subjects can in part be explained by the fact that they were asked to produce other types of expiratory maneuvres as well in the time limited by the duration of the bronchial anaesthetic. Despite practical problems due to mucus impaction, the asthmatics produced, however, more useful results.

Due to the invasive character of the experiments it was difficult and fatiguing for the subjects to perform adequate MEFV maneuvres repeatedly. Not all subjects were able to produce reliable results throughout the full FVC range and/or at all five positions. Typical problems were fits of coughing, increased mucus production with the need to swallow and premature running out of local anaesthetic. At some positions in some subjects no reliable data could be obtained due to wedging of the PS probe especially at low lung volumes. Accepted maneuvers could still contain artifacts over a certain volume part. These parts were omitted in the final analysis.

The asthmatics were pretreated with maximal bronchodilation and anti-inflammatory treatment and their pulmonary function testing did not differ significantly from that of the normal volunteers. Therefore, we assumed homogeneously emptying of the lung parts in both groups and used total expiratory flow, measured at the mouth and corrected for local Plat, for the calculations. The intrabronchial cross sectional areas (positions 0, 1 and 2) are therefore in fact 'functional' cross sectional areas related to the total cross section at the corresponding levels, assuming that all airways at the same level behave like the 'PS probe airway'. Since choke points were identified in the trachea as well in the mainstem and lobar bronchi (i.e. the large airways) intralobar differences in emptying reflecting small regional variations have probably not affected the calculations (9). However, it is necessary to assume that the airways of the same generation contribute uniformly to flow. The Pitot static probe itself diminished the local cross sectional area and may have caused airflow obstruction or even collapse of an airway around the PS probe. Therefore the PS probe may have influenced intrabronchial pres-

sures and may have artificially induced a chokepoint. This may partly explain the differences between the two MEFV curves in Fig. 4a. Since it is difficult to predict what Plat and local flow would have been without the PS probe *in situ*, the 'measured' A values in the present study were not corrected for the cross sectional area of the PS probe. The cross sectional area of the PS probe was 0.07 cm^2 and the 'measured' A at the level of the most peripheral position was 0.7-1.2 cm^2 in the healthy subjects and 0.6-0.8 cm^2 in the asthmatics (2). These A values are measured at the entrance of the lower lobe and represent the total functional cross sectional area of 4 airway branches at this level. The estimated mean A, during forced expiration, of the individual airway containing the PS probe was therefore 0.15-0.3 cm^2, and therefore still larger than the dimension of the PS probe.
Expiration from TLC level to RV level caused the PS probe, being fixed by its catheters, to move upstream with shortening of the airways. Although the relative motion within the trachea was less than two cartilage rings, it meant that the 'measured' A did not reflect the A of a fixed airway site.
At all positions the surrounding pressure of the airways was assumed to be the pleural pressure as discussed by Mead et al. (18).

Interpretation of results

Our analysis is based on concepts, related to wave speed determined flow limitation. Although the flow limiting process already starts at peak flow (23) the volume range 100-80 % FVC will incorporate an effort dependent part as well. In the tail of the MEFV curve, at low flow and lung volume, non uniform airway closure and viscous flow limitation may be present and make the interpretation difficult. Model simulations based on the wave speed concept yielded most accurate predictions in the mid part of the MEFV curve (7,11). One may then expect that, during forced expiration, study into wave speed flow limitation will be most fruitful throughout the lung volume ranges 79-60% and 59-40% FVC. Therefore we focused mainly on the pooled data within these two ranges for statistical analysis of flow limitation within the two groups of subjects.
In our study, all factors (except sex as main factor) included in the statistical model, contributed significantly to SI (Table 4). Although this influence was to be expected for volume and posi-

tion, we found also a different behavior according to the between subjects factor 'disease'. Wave speed was almost reached at all PS probe positions in the healthy subjects whereas it was only reached at the most upstream position 0 (and position 1 for 79-60 %FVC) in the asthmatics (Fig. 5a and 5b). These results suggest that flow limitation occurred more upstream in the bronchi in the asthmatics than in the healthy subjects. Downstream of a flow limiting segment the flow chokes or becomes supercritical, meaning that the velocity of expired air exceeds local wave speed. In the latter case the airway segment often becomes more narrow than the FLS and the flow will often decrease with SI increasing above one (28). In the current study, the distribution of positions with 'measured' SI > 1.2, indicative of local supercritical flow and therefore of positions downstream of the FLS, support both the occurrence of flow limitation in central airways and the conclusion that the site of flow limitation is located more upstream in the asthmatic subjects compared to the healthy subjects.

The finding of wave speed flows *in vivo* in human central airways in the current study is in agreement with the location of FLS in central airways in intact dogs (10,20,28,33) and in humans (13,16) as well as in excised dog and human lungs (7,19,32).

If one adds the lung volume ranges 100-80% FVC and 39-20% FVC to the analysis, an upstream shift of the SI=1 site with decreasing volume can be noticed (Table 3a,b): A representative example of this shift is shown in Fig. 4a and is related as well with an increase in airway compliance at a more upstream located airway segment (Fig. 4b). At high inflation level (100-80% an 79-60% FVC) mean 'measured' SI was between about 0.8 and 1.2 at all positions in the healthy subjects. At 39-20% FVC this was only true for the most peripheral position 0. On average, 'measured' SI values in the central airways decreased with decreasing volume. The asthmatics showed the same pattern although less clear. An upstream shift of CP with decreasing volume is consistent with e.g. studies in dogs by Smaldone and Bergofsky (32), by Pedersen (28) and by Lambert, using a mathematical model (11).

In neither groups of subjects the PS probe could be placed in sufficiently peripheral airways to measure SI significantly smaller

than one. The intrabronchial sites with SI ≥ 1 are indicative of local supercritical flow extending further downstream in the healthy subjects than in the asthmatics, but do not explain where the most upstream position with SI = 1 is located. Therefore, the SI results in our study can not inform us about the real intrabronchial position of FLS at different lungvolumes in both groups nor can we conclude definitively that FLS is located more peripherally in the asthmatics.

A related study by Pedersen et al. of flow limitation at peak flow (23) showed smaller maximum SI values in the central airways at peak flow in stable asthmatics than in the healthy subjects. They hypothesised but could not confirm that this was due to a lower local Caw in the asthmatics.

Brackel et al. described, in the same groups of subjects as the current study but irrespective of flow limitation, stiffer and more narrow airways in the asthmatics during forced expiration, especially at the most upstream central airway positions (2). They suggested that these differences from the healthy subjects may be related to airway remodeling caused by chronic asthmatic airway inflammation (2). A lower airway compliance and smaller A may explain the difference in distribution of sites with SI = 1 (CP's) between the two groups. Analysis of the 'cases' with 0.8 ≤ 'measured' SI ≤ 1.2 showed indeed significantly lower 'measured' A and Caw values at position 0 in the asthmatics, compared to the normals, without a difference in local V'ws (Table 6). This indicates that a lower local Caw, resulting in a higher V'ws, counterbalances a lower A, causing a lower V'ws. The differences in overall pulmonary function between healthy and asthmatic subjects (Table 1) are therefore likely to be due to properties of more peripheral airways than those 'measured' with the PS probe.

The position of the FLS is determined by the local properties of the airway (A and Caw) and the upstream resistance. Therefore we also examined the loss of pressure (Pfr = Palv-Ptot) and the resistance (Rfr = Pfr/V'PS) upstream from the PS probe over volume range 79-60% and 59-40% FVC. To interpretate Pfr well it is important to realize that Pfr includes viscosity dependent pressure loss in the peripheral airways as well as density dependent pressure losses upstream from the PS probe. Macklem found low values for peripheral flow resistance compared to total pulmonary flow resistance at high and mid lung volumes in dogs

(14). Pedersen showed that viscosity dependent losses may not be very important in healthy subjects (27). Wagner et al. showed that peripheral airway resistance was 7 times higher in asthmatics compared to normals, although it contributed little to total airway resistance (36). Therefore Pfr and Rfr may play a role in the asthmatics in spite of pretreatment. We constructed maximal flow static recoil curves (MFSR curves) from the MEFV and the Pel/V curves within each subject and compared these between the healthy and asthmatic subjects (unpublished results). Pel was slightly but not significantly lower in the asthmatics whereas lung compliance was comparable. In the volume range 79-40% FVC, the slope of the mean MFSR curve within each group was comparable between the groups of healthy and asthmatics subjects. This suggested that airway conductance upstream from the FLS and therefore viscosity dependent pressure losses in the periphery were on average comparable in both groups although the model on which the MFSR analysis is based (12) can be considered as a simplification of the mechanics of a forced expiration.

The total pressure loss upstream from position 0 was, on average, higher in the healthy subjects. This finding may be related to the fact that the healthy subjects received no pretreatment with systemic corticosteroids or maximal bronchodilation. Another explanation could be that in the group of healthy subjects more CP's or the actual FLS existed upstream from position 0 and that in the asthmatics these were mainly located around the lower lobe. This could, however, not be confirmed in the current study. In both groups Pfr and Rfr were relatively low at position 0 compared to more central positions. At mid trachea (pos.4) Pfr was equal and Rfr almost equal between the healthy and asthmatic subjects. This indicates that, during forced expiration, the largest pressure drop occurs in the central airways .

Within equal disease status and volume range, Pfr and Rfr were significantly lower in the females compared to the males at all PS probe positions (Table 4). As there was no indication for a decreased airway patency according to the routine lung function parameters (FEV1, FEV1/VC) in the female subjects, this suggests that in the females the main pressure drop occurred in the central airways. This is in agreement with a lower A in the central airways in the females, as described by Brackel et al. (2).

If peripheral (viscosity dependent) pressure losses are comparable between the healthy and asthmatic group of subjects, the Pfr and Rfr findings, in combination with the SI results, suggest that in the healthy subjects positions with SI = 1 are located throughout the central airways and probably even upstream from position 0 during forced expiration. We do not know where in the periphery CP's originate or where actual FLS is located. In the asthmatics positions with SI = 1 are only found in the airway segment near Pos.0 one (and Pos.1 at high lung volume). The effect of a local smaller A in the asthmatics on the formation of a CP (or even FLS ?) near position 0 may have been enhanced by the insertion of the PS probe. Both the smaller A and the presence of the PS probe explain the significantly higher Pca and more negative Ptm values at comparable flows in the asthmatics at Pos.0 (Table 6).

CONCLUSION

Considering all the technical limitations as described and discussed above, this study suggests that valuable information can be obtained about the relation between central airway properties, flow limitation / choke point formation, intrabronchial pressure loss and airway resistance by use of the wave speed concept in vivo in human airways. In (maximally bronchodilated) asthmatic patients pressure loss and airway resistance upstream from the lobar bronchi were lower compared to normal subjects. Airway compliance was lower and cross sectional area was smaller at the lobar bronchi in these subjects. The latter may explain that FLS was probably confined at or peripheral to the lobar bronchi in the asthmatic subjects in contrast to the healthy subjects. The healthy subjects had positions with SI ≈ 1 distributed along all central airways and probably upstream from the lobar bronchi as well, which means that also in healthy subjects FLS may be in the lobar bronchi or more peripherally, if we define FLS as the most upstream site with SI = 1. The effect of a smaller cross sectional area on maximal flow in the asthmatics is probably partially counterbalanced by a lower airway compliance. This may explain that changes in area and/or airway elastic properties may not be detected by conventional lung function measurements like MEFV curves.

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6

The maximal flow static recoil curve and its relation to bronchial mechanics in healthy and asthmatic subjects

submitted

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ABSTRACT

The relation between airway cross sectional area (A) and the transmural pressure (Ptm) describes airway compliance (Caw = dA/dPtm). Caw at the flow limiting site (FLS) in the airways may be estimated from the slope of the Maximal Flow Static Recoil (MFSR) curve (Pedersen, O.F., Acta.Physiol.Scand.100: 139-53, 1977). In an earlier study we obtained *in vivo* dynamic A and Caw values at 5 positions between the right lower lobe and mid trachea, using an esophageal balloon and a Pitot static probe (Brackel H.J.L., Am.J.Respir.Crit.Care Med., in press). The purpose of the current study was to evaluate MFSR derived airway compliance as a non invasive measure for airway elastic properties. We examined 14 healthy subjects and 10 patients with stable, long-lasting asthma. *Results:* The appearance of MFSR derived A/Ptm curves reflected jumps in the FLS location and A and Caw decreased with decreasing lung volume, like in the Pitot study. The correlation between MFSR derived A and Caw values with the Pitot probe results, however, was poor. Furthermore, the MFSR analysis was not sensitive enough to reflect changes in Caw, demonstrated with the Pitot probe, in patients with mild to moderate asthma.

INTRODUCTION

The relation between the compressibility of intrathoracic airways and the occurrence of flow limitation during forced expiration has not been completely understood for many decades. Mead et al. (24) postulated that once flow is limited at a given lung volume, an 'Equal Pressure Point' (EPP) with an equal intrabronchial and peribronchial (id est intrapleural) pressure exists in the intrathoracic airways. Where the airways downstream from EPP will be compressed, the upstream airways will not. The bronchial tree was considered to be an elastic system, emptying through an upstream part with a fixed resistance (Rus), in series with a variable resistance in the downstream airway. The lung elastic recoil pressure (Pel) was regarded to be the driving pres-

sure for the upstream part and therefore considered as the most important determinant of maximal flow (V'max). Pride and coworkers (39) extended the EPP model and compared flow limitation with the behavior of a 'Starling' resistor with an upstream driving pressure Pel, plus a critical transmural pressure (Ptm'), the latter being the transmural pressure causing an elastic airway segment to collapse. After the introduction of Ptm', the importance of airway wall properties as compressibility and/or tone of the flow limiting airway segment in addition to Pel as determinants of V'max was emphasized. Leaver et al. calculated Ptm' as the pressure axis intercept of the slope of the MFRS curve and regarded this as an index of collapsibility of the flow limiting segments in the airway (19). The approach by Mead et al. and by Pride et al., however, was mainly based on a longitudinal pressure distribution in the airways with Rus and Ptm' being regarded as rather static variables independent of flow. Their concept could not really explain the mechanism of flow limitation. Influences of airflow properties (speed of gas, density, and viscosity) in relation with airway wall properties were only partly taken into account.

Dawson and Elliott (7;8) recognized that the 'wave speed' concept, known from fluid carrying systems, also applied to the airways and stated that maximum flow through an airway is only attained when the velocity of air equals the propagation speed of a pressure wave of gas through the airway. The latter is called the tube wave speed and depends on the density (ρ) of the gas and the compliance of the airway wall. When defining airway compliance (Caw) as the relation between the transmural pressure (Ptm) and the local airway cross sectional area (A) ($Caw = dA/dPtm$), wave speed flow (V'ws) can be described according to the equation: $V'ws = A \bullet [A/(\rho \bullet dA/dPtm)]^{0.5}$ (7;37). A smaller A and larger Caw (and/or larger ρ) will decrease V'ws and vice versa. In the wave speed concept of flow limitation, Pel and the pressure loss upstream from the flow limiting site (Pfr) will determine local Ptm, and therefore local A. V'ws depends therefore indirectly on the driving pressure Pel and Pfr.
In accordance with the wave speed concept (37), Pedersen and coworkers showed in a mechanical model (35) and in healthy subjects (36) that the elastic airway properties at flow limiting

sites may be estimated from the slope of the Maximal Flow Static Recoil (MFSR) curve at corresponding volumes. The MFSR derived A/Ptm curve is then regarded as the compliance curve for a single airway, behaving exactly the same as the sequence of flow limiting segments of the complex system of intrathoracic branched airways, partly imbedded in the lung parenchyma (36). Using comparable equations, local dynamic A/Ptm curves can also be constructed from peri- and intrabronchial pressures, measured by an intrabronchially positioned Pitot static probe, an esophageal balloon and the airflow during forced expiration. This *in vivo* application of the wave speed concept was described by Pedersen et al. in a study in dogs (37) and applied by Brackel and coworkers in a study in asthmatics and healthy volunteers (5).

In the current study, MFSR derived airway elastic properties are compared with airway compliance measured by a Pitot static probe located at 5 different positions within the central airways of healthy young adults and patients with mild to moderate asthma. The purpose of the present study is to evaluate whether airway compliance obtained from the MFSR curve can be used to detect changes in airway wall elastic properties, possibly reflecting structural asthmatic remodeling of the airway wall.

THEORY AND BASIC CALCULATIONS

For reasons of simplicity, it is supposed that the flow limiting segments of the human airway can be represented by a theoretical single elastic airway, behaving in exactly the same way as the complex system of branched human airways during forced expiration (34;36). Airway compliance (Caw = dA/dPtm) derived from the MFSR curve reflects the elastic properties of the airway when and where flow is limited and does not indicate the exact site of flow limitation within the airways (36). Further assumptions are that flow (V') is turbulent, with a blunt velocity profile; that V'max is reached throughout the volume range studied and that the viscosity dependent pressure loss (Pfr) from the alveoli to the flow limiting segment is negligible.

During its course the gas moving towards the thoracic outlet accelerates because of downstream tapering of the total cross sectional airway area. The convective acceleration results in a drop (Pca) of the driving intrabronchial pressure. Friction, determined by airway dimensions, the density (ρ) and viscosity (μ) of the expired gas normally causes an extra loss of the driving pressure. Downstream from the equal pressure point (EPP), the airways will be compressed by the negative transmural pressure (Ptm). The intraluminary lateral pressure (Plat) decreases with increasing flow and causes the transmural pressure (Ptm = Plat - pleural pressure Ppl) to become more negative and, and in case of an elastic airway, its cross sectional area (A) to decrease further (34). The pressure drop due to convective acceleration (Pca) can be described by the Bernoulli equation: $Pca = \frac{1}{2} \bullet \rho \bullet (V'/A)^2$. In case of the assumptions mentioned above the following three equations can be derived (34;37) (see appendix):

$$Pel = \tfrac{1}{2} \bullet \rho \bullet V'^2/A^2 + Ptm \qquad (I)$$

$$dV'max/dPel^\circ = A^{\circ 2}/(\rho \bullet V'max) \qquad (II)$$

$$dA^\circ/dPtm^\circ = A^{\circ 3}/(\rho \bullet V'max^2) \qquad (III)$$

(The suffix$^\circ$ indicates the situation when and where flow is limited. A is cross sectional area (cm^2), Ptm is transmural pressure (kPa), V' is flow (l/s), V'max is maximal flow (l/s), ρ is density (g/cm^3))

These equations indicate that A°, Ptm° and $dA^\circ/dPtm^\circ$ can be calculated using the values of V', Pel and the slope of an MFSR curve. The A/Ptm curve calculated from the MFSR curve represents therefore the compliance of the flow limiting airway segments during forced expiration. Equation III is analogue to the equations by Dawson and Elliott (7) and states that V'max can be calculated at any value of A when the local tube law ($dA/dPtm$) is known. At the higher lung volumes, where Pfr is relatively small, the calculation of airway compliance (Caw = $dA/dPtm$) may be more accurate then at the low lung volumes when viscosity dependent flow limiting mechanisms may be expected to occur.

Table 1 Anthropometric and spirometry data of healthy and asthmatic subjects.

	Age yr	height cm	TLC %pred	RV / TLC	FVC %pred	FEV1 %pred	FEV1 / FVC	PEF %pred
8 healthy f	25.8±3.9	173±4	104±9	0.28±0.05	108±9	106±14	0.85±0.06	109±13
6 healthy m	26.5±6.9	187±8	105±11	0.22±0.03	114±7	108±7	0.79±0.08	121±10
healthy f+m	26.1±5.1	179±9	104±9	0.26±0.05	111±8	107±11	0.83±0.07	114±13
3 asthma f	24.9±4.3	166±4	112±25	0.31±0.03	104±30	86±9	0.75±0.16	87±7
7 asthma m	21.1±3.4	182±8	96±10	0.25±0.05	94±8	85±7	0.76±0.04	91±17
asthma f+m	22.2±3.9	177±10	101±16	0.27±0.05	97±16	85±7	0.76±0.09	90±14
p (f+m)	0.06	0.56	0.50	0.89	0.01	<0.001	0.05	<0.001

f=female, m=male. Asthmatic subjects: values after bronchodilation and anti-inflammatory treatment, values: means ± sd, p: p-value according to two sample T-test comparing healthy and asthmatic subjects.

SUBJECTS AND METHODS

Subjects

All measurements were performed in 24 non-smoking young adults: 8 female and 6 male healthy subjects and 3 female and 7 male patients with moderate to severe (28) asthma according to ATS criteria (1), since early childhood. The mean age and anthropometric data are given in Table 1. The patients used maintenance treatment with inhaled corticosteroids for at least three years prior to the study. They were atopic, defined as a total IgE > 100 IE and a positive radio allergosorbent test for at least one inhaled allergen, and demonstrated bronchial hyperresponsiveness. All asthmatics were pretreated with a tapering course of prednisolone (45 mg on day 1, 25 mg on study day 7) in addition to their regular maintenance treatment. The aim was to minimize possible persistent airway wall edema and hypersecretion due to chronic bronchial inflammation. Measurements were postponed for at least two weeks after recovery in case of a respiratory infection or an exacerbation within one month before scheduled measurements.

All subjects performed a dose-response curve with an inhaled bronchodilator one week prior to the prednisolone course. The

dose of the β-2-agonist that resulted in maximal bronchodilation (mostly 1 mg terbutaline) was inhaled by all asthmatic subjects within1.5 h before the MFSR measurements and the Pitot static probe (PS probe) experiment. The healthy subjects obtained no β-2-agonist.
The medical ethics committee of the University Hospital Rotterdam gave approval to the study. It was conducted in conformity with the principles embodied in the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Pulmonary fuction

Baseline pulmonary function tests consisted of at least three maximal expiratory flow-volume curves (MEFV) with measurement of expiratory flow, FVC, FEV1 and peak expiratory flow (PEF); body plethysmography with determination of total lung capacity (TLC) and residual volume (RV) and quasi static pressure volume (PV) measurements (results in Table 1).
Reproducibility of repeated flow-volume measurements was checked according to ATS criteria (2), superimposing the flow-volume curves on line by computer.
The volume constant plethysmograph and the pneumotachometer with a heated Lilly type head were part of a 'Jaeger Masterlab' system (Jaeger, Würzburg, Germany).
Calibration of lung function equipment was based on a standardized procedure (40). Lung function results are expressed as percentage of the predicted values according to the summary equations of the European Coal and Steel Community (ECCS) (40).
Esophageal pressure, as the equivalent of pleural pressure, was measured using an 8.5 cm long, 2 cm perimeter latex balloon (International Medical Products, Zutphen, The Netherlands) containing 1.5 ml of air and positioned in the lower end of the esophagus. The distance of the tip of the balloon to the tip of the nose was (1/5•height + 9) cm according to the method described by Zapletal (height in cm) (47). Several quasistatic deflation pressure volume curves (P/V curves) were obtained according to the guidelines of the ECCS (40).
Two deep breaths to TLC prior to each measurement controlled volume history.

MFSR-A/Ptm analysis: measurements and calculations

Out of three comparable MEFV curves a composite MEFV curve was constructed by computer according to the envelope method by Peslin (38) in order to obtain within each subject the most maximal expiratory flow at each volume level.

Three comparable Pel/V curves within one subject were matched at TLC and an average Pel/V curve was constructed from the mean of the three pressure values of the individual P/V curves at each 2% TLC level.

The average Pel/V curve was matched at TLC with the composite MEFV curve. A Maximal Flow Static Recoil curve (MFSR curve) was constructed from the pressure and flow values at each subsequent 2% TLC level. The MFSR curve between 86% TLC and 40% TLC was described by a 3rd degree polynomial fit with a coefficient of determination of $R^2 > 0.990$. In case of 'knees' in the MFSR curve maximal three polynomials were used. Parts of the MFSR curve that could not be described by a polynomial with a R^2 of > 0.990 were not used for further analysis. Subsequently, at each 2% TLC level, the actual (measured) Pel values, V'max values derived from the polynomial and the MFSR slope values ($k = dV'max/dPel$) of the MFSR fit were used for calculation of A and Ptm according to the above described equations. An A/Ptm curve was constructed using the A and Ptm values at each 2% TLC level calculated by equations 8 and 10. The A/Ptm curves were fitted by a 2nd degree polynomial regression with a coefficient of determination of $R^2 > 0.999$. In case of "jumps" in the A/Ptm curve, maximal three regressions were used. The A values from the A/Ptm polynomial(s) were used for further analysis. Airway wall compliance at each 2% TLC level was calculated as the slope of the A/Ptm fit.

***In vivo* Pitot static probe study**

For a detailed description of equipment, experiments and calculations we refer to the studies by Pedersen et al. based on similar experiments in dogs (37) and to related studies by Pedersen (32) and Brackel et al. (5) in the same groups of subjects.

In summary: a Pitot static Probe (PS probe) with an end hole and 6 lateral holes was subsequently positioned at 5 different intrabronchial positions between the right lower lobe and mid trachea (Fig. 1) for measurement of, respectively, impaction pressure (Ptot) and lateral airway pressure (Plat) during MEFV maneuvers. The local pressure drop due to convective acceleration was

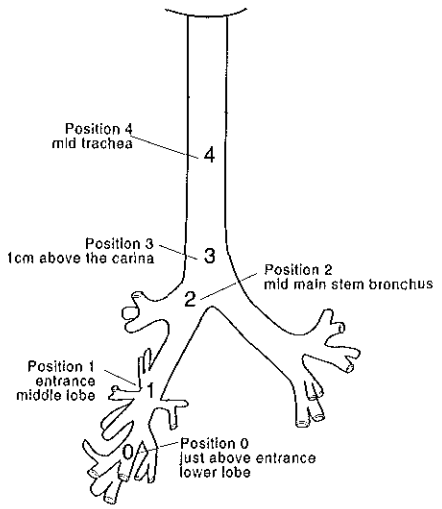


Figure 1

Bronchial tree with Pitot static probe positions

calculated as (Pca = Ptot - Plat). An esophageal balloon was used for indirect measurement of peribronchial (pleural) pressure Ppl and enabled the calculation of the local transmural pressure (Ptm = Plat - Ppl). Flow at the PS probe (V'ps) was calculated from the mouth flow (V'm), measured by a non heated Fleisch type no. 3.5 pneumotachograph. Assuming a blunt velocity profile and incompressible medium, the Bernoulli equation ($Pca = 50 \bullet \rho \bullet V'^2/A^2$ (ρ: density in g/cm^{-3}, cross sectional area A in cm^2, P: kPa, V': l/s)) enables calculation of A at the PS probe if Pca and V' at the PS probe (V'ps) are known. The change of A with change in Ptm is a measure of airway compliance ($Caw = dA/dPtm$). Specific airway compliance (sCaw) was calculated as sCaw = Caw/A.

If local A and Caw are known, the local maximal flow (i.e. wave speed flow $V'ws = A \bullet [10 \bullet A/(\rho \bullet Caw)]^{0.5}$ (32)) and the speed index SI = V'ps/V'ws can be calculated. An SI value of approximately 1 indicates a local choke point or the occurrence of flow limitation (7;34;37). For each intrabronchial PS probe position, the PS probe derived results of each parameter were averaged within each 20% FVC volume range (100%-80%, 79%-60%, 59%-40%, 39%-20% FVC) as described by Brackel et al. (5).

In the following text MFSR derived variables are specified with the suffix 'm' and PS probe derived variables with 'p'.

We assumed that the expiratory flow during the MFSR measure-

ments represents the maximal attainable flow determined by a flow limiting segment (FLS) occurring somewhere in the airways. Therefore, the MFSR derived variables were compared only with the corresponding PS probe derived A_p, Caw_p and $sCaw_p$ selected for the condition $0.8 < SI < 1.2$, indicating a local choke point or flow limitation. The MFSR and PS probe measurements were supposed to match at TLC level. With regard to each variable, the average of all selected PS probe derived results within each of the four 20% FVC volume ranges was compared with the average of the MFSR derived results within a TLC range corresponding with the 20% FVC range within each group of subjects.

STATISTICS

The lung function characteristics were compared between asthmatics and healthy subjects using two paired T-tests. A p value < 0.05 was considered to be significant.
The (from the MFSR relation derived) k and Ptm_m, A_m, Caw_m and $sCaw_m$ values between 80% - 40% TLC were compared between healthy subjects and patients with asthma using a mixed model of analysis of variance with random coefficients to analyze the relation of these variables with TLC. We started with a full quadratic model permitting differences between healthy and asthmatic subjects:

Predicted variable=
$\beta_0 + \beta_1 \bullet \text{disease} + \beta_2 \bullet (\text{TLC-60}) + \beta_3 \bullet [(\text{TLC-60}) \bullet \text{disease}] +$
$\beta_4 \bullet (\text{TLC-60})^2 + \beta_5 \bullet [(\text{TLC-60}) \bullet \text{disease}]^2.$

The factor '60' was introduced as a reference of %TLC with respect to the middle of the range 80%-40% TLC for calculation simplicity; disease is disease status (1 = healthy and 0 = asthma). The model was reduced to a restricted model excluding terms with non significant coefficients in a hierarchical way. A level of significance of $p<0.1$ was used in this MFSR analysis.
Within each subject, the (from the PS probe derived) variables A_p, Ptm_p, Caw_p and $sCaw_p$ within a volume range 100%-80%, 79%-60%, 59%-40%, 39%-20% FVC were logarithmically

transformed and averaged. Statistical analysis and comparison between the healthy and asthmatic subjects were performed applying rmANOVA as described by Brackel et al. (5)
The MFSR derived variables and the PS probe derived variables with $0.8 < SI < 1.2$ were compared within each group of subjects, using a Bland and Altman analysis (4) and a two paired T-Test with a p value < 0.05 considered to be significant.

RESULTS

Subjects

Both groups were comparable with regard to age, height, TLC, RV/TLC and FEV1/FVC ratio. FVC, FEV1 and PEF values were lower in the asthmatic subjects (Table 1).

MFSR analysis

Table 2 gives the coefficients of the different predicted variables according to the most restricted model. The mean (+/- 1 SD) MFSR curve for healthy and asthmatic subjects is given in Fig. 2. Predicted expiratory flow (V'_m) per 2% TLC level was, on aver-

Table 2

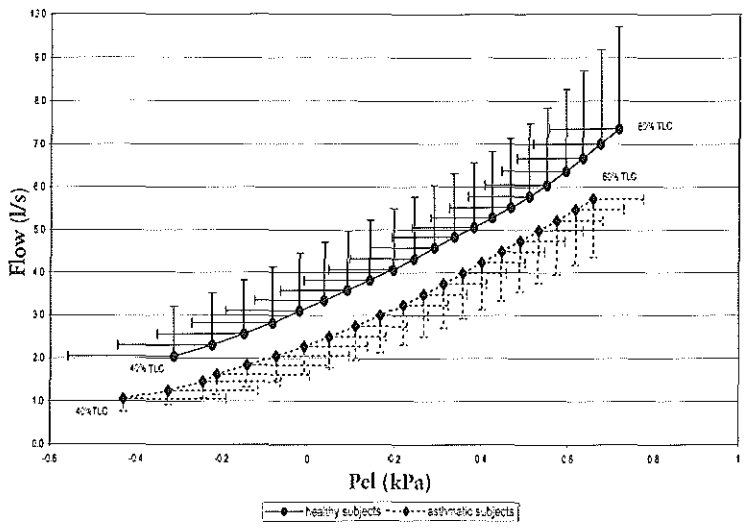
Variable description according to the most restricted model of MFSR analysis for each variable: predicted variable = $\beta_0 + \beta_1 \bullet$disease $+ \beta_2 \bullet$(TLC-60) $+ \beta_4 \bullet$(TLC-60)^2.

Variable	β_0	β_1	β_2	β_4
V'm	3.363294	1.169439	0.124448	-
p	0.0001	0.0068	0.0001	-
Pel_m	0.261940	-	0.025740	-0.0002546
p	0.0001		0.0001	0.0002
K	0.569371	-	0.013060	-
p	0.0001	-	0.0006	
Caw_m	0.260341	-	0.004336	-
p	0.0001	-	0.0236	
A_m	1.361493	0.340338	0.041236	-
p	0.0001	0.0199	0.0001	-
$sCaw_m$	0.167449	-	-0.002609	-
p	0.0001	-	0.01	-

V'm: mouth flow (l/s), Pel: static recoil pressure (kPa), K: slope of the MFSR curve l/s/kPa), Caw_m: airway compliance ($dA_m/dPtm_m$, cm^2/kPa), A_m: cross sectional area (cm^2), $sCaw_m$: specific airway compliance (Caw/A, 1/kPa), suffix 'm': MFSR derived data, disease: disease status (healthy=1, asthma=0), p: p-value according to most restricted model.

Figure 2

Mean MFSR curve in healthy and asthmatic subjects.



values represented as group means ± 1 standard deviation.

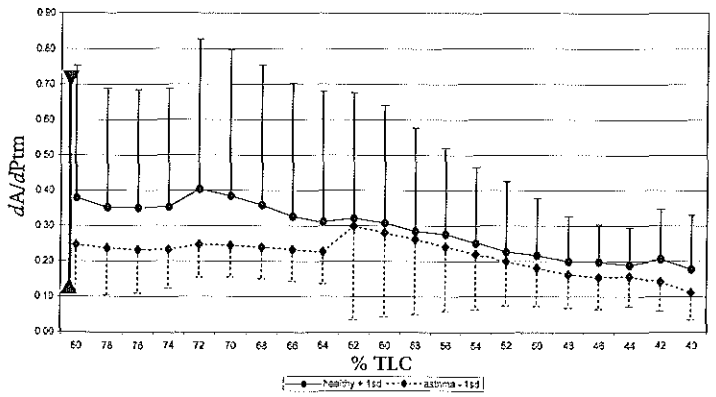
MFSR: Maximal Flow Static Recoil, Flow: mouth flow, Pel: Lung elastic recoil pressure, TLC: Total Lung Capacity,.

age, 1.17 l/s higher in the healthy subjects and decreased linearly with decreasing lung volume. Predicted lung elastic recoil pressure (Pel) was slightly, but not significantly lower in the asthmatic subjects (Fig. 2) and showed a curvy linear relation with lung volume. The predicted slope k of the MFSR curve decreased linearly with decreasing volume and did not differ significantly between the healthy and asthmatic subjects. Figure 3a, 3b and 3c give the mean +/- 1sd of the measured Caw_m, A_m and $sCaw_m$ versus %TLC levels in each group of subjects. Caw_m and A_m decreased significantly and $sCaw_m$ increased slightly although significantly with decreasing lung volume in both the healthy and the asthmatic subjects. Airway compliance Caw_m was slightly but not significantly lower per 2% TLC level in the asthmatics. A_m was, on average, 0.34 cm^2 higher in the healthy subjects. $sCaw_m$ differed not significantly between both groups.

In 7 out of 14 healthy subjects and 2 out of 10 asthmatics the MFSR curve showed one or two 'knees' in the shape of the curve. Not in all subjects the whole MFSR curve and/or the A_m/Ptm_m curve could be covered with one or more fits with an $R^2 > 0.990$, causing missing data at one or more of the 2%TLC levels in some subjects. All A_m/Ptm_m curves were concave to the Ptm_m

Figure 3a

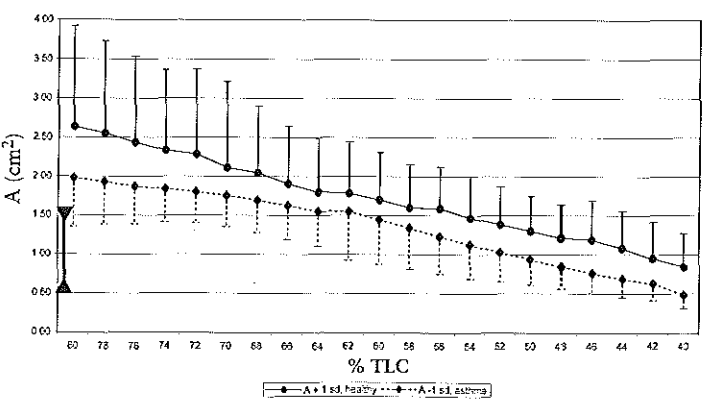
Mean MFSR derived airway compliance (Caw) versus lung volume



Caw: airway compliance (dA/dPtm, cm^2/kPa), A: airway cross sectional area, Ptm: transmural pressure,TLC: Total lung capacity, sd: standard deviation.
▼▲ :value range of corresponding variable as measured *in vivo* during Pitot static probe study.

Figure 3b

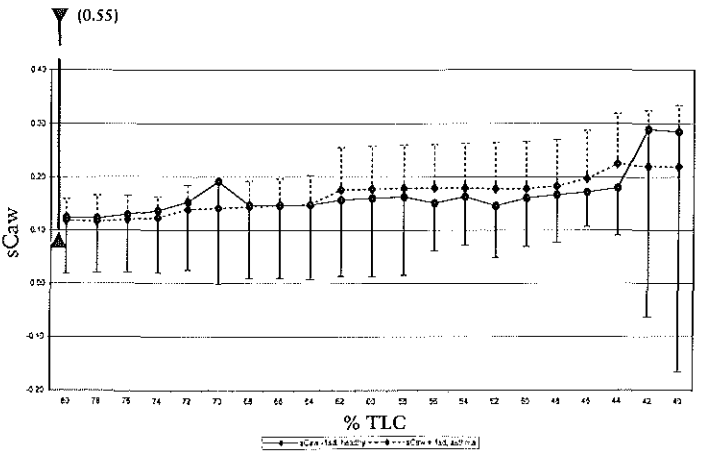
Mean MFSR derived airway cross sectional area (A) versus lung volume



A: airway cross sectional area, TLC: Total lung capacity, sd: standard deviation.
▼▲ : value range of corresponding variable as measured *in vivo* during Pitot static probe study.

Figure 3c

Mean MFSR derived specific airway compliance (sCaw) versus lung volume



sCaw: specific airway compliance (sCaw = Caw/A, 1/kPa), TLC: Total lung capacity, sd: standard deviation, ▼▲ : value range of corresponding variable as measured *in vivo* during Pitot static probe study.

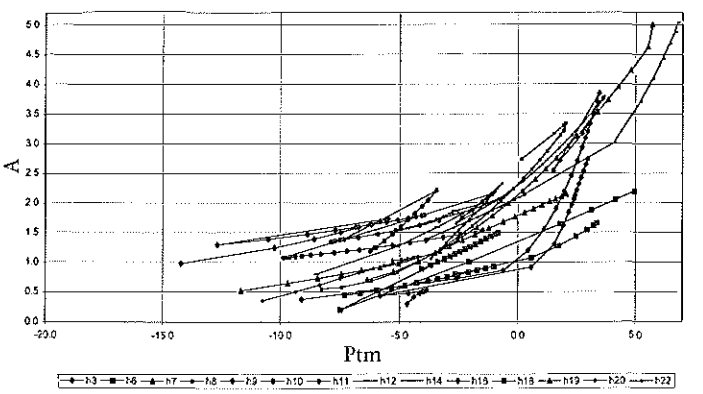
axis. In most of the healthy subjects and in only one of the asthmatics the A_m/Ptm_m curves had a composed appearance with an ascending and a descending branch with decreasing lung volume (Fig. 4).

Pitot static probe $dA_p/dPtm_p$ study

The results of the *in vivo* PS probe measurements are extensively described by Pedersen (32) and Brackel et al. (5). Especially in the upstream part of the central airways significantly lower Caw_p

Figure 4a

MFSR derived A/Ptm curves in individual healthy subjects. (80%-40% TLC)



A: cross sectional area (cm^2), Ptm: transmural pressure (kPa), TLC: Total lung capacity, h: healthy subject.

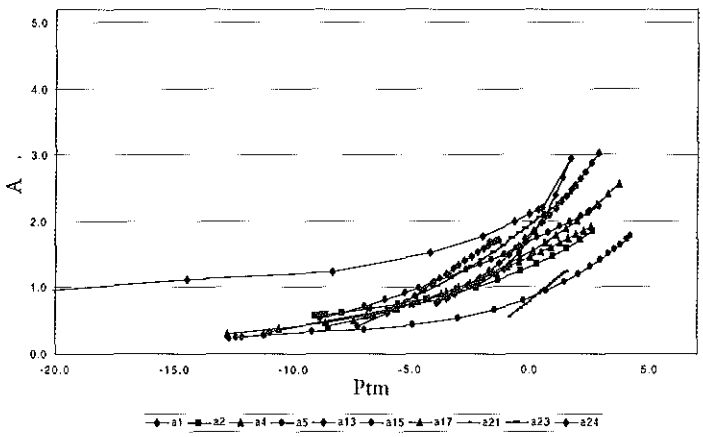


Figure 4b

MFSR derived A/Ptm curves in individual asthmatic subjects. (80%-40% TLC)

A: cross sectional area (cm^2), Ptm: transmural pressure (kPa), TLC: Total lung capacity, a: asthmatic subject.

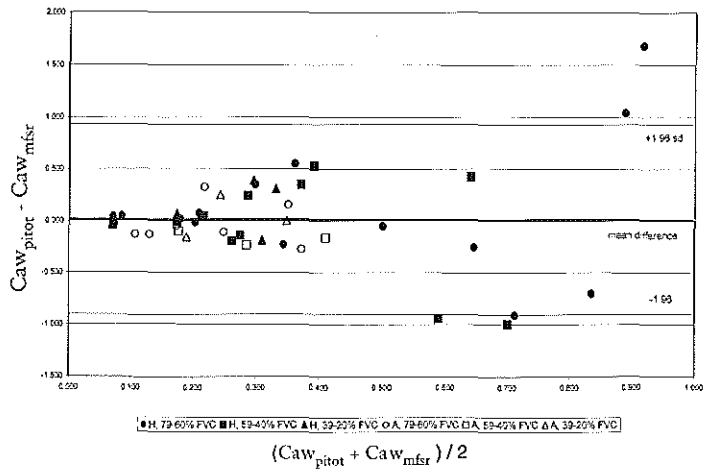
and $sCaw_p$ values were found in the asthmatic subjects, indicating more stiffly central airway behavior during forced expiration. A_p and Caw_p decreased with decreasing volume in contrast with $sCaw_p$. The latter was not determined by volume. The range of mean Caw_p , A_p and $sCaw_p$ values is given in figures 3a, 3b and 3c. Choke points (indicating local flow limitation and defined as PS probe positions with $0.8 < SI < 1.2$) were formed at all central airway positions in the healthy subjects and only at the most upstream PS probe position in the asthmatics (unpublished results) (Chapter 5).

Comparison of MFSR and PS probe derived variables

Fig. 5a, 5b and 5c represent Bland and Altman plots in which Caw_m, A_m and $sCaw_m$ are compared with the directly measured PS probe results under the condition $0.8 < SI < 1.2$. Mean Caw_m did not differ significantly from Caw_p. However, the precision (± 1.96 standard deviation) of the comparison was low, although the random variations increased with the magnitude of Caw, indicating a more stable variation coefficient of the differences. No significant correlation between bias and magnitude of Caw was present. A_p values were over the whole volume range smaller then the A_m values; the difference increased significantly with increasing A ($p < 0.001$) (Fig. 5b). A significant bias was present,

Figure 5a

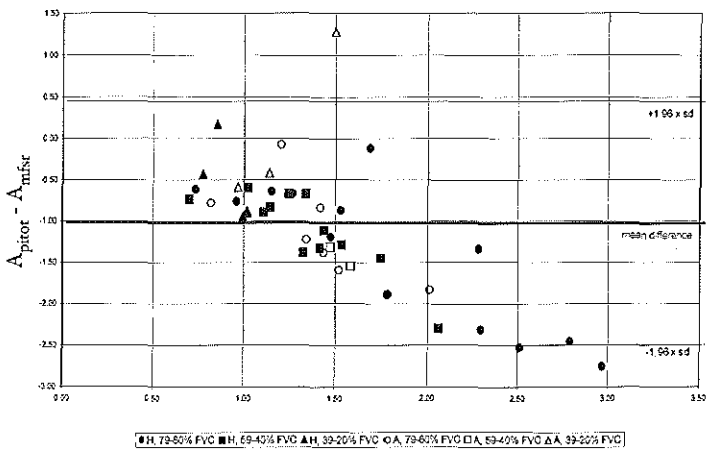
MFSR and Pitot static probe derived airway compliance (Caw), Bland-Altman plot.



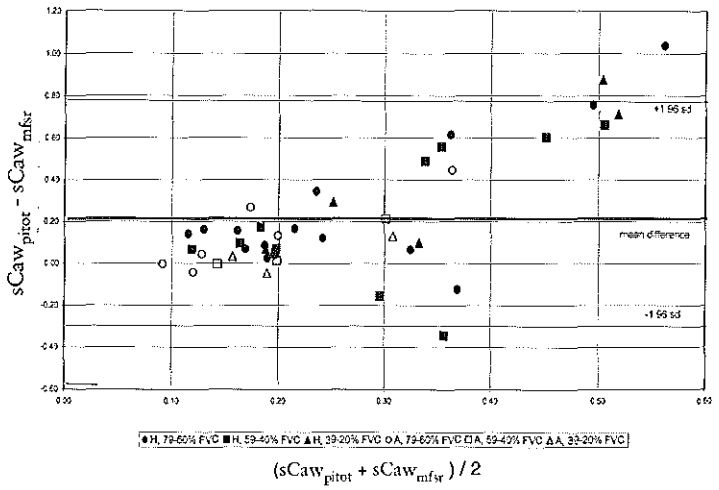
H: healthy subjects, A: asthmatic subjects, FVC: Forced vital capacity, C: airway compliance (cm^2/kPa), pitot: derived from Pitot static probe measurement, mfsr: derived from MFSR curve.

Figure 5b

MFSR and Pitot static probe derived airway cross sectional area (A), Bland-Altman plot.



H: healthy subjects, A: asthmatic subjects, FVC: Forced vital capacity, A: airway cross sectional area (cm^2), pitot: derived from Pitot static probe measurement, mfsr: derived from MFSR curve.



$sCaw_{pitot} - sCaw_{mfsr}$

$(sCaw_{pitot} + sCaw_{mfsr}) / 2$

Figure 5c

MFSR and Pitot static probe derived specific airway compliance (sCaw), Bland-Altman plot.

H: healthy subjects, A: asthmatic subjects, FVC: Forced vital capacity, sCaw: specific airway compliance (1/kPa), pitot: derived from Pitot static probe measurement, mfsr: derived from MFSR curve.

causing A_p to be on average -1.05 (SD 0.75) cm^2 lower than A_m ($p < 0.001$). The lower A_p values caused $sCaw_p$ to be significantly larger then $sCaw_m$ ($p< 0.001$). The difference was on average 0.21 1/kPa (SD 0.29) and increased significantly with increasing sCaw ($p< 0.001$) (Fig. 5c). No clear difference in behavior of the different variables was found between the healthy volunteers and the patients with asthma. The low precision visible in Fig. 5a and 5c becomes also apparent from the absence of a significant correlation between Caw_m and Caw_p or between $sCaw_m$ and $sCaw_p$. A_m correlated, however, with A_p in the group of healthy subjects; regression analysis yielded the equation $A_m = 0.33+1.90 \bullet A_p$ ($R^2=0.51$, $p< 0.001$).

DISCUSSION

The purpose of the current study was firstly to compare MFSR derived elastic airway properties between healthy and asthmatic subjects. Secondly, to evaluate whether airway compliance as derivative of the MFSR curve can be used as an alternative of *in vivo* measurements.

The results indicate that Caw_m, as derivative of the MFSR curve, does not differ between healthy young adults and subjects with stable mild asthma. This is in contrast with the PS probe derived Caw_p results. However, the accuracy and meaning of MFSR derived variables is questionable as the exact location of FLS is not defined and may differ between both groups and large random errors are present. Although mean Caw showed no appreciable difference, a considerable difference existed between both types of measurements with regard to A and sCaw. The MFSR data appeared to be most reliable near peak expiratory flow where flow limitation may be expected to occur in the central airways, where the PS probe measurements were performed. It may therefore be concluded that the intrabronchial measurement of central airway compliance can not be replaced by a less invasive and a less complex deduction of airway compliance from MFSR curves.

Subjects, technical aspects, spirometry, analysis

The complexity of the invasive and the time consuming nature of the PS probe experiments hampered the inclusion of more volunteers. Therefore, a complete match between the two groups of subjects could not be obtained (Table 1). However, no significant differences in FEV1/FVC as measure for airway patency or in TLC were found. The invasive nature of the intrabronchial PS probe part of study obliged us to select patients with only mild to moderate asthma. This may explain partly that we found no significant differences in Caw_m or $sCaw_m$ between the two groups, in contrast with the lower Caw_p and $sCaw_p$ in the patients with asthma (5). Only the asthmatic subjects were pretreated with a β-2-agonist and systemic corticosteroids. A lower tone of bronchial smooth muscle, may have caused artificially more compliant airways in the astmatic subjects (29;30). Therefore Caw_m results may have been lower and the difference in Caw_p and $sCaw_p$ may have been even larger prior to bronchodilation.

For a discussion about the technical aspects of the PS probe study and their limitations we refer to related papers by Pedersen et al. in dogs (37) and Pedersen et al. (32) and Brackel et al. (5). The MFSR analysis is based on a mono-alveolar, mono-airway-model, which is supposed to generate and maximize flow in the same way as the *in vivo* lung, with the flow limiting segments placed in series in the bronchial tree. Several issues will therefore be addressed.

Applying the model to the real *in vivo* situation does not take into account the effects of uneven ventilation of different lung units. For normal lungs this is probably justified (36) as the lungs behave in a more homogeneous fashion during fast expirations (25). We tried to minimize the possible limitations in the asthmatic subjects by maximal bronchodilation and reduction of airway inflammation and by limiting the analysis to high mid lung volumes where the problem of uneven ventilation will be less.
In both groups, Pel values per 2% TLC level were, on average, lower than the scarcely available normal values (9;46). This may be explained by a larger volume of air in the esophageal balloon (1.5 ml instead of 0.5 ml), necessary because the PS probe measurements were performed during forced expiratory maneuvers as well. A larger balloon volume causes a shift of the static PV curve to smaller elastic recoil values although the shape of the PV curves is not changed. Although not significant, values of elastic recoil pressure were somewhat smaller in the asthmatic subjects without a difference in lung compliance (Fig.2, Table 2). Lower Pel values in the asthmatics are in agreement with findings by McCarthy et al. (22), Colebatch et al. (6) and Finucane et al. (11) and involve probably tissue stress relaxation (11). A lower Pel will lead to a leftward shift of the MFSR curve without a change in MFSR slope (Fig. 2). A decrease in Pel will lead to a lower expiratory flow and upstream shift of the Equal Pressure Point and possibly of the FLS. A lower expiratory flow may partly explain the significantly lower calculated A (equation 'j' in the appendix) in the asthmatic subjects (Table 2). A potential shift of FLS in the patients with asthma to upstream airway segments with different characteristics may therefore complicate the interpretation of the Caw_m , A_m , and $sCaw_m$ results.
In contrast to the MEFV curves, lung elastic recoil pressure (Pel) was measured in a quasi static situation. MFSR curves only represent the dynamic conditions when static lung recoil pressure (Pel) can be considered equal to dynamic lung recoil pressure. This is the case only if lung tissue resistance is small, and there is no inequality of ventilation (31). Results of a study on excised dog lobes (45) and re-evaluation of a study by Bar-Yishay and Wilson (3) by Webster et al. (45) indeed indicated that recoil of the lung during forced expiration is adequately modeled by the quasi static Pel/V relationship.

Compression of intrathoracic air during forced expiration causes a discrepancy between flow volume curves, based on either intrathoracic volume or on volume changes from the integration of airflow (16). From recordings of alveolar pressure (Palv), presented in an earlier paper (32), it can be concluded that in the largest range of analysis (80%-40% FVC), no significant changes in Palv occur. *d*V'max/*d*Pel values are, therefore, probably not appreciably influenced by differences in compression of air in the largest range of analysis (80-40% FVC).

During the MFSR experiments, we were not informed about the actual intrathoracic pressures in the healthy subjects and the patients with asthma, but had no reason to believe that the two groups differed in this aspect. MFSR derived Ptm_m values per 2% TLC level were comparable between both groups. Moreover, we found no large differences between the groups in airway patency or in TLC.

We had no actual control of possibly less then maximal expiratory flows or the occurrence of negative effort dependence (12;24). Therefore, we used a composite MEFV curve according to the envelope method by Peslin (38) in order to obtain the most maximal expiratory flow at each volume level for each subject. Although relatively more asthmatic male subjects participated and anthropometric data and TLC were comparable between both groups, $V'max_m$ was on average 1.17 l/s per 2% TLC level lower in the subjects with asthma (table 2) and predicted A_m was on average 0.34 cm^2 lower in the subjects with asthma. As A_m is calculated from $V'max_m$, the lower $V'max_m$ explains the lower A_m value.

Although, as already stated, the lower Pel may cause an upstream shift of the FLS, lower V'_m and/or A_m results may indicate that some (irreversible?) airway obstruction still existed in the asthmatics, despite pretreatment with bronchodilation and corticosteroids. The decrease in A_m with decreasing lung volume was also found in the PS probe study (5) and is in agreement with the findings by Hoffstein and associates (13) and by Hughes and coworkers (14). At a fixed position in the airways, a decrease in A during forced expiration can be explained by dynamic compression. However, A may also decrease directly related to volume, because of diminishment of axial tension or a decrease in tethering from surrounding lung tissue.

A_m reflects, however, the total cross sectional area of the airways at the level of the FLS and one might expect the FLS to move upstream during expiration (18;36;41). According to the trumpet model of the bronchial tree an upstream shift of FLS would imply a shift to an airway level with a larger A and larger Caw. The finding of lower A_m in combination with decreasing lung volume therefore suggests that the location of FLS remains more or less stable or that the volume effects are relatively stronger than that of an upstream shift of FLS. However, we do not know whether dynamic compression during forced expiration may result in a relative lower A of the more upstream located, more compliant airways. The MFSR analysis does not allow a clear separation between those effects.
In contrast with the Caw_p and the $sCaw_p$ results in central airways, Caw_m and $sCaw_m$ per 2% TLC level showed no significant difference between healthy and asthmatic subjects. This is difficult to interpret because we are not informed about the exact intrabronchial location of the FLS in the MFSR study. The decrease of Caw_m with decreasing lung volume (Fig. 3a, Table 2) agrees with a report by Suki et al. (44). They found that in calfs' tracheas, when length tension is reduced during exhalation, cartilage rings move towards each other and result in stiffer airways. However this decrease in Caw_m is inconsistent with an important shift of the FLS to more peripheral, more compliant airways during expiration. The slight, but significant increase in sCaw with decreasing lung volume (Fig. 3c, Table 2) suggests that the effect of a decrease in lung volume is stronger on A than on Caw.

The MFSR-*d*A/*d*Ptm analysis is only valid if A is determined only by Ptm and local airway compliance. When FLS is intrapulmonary, *d*A/*d*Ptm reflects the elastic properties of airways attached to lung parenchyma, instead of the elastic properties of the airways alone. Studies in intact dogs (17;27;42), by Macklem in human subjects (20;21) and in excised dog and human lungs (15;26;41), show the formation of the FLS in the central airways. During forced expiration from TLC, the FLS moves upstream to the lobar and segmental bronchi. Smaldone (43) studied the location of FLS near residual volume in humans: FLS moved upstream during expiration but was found in the central airways in all subjects, even at RV. At a constant volume multiple FLS

could be located, all in parallel bronchi. When we extend the findings by Smaldone to our study and limit our analysis to the volume range 80-40%TLC, the FLS is probably located at comparable positions in the central airways in the group of asthmatic as well as in the healthy subjects. This assumption is supported by the Caw_m and A_m results described above and by the PS probe results as well: choke points, defined as locations with $0.8<SI<1.2$ occurred in the central airways in the healthy subjects and at the lower lobe in the asthmatic patients. However, the PS probe results do not exclude the possibility that wave speed is also reached in more peripheral airways that could not be reached by the PS probe.
In the calculations used, it is assumed that the intrabronchial air velocity profile is blunt. For reasons stated above, we felt justified to assume that FLS was located in the central airways in the volume range studied. Experiments in dogs show that converging airflow with a high Reynolds number is found at the choke point in dogs' trachea's (10). Pedersen showed the same in experiments using a mechanical model (34).

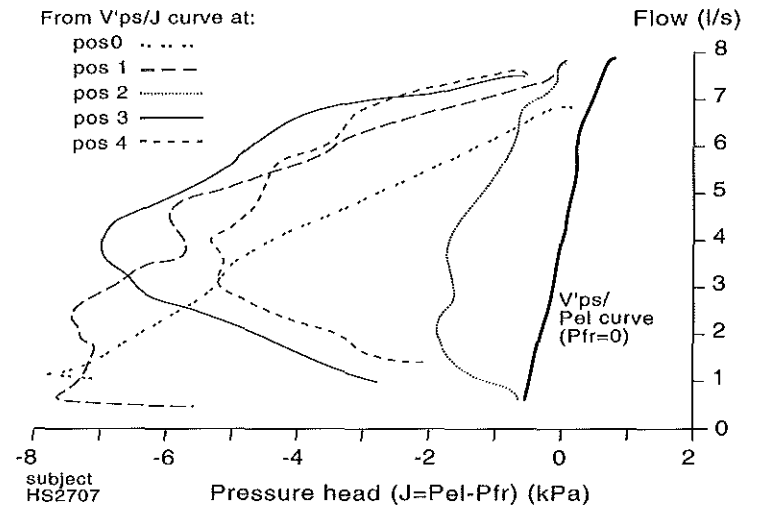
The most important assumption in the MFSR analysis is that the pressure loss due to friction (Pfr) is neglected in the calculations of $dA/dPtm$. No significant differences between the healthy and asthmatic subjects were found in the slope k of the MFSR curve (Table 2). This suggests that the airway conductance upstream from the FLS, and therefore the viscosity dependent pressure losses in the periphery of the lung, are comparable in both groups, according to the model by Leaver and coworkers (19). Therefore comparison of MFSR derived variables between the two groups seems justified. The decrease of k with decrease in volume (Table 2) is in agreement with an increase in airway resistance with decreasing volume.
Neglect of Pfr in the calculation may lead to underestimation of A_m, Ptm_m may be an overestimate of the true Ptm and the airways may seem to be stiffer than they actually are (35). Therefore, negligence of Pfr may (partially) explain the poor agreement of A_m and Caw_m with A_p and Caw_p respectively.
The MFSR derived A/Ptm relationship describes theoretically the compliance of a composite airway (with no frictional pressure losses) that would give the same maximal flow as observed on

the MFSR curve. Studies in a model (35) support the question, whether A/Ptm curves 'contained' in the derived A/Ptm curve(s), really exist. Another study in dogs (37) showed that the measured A/Ptm curve did not differ from the MFSR derived A/Ptm curve at the level of the right lower lobe bronchus of a dogs' lung. The question remains whether this is also true in human subjects.
The peripheral pressure loss may be divided into viscosity dependent and density dependent pressure losses. Pedersen and Nielsen showed that MFSR derived A/Ptm curves on air and on an SF_6/O_2 mixture (higher density, lower viscosity) were identical (36). Since a decrease in the viscosity lower than air made no difference with regard to the measurement of A, this indicated that viscosity dependent pressure loss was minimal. Furthermore, maximal flows on air and on the SF_6/O_2 mixture, were identical after correction for density (33) in healthy young subjects (Pedersen, unpublished results). Since density dependent pressure losses can not be detected this way, we do not know whether these play a significant role.

By use of the flow at the PS probe (V'ps), we constructed 'PS probe' derived V'ps/Pel curves (as an equivalent of an MFSR curve) in five healthy subjects. In each subject, the *in vivo* measured V'ps/Pel curves were compared with the V'ps/J curve (J = Pel-Pfr) and the V'ps/Pel derived A/Ptm curve with the actual measured A/Ptm curves at different PS probe positions in the central airways (example: Fig. 6a, 6b). The horizontal difference between the V'ps/Pel curve and the V'ps/J curves reflects the frictional pressure loss Pfr upstream from the PS probe. Most of the V'ps/J curves were rather close to the V'ps/Pel curves near peak expiratory flow, where flow is limited in most subjects (32). With the PS probe in more upstream positions and at decreasing flows, the curves deviated more from the V'ps/Pel curve, indicating an increase of Pfr. (O.F. Pedersen, personal communication). These *in vivo* results indicate that, only at peakflow, MFSR derived airway parameters reflect central airway characteristics correctly .
Most MFSR derived A/Ptm curves in the healthy subjects showed a similar appearance. They consisted of two 'legs' (both concave to the Ptm axis): one, beginning at the left and ascending along the upper side of the angle towards a top and a second with a

Figure 6a

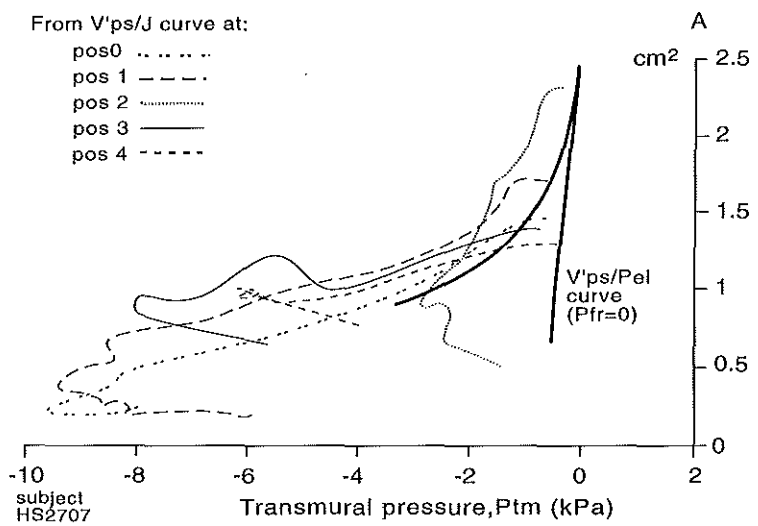
V'ps/Pel and V'ps/J curves during a Pitot static probe experiment



V'ps: flow at the Pitot static probe (l/s), Pel: lung elastic recoil pressure (kPa), Pfr: frictional pressure loss (kPa), Pos: Pitot static probe position (see figure 1), J: Pressure head at Pitot static probe. (explanation: see text)

Figure 6b

Pitot static probe derived A/Ptm curves compared with the A/Ptm curve derived from the V'ps/Pel curve during Pitot static probe experiment.



V'ps: flow at the Pitot static probe (l/s), Pel: lung elastic recoil pressure (kPa), Pos: Pitot static probe position (see figure 1). (explanation: see text)

descending branch to the left along the lower side of the angle (Fig. 4a). This pattern resembled the A/Ptm curves derived from the above described V'ps/Pel curves (example: Fig. 6b) and agreed with findings in model and human studies by Pedersen (36),(35). The pattern can be explained by an upstream motion (or jump) of the FLS from one part of an airway segment or bronchial generation to another segment or generation with different elastic behavior (36). Flow limitation starts at the upper leg. During expiration the movement along the A/Ptm curve is upward and right, reaching the apex and then down along the right leg. In the V'ps/Pel derived A/Ptm curves (example Fig. 6b), the ascending leg, corresponding to the very early phase of flow limitation was in many subjects close to the actually measured A/Ptm relationship of the central airways. In some subjects the descending leg was almost identical to the PS probe determined A/Ptm curve for the most upstream PS probe position. This suggests that the two legs of the MFSR derived A/Ptm curve reflect flow limitation beginning in the most central airways (ascending A/Ptm leg) and later in more upstream airways (descending leg) as described earlier by Pedersen (35;36). In the current study only one asthmatic showed a 'two legged' A/Ptm curve, the others had only a descending A/Ptm curve (Fig. 4b), indicating a more upstream located FLS. These findings support that the MFSR derived A/Ptm curve indeed contains 'true' A/Ptm curves related to the compliance of the segments of the bronchial tree.

Comparison of actual measurements

A large part of the PS probe results was obtained at a PS probe position and/or within a volume range where no flow limitation took place. The MFSR derived A_m , Caw_m and $sCaw_m$ results were supposed to reflect the elastic properties at the FLS wherever this is located. Therefore we compared only the A_p, Caw_p and $sCaw_p$ results, selected for the (choke point') condition $0.8< SI<1.2$, with the equivalent MFSR variables. Although the range of Caw_p and $sCaw_p$ values (5) was comparable with the corresponding MFSR derived results (Fig. 3a, 3c), there was no within subjects correlation in the two groups of subjects (Figure 5a, 5b and 5c). This discrepancy between the actually measured values and the large random fluctuations may be explained by the PS probe itself. The subjects were hampered by the PS probe and showed sometimes inability to breathe in or breathe out com-

pletely and /or showed inadequate force during the PS probe experiments in spite of maximal encouragement. Therefore matching of the MFSR and PS probe measurements may not have been totally accurate. More important, all PS probe derived results were obtained in the central airways whereas a large part of the MFSR derived results probably reflect characteristics of more upstream located airways. The latter explanation may be supported by the finding of a significant larger MFSR derived A_m (Fig. 5b) since in both studies the measured A reflects the total functional cross sectional area of all airways at the level of measurement in the bronchial tree.
The PS probe results indicate stiffer central airway behavior during forced expiration in the asthmatic subjects, as described by Brackel et al. (5). The MFSR derived A/Ptm curves suggest that airway stiffness at FLS (located in more peripheral airways?) is not different between the healthy and asthmatic subjects. We are, however, not informed whether the intrabronchial location of FLS in the healthy and in the asthmatic subjects can be compared.

In conclusion

Under certain assumptions, deduction of the A/Ptm relationship from the MFSR curve according to the wave speed concept may yield airway characteristics at the site where and when flow is limited during forced expiration. This is probably mainly the case near peak expiratory flow where the FLS is located most downstream and where frictional losses are minimal. Appearance of the MFSR derived A/Ptm curves reflected jumps of the FLS between airway segments like the PS probe results suggested. Both methods showed that Caw and A decrease with decreasing lung and that sCaw is relatively volume independent. The absence of knowledge about the exact location of the FLS and negligence of frictional losses may explain why the MFSR analysis is not sensitive enough to reflect changes in airway compliance demonstrated with an intrabronchially placed Pitot static probe, in patients with mild to moderate asthma.

The current study suggests firstly that MFSR curve derived variables are related to flowlimiting airway segments located upstream from the lower lobe bronchus, being the most upstream bronchus reached by the Pitot static probe. Secondly, that the site

of flow limitation remains rather stable during forced expiration in healthy as well as in asthmatic subjects. Furthermore: MFSR derived elastic properties are not sensitive enough to reflect changes in airway compliance, demonstrated with an intra-bronchially placed Pitot static probe, in patients with mild to moderate asthma.

APPENDIX

Mathematical relation between dV'max/dJ and dA/dPtm, A and Ptm

Under the assumptions:
- flow is incompressible and has a blunt profile
- airway cross sectional area A depends only on transmural pressure Ptm (A=f(Ptm) the following mathematics can be derived:

$Pca = \frac{1}{2} \bullet \rho \bullet (V'^2/A^2)$ (Bernoulli equation, ρ: density) (a)

$J = Pel - Pfr$ (b)

$Ptm + (-Pel) + Pfr + Pca = 0$ (Pressure walk by Mead (23)) (c)

equation (a),(b) and (c) ==>

$Ptm - J + \frac{1}{2} \bullet \rho \bullet (V'^2/A^2) = 0$ (d)

solving equation (d) for V' ==>

$V' = A \bullet [(2/\rho) \bullet (J-Ptm)]^{0.5}$ (e)

If A is a unique function of Ptm (A = f(Ptm) (tubelaw)), flow V' becomes a function of Ptm at each value of J (V' = g(Ptm)) and can be described by an iso J-V'-Ptm curve.
From equation (e) follows (34):

$$dV'/dPtm = (dA/dPtm) \bullet [(2/\rho) \bullet (J-Ptm)]^{0.5} + \frac{1}{2} \bullet A \bullet (-2/\rho) \bullet [(2/\rho)(J-Ptm)]^{-0.5} \quad (f)$$

At a maximal value of V' (V'max) along the V'-isoJ-curve: $dV'/dPtm = 0$. Therefore:

$$(dA/dPtm)\bullet[(2/\rho)\bullet(J-Ptm)]^{0.5} - (A/\rho)\bullet[(2/\rho)\bullet(J-Ptm)]^{-0.5} = 0 \Longrightarrow$$

$$(dA/dPtm)\bullet(2/\rho)\bullet(J-Ptm) = A/\rho \qquad (g)$$

equation (a), (c) and (g), and neglecting Pfr ==>

$$dA/dPtm = A^3/(\rho\bullet V'max^2) \qquad \text{and} \qquad (h)$$

$$V'max = A\bullet[(A/\rho)\bullet(dPtm/dA)]^{0.5} \qquad (i)$$

If A°, Ptm° and J° are the values at the flow limiting segment related to maximal flow we get from (e):

$$V'max = A^\circ\bullet[(2/\rho)\bullet(J^\circ-Ptm^\circ)]^{0.5}$$

Differentiation with respect to J° ((34)):

$$dV'max/dJ^\circ = (A^\circ/\rho)\bullet[(2/\rho)\bullet(J^\circ-Ptm^\circ)]^{-0.5}$$

Substituting $J^\circ-Ptm^\circ = Pca^\circ = \frac{1}{2}\bullet\rho\bullet(V'max/A^\circ)^2$ ==>

$$dV'max/dJ^\circ = A^{\circ 2} / (\rho\bullet V'max)$$

Solved for A° ==>

$$A^\circ = [(\rho\bullet V'max)\bullet(dV'max/dJ^\circ)]^{0.5} \qquad (j)$$

A° can therefore be calculated from V'max and the slope of the V'max-J curve at the corresponding V'max point. Ptm° can be calculated from (d) and the calculated A° value.

If Pfr is small, J resembles Pel (equation (b)). The Maximal Flow Static Recoil curve (MFSR curve), which approximates the V'max/Pel curve, can then be used to calculate A°. Ptm° and airway compliance $dA^\circ/dPtm^\circ$ at the Flow Limiting Segment which determines V'max.

Combining equations (i) and (j) links the V'max/J and the A/Ptm curve:

$$(1/V'max)\bullet(dV'max/dJ^\circ) = (1/A^\circ)\bullet(dA^\circ/dPtm^\circ)$$

both sides multiplied with V'max gives:

$$dV'max/dJ^\circ = (V'max/A^\circ)\bullet(dA^\circ/dPtm^\circ) \qquad (k)$$

Equation (k) states that the slope of the V'max-J curve (or at small Pfr, the MFSR curve) can be represented by airway compliance ($dA^\circ/dPtm^\circ$) multiplied by the wave speed at the FLS ($V'max/A^\circ$). In other words the slope of the MFSR curve (Rs in the terminology of Pride et al. (J.Appl.Physiol. 23: 646-662, 1967)) and not the intercept with the Pel axis (Ptm', as described by Leaver (19)) is related to airway compliance at FLS. Ptm' is an extrapolated Ptm value, indicating the transmural pressure at which the last airway closes during expiration.

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7

Wave-speed-determined flow limitation at peak flow in normal and asthmatic subjects

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ABSTRACT

The purpose of this study was to examine whether peak expiratory flow is determined by the wave speed flow limiting mechanism. We examined 17 healthy subjects and 11 subjects with stable asthma, the latter treated with inhaled bronchodilators and corticosteroids. We used an esophageal balloon and a Pitot static probe positioned at five locations between the right lower lobe and midtrachea to obtain dynamic area transmural pressure (A-Ptm) curves as described (O.F. Pedersen, B.Thiessen, and S. Lyager *J.Appl.Physiol.* 52: 357-369,1982). From these curves we obtained cross sectional area (A) and airway compliance (Caw = dA/dPtm) at PEF, calculated flow at wave speed {V'ws = $A[A/(Caw \bullet \rho)]^{0.5}$, where ρ is density}, and speed index is (SI = V'/V'ws). In 13 of 15 healthy and in 4 of 10 asthmatic subjects, who could produce satisfactory curves, SI at PEF was > 0.9 at one or more measured positions. Alveolar pressure continued to increase after PEF was achieved, suggesting flow limitation somewhere in the airway in all of these subjects. We conclude that wave speed is reached in central airways at PEF in most subjects, but it cannot be excluded that wave speed is also reached in more peripheral airways.

INTRODUCTION

Peak expiratory flow is defined as the highest flow achieved at the mouth during a maximally forced vital capacity (FVC) maneuver, starting at full inspiration (1;19).

As first pointed out by Fry et al. (6), there is a unique relationship among transpulmonary pressure, expiratory flow, and lung volume so that, during a forced expiration, flow reaches a maximal value before pressure does. When flow has become maximal, that is, when flow at a given lung volume does not increase further when pressure increases, the expiratory flow has been defined as 'effort independent'.

Hyatt et al. (9) initially estimated the effort independent part of the maximum expiratory flow volume curve to begin at ~ 50%

of vital capacity (VC). This estimate was later increased to 60% (8). Mead et al. (15) demonstrated levels of 70 % VC or higher in five normal subjects. Van de Woestijne and Zapletal (27), requiring at least five points to define a plateau after a maximum on an isovolume pressure flow curve, found that the effort independent portion extended to 82% and that PEF was found at 88% VC in the examined subjects. This indicates that PEF may indeed be obtained at near flow limiting conditions. This is supported by Volta et al (25), who applied a negative pressure pulse at the mouth and found no change in PEF in nine normal subjects applying maximal efforts. A different approach can be made by applying the analysis by Dawson and Elliott (4). This approach shows that flow (V') through an airway segment becomes maximal when the linear velocity reaches the speed of a pressurewave propagation through the airway. Wavespeed flow (V'ws) depends on the cross sectional area (A), airway compliance (Caw = dA/dPtm), which is the slope of the curve describing A as a function of distending transmural pressure (Ptm), and the density (ρ) of the gas , to the equation:

$$V'ws = A\,[A/(\rho \bullet Caw)]^{0.5}$$

It can be seen that V'ws will decrease, when A becomes smaller, and Caw and ρ become larger. V'ws indirectly depends on the lung elastic recoil pressure (Pel) and the pressure loss (Pfr) upstream from the flowdetermining segment, which Dawson and Elliott (4) called the 'choke point', because a decreased pressure head (J = Pel - Pfr) will make the distending pressure (Ptm) smaller and, accordingly, make A smaller.

If PEF is limited by the wave speed, then it should occur when the velocity of the accelerating flow reaches wave speed at some point in the airway. At that point, the speed index (SI = V'/V'ws) will be equal to one.

As described in studies in dogs (16), V'ws can be measured at different locations in the airways from data obtained with a Pitot static probe, an esophageal balloon, and expiratory flow.

The purpose of the present study was to measure SI during FVC maneuvers at different locations in the airway of healthy and stable asthmatic subjects to obtain support for the hypothesis that PEF is determined by the wave speed flow limiting mechanism.

MATERIALS AND METHODS

Subjects

The experiments were performed in 28 adults, 17 healthy and 11 with asthma. All subjects were non-smokers and none had a history of cardiovascular or other diseases apart from asthma in the group of patients. Three of the healthy subjects were examined in 1979 but were included in the present study because they were measured according to the same principles and with use of the same equipment with recording on tape. All healthy subjects had routine lung function results within the normal range and, except for the three subjects examined on the previous occasion, their response to inhalation of 1 mg of terbutaline was examined and showed no significant change from baseline. All the asthmatic subjects had asthma before the age of 5 yr and used maintenance treatment with inhaled corticosteroids for at least 3 yr. They had previously demonstrated bronchial hyperresponsiveness with a 20% fall from baseline forced expiratory volume in 1 s (FEV1) after inhalation of <160 μg histamine and were atopic, defined as a total immunoglobulin E antibody concentration of > 100 IU and a positive radio allergosorbent test for at least one inhaled allergen (in most cases, the house dust mite). All patients with asthma were in a stable period. If an asthma exacerbation had occurred within 1 mo before scheduled measurements, the experiments were postponed for at least 2 wk. In an attempt to minimize bronchial obstruction because of edema or hypersecretion at the time of measurements, all asthmatic subjects were pretreated with a 7 day course of prednisolone in addition to their regular treatment. Within 1.5 h before introduction of the intrabronchial Pitot static probe, all asthmatic subjects inhaled a dose of β-2 agonist, which resulted in maximal bronchodilatation during a doseresponse curve obtained 1 wk before the prednisolone course.

Equipment

A Pitot static probe, as previously described (16), was used, slightly modified from the one described by Macklem and Mead (13). It is a device with an end hole for measurement of impaction pressure (Ptot) and a number of side holes for measurement of lateral airway pressure (Plat). It was provided with two 1.57 mm internal diameter Polystan tubes that were 100 cm

long. These tubes and an identical tube from an esophageal balloon [for measurement of the pleural pressure equivalent (Ppl)] were connected to three identical pressure transducers (EMT34, Elema Schönander, Stockholm, Sweden) and via EMT 311 amplifiers to an electronic subtractor. Three pressure differences were obtained: Pca = Ptot - Plat, J = Ptot - Ppl, and Ptm = Plat - Ppl, where Pca is the pressure needed for convective acceleration, i.e., for acceleration of the gas molecules so that they can pass a given cross section of the airway at a given flow. J is a fluid mechanical term defined as the pressure head, and Ptm is the transmural pressure. The pressures were calibrated daily with a mercury manometer providing ±10 kPa.

Mouth flow (V'm) was measured by a non heated Fleisch no 3.5 pneumotachograph. The pressure drop across the flow head was measured with a Validyne MP45 transducer (Northridge, Ca) fitted with a 2- kPa diaphragm and connected to a Validyne amplifier. Flow was calibrated by the integration procedure (23), introducing 9 liters of air through the flow head with a 1-liter syringe. The amplification was adjusted so that the integrated flow signal provided the same output as an integrated 1-s pulse reference flow, which was then by definition 9 l/s. The geometry of the inlet to the flow head was optimized so that the deviation from linearity was <5% up to 15 l/s.

V'm and the pressure signals, Pca, Ptm, and Ppl, were visible online on an AT computer (Olivetti PCS-286 with a 80287 mathematical coprocessor). In this way it was possible to assess the results directly. Especially, it was possible to detect malfunctioning of the Pitot static probe, as in case of obstruction of one or more of the holes. The signals of approved maneuvers were saved for subsequent calculations.

Tuning of catheters

The Pitot static probe and the esophageal balloon were enclosed in an airtight tube to which a sine pump could be attached and deliver pressure swings of ≈10 kPa. The three pressure differences were displayed on an oscilloscope. With the pump running at the slowest possible speed (~ 1 Hz), the amplifications were adjusted so that the differences between them were zero. Then, the speed of the pump was increased to its maximum (~ 8 Hz), and the resistance and length of the individual catheters were adjusted to minimize the excursions. In this way, the error in the pressure dif-

ferences could be reduced to <1% of the pressure swings. The 90% rise time to a square wave pressure input was <10 ms.
An x-y oscilloscope was finally used to tune the Pca pressure signal to the V'm signal. Via a Y-tube, the Pitot static probe was positioned in an (15-mm inner diameter rigid tube connected to the pneumotachograph. According to the Bernoulli equation, Pca equals $\rho \bullet (V'/A)^2/2$, were A is the cross sectional area. For a blunt flow profile and a constant A, Pca and V' must be in phase. The pneumotachograph was supplied with catheters identical to those of the Pitot static probe, and the length of these was adjusted until the x-y recording showed a closed loop as a response to a peak flow maneuver through the tube.

Test of Pitot static probe

Figure 1 shows results of testing the Pitot static probe for accelerating and decelerating flows. Measured areas for different straight tubes are drawn against Pca. The true dimensions of the tubes are given at the corresponding horizontal lines. Because the probe measures the area around it, a slight but constant underestimation of the tube dimension is expected. This is important especially for the narrowest tube, where, in Fig.1, the dashed line is the true area minus 0.07 cm^2, the area occupied by the probe. Except for the largest areas, the accuracy is in the range of ±10%.

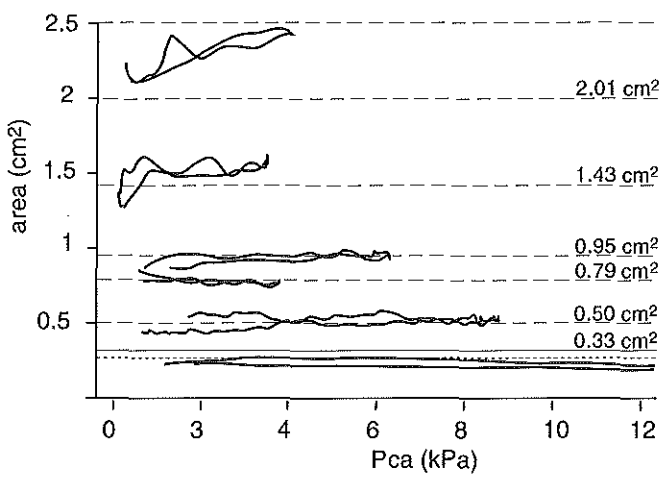


Figure 1

Tests with Pitot static probe in rigid tubes, cross sectional areas of which are marked as solid lines. Area is measured as a function of pressure needed for convective acceleration (Pca). Interrupted line for narrowest tube is area corrected for cross sectional area of probe (= 0.07 cm^2; cf. text).

Experimental procedure

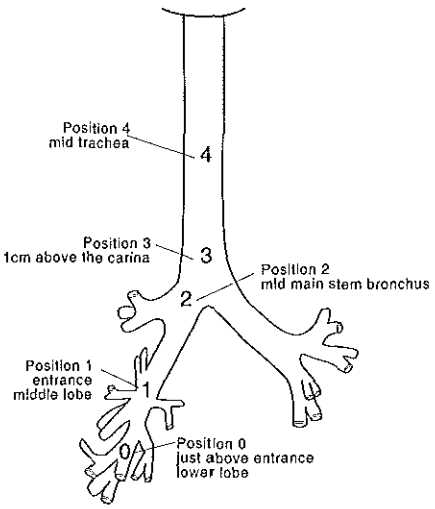
Initial lung function tests were performed on a separate day before the Pitot study. These included measurements of FEV1, FVC, PEF, total lung capacity (TLC), and maximum expiratory flow volume curves. Furthermore, quasi static pressure volume curves were measured according to Zapletal et al. (28). The balloon was introduced via one nostril to a position in the esophagus where the pressure was most negative during maximal inspiration. The balloon was filled with 1.5 ml of air and stayed *in situ* throughout the experiment.

On the day of the Pitot study the subject was premedicated with 0.5 mg atropine intramuscularly 1 h before the introduction of the Pitot static probe to minimize mucous production and prevent a vasovagal reaction. No sedatives were used. Local anesthesia was given as follows: mouth and pharynx, 10% Xylocaine or 4% lidocaine spray; vocal cords, trachea and bronchial tree: 0.5% novesine solution, 20 ml maximally, or lidocaine 1%, 10 ml maximally. Anesthesia was given on demand through the bronchoscope. A cuffless endotracheal (ET) tube was placed over the bronchoscope. After introduction of the bronchoscope into the trachea, the ET tube was passed between the vocal cords, and the bronchoscope was pulled back. The Pitot static probe with its two catheters was placed into the trachea through the ET tube, which was then removed. Subsequently, the bronchoscope was reintroduced and the Pitot static probe was placed at the most peripheral position *(position 0),* with the tip of the probe just above the entrance to the right lower lobe (the left lower lobe in one subject). After the position of the two catheters was checked, the Pitot static probe was pulled back until four other positions were reached.These were, respectively, middle lobe entrance, mid main stem bronchus, 1 cm above the main carina, and mid trachea (Fig. 2). The distance between the positions was determined individually by measuring, at the mouth, the distance the catheter was pulled back between positions. Next, the Pitot static probe was repositioned in its most peripheral position, the bronchoscope was carefully withdrawn, and the two catheters were pushed through and secured in two tightly fitting side holes in the specially designed mouthpiece. Finally, the free ends of the catheters were connected to the pressure transducers, and the mouth piece was connected to the pneumotachograph.

The subjects were measured while sitting upright in a chair and

Figure 2

Bronchial tree with Pitot static probe positions



wearing a noseclip. Before each measurement the two Pitot probe catheters were each flushed forcefully with at least 2 x 50 ml of air to remove secretions from the end and side holes of the probe. Most of the subjects were asked to perform two types of forced expiratory maneuvers from TLC to residual volume. One was an ordinary FVC maneuver, the other a 'huff' maneuver, with performance of a number of sequential peak flows without closing the vocal cords. Some of the healthy subjects were also asked to perform relaxed expirations from TLC (sighs). At each position, starting with the most peripheral, each procedure was repeated until acceptable results were obtained or a maximum of 4 to 5 maneuvers was performed.

Calculations

The data acquisition and calculation applied Asyst software (version 3.10, Asyst Software Technologies, Rochester, NY). From the inputs V'm, Pca, Ptm and Ppl, the parameters in Table 1 were calculated at PEF of the maximum expiratory maneuvers and for the first peak of the huff maneuvers. Caw was calculated as dA/dt divided by $dPtm/dt$ by using a Asyst software routine applying a first order differentiation of a second degree polynomial fitted to three points corresponding to the peak.

The schematic drawing Fig. 3 may help explain some of the calculated relationships. *Equations 1 to 3* define the measured variables, which also included V'm. *Equations 4-15* define derived variables. A few of the equations can be commented on.

Table 1. Parameter definitions and equations

Definition	Equation (No.)	Equation	Unit of Measure
Pressure for convective acceleration	*(1)*	$Pca = Ptot - Plat$	kPa
Transmural pressure	*(2)*	$Ptm = Plat - Ppl$	kPa
Transpulmonary pressure	*(3)*	$Ptp = Pm - Ppl$	kPa
Alveolar pressure	*(4)*	$Palv = Pel + Ppl$	kPa
Downstream pressure drop	*(5)*	$Pd = Ptm - Ptp$ $= Plat - Pm$	kPa
Upstream pressure loss	*(6)*	$Pfr = Palv - Ptot$	kPa
Pressure head	*(7)*	$J = Ptot - Ppl$ $= Pca + Ptm$ $= Pel - Pfr$	kPa
Lateral pressure	*(8)*	$Plat = Ptm + Ppl$	kPa
Gas density at probe	*(9)*	$\rho_{Plat} = \rho_{PB} (P_B + Plat) / P_B$	kg/m^3
Flow at probe	*(10)*	$V'_{Plat} = V'm \bullet P_B / (P_B + Plat)$	l/s
Approximated thoracic gas volume change from TLC	*(11)*	$V_{Ppl} = (P_B / Vm \bullet dt + TLC \bullet Ppl) / (P_B + Ppl)$	l
Airway cross sectional area	*(12)*	$A = V'_{Plat} (50 \rho_{Plat} / Pca)^{0.5}$	cm^2
Airway compliance	*(13)*	$Caw = dA/dPtm$	cm^2/kPa
Wave speed flow	*(14)*	$V'ws = A[10A/(\rho_{Plat} \bullet Caw)])^{0.5}$	l/s
Speed index	*(15)*	$SI = V'Plat/V'ws = (2Pca \bullet Caw/A)^{0.5}$	

Ptot, impaction pressure; Plat, lateral airway pressure; Ppl, pleural pressure; Pm, pressure at mouth; Pel, lung elastic recoil pressure; ρP_B, weighted density of expired gas at 37°C by using Boyle's law; P_B, barometric pressure; V'm, mouth flow; Vm, volume at mouth; TLC, total lung capacity.

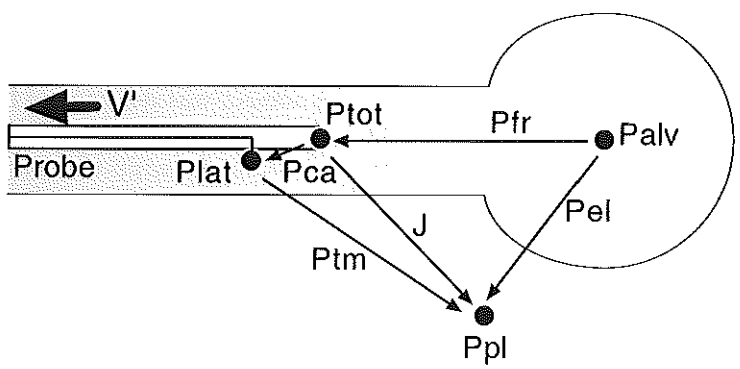


Figure 3

Pressures and pressure differences measured in airway (cf. Table 1). V': flow, Ptot: impaction pressure, Pfr: pressure loss (upstream), Palv: alveolar pressure, Plat: lateral airway pressure, J: Pressure head, Ptm: transmural pressure, Ppl: pleural pressure, Pel: lung elastic recoil pressure.

In *Eq.9*, gas density at the probe ρ_{PB} was calculated as the weighted density at 37°C of expired gas from data presented by Radford (20) to be 1.13 kg/m^3, by use of Boyle's law. In *Eq. 10*, flow at the probe was similarly calculated by use of Boyle's law. In *Eq. 11*, to correct for the effect of gas compression (10), especially in the matching of dynamic volumes with volumes measured quasi statically during determination of the static Pel, the expired volume from TLC was corrected for the influence of Ppl only. At PEF, this represents the largest part of alveolar pressure (Palv), which ideally should have been used in the correction. This correction was only done for positive Ppl. *Equation 12* calculated A from the Bernoulli equation under the assumption of blunt velocity profile. *Equation 15* was derived from *Eqs.12 and 14*. V'm was not corrected to BTPS conditions, and no attempt was made to correct for the difference between the composition of air and the alveolar gas. That correction will introduce a small, but systematic, error considered to be of no significance in the present study.

Selection criteria

Curves with obvious errors (evidence of blocked holes in or wedging of the Pitot static probe) were not saved. In the unselected data, there was a considerable variation in Caw with many negative values that cannot be used in calculation of SI (*Eq.15* in Table 1). This scatter was considerably decreased only if values of Caw for Pca > 1.3 kPa were selected, but negative values of Caw were still found. We therefore excluded curves with extreme values of (Caw <-10 and Caw > 5 cm^2 /(kPa) and with SI > 1.3, or rather SI^2 > 1.69 that could be calculated also for negative values of Caw. (cf.Discusion). The criteria Pca > 1.3 kPa was not used for examination of the distributions of the variables (except Caw) within the airways.

Statistics

The maximum SI in the airway of a subject was determined by first choosing the curve with the highest PEF (or first huff peak) among repeated measurements (replications) with the same maneuver and at the same position of the probe, and next the highest SI among positions was determined. Group means were compared by nonparametric tests. Multivariate analysis of variance and regression analysis were applied to provide estimates of differences between groups stratified for disease, gender, and probe position. $p < 0.05$ was chosen as the significance level.

RESULTS

Initial spirometry

Table 2 shows the anthropometric data for the men and woman in the two groups and the results of the initial spirometry. The predicted values of FEV1, FVC, PEF, and TLC were calculated according to the European Community for Coal and Steel standard (18). There was no significant difference in age. In men, the Wilcoxon rank sum test showed that the percent predicted values of all four parameters were significantly smaller in those with asthma than in the healthy subjects. In woman there was no such difference.

Data selection analysis

The healthy subjects, on average, performed 17 maneuvers (range 12-20). The corresponding number for the asthmatic subjects was 27 (range 11-33). This indicates a greater difficulty in getting satisfactory curves in the latter, mostly because of coughing by subjects and blocking of the holes of the Pitot static probe by secretions.

Not all subjects performed maneuvers or produced reliable results with the probe at all five positions. In the following, positions means probe position if not used in other contexts.The average number of missing positions was the same in the healthy

Table 2. Anthropometric data and initial spirometry of healthy and asthmatic subjects

Group	Age, yr	Height m	FEV1, %pred	FVC, %pred	PEF, %pred	TLC,%pred
Healthy subjects						
M	25.6±5.7	1.85±0.08	111±12	113±7	113±16	108±13
F	25.3±4.1	1.74±0.05	106±14	108±9	108±13	104±9
Asthmatic subjects						
M	20.6±3.3	1.84±0.07	83±6	91±8	90±16	93±8
F	25.3±3.6	1.65±0.03	93±16	105±25	93±13	110±21

values are means ± sd; *n*=9 and 8 healthy men and women and 7 and 4 asthmatic men and women, respectively. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; TLC, total lung capacity; pred, predicted; M, male; F, female.

and asthmatic subjects (0.6, range 0-3).
The average number of replications of pooled FVC and huff maneuvers for each subject at the same positions and satisfying the selection criteria was 2.1 (range 1-6) in healthy subjects and 4.7 (range 1-7) in the asthmatic subjects. This indicates that despite greater difficulties the asthmatic subjects provided more useful results than the healthy subjects. Analysis of the replications showed that within positions there was no difference between values obtained from huff vital capacity maneuvers and FVC maneuvers. The variation coefficient (SD/mean) was 0.26 for SI compared with only 0.08 for PEF. The variation coefficient for SI was not different for the two groups.
Because of the selection criteria, $-10 < Caw < 5$ $cm^2(kPa)^{-1}$ and $SI^2 < 1.69$, 97.2% of the curves could be used. By use of the further requirement of $Pca > 1.3$ kPa, this figure was reduced to 45% in the healthy subjects and 47% in the asthmatic subjects.

Measurements in subjects

Figures 4-6 show examples of recordings of different types of expiratory maneuvers from a healthy subject with the Pitot static probe positioned in the lower part of the trachea.
Figure 4 describes curves obtained during a maximum expiratory flow volume maneuver. In Fig 4A, flow at the Pitot static probe (i.e. V'_{Plat}), pressures, and SI are plotted vs. V_{Ppl}, which is an approximation of the thoracic gas volume change (see Calculations). It can be seen that SI is smaller than one (subcritical conditions) before PEF is reached and close to one at PEF. After PEF, SI apparently becomes >1 (supracritical conditions).
In Fig.4 B, A at the probe is plotted vs. Ptm. Because this curve is slightly irregular, a fourth degree polynomial fit was applied for calculation of Caw, which is the slope of the curve, and this Caw was subsequently used in the calculation of SI, shown in Fig.4A, *bottom*. During expiration, Ptm decreases (see Fig.4a,*top*) and A decreases. At the A-Ptm curve, PEF is reached at the arrow (Fig 4B).
Fig 4 C shows that Palv continues to increase when PEF is reached, forming a closed loop for the entire expiration.
Figure 5 shows a set of curves obtained during a submaximal expiration in the same subject with the same position of the Pitot static probe as in Fig. 4. The curve has no clear peak, lower flow than the maximal expiration, and SI <1 during the upper 40-

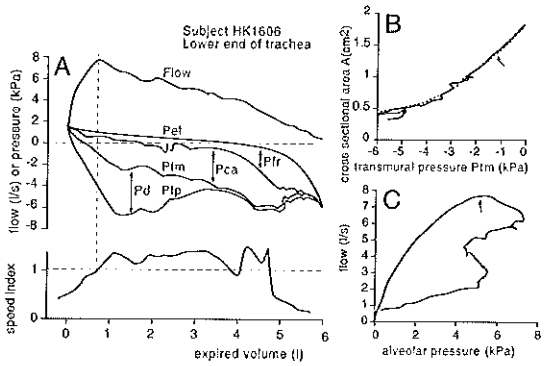


Figure 4

Maximal effort flow volume maneuver in healthy male subject (subject HK1606). A: flow and pressures vs. expired volume corrected for gas compression (top; cf. Table 1, Fig. 3) and Speed Index as a function of the same volume (bottom; cf. text). Ptp: transpulmonary pressure, Pd: downstream pressure drop. B: on line calculated cross sectional area (A)-Ptm curve. Dashed curve, fitted 5th-degree polynomial; arrow: peak expiratory flow. C: flow as a function of Palv

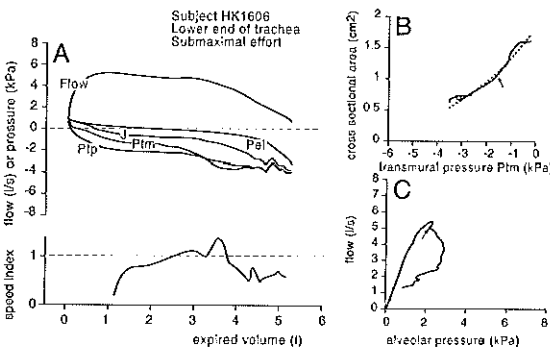


Figure 5

Submaximal effort flow volume maneuver in same subject and with same Pitot static probe position as in Fig. 4. A-C are defined as in Fig. 4.

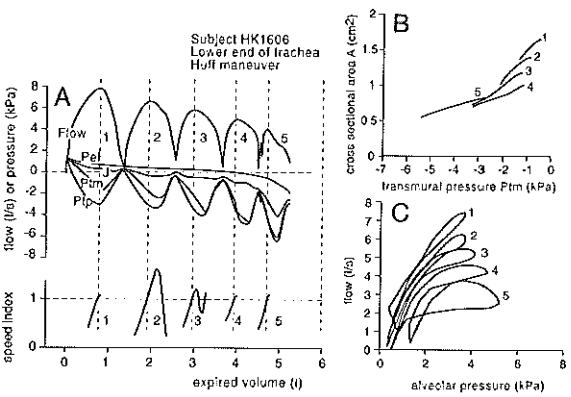


Figure 6

Maximal effort 'huff' flow volume maneuver in same subject with same Pitot static probe position as in Fig. 4. 1-5: peaks, curve segments related to peaks 1-5, and polynomial fits corresponding to A-Ptm curve segments 1-5 in A, B, and C, respectively. A-C are defined as in Fig. 4.

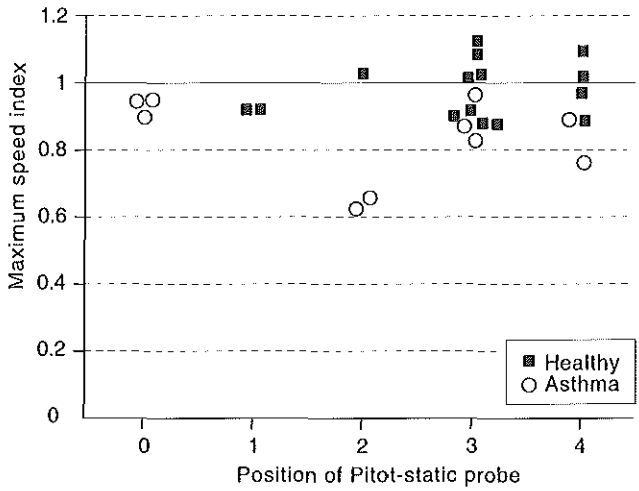


Figure 7

Maximum measured Speed Index at peak expiratory flow (PEF) among positions plotted against position for each healthy subject and asthmatic subject.

50% of the FVC. At some point, however, SI becomes unity, and the flow volume curve follows the course of the maximal curve, as seen by comparison with Fig. 4, indicating that flow limitation has now occurred at the given position. This happens at a lower Ptm and A, and at a lower Palv than in Fig. 4. The shape of the V'- Palv curve is different. After the maximum flow is reached, Palv and V' both decrease until SI equals one (Fig. 5C, arrow). Then, Palv increases again with decreasing flow, just as was the case in Fig. 4 when SI > 1.

Figure 6 shows results from a huff flow volume maneuver of the same subject and the same position as in Figs. 4 and 5. There are five peaks in the series of huffs. During each huff, SI increases abruptly and becomes unity near the peak. The curves in Fig. 6, *B* and *C*, show a clear volume dependence of both of the A-Ptm curves and the V'-Palv curves. Similar curves could be obtained from asthmatic subjects, but in these subjects, SI in the trachea, especially at lower lung volumes, was generally smaller than in the healthy subjects.

In Fig. 7, the maximum SI among probe positions for each subject is plotted for the healthy and asthmatic subjects (one data point for each subject). Two healthy women (with SI <0.6) and one asthmatic woman (with SI = 0.77) showed evidence of submaximal effort, with pressure flow patterns as shown in Fig. 5. They could not produce Pca > 1.3 kPa and therefore their data

were not included in Fig. 7. The remaining subjects included 15 healthy subjects (6 women and 9 men) and 10 asthmatic subjects (3 women and 7 men). Among the healthy subjects, 13 of 15 had SI ≥ 0.9, but the same was true for only 4 of 10 asthmatic subjects (p = 0.22, Fisher test). The distribution of maximum SI among probe positions was not different between healthy and asthmatic subjects, although only 3 of 15 healthy subjects compared with 5 of 10 asthmatic subjects had maximum SI peripheral to the trachea (p = 0.13, Fisher test).

Analysis of data from the two groups described in Fig. 7 is presented in Table 3. The only significant difference between the two groups was an apparently smaller SI in the asthmatic subjects. A similar analysis (not shown), including values only from the most peripheral position (*position 0*), showed no significant differences between the two groups. Five healthy subjects (1 woman and 4 men) were compared with eight asthmatic subjects (3 women and 5 men).

Because of missing data a lege artis multivariate analysis including all subjects could not be performed. Therefore, we initially analyzed probe positions central to position 0 where a number of healthy subjects had no measurements, and we included only subjects with no missing data. This analysis showed that the few

Table 3. Comparison of healthy and asthmatic subjects at probe position with largest measured SI

Variable	Healthy subjects	Asthmatic subjects	p-value*
PEF, l/s	7.29±2.09	7.16±2.63	0.82
Volume to PEF (l)	0.90±0.45	0.84±0.27	0.78
Palv, kPa	6.80±2.61	7.26±2.22	0.37
Pel, kPa	1.01±0.36	0.82±0.18	0.13
Ppl, kPa	5.80±2.74	6.44±2.24	0.35
Pca, kPa**	2.89±1.74	3.29±2.21	0.47
J, kPa	-0.29±0.64	-0.46±1.35	1.00
Pfr, kPa	1.30±0.58	1.28±1.43	0.58
Pd, kPa	2.61±3.04	2.68±2.47	0.54
A,cm^2	1.15±0.49	1.03±0.40	0.62
Ptm, kPa	-3.18±2.09	-3.75±2.37	0.51
Caw, cm^2/kPa	0.27±0.20	0.13±0.07	0.12
SI	0.98±0.09	0.84±0.12	0.01

values are means ± sd; n = 15 healthy subjects (6 women and 9 men) and 10 asthmatic subjects (3 women and 7 men). (* Wilcoxon, nonparametric test. ** Only curves with Pca > 1.3 kPa entered analysis. Two healthy and 1 asthmatic woman were excluded for that reason.

Table 4. Multiple regression analysis including unselected data from 8 healthy and 6 asthmatic subjects male with no missing data for position >0

Parameter	Constant	Condition	Positions 1-4	R^2
PEF, l/s	8.63	-1.19	0	0.14
Volume to PEF, liters	0.92	0	0	0
Palv, kPa	5.80	1.40	0	0.14
Pel, kPa	1.12	-0.28	0	0.14
Ppl, kPa	4.68	1.68	0	0.17
Pca, kPa	0.62	0	0.45	0.20
J, kPa	0.65	-1.08	-0.26	0.28
Pfr, kPa	0.50	0.80	0.25	0.22
Pd, kPa	4.95	0	-0.70	0.16
A,cm^2	2.41	-0.36	-0.21	0.18
Ptm, kPa	0.05	-1.14	-0.71	0.30
Caw*, cm^2/kPa	0.16	0	0	0

Condition: healthy = 0, asthmatic = 1. Example: Pfr = 0.50 + 0.80 (condition) + 0.25 (position). Other parameters are similarly estimated. Zeros indicates no significant influence. Data for *position 0* have been excluded. *Only calculated for Pca > 1.3 kPa.

women behaved differently from the men. Consequently, we decided in a final analysis to compare only eight healthy men with six asthmatic men. In this analysis, variance homogeneity (Cochran's and Bartlett's tests) was present for all parameters examined, except Caw, which varied much more in the healthy than in the asthmatic subjects. The results, shown in Table 4, include statistically significant coefficients in a multiple linear regression analysis. The main findings are the following. There is a smaller PEF in asthma despite higher effort (Palv, Ppl). At a given position in the airway, Pfr in asthmatic subjects is larger and Ptm is smaller than in healthy subjects, and A is smaller. Caw seems to be uninfluenced by asthma and probe location. More central probe locations cause J, Ptm, A, and Pd to decrease and Pfr and Pca to increase, as would be expected. It should be noted that the separate analysis of the most peripheral probe position showed no difference between the groups.

DISCUSSION

The purpose of the present study was to examine whether peak expiratory flow is determined by the wave speed flow limiting mechanism (4) and whether the mechanics of the forced expiration differs between healthy and stable asthmatic subjects. For that purpose we used a method previously applied in dogs (16). We used a Pitot static probe as originally used by Macklem and Wilson in 1965 (14). As pointed out by these authors, this method is technically difficult, and therefore should be discussed.

Technical problems

The crucial points are the measurements of Pca = Ptot - Plat with the Pitot static probe and Ptm = Plat - Ppl by further use of the esophageal balloon. Fig. 2 shows that the area in stiff tubes could be measured reasonably well, even for small values of Pca. Areas > 2 cm^2, however, may have been overestimated by 10 - 15 %. About 18 % of the measured areas were > 2 cm^2 and were mostly found in tall healthy men. The position of the probe should be axial in the airway. With the given design of the probe, we found in the previous study (16) that an angle up to 20° changed measured A <10% in a single experiment. In that study we also found that, in a converging part of the airway, the area is measured rather accurately but, because of separation of flow from the airway walls, the area in a diverging airway may be underestimated if the probe is in the middle of the lumen or overestimated if the probe is near the wall. In the present study we found decreasing areas when the probe was moved up in the trachea (Table 4), and therefore the measurements may be more accurate than indicated in Fig. 1.

The measurements in the bronchial tree supply a 'functional' cross sectional area related to the total cross section of the airway. It is assumed that all airways at the same level behave like the airway containing the probe. On the other hand, analysis of overall airway behavior is necessary for determination of the overall flow limitation.

Nonhomogeneous emptying of the lungs will probably influence total flow very little because as soon as flow limitation occurs in one airway, flow through the others will speed up (21). Consequently, SI may be large in one parallel airway and small in

another one. SI determined by the present method is a weighted value that assumes that all parallel airways behave similarly. In the present study, the asthmatic and the healthy subjects did not differ a great deal, and we believe that nonhomogeneous emptying is of minor importance for the interpretation of the results of the bronchial measurements.

Another factor that may influence the interpretation is that the probe will move towards the periphery during the expiration, when the airways shorten. This was examined by having the subjects perform a slow vital capacity expiration with the bronchoscope in a fixed position. The relative motion was less than the distance between two cartilage rings. With the probe in a very peripheral position, Ptm includes transparenchymal pressure, and we do not know the significance of this. In the present study all positions were extrapulmonary, but intrathoracic. Therefore, we believe that the measured Ptm reflects transmural pressure only.

Interpretation of results

We believe that PEF is reached when SI equals one for the first time somewhere in the airway, and we define the flow determining site as the most upstream point in the airway where this happens. In theory, SI at PEF cannot be > 1 because at supracritical velocities (SI > 1) flow becomes less than maximal (16) and hence less than flow at an SI of one that necessarily must precede flow at SI > 1. Later, during the expiration, the velocity may become supracritical, but only downstream of the flow determining site. With this in mind, we found it justifiable to discard values of SI > 1.3 at PEF.

Repeated measurements of the same subjects at the same positions showed a large variation of SI. However, the performance varied greatly between individual tests, which is only natural because of the inconvenience of the catheters. This is reflected in a large variability of Pca, Caw, and A, which are all determinants of SI (*Eq.15* in Table 1). This was especially marked when Pca <1.3. Typical problems were coughing by subjects, mucus blocking the holes of the probe, and occasional wedging of the probe, especially at the most peripheral positions. Because Caw was determined as a quotient of two slopes, it is especially sensitive to noise in the measurement. As seen in Figs. 4-6, SI changes rapidly near PEF, which means that small changes in flow around PEF are associated with large changes in SI. This is an additional

source of variation. With the given coefficient of variation, we estimated that a measured SI > 0.9 would not be different from an SI of one.

Despite the technical difficulties, the results in Figs. 4-6 clearly support the hypothesis that SI at PEF in the central airways in a normal subject is very close to unity. This means that at PEF the air velocity reaches wave speed. We also found that with submaximal effort, SI at PEF will be <1, when the peak of flow occurs before the perimeter of the maximum expiratory flow volume curve is reached. With slightly less initial effort, the peak in Fig. 5 (defined as the maximum flow during the expiration) might have been reached at the perimeter where SI equals one, but at a much lower lung volume. PEF is clearly effort dependent, but if it is reached at the perimeter of the maximum expiratory flow volume curve, it is determined by the wave speed.

The fact that PEF is close to wave speed flow in the central airways does not necessarily imply that the flow is determined in the central airways. We believe that PEF is reached at the moment when air velocity for the first time during the expiration just reaches wave speed at some point in the airway, i.e., before dynamic compression occurs and before frictional pressure losses because of dynamic compression can be detected. If the flow determining site is defined as the most upstream point in the airway where SI first becomes unity, we cannot be sure that we have reached the flow determining site with the probe, even if SI equals one.

There may be two reasons for a local SI <1 at PEF. First, the effort may be too small so that wave speed is not reached anywhere in the airway. In the case of flow limitation at PEF, we saw that Palv continued to increase after PEF was reached (Fig. 4). The explanation for this is that when flow limitation occurs, the resistance (Palv/V') and the driving pressure (Palv) increase proportionally, keeping V' unchanged at the given lung volume. If we consider a short interval encompassing PEF, then the volume will not change very much within that interval, and we can consider the pressure flow curve within the interval equal to a segment of an isovolume pressure flow curve. If this curve has a maximum at PEF, so that V' decreases for increasing pressure after PEF is reached, then PEF can be considered a maximal flow. If we expand the interval around PEF, the decrease of V' after

PEF is related to the decrease in maximum flow with volume.
If PEF is reached with submaximal effort and no flow limitation, this phenomenon will not take place. When V' declines after PEF is reached, pressure will also decrease like in a stiff tube. However, as the resistance of the airways increases with decreasing lung volume, the curve in Fig. 5 will not completely follow the same path down. When the decreasing V' eventually reaches the flow volume perimeter (arrow), SI becomes unity. Flow and pressure will no longer be in phase, and flow decreases more rapidly than pressure.
The reason why previous investigators did not find flow limitation at PEF may have to do with the definition of flow limitation. According to the classic definition, flow limitation occurs when flow reaches the maximum or plateau of an isovolume pressure flow curve. It is very difficult to construct isovolume pressure flow curves near TLC, and flow limitation at PEF is difficult to demonstrate in this way. Fry and Hyatt (7), however, believed that if a subject is able to create a sufficient intrathoracic pressure, such a maximum could be demonstrated. In the present study, assuming that flow limitation occurs at wave speed, we can get around this problem because SI can be determined during the actual forced expiration.
As pointed out by Fry and Hyatt (7), the addition of an external resistance will move the maxima of the isovolume pressure flow curves toward higher pressures. Addition of an external resistance may therefore lead to insufficient pressure for maximal flow. This is illustrated in Fig. 8 (O.F. Pedersen, unpublished observations), where data in *A* and *B* were obtained in a healthy subject performing forced expirations through a 13 and a 6.5 mm orifice, respectively. The subject was sitting in a volume displacement body plethysmograph equipped to measure Palv. In Fig. 8, *C* and *D*, similar curves were obtained with a servo controlled piston pump replacing the subject. In the piston pump, dynamic compression cannot occur, and the pressure flow curves are alone determined by the two orifices and the driving pressures. For the human subject blowing through the 13 mm orifice, peak flow occurs before peak pressure, indicating dynamic compression at PEF. The 6.5 mm orifice, however, imposes a resistance so large that flow limitation is not reached at PEF. The flow follows closely the pressure flow curve of the orifice. Peak flow

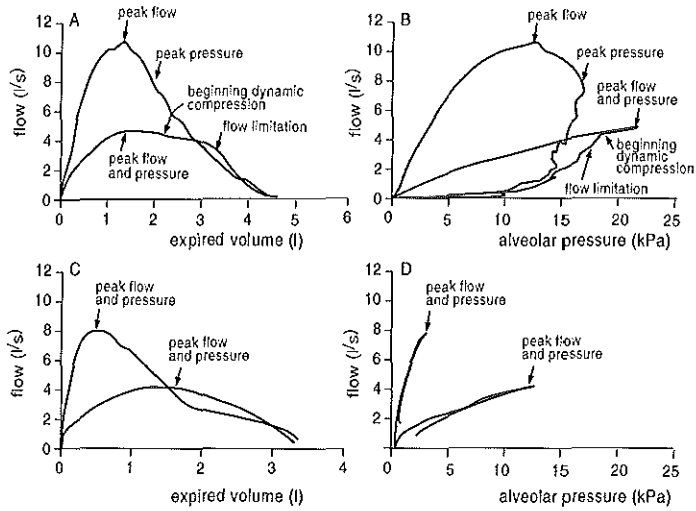


Figure 8

Maximum expiratory flow-volume and flow-pressure curves in a healthy subject seated in a plethysmograph equipped to measure alveolar pressure (A and B) and with a servo-controlled piston pump (C and D). Curves with higher flows in A-D were obtained in subject (or with pump) by expiration through a 13-mm orifice. For curves with lower flows, orifice diameter was 6.5 mm. Arrows, corresponding events in healthy subject and with use of pump (cf. text).

and peak pressure are reached simultaneously, just as with use of the piston pump. With decreasing flow after PEF, flow initially follows the pressure flow curve for the orifice, but at some point dynamic compression of the airways or volume related changes in the airways cause the resistance to increase and flow to deviate from the curve for the orifice. At the point where the flow volume curve indicates flow limitation, the deviation is marked. The pattern in Fig. *5* is not as clear but indicates the same phenomenon. We therefore believe that when Palv continues to increase markedly after PEF is reached, it is a sign of flow limitation at PEF somewhere in the airway, whereas simultaneous pressure and flow peaks indicate that flow limitation at PEF may not have occurred.

The second reason for SI <1 at PEF may be that the flow determining site is not within reach of the probe. We found SI <1 at all positions in some subjects, mostly asthmatic subjects. This could

be explained by a location of the flow determining segment peripheral to the most upstream position of the probe. In that case, SI at the probe may be <1 but the Palv will continue to rise after PEF is reached, as we found for all subjects in Fig. 7. The finding that the upstream Pfr was not increased in these cases is probably because of PEF just being reached and dynamic compression not yet having been fully established.

The huff curves (Fig. 6) show that SI equals one not only at the first peak corresponding to PEF but also at subsequent peaks. The Palv flow curves indicate flow limitation at the three last peaks, but not clearly at the first two peaks at the higher lung volumes, where inspiration was initiated as soon as flow became maximal. Figure 6 also shows that the relationship between A and Ptm, i.e., the 'tube law', is volume dependent, mostly at higher lung volumes. For a given Ptm, A becomes smaller with decreasing volume, and the slope of the curve becomes smaller. This is in agreement with the findings of Macklem and Wilson (14). The smaller A with decreasing lung volumes could be explained by decrease of dilating forces because of changes in axial tension, and the smaller compliance by stiffening of the airways when the cartilages approach each other with shortening of the airways, as shown for calf tracheae (22).

Figure 7 shows that the position of the highest measured SI, which most closely reflects the flow determining site at PEF, is not different between healthy and asthmatic subjects, although SI appears smaller in the asthmatic subjects, in whom there is a slight tendency for a more peripheral location. Table 3 shows that this smaller SI most likely is because of a smaller Caw (*Eq. 15* in Table 1), but Table 4, which also includes data for positions with less than maximal SI, does not support this.

Table 4 displays some significant differences between the healthy and the asthmatic subjects. In the following we try to explain these differences.

If, as a first approach, we assume that flow is determined in the central airways in both groups, the following differences are consistent: a smaller Pel and a larger Pfr in the asthmatic subjects will decrease J (Table 1, Eq. 7), and a decreased J will decrease the maximal flow via a decreased Ptm, leading to a smaller A. The finding of a larger driving pressure (Palv = Ppl + Pel) at PEF in the asthmatic subjects is interesting and contrary to what

should immediately be expected. Studies by Campbell et al. in 1957 (2) clearly indicated that airway obstruction with flow limitation caused the esophageal pressure at PEF (maximal effective intrathoracic pressure) to decrease. This is supported by studies of flow maxima of isovolume pressure flow curves of Potter et al. (17). On the other hand, increased downstream resistance will increase Palv at PEF by moving the flow maxima toward higher pressures (7). In that case, an increased Palv at PEF in the asthmatic subjects would most likely be because of an increased downstream pressure drop due to dissipation of the excess pressure, but this could not be demonstrated. The downstream resistance, however, was slightly, although not significantly, larger in the asthmatic subjects ($p = 0.07$). Because of the difficulties in determining Caw, especially in the healthy subjects, with a larger fraction of negative values, a proper statistical evaluation of Caw could not be performed, and it could not be determined whether the finding of the lower SI in Table 3 could be because of a generally lower Caw among the stable asthmatic subjects. Stiffer central airways could explain not only smaller SI but also a more upstream location of the flow determining sites in the asthmatic subjects compared with the healthy subjects, findings that were only indicated in the present study.

It is noteworthy that Pfr upstream of the most peripheral positions and the pressures here were identical in the two groups of subjects and that the differences between the groups only became evident at more downstream positions (Table 4). Therefore, peripheral airway obstruction is unlikely to play a part in the observed difference between the groups. The slightly smaller Pel, however, might contribute.

The smaller Pel found at PEF for the asthmatic subjects in the multivariate analysis could be because of a larger expired volume at PEF. Table 4 showed that, when the value is measured in absolute terms, this was not the case. Measured relative to FVC, the fraction was 0.14 ± 0.05 in the healthy subjects, 0.15 ± 0.04 in the asthmatic subjects. This is very close to the median value in a population study by Lebowitz et al.(12). The absence of a difference in volume to PEF indicates that the smaller Pel in the asthmatic subjects most likely is because of other factors. A possible explanation could be related to the bronchodilator treatment and subsequent relaxation of the alveolar ducts (24) or

maximal bronchodilatation (3;5). In our attempt to compare asthmatic subjects with healthy subjects, we realize that the interpretation might have been easier if the healthy subjects had also received bronchodilator treatment, but the present study design was chosen to give a more realistic comparison.
It is interesting that SI at PEF can be close to one at many locations in the airway, even at different lung volumes. This may be more than a coincidence, because in that way local strain is minimized and the airways are better protected against damaging effects of severe local dynamic compression. Evolution may have played a part by favoring airways with the most appropriate structure.

Modeling of expiratory flow

Lambert et al. (11) made a fluid mechanical analysis of the maximum expiratory flow. The analysis was partly based on airway properties obtained from excised human lungs and partly from data of Weibel (26). They predicted that the most proximal locations of the flow determining site at high lung volumes were in the main or lobar bronchi and that Ptm at flow limitation would be slightly positive or close to zero. This means that the flow determining sites were upstream to or at the equal pressure points. We found that at PEF the SI was equal to unity in the trachea in most cases, supporting flow limitation in the trachea, but we could not exclude that SI would be unity also at more upstream locations. We found Caws different from those, on which the computational model was based. Contrary to our expectations, we did not find that the compliance at PEF increased significantly with peripheral motion of the probe, but Ptm increased. At Ptm measured in our study, the Caw read from the curves presented by Lambert et al. (11) had almost the same value in the trachea, but in the lobar bronchi it was much larger. This may explain why they did not find flow limitation in the trachea at high lung volumes but in the bronchi instead (cf. *Eq.15* in Table 1). Other factors may contribute: our curves were measured during dynamic conditions, in which invagination of the membranous parts of the airways and axial tension may change the A-Ptm curves in a way that is not accounted for in the model.

Main conclusions and implications

The main conclusion of the present work is that when PEF is reached the SI is close to unity in the central airways of most subjects. Among those with SI <1 in the measured airways (mostly asthmatic subjects), the shape of the Palv-flow curves usually indicated that flow limitation at PEF took place at some point in the airway. This may be in more peripheral airways, beyond the reach of the probe. Therefore, this work supports that PEF in general is determined by the wave speed flow limiting mechanism.

If PEF is obtained with submaximal effort, it is determined by the wave speed flow limiting mechanism, if PEF is reached at the perimeter of the maximum expiratory flow volume curve.

These findings have consequences for the interpretation of PEF. If PEF is determined by the wave speed flow limiting mechanism, it will be determined by three main factors: Pel, upstream Pfr, and relationship between distending pressure (Ptm) and A at the most upstream positions where SI equals one. PEF will be large when Pel is large, Pfr is small, A is large, and Caw is small. PEF will increase with increasing effort because wave speed is reached at a higher lung volume (higher Pel and smaller upstream Pfr).

In the present study, stable asthmatic subjects had smaller maximum SI in the measured airways than did healthy subjects. This might be related to decreased Caw, but this could not be confirmed.

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8

Summary and general discussion

Samenvatting

SUMMARY

The concept of structural and functional changes in the airway wall (airway remodeling) as the result of chronic asthmatic inflammation is widely accepted nowadays. However, the relationship between (persistent) airflow obstruction and bronchial hyperresponsiveness as characteristic features of asthma on the one hand and airway remodeling on the other is still poorly understood. Also we do not know when airway remodeling develops, whether and to what extent it exists in young patients with asthma and what risk factors are involved. In general, conventional lung function techniques such as MEFV curves are unsuitable to detect structural changes due to asthmatic remodeling.
The wave speed concept of flow limitation relates airway elastic properties, airway resistance and elastic recoil to the maximal attainable expiratory flow. No *in vivo* studies with regard to airway compliance and/or the site of flow limitation based on the wave speed concept have yet been performed in humans. The effects of (possibly) remodeling of the airway wall on the elastic properties of the airway wall and on the mechanism of flow limitation are unknown.

This thesis adresses both aspects and describes the first *in vivo* (patho-)physiological studies of expiratory flow limitation and bronchial mechanics in healthy subjects and patients with long-lasting asthma.
The primary objective of these studies was to answer the following questions: 1) Does airway compliance, as a measure of (remodeled) airway structure, differ between healthy controls and patients with asthma? (Chapter 4). 2) Where does flow limitation, based on the wave speed concept, occur *in vivo* in human airways? (Chapter 5). 3) Does chronic airway inflammation (and possible airway wall remodeling) lead to a change in the site of flow limitation in patients with asthma? (Chapter 5). 4) Can airway elastic behavior be meaningfully described by airway compliance curves derived from MFSR curves? (Chapter 6) and 5) Is Peak Expiratory Flow only determined by effort or by flow limitation as well? (Chapter 7).

In this chapter a summary of the findings and conclusions within each chapter is presented, a short synthesis is given and limitations of the studies are discussed and suggestions for future research will are described.

In Chapter 1 a general introduction is given to the thesis and the aims of the study are outlined.

In Chapter 2 the current understanding of the relation between asthmatic inflammation of the airway and the occurrence of remodeling of the airway wall is summarized. Features of asthma and remodeling are related to determinants of expiratory flow limitation.

In Chapter 3 the evolution of our understanding of expiratory flow limitation is described. The theoretical basis for the experiments is described and elaborated in the following chapters. The wave speed concept of flow limitation explains that the coupling of geometry, size and compliance of the airways with pressure distribution and flow results in flow limitation (Fig. 10). Local maximal flow is reached when the local speed of air equals the local wave speed, i.e. the speed at which a pressure disturbance travels through an elastic tube (an airway). These characteristics define a choke point. The airway segment with the lowest maximal flow determines the maximal flow for the whole bronchial tree and is called the flow limiting site (FLS).
Although the wave speed theory is an all embracing concept, the phenomenon of expiratory flow limitation has not been solved completely. In the *in vivo* studies described in this thesis, we applied the wave speed concept to analyse the results of intrabronchial measurements during forced expiration in order to obtain more insight in qualitative and quantitative features (of abnormalities) of airway mechanics in healthy as well as in asthmatic subjects.

In Chapter 4 a study of the dynamic elastic properties of the central airways during forced expiration in 14 healthy and 10 young adults with long-lasting asthma is described. The patients with asthma were pretreated with a β-2-agonist and systemic corticosteroids. The relationship between airway cross sectional area (A)

and transmural pressure (Ptm) was regarded as a measure of airway compliance (Caw = $dA/dPtm$). A/Ptm curves were obtained during forced expiration, using an esophageal balloon and a Pitot static probe positioned at five positions between the right lower lobe and mid trachea. Cross sectional area (A), airway compliance (Caw) and specific airway compliance (sCaw = Caw/A) were obtained from the A/Ptm curves. We found that the cross sectional area A was significantly larger in males than in females and that Caw and sCaw decreased with decreasing lung volume. The most important finding, however, was that Caw and sCaw were significantly lower in the patients with asthma. The latter supports the concept that chronic asthmatic airway wall inflammation may result in remodeling of the airway wall, even in relatively young patients with mild to moderate asthma who were treated with inhaled corticosteroids for several years. Furthermore, we concluded that asthmatic remodeling probably leads to stiffening of the (central) airways.

In **Chapter 5** we investigated the occurrence and the behavior of flow limitation during forced expiration in the same group of 14 healthy and 10 asthmatic subjects. From the above described A/Ptm curves we obtained airway cross sectional area (A) and airway compliance (Caw = $dA/dPtm$). We calculated air speed (v = V'/A), flow at wave speed (V'ws), wave speed (c = V'ws/A) and the Speed Index (SI = V'/V'ws = v/c) according to the equations derived from the wave speed concept of flow limitation (chapter 3).
Despite all technical and practical limitations, the results indicate that the wave speed concept can be applied *in vivo* in humans in order to obtain more insight in the development and the site of flow limitation. SI values ≈1, indicative of a local choke point, were found at all 5 Pitot static probe positions in the healthy subjects but only at the two most upstream positions in the subjects with asthma. In other words, the flow limiting behavior of the central airways is changed in patients with asthma.
The difference in choke point distribution between healthy and asthmatic subjects may be explained by changed local airway wall properties possibly due to chronic asthmatic airway inflammation (chapter 4). It was not possible to position the Pitot static probe in airways upstream from the lower lobe bronchus.

Therefore, it can not be excluded that wave speed was also reached in more peripheral airways and/or that the FLS was located beyond the most upstream Pitot static probe position.

In Chapter 6 airway compliance (Caw), derived from the relation between forced expiratory flow and static recoil is evaluated. Theoretically, airway elastic properties at the flow limiting site in the bronchial tree may be estimated from the slope of Maximal expiratory Flow Static Recoil (MFSR) curves under the assumption that pressure loss due to friction is negligible. The MFSR curve is relatively easy to construct and may therefore be applicable in larger groups of patients with asthma. This makes the MFSR curve a potential tool for the evaluation of airway compliance as a measure of airway remodeling. We compared MFSR derived airway characteristics with the corresponding Pitot static probe results.
The appearance of MFSR derived A/Ptm curven reflected jumps in the location of the flow limiting segment during expiration. MFSR derived airway compliance and airway cross sectional area decreased with decreasing lung volume. These findings were in accordance with the Pitot static probe results. Therefore, MFSR derived airway characteristics may reflect qualitatively the behavior of flow limitation.
However, the correlation of MFSR derived airway characteristics (A_m, Caw_m and $sCaw_m$) with the corresponding *in vivo* Pitot static probe results was poor. Furthermore, the MFSR analysis was not sensitive enough to reflect changes in Caw in the patients with asthma, as demonstrated with the Pitot probe. This may be due to the fact that the 'real' location of the flow limiting segment differed between the healthy and the asthmatic subjects and/or may be due to the presence of different frictional pressure losses in both groups. We conclude that the MFSR curve is not suitable to evaluate (changes in) airway compliance in healthy subjects and/or patients with asthma.

In Chapter 7 is reported whether peak expiratory flow (PEF) is determined by the wave speed flow limiting mechanism. Although PEF is widely used in the assessment of bronchial patency in asthma, especially in the home situation, it is by many clinicians regarded to be mainly effort dependent.

Using a Pitot static probe positioned at 5 different positions in the central airways and an esophageal balloon, we obtained Speed Index values in 17 healthy controls and in 11 subjects with stable asthma. Speed Index values near unity reflect wave speed determined flow limitation. In 13 out of 15 healthy controls and in 4 out of 10 asthmatic subjects, from whom satisfactory curves could be obtained, SI at PEF was > 0.9 at one or more Pitot static probe positions. Alveolar pressure further increased after PEF was reached, also among those (mostly asthmatic) subjects with Speed Index values < 1. These findings indicate that at PEF flow limitation occurs at some point in the airway. We conclude that in general PEF is determined by the wave speed flow limiting mechanism.

GENERAL DISCUSSION

The explanation of flow limitation involves a complicated interdependence of airway compliance, elastic recoil of the lung, geometry of the bronchial tree and pressure loss due to friction. The end result is reflected mainly by the shape of the maximal expiratory flow volume (MEFV) curve and also by the included absolute values of flow and volume. The MEFV curve is relatively easy to obtain, highly reproducible within individual subjects and sensitive to a reduced patency of the airways. Therefore it is widely used in clinical practice as well as in e.g. epidemiological surveys, especially in diseases characterized by airway obstruction. However the MEFV curve does not inform us whether, why and where flow limitation takes place, especially in case of abnormalities in MEFV shape and/or expiratory flow values. Moreover, a 'normal' MEFV curve does not exclude pathology of the lung and/or the bronchial tree.

Therefore, we applied **intrabronchial** measurements during forced expiration in order to obtain more insight in the location and behavior of flow limitation *in vivo* in humans. Furthermore, we examined whether and to what extent potential changes in airway compliance and/or airway behaviour with regard to flow limitation in asthma can be detected by this method.

On theoretical grounds one might expect that persisting or severe

airway inflammation may result in (irreversible) histological and structural changes. These may affect airway mechanical properties and may lead to functional abnormalities and possibly an increase in symptoms. Therefore we compared a group of patients with stable, long lasting, mild to moderate asthma with a group of healthy subjects.

Both groups were relatively small. However one should realize that these volunteers were subjected to very unpleasant and time consuming experiments. We are very thankfull that they participated throughout the whole study because invasive studies with intrabronchial measurements of airway mechanics, such as described in this thesis, are necessary to assess to what extent structural abnormalities contribute to or correlate with the development of functional and histological changes and symptoms. These studies are often proposed for but rarely conducted.

The level of lungfunction was comparable in both groups. This finding is may be reassuring with regard to the development and/or existence of functional changes in asthma. However, the patients studied may not be representative for the (relatively small) group of patients with more severe asthma.

In spite of the small number of subjects, statistical analysis showed that the cross sectional area of the central airways in the patients with asthma was significantly lower and that the central airways behaved more stiffly during forced expiration.

According to the wave speed concept, stiffer airways have higher wave speeds and therefore higher maximal flows. On the other hand, lower airway cross sectional areas will result in a lower maximal flow values. This seems to be in contrast with the fact that the MEFV curves of the asthmatic subjects participating in the study, showed neither significant bronchial obstruction nor higher expiratory flows. The potential effect of lower local airway compliance (i.e. higher wave speed flow) is probably partially counterbalanced by a lower local cross sectional area, causing a lower wave speed flow. In other words: we found that the 'normal' lungfunction in the asthmatics can be explained by the combination of two compensatory abnormalities.

These findings explain why 'normal' MEFV curves may not exclude changes in airway structure related to asthmatic airway inflammation. A plausible explanation for the changes in airway cross sectional area and airway compliance is remodelling due to

chronic asthmatic airway inflammation. However, one can not exclude that these 'abnormalities' existed in the patients with asthma already prior to the development of symptoms.
Increased stiffness of the airway wall will impose a greater load in bronchial smooth muscle during bronchoconstriction, and therefore has, to a certain degree, a protective effect. However, it does not rule out the appearance of excessive bronchoconstriction related to bronchial hyperresponsiveness, because many factors causing thickened airways also contribute to excessive airway narrowing.
The possible long-term effects of the functional abnormalities in patients with asthma, described in this thesis, remain unknown.
Intrabronchial pressure measurements enabled us to analyze the factors determining peak expiratory flow (PEF) in detail. Until recently, PEF was regarded to be effort dependent, in contrast with the flows in a later phase of forced expiration. This implicated that PEF was regarded to be inferior to FEV1, the golden standard of airway patency. However, our results indicate that in most subjects PEF is determined by the same flow limiting mechanisms that occur in the so-called 'effort independent' phase of forced expiration. These findings have consequences for the interpretation of PEF. If PEF is determined by the wave speed flow limiting mechanism, it will be determined by three main factors: lung elastic recoil pressure (Pel), pressure loss due to friction (Pfr), and the airway compliance at the most upstream positions in the bronchial tree where the Speed Index equals one. PEF will be large when Pel is large, Pfr is small, cross sectional area is large and airway compliance is low. PEF will increase with increasing effort because wave speed is reached at a higher lung volume and therefore at a higher Pel and lower Pfr.

Practical aspects and limitation of the experiments

The invasive nature and time consuming complexity of the experiments hampered inclusion of more healthy and asthmatic volunteers in the study. This also stopped us from repeating the Pitot static probe experiment in order to test reproducibility of the results. Despite an optimal anesthetized pharynx, larynx and bronchial tree, most of the volunteers found it difficult to perform 30-40 MEFV maneuvers adequately with an intrabronchial Pitot static probe in situ. Typical problems were fits of coughing or increased mucus production with a need to swallow.

Sometimes we had to stop the measurements due to premature cessation of local anesthetic effect. For the same reasons, not all subjects could repeatedly exhale a full FVC, despite being instructed and encouraged to do so. Furthermore the Pitot static probe could get blocked in wedge position in a bronchial branch and/or one or more side holes of the probe could clog up by mucus.

These practical problems explain why in some subjects no reliable data could be obtained at all probe positions or throughout the full FVC range. The variation of results within an individual subject was relatively large.

These factors obliged us to apply a statistical model to describe the behavior of: the airway compliance, the cross sectional area, the specific airway compliance, the transmural pressure, the pressure loss due to friction, the airway resistance upstream from the probe and also of the Speed Index (SI) in relation to the intrabronchial position of the probe, the lung volume and the disease status of the subjects.

Despite the practical problems and technical limitations as described in the subsequent chapters, the behavior of flow limitation during forced expiration was as we theoretically had expected. This was also true for the change in airway compliance (Caw) and cross sectional area A when the Pitot static probe position and/or volume changed and for the difference in cross sectional area A between male and female subjects. Therefore, we feel justified to state that the application of intrabronchial measurements is a reliable tool to study airway mechanics during forced expiration *in vivo* in humans.

The measurements were restricted to the central airways (trachea – lower lobe bronchus). Therefore we were not informed of what takes place upstream from the lower lobe, being the most upstream Pitot static probe position. This has consequences for the interpretation of the Speed Index results. SI values near unity indicated existence of local choke points in the healthy subjects as well as in the patients with asthma. However, based on the SI results the occurrence of choke points or even a flow limiting segment upstream from the lower lobe could not be excluded.

In conclusion

For the first time in medical research we were able to derive *in vivo* local bronchial mechanical properties in healthy volunteers and in patients with asthma. Despite the restrictions mentioned above we were able to draw the following main conclusions (Figure 1):

1) Central airways in the patients with asthma are more narrow and behave more stiffly during forced expiration.
2) Flow limitation takes place in the central airways in human subjects.
3) The distribution of sites with choke points and/or flow limitation has moved upstream in the patients with asthma.
4) Maximal Flow Static Recoil curves are not suitable to evaluate (changes in) airway compliance.
5) Peak Expiratory Flow is determined by the wave speed flow limiting mechanism.

Several studies show that structural changes occur predominantly in small airways but also in large airways in cases of non fatal asthma. The finding of stiffer central airways in patients with stable asthma strongly supports the hypothesis that remodeling does occur in central airways, even in patients with mild to moderate asthma and under prolonged treatment with inhaled corticosteroids. We could not predict whether decreased compliance could also be found in the more peripherally localized and intrapulmonary airways, as our measurements were restricted to the central airways. The finding that the elastic behavior of airways changes in a group of relatively young subjects with well treated, mild to moderate asthma suggests that our current therapeutic measures insufficiently prevent airway remodeling. However, one can not exclude the possibility that patients with asthma are characterized by other measures of airway diameter and/or airway elastic properties, perhaps even at birth or early in life. As long as the long term effects of functional abnormalities are unknown, we stress the importance of identifying the risk factor(s) for remodeling and to develop other, better (preventive) treatment strategies.

Suggestions for future research

Airway mechanics:

In our opinion, the studies described in this thesis reached the limit of the capability of conventional lung function techniques combined with invasive techniques with the aim to study airway

mechanics *in vivo* in humans. However, other aspects that should and can be addressed with the same techniques are: the volume dependency of airway compliance, the effects of bronchodilatation and/or bronchial constriction on bronchial mechanics, the reproducibility of the findings and follow-up in time of the different results, especially in the patients with asthma. Results with regard to these aspects will improve the interpretation of the findings described in this thesis and extend our knowledge of the *in vivo* behaviour of human (central) airways. Comparable studies in excised human central airways in an *in vitro* experimental setup may provide indirect information on e.g. the importance of the intrathoracic tissue – (central) airway interaction with regard to airway mechanics.
Furthermore, *in vivo* derived data on airway compliance, airway cross sectional area, transmural pressure, pressure loss due to friction, volume dependency of different parameters, etc., should be used to improve further the (limited number of) available computational models, in order to extend the knowledge and our understanding of the complex system of airway mechanics.
Other, non invasive, ways to study airway mechanics *in vivo* in humans should be developed. Modern methods, such as dynamic high resolution computed tomography scans, including the construction of a three dimensional model of the bronchial tree, and/or video imaging of the lungs and airways may provide tools for such studies. It is understood that abnormalities in the parenchyma-airway interactions may play a key role in the pathogenesis of chronic or even acute airflow obstruction. Therefore these studies should not be limited to the large, central airways.

Remodeling:
In the current studies we were not able to perform bronchial biopsies in order to assess features and/or the extent of airway inflammation or airway remodeling in the subjects with asthma studied. Future studies should preferably combine physiological and histological data in the same group of patients. We are not informed whether airway mechanical abnormalities are the result of remodeling caused by chronic airway inflammation or that these abnormalities are pre-existing features in subjects with asthma. Nor do we know whether airway remodeling can be pre-

vented or reversed by anti-inflammatory treatment. Studies of airway mechanics at an early stage of asthma and before and after a prolonged period of anti-inflammatory therapy may provide answers to these questions. However, this will probably lead to (invasive) studies in (young) children with asthma and therefore to medical ethical problems. Furthermore, detailed knowledge of the airway geometry at different ages is required for such studies and is lacking at the moment.
New approaches to the study of the functional consequences of airway remodeling should be developed. Measuring the effects of deep inhalation on lung function is e.g. a promising, easy to perform and simple test to evaluate the structural changes occuring in the airways and to monitor the effectiveness of therapy.

The present challenge is to combine (new) knowledge on physiology, morphology and the molecular basis of asthma, with in vitro studies and mathematical models to provide more information about the basic mechanisms underlying the relation between bronchial hyperreactivity, (severe) airway obstruction and the histological and molecular abnormalities in asthma.

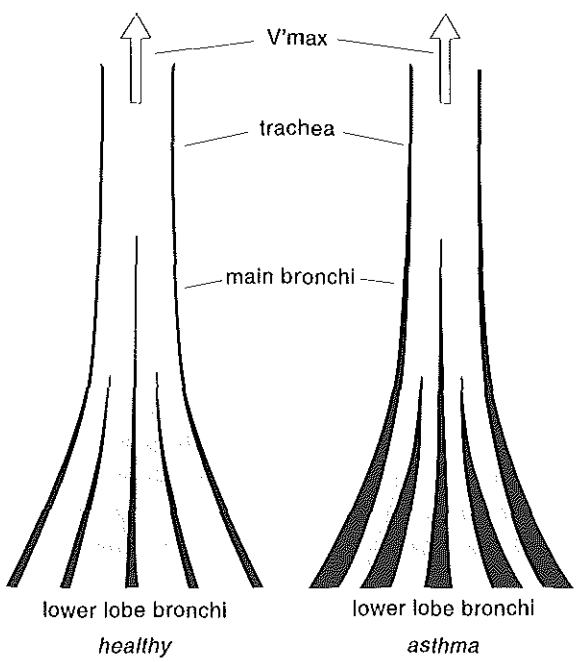

Figure 1

Schematic view of findings in this thesis.
Left panel: central airways in healthy subjects.
Right panel: in patients with asthma the upstream segments of the central airways are stiffer. This may result in a larger maximal expiratory flow (V'max). However, a lower local cross sectional area (partially) counter balances this effect. The distribution of chokepoints (Speed Index ≈1) is located more upstream (shaded area).

SAMENVATTING

Algemeen wordt aangenomen dat de chronische ontsteking in de luchtwegen bij patiënten met astma leidt tot structurele en functionele veranderingen van de luchtwegwand ('remodeling'). Of er een verband bestaat tussen karakteristieke kenmerken van astma als (persisterende) luchtweg obstructie en bronchiale hyperreactiviteit enerzijds en 'remodeling' van de luchtwegen anderzijds is onduidelijk. Wanneer 'remodeling' ontstaat en hoe 'remodeling' de prognose van astma beïnvloedt, is onbekend. Ook zijn we niet op de hoogte óf en in welke mate 'remodeling' aanwezig is bij jonge patiënten met astma en zijn de risicofactoren voor het optreden van 'remodeling' nog niet in kaart gebracht.

Flowlimitatie houdt in dat de expiratoire volumestroom aan een maximum gebonden is. Het 'wave speed' concept verklaart flowlimitatie uit de interactie tussen de elastische eigenschappen van de luchtwegen, de luchtwegweerstand en de elastische retractiekracht van de long. Tot op heden zijn er bij de mens geen *in vivo* studies, gebaseerd op het 'wave speed' concept, naar het optreden en de locatie van flowlimitatie binnen de bronchiaalboom uitgevoerd. De *in vivo* effecten van mogelijke structurele veranderingen in de luchtwegwand bij astma op de elastische eigenschappen van deze luchtwegen en op het mechanisme van flowlimitatie zijn eveneens onbekend.

Dit proefschrift behandelt deze beide aspecten en beschrijft de eerste, *in vivo* uitgevoerde, (patho-)fysiologische studies naar flowlimitatie en de mechanica van de centrale luchtwegen tijdens geforceerde uitademing bij zowel gezonde personen als bij patiënten met astma.

Hoofdstuk 1 geeft een algemene introductie over astma en flowlimitatie en beschrijft het doel van de verschillende studies.

Hoofdstuk 2 geeft een samenvatting van de huidige inzichten in de relatie tussen chronische astmatische ontsteking van de luchtwegen en 'remodeling' van de luchtwegwand. Factoren die bepalend zijn voor expiratoire flowlimitatie worden in verband

gebracht met kenmerken van astma en 'remodeling'.

Hoofdstuk 3 is een historisch overzicht van de ontwikkeling van ons denken over het complexe mechanisme van expiratoire flowlimitatie en beschrijft de theoretische basis van de uitgevoerde experimenten.
Beschreven wordt hoe flowlimitatie verklaard kan worden uit de interactie van architectuur, lengte, dwarsdoorsnede oppervlak en elastische eigenschappen van de luchtwegen enerzijds en anderzijds de volumestroom en de verdeling van intrathoracaal aanwezige drukken in en rond de luchtwegen. De maximale volumestroom locaal in een luchtweg wordt bereikt als de locale snelheid van de lucht gelijk wordt aan de locale 'wavespeed'. De 'wavespeed' is de snelheid waarmee een drukgolf zich verplaatst door het gas in een elastische buis (i.e. luchtweg). De plaats waar de 'wavespeed' wordt bereikt is het 'chokepoint'. Het luchtwegsegment met de laagst maximaal haalbare volumestroom bepaalt de maximale volumestroom voor de gehele bronchiaalboom en wordt het 'Flow Limiterend Segment' genoemd. Ofschoon het 'wave speed' concept als een alles omvattende theorie wordt beschouwd, is de ingewikkelde puzzel van de expiratoire flowlimitatie hiermee nog niet geheel opgelost.
In de *in vivo* experimenten, die in dit proefschrift beschreven worden, wordt de 'wavespeed' theorie gebruikt om de resultaten van intrabronchiale en intrathoracale drukmetingen tijdens geforceerde uitademing te analyseren. Het doel is om, *in vivo*, meer inzicht te verkrijgen in de kwalitatieve en kwantitatieve aspecten van luchtwegmechanica tijdens geforceerde uitademing bij zowel gezonde personen als bij patiënten met astma. Afwijkingen in luchtweg mechanica bij astma kunnen het gevolg zijn van structurele afwijkingen in de wand van de luchtweg tengevolge van chronische astmatische ontsteking.

Hoofdstuk 4 beschrijft een studie naar de dynamische elastische eigenschappen van luchtwegen tijdens geforceerde uitademing bij 14 gezonde jong volwassenen en 10 jong volwassenen met astma. De metingen bij de patiënten met astma werden uitgevoerd na maximale luchtweg verwijding en na voorbehandeling met een kuur systemische corticosteroïden. Met behulp van een ballon in de oesophagus en een intrabronchiaal geplaatste 'Pitot-static

probe' werden drukmetingen verricht tijdens de meting van de geforceerde uitademing. Een Pitot-static probe is een dun buisje met een opening aan de tip waarmee de voorwaarts gerichte druk gemeten wordt en zij-openingen voor het bepalen van de zijwaarts gerichte druk in de luchtweg. Uit de op deze manier verkregen druk- en volumestroom-gegevens werd het dwarsdoorsnede oppervlak (A) ter plaatse van de probe berekend en de lokaal aanwezige druk over de luchtwegwand (de transmurale druk Ptm). De ratio tussen de verandering in A en de verandering in Ptm werd beschouwd als een maat voor de compliantie van de luchtweg. (Caw = $dA/dPtm$). De Pitot-static probe was gepositioneerd op 5 plaatsen in de centrale luchtwegen: van het midden van de trachea tot bij de ingang van de rechter onderkwab. A, Caw en de specifieke luchtweg-compliantie sCaw (sCaw = Caw/A) werden afgeleid van de A/Ptm-curven.
De resultaten wezen uit dat het dwarsdoorsnede-oppervlak A bij mannen significant groter is dan bij vrouwen en dat Caw en sCaw afnemen met afnemend longvolume. Dit komt overeen met andere niet-invasieve onderzoeken en/of theorieën in de literatuur. De meest belangrijke bevinding is echter dat Caw en sCaw significant lager zijn bij de patiënten met astma. Dit wijst op een afname van de elastische eigenschappen van de astmatische luchtweg. Deze resultaten ondersteunen het concept dat bij astma chronische ontsteking van de luchtweg kan leiden tot structurele verandering van deze luchtweg en dat dit zelfs al bij relatief jonge patiënten met mild tot matig astma die volgens de huidige richtlijnen behandeld worden, kan optreden. Verder tonen de resultaten dat 'remodeling' kan leiden tot 'verstijving' van de luchtwegen.

In **hoofdstuk 5** wordt het optreden en het gedrag van flow limitatie tijdens geforceerde uitademing onderzocht in dezelfde groep van 14 gezonde en 10 personen met astma. Uit de boven beschreven A/Ptm-curven berekenden wij het dwarsdoorsnede oppervlak A en de luchtweg compliantie (Caw = $dA/dPtm$). Gebruik makend van de vergelijkingen die afgeleid werden van het 'wavespeed' concept van flowlimitatie (hoofdstuk 3) werden de volumestroom (V') tijdens 'wavespeed'-conditie (V'ws), de verplaatsings-snelheid van de lucht (v = V'/A), de wavespeed (c = V'ws/A) en de Speed Index (SI = V'/V'ws = v/c) berekend.

Ondanks de technische en praktische beperkingen, geven de resultaten aan dat het wavespeed concept *in vivo* bij de mens toepasbaar is om meer inzicht te verkrijgen in de ontwikkeling en de localisatie van flowlimitatie tijdens geforceerde uitademing.
SI-waarden rond de één wijzen op het bestaan van een locaal chokepoint en werden bij de gezonden bij alle 5 de Pitot-static probe posities gevonden. Daarentegen werd bij de patiënten met astma deze conditie alleen bij de twee meest stroomopwaarts gelegen posities gevonden. Met andere woorden: het flow-limiterend gedrag van de centrale luchtwegen is anders bij de patiënten met astma. Het verschil in de verdeling van 'choke-points' tussen gezonden en astmatici kan verklaard worden vanuit veranderde luchtwegwand-eigenschappen, mogelijk gerelateerd aan chronische luchtwegwand ontsteking (hoofdstuk 4). Het was niet mogelijk om de Pitot-static probe te plaatsen in luchtwegen stroomopwaarts van de onderkwabs bronchus. We kunnen daarom niet uitsluiten dat 'wavespeed' ook bereikt wordt in de meer 'perifere' luchtwegen en/of dat het Flow Limiterend Segment stroomopwaarts van de onderkwabs bronchus gelegen is.

Hoofdstuk 6 vergelijkt de luchtweg-compliantie (Caw), die bepaald word uit de relatie tussen de volumestroom tijdens geforceerde uitademing en de statische elastische retractie kracht van de long met de Caw-resultaten verkregen met behulp van de Pitot-static probe. Op theoretische gronden kunnen de elastische eigenschappen ter plaatse van het Flow Limiterend Segment (FLS) afgeleid worden uit de helling van de 'Maximale expiratoire Flow - Statische Retractie kracht'-curven (MFSR-curven) onder de aanname dat het intrabronchiale drukverlies ten gevolge van frictie verwaarloosbaar is. De MFSR-curve is relatief gemakkelijk te construeren en zou daarmee toepasbaar zijn in grotere groepen patiënten met astma. Dit maakt de MFSR-curve tot een potentieel (non-invasief) instrument voor onderzoek naar de elastische eigenschappen van luchtwegen als maat voor luchtweg-'remodeling'. We vergeleken luchtweg-eigenschappen afgeleid uit de MFSR-curven met de resultaten verkregen uit de studies met de Pitot-static probe.
De vorm van de MFSR-afgeleide A/Ptm-curven wees erop dat de intrabronchiale localisatie van het FLS verspringt, cq. verschuift

tijdens de (geforceerde) uitademing. Het dwarsdoorsnede oppervlak A en de luchtweg-compliantie Caw, afgeleid van de MFSR-curven, namen af met afnemend longvolume. Deze bevindingen zijn in overeenstemming met de resultaten afgeleid van Pitot static probe studie. Dit impliceert dat MFSR- afgeleide luchtweg-eigenschappen kwalitatief het gedrag van de luchtwegen tijdens flowlimitatie kunnen weergeven. De kwantitatieve correlatie tussen de resultaten van de MFSR-afgeleide variabelen (A_m, Caw_m en $sCaw_m$) met de overeenkomstige Pitot-static probe variabelen was echter matig tot slecht. Verder was het niet mogelijk om met de MFSR-analyse verschillen in Caw en/of sCaw tussen de gezonden en de patiënten met astma aan te tonen zoals beschreven in hoofdstuk 4. Dit laatste kan verklaard worden uit een mogelijk verschil in de intrabronchiale locatie van het FLS tussen gezonden en patiënten met astma en/of door verschillen in drukverlies door frictie tussen beide groepen. De conclusie is dat de MFSR-curve niet geschikt is om (veranderingen in) luchtweg-compliantie te evalueren bij gezonden en/of patiënten met astma.

In **hoofdstuk** 7 wordt onderzocht in hoeverre de piekstroom (peak expiratory flow, PEF) wordt bepaald door het 'wavespeed' flow-limiterende mechanisme. Ofschoon de PEF veelvuldig gebruikt wordt als maat voor (veranderingen in) luchtweg doorgankelijkheid bij astma, wordt deze door de meeste clinici beschouwd als zijnde voornamelijk inspanningsafhankelijk.
Met behulp van een Pitot-static probe, gepositioneerd op 5 verschillende plaatsen in de centrale luchtwegen, en een oesophagus ballon, werden Speed-Index waarden verkregen bij 17 gezonde personen en 11 personen met astma (zie hoofdstuk 5). Speed-Index waarden rond de één geven aan dat sprake is van 'wavespeed' bepaalde flow-limitatie. Bij 13 van de 15 gezonde personen en bij 4 van de 10 patiënten met astma, bij wie geschikte curven verkregen konden worden, werd een SI-waarde rond de één gevonden bij een of meerdere posities van de Pitot-static probe bij het bestaan van PEF. Verder bleek dat de alveolaire druk verder toenam nadat de PEF werd bereikt, ook bij de (vooral astmatische) personen met SI-waarden kleiner dan één. Deze bevindingen geven aan dat tijdens de PEF ergens in de luchtwegen flow-limitatie optreedt. Onze conclusie is dat, bij voldoende inspanning, de piekstroom in het algemeen bepaald

wordt door het 'wavespeed' flow-limiterende mechanisme binnen de luchtwegen.

In de **algemene discussie** worden bovenstaande bevindingen nader geinterpreteerd. Het feit dat bij de patiënten met astma een vrijwel normale longfunctie gevonden werd, zonder 'obstructieve' flow-volume curven, kan verklaard worden doordat, volgens de 'wavespeed theorie', het effect van een lager dwarsdoorsnede oppervlak van de luchtweg (leidend tot een lagere maximale volumestroom) gecompenseerd wordt door het effect van een lagere luchtweg compliantie (resulterend in een hogere maximale volumestroom). Een 'normale' flow-volume curve sluit derhalve veranderingen in de structuur van de luchtwegen niet uit.

De bevinding dat de elastische eigenschappen van luchtwegen bij, volgens de huidige inzichten behandelde, jong-volwassen patiënten met astma verschillen van die van gezonden, suggereert dat onze huidige medicamenteuze aanpak van astma onvoldoende instaat is om 'remodeling' te voorkomen cq. te verhelpen. We moeten ons realiseren dat de risico-factoren en tevens de lange termijn effecten van de gevonden afwijkingen onbekend zijn.

De conclusie dat piekstroom meestal bepaald wordt door het wavespeed mechanisme heeft consequenties voor de interpretatie van de piekstroom: de piekstroom zal hoog zijn bij een hoge elastische retractiedruk van de long (Pel), een laag drukverlies door frictie (Pfr), een groot dwarsdoorsnede-oppervlak van de luchtweg en een lage luchtwegcompliantie. De piekstroom zal toenemen met toenemende inspanning omdat de 'wavespeed' bereikt wordt bij een hoger longvolume en daarom bij een hogere Pel en een lagere Pfr.

De praktische en technische beperkingen van de studies worden besproken en tevens worden aanbevelingen voor nader onderzoek gedaan.

De grootste uitdaging is om de (nieuwe) kennis over fysiologie, morphologie, histologie en de moleculaire basis van astma te combineren met *in vitro* studies en mathematische modellen. Op deze manier kan meer informatie verkregen worden over het basale mechanisme dat ten grondslag ligt aan de relatie tussen bronchiale hyperreactiviteit en het optreden van (acute en/of ernstige) luchtwegobstructie enerzijds en de histologische en moleculaire veranderingen bij astma anderzijds. Verder mag verwacht worden dat zo de kans vergroot wordt om nieuwe therapeutische en preventieve interventies bij astma te ontwikkelen.

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CURRICULUM VITAE

Hein Brackel was born in Tilburg, The Netherlands, on April 13th 1956. He passed his secondary school exam (Gymnasium β) at the 'St. Bernardinus college' in Heerlen in 1974. His medical training started the same year at the Medical Faculty of the University of Leiden. In 1982 he obtained his medical degree and started his specialist training in paediatrics first in the Juliana Childrens Hospital in The Hague (head: dr. H.E. Zoethout) and later at the Childrens Clinic of the Academic Hospital Leiden (head: Prof. Dr. L.J. Dooren). He was registred as paediatrician in 1986. He worked as a general paediatrician in the Sophia Childrens Hospital in Rotterdam (head: Prof.dr. H.K.A. Visser) before he followed a clinical and research fellowship in paediatric pulmonology at the department of Paediatric Respiratory Medicine (head: Prof.dr. K.F. Kerrebijn) in the same hospital from 1987 – 1990 under auspicies of the Dutch Asthma Foundation. From Januari 1990 till March 1992 he worked as a staff paediatric pulmonologist at the same department. In March 1992 he became head of the department of Paediatric Respiratory Medicine of the Wilhelmina Childrens Hospital in Utrecht (head: 1992: Prof.dr. J.W. Stoop, 1998: Prof.dr. J.L.L. Kimpen).

Hein Brackel is married to Marianne Welten (1957, MD primary health care), and they have three children: Caroline (1985), Annemieke (1986) and Bart (1988)

CURRICULUM VITAE

Hein Brackel werd geboren op 13 april 1956 te Tilburg. In 1974 behaalde hij het eindexamen Gymnasium-β aan het St. Bernardinus college te Heerlen. Datzelfde jaar begon hij met de studie Geneeskunde aan de Rijks Universiteit te Leiden waar hij in 1982 het artsexamen behaalde. Tijdens deze periode was hij werkzaam als student-assistent pathologie, lid van het bestuur van de Medische Faculteit Leidse Studenten en maakte enkele jaren deel uit van de faculteitsraad als student-vertegenwoordiger. In juni 1982 werd hij arts-assistent kindergeneeskunde in opleiding in het Juliana Kinderziekenhuis te 's Gravenhage (opleider: dr. H.E. Zoethout). De academische stage Kindergeneeskunde werd doorlopen in de Kinderkliniek van het Academisch Ziekenhuis Leiden (opleider: Prof.dr. L.E. Dooren) waarna hij in juli 1986 als kinderarts werd geregistreerd. Vervolgens was hij als algemeen kinderarts gedurende een half jaar werkzaam in het Sophia Kinderziekenhuis te Rotterdam (hoofd: Prof.dr. H.K.A. Visser). Aansluitend begon zijn fellowship Kinderlongziekten op de afdeling Kinderlongziekten van het Sophia Kinderziekenhuis (Opleider: Prof.dr. K.F. Kerrebijn) onder auspiciën van het Nederlands Astma Fonds. Vanaf januari 1990 was hij als staflid op deze sub-afdeling werkzaam. Tijdens deze periode werd de basis gelegd voor dit proefschrift. In maart 1992 werd hij aangesteld als hoofd van de sub-afdeling kinderlongziekten in het Wilhelmina Kinderziekenhuis te Utrecht (hoofd: 1992: Prof.dr. J.W. Stoop; 1998: Prof.dr. J.L.L. Kimpen)

Hein Brackel is getrouwd met Marianne Welten (1957, stafarts Jeugdgezondheidszorg Thuiszorg Stad Utrecht). Samen hebben zij drie kinderen: Caroline (1985), Annemieke (1986) en Bart (1988)

LIST OF ABBREVIATIONS

A	Cross sectional area
A°	A at FLS
ATS	American Thoracic Society
c	Wave speed
Caw	Airway compliance
COPD	Chronic obstructive pulmonary disease
CP	Choke point
dA/*d*Ptm	Airway compliance
DD	Density Dependence
EPP	Equal Pressure Point
ECCS	European Community for Coal and Steel
FEV1	Forced expiratory volume in 1 second
FLS	Flow Limiting Segment
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
HeO_2	Heliox, 80% He and 20% O_2
IVPF	IsoVolume Pressure Flow
J	Pressurehead; Intrabronchial pressure head relative to pleural pressure
J°	J at FLS
Lbr	Length of bronchus
μ	Viscosity
MEF	Maximal expiratory flow
MEFV	Maximal expiratory flow volume
MFSR	Maximal Flow Static Recoil
O_2	Oxygen
P	Pressure (if not defined as difference, P is related to atmospheric pressure)
Palv	Alveolar Pressure (Palv = Ppl + Pel)
Pbr	Intrabronchial pressure (= Pibr)
Pca	Pressure loss due to convective acceleration ($Pca = ½\bullet\rho\bullet(V'^2/A^2)$)
PEF	Peak Expiratory Flow
Pel	Lung elastic recoil pressure
Pfr	Pressure loss due to friction
Pibr	Intrabronchial pressure (= Pbr)
Plat	Laterally directed intrabronchial pressure

Poes	Esophageal pressure
P_{Pb}	Peribronchial pressure
Ppl	Pleural pressure
PS probe	Pitot Static probe
Ptm	Transmural pressure (Ptm = Plat-Ppl)
Ptm^{o}	Ptm at FLS
Ptm'	Critical transmural pressure according to Pride et al.
Ptot	Impaction Pressure = Pressure measured at endhole PS-probe
PV	Pressure Volume
ρ	Density
Rds	Resistance downstream from EEP
Re	Reynolds number
Rfr	Resistance upstream from the PS probe
Rs	Upstream resistance according to Pride et al. (= (Pel-Ptm')/V'max).
Rus	Resistance upstream from the EEP
RV	Residual Volume
sCaw	Specific airway compliance
SI	Speed index
TLC	Total lung capacity
v	Velocity, airspeed
V	Volume
VC	Vital Capacity
V'	Flow
V'm	Mouth expiratory flow (= V'mo)
V'max	Maximal expiratory flow
$V'max^{o}$	Maximal flow predicted from A/Ptm curves or isoJ-V-Ptm curve
V'mo	Mouth expiratory flow (=V'm)
V'ps	Flow at the PS probe
V'ws	Flow at wave speed