Evaluation of pulmonary resistance and maximal expiratory flow measurements during exercise in humans

KENNETH C. BECK, ROBERT E. HYATT, PANAGIOTIS MPOUGAS, AND PAUL D. SCANLON
Pulmonary Function Laboratory, Division of Pulmonary and Critical Care Medicine, Mayo Clinic and Foundation, Rochester, Minnesota 55905

Beck, Kenneth C., Robert E. Hyatt, Panagiotis Mpougas, and Paul D. Scanlon. Evaluation of pulmonary resistance and maximal expiratory flow measurements during exercise in humans. J. Appl. Physiol. 86(4): 1388–1395, 1999.—To evaluate methods used to document changes in airway function during and after exercise, we studied nine subjects with exercise-induced asthma and five subjects without asthma. Airway function was assessed from measurements of pulmonary resistance (RL) and forced expiratory vital capacity maneuvers. In the asthmatic subjects, forced expiratory volume in 1 s (FEV1) fell 24 ± 14% and RL increased 176 ± 153% after exercise, whereas normal subjects experienced no change in airway function (RL = 3 ± 8% and FEV1 = 4 ± 5%). During exercise, there was a tendency for FEV1 to increase in the asthmatic subjects but not in the normal subjects. RL, however, showed a slight increase during exercise in both groups. Changes in lung volumes encountered during exercise were small and had no consistent effect on RL. The small increases in RL during exercise could be explained by the nonlinearity of the pressure-flow relationship and the increased tidal breathing flows associated with exercise. In the asthmatic subjects, a deep inspiration (DI) caused a small, significant, transient decrease in RL 15 min after exercise. There was no change in RL in response to DI during exercise in either asthmatic or nonasthmatic subjects. When percent changes in RL and FEV1 during and after exercise were compared, there was close agreement between the two measurements of change in airway function. In the groups of normal and mildly asthmatic subjects, we conclude that changes in lung volume and DIs had no influence on RL during exercise. Increases in tidal breathing flows had only a minor influence on measurements of RL during exercise. Furthermore, changes in RL and in FEV1 produce equivalent indexes of the variations in airway function during and after exercise.

esophageal manometry; forced vital capacity; pulmonary function

THE FUNCTION OF THE AIRWAYS during exercise can be determined in a number of ways. The most common noninvasive method is the maximal forced vital capacity (FVC) maneuver to obtain the forced expiratory volume in 1 s (FEV1) and maximal flows at various lung volumes [e.g., the peak expiratory flow and maximal expiratory flow at 50% of the expired volume (PEF and FEF50, respectively)]. The FVC maneuver has certain drawbacks. It requires good cooperation and a near-maximal effort on the part of the subject, and the effort must be reproducible if comparisons are to be made among various conditions (19). Additionally, the deep inspiration (DI) required for the FVC maneuver may affect airway function, particularly in individuals with asthma (7, 12, 20, 22).

Airway function can also be assessed by using measurements of airway resistance or pulmonary resistance (RL). Airway resistance requires body plethysmography that is difficult to apply to exercising subjects. RL on the other hand can be measured with an esophageal balloon and requires only continuous registration of flow and pressure signals. Both airway resistance and RL are affected by changes in lung volume (5, 6, 16, 25, 32) and by changes in flow (25) at which the measurements are made, the latter due to nonlinearity of the transpulmonary pressure vs. flow relationship. Thus interpretation of RL measurements during exercise should take into account the possible effects of increases in airflow, which could cause overestimation of RL, and increases in lung volume, which could cause underestimation of RL. An additional drawback to RL measurements is the discomfort associated with esophageal balloon placement.

Both RL and the FEV1 have been used to assess responses during exercise in normal subjects and individuals with asthma (3, 21, 28, 31). To our knowledge, only one study has compared the two types of measurements in the same subjects (31). However, this study did not take into consideration possible effects of changes in lung volume or flow.

The major purpose of the present investigation was to compare maximal flows from FVC maneuvers to RL measurements during exercise in normal individuals and subjects with mild exercise-induced asthma. These two estimates of airway function are not necessarily equivalent. During the FVC maneuver, airways are dynamically compressed and static lung recoil is the driving pressure for expiratory flow (24). Airways are rarely compressed during RL measurements, and the pertinent driving pressure is alveolar. We measured RL by two methods, one that should be insensitive to changes in flow and the other that allowed evaluation of the effects of changing flows. We evaluated the possible confounding effects of changes in lung volume on RL measurements, and we evaluated the acute effects of a DI on RL.

METHODS

Subject Recruitment

Nine subjects with a history of exercise-induced asthma and five subjects without asthma were recruited from the local population by general advertisement. All subjects signed a written informed-consent form approved by the Mayo Institutional Review Board. Subjects with asthma were not...
taking inhaled or oral corticosteroid medications and were asked to withhold inhaled β-agonists for 12 h before each study. Subjects in the asthma group were screened for exercise-induced asthma by using an incremental exercise protocol on a stationary cycle ergometer while breathing dry room air as described previously (3). All subjects completed the two additional exercise studies on separate days within a 2-wk period. The subjects with asthma were asymptomatic at the time of study.

Spirometry

Spirometry was performed with the subject wearing a noseclip and connected directly by a mouthpiece to a screen-type pneumotachograph with a ±2 cm H₂O differential pressure transducer. The transducer signal was digitized at a rate of 100 s⁻¹, and the flow data were digitally linearized (34) and then integrated to produce the volume signal. The pneumotachograph was calibrated before each study by using a 3-liter air-filled syringe. Integrated volumes were required to be within ±3% of the syringe volume across a range of flows from ~0.5 to >6.0 l/s. To correct flow and volume measurements to BTPS conditions, expired temperature was assumed to be 28–32°C, saturated (18), the actual value being adjusted to minimize drift in the volume signal (see Rl Measurements).

To perform spirometry, subjects inspired fully, then exhaled forcefully into the mouthpiece for at least 6 s when at rest and for 3 s during exercise. Because of the timing difference imposed on the measurements, vital capacity changes were not reported in this study. FEV₁, PEF, and FEF₅₀ were calculated from the best FVC maneuver. For the purposes of the FEF₅₀ calculations, it was assumed that total lung capacity (TLC) was unchanged by exercise (30); thus comparison was made at the same lung volume below full inflation. Baseline measurements satisfied the acceptability and reproducibility criteria suggested by the American Thoracic Society (27). The maneuver with the largest sum of FVC, FEV₁, and PEF/3 was selected to represent preexercise values. PEF/3 was added to the standard selection criteria to ensure maximal efforts, thus controlling for the inverse effort dependence of FEV₁ (19). To minimize subject fatigue, only one maneuver was required at each time point during and after exercise.

Rl Measurements

Rl was calculated by two methods from raw data streams stored in computer files. We used a digital equivalent of the "electrical subtraction" technique of Mead and Whittenberger (25) (Rl,MW) and an isovolume technique (Rl,iso) similar to that of Frank and colleagues (9). The esophageal balloon placement through the nares into the subject's esophagus has been described previously (2). Transpulmonary pressure (Ptp) was used as the difference between esophageal pressure and lateral air pressure measured at the mouth. Transducers were calibrated before each study. Before data analysis, the BTPS correction factors of the flow and volume signals were adjusted to minimize drift in the volume channel so that the volumes recorded at full inspirations at the beginning and end of each recording were equal. This technique did not take into account possible real drift in the volume signal because of CO₂ production (VCO₂) < O₂ consumption (VO₂). We felt this effect was probably minimal because the subjects were exercised near their anaerobic threshold, where VCO₂ = VO₂.

Rl,MW. From the continuous raw data record of spontaneous breathing, individual breaths were analyzed to determine dynamic lung compliance (Cl,dyn) and Rl,MW by using

\[
\Delta P_{tp} = \frac{\Delta V_L}{Cl,dyn} + V \cdot Rl,MW
\]

where \(\Delta V_L\) and \(\Delta P_{tp}\) indicate the change in lung volume and Ptp during the breath, respectively, and V indicates mouth flow. Cl,dyn was obtained by taking the ratio of the tidal volume to \(\Delta P_{tp}\) between points of zero flow at end inspiration and end expiration. Rl,MW was obtained by linear regression of V vs.

\[
\Delta P_{tp} - \frac{\Delta V_L}{Cl,dyn}
\]

for flow between ±1.0 l/s. Before analysis, data for each breath were inspected on a plot of volume vs. Ptp, and breath volumes that did not match at end expiration compared with at the beginning of inspiration or Ptp signals that showed obvious aberrations (from esophageal spasms or swallowing) were rejected from further analysis.

Rl,iso. The same breaths were used to determine Rl,iso, which was calculated by using

\[
Rl,iso = \frac{Ptp,E - Ptp,I}{V_E - V_I}
\]

where Ptp,E - Ptp,I and V_E - V_I refer to the differences in Ptp and V between expiration and inspiration at a given volume below TLC. Because these points were picked according to the volume, the flow was unconstrained and likely increased with exercise. To assess the effects of increasing tidal breathing flows on Rl,iso, we used isovolume pressure-flow (IVPF) curves to model changes in Rl,iso that would be expected because of the increase in airflows during exercise, as described in the Appendix.

Exercise Evaluations

Exercise studies were performed on an electrically braked stationary cycle ergometer. The inspiratory port of the breathing valve was connected to a large gas bag (weather balloon) that was kept inflated by dry gas from a compressed-air cylinder. Dry air at room temperature has been shown to be nearly as effective as cold, dry air in inducing bronchospasm after exercise (1, 8, 14, 29). All subjects completed an initial screening evaluation as described previously (3), followed on different days by a submaximal exercise study (see below).

Submaximal Exercise

Six-minute periods of constant-load exercise of moderate intensity (60–65% of the subject's maximal capacity, from the initial evaluation) were utilized. After preexercise spirometry, IVPF curve generation, and baseline Rl measurements, the external power output was set to a low value for a 3-min warm-up period, followed by 6 min at the target exercise intensity and finally 3 more min at low intensity for a cool-down period. Two 3-min continuous recordings of mouth flow, integrated volume, and pressures were obtained, starting 1.5 min before power output was increased to the target level and starting 1.5 min before cool-down. A full inflation to TLC followed by an FVC maneuver was performed at the beginning and end of these recordings to obtain the reference volumes at full inflation used for drift correction and for spirometry data. Thus each 3-min recording interval spanned a change in exercise intensity and allowed determination of spirometry and Rl late in warm-up, early and late in exercise, and early in the postexercise period. Spirometry and 2-min
recorderings were also obtained at 5, 10, and 15 min after exercise.

DI

The effects of DI associated with spirometry on RL,iso and RL,MW were evaluated at rest, at the beginning of the two 3-min recording intervals, and postexercise. The effects of DI were determined by using paired t-tests on the differences in 4- to 6-breath averages of RL taken before and within 60 s after the DI.

Statistical Analysis

Comparisons between phases of exercise within individuals were made by using paired t-tests. Unpaired t-testing was used to test for differences in preexercise spirometry between the asthmatic and nonasthmatic groups. Both P < 0.05 and P < 0.01 are listed in RESULTS.

RESULTS

Physiological Characteristics of Subjects (Table 1)

Compared with the nonasthmatic subjects, the asymptomatic asthmatic subjects had lower expiratory flows (P < 0.01), particularly FEF50, and there was a nonsignificant tendency for the asthmatic subjects to have higher RL,MW and RL,iso (P > 0.1). The asthmatic subjects experienced a drop in FEV1 averaging 14% (P < 0.01) and an increase in RL,MW of 176% after exercise at 60%-65% of their maximal work rate. Normal subjects showed no significant change in either FEV1 (±4 ± 5%) or RL,MW (±3 ± 8%).

Effects of Lung Volume on RL

The effects of lung volume on RL were evaluated by plotting the inverse slope of the preexercise IVPF curves (1/K, Eq. A1 in the APPENDIX, which has units of resistance) against lung volume below TLC (Fig. 1). In only one subject was the slope of the IVPF curve strongly dependent on lung volume. The lung volumes at which RL,iso data were obtained at rest and exercise are indicated on the volume axes (R and Ex, respectively). In two subjects in each group this volume increased by ~0.4 liter during exercise, which had little effect on resistance. Expected changes in RL over a comparable volume range (indicated by dotted lines) assume that airways expand homogeneously with lung parenchyma and changes in tissue resistance are minimal (15).

Effects of Changing Airflows on RL

Figure 2 compares mean values for RL,iso (circle), RL,MW (square), and the modeled change in RL,iso (dotted lines; based on IVPF curves, APPENDIX) during exercise and in the postexercise period. In both asthmatic and nonasthmatic subjects, RL,iso increased slightly during exercise compared with preexercise, but the increase in RL,iso did not attain significance in either group (P > 0.10). RL,MW stayed constant in the asthmatic subjects but fell slightly (P < 0.05) in the normal subjects. RL,iso was expected to increase slightly with increasing tidal breathing flows, on the basis of the shape of the IVPF curve (dashed curve). Note that RL,MW is determined in a constant range of flow (~1 l/s) and is therefore not expected to be affected as much by changes in tidal breathing flows. After exercise, the marked increase in

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Values are means ± SD, n, No. of subjects. FVC, forced vital capacity; PEF, peak expiratory flow; FEV1, forced expiratory volume in 1 s; FEF50, forced expiratory flows at 50% of exhaled FVC; RL,MW and RL,iso: pulmonary resistance by Mead and Whittenberger (25) and isovolume technique, respectively; IC, inspiratory capacity. Predicted (Pred) values from Miller et al. (26) and Knudson et al. (17).

* Significant difference between groups, unpaired t-test, P < 0.01.
R_{L,iso} and R_{L,MW} in the asthma group demonstrates induced bronchoconstriction. In the normal subjects, R_{L,iso} followed the pattern predicted by the IVPF curve model after exercise, indicating no overall change in airway function, and R_{L,MW} returned to preexercise values.

Effects of DI on RL

The average R_{L,MW} and R_{L,iso} before and 30–60 s after DI at rest and during and after exercise are shown for each group in Fig. 3. In eight of the nine asthmatic subjects, DI caused a slight increase in R_{L,MW} and R_{L,iso} before exercise, although both changes just failed to reach significance by paired t-test (P > 0.05). DI caused a transient but statistically significant decrease in R_{L,iso} and R_{L,MW} when measured 15 min after exercise in the asthmatic subjects.

Changes in Forced Expiratory Flows and RL During and After Exercise

Mean data for spirometric variables are shown in Fig. 4. In the asthma group, there was a nonsignificant trend for forced expiratory flows to increase during exercise but a significant decrease in flows (FEV_{1}, −24 ± 14%) occurred after exercise. A possible mechanism for an increase in forced expiratory flows would be a slightly reduced effort by the subjects, leading to paradoxical increase in flows (19). The
average Ptp generated by the asthmatic subjects at PEF were the same during exercise (−114 ± 50 cmH₂O) compared with preexercise (−115 ± 48 cmH₂O), indicating a similar degree of effort in the early part of the forced expiratory maneuver in both conditions. The normal subjects showed a transient decline in FEV₁ at one point during exercise (P < 0.05) not reflected in the PEF or FEF₅₀, but no significant changes were seen after exercise.

Mean data for RL are shown in Figs. 2 and 3. The changes in RL,iso and RL,MW in the asthma group were small and not statistically significant during exercise, similar to the spirometry data. The asthmatic subjects experienced a considerable increase in both RL,iso and RL,MW after exercise (RL,MW 176 ± 153%), also consistent with the decline in spirometric flows. There was good agreement between the two indexes of changes in airway function during and after exercise (r² = 0.58, P < 0.01) (Fig. 5).

**DISCUSSION**

Our results showed 1) there was no consistent effect of changes in lung volume on measurements of RL during exercise in subjects either with or without mild asthma; 2) with exercise, the slight increase in RL,iso was consistent with the increase in tidal breathing flows and the nonlinearity of the pressure vs. flow relationship, indicating no actual change in airway

Fig. 4. Values (means ± SD) for forced expiratory volume in 1 s (FEV₁; top), peak expiratory flow (PEF), and maximal expiratory flow at 50% of rest FVC (FEF₅₀; bottom) in asthmatic (A) and nonasthmatic subjects (B). Significant differences compared with preexercise: *P < 0.05; **P < 0.01 (paired t-tests).

Fig. 5. Percent changes compared with preexercise in FEV₁ compared with percent changes in RL,MW during and after exercise in asthmatic subjects. Each data point represents 1 observation in 1 subject. Data for nonasthmatic subjects, which would form a cluster of points around (0,0), are not shown for clarity. Heavy diagonal line, linear regression (r² = 0.57).
function; 3) DI caused a small transient decrease in RL after exercise in the asthmatic subjects but had little immediate effect on RL during exercise in either group of subjects; 4) RL,iso and RL,MW gave similar results; and 5) changes in RL and FEV₁ indicated similar changes in airway function during and after exercise.

Effects of Lung Volume on RL

Because of the mechanical interdependence of airways and lung parenchyma, increasing lung volume increases the tethering forces on intraparenchymal airways, resulting in an expected decrease in RL as lung volume increases (15). We found little effect of increasing lung volume on RL in the limited volume range encountered during exercise. The resistance vs. volume relationship in our study was derived from IVPF curves constructed from near-vital capacity breaths with varying flows rather than from tidal breathing. To our knowledge, no one has reported effects of lung volume on RL by using this technique. Whether upper airway effects or other technique differences account for the generally smaller effect of lung volume in our study compared with previous studies remains to be determined.

Effects of Increasing Flows on RL,iso

Several studies have demonstrated the nonlinear relationship of Ptp to flow at any given lung volume (11, 24, 25). The increasing flows of exercise would be expected to increase RL, although the amount of this increase has not been previously measured. By referring to IVPF curves generated before exercise, we documented the degree to which the increasing flows of exercise should increase RL,iso. The increase in RL,iso found was small in our subjects and of a magnitude predicted by the nonlinearity of the pressure-flow relationship. In subjects with more advanced lung disease, the effect of increasing flow is likely to be larger because of the increased curvature of the IVPF curve in the lower flow range (11, 32).

In studies using RL measurements where substantial increases in flow are encountered, either of two approaches can be used. Measurements of RL can be restricted to low inspiratory and expiratory flows, as in the Mead and Whittenberger technique (25). Alternatively, the IVPF curve technique described in this study can be employed to document the effect of increasing flows.

Effects of DI on Lung Function During Exercise

A potential problem in assessing airway function by spirometry is that the DI required for the maneuver may induce either transient bronchodilation or bronchoconstriction (7, 10, 12, 22). We investigated the effect of DI on assessment of airway function by measuring RL before and after each DI associated with the FVC maneuvers. DI decreased RL 15 min after exercise in the asthma group. However, there was no consistent change in RL in the 30- to 60-s period after each DI during any other phase of the study in either group of subjects. We have no information on whether our results apply to subjects with more severe asthma or other forms of obstructive lung disease.

In an additional separate study in the same nine asthmatic subjects, we compared the pattern of RL,MW change before, during, and after exercise when no FVC maneuvers were performed. The pattern of changes was not statistically different from that in Figs. 2 and 3 (data not shown).

Airway Function During Exercise

Results from previous studies by using a variety of methods do not provide a consistent picture concerning changes in airway function during exercise in either normal subjects (13, 16, 30, 33) or subjects with asthma (3, 21, 28, 31). A major purpose of this study was to
compare R L and maximal expiratory flows during exercise in normal and mildly asthmatic subjects. Both measurements indicated similar patterns of change in airway function (Figs. 2–4), namely, no consistent change during exercise in either group and bronchoconstriction in the asthmatic subjects after exercise.

The inconsistency in results among the various studies of airway function during exercise may be related, in part, to differences in technique. Three groups reported a dramatic fall in R L during exercise in normal subjects by using techniques that require the subject to increase respiratory rate (16, 21, 33). Two of these reported that the reduction in R L was blocked by treatment with anticholinergic drugs but was not affected by treatment with β-blockers. In contrast, studies reporting R L, MW or R L, iso measured during spontaneous breathing all report no change in R L during exercise in normal subjects (28, 30, 31), results that are similar to ours using the same technique. When taken together, the results from these studies suggest that there may be a vagally induced increase in R L caused by panting before exercise (16, 33) but that during exercise, vagal tone is abolished and airways are maximally dilated. These reflex changes in airway function do not occur during unconstrained breathing. Two studies have reported R L, MW measurements in asthmatic subjects during exercise with mixed results. Stirling and colleagues (28) reported a 20% fall in R L, MW during exercise of up to 12-min duration, and Suman and co-workers (31) documented an early fall in R L, iso, but by 5 min of exercise R L, iso had returned to preexercise levels. The latter result is similar to the changes we documented after 5 min of exercise. We can only speculate that the differences among these studies in asthmatic subjects can be caused by differences in the populations studied, the level of exercise attained, or exercise modality (Stirling and colleagues and Suman and co-workers used treadmill exercise). In addition, small differences in exercise protocol could account for some of the differences. We included a 3-min warm-up period before increasing intensity to the target level, which may not have been included in other protocols.

The use of spirometry to document changes in airway function during exercise has been criticized because of the possible inability of subjects to perform maximal expiratory maneuvers during strenuous exercise (23). We did not find this to be the case. The Ptp values generated by the asthmatic subjects at the time of PEF were not different during exercise compared with preexercise, indicating that subjects are capable of providing adequate effort to perform spirometry during exercise. Furthermore, the FEV 1 data were not affected by the effort dependence that has been documented in patients with chronic obstructive lung disease (19). Thus, despite the differences in lung mechanics during resistance and maximal expiratory flow measurements, the results were similar with either technique.

APPENDIX

To quantify the effect of increasing flow during exercise, we calculated R L, iso by using preexercise IVPF curves [R L, iso (model)] as follows. We obtained a series of IVPF curves at rest for each subject (Fig. 6). Then we could plot the exercise flows (V) used in the R L, iso measurement on a graph of the preexercise IVPF curve obtained at the same lung volume. If the measured R L, iso increased during exercise but the Ptp vs. V data fell on the control IVPF curve, then the increase in R L, iso would be due to the nonlinearity of the pressure-flow relationship and would not represent bronchoconstriction. Data not falling on the control IVPF curve could reflect either bronchoconstriction or bronchodilation. Thus the method documents the increases in R L secondary to increases in flow. It also controls for increases in lung volume by referring to isopleths of constant volume below TLC. The changes in resistance estimated from the IVPF curves are indicated in Fig. 2 (dotted lines). The slight increase in R L, iso(model) was close to the measured increase in R L, iso, indicating no change in airway function occurred.

Before exercise, subjects generated IVPF curves as described previously (4). With the esophageal balloon in place, the subject performed nearly full vital capacity inspiratory and expiratory maneuvers with increasing effort. This procedure was repeated as many times as needed to cover inspiratory and expiratory flows from <0.5 to >4.0 l/s over most of the volume range from ~80% TLC to near residual volume. The resulting V and lung volume signals were adjusted to minimize drift in the volume signal as described above. A family of IVPF curves was constructed by plotting Ptp and V values at constant volume levels, several of which are shown in Fig. 6. To use these data for calculation of R L, iso(model), lines were fitted to the data for each volume level in each subject by an iterative fitting procedure that minimized the mean square deviation from the equation

$$P_{tp} = K_1 \cdot V_E + K_{2,E} \cdot V_E^2 \ (\text{expiratory flow})$$

(A1)

$$P_{tp} = K_1 \cdot V_I + K_{2,I} \cdot V_I^2 \ (\text{inspiratory flow})$$

where K 1 indicates the inverse slope of the IVPF curve around zero flow. K 2,E and K 2,I are separate parameters fitted to the expiratory and inspiratory portions (i.e., V E and V I), respectively, that added curvature. By using Eq. 1, a pair of Ptp EIVPF and Ptp IIVPF points could be determined from the measured V E and V I that had been used to calculate R L, iso. By using these estimated pressures, R L, iso(model) was calculated from

$$R_L, iso(model) = \frac{P_{tp, EIVPF}(V_E) - P_{tp, IIVPF}(V_I)}{V_E - V_I}$$

(A2)

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Address for reprint requests and other correspondence: K. C. Beck, Pulmonary Function Laboratory, Division of Pulmonary and Critical Care Medicine, Mayo Clinic and Foundation, Rochester, MN 55905.

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