INCREMENTAL EXERCISE TESTING IN PLEUROPULMONARY DISEASE DUE TO INHALATION OF INORGANIC DUSTS: PHYSIOLOGIC DEAD SPACE AS THE MOST SENSITIVE INDICATOR

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INTRODUCTION

Evaluation of dyspnea, and of respiratory impairment and disability, is of great social and economic importance, let alone physiologic and clinical interest, in patients thought to have pulmonary and/or pleural fibrosis secondary to inhalation of inorganic dusts.[1-7] The relationship of abnormalities on exercise to those in standard pulmonary function tests (performed at rest) is controversial. Cotes[2] has recently concluded that "loss of exercise capacity cannot be predicted with acceptable accuracy from the 4 commonly used lung function indices (FVC, FEV_1, FEV_1/FVC, D_LCO_{SB}) alone or in combination."

We have correlated FVC and D_LCO_{SB} (henceforth further abbreviated as D_L) with a number of exercise variables (both invasive and non-invasive) in 43 patients undergoing maximal incremental exercise to evaluate likely pulmonary and/or pleural fibrosis due to inhalation of inorganic dusts (in 35 patients, the dust was asbestos). Our results indicate that an abnormal D_L predicts excessive dead space ventilation often present at rest, and conversely, that this abnormality of gas exchange is frequently present even when D_L is normal.

METHODS

Standard pulmonary function tests were performed according to the recommendations of the American Thoracic Society.[8,9] Predicted values for spirometry were modified[10] from an earlier publication of Morris[11] and for D_L CO_{SB} and TLC_{SB} were those separately established by this laboratory[12] for current smokers, ex-smokers and nonsmokers.

Incremental exercise testing was performed using a model 2000 Medical Graphics, Inc., breath-by-breath system which employs a pneumotachygraph to obtain expiratory flows and volumes, an infra-red CO_2 analyzer, and a zirconium fuel cell O_2 analyzer. Exercise was performed on a bicycle ergometer which increments 5 to 25 watts per minute. The patient sat quietly on the bicycle while adjusting to the nose clip, mouthpiece, ear oximeter (Hewlett-Packard model 47201 A), electrocardiographic leads and radial artery catheter. Measurements were then made sitting, during unloaded cycling, during incremental cycling and several times following exercise. Exercise was terminated when the patient was unable to continue (usually limited by dyspnea) or if there were untoward changes in the electrocardiogram, blood pressure or O_2 saturation.

A microprocessor collected flow, F_ECO_2, and F_EO_2 data and computed O_2 consumption and CO_2 production for each breath. A separate computer (TEKTRONIX 4052 A) stored, analyzed and displayed data. Primary measurements included tidal volume, respiratory frequency, inspired and expired O_2 and CO_2 concentrations and heart rate (HR). These allow immediate calculation of such parameters as minute ventilation ($\dot{V}E$), O_2 consumption ($\dot{V}O_2$), CO_2 production ($\dot{V}CO_2$), respiratory equivalent (R; $\dot{V}CO_2$ /$\dot{V}O_2$), VE/$\dot{V}CO_2$, $\dot{V}E$/$\dot{V}O_2$, O_2 pulse ($\dot{V}O_2$/HR) etc. Arterial blood was blood sampled every one to two minutes. Samples were stored in ice and analyzed immediately after the test on a Radiometer model ABL30. Entry of these results permits the system to calculate and print values for dead space ventilation (as a percentage of tidal volume, V_D/V_T) and alveolar-arterial differences for PO_2 (A-aDO_2) during all phases of the test.

Ventilatory response was evaluated as the slope of $\dot{V}E$ vs. $\dot{V}O_2$ before ventilatory anaerobic threshold is reached; excessive values are ≥ 30.[13] Limit values for other tests are: FVC <80% of predicted, FEV_1/FVC <0.70 up to age 59 years and <0.65 beyond age 59, D_L <75% of predicted, $V_D/V_T \geq 0.35$ at rest and ≥ 0.25 on exercise ($\dot{V}O_2$ 1.0L)[14] and A-a DO_2 35 Torr during exercise.[4]

RESULTS

Of the 43 patients tested, 35 were studied because of occupational exposure to asbestos; several of these had normal chest radiographs and one-third had only pleural thickening. Of the remaining 8 patients, 6 were occupationally exposed to hard metal (half had normal chest radiographs) and 2 to beryllium (both had abnormal radiographs). D_L was not available on 4 patients. Dyspnea was equivocal in 9 patients, present in 29 and absent in 5. Because of the small number of patients without dyspnea, correlation with physiologic variables was not possible. It was noted that the 5 patients who did not complain of dyspnea had normal D_L (vs. 14 of the 26 with dyspnea) and 4 of the 5 had normal ventilatory responses (vs. 18 of 27 with dyspnea).

Mean values of the most important pulmonary function tests (FVC, D_L) and exercise variables ($\dot{V}E$ at $\dot{V}O_2$ 1.0L, V_D/V_T at $\dot{V}O_2$1.0L) and of V_D/V_T at rest are shown in Table I.

Table I

Mean Values of Pulmonary Function and Exercise Tests

Variable	Mean	SD
FVC (% pred)	80.2	18.2
D_L (% pred)	80.7	24.9
$\dot{V}E$ 1.0L (L/min)	30.2	9.73
V_D/V_T Rest (x 100)	35.9	8.6
V_D/V_T 1.0L (x 100)	28.8	9.9

Prevalence of Abnormal Test Results (Table II)

Of the patients studied, 18 (of 43) had a reduced FVC (42%), 15 (of 39) a reduced D_L (38%), 10 (of 41) increased ventilatory responses (24%) and 8 (of 41) an elevated A-a DO_2 (20%). The highest prevalence of abnormality was for V_D/V_T at rest and/or exercise (measured at a $\dot{V}O_2$ of 1.0L): 31 of 43 patients (72%). Of these 31, 19 were abnormal under both conditions, 5 at exercise only and 7 at rest only (4 of these did not have exercise values or did not reach a $\dot{V}O_2$ of 1.0L). Hence, 24 of 39 patients (62%) showed abnormal V_D/V_T at exercise and 26 of 43 (60%) did so at rest.

Correlations with D_L (Table III)

Of the 39 patients with D_L, 15 had abnormal values for this test (as stated above):

D_L (percent predicted) showed a moderate correlation with FVC (r=0.315, P 0.05) (Table III). Comparison of abnormal results for the two tests is shown in Table IV. 15 patients had abnormal values for FVC; 8 were abnormal for both tests, 17 normal for both, 7 abnormal only for D_L and 7 abnormal only for FVC.

D_L (percent predicted) correlated with V_D/V_T at rest (r= −0.274, p <0.1) and more strongly on exercise (r= −0.554, p 0.0005) (Table III). Comparison of abnormal results for D_L and for V_D/V_T is shown in Table V. 27 patients had abnormal values for V_D/V_T; 13 were abnormal for both, 10 normal for both, 14 abnormal for V_D/V_T alone and 2 abnormal for D_L alone. Thus, of the 15 patients with abnormal D_L, 13 (87%) had abnormal V_D/V_T yet 14 of the 24 (58%) with normal D_L still had abnormal V_D/V_T.

Only 8 patients had abnormal A-a DO_2 (Table VI); 6 were abnormal for both tests, 22 normal for both, 2 abnormal for A-a DO_2 alone and 8 abnormal for D_L alone. Of the 8 patients with abnormal A-a DO_2, only 2 had a normal D_L.

Only 9 of the 39 patients had abnormal $\Delta\ \dot{V}E/\ \Delta\ \dot{V}O_2$ (Table VII); 5 of the 9 had abnormal D_L.

Correlations with FVC (Table III)

FVC (percent predicted) correlated with V_D/V_T both at rest (r= −0.359, p 0.02) and on exercise (r= −0.436, p <0.006).

Correlations with Exercise $\dot{V}_E$ (Table III)

Exercise $\dot{V}_E$ (at a $\dot{V}O_2$ of 1.0 L[2] showed a weak correlation

Table II

Frequencies of Abnormal Test Results in 43 Patients with Suspect Pleuropulmonary Disease Due to Inorganic Dusts

FVC	42%	(18/43)
(FVC	38%)	(15/39)
D_L	38%	(15/39)
$\dot{V}O_2$ peak < 75% pred	28%	(12/43)
Δ VE/ Δ VO_2	24%	(10/41)
A-a DO2	20%	(8/41)
Resp. Rate > 50/min		0
Resp. Rate > 40/min	21%	(9/43)
V_D/V_T:		
Rest and/or 1.0L	72%	(31/43)
Rest	60%	(26/43)
1.0L	62%	(24/39)

Table III
Pearson Correlation Coefficients for Pulmonary Function and Exercise Tests

	$\dot{V}E$	FVC	D_L	V_D/V_T Rest	V_D/V_T 1.0L
$\dot{V}E$ 1.0L	1.00000	-0.22962	-0.41311*	0.38629*	0.48455*
FVC	-0.22962	1.00000	0.31537*	-0.36191*	-0.44035*
D_L	-0.41311*	0.31537*	1.00000	-0.27351	-0.55392*
V_D/V_T Rest	0.38629*	-0.36191*	-0.27351	1.00000	0.66262*
V_D/V_T 1.0L	0.48455*	-0.44035*	-0.55392*	0.66262	1.00000

* $p \leq 0.05$

Table IV
FVC vs. D_LCO_{SB}

	Abnormal FVC (15)	Normal FVC (24)
Abnormal D_L (15)	8	7
Normal D_L (24)	7	17
No D_L (4)	3	1

with FVC ($r= -0.230$, p 0.15), a strong correlation with D_L ($r= -0.413$, p 0.009) and strong correlations with V_D/V_T both at rest ($r= 0.386$, p 0.0115) and even more so on exercise ($r= 0.485$, p 0.0021).

$\dot{V}O_2$ Max

Of the 43 patients, 31 (72%) were able to reach a peak $\dot{V}O_2$ ≥75% of predicted. The 12 who were not able were more likely to manifest other abnormalities, e.g., 10 had abnormal V_D/V_T (vs. 20 of the 31 with normal $\dot{V}O_2$ max) and 8 had abnormal FVC (vs. 7 of the 31 with normal $\dot{V}O_2$ max). Of the 10 with decreased $\dot{V}O_2$ max who performed D_L, 6 had abnormal D_L (vs. 9 of the 29 with normal $\dot{V}O_2$ max). Nevertheless, 12 of the 18 patients with abnormal V_D/V_T both at rest and on exercise were able to achieve a $\dot{V}O_2$ max ≥75% of predicted.

Respiratory Pattern

No patient reached a respiratory rate > 50 min; 9 (21%) reached a rate between 41 and 50. Nine patients achieved a V_T/VC ratio ≥0.70; 6 of these 9 had normal FVC. The 2 patients whose V_T/VC exceeded 0.80 both had reduced FVC.

DISCUSSION AND CONCLUSIONS

Our goals were to assess (1) "invasive" variables requiring sampling of arterial blood and (2) the responses to incremental exercise both non-invasive ($\dot{V}E$, $\Delta\dot{V}E/\Delta\dot{V}O_2$, respira-

Table V
V_D/V_T vs. D_LCO_{SB}

	Abnormal V_D/V_T (31)			Normal V_D/V_T at rest and at $\dot{V}O_2$ = 1.0L (12)
	At rest and at $\dot{V}O_2$ = 1.0L (19)	At rest only* (7)	At $\dot{V}O_2$ = 1.0L only (5)	
Abnormal D_L (15)	10	1	2	2
Normal D_L (24)	8	3	3	10
No D_L (4)	1	3	0	0

* Includes inability to reach $\dot{V}O_2$ = 1.0L or no sample obtained.

Table VI
A-a DO2 vs. D_LCO_{SB}

	Abnormal A-a DO2 (8)	Normal A-a DO2 (33)
Abnormal D_L (14)	6	8
Normal D_L (24)	2	22
No D_L (3)	0	3

tory rate and tidal volume) and invasive (V_D/V_T, A-a DO_2) compared with standard pulmonary function tests (FVC, D_L). Our patients demonstrated the full spectrum of disease from radiographically inapparent to minimal (1/0 irregular opacities and/or pleural thickening) to advanced diffuse pulmonary fibrosis. Most complained of dyspnea.

V_D/V_T was the most sensitive indicator of abnormality, being increased in 31 of 43 patients (72%), many of whom had normal FVC and/or D_L. The most useful comparison was with D_L; 13 of the 15 patients with abnormal D_L had abnormal V_D/V_T. It may, therefore, be said that a decreased D_L predicts abnormal V_D/V_T and that measuring the latter is then not required to detect disease. However, more than half the patients (58% or 14 of 24) with normal D_L still had abnormal V_D/V_T.

FVC was as likely to be abnormal as D_L (each was decreased in 15 of 39 patients who had both tests, or 38%). Abnormality of one was not very likely to predict abnormality of the other; roughly half the patients with an abnormal FVC had a normal D_L and vice-versa.

A-a DO2 and ventilatory response during exercise were least likely to be abnormal (in 20% and 24%, respectively). Widening of the A-a DO2 was associated with an abnormal D_L. No patient demonstrated a respiratory rate >50/min.

Table VII
$\Delta\dot{V}E/\Delta\dot{V}O_2$ vs. D_L

	Abnormal $\dot{V}E/\dot{V}O_2$ (10)	Normal Δ VE/ Δ VO_2 (31)
Abnormal D_L (15)	5	10
Normal D_L (24)	4	20
No D_L (2)	1	1

About three-quarters of the patients reached a $\dot{V}O_2 \geq 75\%$ of predicted maximum, demonstrating their motivation to perform. Many patients with manifest abnormalities achieved this level of work, e.g., two-thirds (12 of 18) of those with abnormal V_D/V_T both at rest and on exercise.

Of the 31 patients with abnormal V_D/V_T at rest or exercise, this was manifest in the majority (26 patients or 84%) at rest. It may thus be inferred that exercise is not usually necessary to demonstrate this derangement of gas exchange.

$\dot{V}_E$ at an exercise level corresponding to a $\dot{V}O_2$ of 1.0L/min has been advocated as a useful non-invasive measurement which additionally does not require maximal effort.[2] It was strongly correlated with D_L and with V_D/V_T both at rest and even more so at (the same level) exercise. An important consideration is whether anaerobic threshold (AT) has been reached before this level of exercise, which would increase $\dot{V}_E$ non-linearly; almost all our patients had a normal AT, beyond a $\dot{V}O_2$ of 1.0L.

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