

Measurement of Lung Diffusion and Cardiac Output with a Single Breath Gas Absorption Method During Graded Exercise Testing: Reference Values for Clinical Testing

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Abstract: Measurement of lung diffusion and cardiac output with a single breath gas absorption method during graded exercise testing: reference values for clinical testing.

Objective: The evaluation of ventilation and gas exchange has become a standard part of clinical exercise testing. We sought to assess the practicality of integrating measurements of lung diffusion for carbon monoxide (D_LCO) and non-invasive cardiac output (using pulmonary capillary blood flow Q_C) into our clinical graded exercise tests. Our objective was to define the responses in normal subjects so that impairment could be detected in patients suspected of having pulmonary or pulmonary vascular disease despite normal resting D_LCO and Q_C . We conducted incremental exercise tests on 20 normal volunteers at 6 levels of exercise ranging between rest and 75% of their measured maximum. The investigational method is based on absorption of CO (for D_LCO) and acetylene (for Q_C) into the pulmonary circulation during a single slow exhalation. The subjects averaged 35 years of age with a maximum work capacity of 76% of predicted maximum.

Results: The values increased linearly with workload (Q_C in L/min = $3.5 + 6.5 \cdot VO_2$ in L/min, and D_LCO in ml/min/mmHg = $18.7 + 10.2 \cdot VO_2$ in L/min). From baseline levels the Q_C increased more than two-fold and the D_LCO increased by 50%. The mean deviation of individual measurements from the patient's regressed response was 9.9% and 6.6% respectively.

Conclusions: We found the procedure easy to include in our standard graded exercise protocol and the single breath technique readily performed. Normative values were obtained for measurements expressed as a percentage of individual maximum and as actual VO_2 . At a moderate level of exercise (VO_2 1.0 liter) the D_LCO and Q_C should increase at least 20% and 65% respectively above baseline. Since the response of Q_C and D_LCO to progressive exercise offers pathophysiological information of clinical interest, its application can now be characterized in patients with different disorders including those with normal resting Q_C and D_LCO .

Keywords: Cardiopulmonary exercise testing, diffusing capacity of the lung, cardiac output, single breath gas absorption, pulmonary capillary blood flow.

INTRODUCTION

The concept of evaluating the integrated responses of ventilation, circulation and skeletal muscle to exercise is well accepted [1, 2]. During graded exercise testing (GXT), measurements of heart rate, ECG rhythm/morphology, ventilation, metabolic responses and gas exchange are now standard. Measurements of cardiac output and lung diffusion (D_LCO) during GXT would be of great interest but are far less frequent because of technical difficulties. Cardiac output is frequently measured before and after many therapeutic interventions, usually by invasive techniques. Pulmonary capillary blood flow (Q_C) is similar to cardiac output in the

absence of cardiac or pulmonary anatomical shunts. An easily performed non-invasive estimate of Q_C during graded exercise would be well suited to serial studies of patients treated medically for heart failure or after surgical procedures including left ventricular assist and heart transplant. Evaluation of the expected increase of D_LCO with exercise can illuminate the mechanism for exercise intolerance in patients with normal or near normal D_LCO at rest. This is a common problem in pulmonary and occupational medicine. In two large groups of patients with minimal interstitial lung disease (asbestosis [3] and sarcoidosis [4]) studies by the senior author found failure to decrease deadspace ventilation during GXT to be the most sensitive indicator of disease. This requires an arterial line and serial sampling during progressively more intense exercise. Serial non-invasive measurements of D_LCO , demonstrating failure to recruit and expand the pulmonary capillary bed, would be similarly useful. Studies of Q_C and

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D_LCO during GXT have suggested their promise as prognostic indicators [5-8].

A steady exhalation single breath method for measuring Q_C and D_LCO is commercially available as a research tool (SensorMedics Vmax System, Yorba Linda, California). The integration of these measurements into a system used for graded cardiopulmonary exercise testing suggested the possibility of measuring changes in Q_C and D_LCO throughout a standard GXT. Most single breath measurements of Q_C and D_LCO have been made in steady state exercise. One such study tested subjects during successive stages following return to baseline, but two to three days were necessary to complete each study [9].

To evaluate this feasibility, GXTs using a bicycle ergometer were conducted incorporating the Q_C and D_LCO measurements along with traditional ventilatory and gas exchange parameters in 20 normal volunteers. The increases in Q_C and D_LCO at progressive workloads (expressed both as a percentage of maximum VO₂ and as VO₂ in L/min at standard levels) in these normal subjects provide guidelines for assessing these responses in patients.

MATERIALS AND METHODS

Description of Technique

The "intradbreath" (IB) method employed in this study has been compared to invasive methods [10-12] and its use demonstrated during steady state exercise [9, 13, 14] and ramp protocols [15]. The IB technique measures the absorption of acetylene (for Q_C) and carbon monoxide (for D_LCO) continuously, using a rapid response infra-red analyzer, during a single steady exhalation. Readings are normalized for lung volume with the use of a third, inert gas, methane. The calculations are based on gas measurements from the alveolar plateau of exhalation, which is clearly

demonstrated with the rapid gas analyzer. This single breath method does not require a breath hold. Exhalation following a full inhalation must be maintained at a steady flow of less than 1 L/sec for greater than 3 seconds after clearing the dead space (Fig. 1). This is accomplished by proper coaching and the use of a slight expiratory resistance. The theoretical basis of the method is fully described in previous reports [9, 10].

The 20 tests were conducted on normal subjects. Prior to the GXT, which included the investigational IB measurements, each subject performed standard pulmonary function tests and a standard maximal GXT. For each investigational GXT, six work loads were selected starting at rest and proceeding in similar increments to a goal of 75% of that subject's maximum VO₂. These work loads were equivalent to 31%, 42%, 53%, 64% and 75% of the VO₂max. The IB measurements were made at each of these six standardized levels, so that the response to increasing work load could be evaluated with regard to actual work load (expressed as VO₂ in liters/min) as well as standardized to each subject's maximum VO₂ (expressed as a percentage of maximum VO₂) [2]. A single IB measurement of Q_C and D_LCO was made during the last minute of a three minute interval at each work level.

The data shown graphically in Fig. (1) were displayed following each test to assure that expiratory flow was steady and < 1 liter/minute, that dead space had been cleared, and that gas concentrations were stable and measured over the appropriate interval, 25%-75% of the exhaled vital capacity.

Selection of Subjects

Subjects were recruited from the medical and technical staffs of Mary Immaculate Hospital, Jamaica, NY and reflected their ethnic, age and gender distribution. All subjects considered themselves reasonably fit and active but

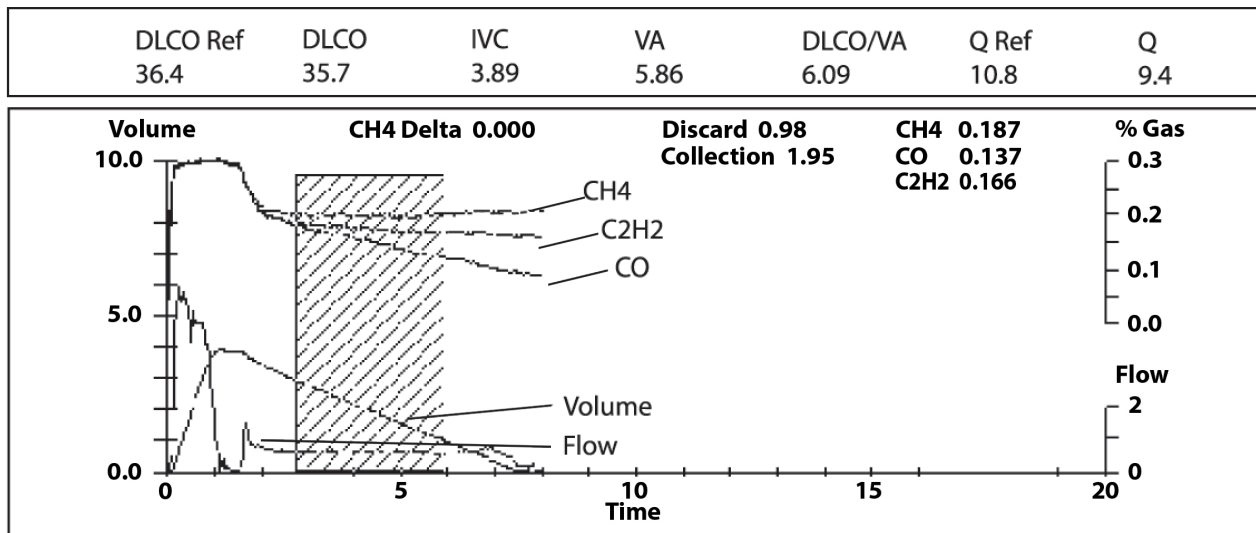


Fig. (1). Intradbreath maneuver. The display depicts a successful Intradbreath maneuver at 60 watts of steady state exercise. IB-D_LCO = 35.7 and IB-Q_C = 9.4. Lung Volume is on the left axis, while the right axis indicates the gas concentrations and expiratory flow rate. The hatched area indicates the period of exhalation selected by the computer for analysis; after discarding 0.98 liters of dead space sample, steady slow exhalation of 1.95 liters over approximately 3.3 seconds was evaluated. Generally, a steady expiratory flow of less than 1 liter per second for a minimum of 3 seconds after clearing dead space is required for a reliable measurement. The operator can override the computer selection.

not athletic and were free of any significant medical disorder. Informed consent was obtained and the study was conducted under the supervision of the Institutional Review Board of Mary Immaculate Hospital.

Evaluation Methods

Differences between means of Q_C, D_LCO and VO₂ at the six workloads were evaluated using t-tests, pooled or paired as appropriate. Linear regression equations describing the increase of Q_C and D_LCO with exercise were calculated for each patient, and then averaged for the population. Variation among regression responses to exercise were evaluated using 95% confidence limits. A p<0.05 was prospectively defined as statistically significant. Unless indicated otherwise ± denotes standard deviation. All descriptive and comparative statistics were calculated using either Microsoft Excel (Microsoft Corporation, Redmond WA) or SPSS 11.0 (SPSS, Inc. Chicago, IL).

RESULTS

The demographics, pulmonary function, and GXT results of the subjects are described in Table 1. The subjects' ages ranged between 25 and 62 years. Seven of the 20 subjects were female; 11 were of Asian origin. Subjects were of normal height and weight. Their pulmonary function was characterized as low normal [16, 17]. This is consistent with the ethnicity of a majority of them since many Asian ethnic groups show low normal or slightly decreased values when compared to pulmonary function predicted values for Caucasians. Their fitness was typical of normal unconditioned adults with a maximum VO₂ of approximately 27 ml/min/kg and a normal anaerobic threshold. Baseline data were complete for all subjects. Only 3 subjects did not complete the appropriate IB expiratory maneuver at one single stage of exercise; this was due to a temporary obstruction in the gas sample line.

Table 1. Characteristics of the 20 Subjects Performing Graded Exercise Tests

	Mean	sd	Range
Age	35	10	25-62
Gender % Female	35		
Height (cm)	169	9	138-163
Weight (kg)	72	14	50-110
FVC (% predicted) [16]	94	12	78-107
FEV1 (% predicted) [16]	90	12	74-110
D _L CO (% predicted) [17]	95	16	69-126
VO ₂ - max (ml/kg/min)	27	7	19-46
VO ₂ - max (L/min)	1.96	0.66	1.11-3.10
VO ₂ -max (% predicted) ²	76	18	38-110
VO ₂ -AT (ml/kg/min)	16	4	10-24
VO ₂ - AT (L/min)	1.16	0.37	.75-1.99
VO ₂ - AT (% predicted max) ²	46	11	22-69
HR max	167	14	150-194

AT= anaerobic threshold, HR= heart rate (beats/min).

The results of the investigational GXT for the six stages of exercise are described in Table 2. The tests covered a range from rest (VO₂ = 0.35 ± 0.11 L/min) to 76% ± 13% of maximum (VO₂ = 1.43 ± 0.38 L/min). There was a statistically significant increase in VO₂ (p<0.001) and pulmonary capillary blood flow (p<0.05) between each successive stage of exercise. The increase in lung diffusion was significant (p<0.05) between all the stages except 2 & 3 and 4 & 5.

Table 2. Graded Exercise Test Results at Six Workloads

Stage	Rest	2	3	4	5	6
% VO₂ max						
mean	19	32	43	55	64	76
sd	5	9	9	12	14	13
VO₂ (L/min)						
mean	0.35	0.59	0.81	1.02	1.20	1.43
sd	0.11	0.16	0.20	0.25	0.32	0.38
VO₂ (ml/kg/min)						
mean	5.0	8.4	11.4	14.4	16.9	20.2
sd	1.7	2.1	2.5	3.0	3.5	4.3
IB-Q_C (L/min)						
mean	5.3	7.7	8.5	9.9	10.7	12.4
sd	1.5	2.2	1.9	2.1	2.5	3.1
IB-D_LCO (ml/mmHg/min)						
mean	21.5	25.5	26.5	29.1	30.5	32.3
sd	4.9	7.3	7.6	7.9	8.2	9.1

IB-Q_C= intrabreath pulmonary capillary blood flow, IB-D_LCO= intrabreath lung diffusion, sd= standard deviation.

The pulmonary capillary blood flow (Q_C) of the group increased more than two-fold from baseline values (95% confidence limits: 205% - 277%). The Q_C response to increased exercise, as determined by linear regression, was:

$$Q_C \text{ (L/min)} = 3.5 + 6.5 * VO_2 \text{ (L/min)}, (r = .81)$$

The lung diffusion increased about 50% above baseline (95% confidence limits: 139% - 163%). The D_LCO response to increased exercise, as determined by linear regression, was:

$$D_LCO \text{ (ml/mmHg/min)} = 18.7 + 10.2 * VO_2 \text{ (L/min)}, (r = .84)$$

Non linear regression did not improve the correlation for either parameter. There was no statistically significant difference in the regression with regard to gender, allowing pooling of the data. The standard error of the response to exercise (i.e., slope) for Q_C and D_LCO was 0.6 L/min and 1.2 ml/mmHg/min respectively.

Because only one measurement of Q_C and D_LCO could be made at each work load, we evaluated the reliability of individual measurements by comparing each of the six measurements to the regression for that subject. The mean variation from the regression for Q_C and D_LCO were

9.9% ± 4.6% and 6.6% ± 3.6% respectively. We also evaluated these differences to determine how many individual measurements were excessively deviant from the regression. Excessive deviation was defined to be 20% or 2 L/min for Q_C and 20% or 5 ml/mmHg/min for D_LCO , whichever was larger. Only 4 measurements of both responses (<4% of the total) met the criteria for excessive deviation.

The increase above resting levels for both Q_C and D_LCO across the range of workloads (expressed as VO_2 L/min) can be seen in Fig. (2). At a moderate workload expressed in VO_2 as liters/minute ($VO_2 = 1.0$ L/m), the D_LCO is expected to increase to at least 120% of resting level and the Q_C to at least 165% of the resting level. The increase above resting levels for both Q_C and D_LCO across the range of workloads expressed as a percentage of maximum VO_2 , can be seen in Fig. (3). At 50% of maximum VO_2 , D_LCO can be expected to increase to at least 120% of resting level and Q_C can be expected to increase to at least 160% of the resting level.

DISCUSSION

Previous studies of exercise response in cardiac output and lung diffusion have used various methods to measure these variables. Several have made these measurements at a single level of exercise characterized by heart rate alone [14, 18]. The intrabreath (IB) technique is well suited to making these measurements during progressive exercise, since it requires only a single deep breath and does not require a fixed breath hold. Its development has been made practical by economical rapid infra-red gas analyzers and increasing computational power, both required for the continuous measurements and complex calculations. It is now available as an option in a standardized commercial instrument.

We made Q_C and D_LCO measurements at 6 stages of exercise ranging from rest to an average of 76% of each

subject's maximum in GXT's in 20 normal subjects. Increases in these measurements reflect the ability of the pulmonary capillaries to distend and recruit during exercise.

We found the Q_C response to increased exercise to be: Q_C (L/min) = 3.5 + 6.5 * VO_2 (L/min). This is consistent with the literature. In 1962 Wade and Bishop characterized the normal response of cardiac output to exercise by a linear increase with increased work, defined by the equation cardiac output (L/min) = 4 + 6 * VO_2 (L/min) (±2 L/min SEE) [19]. Others have suggested normalization for weight (cardiac output (L/min) = .06*wt (kg) +5* VO_2 (± 1 L/min) [2].

The increase in Q_C in our normal subjects using the IB technique during progressive exercise is similar to the increases reported by previous investigators using the rebreathing or IB techniques and different exercise increments. Hsia and coworkers [20] have reported both Q_C and D_LCO (see below) using a rebreathing method in 44 normal subjects at 25%, 50% and 80% of each individual's maximum workload. At 80% of maximum, Q_C increased 134% in males and 100% in females. The magnitude was similar in our study, although we did not note a difference between genders. Wilson [9], using the IB technique at various steady state exercise levels separated by return to baseline in 10 normal subjects, reported Q_C (L/min) = 5.2 + 5.1 * VO_2 (L/min) ± (1.7 L/min SEE), very similar to our Q_C/VO_2 relationship. Huang, MacIntyre and coworkers [14] have used the IB method at a single level of exercise. At a level similar to our stage 4 (which is 55% of maximum VO_2), they reported Q_C increases of 89% for 30 year old men and 102% for 30 year old women, very similar to the 87% we reported for both sexes with an average age of 36 years. More recently, Blevins and coworkers [15], using the Intrabreath technique for Q_C , reported similar regressions for Q_C vs VO_2 to ours and noted that these were stable over time

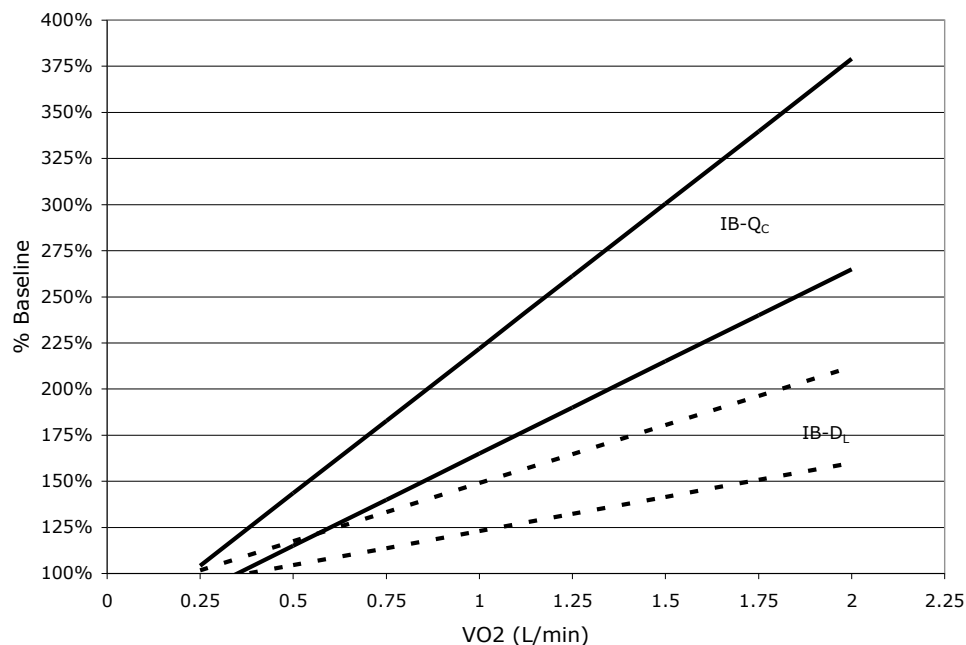


Fig. (2). Response to Exercise (VO_2 ; L/min). The upper two solid lines describe the 95% SEE boundaries of the cardiac output (IB- Q_C) response above baseline to increasing exercise. The bottom two dashed lines describe the 95% SEE for lung diffusion (IB- D_LCO) response to increasing exercise.

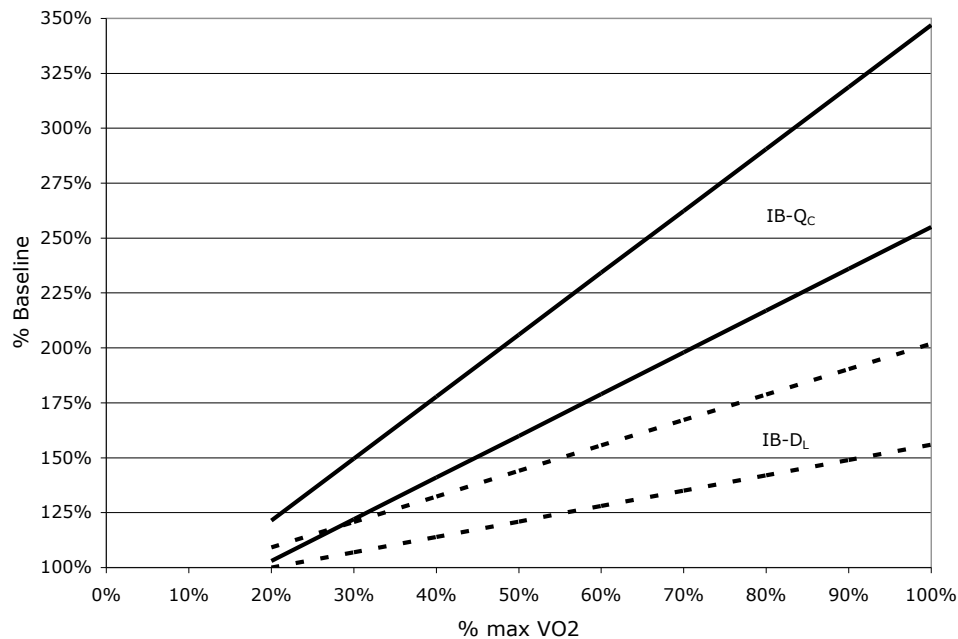


Fig. (3). Response to Exercise (% maxVO₂). The upper two solid lines describe the 95% SEE boundaries of the cardiac output (IB-Q_c) response above baseline to increasing exercise. The bottom two dashed lines describe the 95% SEE for lung diffusion (IB-D_LCO) response to exercise.

and technique (fixed load vs ramp). They did not measure D_LCO .

In patients with cardiac disease, a blunted response to exercise (i.e., less than normal increase with exercise) has been found to be prognostic. In a series of 46 post-myocardial infarction patients, Bigi found that a blunted cardiac output response to exercise at discharge was a better indicator of cardiovascular risk than ECG changes [7]. In a study of 185 heart failure patients using thermal dilution, Chomsky identified the strong independent prognostic value of a blunted cardiac output response to exercise [5]. Resting D_LCO is decreased in heart failure [21], attributable to decreased D_m ; both D_L and D_m correlated with VO_{2max} and inversely with pulmonary vascular resistance.

In our subjects, we found the average D_LCO response to progressive exercise, determined with linear regression to be: D_LCO (ml/mmHg/min) = 18.7 + 10.2* VO_2 (L/min). Hsia *et al.* [20], using the rebreathing method, reported increases of 65% in men and 26% in women at 80% of maximum VO_2 , within a range similar to our results. In three normal subjects, reported by Potts and coworkers, increases in D_LCO measured by the three equation method at 90% of peak exercise, ranged from 61% to 75%, consistent with our regression for this somewhat greater level of exercise [22]. Wilson *et al.*, in a study of 10 fit individuals with the IB technique, reported somewhat higher values at lower levels of exercise, but not as much of a percent increase with increasing exercise. (D_LCO (ml/mmHg/min) = 34 + 7* VO_2 (L/min)) [13]. However, one of their ten subjects, who was the only female and significantly older and less fit, attained levels similar to that seen in our group. Table 2 shows that at 55% of maximum VO_2 , D_LCO in our subjects (mean age 36 years) increased 35% from baseline. Consistent with the results in our population, Haung *et al.* reported a predicted increase of approximately 30% in D_LCO from rest to an

exercise level of 58% of the predicted maximum heart rate, in their study of 100 normal subjects using the IB technique [18]. The predicted increase for a 30 year old male was 33% and for a 30 year old female 24%. These investigators recently reported slightly lower increases in a slightly older study population (mean 40 age years). This increase was 29% in 56 men and 18% in 49 women [17]. Again, we did not observe a gender difference. Kendrick and Laszlo [26] Studied 80 normal subjects evenly distributed by sex and age (from 20-59) and concluded that the rate of increase in D_LCO with increasing exercise is not affected by age and is slightly less in females.

Recent investigators have compared DL for nitric oxide with that for CO during incremental exercise, noting a linear increase in both and a constant ratio for the two measurements [23, 24]. Since D_LNO is not limited by pulmonary capillary blood volume, it is equal to D_M .

Both D_LCO and D_LNO decrease at 2 hours after maximal exercise (to exhaustion) [25], unlike their linear increase during progressive submaximal exercise.

Failure to increase D_LCO during exercise has been reported in a few studies to reflect subclinical pulmonary impairment. Using the IB technique, Mitchell and coworkers found that, in a group of 30 seven year old children, survivors of bronchopulmonary dysplasia were unable to increase D_LCO above resting levels at moderate exercise despite modest increases in Q_C [27]. This inability to increase D_LCO was not seen in either of their control groups of former preterm or term infants. In adults, a recent study noted significantly increased post-operative morbidity associated with failure to improve lung diffusion by more than 10% from rest to high levels of exercise in pre-surgical lung resection patients [6]. Reduction of D_LCO as a consequence of chronic pulmonary hypertension has been

identified as an important factor in the limitation of peak exercise in patients with heart failure [21].

Individual intrabreath D_LCO and Q_C measurements have considerable variability. Similar variability is found in cardiac output measured by other techniques during exercise. Average coefficient of variations of Q_C of 8.7% and 12% using the intrabreath method at rest were reported by Elkayam [10] and Blevins [15]. This is comparable to our experience during exercise, an average deviation from the regression of 9.9% and 6.6% for Q_C and D_LCO respectively. We also found that less than 4% of the individual measurements were excessively deviant. Unfortunately only a single IB measurement of D_LCO and Q_C can be made at each level of exercise when using incremental protocols with stages of 3 minutes or less. Variability can be addressed in two ways. It can be averaged out by looking at the trend in repeated single measurements with increasing exercise as was done in this study or by averaging repeated measurements at fewer more prolonged workloads. Some bias will exist between the IB Q_C , which measures unshunted pulmonary blood flow, and true cardiac output. This bias should be considered in evaluating the results in abnormal populations with the potential for intra cardiac and pulmonary shunts.

We presented our D_LCO and Q_C results in three different metrics. The first approach presented the actual D_LCO and Q_C values increasing as a function of the metabolic workload (VO_2 L/min). The other two approaches compared percentage increases from baseline in D_LCO and Q_C with incremental exercise to absolute workload (VO_2 L/min) and to percent of individual maximum. The latter approach was undertaken to adjust for differences in exercise capacity associated with age, size and gender. Use of response above baseline, while appealing, is limited by the need for careful baseline measurement.

Based on these limitations it would appear that assessment of the slope of the response to exercise (Q_C/VO_2 and D_LCO/VO_2) would be the most useful approach to interpretation. This approach is well suited to making single repeated measurements during an incremental GXT as used in this investigation and by Chomsky [5] or at several levels of steady state exercise as advocated by Jones [2]. Alternatively measurements at rest and at one level of moderate exercise might be used as a simple assessment of response in these variables. Our data show that D_LCO increased by at least 20% and Q_C by at least 50% from resting levels at 50% of maximum, suggesting that we can apply these guidelines to simplify exercise testing. These findings are consistent with the two studies by the Duke group [15, 18]. Using measured VO_2 rather than percentage maximum, similar increases can be expected at 0.9 L/min VO_2 . Several measurements can be made at such a workload to eliminate an aberrant value. Furthermore, these workloads are generally below the anaerobic threshold and thus easily tolerated by most subjects.

CONCLUSIONS

We found the intrabreath procedure easy to integrate into our clinical GXT. Furthermore our results with normal volunteers during incremental exercise, a methodology well suited to clinical practice, were consistent with published

expectations from research protocols using steady state exercise requiring multiple days to complete. Our findings are acceptably reliable to use for clinical reference. While a strong physiological rationale supports the likely prognostic potential of these measurements, there is a paucity of clinical data. We intend, and recommend to others, to include these measurements in the standard diagnostic GXT so that information on pulmonary blood flow and lung diffusion response to exercise in various abnormal populations can be fully characterized.

CONFLICT OF INTEREST

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