# Detection of expiratory flow limitation during exercise in COPD patients

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**Koulouris, Nickolaos G., Ioanna Dimopoulou, Päivi Valta, Richard Finkelstein, Manuel G. Cosio, and J. Milic-Emili.** Detection of expiratory flow limitation during exercise in COPD patients. *J. Appl. Physiol.* 82(3): 723–731, 1997.—The negative expiratory pressure (NEP) method was used to detect expiratory flow limitation at rest and at different exercise levels in 4 normal subjects and 14 patients with chronic obstructive pulmonary disease (COPD). This method does not require performance of forced expirations, nor does it require use of body plethysmography. It consists in applying negative pressure ($-5$ cm$H_2O$) at the mouth during early expiration and comparing the flow-volume curve of the ensuing expiration with that of the preceding control breath. Subjects in whom application of NEP does not elicit an increase in flow during part or all of the tidal expiration are considered flow limited. The four normal subjects were not flow limited up to 90% of maximal exercise power output ($\dot{W}_{max}$). Five COPD patients were flow limited at rest, 9 were flow limited at one-third $\dot{W}_{max}$, and 12 were flow limited at two-thirds $\dot{W}_{max}$. Whereas in all patients who were flow limited at rest the maximal $O_2$ uptake was below the normal limits, this was not the case in most of the other patients. In conclusion, NEP provides a rapid and reliable method to detect expiratory flow limitation at rest and during exercise.

negative expiratory pressure; chronic obstructive pulmonary disease; exercise performance; dynamic hyperinflation

THE HIGHEST PULMONARY ventilation that a subject can achieve is ultimately limited by the highest flow rates that can be generated. Most normal subjects do not exhibit expiratory flow limitation, even during maximal exercise (2, 10, 13). In contrast, patients with chronic obstructive pulmonary disease (COPD) may exhibit expiratory flow limitation at rest or at low work rates, as first suggested by Potter et al. (25). They observed that patients with severe COPD often breathe tidally along their maximal expiratory flow-volume curve and suggested that this reflects the presence of expiratory flow limitation (i.e., inability to further increase flow at a given lung volume). By use of this approach, expiratory flow limitation has been extensively studied in COPD patients at rest and during exercise (1, 10, 17, 28). In many instances, however, the flows obtained during tidal breathing actually exceeded those of the maximal expiratory flow-volume curve (1, 10, 25). Several explanations for this phenomenon have been offered: The first explanation involves thoracic gas compression artifacts. In nearly all previous studies, the flow-volume loops were obtained from measurements of expired gas volume, although Ingram and Schilder (14) pointed out that, to avoid gas compression artifacts, volume should be measured with a body plethysmograph. The second explanation is incorrect alignment of tidal and maximal expiratory flow-volume curves. Such alignment is usually made on the assumption that the total lung capacity (TLC) does not change during exercise and, hence, that changes in inspiratory capacity (IC) reflect changes in end-expiratory lung volume (EELV). Although several investigators have reported that TLC does not change with exercise (21, 28, 32), others found that it increases (11). Furthermore, this approach is based on the assumption that during exercise the subjects can perform a truly maximal inspiration. During exercise, however, some COPD patients may be incapable of performing IC maneuvers. The third explanation is the effect of previous volume and time history. The maximal flows that can be achieved during expiration depend on the volume and time history of the preceding inspiration (4, 6, 9, 18). Because, by definition, the previous volume and time history varies between tidal breathing and maximal inspiration, it follows that assessment of flow limitation on the basis of comparison of tidal and maximal flow-volume curves may lead to erroneous conclusions, even if the measurements are done with a body plethysmograph. The fourth explanation is the effect of muscular exercise on lung mechanics. Exercise may result in bronchodilatation and other changes in lung mechanics, which may affect tidal and maximal flow-volume curves (2, 28).

Assessment of expiratory flow limitation may also be based on comparison of tidal flow-volume curves with those obtained during partial forced expirations. In this way, the previous volume history is kept constant. The previous time history should also be kept constant. Indeed, Wellman et al. (31) showed that in normal subjects the flows attained during a partial forced expiratory maneuver depend on the previous time history, similar to the maximal forced vital capacity (FVC) maneuver (4). Whereas normal subjects may be trained to produce partial FVC maneuvers with previous volume and time history similar to that of the preceding tidal breaths, this is seldom feasible in most patients with COPD, especially during exercise.

From the above considerations, it appears that detection of expiratory flow limitation on the basis of comparison of tidal with maximal flow-volume curves is questionable. Recently, however, an alternate approach [negative expiratory pressure (NEP) method] has been introduced (16, 30). This method does not require performance of FVC maneuvers on the part of the patient, nor does it require use of a body plethysmograph. It consists in applying a negative pressure at the

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mouth during a tidal expiration and comparing the ensuing expiratory flow-volume curve with that of the previous control expiration. Accordingly, with this method the volume and time history of the control and test expiration is the same. The NEP technique has been previously applied and validated in mechanically ventilated patients in the intensive care unit by concomitant determination of isovolume flow-pressure relationships (30). It has also been used in stable COPD patients at rest (16). The present investigation is designed to test the feasibility of using this method during exercise in COPD patients and normal subjects and to assess the implications of flow limitation on exercise performance. We have also assessed expiratory flow limitation by comparison of tidal with maximal expiratory flow-volume curves.

## METHODS

Four normal subjects and 14 patients with COPD ranging from mild to severe were studied. Their anthropometric characteristics and lung function data are given in Table 1. All COPD patients, who were recruited from the respiratory outpatient clinic, were in a stable clinical and functional state at the time of the study and had no contraindications for exercise testing. None had a history of obstructive sleep apneas (OSA) or any evidence of upper airway obstruction. Routine spirometry was performed with a calibrated dry spirometer (1070 system, Medical Graphics, Minneapolis, MN), and thoracic gas volumes were determined with a body plethysmograph (P. K. Morgan, Kent, UK). The predicted normal values for spirometric measurements were those of Morris and co-workers (20), and for thoracic gas volumes the values of Goldman and Becklake were used (8). The study was approved by the local Ethics Committee. All subjects gave informed consent.

Figure 1 depicts the experimental setup used to assess expiratory flow limitation. A flanged plastic mouthpiece is connected to a Fleisch no. 3 or 4 pneumotachograph (Fleisch, Lausanne, Switzerland) and a T tube. One side of the T tube is open to the atmosphere, and the other side is equipped with a one-way pneumatic valve that allows for the subject to be rapidly switched to negative pressure generated by a vacuum cleaner (Hoover Heavy Duty Portapower, model S7065–060, Hoover, Dayton, OH). The pneumatic valve (occlusion valve setup, series 9300, Hans Rudolph, Kansas City, MO) consists of an inflatable balloon connected to a gas cylinder filled with helium and a manual pneumatic controller (Hans-Rudolph control switch 9301). The latter permits remote-control balloon deflation, which is accomplished quickly (30–60 ms) and quietly, allowing rapid exposure to negative pressure during expiration (NEP). The NEP (usually set at about $-5$ $cmH_2O$) (16) could be adjusted with a potentiometer (Powerstat, Superior Electric, Bristol, CT).

Airflow was measured with the heated Fleisch pneumotachographs connected to a differential pressure transducer

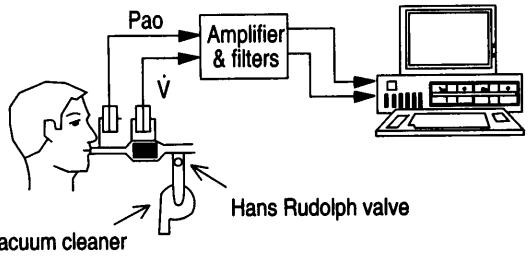


Fig. 1. Schematic diagram of equipment setup. Pao, pressure at airway opening; $\dot{V}$, flow.

(Validyne MP45, $\pm 2$ $cmH_2O$). This is one of the most symmetrical transducers available, with a common-mode rejection ratio of 70 dB at 30 Hz (7). The response of the pneumotachographs, calibrated with a rotameter, was linear over the experimental range of flows. Pressure at the airway opening (Pao) was measured through a side port on the mouthpiece using a differential pressure transducer (Validyne MP45, $\pm 88$ $cmH_2O$). With this system there was no appreciable shift or alteration in pressure amplitude up to 20 Hz. The breathing assembly had a dead space of 220 and 410 ml with Fleisch pneumotachographs no. 3 and 4, respectively, and the corresponding pressure-flow relationships were characterized by the following equations: $P = 0.16\dot{V} + 0.31\dot{V}^2$ and $P = 0.17\dot{V} + 0.22\dot{V}^2$, where P is pressure (in $cmH_2O$) and $\dot{V}$ is flow (in l/s). The Fleisch no. 4 pneumotachograph was used only by the normal subjects. In two normal subjects and two COPD patients we also measured the esophageal pressure (Pes), as previously described in detail (3). The flow and pressure signals were amplified (model 8085, Hewlett-Packard, Waltham, MA) and sampled simultaneously at a rate of 100 Hz using a computer data acquisition system with a built-in 16-bit analog-to-digital converter (AT-Codas, DATAQ Instruments, Akron, OH). Collected data were stored on a computer disk for subsequent analysis. Volume was obtained by numerical integration of the flow signal. The flow signal was corrected for any offset on the basis of the assumption that inspired and expired volume of the preceding control breath were the same (24). This analysis was made using ANADAT data analysis software (ANADAT 5.1, RHT-InfoDat, Montreal, Quebec, Canada).

*Procedure.* On a separate day before the study, all subjects underwent an incremental symptom-limited exercise test on an electrically braked bicycle ergometer (Mijnhardt, Schoudermanterl, Bunnik, The Netherlands) connected to an automated exercise system (model 2000, Medical Graphics, Minneapolis, MN). Subjects cycled at a rate of 50–70 rpm and were encouraged to exercise to the limit of their tolerance. In this way, the maximal mechanical power output ($\dot{W}_{max}$), $O_2$ uptake ($\dot{V}O_{2max}$), ventilation, and heart rate were determined (Table 2). The predicted normal values for $\dot{V}O_{2max}$ and maximal heart rate were those of Jones and Campbell (15). On the study day, each subject underwent steady-state constant workload tests at one-third and two-thirds $\dot{W}_{max}$ at least 2 h after eating or drinking coffee. During these tests the patients breathed

Table 1. *Anthropometric and lung function data of normal subjects and COPD patients*

| | *n* | Age, yr | Height, cm | Weight, %pred | Gender | FVC, %pred | $FEV_1$, %pred | $FEV_1$/FVC, % | IC, %pred | FRC, %pred | TLC, %pred | RV, %pred |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Normal subjects | 4 | 32 ± 3 | 177 ± 8 | 94 ± 6 | 2M, 2F | 106 ± 7 | 108 ± 5 | 83 ± 4 | | | | |
| COPD patients | 14 | 64 ± 9 | 166 ± 8 | 117 ± 20 | 10M, 4F | 78 ± 20 | 58 ± 20 | 53 ± 11 | 80 ± 22 | 149 ± 37 | 117 ± 16 | 173 ± 42 |

Values are means ± SD. IC, inspiratory capacity; FRC, functional residual capacity; TLC, total lung capacity; RV, residual volume; $FEV_1$, forced expired volume in 1 s; FVC, forced vital capacity; COPD, chronic obstructive pulmonary disease; %pred, percentage of predicted.

Table 2. *Maximal exercise data of normal subjects and COPD patients*

| | | | $\dot{V}O_{2max}$ | | | |
|---|---|---|---|---|---|---|
| | *n* | $\dot{W}_{max}$, W | l/min | %pred | $\dot{V}E_{max}$, l/min | $HR_{max}$, beats/min |
| Normal subjects | 4 | 222 ± 55 | 2.79 ± 0.69 | 118 ± 22 | 95 ± 17 | |
| COPD patients | 14 | 90 ± 25† | 1.45 ± 0.26† | 85 ± 21* | 51 ± 13† | 139 ± 19 |

Values are means ± SD. $\dot{W}_{max}$, maximal power output; $\dot{V}O_{2max}$, maximal $O_2$ uptake; $\dot{V}E_{max}$, maximal exercise ventilation; $HR_{max}$, maximal exercise heart rate. *$P < 0.02$; †$P < 0.001$.

room air through the equipment assembly while wearing noseclips (Fig. 1). Measurements were also made at rest with subjects seated on the bicycle ergometer in the same position as during exercise. Each subject performed an initial 10- to 15-min trial run of resting breathing to become accustomed to the apparatus and procedure. The time course of Pao, flow, and volume, together with the corresponding flow-volume loops, were continuously monitored on the computer screen. After regular resting breathing had been achieved, the maximal expiratory flow-volume curves were measured. Because flows during FVC depend markedly on previous time and volume history (4), the maneuvers were standardized by using a rapid inspiration to TLC from resting EELV without an end-inspiratory pause. After resting breathing was resumed, a series of three to five test breaths were performed in which NEP (−5 $cmH_2O$) was applied during early expiration and maintained throughout the ensuing exhalation (Fig. 2). Then the subjects were asked to perform three IC maneuvers at intervals of ~30 s. Subsequently, the external workload was set first at one-third and next at two-thirds $\dot{W}_{max}$. After a constant breathing pattern had been reached at each workload, NEP was applied in a manner similar to that during resting breathing. Subsequently, at both levels of exercise, the patients were asked to perform three IC maneuvers at intervals of ~30 s. At each exercise level it was assumed that TLC was reached with the highest IC (21, 32), and this IC was used to place the tidal within the maximal flow-volume loop. In the normal subjects, similar experiments were also carried out at 90% $\dot{W}_{max}$.

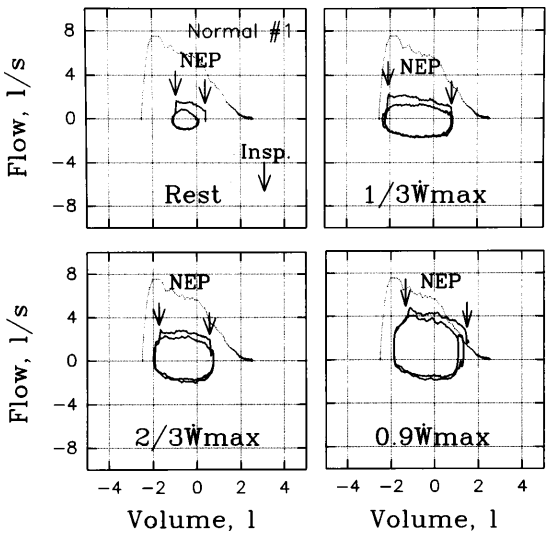


Fig. 2. Flow-volume ($\dot{V}$-V) curves from representative normal subject at rest and at 3 levels of exercise, expressed as a fraction of maximal power output ($\dot{W}_{max}$). Zero volume represents end-expiratory lung volume at rest. In each instance, $\dot{V}$-V loops of 2 consecutive breathing cycles are shown: that of a test breath during which negative expiratory pressure (NEP) of −5 $cmH_2O$ was applied during expiration and that of preceding control breath. NEP was applied during early expiration (1st arrow) and maintained throughout expiration (2nd arrow). In all instances, NEP elicited a sustained increase in flow, reflecting absence of expiratory flow limitation. Dotted line, expiratory $\dot{V}$-V curve obtained during forced vital capacity maneuver.

*Principle of NEP method and data analysis.* The NEP method to detect expiratory flow limitation has been previously described in detail (16, 30). It is based on the principle that in the absence of preexisting flow limitation the increase in pressure gradient between the alveoli and the airway opening caused by NEP should result in increased expiratory flow (Fig. 2). By contrast, in flow-limited subjects, application of NEP should enhance dynamic airway compression downstream from the flow-limiting segments without substantial effect on pressure or flow upstream. Under these conditions, expiratory flow does not change with NEP, except for a brief flow transient (i.e., spike), which in our experiments should mainly reflect a sudden reduction in volume of the compliant oral and neck structures. To a lesser extent, however, enhanced dynamic airway compression and a small artifact due to the common-mode rejection ratio of the system for measuring flow may also contribute to the flow transients. In this connection, it should be noted that the flow spikes can be regarded as a characteristic marker of flow limitation (16, 30).

On the basis of the above considerations, our analysis essentially consists in comparing the expiratory flow-volume curve obtained during a control breath with that obtained during the subsequent expiration in which NEP is applied. Subjects in whom application of NEP did not elicit an increase in flow during part or all of the tidal expiration were considered flow limited. By contrast, subjects in whom flow increased with NEP throughout the control tidal volume ($V_T$) range were considered not flow limited.

In agreement with a previous study (16), application of NEP was not associated with unpleasant sensations or cough, nor was there any evidence of upper airway collapse. Indeed, with NEP the expiratory flow increased (reflecting absence of flow limitation) or did not change (reflecting presence of flow limitation). There was no instance in which application of NEP resulted in a sustained decrease in expiratory flow.

Flow limitation was also assessed by comparison of tidal with maximal expiratory flow-volume curves based on expired volume (13). Hereafter this method is called the "conventional" method. Patients in whom, at comparable lung volumes, flows during tidal expiration were similar to or higher than those obtained during the FVC maneuver were considered "flow limited" (16, 25).

Statistical analysis was made using Dunnett's test of multiple comparisons and unpaired *t*-test, where appropriate. $P \leq 0.05$ was taken as significant. Values are means ± SD.

## RESULTS

Figure 2 depicts flow-volume loops obtained at rest and at three levels of steady-state exercise in a representative normal subject. In all instances the application of NEP resulted in increased expiratory flow over the

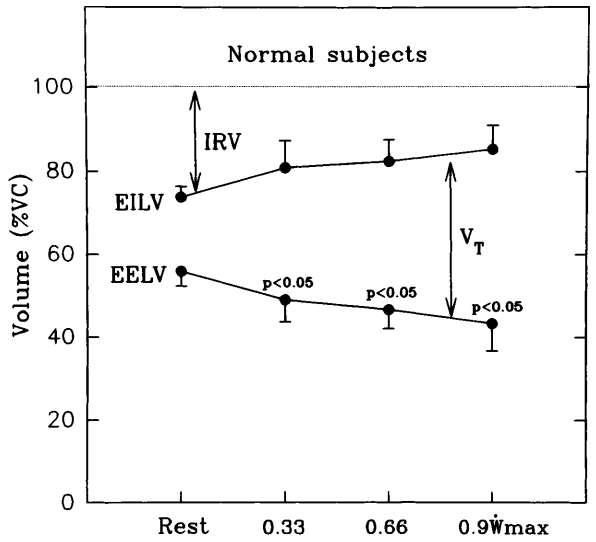


Fig. 3. Subdivisions of lung volume, expressed as percentage of vital capacity (VC), at rest and at different levels of $\dot{W}_{max}$ in 4 normal subjects. EILV and EELV, end-inspiratory and end-expiratory lung volume; IRV, inspiratory reserve volume; VT, tidal volume. ●, Average values; bars, SE. $P < 0.05$, significant change relative to EELV at rest.

entire range of control tidal volume (VT), indicating absence of expiratory flow limitation up to 90% $W_{max}$. Also shown in Fig. 2 is the maximal expiratory flow-volume curve obtained at rest. In all instances the latter exceeded those used to sustain resting and exercise ventilation. With increasing exercise level, the end-inspiratory lung volume (EILV) increased while the EELV tended to decrease. Similar results were found in the other three normal subjects studied. In all instances the results were reproducible with repeated NEP tests. The average values of EILV and EEVL during exercise of the four normal subjects are depicted in Fig. 3.

Figure 4 illustrates flow-volume loops of COPD *patient 4* at rest and during exercise. In all instances, the application of NEP did not elicit an increase in flow, except for a transient increase (i.e., spike) coincident with NEP application. This transient mainly reflects reduction in volume of the airways and heralds flow limitation (see METHODS). Thus, according to NEP, this patient had expiratory flow limitation at rest as well as during exercise. Also shown in Fig. 4 is the maximal expiratory flow-volume curve. The tidal expiratory flows largely exceeded the maximal flows at rest and during exercise. Thus, according to the conventional method for detecting flow limitation, this patient would also be classified as flow limited. In this patient, EILV and EELV increased progressively with increasing exercise load. Similar results were found in *patients 2, 5, 8,* and *14*.

Figure 5 depicts results obtained in COPD *patient 1*, who, according to the NEP test, was not flow limited at rest but became flow limited at one-third and two-thirds $\dot{W}_{max}$. At rest the tidal flows were essentially superimposed on the maximal expiratory flow-volume curve, whereas during exercise the tidal flows exceeded the maximal expiratory flow-volume curve. Thus at rest the patient would be classified as flow limited with the conventional method but not flow limited with the NEP test. During exercise, flow limitation was detected with both methods. However, at one-third $\dot{W}_{max}$, flow limitation with NEP encompassed only the last 30% of VT, whereas the maximal expiratory flow-volume curve was superimposed with a larger fraction of the tidal expiratory flow-volume curve (~70% VT). In this patient, EILV was close to TLC even at rest, and during exercise there was little change in EELV or VT.

Figure 6 depicts the time course of flow, volume, Pao, and Pes during a control breath and the subsequent expiration with NEP, together with the corresponding flow-volume and Pes-volume loops, at rest in a COPD patient who was flow limited and in a normal subject. In the flow-limited patient, the time course of flow, volume, and Pes was not affected by NEP, except for the characteristic initial flow transient. Apart from the latter, the flow-volume and Pes-volume loops obtained with NEP were essentially the same as in the preceding control breath. This indicates that NEP did not elicit changes in respiratory muscle activity. By contrast, in the non-flow-limited subject, the increase in flow elicited by NEP was associated with a slower increase in Pes at any given time during expiration (Fig. 6*Ba*). An increase in flow would per se be expected to result in more negative Pes at any given time of expiration because of *1*) increased pressure dissipations due to the Newtonian resistance of the chest wall, *2*) decreased elastic recoil pressure of the chest wall due to faster lung deflation, and *3*) increased antagonistic pressure exerted by the breaking action of the inspiratory muscles, which are active during expiration (19, 27). That is, during pliometric contraction the force exerted by a muscle increases with increased velocity of lengthening (19). With NEP, Pes at any given volume was more negative than during the control expiration (Fig. 6*Bb*). Apart from *mechanisms 1* and *3*, this phenom-

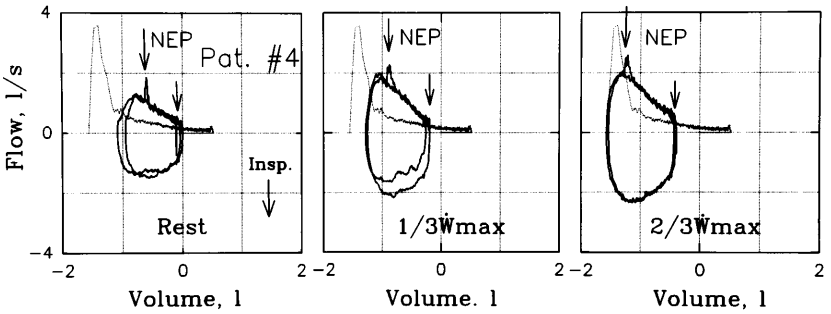


Fig. 4. $\dot{V}$-V curves, as in Fig. 2, from *patient 4* with chronic obstructive pulmonary disease (forced expired volume in 1 s = 33% predicted). In all instances, there was no change in expiratory flow with NEP, except for a flow transient (spike) at onset of NEP application. Such relationships indicate presence of expiratory flow limitation at rest and during exercise. Insp, inspiration.

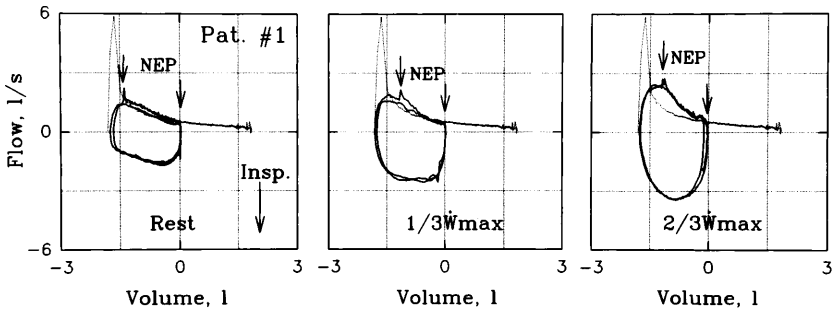


Fig. 5. V̇-V curves, as in Fig. 2, from *patient 1* with chronic obstructive pulmonary disease (forced expired volume in 1 s = 45% predicted). With NEP, flow increased at rest but not during exercise, indicating that expiratory flow limitation was present at both levels of exercise but not at rest. With conventional test, patient would be classified as flow limited at rest and during exercise.

enon was also related to the postinspiratory activity of the inspiratory muscles (PIIA) (19, 27). Indeed, even if the magnitude and rate of decay of PIIA were the same with and without NEP, Pes at any given lung volume should be lower with NEP, because, as a result of faster exhalation, PIIA has less time to decay. Thus, also in the subject without flow limitation, there was no evidence that NEP elicited appreciable changes in activity of the respiratory pump muscles. Similar results were found in the other two subjects in whom Pes was measured.

According to the NEP results, our 14 COPD patients could be subdivided into four groups: *1*) flow limited from rest ($n$ = 5), *2*) flow limited from one-third $\dot{W}_{max}$ ($n$ = 4), *3*) flow limited from two-thirds $\dot{W}_{max}$ ($n$ = 3), and *4*) not flow limited up to two-thirds $\dot{W}_{max}$ ($n$ = 2). Assessment of flow limitation based on comparison of tidal with maximal flow-volume curves yielded different results (Table 3). With the conventional method, nine COPD patients would have been classified flow limited at rest, whereas with NEP flow limitation was present in only five of the COPD patients. Similarly, at one-third $\dot{W}_{max}$, 12 patients were flow limited according to the conventional method but only 9 were flow limited with NEP. Furthermore, one patient who was not flow limited according to the conventional method was found to be flow limited with NEP. Thus, at one-third $\dot{W}_{max}$, consistent results were obtained with the two methods in only 8 patients, whereas consistent results were found in 10 patients at two-thirds $\dot{W}_{max}$.

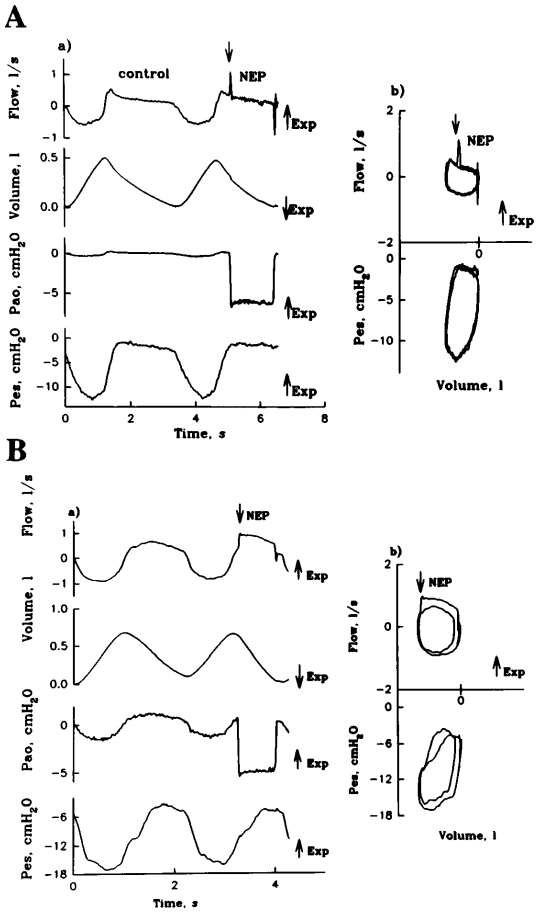


Fig. 6. Time course of flow, volume, Pao, and esophageal pressure (Pes) during a control breath (*a*) and subsequent expiration with NEP, together with corresponding flow-volume and Pes-volume relationships (*b*), at rest from a flow-limited patient with chronic obstructive pulmonary disease (*A*) and a normal subject (*B*).

In all our COPD patients who were flow limited from rest or one-third $\dot{W}_{max}$, flow limitation at two-thirds $\dot{W}_{max}$ encompassed >60% of the VT (flow-limited range 64–78% VT; Fig. 5). In contrast, in the three patients who became flow limited only at two-thirds $\dot{W}_{max}$, flow limitation at this level of exercise was 13–55% of control VT.

The presence of flow limitation at rest implies that the increased ventilation during exercise should be associated with dynamic pulmonary hyperinflation (25, 26). Indeed, in our COPD patients who were flow limited at rest, the EELV increased significantly at both exercise levels studied (Fig. 7, *left*). Similarly, in the patients who became flow limited at one-third $\dot{W}_{max}$, there was a significant increase in EELV only at two-thirds $\dot{W}_{max}$ (Fig. 7, *middle*). In contrast, in the other patients there was no significant change in EELV over the entire exercise range studied (Fig. 7, *right*).

Table 3. *Comparison of NEP and conventional method of detecting expiratory flow limitation in COPD patients*

| Method | | | Exercise Level | |
|---|---|---|---|---|
| NEP | Conventional | Rest | 1/3 $\dot{W}_{max}$ | 2/3 $\dot{W}_{max}$ |
| FL | FL | 5 | 8 | 10 |
| NFL | FL | 4 | 4 | 2 |
| FL | NFL | 0 | 1 | 2 |
| NFL | NFL | 5 | 1 | 0 |

NEP, negative expiratory pressure; Conventional, method based on comparison of tidal and maximal expiratory flow-volume curves; FL, flow limited; NFL, not flow limited; $n$ = 14.

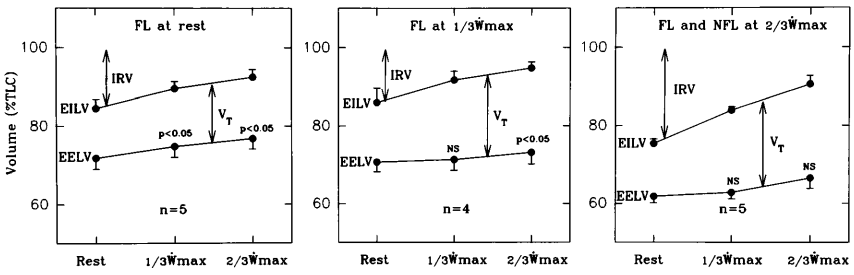


Fig. 7. Subdivisions of lung volume, expressed as percentage of total lung capacity (TLC), at rest and different exercise levels in 3 groups of patients with chronic obstructive pulmonary disease: flow limited (FL) at rest, flow limited at one-third $\dot{W}_{max}$, and flow limited or not flow limited at two-thirds $\dot{W}_{max}$. ●, Average values; error bars, SE.

The five COPD patients who were flow limited from rest exhibited a significantly lower IC (percent predicted) than the other COPD patients (Table 4). If flow limitation is present at rest, with a concomitant decrease in IC, $V_{T_{max}}$ during exercise should also be reduced. Indeed, a very low $V_{T_{max}}$ was a characteristic feature of the five COPD patients who were flow limited from rest (Fig. 8). In four of these patients the low $V_{T_{max}}$ was associated with a low maximal ventilation, whereas severe tachypnea was present in the fifth patient. In all five of these patients the values of $\dot{V}O_{2max}$ (percent predicted) were below the normal range (<80% predicted). In contrast, in only two of the other nine COPD patients was the $\dot{V}O_{2max}$ below the normal range (77 and 78% predicted, respectively). However, there was no significant difference in $\dot{V}O_{2max}$ (percent predicted) among the three groups of COPD patients (Table 4), probably mainly reflecting the small number of patients studied.

In the COPD patients who were flow limited from rest, forced expired volume in 1 s ($FEV_1$) and FVC were significantly more impaired than in the other COPD patients (Table 4). Figure 9 depicts the individual values of $FEV_1$ (percent predicted) of the COPD patients classified according to NEP. Although four of the five patients who were flow limited from rest had severe airway obstruction ($FEV_1$ < 49% predicted), one had only moderate airway obstruction ($FEV_1$ = 63% predicted) (22). Furthermore, a patient with severe airway obstruction was not flow limited at one-third $W_{max}$, and another was not flow limited even at two-thirds $W_{max}$.

Figure 10*B* depicts the $\dot{V}O_{2max}$-$FEV_1$ relationship of the 14 COPD patients and the 4 normal subjects. Although the correlation was highly significant, there was considerable scatter of the data. Less scatter was found when $\dot{V}O_{2max}$ was correlated with $V_{T_{max}}$ (Fig. 10*A*).

## DISCUSSION

The present results indicate that NEP provides a simple and reliable method for on-line detection of expiratory flow limitation at rest and during exercise. Flow limitation at rest is associated with low values of $\dot{V}O_{2max}$ and $V_{T_{max}}$, which are probably mainly due to dynamic pulmonary hyperinflation (3, 21, 26). In agreement with previous results obtained in COPD patients at rest (16), the present study indicates that the conventional method for detecting flow limitation based on comparison of tidal with maximal flow-volume curves is not reliable. Before further discussion of the present

Table 4. *Anthropometric, lung function, and maximal exercise data of COPD patients at each exercise level*

| | FL at Rest | FL at 1/3 $\dot{W}_{max}$ | FL and NFL at 2/3 $\dot{W}_{max}$ | *P* (ANOVA, all groups) |
|---|---|---|---|---|
| Age, yr | 63 ± 12 | 62 ± 8 | 68 ± 5 | NS |
| Height, cm | 163 ± 6 | 171 ± 7 | 166 ± 9 | NS |
| Wt, %pred | 114 ± 12 | 121 ± 33 | 117 ± 19 | NS |
| Gender | 4 M, 1 F | 3 M, 1 F | 3 M, 2 F | |
| FVC, %pred | 60 ± 8 | 77 ± 7* | 97 ± 20* | <0.005 |
| $FEV_1$, %pred | 40 ± 9 | 57 ± 16* | 75 ± 19* | <0.02 |
| $FEV_1$/FVC, % | 50 ± 15 | 52 ± 11 | 56 ± 9 | NS |
| IC, %pred | 66 ± 7 | 73 ± 17* | 100 ± 24* | <0.03 |
| FRC, %pred | 167 ± 52 | 142 ± 25 | 135 ± 23 | NS |
| TLC, %pred | 120 ± 23 | 109 ± 5 | 120 ± 16 | NS |
| RV, %pred | 198 ± 43 | 163 ± 49 | 157 ± 29 | NS |
| RV/TLC, % | 62 ± 9 | 53 ± 8 | 50 ± 5 | NS |
| $\dot{W}_{max}$, W | 73 ± 25 | 94 ± 22 | 105 ± 20 | NS |
| $\dot{V}O_{2max}$, %pred | 69 ± 7 | 92 ± 25 | 95 ± 21 | NS |
| $\dot{V}E_{max}$, l/min | 41 ± 10 | 56 ± 10 | 57 ± 11 | NS |
| $V_{T_{max}}$, liters | 0.99 ± 0.16 | 1.52 ± 0.19† | 1.63 ± 0.17† | <0.001 |
| $f_{max}$, breaths/min | 42 ± 14 | 38 ± 8 | 35 ± 4 | NS |
| $HR_{max}$, beats/min | 131 ± 25 | 134 ± 8 | 152 ± 14 | NS |
| $HR_{max}$, %pred | 92 ± 22 | 86 ± 4 | 98 ± 9 | NS |
| $Sa_{O_{2max}}$, % | 90 ± 4 | 91 ± 2 | 95 ± 2 | NS |

Values are means ± SD. M, male; F, female; $V_T$, tidal volume; f, respiratory rate; $Sa_{O_{2max}}$, maximal $O_2$ saturation; ANOVA, analysis of variance. *$P < 0.05$, †$P < 0.001$ relative to FL at rest.

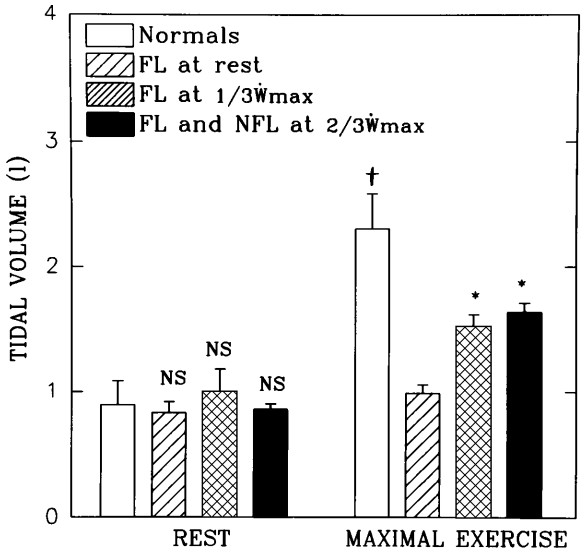


Fig. 8. Average $V_T$ at rest and $\dot{W}_{max}$ of normal subjects and 3 groups of patients with chronic obstructive pulmonary disease. Error bars, SE. *$P < 0.001$, relative to FL at rest. Maximal $V_T$ of normal subjects were significantly higher than those of patients with chronic obstructive pulmonary disease (†$P < 0.001$).

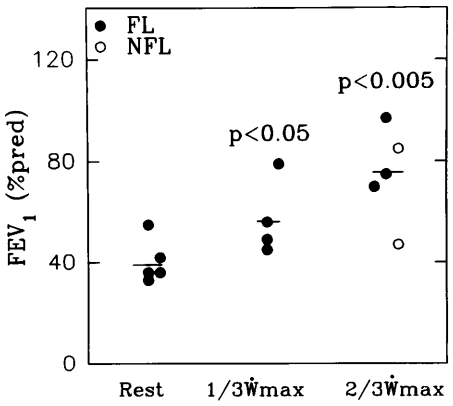


Fig. 9. Individual values of forced expired volume in 1 s ($FEV_1$) of 5 patients with chronic obstructive pulmonary disease who were flow limited from rest, 4 who were flow limited from one-third $\dot{W}_{max}$, 3 who were flow limited from two-thirds $\dot{W}_{max}$, and 2 who were not flow limited up to two-thirds $\dot{W}_{max}$.

results, however, some methodological considerations are required.

*Methodological considerations.* The NEP technique for recognizing flow limitation has been validated in patients during controlled mechanical ventilation by concomitant determination of isovolume flow-pressure relationships (30). These patients, however, were intubated (upper airways bypassed), and respiratory muscle activity was absent. It has been long established, however, that application of NEP to intact (nonintubated) subjects can result in upper airway narrowing and collapse. Suratt et al. (29) measured the ability of the pharyngeal airway to resist collapse in the face of NEP in awake supine patients with OSA. They found that the pressures required to produce collapse ranged from $-11$ to $-40$ $cmH_2O$, which is considerably more subatmospheric than our value of NEP ($-5$ $cmH_2O$). Furthermore, our subjects were studied in the sitting position, and none had a history of OSA or any evidence of upper airway obstruction. Not surprisingly, therefore, we did not find any instance of airway closure in our study. This is in agreement with a previous study in which NEP of $-5$ $cmH_2O$ was applied to COPD patients at rest in the sitting and the supine position (16).

Although there was no airway collapse, application of NEP could have resulted in increased flow resistance due to passive upper airway narrowing. This would imply that the increase in flow with NEP observed in our normal subjects and non-flow-limited COPD patients was in part counterbalanced by a concomitant increase in flow resistance. In the limit, the increase in resistance could be such that, with NEP, expiratory flow would not change at all, and hence the NEP test would not be valid. A similar scenario could be argued in terms of modulation of respiratory muscle activity: in the face of NEP, the expiratory flow could be maintained unchanged by appropriately modulating the respiratory pump muscle activity. However, such perfect and immediate load compensation is highly unlikely and has not been previously reported in the vast literature dealing with respiratory loading (19). Furthermore, our measurements of Pes indicate that NEP does not elicit appreciable changes in activity of the respiratory pump muscles (Fig. 6). In this connection, it should be noted that in humans NEP increases the activity of the upper airway muscles, which tends to maintain the upper airway dilated (12). In this context, it should also be noted that most of our subjects were also studied with different values of NEP (range $-5$ to $-10$ $cmH_2O$). In the non-flow-limited subjects the increase in flow was proportional to NEP magnitude, whereas in the flow-limited patients flow did not change indepedent of NEP value. It should be stressed that in flow-limited patients an increase in airway resistance with NEP should not necessarily result in decreased flow. Indeed, Valta and co-workers (30) used added expiratory resistances to detect expiratory flow limitation and found that in flow-limited patients expiratory flow did not change with added expiratory resistances until this reached a critical value. Such behavior is consistent with flow limitation. Similarly, in flow-limited patients an increase in expiratory pump muscle activity associated with NEP should also result in no change in expiratory flow.

*Flow limitation and exercise performance.* In agreement with previous reports (2, 10, 13), we found that in normal young subjects there is no evidence of expiratory flow limitation during submaximal exercise (up to

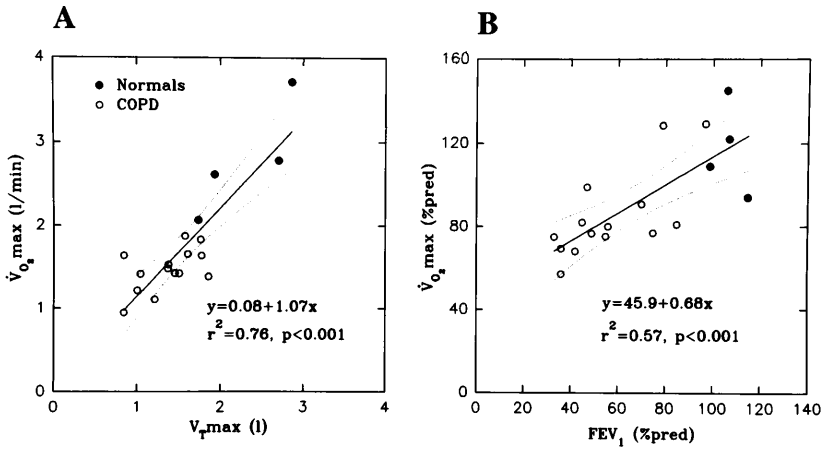


Fig. 10. $\dot{V}O_{2max}$-maximal VT ($VT_{max}$) relationship (*A*) and $\dot{V}O_{2max}$-$FEV_1$ relationship (*B*) in 14 patients with chronic obstructive pulmonary disease (COPD) and 4 normal subjects. Average regression lines and 95% confidence limits are shown.

90% $\dot{W}_{max}$). By contrast, most of our COPD patients were flow limited at rest or during light exercise (one-third $\dot{W}_{max}$). Two COPD patients, however, were not flow limited even at two-thirds $\dot{W}_{max}$. In the patients who were flow limited from rest, the values of $\dot{V}O_{2max}$ were below the normal limits. This was associated with a low $V_{T_{max}}$ (Fig. 8), probably reflecting severe dynamic pulmonary hyperinflation. If flow limitation is present during resting breathing, any further increase in ventilation should result in enhanced pulmonary hyperinflation, which is associated with increased inspiratory work due to intrinsic positive end-expiratory pressure and impaired inspiratory muscle function, and will necessarily limit $V_{T_{max}}$ (3, 21, 26). Indeed, in these patients, pulmonary hyperinflation tended to be more pronounced not only at rest (Table 4) but also during exercise (Fig. 7).

Whereas in all five COPD patients who were flow limited at rest the values of $\dot{V}O_{2max}$ were <80% of predicted, this was the case in only two of the other nine patients. Furthermore, in two of these nine patients, $\dot{V}O_{2max}$ was 129% of predicted. This suggests that, in the patients who are not flow limited at rest, exercise performance is not necessarily limited by ventilatory constraints, as is the case in the patients who are flow limited at rest. This suggests that the abnormally low values of $\dot{V}O_{2max}$ exhibited by two of the COPD patients who were not flow limited at rest (77 and 78% predicted) probably reflect physical deconditioning due to a sedentary life (1).

*Flow limitation and dynamic pulmonary hyperinflation*. Pulmonary hyperinflation is defined as an increase in functional residual capacity (FRC) above predicted normal. This may be due to an increase in the relaxation volume ($V_r$) of the respiratory system resulting from loss of lung elastic recoil (e.g., emphysema) or to dynamic pulmonary hyperinflation, which is said to be present when FRC exceeds $V_r$ (26). Predictably, the group of patients who exhibited expiratory flow limitation at rest had, on average, a higher FRC (percent predicted) and a lower IC (percent predicted) than the other COPD patients (Table 4). This was probably due to dynamic hyperinflation caused by expiratory flow limitation as well as increased $V_r$. The COPD patients who were not flow limited at rest also exhibited an increase in FRC and a decrease in IC, although it was less pronounced than in the other patients. In this case, the hyperinflation probably reflected increased $V_r$, as well as dynamic hyperinflation, which may be present in the absence of flow limitation. This tends to occur when expiration is impeded (e.g., increased airway resistance, persistent contraction of inspiratory muscles during expiration) or when expiratory time is shortened (19, 23, 26). Lung units with slow time constant may exhibit dynamic hyperinflation during resting breathing in the absence of overall expiratory flow limitation. Such regional dynamic hyperinflation may also contribute to the increase in FRC in the COPD patients who are not flow limited at rest.

In agreement with previous studies (1, 10, 17, 21, 25, 28, 32), we found that whereas in normal subjects there was a reduction in EELV with exercise, this was not the case in the COPD patients in whom the changes in EELV were mainly dictated by flow limitation. Indeed, in the patients who were flow limited at rest the EELV increased significantly at both levels of exercise studied (Fig. 7, *left*), whereas in those who became flow limited at one-third $\dot{W}_{max}$ the EELV increased significantly at two-thirds $\dot{W}_{max}$ (Fig. 7, *middle*). In the remaining five patients there was no significant change in EELV with exercise. In this connection, it should be noted that the latter group of patients included two individuals who were not flow limited even at two-thirds $\dot{W}_{max}$. Nevertheless, in both patients the EELV did not decrease with exercise, as in normal subjects. This probably reflects the fact that during exercise in these two patients the lung units with the lowest time constant exhibited dynamic hyperinflation, and, as a result, the overall EELV did not change significantly.

Pellegrino et al. (23) suggested that compression of the airways downstream from the flow-limiting segment may elicit a flow reflex mechanism that influences the breathing pattern by terminating expiration prematurely, thus increasing the EELV. In this way, ventilation may be increased with flow limitation being absent over most of the $V_T$, and hence flow limitation should be found only near end expiration. Results consistent with this hypothesis were found by Babb et al. (1) in patients with mild-to-moderate airflow obstruction. This, however, does not appear to be the case in our COPD patients in whom the values of $FEV_1/FVC$ were lower than those in the patients studied by Babb et al. (53 ± 11 vs. 74 ± 8% predicted). Indeed, in the nine COPD patients who were flow limited from rest or one-third $\dot{W}_{max}$, flow limitation at two-thirds $\dot{W}_{max}$ encompassed 64–78% of $V_T$. Furthermore, in the three patients who became flow limited only at two-thirds $\dot{W}_{max}$, there was no significant increase in EELV, although flow limitation was present over 13–55% of $V_T$. Thus in our COPD patients the increase in EELV with exercise appears to be mainly a passive response to expiratory flow limitation.

O'Donnell and Webb (21) showed that in COPD patients there is a close association between the increase in EELV and the severity of dyspnea. A similar association has been found between the degree of flow limitation at rest and chronic dyspnea (Medical Research Council score) (5).

In conclusion, the NEP method provides a simple and reliable method for detecting expiratory flow limitation at rest and during exercise. The method does not require body plethysmography or the patient's cooperation and coordination and can be applied in any desired body posture. In our COPD patients, flow limitation at rest was associated with impaired exercise capacity mainly due to pulmonary hyperinflation.

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