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


Wave-speed-determined flow limitation at peak flow in normal and asthmatic subjects. J. Appl. Physiol. 83(5): 1721–1732, 1997.—The purpose of this study was to examine whether peak expiratory flow is determined by the wave-speed-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 (V̇ws = A/[Caw(ρ+Caw)]0.5), where ρ is density and speed index is (SI = V̇/V̇ws). 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.

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 (23), 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. (26), 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 (2). This approach shows that flow (V̇) through an airway segment becomes maximal when the linear velocity reaches the speed of a pressure-wave propagation through the airway. Wave-speed flow (V̇ws) 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, according to the equation

\[
V̇ws = A/[Caw(\rho+Caw)]^{0.5}
\]

It can be seen that V̇ws will decrease, when A becomes smaller, and Caw and ρ become larger. V̇ws indirectly depends on the lung elastic recoil pressure (Pel) and the pressure loss (Pfr) upstream from the flow-determining segment, which Dawson and Elliott (2) 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 = V̇/V̇ws) will be equal to one.

As described in studies in dogs (16), V̇ws 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 nonsmokers, 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 radioallergosorbent 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 β₂ agonist, which resulted in maximal bronchodilatation during a dose-response 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 (Pr) and a number of side holes for measurement of lateral airway pressure (Plat). It was provided with two 1.57-mm-internal diameter Polysant 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 = Pr − Plat, J = Pr − 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 (Vm) was measured by a nonheated 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 (24), 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.

Vm and the pressure signals, Pca, Ptm, and Ppl, were visible on-line on an AT computer (Olivetti PCS-286 with 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 wave 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 differences 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 Vm 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 ρ(VA)²/2, where 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

![Fig. 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 cm²; cf. text).](http://jap.physiology.org)
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 cm², the area occupied by the probe. Except for the largest areas, the accuracy is in the range of ±10%.

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, tracheal entrance, mid-main stem bronchus, 1 cm above the main bronchus, 1 cm above the carina, and midtrachea (Fig. 2). The distance between the entrances was reached. These were, respectively, middle-lobe entrance, right lower lobe entrance, middle-lobe entrance, 1 cm above the main carina, and midtrachea (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 mouthpiece was connected to the pneumotachograph.

The subjects were measured while sitting upright in a chair and wearing a noseclip. Before each measurement the two Pitot-probe catheters were each flushed forcefully with at least 2 × 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 4–5 maneuvers was performed.

Calculations. The data acquisition and calculation applied Asyst software (version 3.10, Asyst Software Technologies, Rochester, NY). From the inputs, Vm, 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 d²Ptm/d(Vm·Pca)/dr, where the pressure was most negative during maximal inspiration.

The schematic drawing in Fig. 3 may help explain some of the calculated relationships. Equations 1–3 define the measured variables, which also included Vm. Equations 4–15 define derived variables. A few of the equations can be commented on. In Eq. 9, gas density at the probe Pgas was calculated as the weighted density at 37°C of expired gas from data presented by Radford (20) to be 1.13 kg/m³, by use of

Table 1. Parameter definitions and equations

<table>
<thead>
<tr>
<th>Definition</th>
<th>Equation (No.)</th>
<th>Unit of Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure for convective acceleration</td>
<td>(1)</td>
<td>kPa</td>
</tr>
<tr>
<td>Transmural pressure</td>
<td>(2)</td>
<td>kPa</td>
</tr>
<tr>
<td>Transpulmonary pressure</td>
<td>(3)</td>
<td>kPa</td>
</tr>
<tr>
<td>Alveolar pressure</td>
<td>(4)</td>
<td>kPa</td>
</tr>
<tr>
<td>Downstream pressure drop</td>
<td>(5)</td>
<td>kPa</td>
</tr>
<tr>
<td>Upstream pressure loss</td>
<td>(6)</td>
<td>kPa</td>
</tr>
<tr>
<td>Pressure head</td>
<td>(7)</td>
<td>kPa</td>
</tr>
<tr>
<td>Lateral pressure</td>
<td>(8)</td>
<td>kPa</td>
</tr>
<tr>
<td>Gas density at probe</td>
<td>(9)</td>
<td>kg/m³</td>
</tr>
<tr>
<td>Flow at probe</td>
<td>(10)</td>
<td>l/s</td>
</tr>
<tr>
<td>Approximated thoracic gas volume change from TLC</td>
<td>(11)</td>
<td>liters</td>
</tr>
<tr>
<td>Airway cross-sectional area</td>
<td>(12)</td>
<td>cm²</td>
</tr>
<tr>
<td>Airway compliance</td>
<td>(13)</td>
<td>cm³/kPa</td>
</tr>
<tr>
<td>Wave-speed flow</td>
<td>(14)</td>
<td>l/s</td>
</tr>
<tr>
<td>Speed index</td>
<td>(15)</td>
<td></td>
</tr>
</tbody>
</table>

\[ Pr, \text{impaction pressure; } Plat, \text{ lateral airway pressure; } Ppl, \text{ pleural pressure; } Pm, \text{ pressure at mouth; } Pel, \text{ elastic recoil pressure; } \rho_p, \text{ weighted density of expired gas at } 37°C \text{ by using Boyle's law; } P_b, \text{ barometric pressure; } V_m, \text{ mouth flow; } V_p, \text{ volume at mouth; } \text{TLC, total lung capacity.} \]

![Fig. 2. Positions of Pitot-static probe in bronchial tree.](http://jap.physiology.org/)
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 P\text{el}, the expired volume from TLC was corrected for the influence of P\text{pl} only. At P\text{EF}, this represents the largest part of alveolar pressure (P\text{a}), which ideally should have been used in the correction. This correction was only done for positive P\text{pl}. Equation 15 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. DISCUSSION). The criterion 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 P\text{EF} (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.

FIG. 3. Pressures and pressure differences measured in airway (cf. Table 1). \( V \), flow; \( P_T \), impaction pressure; \( P_{fr} \), pressure loss (upstream); \( P_a \), alveolar pressure; \( P_{lat} \), lateral airway pressure; \( J \), pressure head; \( P_{tm} \), transmural pressure; \( P_{pl} \), pleural pressure; \( P_{el} \), elastic recoil pressure.

RESULTS

Initial spirometry. Table 2 shows the anthropometric data for the men and women in the two groups and the results of the initial spirometry. The predicted values of FEV\(_1\), 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 women, 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 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, \(-10 < \text{Caw} < 5\ \text{cm}^2(\text{kPa})^{-1}\) and \(\text{SI}^2 < 1.69\), 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.

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Age, yr</th>
<th>Height, m</th>
<th>FEV(_1), %pred</th>
<th>FVC, %pred</th>
<th>PEF, %pred</th>
<th>TLC, %pred</th>
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<tbody>
<tr>
<td>Healthy Subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>25.6 ± 5.7</td>
<td>1.85 ± 0.08</td>
<td>111 ± 12</td>
<td>113 ± 7</td>
<td>113 ± 16</td>
<td>108 ± 13</td>
</tr>
<tr>
<td>F</td>
<td>25.3 ± 4.1</td>
<td>1.74 ± 0.05</td>
<td>106 ± 14</td>
<td>108 ± 9</td>
<td>108 ± 13</td>
<td>104 ± 9</td>
</tr>
<tr>
<td>Asthmatic Subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>20.6 ± 3.3</td>
<td>1.84 ± 0.07</td>
<td>83 ± 6</td>
<td>91 ± 8</td>
<td>90 ± 16</td>
<td>93 ± 8</td>
</tr>
<tr>
<td>F</td>
<td>25.3 ± 3.6</td>
<td>1.65 ± 0.03</td>
<td>93 ± 16</td>
<td>105 ± 25</td>
<td>93 ± 13</td>
<td>110 ± 21</td>
</tr>
</tbody>
</table>

Values are means ± SD; \( n = 9 \) and 8 healthy men and women and 7 and 4 asthmatic men and women, respectively. \( \text{FEV}_1 \), forced expiratory volume in 1 s; \( \text{FVC} \), forced vital capacity; \( \text{PEF} \), peak expiratory flow; \( \text{TLC} \), total lung capacity; pred, predicted; M, male; F, female.
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 $>1$ (supercritical conditions).

In Fig. 4B, 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).

Figure 4C shows that PA 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--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 Pa than in Fig. 4. The shape of the V-Pa curve is different. After the maximum flow is reached, PA and V both decrease until SI equals one (Fig. 5C, arrow). Then, PA 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 the A-Ptm and V-Pa 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

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**Fig. 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 PA.
Fig. 5. Submaximal effort flow-volume maneuver in same subject as and with same Pitot-static probe position as in Fig. 4. A-C are defined as in Fig. 4.

Fig. 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.
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 probe 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 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 as follows. There is a smaller PEF in asthma despite higher effort (PA, 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.

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy Subjects</th>
<th>Asthmatic Subjects</th>
<th>P* Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEF, l/s</td>
<td>7.29 ± 2.09</td>
<td>7.16 ± 2.63</td>
<td>0.82</td>
</tr>
<tr>
<td>Volume to PEF, liters</td>
<td>0.90 ± 0.45</td>
<td>0.84 ± 0.27</td>
<td>0.78</td>
</tr>
<tr>
<td>Pa, kPa</td>
<td>6.80 ± 2.61</td>
<td>7.26 ± 2.22</td>
<td>0.37</td>
</tr>
<tr>
<td>Pel, kPa</td>
<td>1.01 ± 0.36</td>
<td>0.82 ± 0.18</td>
<td>0.13</td>
</tr>
<tr>
<td>Ppl, kPa</td>
<td>5.80 ± 2.74</td>
<td>6.44 ± 2.24</td>
<td>0.35</td>
</tr>
<tr>
<td>Pca, kPa</td>
<td>2.89 ± 1.74</td>
<td>3.29 ± 2.21</td>
<td>0.47</td>
</tr>
<tr>
<td>J, kPa</td>
<td>-0.29 ± 0.64</td>
<td>-0.46 ± 1.35</td>
<td>1.00</td>
</tr>
<tr>
<td>Pfr, kPa</td>
<td>1.30 ± 0.58</td>
<td>1.28 ± 1.43</td>
<td>0.58</td>
</tr>
<tr>
<td>Pd, kPa</td>
<td>2.61 ± 3.04</td>
<td>2.68 ± 2.47</td>
<td>0.54</td>
</tr>
<tr>
<td>A, cm²</td>
<td>1.15 ± 0.49</td>
<td>1.03 ± 0.40</td>
<td>0.62</td>
</tr>
<tr>
<td>Ptm, kPa</td>
<td>-3.18 ± 2.09</td>
<td>-3.75 ± 2.37</td>
<td>0.51</td>
</tr>
<tr>
<td>Caw, cm²/kPa</td>
<td>0.27 ± 0.20</td>
<td>0.13 ± 0.07</td>
<td>0.12</td>
</tr>
<tr>
<td>SI</td>
<td>0.98 ± 0.09</td>
<td>0.84 ± 0.12</td>
<td>0.01</td>
</tr>
</tbody>
</table>

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.

### DISCUSSION

The purpose of the present study was to examine whether peak expiratory flow is determined by the wave-speed flow-limiting mechanism (2) 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 it should be discussed.

Technical problems. The crucial points are the measurements Pca = Pr – Plat with the Pitot-static probe and Ptm = Pat – Ppl by further use of the esophageal balloon. Figure 2 shows that the area in stiff tubes could be measured reasonably well, even for small values of Pca. Areas > 2 cm², however, may have been

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Constant</th>
<th>Condition</th>
<th>Positions 1-4</th>
<th>r²</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEF, l/s</td>
<td>8.63</td>
<td>-1.19</td>
<td>0</td>
<td>0.14</td>
</tr>
<tr>
<td>Volume to PEF, liters</td>
<td>0.92</td>
<td>0</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>Pa, kPa</td>
<td>5.80</td>
<td>1.40</td>
<td>0</td>
<td>0.14</td>
</tr>
<tr>
<td>Pel, kPa</td>
<td>1.12</td>
<td>-0.28</td>
<td>0</td>
<td>0.14</td>
</tr>
<tr>
<td>Ppl, kPa</td>
<td>4.68</td>
<td>1.68</td>
<td>0</td>
<td>0.17</td>
</tr>
<tr>
<td>Pca, kPa</td>
<td>0.62</td>
<td>0</td>
<td>0.45</td>
<td>0.20</td>
</tr>
<tr>
<td>J, kPa</td>
<td>0.65</td>
<td>-1.08</td>
<td>-0.26</td>
<td>0.28</td>
</tr>
<tr>
<td>Pfr, kPa</td>
<td>0.50</td>
<td>0.80</td>
<td>0.25</td>
<td>0.22</td>
</tr>
<tr>
<td>Pd, kPa</td>
<td>4.95</td>
<td>0</td>
<td>-0.70</td>
<td>0.16</td>
</tr>
<tr>
<td>A, cm²</td>
<td>2.41</td>
<td>-0.36</td>
<td>-0.21</td>
<td>0.18</td>
</tr>
<tr>
<td>Ptm, kPa</td>
<td>0.05</td>
<td>-1.14</td>
<td>-0.71</td>
<td>0.30</td>
</tr>
<tr>
<td>Caw, cm²/kPa</td>
<td>0.16</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Condition: healthy = 0, asthmatic = 1. Example: Pfr = 0.50 + 0.80 (condition) + 0.25 (position). Other parameters are similarly estimated. Zeros indicate no significant influence. Data for position 0 have been excluded. *Only calculated for Pca > 1.3 kPa.
overestimated by 10–15%. About 18% of the measured areas were > 2 cm² 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° in the airway. With the given design of the probe, 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 interpretation is that the probe will move toward 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 PAv continued to increase after PEF was reached (Fig. 4). The explanation for this is that when flow limitation occurs, the resistance (PAv) and the driving pressure (PA) 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 \( P_A \). 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 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 \( P_A \) continues to increase.

**Fig. 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).
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 PA 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 PA-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 (PA = 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 (3) 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 PA at PEF by moving the flow maxima toward higher pressures (7). In that case, an increased PA 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 and 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 (25) or maximal bronchodilation (4, 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 (27). 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 PA-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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