Control of Breathing in Children with Interstitial Lung Disease

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Summary

Control of breathing at rest was studied in 14 children (4-16 years old) with interstitial lung disease (ILD). Four of them were tested several times. Breathing pattern and the mouth occlusion pressure ($P_{0.1}$) were measured. Results in ILD children were compared to values in healthy children previously reported. Respiratory frequency and minute ventilation were increased ($P < 0.02$). Inspiratory time (TI) was shortened ($P < 0.001$), the shortening in TI being significantly related to the increase in lung elastance (EL). The ratio of TI to the total duration of the respiratory cycle (TI/TTOT) was lowered ($P < 0.01$). Tidal volume (VT) both in ml and normalized for body weight (BW) was normal. $P_{0.1}$ was higher than predicted. The increase in $P_{0.1}$ was significantly related to change in arterial O_2 pressure (PaO_2) which was reduced in 10 cases. There was a significant relationship between the increase in $P_{0.1}$ and in EL. The increase in mean inspiratory flow (VT_{BW}/TI) was related to the increase in EL. But VT_{BW}/TI was not increased as much as $P_{0.1}$. Consequently the effective inspiratory impedance was enhanced. This high effective inspiratory impedance was related to the increased lung elastance.

Speculation

Increase in the neural drive in ILD children appears to be due to hypoxemia and/or to the increased elastic load. The effects of the elastic load on the control of breathing are probably vagally-mediated.

In adults with interstitial lung disease (ILD) increase in respiratory frequency and minute ventilation have been previously observed suggesting an increased inspiratory drive (13). More recently the mouth occlusion pressure generated 0.1 sec after airway occlusion at the end expiratory level ($P_{0.1}$) was measured in ILD adults and found enhanced (2, 3, 17, 18). Because $P_{0.1}$ is related to the inspiratory neural drive (5, 21), its increase in ILD adults is in agreement with the previous hypothesis (13).

The aim of the present study was to analyze the breathing pattern and to measure $P_{0.1}$ in 14 children with ILD during resting breathing. Changes in control of breathing in ILD children were related to lung mechanics and to pulmonary gas exchange data.

MATERIALS AND METHODS

Fourteen children with ILD were tested. Their age and weight are reported in Table 1. Parental consent for each child was obtained. In all the cases the x-ray data were in favor of ILD. The etiology of ILD was based on histologic (eight cases), immunologic (four cases of hypersensitivity pneumonitis) or viral (two cases) findings (Table 1). Four of them were tested several times (No. 1, 4, 7, 14, Table 1). In all of them pulmonary function tests were performed. Vital capacity (VC), functional residual capacity (FRC), total pulmonary resistance (RL), dynamic and/or static lung compliance (CL) measured in the tidal volume range, lung

transfer factor for CO (TLCO) and blood gases were determined, using methods previously described (7). During the same test the latter parameters and control of breathing were measured.

For the study of control of breathing, the children were studied awake in the sitting position. None had received any premedication. They breathed room air with a mouth piece and a nose-clip through a pneumotachograph (Fleish no. 1 for children younger than 8 years, and no. 2 for children older than 8 years). The pneumotachograph was attached to a two-way valve that separated the inspiratory from the expiratory line. Instrumental dead space amounted to 45 ml in the children less than 8 years and 70 ml for the others.

Breathing pattern was analyzed on at least 10 respiratory cycles under resting breathing conditions in terms of tidal volume (VT), inspiratory and expiratory volume (TI, TE), total duration of the respiratory cycle (TTOT) and minute ventilation (V̇E). Tidal volume was normalized for body weight (BW). The mean inspiratory flow was calculated in terms of VT_{BW}/TI.

The mouth occlusion pressure was measured with a pressure transducer (Statham ± 50 cmH_2O). Airway occlusions were performed by inflating a 3-cm long balloon placed on the respiratory line during expiration. The inspiratory line was occluded for 0.3–0.7 sec. Great care was taken to avoid any leak around the mouth piece during the occlusions. Occlusions were repeated at least five times at intervals of at least 1 min. In four children (cases no. 1, 7, 9, 14) $P_{0.1}$ was also measured after O_2 breathing. This was done by connecting a bag of pure oxygen to the inspiratory line. The subjects breathed O_2 during two consecutive respiratory cycles. $P_{0.1}$ was measured 8–12 sec after O_2 inhalation (9).

Results in ILD children were compared to breathing pattern and $P_{0.1}$ values previously reported in healthy children (9). The paired *t* test was used in order to compare the ILD's values with the predicted ones according to the equation of regression previously reported between each variable and age (9).

RESULTS

Results of pulmonary function tests expressed as % of the predicted values are reported in Table 1. In Table 2 the components of breathing pattern and mouth occlusion pressure ($P_{0.1}$) are included. It can be seen that respiratory frequency was higher ($P < 0.02$) (Fig. 1, upper panel), inspiratory time (TI) shorter ($P < 0.001$) (Fig. 1, middle panel), TI/TTOT ratio lower ($P < 0.001$) (Fig. 1, lower panel), minute ventilation greater ($P < 0.02$) in ILD than in healthy children (9). Tidal volume was in the normal range, both expressed in absolute values (ml) or normalized for body weight. VT_{BW}/TI was significantly increased ($P < 0.001$) (Fig. 3, upper panel), and $P_{0.1}$ higher than predicted ($P < 0.001$) (Fig. 2). There was a significant relationship between $P_{0.1}$ and both $V̇E_{BW}$ ($r = 0.49$, $P < 0.05$) and VT_{BW}/TI ($r = 0.70$, $P < 0.001$). The ratio of $P_{0.1}$ to VT_{BW}/TI, that is the effective inspiratory impedance, was calculated, it was significantly greater than predicted ($P < 0.01$) (Fig. 3, lower panel).

Control of breathing data were compared to changes in lung

Table 1. *Pulmonary function tests*[1]

Case	Sex	BW (kg)	Age (yr)	Diagnosis	VC[3]	FRC[3]	TLCO[3]	RL[3]	CL[3]	EL[3]	PaO$_2$ (mmHg)	PaCO$_2$ (mmHg)
1	M	17	5	LIP[2]		70	33	111	36	276	82 (97)	31
		17	5.6			81	40	86	22	380	80 (90)	36
		18.5	6			97	51	95	28	353	77 (87)	35
2	F	24	6	HP		77	59	93	69	145	70 (80)	34
3	F	20	6	D		85	76	101	55	182	84 (95)	30
4	M	42	14.4	HP	28	83	53	148	23	457	58 (63)	33
		42	14.6		57	94	59	124	59	169	81 (87)	36
		48	15.3		75	88	73	100	69	131	87 (94)	36
5	F	31	11	HP	70	96	90	107	73	134	98 (95)	33
6	F	32	12	NPD[2]	39	88	60	100	22	447	85 (91)	35
7	M	32	12	PH[2]	66	147	52	176	43	230	82 (88)	35
		34	13		69	124	59	128	58[4]	174	83 (88)	37
		34	14		60	126	52	162	46[4]	227	79 (85)	34
8	F	26	12	NPD[2]	78	100	80	105	73[4]	148		
9	F	36	14	PVD[2]	68	87	37	111	38[4]	262	73 (79)	34
10	M	17.5	7.9	NPD[2]		131	93	132	44[4]	224	84 (91)	36
11	F	20	7.3	VIP[2]		108	62	104	49	200	86 (94)	36
12	M	15.5	4.5	VIP		102		97	51	198	92 (105)	32
13	F	24	9.6	HP	86	75	57	126	44[4]	227	71 (77)	38
14	F	15.5	6.6	VIP[2]		87	67		36	280	80 (90)	35
		15.5	6.8			78			31	286	73 (83)	36

[1] BW, body weight; y, years; LIP, Lymphoid Interstitial Pneumonia; HP, Hypersensitivity Pneumonitis; D, Dermatomyositis; NPD, Nieman Pick's Disease; PVD, Pulmonary vascular disease; VIP, Viral Interstitial Pneumonia; PH, Pulmonary Hemosiderosis.

[2] Lung biopsy. VC, vital capacity; FRC, functional residual capacity; TLCO, lung transfert for CO; RL, lung resistance; CL, dynamic lung compliance; EL, lung elastance; PaO$_2$ is expressed in absolute terms and as % of the predicted values in brackets.

[3] As % of predicted values.

[4] Static lung compliance.

Table 2. *Breathing pattern and mouth occlusion pressure*[1]

Case	P$_{0.1}$ (cm H$_2$O)	(*)	f (m^{-1})	TI (s)	TI/TTOT	VT (ml)	VT (ml·kg^{-1})	V̇E$_{BW}$ (ml·kg^{-1} m^{-1})	VT$_{BW}$/TI (ml·s^{-1}· kg^{-1})	P$_{0.1}$/VT$_{BW}$/TI (cm H$_2$O/ml· kg^{-1}·s^{-1})
1	4.5		32	0.9	0.48	206	12.2	390	13.4	0.336
	5.6		43	0.6	0.40	184	10.5	441	19.3	0.305
	8.7	6.2	38	0.6	0.37	222	12	456	20.7	0.420
2	5.2		32	0.8	0.42	225	11.7	378	11.7	0.444
3	5.3		38	0.8	0.47	186	9.3	353	12.2	0.434
4	5.5		47	0.5	0.42	272	6.5	306	12.2	0.450
	2.2		23	1.1	0.42	426	9.2	212	8.4	0.257
	2.6		21	1.2	0.41	461	9.6	202	8	0.325
5	2.6		24	0.9	0.37	264	8.5	204	9.1	0.286
6	5		25	0.8	0.35	275	8.6	215	10.4	0.487
7	2.9		19	1.4	0.43	430	13.9	264	9.9	0.298
	2.6	2.3	18	1.5	0.44	445	13	234	9	0.284
	2.9		19	1.3	0.39	357	10.5	189	8.3	0.280
8	1.9		22	1	0.37	284	10.9	239	10.9	0.362
9	3.4	2.8	21	1.1	0.39	372	10.3	206	9.4	0.261
10	3.5		26	1.1	0.45	248	14.2	368	13.5	0.332
11	3.2		20	1.3	0.42	243	12.2	243	9.8	0.331
12	5.6		36	0.7	0.44	189	12.1	436	16.8	0.345
13	3.4		16	1.7	0.46	389	16.2	259	9.5	0.316
14	6.8		46	0.5	0.42	190	11.9	547	21.6	0.417
	9.2	8	50	0.5	0.43	170	11	550	22	0.418

[1] P$_{0.1}$, mouth occlusion pressure 0.1 s. after the onset of inspiration; (*) P$_{0.1}$ measured 8–12 sec after the onset of O$_2$ inhalation; f, respiratory frequency; TI, inspiratory time; T$_{TOT}$, total duration of the respiratory cycle; VT, tidal volume; VT$_{BW}$, VT normalized for body weight; V̇E$_{BW}$: minute ventilation normalized for body weight; and VT$_{BW}$/TI, mean inspiratory flow normalized for body weight.

mechanics and to gas exchange abnormalities. In Fig. 4, PaO$_2$ was related to P$_{0.1}$, both expressed as % of predicted values: the lower was PaO$_2$ the higher was P$_{0.1}$, ($r = 0.57$, $P < 0.01$). The increase in lung elastance (EL) (Table 1), expressed as % of predicted values was correlated with the increase in P$_{0.1}$ ($r = 0.78$, $P < 0.01$) for the whole ILD group (Fig. 5, upper panel). In the lower panel of Fig. 5, only P$_{0.1}$'s patients with normal PaO$_2$ and with P$_{0.1}$ measured

after O$_2$ breathing (cases 1, 7, 9, 14, Table 2) were taken into account and compared to the corresponding changes in EL ($r = 0.66$, $P < 0.001$). There was no significant relationship between P$_{0.1}$ and the decrease in TLCO, whereas EL and TLCO were significantly correlated ($r = 0.45$, $P < 0.05$). The increase in EL was significantly related to the shortening in TI ($r = 0.55$, $P < 0.01$) (Fig. 6, upper panel), to the increase in VT$_{BW}$/TI ($r = 0.52$, $P <$
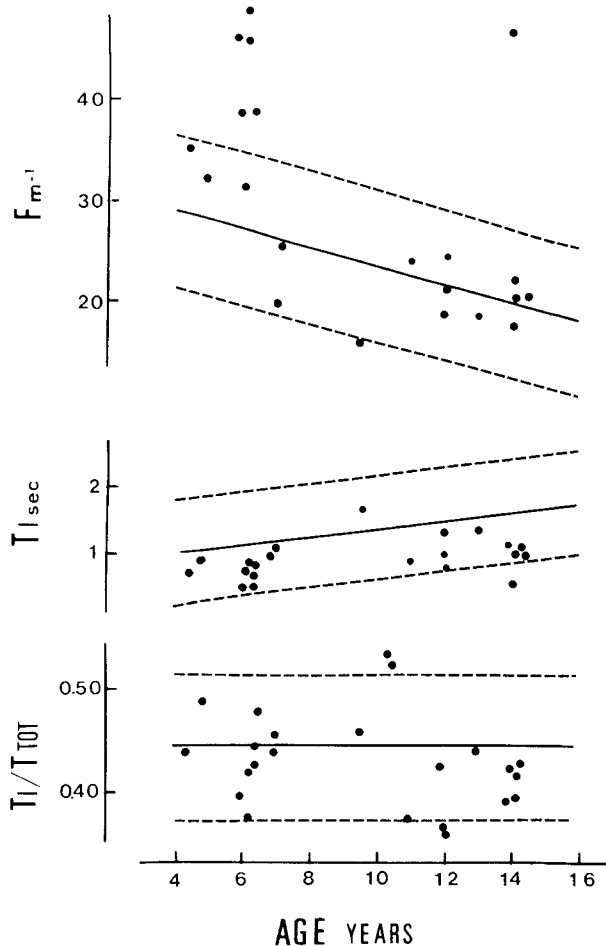
Fig. 1. Plots of respiratory frequency (f) in breath per min (*upper panel*), inspiratory time (Ti) in second (*middle panel*), and the ratio of Ti to the total duration of the respiratory cycle (Ti/Ttot)(*lower panel*) versus age in ILD children. Full and dotted lines indicate mean ± 2 S.D. in healthy children (9), full circles are values in ILD children.

Fig. 2. Mouth occlusion pressure ($P_{0.1}$) and cmH_2O plotted against age. Symbols as in Figure 1.

Fig. 3. Mean inspiratory flow (V_{TBW}/Ti) in $ml \cdot kg^{-1} \cdot sec^{-1}$ (*upper panel*) and ratio of $P_{0.1}$ to V_{TBW}/Ti (*lower panel*) plotted against age. Symbols as in Figure 1.

0.02) (Fig. 6, middle panel) and to the effective inspiratory impedance ($r = 0.55$, $P < 0.01$) (Fig. 6, lower panel). During the follow-up studies in cases 1, 4, 8, 14 (table 1 and 2) the changes in control of breathing variables were also correlated with the changes in lung mechanics and in gas exchange.

DISCUSSION

Breathing pattern and mouth occlusion pressure ($P_{0.1}$) change with age, as we have previously shown (9). Thus children with respiratory disease have to compared to healthy children of the same age.

As in adults resting respiratory frequency, minute ventilation were increased in ILD children (2, 12, 13, 17). In our population VT was normal as Renzi (17) observed in ILD adults while Camus (2) reported a decreased VT. We found a significantly reduced V_{TBW}/Ti because of a shortening in Ti. The shortening in Ti was significantly related to the increase in lung elastance (EL) (Fig. 6, upper panel). Ti was shorter than TE, thus the Ti/Ttot ratio was significantly lowered. In contrast•ILD adults have normal Ti/Ttot ratio at rest (2, 17) and during CO_2 breathing (3). A greater shortening in Ti in ILD children may reflect stronger afferent reflexes originating from lung (14) or chest wall (16) than in adults.

$P_{0.1}$ was significantly higher than predicted in our ILD children as reported in adults (2, 3, 17, 18). $P_{0.1}$ depends on the neural drive and the advantage of the respiratory muscles as pressure generators (5).
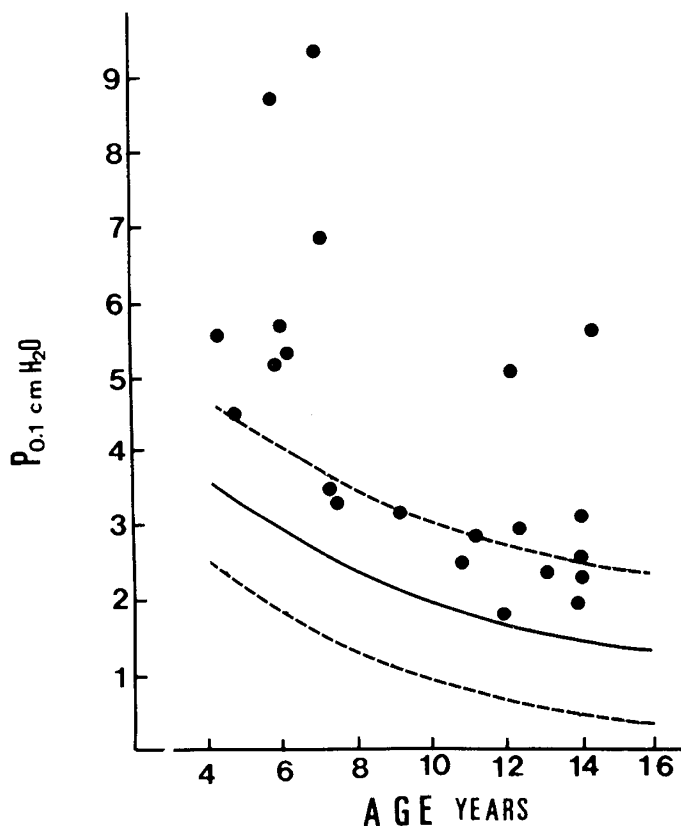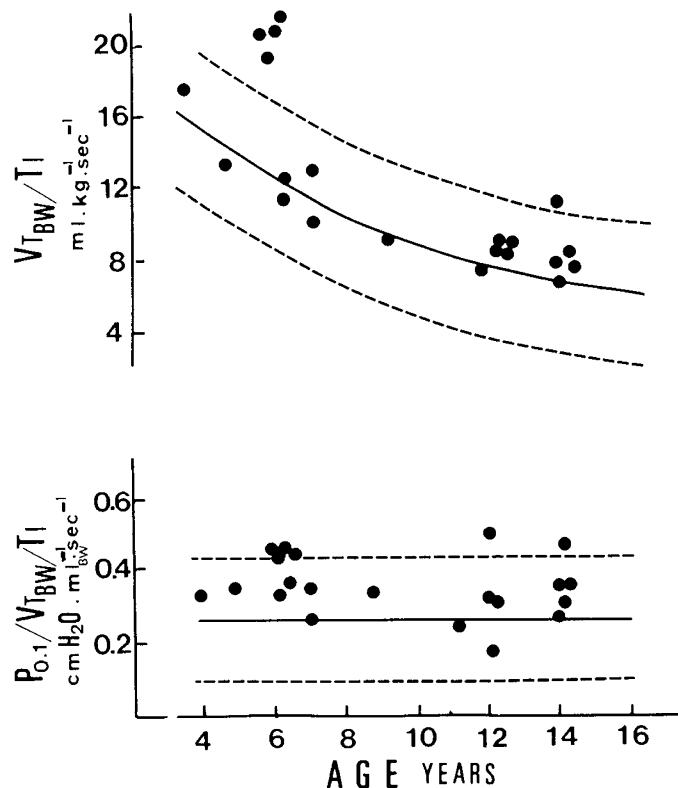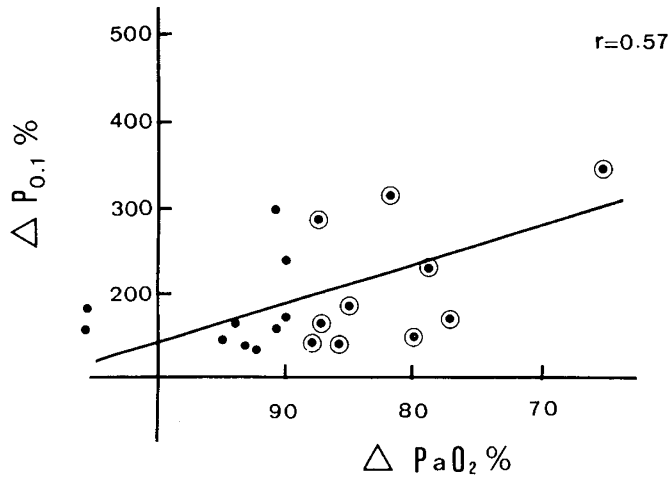
Fig. 4. Relationship between change in PaO_2 and increase in $P_{0.1}$ both expressed as % of predicted values. Full circles indicate results of ILD children with PaO_2 in the normal range, and double circles values in ILD children with PaO_2 significantly reduced.

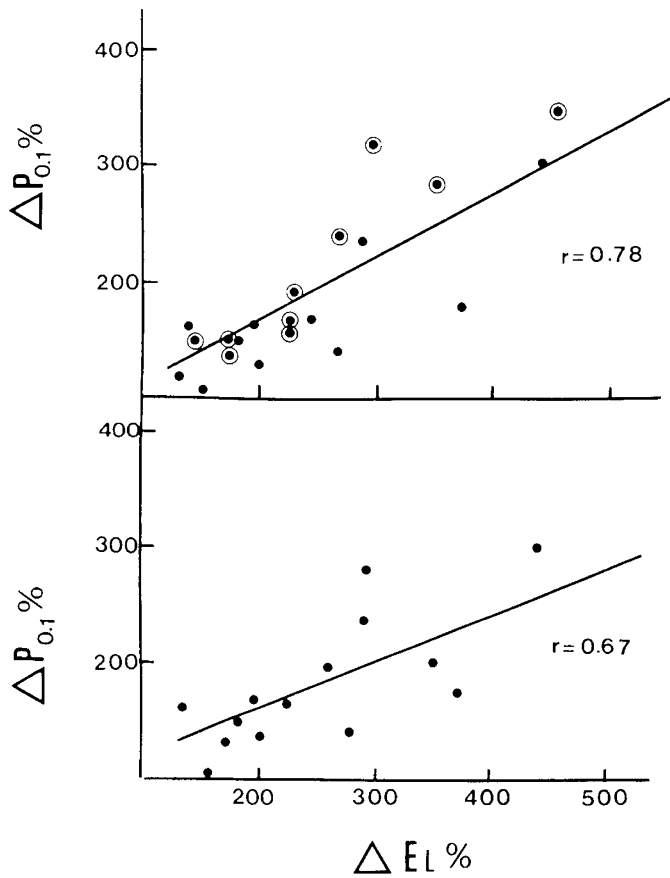hood a significant relationship between the decrease in lung volumes and in lung compliance (7), which suggested no change in thoracic compliance. On the other hand the inspiratory muscle action is affected by changes in the end-expiratory volume [functional residual capacity (FRC) (6)]. A decrease in FRC results in longer inspiratory muscle length, and hence promote an increased $P_{0.1}$ (5). Burki did not find any significant correlation between $P_{0.1}$ and change in FRC in healthy subjects, but Camus (2) in ILD adults observed an increase in $P_{0.1}$ when FRC decreased. A decreased FRC was observed in several ILD children (Table 1); however, in spite of the possible influence of the reduced FRC in these cases, the higher $P_{0.1}$ probably reflects also a greater neural drive which may be related in part to gas exchange abnormalities and/or to changes in lung mechanics.

In ten cases, PaO_2 was significantly reduced (Fig. 4, double circles), only one patient had severe hypoxemia (case no. 4). A close relationship was observed between the changes in PaO_2 and in $P_{0.1}$ (Fig. 4), the lower was PaO_2, the higher was $P_{0.1}$. The results are in agreement with previous reports of increase in $P_{0.1}$ with hypoxia in healthy adults (11) and in hypoxemic children with chronic bronchial obstruction (8).
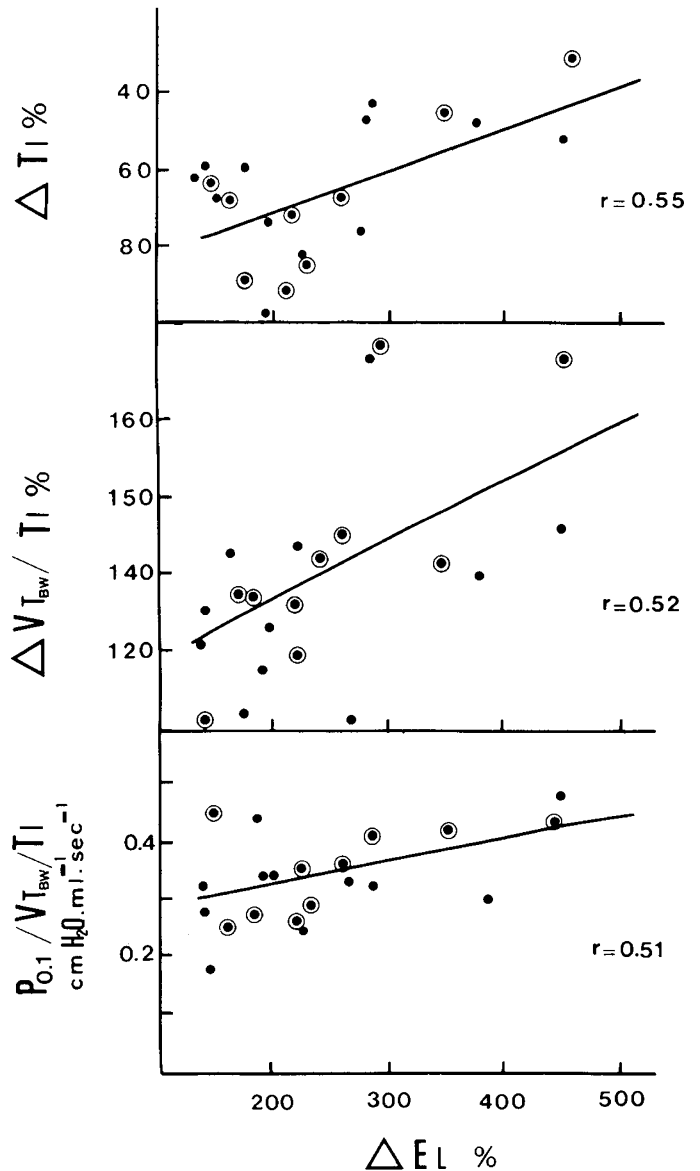

Fig. 5. Relationship between increase in lung elastance (E_L) and in $P_{0.1}$, both expressed as % of predicted values. In the upper panel results of the whole ILD group are given, in the lower panel only $P_{0.1}$ of patients with normal PaO_2 and of four hypoxemic patients after O_2 breathing are plotted *versus* the corresponding increase in E_L. Symbols as in Figure 4.

Fig. 6. Relationship between increase in E_L and shortening in T_I (*upper panel*), increase in mean inspiratory flow (VT_{BW}/T_I) (*middle panel*) and effective inspiratory impedance ($P_{0.1}/VT_{BW}/T_I$) (*lower panel*). E_L, T_I, and VT_{BW}/T_I are expressed as % of predicted values. Symbols as in Figure 4.

A high $P_{0.1}$ could be attributed to change in the effectiveness of the inspiratory muscle force. In ILD adults muscle force and thoracic compliance were found to be not modified (4). Our children did not perform maximal static inspiratory efforts, so we do not know the values for their maximal static inspiratory pressures. But we have previously reported in ILD during child-

If hypoxemia may partially explain the high $P_{0.1}$ in ILD, changes in lung mechanics must be also considered. RL of our patient was in the normal range (that is 100 % ± 50 of predicted) except in case no. 7 (Table 1), thus afferent reflexes originating from central airways (14) probably were not involved in the increased neural drive. A decreased lung compliance and thus an increased lung elastance (EL) (Table 1) were present in all the cases. In five children dynamic and static EL were measured and found equal, in these cases increase in EL reflects the enhanced elastic load. In the others cases only dynamic EL was obtained. Increase in dynamic EL may reflect the enhanced elastic load; however, it may be due in part to a ventilatory asynchronism resulting from unequal changes in the calibre of the peripheral airways. In our population of ILD children increase in EL was significantly correlated with the increase in $P_{0.1}$ (Fig. 5, upper panel). In children with decreased PaO_2 (double circles) (Fig. 5, upper panel), both increased chemical drive and elastic load are associated to explain high $P_{0.1}$. Thus, in order to suppress the effects of hypoxemia, we plotted the $P_{0.1}$ of the normoxemic patients and the $P_{0.1}$ of four hypoxemic patients obtained after O_2 breathing versus the corresponding increase in lung elastance (Fig. 5, lower panel). In this way, the increase in $P_{0.1}$ was related only to the increase in EL. The significant correlation ($r = 0.68$, $P < 0.01$) suggests that increased EL enhances neural drive probably by way of afferent reflexes originating from the lungs (12, 14). The augmenting of the elastic load on $P_{0.1}$ was previously demonstrated in healthy (19) and in ILD adults at rest (17) and during exercise (20). Increased neural drive in response to elastic load is presumed vagally-mediated. In animals with experimentally induced ILD (15) and in humans (10), modification of breathing pattern was reported by blocking the vagus nerve; however, recently Savoy (18) did not observe any change in control of breathing after xylocaïne inhalation in ILD adults.

ILD children had a greater effective inspiratory impedance than healthy children (Fig. 3, lower panel). The effective inspiratory impedance is the ratio between the rate of mouth pressure potentially available for inspiration ($P_{0.1}$) and the resulting flow (V_{TBW}/T_I). In ILD children both $P_{0.1}$ and V_{TBW}/T_I were increased (Fig. 2 and 3, upper panel), but V_{TBW}/T_I was not as much increased as $P_{0.1}$ because of the changes in lung mechanics. In fact the increase in the effective inspiratory impedance was significantly correlated with the increase in EL (Fig. 6, lower panel). Such relationship has been reported in ILD adults during CO_2 breathing and during maximal exercise (8, 20).

We did not find any correlation between diffusion defect and increase in $P_{0.1}$. Thus, receptors located in the interstitium do not seem to be involved with changes in control of breathing in our ILD children.

We conclude that ILD in children is associated with increased neural drive which is related to hypoxemia and increased lung elastance.

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