Expiratory flow limitation

HYATT, ROBERT E. Expiratory flow limitation. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 55(1): 1–8, 1983.—The first major advance in understanding expiratory flow limitation of the lungs came with the description of isovolume pressure-flow curves. These curves documented the existence of a volume-dependent limit to maximal expiratory flow and led directly to the description of the maximal expiratory flow-volume (MEFV) curve. Definitive modeling of flow limitation awaited the description of a localized mechanism that dominated the flow-limiting process. The phenomenon of wave speed limitation of flow was shown to apply to the airways and provided the needed localized mechanism. Using this concept and recent data on airway mechanics and the frictional losses in the flow, a computational model of the MEFV curve has been developed. Further progress will require modeling of inhomogeneous emptying in diseased lungs, perfecting noninvasive techniques of estimating pertinent airway characteristics, and improving techniques for increasing the signal-to-noise ratio in MEFV curves.

forced vital capacity maneuver; maximal expiratory flow-volume curve; isovolume pressure-flow curve; wave speed

THIS REVIEW will focus on the evolution of our understanding of expiratory flow limitation. We will identify some of the major remaining gaps in our understanding and suggest areas where future advances in knowledge seem likely. Little will be said about the application of tests of maximal expiratory flow to disease detection or about comparison of such tests with other tests of airway function.

Forced expiration has been used for many years to assess pulmonary function (14, 45). The most commonly used procedure has been the forced vital capacity (FVC) maneuver with recording of volume as a function of time, the spirogram. This procedure consists of having the subject inhale maximally and then immediately exhale as rapidly, completely, and forcefully as possible. It is well established that this test is reproducible and sensitive to disease. For example, reductions in the volume expired in the first second, the FEV₁, are associated with either acute or chronic airway disease, such as asthma, chronic bronchitis, and emphysema.

However, as has been true for many procedures, for years it was not understood why the procedure was so useful in evaluating pulmonary function. Dayman (5) in 1951 noted that the intrathoracic airways behaved as check valves and documented the importance of lung recoil in setting maximal flow (Vmax) in both health and disease. Campbell and associates (2) expanded on these ideas and noted that at Vmax there was a dissociation between transpulmonary pressure and expiratory flow. However, it was the work of Fry and colleagues (11) that provided the key observation. They measured pressure-flow relations at a fixed lung volume and constructed isovolume pressure-flow (IVPF) curves which showed that during expiration flow became limited at modest positive transpulmonary pressures. In other words, above a certain transpulmonary pressure at a given lung volume, flow did not increase with driving pressure. Three such curves from a normal subject are plotted in Fig. 1B. These curves were obtained with the subject seated in a body plethysmograph and breathing repeatedly with increasing effort through the lung volume of interest. Only flow and transpulmonary pressure values at the specific volume of interest are used to construct the IVPF curve. Thus each curve relates transpulmonary pressure to flow at a different lung inflation. Curve A relates pressure to flow at a volume of 0.8 liters from total lung capacity (TLC). Curve B was measured at 2.3 and curve C at 3.0 liters from TLC. Note that on curve A, measured at high lung inflation, flow increases as pressure increases, and there is no defined limit. On the other hand, on curves B and C, measured at lower lung volumes, there are expiratory maxima. Flow increases with pressure until maxima are reached at points B and C; beyond these points further increases in pressure produce no change in flow. This then explains why the FVC maneuver was so useful. Over most lung volumes there was a reproducible limit to expiratory flow; thus not effort but some property of the lungs determines maximal expiratory flow.

Vmax on the IVPF curves decreases with decreasing
lunge inflation and can be reached with relatively moderate expiratory efforts (i.e., transpulmonary pressures of 10–40 cmH₂O). It was only a question of time before the maximal expiratory flow-volume (MEFV) curve was described (12, 17, 18). All that was required was to plot flow against lung volume during a forced expiration. This has been done in Fig. 1A for the three curves in Fig. 1B. The greatest expiratory flow, point A, achieved in curve A is plotted against its corresponding volume and so forth for points B and C. If one recorded IVVV curves over a wide range of lung inflations and plotted the expiratory flows and volumes in the same manner, the full MEFV plot shown in Fig. 1A could be constructed. Clearly, in practice one does not construct MEFV curves in this manner. As noted above, the subject breathes into a system in which flow and volume are measured simultaneously. The flow signal is placed on the Y-axis and the volume signal on the X-axis of a suitable X–Y recorder. The subject then performs the FVC maneuver, yielding the MEFV curve. Thus, over almost the entire vital capacity (VC) there is a limit to expiratory flow that can be defined without measuring transpulmonary pressure. Furthermore V max at a given volume is reproducible.

Once it had been established that there was a limit to expiratory flow, investigators became interested in studying the mechanism(s) that led to expiratory flow limitation. Such flow limitation, or autoregulation of flow, had been seen in various vascular beds but had not been described for the lung. Mead, in 1958, commenting on the paper in which the MEFV curve had been described (17), predicted that understanding the phenomenon of expiratory flow limitation would keep researchers busy for at least 10 years. As usual, he was correct.

In 1958, Fry (9) described a mathematical model of flow along an elastic bronchial segment. He related the pressure gradient at a point in the segment to the physical properties of the gas, the flow, and the tube dimensions which varied as a function of transmural pressure. He showed that in such a system expiratory flow limitation could occur at some point in the segment. He also pointed out that upper airway resistance, the resistance downstream or mouthward of the flow-limiting point, would have little effect on V max; V max was determined by the physical properties of the intrathoracic system. He also suggested that perturbing the system by varying gas properties might provide important additional information. As is well known, this prediction was correct, as seen by the large numbers of studies in recent years investigating the effects of varying gas properties, especially gas density, on V max. However, in 1958 Fry (9) could not carry the modeling further, primarily because there were little detailed data on the anatomy or geometry of the airways, the mechanical properties of the airways, or the flow regimes occurring within the bronchial tree.

The result was that despite this important start, very little progress was made in the next nine years in understanding the mechanism of flow limitation. However, during that period important pieces of data were accumulated, data that were to aid considerably in advancing our understanding. For example, the paper of Martin and Proctor (29) provided the first detailed description of the elastic behavior of various portions of the airway. The classic work of Weibel (46) appeared in 1963 and provided a basis for modeling the geometry of the branching airway system. Also important in making appropriate measurements of MEFV curves was the introduction of the volume displacement body box by Mead in 1960 (30) and the recognition by Mead, and the documentation by Ingram and Schilder (20), of the importance of controlling for gas compression in the evaluation of maximal expiratory flow. Very important contributions were made by Macklem and his colleagues (26–28) by directly measuring intrabronchial pressure in humans during forced expiration. They also provided estimates of the dimensions of the airways during forced expiration and of the location in the airways of the flow-limiting point.

Then in rather rapid succession three important papers appeared. Two dealt with a descriptive or operational approach to flow limitation. Mead and associates (33) analyzed forced expiration in terms of the equal pressure point (EPP) concept. Briefly, according to this approach, once flow was limited at a given lung volume there was a site in the intrathoracic airways where intrabronchial and extrabronchial pressures were equal, the EPP. Driving pressure from alveolus to EPP was the static recoil of the lung (Pel) at that volume. Airways downstream, or mouthward, of the EPP would be compressed, whereas those upstream, or alveolarward, would.

**FIG. 1.** Three isovolume pressure-flow curves from normal subject are shown in panel B. Curves A–C were measured at volumes of 0.8, 2.3, and 3.0 liters, respectively, from total lung capacity. Transpulmonary pressure is difference between pleural (estimated by esophageal balloon) and mouth pressures. Panel A is flow-volume plot for same subject. Maximal expiratory flows are plotted vs. their corresponding volumes at points (•) A–C and define maximal expiratory flow-volume curve (solid line).
be. Thus an upstream resistance could be defined as pressure divided by $V_{\text{max}}$. This paper reemphasized the importance of recoil pressure in determining $V_{\text{max}}$ and analyzed factors affecting the upstream resistance in a productive manner. At about the same time, Pride and associates (41) compared flow limitation with the behavior of a Starling resistor, or a “waterfall.” They emphasized that under conditions of flow limitation, the flow downstream, or mouthward, pressure did not affect $V_{\text{max}}$. This work also emphasized the importance of the compressibility and tone of the airways at the flow-limiting point.

However, the above analyses, although providing some very important insights into the phenomenon, did not explain the mechanism of flow limitation. Fry in 1968 (10) restudied the problem by using a systems analysis approach to the mechanics of expiratory flow. He pointed out that if 1) the total cross-sectional area of the bronchial tree $(A)$ could be defined as a function of transpulmonary pressure $(P_{L})$ and position along the tree $(x)$,

$$ A = f(P_{L}, x) \tag{1} $$

and 2) the pressure gradient $(dP/dx)$ in the airways could be described as a function of area, position, and flow $(V)$

$$ dP/dx = f(A, x, V) \tag{2} $$

then for a given flow this coupled set of equations could in principle be integrated from the alveolus to the trachea. Fry showed that for some airway pressure-area curves there was a maximum value of expiratory flow for which a solution of these equations existed. In large part, this important contribution was made possible by the advent of rapid computing techniques and by the recent knowledge that had been accumulated regarding the geometry of the airways and their mechanical properties. However, there were still insufficient data to permit Fry to make reliable estimates of all the system parameters. The work could not be carried further, although it was clear that his goal was to develop a detailed mathematical model which when applied to a given MEFV curve would permit estimates of pertinent mechanical variables.

Since it did not appear productive to pursue the task of developing a complete mathematical model, attention was directed by several investigators to the possibility that there might be localized mechanisms that were dominant in producing flow limitation (24, 39, 40). It was postulated that if one assumed that most of the frictional pressure loss occurred in the peripheral airways, and if the convective acceleration pressure loss occurred primarily in the central airways, one could apply the following expression

$$ P = P_{e}L - \Delta P_{fr} - 1/2 \rho V^{2}/A^{2} \tag{3} $$

where $P$ is lateral airway pressure, $\Delta P_{fr}$ is frictional head loss, $\rho$ is gas density, and the third term on the right is the pressure loss due to convective acceleration, the Bernoulli effect. The idea was that if one knew the pressure-area behavior of the central airways, the frictional pressure losses, and the static recoil pressure, one should be able to predict maximal expiratory flow. In other words, knowing the area available for the flow from the pressure-area behavior of the airways and the area required for the flow from the Bernoulli expression, one could obtain a unique solution for $V_{\text{max}}$. In studies of excised human lungs, Hyatt and associates (19) measured the pressure-area behavior of the central airways and the frictional pressure drop occurring upstream of the flow-limiting point. It was possible to solve Eq. 3 graphically and to predict $V_{\text{max}}$ at various volumes in a given lung. Predicted flows agreed well with those measured in excised lungs, except at low lung volumes. Similar approaches were reported by other workers in human (35) and dog lungs (22, 36). These studies clearly showed that when the recoil pressure of the lung and the peripheral friction losses were taken into account, over most of the lung volume $V_{\text{max}}$ could be understood in terms of the coupling between airway compliance and the pressure drop due to the convective acceleration of the flow.

However, one major problem still existed. None of the models was able to predict a plateau on the IVPF curve, which of course is the hallmark of flow limitation. The fact that flow plateaus were found in spite of drastic changes in volume and lung properties suggested a crucial and perhaps localized mechanism that fixed the flow once the pressure drop in the system was large enough. The answer to this perplexing problem was supplied by Dawson and Elliott (4, 6). They pointed out that elastic tubes cannot carry a fluid at a mean velocity greater than the speed at which pressures will propagate along the tube. The velocity at which pressures will propagate in a given tube is the tube wave speed. The pertinent wave speed is the speed at which a small disturbance travels in a compliant tube filled with fluid. In the arteries, this is the speed at which the pulse propagates. Wave speed flow ($V_{w}$) can be predicted by the following equation

$$ V_{w} = A \left[ \frac{A}{\rho} \left( \frac{dA}{dP} \right) \right]^{0.5} \tag{4} $$

where $dA/dP$ is the compliance of the tube at a particular point on its pressure-area curve. From this relationship it is seen that wave speed decreases with a decrease in area, an increase in density, and an increase in compliance of the tube. With low expiratory flows wave speed is high, but as the flow increases, the central airways narrow and move onto the more compliant portion of their pressure-area characteristic and wave speed falls. As this process continues with increasing flow, a point will be reached where the local wave speed (predicted by Eq. 4) equals the airflow, and flow limitation will occur; the location at which the limitation occurs is called the choke point.

The equation for wave speed and its significance in limiting flow can be determined from the partial differential equations describing the physical laws that govern flow (4, 16). However, one can obtain an intuitive appreciation for wave speed limitation from the following considerations. Basically one wishes to understand how the wave speed mechanism can produce plateaus on IVPF curves. The critical point to keep in mind is that on the plateau, flow is independent of the downstream pressure; this is the so-called “waterfall” or Starling
resistor effect. Keeping in mind that we are dealing with an isovolume condition, it is clear that at low flows, wave speed is high because the airways show little compression (large area) and are on the flat part of their pressure-area characteristic (they are stiff). A drop in pressure at the outlet will be transmitted upstream at a speed that is diminished only slightly by the counteracting effect of airflow velocity. As flow increases, the speed at which a downstream pressure disturbance (a drop in pressure) can be transmitted upstream will fall because 1) wave speed is decreasing and 2) the opposing effect of the airflow velocity is increasing. When the speed (predicted by the wave speed equation) no longer exceeds the speed of expiratory flow, the pressure disturbance can no longer propagate upstream and affect the flow. In essence, the downstream pressure change is no longer "seen" by the upstream driving pressure, and flow becomes independent of, or uncoupled from, downstream pressure. When this occurs, the system is flow limited, and one has the waterfall phenomenon. Further decreases in downstream pressure serve only to compress the airways downstream of the choke point and of course have no effect on the flow. In summary, pressure disturbances below the choke point cannot be propagated upstream, since they are traveling in a medium that is moving in the opposite direction with a velocity that equals the velocity at which the pressure can be propagated.

Another important piece of information was provided by Reynolds and Lee (42) who developed a simple description of the frictional airway losses from studies of expiratory flow in models and bronchial casts. This information, plus the wave speed concept, made it feasible to return to the task of developing a detailed computational model of expiratory flow and to complete, in at least a preliminary fashion, the task begun by Fry in 1958 (9). Details of the computational model were published recently (25) and will not be described in detail here. In brief, by taking into account the pressure losses in the flow and the distributed airway compliance, it was possible to predict the pressure distribution in the airways and to generate IVPF and MEFV curves that predicted flows very close to those measured in excised human lungs. The model was also successful in predicting MEFV curves when the lungs were ventilated with 80% He-20% O2, as well as 100% SF6. Other features of the model's predictions, such as lung conductance, density and viscosity dependence of Vmax, and the pressure required to reach Vmax agreed well with published data. This model represents a very encouraging step forward. Lambert (23), for example, has simulated peripheral airway disease by reducing cross-sectional area of the distal airways by 50%. This produced scooping of the MEFV curve, particularly at low lung volumes, and also a marked reduction in density dependence of flow. Both these changes are consistent with current thinking regarding the effect of peripheral airway disease on maximal expiratory flow. Lambert (23) has also studied the sensitivity of maximal expiratory flow to changes in the model's parameters. This is a first step in defining the uniqueness of the model; i.e., the range of parameter values that are consistent with the data. Clearly the more narrow the range, the greater will be the informational content of the MEFV curve.

It should be pointed out, however, that the wave speed phenomenon does not appear to be the only mechanism by which flow limitation can occur. There is evidence that flow at low lung volumes may be determined by viscous flow limitation. In this case, the limiting flow is determined by the coupling between viscous losses in the flow and tube compliance; limitation at wave speed, i.e., the coupling between tube compliance and convective losses, is not the significant mechanism. For example, Shapiro (43) has described purely viscous flow limitation in a compliant tube. Fry et al. (13) have used the Starling resistor model to show how viscous flow limitation might occur. In the study of Hyatt et al. (19) it was not possible to predict Vmax at low volumes in excised lungs utilizing reasonable estimates of peripheral airway area and compliance. This led these investigators to suggest that the wave speed theory cannot predict flows consistent with those measured over the lower 25% of the VC. Finally the model of Lambert et al. (25) described above also predicts that at low lung volumes flow limitation is predominantly a result of viscous limitation. An example is shown in Fig. 2 where the solid line defines the maximal wave speed flow in the sixth generation. The dashed line represents the model's prediction of airflow in the sixth generation at a recoil pressure of 2 cmH2O. It can be seen that the dashed pressure-flow curve approaches a plateau value at a pressure of -2 cmH2O, well before wave speed limitation is reached, which would occur at a pressure of -13 cmH2O. In this situation flow speed (1.2 l/s) is significantly below wave speed (2.0 l/s) at the pressure at which the plateau begins. Of course, eventually wave speed is reached well out on the plateau. These observations should not be taken, however, as minimizing the tremendous contribution made by the concept of wave speed limitation.

A very useful discussion of the implications of wave speed flow limitation can be found in the article by Mead (32). Mead discusses how the wave speed flow depends on the interrelations among intrinsic features (such as

![Fig. 2. Model prediction of viscous flow (V) limitation. Solid line defines maximal wave speed for 6th generation. Dashed line present isovolume pressure-flow curve at recoil pressure (P) of 2 cmH2O. See text for further discussion.](image)
pressure-area behavior of the bronchi and the fluidity and an extrinsic feature of the system, i.e., the transmural pressure. The transmural pressure depends on the static recoil of the lung and the intraluminal and convective pressure losses along the airway. He examines this extrinsic feature by taking a "pressure walk" across the airway, through the parenchyma, and down the airway to the starting point, the open point. Mead points out that this approach is patterned after that used by Fry in 1968 (10) as a bookkeeping device. Anyone interested in delving into the concept of flow limitation would do well to start by taking this delightful "walk" with Mead. He should also read the papers by Mead et al. (33), Pride et al. (41), Fry (10), Lambert et al. (25), and Wilson et al. (47). These papers provide an excellent background for exploring the topic further.

This then brings us up to date. What challenges lie ahead? Clearly more work needs to be done on the modeling, for the ultimate goal is to estimate parameters by fitting models to data, the so-called general inverse problem. More precise data are needed on the pressure-area characteristics of the airways as a function of location in the lung. In addition, the model described by Lambert et al. (25) needs to be modified to the geometry described by Horsfield and Cumming (15). How much difference will switching from the symmetrical model of Weibel to the asymmetric model of Horsfield and Cumming make? Developing an asymmetric model will present a difficult challenge but is an important step to modeling diseased lungs. The modeling of flow from an asymmetric lung must satisfy the physical principle that the pressure in the stream from two nonuniform regions must match at the point where the branches join. Computations seem possible if the number of differing regions is small, but if the number gets large the computation may become unmanageable. On the other hand, the nonuniformity or inhomogeneity of emptying may be self-limiting. For example, in a region that initially empties relatively rapidly because of low airway resistance, recoil pressure will drop rapidly and an inhomogeneous driving pressure will develop that will reduce the inhomogeneity of regional flow. There may therefore be limits on the inhomogeneity of regional flow and volume, and these limits may apply to some extent to the inhomogeneity found in disease. Work should continue on "exposing" inhomogeneous emptying in health and disease, following the leads suggested by Mead and colleagues (16, 31). Mead has analyzed the configuration of the MEFV curve and has made some estimates of what changes in curvature would be required to detect inhomogeneous emptying. The Boston group has also explored the ability of varying the time course of flow limitation to uncover inhomogeneous emptying (34). One would anticipate that flow at 50% VC would be higher on a partial flow-volume curve initiated from 60% VC than on the MEFV curve if there are large discrepancies in emptying among different regions of the lung. The magnitude and significance of such discrepancies need to be determined.

Another complexity is the possibility that during forced expiration, multiple choke points may exist in series at different sites in the lung; this could decrease inhomogeneous emptying. Mead has recently suggested that this may be the case (32). If this proves to be true, what are the implications of such behavior on our modeling efforts? Viewed differently, it is impressive that the system is so orderly and reproducible during forced expiration. The uniformity of the flow-limiting process in the very complicated, branching airway network represents a rather remarkable engineering accomplishment!

Currently we have a good catalogue of the important determinants of $V_{max}$. Even as work on more sophisticated modeling is proceeding, there are still interesting and important problems that need to be addressed. What might be called the forward problem should be studied; i.e., given an individual static lung pressure-volume curve and some estimate of central airway compliance, is it possible to predict that subject's MEFV curve in part or full? Recent work by Fredberg and associates (8) and by Jackson et al. (21) suggests that it may be possible to obtain data on the area and compliance of the central airways. These data, coupled with better estimates of peripheral resistance which may be obtained by manipulation of gas properties, might allow the forward problem to be addressed even before a totally satisfactory computational model is available. Evidence in support of this is found in the recent paper by Osmanliev and associates (38) in which a good correlation between the size of the trachea and the FEV1 is shown. Castile et al. (3) showed that elastic recoil pressure and estimates of airway size correlated with $V_{max}$.

There are other specific questions to answer. One that has intrigued the author for a number of years is the parallel shift of the MEFV curve not infrequently seen during the induction of mild attacks of bronchospasm in asthmatic subjects (37). This shift in the curve with an increase in residual volume (Fig. 3) has never been fully explained. Although the original explanation offered by Olive and Hyatt (37) is probably too simplistic, a better explanation has not been forthcoming. Success in modeling the parallel shift of the MEFV curve may provide important insight into the pathophysiology of asthma.

![FIG. 3. Maximal expiratory flow-volume (MEFV) curves from subject with asthma. Patient was asymptomatic during control period (solid line). Symptoms including wheezing were induced by inhaling extract of ragweed. Note parallel shift in postchallenge MEFV curve (dashed line). TLC, total lung capacity.](image-url)
It is important to note that currently three models are theoretically capable of providing information regarding the physical properties of the lung from noninvasive measurements. One models flow as a function of volume (25); one models total respiratory impedance (Zrs) as a function of oscillation frequency (ω) (7); and another, the airway area acoustic reflection technique (8, 21), predicts airway area (AAR) as a function of distance (x). Each of these measures, namely V(V), Zrs(ω), and AAR(x), can be predicted from a single common description of the bronchial tree, its branching nature and geometry, gas physical properties, and the airway wall and tissue properties. An important and potentially productive area of investigation will be to determine whether these three techniques provide additive information regarding lung mechanics. For example, in each model one can change the properties of the airways at a given site and observe the effects these changes have on the output of the MEFV, area-distance, and impedance models. Although not a simple task, the substantial progress made in recent years suggests that studies describing the relative sensitivity of these three measures to various airway and lung parameters will be forthcoming in the near future.

In the author's opinion the inability to define a person's "true" MEFV curve has hampered progress not only in the understanding of flow limitation but also in the application of forced expiration, particularly the MEFV curve, to clinical problems. An important advance in this area has been made recently by Bruce and Jackson (1) and Tien et al. (44) who have shown that by using digital filtering and averaging techniques, one can rather precisely define a unique MEFV curve for an individual. The assumption used is that a given flow corresponds to a unique volume and that we are able to measure flow more precisely than volume. The work to date looks encouraging, and I would predict that once flow-volume curves are routinely handled in this manner, much of the variability that has plagued the evaluation of density dependence and inter- and intransubject comparisons will be greatly reduced. Of course, further steps may be needed to reduce inter-subject variability, such as taking into account lung elastic recoil and some indirect measurement of airway area.

These then are only some of the challenges and opportunities that lie ahead. I would suggest that there is sufficient work to keep energetic imaginative investigators profitably occupied for many years. The phenomenon of expiratory flow limitation is clearly not solved. However, as one of my colleagues said, "We are still confused, but at a much higher level."

REFERENCES


Review


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