PULMONARY FUNCTION IN HYPERTHYROIDISM *

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Previous investigators, including Peabody and Wentworth in 1917 (1), have described dyspnea and a decreased vital capacity in hyperthyroid patients (2, 3). Following successful therapy of hyperthyroidism, an increase in the vital capacity to normal levels has been observed. The precise relationship of these changes to other measurable derangements of pulmonary or cardiac function has not been determined. Therefore, the present study was undertaken using recently developed techniques to determine the correlation between the changes in vital capacity in hyperthyroidism and changes in *1*) lung compliance, *2*) strength of the respiratory muscles, *3*) airway resistance, or other factors. Also, an attempt has been made to explain the symptom of dyspnea associated with hyperthyroidism (4, 5) in the absence of obvious congestive heart failure.

MATERIALS AND METHODS

Patients. The patients studied were from the wards or clinics of the Philadelphia General Hospital or the Hospital of the University of Pennsylvania. The diagnosis of hyperthyroidism was based upon *1*) clinical evaluation, *2*) I^{131} uptake by the thyroid gland, *3*) basal metabolic rate, and *4*) serum protein-bound iodine.

Thirteen patients, 12 of whom were female (Table I), were studied. The ages ranged from 21 to 55 years (mean age 41). In addition to other symptoms of hyperthyroidism, 9 patients had decreased exercise tolerance. Four described "hard breathing" or "inability to get enough air" on moderate exercise and 5 had shortness of breath on mild exertion. There was none with difficult breathing at rest.

One patient (RR) had acute pulmonary edema 1 month prior to study, treated with digitalization, low salt diet, and bed rest. Although she had not received antithyroid medication, there was no evidence of congestive failure at the time of the pulmonary function studies. Electrocardiographic, X-ray and fluoroscopic studies were within normal limits. Patient SC had been in mild congestive heart failure but was not believed to be in failure at the time of the studies.

Fluoroscopic and X-ray examinations were carried out in all patients to determine whether there was tracheal compression by an enlarged thyroid gland. No definite tracheal compression was observed except in RR.

Methods. Inspiratory capacity, expiratory reserve volume, and vital capacity were measured with a 13 L spirometer. Distribution of inspired air was measured by the nitrogen meter single breath test (6). Maximal breathing capacity was measured by inspiring from a 120 L spirometer through a low resistance valve. Respiratory rate, tidal volume, and minute volume at rest and during the third to seventh minutes of exercise were measured using the 120 L spirometer. The minute volume was corrected to BTPS (body temperature and pressure saturated with water vapor). Exercise studies were performed by walking on a treadmill (slope 4¼°, speed 2.4 mph unless otherwise indicated). Ventilation during exercise was measured with the subjects inspiring air or oxygen. Arterial (brachial) blood samples were obtained while the subjects were breathing air at rest, air during exercise, and oxygen at rest. Arterial blood oxygen content, capacity, and carbon dioxide content were determined using the Van Slyke and Neill apparatus (7). Arterial blood pH readings were made at room temperature using a glass electrode and the correction factors of Rosenthal to convert to 37° C (8). Partial pressures of arterial blood carbon dioxide were calculated by applying the line charts of Van Slyke and Sendroy (9) to the pH and carbon dioxide content values obtained on whole blood.

Oxygen consumption and carbon dioxide production at rest and during the fourth and fifth minutes of exercise were measured by collection of expired gas in a Douglas bag and analysis in a Scholander 0.5 ml gas sample apparatus (10), with correction to 0° C and 760 mm Hg dry. Duplicate samples from each bag were analyzed and required to check within ± 0.05 per cent. Physiological dead space during resting and exercising ventilation was calculated by the Bohr formula (11).

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TABLE I

Physical characteristics, laboratory data before therapy, and results of therapy

Patient	Sex	Age	Ht	Wt	Basal metabolic rate	Radioactive iodine uptake	Protein-bound iodine	Dyspnea*	Antithyroid treatment	Clinical status post-therapy
		yrs	*in*	*lbs*	%	%	*μg/100 ml*			
RR†	F	41	62	131	+72		12.2	xxx		
DS	F	21	66	131	+28	77		xxxx	Propyl.‡ Surgery	Euthyroid
FC	F	41	65	173	+40	78	9.3	xxx	RaI§	Euthyroid
MC	F	52	68	131	+35	91	10.2	xx	RaI	Hypothyroid
LF	F	34	63	103	+52	87	11.0	x	Propyl. Surgery	Euthyroid
SC‖	F	45	64	148	+57	94	11.5	xxxx	RaI	Euthyroid
AT	F	42	68	159		67	11.6	xxxx		
EL	F	34	65	105	+ 3	58	6.5	xxx		
AL¶	F	55	62	107	+63	78	9.5	xxxx	RaI	Euthyroid
HR	F	46	65	124		88	7.5	x		
MB	M	43	73	157	+31	78	9.4	xxx		
EM	F	56	63	162	+70		14.0	x	Propyl.	Euthyroid
EQ	F	33	64	137	+28	59	6.7	xxxx		

* x = No change in exercise tolerance; xx = dyspnea on severe exertion; xxx = dyspnea on moderate exertion; xxxx = dyspnea on mild exertion.

† Episode of acute pulmonary edema 1 month prior to study and compression of trachea by enlarged thyroid observed on fluoroscopy.

‡ *n*-Propylthiouracil.

§ Radioactive iodine-131.

‖ Slight pulmonary congestion.

¶ Aortic stenosis, no clinical evidence of decompensation.

Functional residual capacity (FRC) and airway resistance were measured in the body plethysmograph (12, 13). Lung compliance was measured during normal ventilation by the method of Mead and Whittenberger (14). Maximal inspiratory and expiratory pressures at the mouth were measured against a closed airway using a capacitance manometer.

Apparent CO diffusing capacities (D_L)[1] were estimated by a modification of Krogh's single breath method described previously (15). Alveolar samples were analyzed for CO with an infrared analyzer,[2] and for He and O_2, with a continuous sampling mass spectrometer.[3] Plasma CO tension in equilibrium with mixed venous carboxyhemoglobin was estimated at the start and at the end of each series of breath-holding measurements with a rebreathing technique and subtracted from the alveolar CO tensions in a manner previously described (16) for estimating true CO tension gradients during breath-holding.

Diffusing capacity of the pulmonary membrane (D_M) and pulmonary capillary blood volume (Vc) were calculated from measurements of D_L at more than one alveolar oxygen tension using the following relationship derived by Roughton and Forster (17):

$$1/D_L = 1/D_M + 1/(Vc\theta). \quad [1]$$

D_L and D_M are expressed in ml/(min × mm Hg), and θ is the rate of CO uptake by the red cells in 1 ml of whole blood expressed as milliliters per minute per millimeter Hg plasma CO tension; Vc then is in milliliters. The reciprocal of θ was approximated from the alveolar oxygen tension ($P_{A_{O_2}}$) as follows (17):

$$1/\theta = 0.72 + 0.0058\ P_{A_{O_2}}. \quad [2]$$

The reciprocals of D_L for each subject were plotted against $1/\theta$ and the best straight lines to describe these relationships were determined by the method of least squares. Vc was calculated from the slopes and D_M from the intercepts of these lines at $(1/\theta) = 0$. Since the values of $1/\theta$ are based on an assumed oxygen capacity of 20 vol of gas per 100 ml of blood, estimates of Vc were corrected to the patient's oxygen capacity by multiplying the measured capillary volume by the ratio,

$$\frac{20}{\text{patient's } O_2 \text{ capacity (vol \%)}}.$$

Mean and instantaneous pulmonary capillary blood flows were measured in duplicate by the plethysmographic nitrous oxide method of Lee and DuBois (18).

All measurements at rest were made with subjects seated comfortably in a chair. Three to 16 months after therapy, 7 of the 13 patients were re-evaluated by the endocrine clinics of the University and Philadelphia General Hospitals and were restudied as described above.

[1] The subscript referring to carbon monoxide (CO) is omitted in this paper; D_L, D_M and θ refer to D_{LCO}, D_{MCO}, and θ_{CO}, respectively, unless specifically stated otherwise.

[2] Beckman Instruments, Inc., Fullerton, Calif.

[3] Consolidated Electrodynamics Corporation, Pasadena, Calif.

TABLE II

Lung volumes before and after therapy

Patient	Vital capacity		Residual volume		Functional residual capacity		Total lung capacity	
	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy
	ml		*ml*		*ml*		*ml*	
RR	2,580 (91)*		1,540 (95)		2,000 (88)		4,200 (99)	
DS [7]†	2,460 (67)	2,830 (77)	1,000 (67)	635 (43)	2,180 (94)	2,100 (90)	3,460 (71)	3,465 (71)
FC [6]	2,700 (83)	3,400 (105)	1,190 (66)	1,370 (77)	2,400 (86)	2,630 (94)	3,890 (81)	4,470 (93)
MC [4]	2,480 (77)	3,160 (97)	2,430 (135)	1,390 (77)	3,400 (121)	2,390 (85)	4,960 (104)	4,650 (97)
LF [5]	2,520 (81)	3,040 (97)	1,600 (104)	1,390 (90)	2,600 (116)	2,660 (118)	4,120 (93)	4,440 (101)
SC [3]	2,420 (81)	2,600 (87)	850 (51)	890 (53)	1,920 (81)	1,380 (58)	3,270 (74)	3,490 (79)
AT	2,230 (63)		1,235 (75)		1,870 (76)		3,465 (71)	
EL	3,090 (92)		1,070 (68)		2,480 (102)		4,160 (90)	
AL [3]	3,220 (122)	2,940 (111)	1,990 (120)	1,750 (106)	3,280 (100)	2,700 (88)	5,040 (123)	4,360 (107)
HR	2,590 (83)		1,590 (95)		2,590 (108)		4,180 (92)	
MB	4,625 (95)		1,945 (74)		2,685 (72)		6,570 (93)	
EM [3]	2,640 (100)	3,240 (123)	2,290 (129)	1,315 (74)	2,690 (80)	2,340 (69)	4,940 (118)	4,690 (112)
EQ	3,080 (95)		1,330 (85)		2,460 (106)		4,410 (97)	
Mean	2,820 (87)	3,030 (100)	1,540 (90)	1,250 (74)	2,500 (95)	2,315 (85)	4,380 (93)	4,220 (94)

* Per cent of predicted values in parentheses. Since the predicted values of Needham, Rogan and McDonald (20) were measured at ATPS and the measured values in our subjects were corrected to BTPS, 9% has been added to the predicted figures.
† Number of months between studies in brackets.

Calculations of standard deviations (SD) were performed by conventional methods. The *t* test was used to determine the probability that the observed changes were significant (19).

RESULTS

Lung volumes (*Table II, Figure 1*). The vital capacities of three of the hyperthyroid patients (DS, MC and AT) were significantly less than the predicted normal values of Needham, Rogan and McDonald (20). The other ten patients had vital capacities within the predicted normal range. The mean inspiratory capacity generally was decreased, and the mean expiratory reserve volume generally was greater than predicted, although the deviations from predicted values were not significant. Mean FRC, residual volume, and total lung capacity were within normal limits. It is noteworthy that 3 of 13 patients prior to therapy had total lung capacities less than 75 per cent of predicted values. On the other hand, AL had a total lung capacity of 123 per cent of the predicted value before therapy. The small variations observed are in reference to predicted values, but critical evaluation can be made only by measurement of the lung volumes following successful therapy (Figure 1). No correlation was found between the vital capacity or other lung volumes measured at rest and the dyspnea frequently observed on exercise. The mean vital capacity increased in seven patients who were restudied after treatment ($p < 0.02$). The inspiratory capacity was slightly increased ($p < 0.05$) and the residual volume was not significantly changed. The total lung capacity did not change. These results are similar to those of Richards, Whitfield, Arnott and Waterhouse (21).

Mechanics of breathing (*Table III*). Maximal breathing capacity was less than 80 per cent of predicted values in three patients, according to the prediction formula of Baldwin, Cournand and Richards (22). In contrast to the observation of normal "elastic resistance" in two hyperthyroid patients by McIlroy, Eldridge and Stone (23),

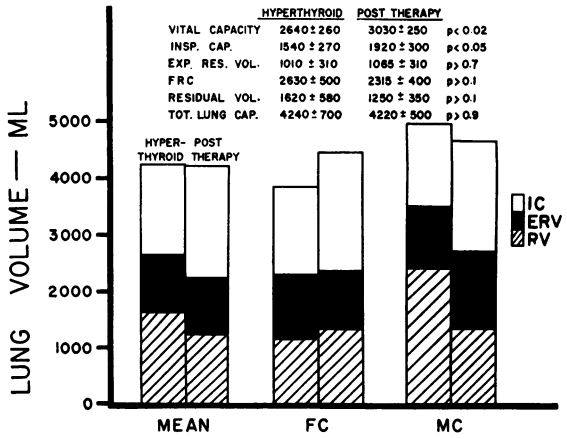

FIG. 1. MEAN LUNG VOLUMES AND STANDARD DEVIATIONS IN 7 PATIENTS BEFORE AND AFTER THERAPY. Patients FC and MC represent variations among group, FC showing an increase in inspiratory capacity post-therapy, and MC an increase in inspiratory capacity and a decrease in residual volume. IC = inspiratory capacity; ERV = expiratory reserve volume; RV = residual volume.

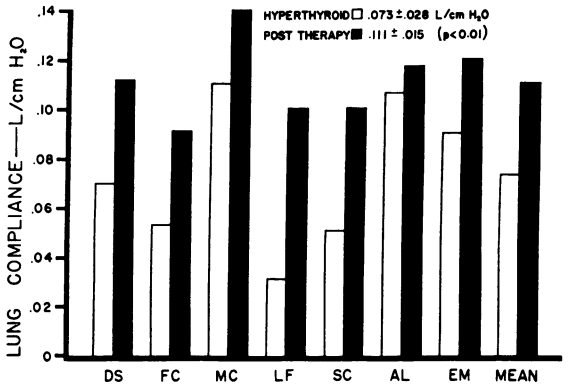

FIG. 2. LUNG COMPLIANCE PRE- AND POST-THERAPY IN 7 PATIENTS.

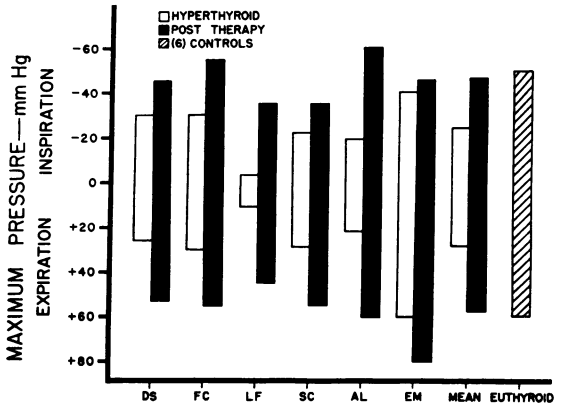

FIG. 3. MAXIMAL INSPIRATORY AND EXPIRATORY PRESSURES MEASURED AT THE MOUTH AGAINST A CLOSED AIRWAY PRE- AND POST-THERAPY.

lung compliance in the present study was lower than the predicted value in practically all the patients. Airway resistance was normal, except in one patient who had a large goiter and a small increase in airway resistance. Maximal pressures measured at the mouth on both inspiration and expiration against a closed airway were decreased significantly when compared to those measured on a control group of six female euthyroid subjects of similar age and body size. One patient, LF, had exceedingly low values of maximal inspiratory pressure before therapy.

After treatment, lung compliance increased to normal levels (Figure 2). Airway resistance measurements were unchanged when compared to the pre-therapy measurements. There were significant increases in maximal inspiratory and expiratory pressures measured at the mouth (Figure 3).

TABLE III

Mechanics of breathing

Patient	Maximal pressures: Inspiration, Before therapy	Maximal pressures: Inspiration, After therapy	Maximal pressures: Expiration, Before therapy	Maximal pressures: Expiration, After therapy	Maximal breathing capacity, Before therapy		Lung compliance, Before therapy	Lung compliance, After therapy	Airway resistance, Before therapy	Airway resistance, After therapy
	mm Hg				*L./min*	*% pred.*	*L./cm H₂O*		*cm H₂O/L./sec*	
RR					59	70			2.94	
DS	30	45	29	53	72	68	0.070	0.112	1.98	1.70
FC	30	55	30	55	123	123	0.053	0.091	1.73	1.14
MC					59	75	0.110	0.140	1.69	1.45
LF	3	35	11	45	92	108	0.029	0.100	1.26	1.48
SC	22	35	29	55	86	100	0.052	0.100	0.90	1.30
AT	20		61		79	82	0.066		1.46	
EL	20		32		77	96	0.092		1.83	
AL	19	60	22	60	87	130	0.106	0.117	0.66	0.83
HR	40		55		78	98	0.090		1.32	
MB*	35		40		146	116	0.015		1.49	
EM	40	45	60	80	88	111	0.090	0.120	0.71	1.04
EQ	15		30		87	95				
Mean	24	46	35	58	86	98	0.076	0.111	1.50	1.27
SD	±11	±9	±16	±11			±0.025	±0.015	±0.60	±0.27
	$p < 0.01$		$p < 0.01$				$p < 0.01$		$p > 0.05$	
Normal	49		60				Female 0.09–0.19		0.7–2.4	
SD	±10		±17				Male 0.14–0.24			

* MB not included in the mean.

TABLE IV

Distribution of inspired air, ventilation, and oxygen consumption before therapy

Patient	Alveolar distribution	Minute volume		Frequency		O_2 consumption		O_2 extraction*	
		Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
	% change (750–1,250 ml)	*L/min/m² BTPS*		*resp./min*		*ml/min/m² STPD*		*%*	
RR	1.0	6.2		21					
DS	1.7	4.4	30.3	16	33	160	515	3.92	4.55
FC	0.8	6.1	24.7	27	42		660		5.25
MC	0.8	6.7	17.8	25	30	208	710	4.10	4.00
LF	0.3	7.3	23.6	30	40	216	420	2.96	3.63
SC	1.5	6.4	27.1†	28	48	200	640	4.25	3.74
AT	0.2	6.4	36.2	29	54	212	810	4.20	3.26
EL	2.5								
AL‡	1.9	5.5		17		182		4.20	
HR	0.8	5.9	27.7	23	43	194	850	3.50	3.64
MB	0.5	8.8	30.1	32	49	175	496	2.50	4.65
EM	0.3								
EQ	0.3	5.6	17.4	25		179	530	3.80	3.62
Mean	1.0	6.3	26.1	25	42	191	625	3.71	4.04
SD		± .3	±5.7	±5	±8	±19	±139	±0.58	±0.6
Mean euthyroid controls§		4.5	12.5	19	20	138	523	4.07	5.51
SD		±0.2	±3.8	±6	±4	±22	±158	±0.94	±1.06
p Values		p <0.01	p <0.01	0.05 >p >0.02	p <0.001	p <0.01	p >0.05	p >0.05	p <0.01

* Ventilation measured during period of oxygen consumption.
† 1 mph, 4¼° slope.
‡ Could not tolerate exercise.
§ Average age 35 yrs; average weight 123 lbs.

Ventilation and gas exchange (Table IV). In all patients studied, distribution of inspired air was within normal limits. Frequency of breathing at rest was increased in hyperthyroid patients compared to that of a group of seven euthyroid females of similar body size and age. The hyperthyroid patients at rest had an increased minute ventilation per unit of body surface area (BSA) with decreased tidal volumes. The respiratory quotient of the hyperthyroid patients was within normal limits at rest. There was a significant increase in minute ventilation in the hyperthyroid patients during exercise on a treadmill (26.1 ± 5.7 L per minute per m²) compared to the minute volume of exercising euthyroid controls (12.50 ± 3.8 L per minute per m²). The increase in minute volume

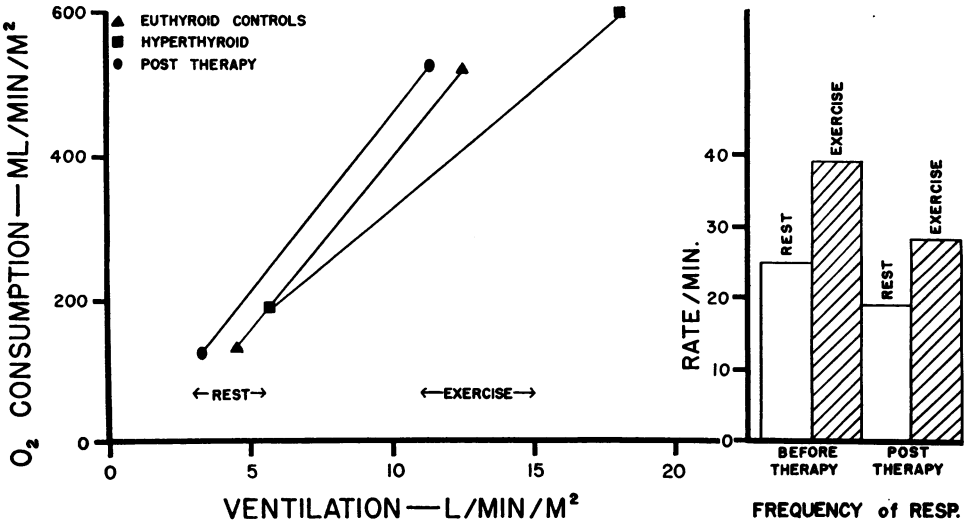

FIG. 4. OXYGEN CONSUMPTION, MINUTE VENTILATION, AND FREQUENCY OF RESPIRATION AT REST AND DURING EXERCISE IN EUTHYROID AND HYPERTHYROID SUBJECTS PRE- AND POST-THERAPY. The mean results for rest and exercise have been connected by straight lines.

TABLE V

Oxygen consumption and ventilation before (B) and after (A) therapy

Patient	Minute volume				Frequency				O_2 consumption				O_2 extraction*			
	Rest		Exercise		Rest		Exercise		Rest		Exercise		Rest		Exercise	
	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
	L/min BTPS				*resp./min*				*ml/min STPD*				%			
DS	7.50	5.33	50.0	21.3	16	13	33	23	265	254	850	932	3.92	4.25	4.55	5.50
FC	11.40	7.55	46.0	19.6	27	25	42			227	1,220	1,150		3.00	5.25	5.90
MC	8.30	3.50	28.8	24.2	25	15	30		340	138	1,160	1,065	4.10	3.94	4.00	6.10
LF	10.65	5.56	34.2	12.3	30	21	40	31	315	216	615	523	2.96	3.90	3.63	5.13
SC	8.00	4.47	49.6	22.0	29	22	48	31	342	210	1,100	770	4.25	4.70	3.74	5.65
AL†	8.03	6.90		43.5	17	16		24	265	254				3.16		
Mean	9.26	5.28	41.72	29.42	25	19	39	28	315	204	989	940	3.81	3.96	4.23	5.66
SD	±1.50	±1.34	±8.6	±4.1	±5	±4									±0.58	±0.36
	$p < 0.01$		$p < 0.01$												$p < 0.01$	

* Ventilation during period of oxygen consumption measurement.
† Unable to tolerate exercise while hyperthyroid.

during exercise was accomplished for the most part by an increase in frequency of breathing in the hyperthyroid subjects (42 ± 8; controls, 20 $\pm$ 4). At rest, mean oxygen consumption per unit BSA was significantly higher in hyperthyroid patients than it was in euthyroid controls, but during exercise oxygen consumption was not significantly different in the patient and control groups (Figure 4).

The oxygen extraction (rate of oxygen consumption divided by minute volume of ventilation) was not significantly different in the hyperthyroid patients and euthyroid controls at rest, but during exercise it was significantly less in the patients than in control subjects.

After treatment, frequency of breathing and minute ventilation during rest and exercise decreased significantly in the seven patients who were restudied (Table V, Figure 4). Oxygen extraction during rest was not significantly different after therapy, but during exercise this ratio increased significantly above the pre-therapy levels.

Dyspnea. The euthyroid subjects accomplished the required exercise without dyspnea. Preceding the exercise test, the hyperthyroid patients were instructed to signal by hand if they experienced respiratory discomfort. In four patients

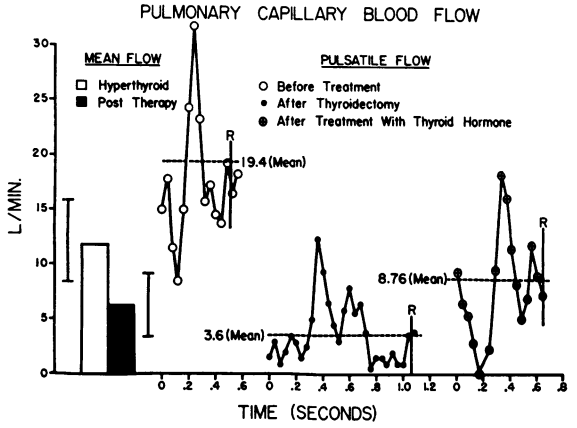

FIG. 5. MEAN PULMONARY CAPILLARY BLOOD FLOW BEFORE AND AFTER THERAPY (ON THE LEFT). Range bars define 1 standard deviation. Pulsatile pulmonary capillary blood flow of Patient DS appears on the right. Flow in liters per minute is on ordinate; time in seconds is on abscissa. 0–R (– – –) indicates one R–R interval on electrocardiogram; ○ = pulsatile flow in Patient DS before therapy; ● = after therapy and prior to clinical appearance of hypothyroidism; ⊕ = after treatment with thyroid hormone.

who so signalled, the inspiratory gas was changed from air to oxygen by manipulation of a hidden valve. In all four subjects dyspnea disappeared and there was a fall in rate of respiration. On re-examination, all patients had noticed improvement in exercise tolerance (Table V). AL, who was unable to tolerate the exercise test prior to therapy, stated that she could climb two or three flights of stairs without discomfort.

Pulmonary capillary blood flow and diffusing capacity. In the hyperthyroid patients at rest, peak levels of pulsatile flow in the pulmonary capillaries reached levels as high as those obtained on normal euthyroid subjects immediately after mild exercise (18). A representative pattern of pulsatile flow in Patient DS is shown in Figure 5. Following remission of symptoms, mean flow rates and peak flow rates decreased (Table VI and Figure 5). The low pulmonary capillary blood flow observed following therapy in three of the patients appears to be related to impending hypothyroidism, since these patients subsequently became grossly hypothyroid. In one of these latter three patients, DS, there was a substantial increase in pulmonary capillary blood flow during therapy with thyroid hormone (Figure 5). Apparent diffusing capacity, true membrane diffusing capacity and pulmonary capillary blood volume at rest were not elevated before treatment of hyperthyroidism and significant changes did not occur

TABLE VI

Pulmonary capillary blood flow ($\dot{Q}_c$), apparent diffusing capacity for CO(D_L) at different alveolar oxygen tensions, true membrane diffusing capacity (D_M) and pulmonary capillary blood volume (V_c) *

	Before treatment							After treatment						
				D_M		V_c					D_M		V_c	
Patient	$\dot{Q}_c$	P_{AO_2}	D_L	Meas.	Pred.†	Meas.	Pred.†	$\dot{Q}_c$	P_{AO_2}	D_L	Meas.	Pred.†	Meas.	Pred.†
RR		113	18.7	30	47	80	66							
		560	10.8											
DS	19.4	99	20.7	72	49	57	69	8.5	124	19.3	48	50	54	72
									230	15.2				
		362	13.0						403	11.9				
		622	8.0						574	9.1				
FC	7.5	105	18.3	34	56	59	80	10.4	120	16.9				
		216	13.2											
		504	9.5											
MC	9.6	112	20.4	48	48	65	68	4.3	144	19.6	63	51	62	73
		469	10.7						428	11.9				
		614	9.1						571	9.4				
LF	12.3	125	18.6	43	41	80	58	8.4	133	18.7				
		314	14.2											
		609	9.2											
SC	7.2	126	15.6	58	51	45	73	3.0	146	14.5	53	56	46	80
		308	10.2											
		609	6.5						581	6.7				
AL	14.0	126	14.7	65	41	50	58	3.1	120	12.4				
		248	11.3											
		423	9.0											
		568	5.8											
EM	12.2	120	14.3					6.2	120	15.0				
AT		129	22.5	56	55	75	79							
		317	16.4											
		608	10.8											
Mean	11.7			48	51	69	64	6.3			55	52	54	75

* Units: $\dot{Q}_c$ is in L/min; D_L and D_M are given in ml/(min × mm Hg); V_c is in ml; P_{AO_2} is given in mm Hg.

† Predicted D_M and V_c were calculated from predicted D_L utilizing the observation that the membrane and corpuscular resistances to CO diffusion in a normal resting subject are approximately equal (17). For this, D_L was predicted with a standard formula using body surface area (15).

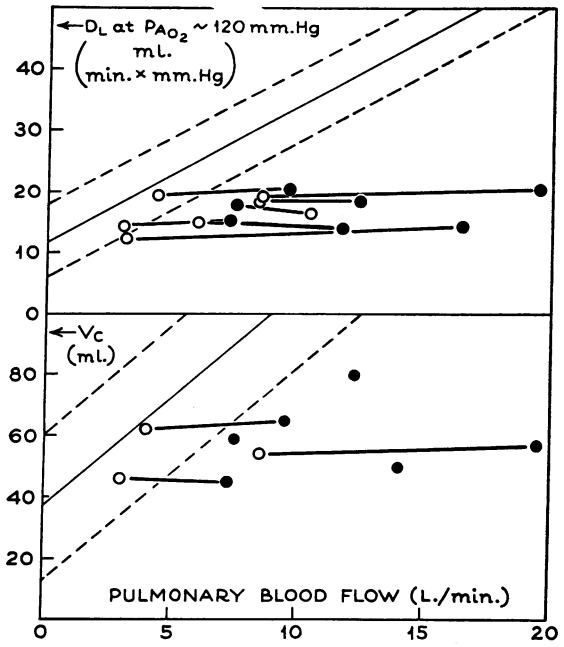

FIG. 6. THE RELATIONSHIPS OF LUNG DIFFUSING CAPACITY (DL) AND PULMONARY CAPILLARY BLOOD VOLUME (V_c) TO PULMONARY BLOOD FLOW. Results for each patient before (●) and after (○) successful treatment of hyperthyroidism have been connected by straight lines. The solid diagonal lines are the regression lines describing the changes in DL and V_c as blood flow was altered by physical activity in 4 normal male subjects (43); the parallel dashed lines delimit two standard errors of estimate on either side of the regression lines.

following successful therapy (Table VI). The absence of any significant correlation between changes of pulmonary blood flow and changes of either diffusing capacity or pulmonary capillary blood volume before and after treatment are illustrated in Figure 6.

Arterial blood gases (Table VII). The arterial oxygen saturation measured in seven of the hyperthyroid subjects was normal at rest and on exercise. There was not an abnormal right to left shunt as indicated by the normal amount of oxygen dissolved in plasma while breathing 100 per cent O_2. Arterial blood carbon dioxide tension and pH were within normal limits, but in several patients decreases in arterial blood P_{CO_2} occurred during exercise. During resting ventilation the total dead space comprised 38 per cent of the tidal volume, but during exercise, the total dead space increased to an average of 50 per cent in the four patients so studied.

DISCUSSION

Vital capacity

The present studies once again demonstrated a decreased vital capacity in some patients with hyperthyroidism. Although the mean pretreatment value was not significantly less than predicted, there were large rises of vital capacity in five of the seven patients restudied after therapy.

The low vital capacity prior to therapy may be related to the low lung compliance and to the muscular weakness which has been observed to accompany the hyperthyroid state (24). However, the fact that the total lung capacities of the group were the same before and after treatment is evidence against changes in lung compliance being the major determinants of the observed changes in vital capacity. An alternative explanation would be that sufficient effort to complete

TABLE VII
Arterial blood studies

Patient	Arterial oxygen saturation		Dissolved oxygen*	pH		P_{ACO_2}	
	Rest	Exercise		Rest	Exercise	Rest	Exercise
	%		*vol %*			*mm Hg*	
DS	98.3	98.4	2.11	7.35	7.32	46	41
FC	95.1		1.77	7.36		42	
MC	97.5	98.7	2.00	7.40	7.33	42	43
LF	98.5	96.6	1.65	7.37	7.35	43	40
SC	94.8	96.1	1.93	7.37	7.38	46	39
AT	97.7	98.6	1.78	7.38	7.32	42	37
MB	99.0	98.3	1.90	7.34	7.41	46	36
Mean	97.3	97.8	1.76	7.37	7.36	44	39
Normal	96–99		>1.5	7.34–7.44		35–45	

* After breathing 99.6% oxygen for 15 minutes.

maximal expiration could not be sustained against *1*) the opposing elastance of the rib cage, *2*) frictional forces in the lung and chest wall, and *3*) increased inspiratory muscle tone (25). Although it is possible that congestion of the lungs with blood is a major factor causing the low vital capacity, the application of tourniquets on several of the hyperthyroid subjects did not elevate vital capacity to predicted or post-therapy levels. Since airway resistance measurements were normal in all but one of the patients, it is unlikely that generalized bronchial obstruction played a prominent part in the observed changes in vital capacity. RR, who had a large goiter with tracheal compression, had a slight increase in airway resistance, which did not decrease after an aerosolized bronchodilator and was therefore probably not due to bronchospasm. The normal values for distribution of inspired air in these patients also is not consistent with diffuse obstructive pulmonary disease.

Compliance

The mechanism of the decreased lung compliance observed in the hyperthyroid patients is not clear at the present time. Five possible mechanisms have been considered: *1*) changes in the FRC; *2*) pulmonary congestion and edema; *3*) increased intrathoracic blood volume; *4*) alterations in the retractile properties of alveolar septa; *5*) a decrease in the number of functioning alveolar units during quiet breathing.

1) *FRC.* A marked decrease or elevation of FRC may affect the lung compliance (*26, 27*). A decrease in FRC may be related to closure of a sufficient number of alveolar units so that an increased "opening pressure" is required (28). An increase in FRC, on the other hand, may be accompanied by an increase or decrease in the lung compliance. If the FRC be sufficiently increased to expand the volume to a position on the pressure-volume curve near its plateau, the compliance would decrease. If, after therapy, the FRC were increased sufficiently so that previously collapsed alveoli were expanded, the compliance would increase. Analysis of our data, however, reveals no significant change in mean pre- and post-treatment FRC to account for the observed changes in lung compliance.

2) *Pulmonary capillary congestion and edema.* We have demonstrated that the peak pulmonary capillary blood flow of the hyperthyroid patients at rest reaches levels greater than that in most euthyroid subjects after moderate exercise. At peak levels of flow, the hydrostatic pressure in the capillaries may force fluid into the interstitial spaces from which colloidal osmotic pressure or lymphatic flow cannot remove it rapidly enough to prevent accumulation. Such an increase in interstitial fluid, although this is pure conjecture, might produce a decrease in pulmonary compliance. Evidence to implicate ventricular failure in the genesis of pulmonary edema in exercising hyperthyroid subjects is lacking. Bishop, Donald and Wade (*29*) measured "wedge" pressures in three resting hyperthyroid subjects and observed an elevation in only one subject without overt congestive heart failure. Our finding of a normal D_M and a normal Vc during rest in these hyperthyroid patients makes the presence of pulmonary edema seem unlikely. Furthermore, in 11 of the 13 hyperthyroid subjects, there was no clinical or X-ray evidence of pulmonary congestion and edema. The normal arterial oxygen saturations at rest and on exercise and the normal airway resistance measurements also would be inconsistent with the presence of pulmonary edema and congestion as causative factors in the decreased compliance.

3) *Changes in intrathoracic blood volume other than in pulmonary capillaries.* An increase in total blood volume has been previously observed in hyperthyroidism (30). However, an increase in intrathoracic blood volume displacing pulmonary gas does not seem likely as a factor in the observed decrease of compliance in view of the normal values for total lung capacity and the failure of tourniquets to elevate the vital capacities to predicted or post-therapy levels in these patients.

4) *Alterations in the retractile properties of alveolar septa.* These alterations might occur as the result of changes in composition, structure, or configuration of the elastic components of the alveolar septa (31). However, evidence relating to such changes caused by hyperthyroidism is not available. Changes in composition of the alveolar mucoid film (*32, 33*) might alter tension at the air-liquid interface of alveoli and of small airways. This also could significantly alter the retractile forces in the lung. Depositions of mucoid mate-

rials have been observed in the orbit and lower extremities of hyperthyroid patients, although there have been no observations of a change in the alveolar mucoid film in hyperthyroidism.

5) Alterations in the number of functioning alveolar units. Lung compliance is the sum of the compliance of the smallest functioning volume units. Occlusion of unstable alveolar units by interfacial forces might result from muscle weakness in hyperthyroidism. Such changes would produce a decreased compliance. Similar decreases in lung compliance have been observed in patients with poliomyelitis (34).

Exercise ventilation and oxygen consumption

The hyperthyroid subjects had significantly greater respiratory minute volumes and rates of respiration during exercise in comparison with post-therapy studies or measurements on euthyroid controls. These findings could be the result of several factors. *1)* Muscular weakness and decreased lung compliance may induce a rapid rate of respiration as a means of minimizing the work necessary to achieve a given ventilation (35, 36). *2)* An abnormally large production of carbon dioxide during exercise may act as a respiratory stimulant. Although these studies do not preclude an increased sensitivity of the respiratory centers to carbon dioxide in hyperthyroid patients, carbon dioxide production and arterial P_{CO_2} during moderate exercise were no greater than they were after therapy or in euthyroid controls. *3)* Increased heat may have been a stimulus to the respiratory center. An increase in rate of respiration and ventilation usually accompanies an increase in body temperature (37). Maley and Lardy (38) and Hoch and Lipmann (39) have demonstrated by *in vitro* techniques that thyroxine produces a biochemical alteration whereby energy in the cell is dissipated as heat rather than by the formation of high energy phosphates. Heat intolerance is a frequent clinical observation in hyperthyroid patients, and many of the patients studied complained of warmth and sweating during the exercise test. *4)* The respiratory center may be stimulated directly by thyroid hormone or its metabolites. Williams, Winters, Clapp and Welt (40) have recently observed an increase in ventilation in animals treated with dinitrophenol. In their experiments, hyperventilation occurred even in the presence of respiratory alkalosis. They postulated that dinitrophenol might act as a respiratory stimulant. Since thyroxine and dinitrophenol have many similar actions, it is possible that thyroid hormone may also exert a direct or indirect effect on the respiratory center. *5)* The subjects who observed dyspnea on exercise experienced rapid relief of this symptom when allowed to breathe 100 per cent O_2 while continuing the exercise, even though arterial oxygen saturation was normal prior to oxygen. Ventilation per unit of oxygen consumption may be decreased when 100 per cent O_2 is administered to certain types of patients, usually those with hypoxia. This may indicate that tissue demand for oxygen may be operative in the increased ventilation observed in patients with thyrotoxicosis.

The decreased oxygen extraction in exercising hyperthyroid patients is probably due to an increase in total dead space ventilation produced by an increased frequency of breathing and an augmented alveolar or parallel dead space ventilation. Similar results in exercising hyperthyroid patients have been reported by Bates (41). Alveolar ventilation appears to have been adequate during exercise as there was no evidence of arterial oxygen unsaturation or carbon dioxide retention in any of the patients studied.

The dyspnea observed in many of the patients, while they were hyperthyroid, did not appear to be related to the size of the goiter or to an increase in minute ventilation accompanying an increase in oxygen uptake (23), but rather to a combination of several factors. In no patient was the airway resistance increased to a level considered sufficient to cause dyspnea of airway obstruction, and the increment of minute ventilation during exercise was consistently greater than that of oxygen consumption. Therefore, the dyspnea of hyperthyroidism appears to be related to other factors such as decreased compliance, decreased respiratory muscular strength (42), increased dead space ventilation, and perhaps an abnormal stimulus to respiration.

Diffusion and capillary blood flow

In each of these hyperthyroid patients the dimensions of the pulmonary capillary bed, as reflected by D_L, D_M and Vc, were essentially normal at rest even though the resting blood flow was

approximately twice to three times normal. Bates has made similar observations in patients with hyperthyroidism during light exercise, showing that DL is low in respect to the oxygen consumption (41), and by inference, even lower in respect to the cardiac output.

These findings in hyperthyroid patients are not inconsistent with reported findings in other circumstances where pulmonary blood flow is increased and DL is not. Ross, Frayser and Hickam (43) have shown that increases of pulmonary blood flow induced by epinephrine or norepinephrine are not accompanied by changes of diffusing capacity; and Turino, Brandfonbrener and Fishman (44) have shown that diversion of the total resting cardiac output through one lung in a man does not increase DL in the over-perfused lung. Therefore, failure to find DL increased during rest in these hyperthyroid patients in response to the increased resting pulmonary blood flow does not necessarily indicate an abnormal response of the vascular bed.

These observations in hyperthyroid patients are of interest because of the still pending question as to which factors control the size of the pulmonary capillary bed. It may be that the pulmonary intravascular pressures are not sufficiently increased by the increased blood flow in hyperthyroidism to cause the capillaries to expand. The data of Bishop and associates (29) indicate that the relationship between pulmonary blood flow and pulmonary arterial pressure is normal in patients with hyperthyroidism, but significant data are not available concerning pulmonary capillary pressure. Thus, the possibility that lung capillaries have failed to expand in these patients, owing to a transmural capillary pressure lower than normal in respect to blood flow, cannot be eliminated. Furthermore, if the low lung compliances observed in these hyperthyroid patients reflect a true change in the elastic properties of the septal tissues of the lung, it is not unreasonable to suspect that septal capillaries are similarly affected. This would mean that the vascular volume would tend to be less than normal for the same transmural pressure difference.

In contrast to the findings in hyperthyroid patients, a close reproducible relationship has been found between pulmonary capillary blood flow ($\dot{Q}c$) and DL in normal subjects at rest and during various grades of exercise (45, 46). It is reasonable to suspect that DL is increased during exercise by passive distention of the capillary bed owing to an increase in intravascular pressure accompanying the increased flow. The observation that an increase in intravascular pressure at constant pulmonary blood flow causes DL to increase in the isolated perfused cat lung (47) confirms this explanation. However, the increase of DL during exercise in normal subjects may be caused by a mechanism or mechanisms other than passive distention of capillaries: *1*) The size of the pulmonary capillary bed may actually remain fixed during exercise but an apparent change of DL, DM and Vc could occur if the relationship between intracorpuscular oxygen tension and the reaction rate (θ) between CO and oxyhemglobin were altered during physical activity. This possibility has not been entirely disproved, but it seems unlikely, since θ is relatively insensitive to the changes of blood pH, CO_2 tension and lactic acid concentrations normally associated with exercise (48–50). *2*) Increased ventilation has been suggested as the principal cause for the increase of DL during exercise (43, 44). Hyperventilation at rest causes DL to increase significantly when measured by steady state methods, but hyperventilation cannot explain the increases of DL, DM and Vc during exercise measured by breath-holding methods (15). The increase of DL by steady state measurements during hyperventilation may be related in part to an associated increase of mean lung volume as suggested by the work of Marshall (51). *3*) The size of the pulmonary capillary bed may be primarily determined by vasomotor activity in small pulmonary blood vessels. For instance, changes in chemical composition of venous blood returning to the lungs during exercise might mediate the observed expansion of the pulmonary capillary bed either by a direct action on the blood vessels or by reflex vasodilatation. In support of this, inhalation of CO_2 by normal subjects has been found to increase DL before significant rises in pulmonary capillary blood flow can be demonstrated (52). In patients with hyperthyroidism, arteriovenous oxygen differences are smaller than normal, therefore, CO_2 tension in mixed blood may be normal or low, providing no stimulus for capillary bed expansion. This possibility requires further evaluation.

TABLE VIII

Right ventricular stroke volume, pulmonary capillary blood volume, and mean transit time for blood through pulmonary capillaries

Patient	Before treatment			After treatment		
	Stroke vol.	V_c	Mean capillary transit time	Stroke vol.	V_c	Mean capillary transit time
	ml	*ml*	*sec*	*ml*	*ml*	*sec*
DS	164	57	0.18	106	54	0.38
FC	62	59	0.47	120	59*	0.34
MC	120	65	0.41	67	62	0.86
LF	111	80	0.39	73	80*	0.57
SC	63	45	0.38	46	46	0.92
AL	127	50	0.21	39	50*	1.01
EM						
Mean	108	59	0.34	75	58	0.68

* These values were assumed to be the same after treatment as they were before treatment.

Transit times through pulmonary capillaries

Another aspect of these data which stimulates speculation concerns the short intervals that red cells apparently remained in lung capillaries of these hyperthyroid patients during one circulation (Table VIII). In normal subjects at rest the average time spent in pulmonary capillaries during a single circulation is about 0.75 second and, during moderate exercise, expansion of the capillary bed tends to keep transit time at 0.5 second or more even though blood flow may be tripled (43). Also, the pulmonary capillary blood volume in normal subjects tends to be larger than the cardiac stroke volume and this insures a fairly uniform time of exposure of red cells to the lung diffusing surface, despite the pulsatile nature of pulmonary capillary flow. In the hyperthyroid patients, the rate of blood flow during rest was doubled or tripled, whereas the volume of the pulmonary capillary bed remained fixed at normal resting dimensions and the capillary blood volume was less than the cardiac stroke volume (Table VIII). Therefore, the mean pulmonary capillary transit time was not only short in these patients, but some red cells must have flowed past the alveolar capillary diffusing surface in much less than the estimated mean transit time, as indicated in the lower half of Figure 7. As a consequence, the oxygen tension gradient between alveolar air and end-capillary blood in the lungs of these patients should have been larger than in normal subjects under the same conditions. In order to estimate the possible magnitude of this increased gradient, approximations of the time course of intracorpuscular oxygen tension during capillary transit in the lung have been constructed for Subject DS, using the Bohr integration procedure (53) (Figure 8). In order to construct these curves, D_L was estimated with Equation 2, assuming that the D_M for oxygen is 1.23 times that for CO and assuming two different average values for θ_{O_2}. Only recently, θ_{O_2} has been measured within the physiological range of oxygen saturations, and although it has been found to remain relatively constant within the range of zero to 85 per cent blood oxygen saturation, θ_{O_2} falls as the oxygen saturation rises above 85 per cent and approaches zero as oxygen saturation approaches completion (54). Assuming that the average θ_{O_2} for blood traversing the

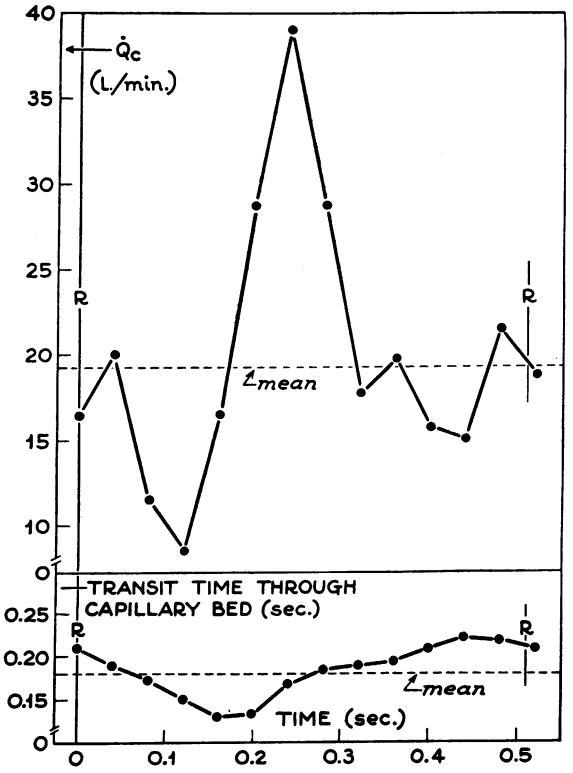

FIG. 7. ESTIMATES OF INSTANTANEOUS FLOW ($\dot{Q}c$) AND TRANSIT TIME THROUGH THE CAPILLARY BED OF RED CELLS ENTERING LUNG CAPILLARIES AT DIFFERENT MOMENTS WITHIN A CARDIAC CYCLE. The subject is DS before treatment of the hyperthyroid condition. The temporal positions of the ECG R waves in relation to flow events are indicated by vertical lines. In making estimates of transit time it was assumed that the pulmonary capillary blood volume remained 57 ml throughout the cardiac cycle (Table VI).

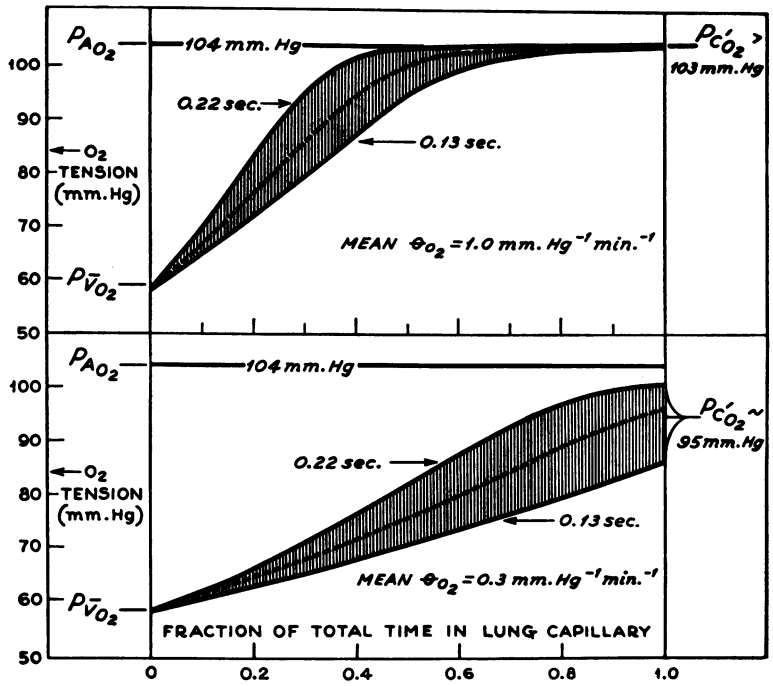

FIG. 8. OXYGEN TENSION IN RED CELLS AS THEY PASS ALONG AN ALVEOLAR CAPILLARY IN SUBJECT DS BEFORE TREATMENT OF HYPERTHYROIDISM. Two limiting values of θ_{O_2} have been assumed. $P_{A_{O_2}}$ and $P\bar{v}_{O_2}$ are the alveolar and mixed venous oxygen tensions, respectively. The dashed curves represent the oxygen tension in a red cell traversing the alveolar capillary bed in the calculated mean transit time (0.175 second, see Figure 7), and the solid lines forming the upper and lower boundaries of the cross-hatched areas represent the oxygen tension in red cells traversing capillaries in the longest and shortest times, respectively, during pulsatile flow (Figure 7). Pc'_{O_2} represents the end-capillary blood oxygen tension after mixing has smoothed out temporal as well as regional non-uniformity of oxygen saturation. Because of the shape of the blood oxygen dissociation curve, the end-capillary oxygen saturation of blood which has remained in the lung capillaries for longer than the mean transit time cannot take up sufficient additional O_2 to make up for the lesser end-capillary O_2 saturation of that blood which has traversed the capillaries in less than the mean transit time. For this reason oxygen tension of the mixed end-capillary blood (Pc'_{O_2}) is less than the oxygen tension of blood which has passed through the alveolar capillaries in the mean transit time, unless, of course, the transit time is constant throughout the cardiac cycle.

capillary bed in DS might reasonably lie between 1.0 and 0.3 mm Hg^{-1} min^{-1} (17), the mean DL_{O_2} would lie between 28 and 11 ml (per minute $\times$ mm Hg), respectively. The curves in Figure 8 were constructed, using these assumptions. The transit times were obtained from the data plotted in Figure 7. The rates of O_2 diffusion at different points along a pulmonary capillary and, consequently, the shape of the O_2 tension rise with time are critically dependent upon the manner in which θ_{O_2} decreases as hemoglobin saturation increases, but even at the lower assumed value for mean θ_{O_2}, the mixed end-capillary O_2 tension in this patient should have been within 10 mm Hg of the alveolar oxygen tension. This end-capillary gradient is still compatible with the normal resting arterial oxygen saturations measured in these patients (Table VII).

SUMMARY

1. The vital capacity was decreased in some, but not all, of the hyperthyroid patients studied.

Following therapy, the vital capacity reached predicted normal or higher levels in the majority of patients restudied.

2. The lung compliance in hyperthyroidism was decreased.

3. Elevation of airway resistance observed in only one patient was insufficent to produce symptoms of respiratory obstruction.

4. Measurements of pressures at the mouth on maximal expiratory and inspiratory effort against a closed airway indicated weakness of the respiratory muscles.

5. On exercise the patients' ventilation was increased in excess of the oxygen uptake when compared to a group of controls of similar age and body size. This was apparently related to an increase in the dead space ventilation due to an increase in frequency of breathing and alveolar dead space ventilation.

6. Following remission of symptoms produced by surgical thyroidectomy, radioactive iodine, or propylthiouracil drugs, the previously described abnormalities reverted to normal levels.

7. In hyperthyroid patients, apparent diffusing capacity of the lung (D_L), pulmonary capillary blood volume (Vc), and membrane diffusing capacity (D_M) at rest were not elevated in the presence of significant elevations of pulmonary capillary blood flow. Reductions of pulmonary capillary blood flow following successful therapy were not associated with significant changes in D_L, Vc, or D_M.

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