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THE EFFECT OF CHANGES IN THE PULMONARY VASCULAR BED PRODUCED BY ATROPINE, PULMONARY ENGORGEMENT, AND POSITIVE-PRESSURE BREATHING ON DIFFUSING AND MECHANICAL PROPERTIES OF THE LUNG *

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Several factors probably have some role in determining the volume of the effectively ventilated pulmonary capillary bed, including pulmonary blood flow, pulmonary vascular pressures, pulmonary blood volume, alveolar and blood gas tensions, and mechanical effects of ventilation.

Others have found that atropine sulfate, 2.0 mg iv, increases cardiac output (1, 2), decreases central venous pressure (1, 2), and affects the distribution of the blood volume as shown by plethysmographic study of extremity venous volume (3). This drug, then, provides an unusual rearrangement of some of the determinants of pulmonary capillary function and, for the present study, was used either alone or in combination with positive-pressure breathing or pulmonary vascular engorgement produced by G-suit inflation.

This study was carried out to provide further information concerning the interaction of cardiac output, pulmonary vascular pressure, and pulmonary blood volume as determinants of the volume of effectively ventilated capillaries by determining the effects of changes in the pulmonary vascular bed produced by atropine, pulmonary engorgement, and positive-pressure breathing on the diffusing and mechanical properties of the lung.

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METHODS

Subjects. These studies were carried out in a group of 17 trained, normal, male subjects with an age range from 22 to 34 and body surface area range from 1.85 to 2.20 m^2. All studies were carried out no sooner than 3 hours after a light meal and after the subjects had rested at least 30 minutes in the laboratory.

Experimental conditions. Observations were made with the subject either supine or sitting, as required by the specific experimental procedure. Data obtained with the subject in different postures were collected on separate days and are not used for comparison. Observations were made before and beginning 10 minutes after the iv administration of 2.0 mg of atropine sulfate.

Several subjects were studied before and during pressure-suit inflation over the lower part of the body, both before and after the administration of atropine sulfate. The suit used is a single-chamber, balloon-type garment [1] that covers the feet, legs, and abdomen and can be inflated to the desired pressure within 5 seconds by a standard Air Force G valve. The suit was laced on the subject carefully to provide even distribution of pressure. All determinations for comparison with those made during suit inflation were carried out with the subject wearing the laced but uninflated suit. All determinations made during suit inflation were carried out after the suit had been inflated to a pressure of 100 mm Hg for 30 seconds, a pressure which, in previous studies, produced a mean rise in central venous pressure of 25 mm Hg in seated subjects (4) and increases of 1.35 mm Hg in intrathoracic pressure, 5 mm Hg in gastric pressure, and 18 mm Hg in rectal pressure in supine subjects (5). Subjects were trained to keep the glottis open during suit inflation to avoid a Valsalva maneuver.

Positive-pressure breathing was carried out from a closed system consisting of a 200-L drum, a Douglas valve, an underwater exhaust for flushing the system,

[1] This full pressure half-suit was made by the David Clark Co., Inc., Worcester, Mass., and in this paper, is referred to as a G suit. This suit, however, is not a standard aviator's G suit and cannot be used in that way, since it provides much more G protection than the standard aviator G suit, which comprises only abdominal, thigh, and skin bladders, but doesn't apply pressure to feet, ankles, knees, hips, and buttocks.

and a CO_2 absorber in the expiratory line (Figure 1). Because of the large volume of the system in relation to the tidal volume and because of a high air-flow rate through an underwater exhaust, respiratory pressure fluctuations in the system were minimal. Regulation of the rate of inflow of compressed air further regulated the pressure in the system. Pulmonary diffusing capacity was measured before and 2 minutes after beginning positive-pressure breathing.

Hemodynamic measurements. Cardiac output was determined in duplicate in the supine position by the indocyanine green dilution method with a Gilford IR 103 densitometer. Dye injections were made into the pulmonary artery during the end-expiratory phase of respiration. Cardiac output was calculated by the Hamilton semilog replotting method (6). Duplicate determinations of cardiac output by this method are reproducible with a mean difference of 3.8% in this laboratory. Duplicate determinations of cardiac output during maintained inflation of the G suit or during positive-pressure breathing showed no greater variability if the dye injections were made during the period 30 seconds to 5 minutes after G-suit inflation or 1 to 3 minutes after beginning positive-pressure breathing. This suggests that within these time limits a reasonably steady state is attained so that the dye dilution method may be used to measure flow reliably.

Intravascular pressures were recorded by Statham P-23D transducers and a multichannel recording system. Pulmonary artery, right atrial, and brachial arterial pressures were recorded simultaneously, referred to the midthoracic level, electronically integrated, and recorded over several respiratory cycles.

Pulmonary blood volume estimations. Changes in pulmonary blood volume after atropine were estimated by the method described by Bondurant, Hickam, and Isley (7) and by Weissler, McCraw, and Warren (8). A Nuclear-Chicago 183-B scaling unit, 1810 radiation analyzer, and DS5-1 probe scintillation counter [2] were used with the 20° collimator. A convenient area in the right mid-lung field, well away from the mediastinal region and well above the diaphragm was selected for counting and marked on the skin. The collimator was applied directly to the skin in an axis perpendicular to the frontal plane of the body at a measured distance from the table top. After background counting over this area, 50 μc of I^{131}-albumin was injected intravenously. Twenty minutes later, counting was begun over the same region and then repeated 10 minutes after the iv administration of 2.0 mg of atropine. In all cases, the counting rate was at least eight times the background rate. Three or more counting periods with a minimum of 1,680 counts each were used before and again after atropine. Between periods, the probe was removed from the skin, redirected, and replaced so that variability in probe placement and orientation could be made random. The variability among such periods was $2.4 \pm 1.5\%$. Further extension of the time allowed for mixing of the administered I^{131}-albumin did not result in a change in the counting rate; consequently, altered counting rates observed after atropine do not represent further dilution of the administered dose. As was observed by Bondurant, Hickam, and Isley (7) and by Weissler, McCraw, and Warren (8), Valsalva maneuvers produced striking decreases in the counting rate over the lung. Percentage of change in pulmonary blood volume after atropine = (counts per minute after atropine − background counts per minute)/(counts per minute before atropine − background counts per minute) × 100.

[2] Nuclear-Chicago Corp., Des Plaines, Ill.

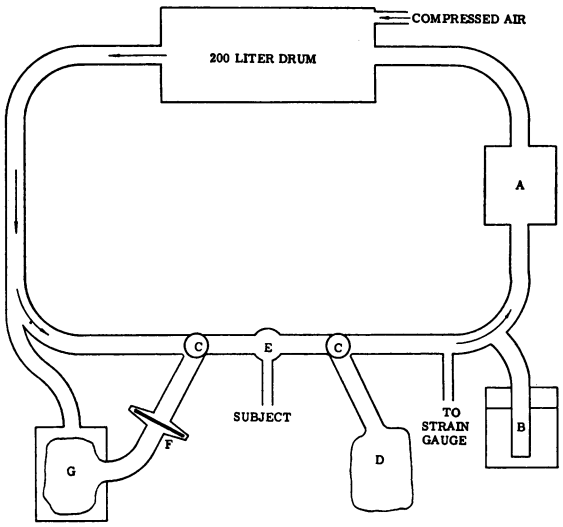

FIG. 1. APPARATUS FOR POSITIVE-PRESSURE BREATHING. A = CO_2 absorber; B = underwater exhaust (pressure in the system is determined by the depth of the exhaust tube under water; pressure fluctuations are minimized by keeping a high flow rate); C = three-way valves; D = bag for collecting alveolar sample; E = Douglas valve; F = pneumotachograph; and G = gas bag containing 0.4% CO. Pressure is maintained by constant flow of compressed air, and recorded directly from a Statham P-23D strain gauge.

Pulmonary diffusing capacity (D_L) and capillary blood volume (V_c) determinations. D_L was determined by a modification of the Krogh breath-holding technique described by Forster and co-workers (9, 10) and as previously carried out in this laboratory (4). For calculation of V_c by the method of Roughton and Forster (11), D_L was determined at two different alveolar O_2 tensions in each subject by using different concentrations of O_2 in the inspired gas mixture. Determinations were made in duplicate under each condition. A period of at least 5 minutes was allowed between D_L determinations. In the group in which the effects of atropine and G-suit inflation were studied, the gas mixture containing 0.4% CO was inspired from a bag in a box connected to a spirometer, so that the inspired volume and breath-holding time were recorded on the spirometer tracing. When the determinations were made with ambient- and positive-pressure breathing before and after atropine, the area in the

TABLE I

Lung volumes, airway resistance, and blood oxygen

	FRC*		Vs		AR		O_2 Cap		O_2 Sat		$V_{D(phys)}$	
	B	A	B	A	B	A	B	A	B	A	B	A
Mean	3.46	3.32	0.61	0.54	1.82	1.45	19.2	19.4	96.0	96.0	139	166
SD	0.81	0.85	0.45	0.24	0.39	0.32	0.7	1.1	1.1	0.7	13	24
p	0.2		0.2		0.05		0.4				0.01	

* FRC = functional residual capacity, liters (BTPS, body temperature, pressure, saturated with water); Vs = slowly ventilated space, liters (BTPS); AR = airway resistance, liters per second per centimeter H_2O; O_2 Cap = arterial blood oxygen capacity, volume per cent; O_2 Sat = oxyhemoglobin saturation, per cent; $V_{D(phys)}$ = physiologic dead space, milliliters (BTPS); B = before atropine; and A = after atropine.

box around the bag containing the inspired mixture was not connected to a spirometer, but rather to the positive-pressure breathing system already described (Figure 1), so that when measurements were made during pressure breathing, the gas mixture was inspired at the pressure at which the subject had been breathing. A pneumotachograph was interposed in the airway near the mouthpiece, and respiratory flow was integrated and recorded on a photographic recorder for determination of the inspired volume and breath-holding time. The apparatus dead space, which is included in the alveolar volume (V_A), was small (< 100 ml) and constant under all conditions. By having the subject regulate the inspired volume, it was possible, in an individual subject, to determine D_L at approximately the same V_A under each condition studied.

D_L was calculated with the Krogh equation (12) as modified by Forster and co-workers (9, 10): D_L (ml CO_{STPD} per minute per mm Hg CO) $= [(V_A)(60)]/[(t)(P_B - 47)] \times [\ln (FA_{CO_0}/FA_{CO_t})]$. V_A is the alveolar volume (STPD, standard temperature, pressure, dry $-$ 0° C, 760 mm Hg); t is the breath-holding time in seconds; $P_B - 47$ is the barometric pressure less the vapor pressure of water at 37° C (in calculations of D_L when subjects were breathing 10 mm Hg positive pressure, this factor was $P_B + 10 - 47$; FA_{CO_0} is the initial alveolar CO concentration calculated by multiplying the inspired CO concentration by the ratio of the expired alveolar He concentration to inspired He concentration; and FA_{CO_t} is the alveolar CO concentration at the end of the breath-holding period as measured in the alveolar sample. A correction for capillary CO tension (P_{CO}) equilibrated with small amounts of CO-hemoglobin present in the blood was made in each determination by subtracting the P_{CO} from both initial and final alveolar CO concentrations as previously described (9).

V_c was calculated by the technique outlined in detail by Roughton and Forster (11). The mean capillary O_2 tension was estimated by the technique suggested by McNeill, Rankin, and Forster (13). θ for the appropriate O_2 tension was obtained from the data of Roughton, Forster, and Cander (14) by using a ratio of red-cell membrane permeability to that of its interior of 2.5, which they found to be the average value. These values for θ were calculated on the basis of a CO capacity of 20 ml per 100 ml blood. Since each subject served as his own control and no significant change in oxygen capacity in an individual subject was noticed under our experimental conditions (Table I), no corrections were made for variations of CO capacity from 20 ml per 100 ml blood. It is true that variations in θ, while not altering the direction of change in an individual, could vary the degree of change. Since the O_2 capacity for this group was actually 19.2 ± 0.7, however, the variability is so small that the statistics would not be altered.

Lung compliance (C_L). C_L was measured by a linear pneumotachograph-integrator system and an esophageal balloon as described by Mead and Whittenberger (15). The expressed values for C_L represent the mean of values obtained over six to ten slow tidal volumes. Just before each determination, the subject made full inspirations so that the C_L changes that Ferris and Pollard (16) found associated with quiet breathing could be avoided. When C_L was determined during G-suit inflation, the subjects breathed into a recording spirometer so placed that they were able to observe their respiratory ex-

TABLE II

Hemodynamic changes after atropine sulfate, 2.0 mg iv, in 13 normal supine subjects

	CI*		HR		SI		RAP		PAP	
	B	A	B	A	B	A	B	A	B	A
Mean	2.96	3.64	65	104	47	35	7	4	19	14
SD	0.42	0.74	9	11	6	8	2	2	5	4
p		0.01	<0.001		<0.001		<0.001		0.005	

* CI = cardiac index, liters per minute per meter squared; HR = heart rate, beats per minute; SI = stroke index, milliliters per meter squared; RAP = mean right atrial pressure, millimeters Hg; PAP = mean pulmonary artery pressure, mm Hg (eight subjects); B = before atropine; and A = after atropine.

TABLE III

Hemodynamic effects of G-suit inflation before and after atropine, 2.0 mg iv, in eight normal supine subjects

	Before atropine		After atropine	
	Control	Suit inflated	Control	Suit inflated
Cardiac index, *L/min/m²*	3.12 ± 0.42	2.95 ± 2.52	3.70 ± 0.76	3.76 ± 0.45
	p = NS		p = NS	
Mean right atrial pressure, *mm Hg*	7 ± 2	15 ± 5	4 ± 2	7 ± 3
	p = 0.01		p = 0.01	
Mean pulmonary artery pressure, *mm Hg*	19 ± 5	26 ± 4	14 ± 5	19 ± 6
	p = 0.01		p = 0.01	

cursions. Each subject practised until he was able to control his breathing to avoid shifts in functional residual capacity (FRC) during suit inflation. C_L was measured before and 30 seconds after abrupt inflation of the G suit to 100 mm Hg before and 10 minutes after atropine.

Arterial blood and physiologic dead space [$V_D(phys)$] measurements. Arterial oxyhemoglobin capacity and saturation were determined spectrophotometrically (17, 18). Arterial P_{CO_2} and the P_{CO_2} of mixed expired gas were determined with a P_{CO_2} electrode system.[3] $V_{D(phys)}$ was determined by the method of Riley and co-workers (19) in seated subjects before and 10 minutes after administration of atropine.

Lung volumes and airway resistance. FRC and airway resistance were determined in the total body plethysmograph by the techniques described by DuBois and associates (20) and DuBois, Botelho, and Comroe (21). Expiratory reserve volume was measured on a Collins Stead-Wells spirometer and subtracted from FRC to obtain residual volume for use in calculation of D_L.

In some subjects, determinations of FRC and volume of the slowly ventilated component of the FRC (V_S) were also carried out by the open-circuit helium technique of Hickam, Blair, and Frayser (22).

Statistics. The effects of atropine, G-suit inflation, and positive-pressure breathing were examined statistically by the "paired comparison" *t*, with each subject serving as his own control (23).

TABLE IV

Change in estimated pulmonary blood volume after atropine, 2 mg iv, in normal supine subjects

Name	Percentage of change in estimated pulmonary blood volume after atropine*
J.W.	−10.5
D.W.	− 1.3
M.L.	−11.2
J.B.	−10.6
B.S.	− 9.8
M.P.	−12.0
Mean	− 9.2
SD	3.9
p	0.005

* (cpm after atropine−background cpm)/(cpm before atropine−background cpm) × 100.

[3] Model 103, Instrumentation Laboratories, Boston, Mass.

RESULTS

Hemodynamic effects of atropine. After atropine, in 13 subjects, cardiac index increased (2.96 ± 0.42 to 3.64 ± 0.74 L per minute per m², p = 0.01), heart rate increased (65 ± 9 to 104 ± 11 beats per minute, p < 0.001), stroke index decreased (47 ± 6 to 35 ± 8 ml per m², p < 0.001), mean right atrial pressure decreased (7 ± 2 to 4 ± 2 mm Hg, p < 0.001), and mean pulmonary artery pressure decreased (19 ± 5 to 14 ± 4 mm Hg, p = 0.005) (Table II).

G-suit inflation did not alter cardiac index either before or after atropine administration (Table III). Before atropine, mean right atrial pressure, measured 30 seconds after suit inflation, was consistently increased (7 ± 2 to 15 ± 5 mm Hg, p = 0.01). After atropine, suit inflation produced a smaller increase in right atrial pressure (4 ± 2 to 7 ± 3 mm Hg, p = 0.01).

Mean pulmonary artery pressure was increased by suit inflation (19 ± 5 to 26 ± 4 mm Hg, p = 0.01). After atropine, mean pulmonary artery pressure was increased only to the preatropine level (14 ± 5 to 19 ± 6 mm Hg, p = 0.01).

Pulmonary blood volume. The data of Table IV demonstrate a consistent decrease, averaging 9.2 ± 3.9%, in the counts detected over the right mid-lung field after atropine in six supine subjects.

D_L and V_c. The data in Tables V and VI demonstrate a decrease in D_L after atropine administration in both seated and supine subjects. In the seated subjects, mean D_L decreased from 25.2 ± 3.4 to 22.0 ± 3.8 ml CO per mm Hg per minute (p = 0.05). In supine subjects, atropine decreased D_L from 31.3 ± 7.3 to 25.5 ± 7.3 ml CO per mm Hg per minute (p = 0.005). In both supine and seated subjects, pulmonary V_c was decreased after atropine (seated, 85 ± 26 to 66 ± 12 ml, p = 0.01; supine, 112 ± 42 to 93 ± 34 ml, p = 0.025). Atropine had no significant effect on V_A.

Before atropine, G-suit inflation increased D_L (25.2 ± 3.4 to 30.6 ± 5.3 ml CO per minute per mm Hg, p = 0.005) and V_c (85 ± 16 to 117 ± 26 ml, p = 0.005), but caused no statistically significant changes in V_A (Table V). After atropine, suit inflation increased D_L (22.0 ± 3.8 to 25.7 ± 5.3 ml CO per mm Hg per minute, p = 0.025) and V_c (66 ± 12 to 79 ± 22 ml, p = 0.05) without significant change in V_A (Table V). After atropine, then, suit inflation increased both D_L and V_c, but not to the high level attained before atropine.

TABLE V

Pulmonary diffusing capacity (D_L), pulmonary capillary blood volume (V_c), and alveolar volume (V_A) in normal seated subjects: the effects of atropine, 2.0 mg iv, and G-suit inflation

Subject	Condition	V_A	D_L	V_c
		ml	*ml/min/mm Hg*	*ml*
J.O.	Seated	4,960	24.4	100
	G suit	5,390	32.4	125
	Atropine	4,390	21.3	83
	G suit	4,120	26.9	115
B.S.	Seated	3,890	20.2	61
	G suit	3,520	22.8	70
	Atropine	3,700	20.1	52
	G suit	3,560	19.6	46
D.F.	Seated	4,910	26.9	84
	G suit	4,530	30.0	125
	Atropine	4,650	18.2	67
	G suit	4,590	21.6	80
D.M.	Seated	4,500	25.8	95
	G suit	4,340	30.9	111
	Atropine	4,370	25.4	55
	G suit	4,400	29.2	67
H.H.	Seated	5,450	22.5	91
	G suit	5,020	26.8	111
	Atropine	5,260	19.1	64
	G suit	5,350	21.9	69
J.M.	Seated	4,760	31.0	100
	G suit	5,000	39.9	159
	Atropine	5,450	28.9	80
	G suit	5,360	37.4	91
J.W.	Seated	3,860	26.0	64
	G suit	3,480	31.1	118
	Atropine	3,880	20.9	60
	G suit	3,475	22.0	83
Mean ± SD	Seated	4,618 ± 582	25.2 ± 3.4	85 ± 16
	G suit	4,468 ± 746	30.6 ± 5.3	117 ± 26
	Atropine	4,528 ± 652	22.0 ± 3.8	66 ± 12
	G suit	4,407 ± 763	25.7 ± 5.3	79 ± 22
p	Seated—atropine	NS	0.05	0.01
	Seated—G suit	NS	0.005	0.005
	Atropine—G suit and atropine	NS	0.025	0.05

TABLE VI

Pulmonary diffusing capacity (D_L), pulmonary capillary blood volume (V_c), and alveolar volume (V_A) in normal supine subjects: the effects of atropine, 2.0 mg iv, and positive-pressure breathing, 10 mm Hg

Subject	Condition	V_A	D_L	V_c
		ml	*ml/min/mm Hg*	*ml*
J.O.	Supine	4,760	23.1	182
	Positive pressure	4,720	24.1	93
	Atropine	4,650	19.1	125
	Positive pressure	4,680	19.9	39
B.S.	Supine	4,510	27.1	56
	Positive pressure	4,200	22.5	27
	Atropine	4,200	17.8	44
	Positive pressure	3,990	10.3	
D.F.	Supine	6,080	32.8	72
	Positive pressure	5,450	23.4	93
	Atropine	4,820	19.3	76
	Positive pressure	5,290	22.3	47
D.M.	Supine	5,140	29.6	125
	Positive pressure	4,900	28.0	117
	Atropine	5,340	28.4	105
	Positive pressure	5,530	28.8	95
H.H.	Supine	4,780	26.2	100
	Positive pressure	4,810	19.4	63
	Atropine	5,120	22.9	80
	Positive pressure	4,810	19.3	100
J.M.	Supine	6,780	45.3	154
	Positive pressure	6,910	42.6	125
	Atropine	7,180	38.4	154
	Positive pressure	7,150	41.3	117
J.W.	Supine	3,840	27.8	91
	Positive pressure	4,050	27.6	83
	Atropine	3,980	24.7	70
	Positive pressure	3,480	21.9	71
B.Mo.	Supine	7,180	38.8	118
	Positive pressure	7,260	35.6	100
	Atropine	7,680	33.7	88
	Positive pressure	7,490	29.4	67
Mean ± SD	Supine	5,380 ± 1,170	31.3 ± 7.3	112 ± 42
	Positive pressure	5,290 ± 1,195	27.9 ± 7.7	88 ± 31
	Atropine	5,370 ± 1,350	25.5 ± 7.3	93 ± 34
	Positive pressure	5,350 ± 1,350	24.1 ± 9.1	76 ± 29
p	Supine—atropine	NS	0.005	0.025
	Supine—positive pressure	NS	0.025	0.025
	Atropine—positive pressure and atropine	NS	NS	NS

Positive-pressure breathing (Table VI) decreased D_L (31.3 ± 7.3 to 27.9 ± 7.7 ml CO per mm Hg per minute, p = 0.025). D_L during positive-pressure breathing (27.9 ± 7.7 ml CO per mm Hg per minute) was not statistically different from D_L after atropine (25.5 ± 7.3 ml CO per mm Hg per minute, p = 0.1). V_c after atropine (93 ± 34 ml) was not statistically different from V_c during positive-pressure breathing before atropine (88 ± 31 ml).

After atropine, the changes observed in D_L and V_c during positive-pressure breathing were not statistically significant. V_A was not affected by positive-pressure breathing either before or after atropine.

C_L. C_L was decreased by G-suit inflation (0.193 ± 0.026 to 0.137 ± 0.046 L per cm H_2O, p = 0.005) (Table VII). Atropine increased C_L (0.193 ± 0.026 to 0.234 ± 0.047 L per cm H_2O, p = 0.025). After atropine, suit inflation de-

creased C_L (0.234 ± 0.047 to 0.201 ± 0.054, p = 0.05), but not to the low level obtained during suit inflation before atropine.

Lung volumes, airway resistance, and blood oxygen. Atropine produced no change in FRC, "slow space," O_2 capacity, or oxyhemoglobin saturation. Airway resistance was decreased slightly after atropine (1.82 to 1.45 L per second per cm H_2O, p = 0.05), and $V_{D(phys)}$ was increased after atropine (139 ± 13 to 166 ± 24 ml, p = 0.01) (Table I).

Summary of results. Table VIII summarizes the effects of atropine, G-suit inflation, and positive-pressure breathing.

DISCUSSION

In the present study, the iv administration of atropine sulfate not only increased heart rate and

TABLE VII

Pulmonary compliance (C_L) in normal seated subjects: the effects of atropine, 2.0 mg iv, and G-suit inflation

Subject	Before atropine A	Before atropine B	After atropine A	After atropine B
J.O.	0.164	0.127	0.241	0.163
B.S.	0.164	0.081	0.147	0.097
D.F.	0.220	0.215	0.273	0.246
D.M.	0.178	0.117	0.192	0.208
H.H.	0.231	0.183	0.270	0.250
J.M.	0.183	0.125	0.213	0.210
J.W.	0.195	0.114	0.285	0.235
B.Mo.	0.216		0.251	
Mean	0.193	0.137	0.234	0.201
SD	0.026	0.046	0.047	0.054

p = 0.005 (B vs. B) ⟷ p = 0.05 (A vs. A)

p = 0.025 (A vs. B) ⟷

* A = before G-suit inflation; B = 30 seconds after G-suit inflation to 100 mm Hg.

TABLE VIII

*Summary of the effects observed**

	Atropine	G suit	Positive-pressure breathing	Atropine + G suit§	Atropine + positive-pressure breathing§
Cardiac index	↑†	NC‡		NC	
Right atrial mean pressure	↓	↑		↑	
Pulmonary artery mean pressure	↓	↑		↑	
Pulmonary blood volume	↓				
Lung compliance	↑	↓		↓	
Pulmonary diffusing capacity	↓	↑	↓	↑	NC
Pulmonary capillary blood volume	↓	↑	↓	↑	NC
Functional residual capacity	NC				
Airway resistance	↓				
Slowly ventilated space	NC				
Physiologic dead space	↑				
Arterial oxyhemoglobin saturation	NC				
Arterial oxygen capacity	NC				

* Conditions are as defined in the section on methods.
† Arrows indicate the direction of statistically significant change (p = 0.05).
‡ NC, no change.
§ Compared with atropine alone.

cardiac index and decreased right atrial pressure and stroke volume, as others have reported (1, 2), but also caused a decrease in pulmonary artery pressure. Previous direct measurements of intrapleural pressure have suggested that atropine probably does not produce changes in intrathoracic pressure (5), and therefore, the observed changes in central vascular pressures should reasonably reflect changes in transmural pressures. In the absence of simultaneous left atrial pressure measurements, consideration of the effects of atropine on pulmonary vascular resistance is speculative, yet, given the combination of increased cardiac output and decreased pulmonary arterial pressure, it can be argued that either pulmonary vascular resistance must have decreased or left atrial pressure decreased considerably more than pulmonary arterial pressure or right atrial pressure.

Acute central vascular engorgement produced by G-suit inflation to 100 mm Hg did not increase cardiac index, measured by dye injection 30 seconds after suit inflation, either before or after atropine. Ross, Frayser, and Hickam (24) previously reported no increase in cardiac output with G-suit inflation. Since all these subjects were supine when studied, the data are not at variance with those of Weissler, Leonard, and Warren (25), who found an increase in cardiac index during G-suit inflation in tilted subjects after atropine. The absence of an increase in cardiac index as a result of an increase in right atrial pressure produced by G-suit inflation for 30 seconds is consistent with the observations of others (26, 27) that acute elevation of previously normal right atrial and pulmonary vascular pressures by iv infusion does not consistently increase cardiac output in normal subjects. A transient increase in cardiac output during the first 30 seconds after G-suit inflation is not excluded.

In the present study, G-suit inflation caused a mean increase in central venous pressure of 8 mm Hg in eight supine subjects. Previous observations in similar subjects have shown that intrapleural pressure rises only an average of 1.35 mm Hg during G-suit inflation (5). After atropine, however, the increase in right atrial pressure produced by G-suit inflation was diminished. Two alternative explanations are suggested for the decrease in central vascular pressure after atropine and for the difference in the effect of G-suit inflation: *a*) after atropine, blood shifts out of the central vascular reservoir into an area that is not effectively compressed by the G suit, or *b*) after atropine, the compliance of the pulmonary vascular reservoir is increased so that blood is contained at a lower pressure, and the blood transferred to the lungs by G-suit inflation is accommodated at a lower pressure.

Our observations with the external counting technique for estimation of change in pulmonary blood volume (Table IV) indicate that there is less blood in the lungs of supine subjects after atropine administration and support the concept that the shift of blood is away from the lung. D_L and V_c, whether measured in seated or supine subjects, were also decreased after atropine administration. Acute central vascular engorgement produced by G-suit inflation moves blood into the lungs (7) and increases D_L (4), again demonstrated in the present study. In these subjects, G-suit inflation after atropine increased central vascular pressures only to about the levels present before atropine was given and caused increases in D_L and V_c to much lower levels than those that were attained during G-suit inflation before atropine.

Fenn, Otis, Rahn, Chadwick, and Hegnauer (28) have shown that there is a shift of blood out of the thorax during positive-pressure breathing. Positive-pressure breathing at 10 mm Hg in normal supine men does not affect cardiac output (5). This does not imply that greater amounts of positive pressure would not decrease cardiac output (29). In the present study, this procedure was associated with decreases in D_L and V_c. After atropine, D_L and V_c were not further decreased by positive-pressure breathing. These decreases in D_L and V_c during 10 mm Hg positive-pressure breathing are not unlike changes previously observed during Valsalva maneuvers (4, 10).

The absence of changes in FRC, slowly ventilated space (V_s), and arterial oxyhemoglobin saturation along with the decreased airway resistance after atropine provide evidence that the effects of atropine on D_L are not the result of restricted distribution of gas inspired for the D_L measurement.

These observations of the effects of atropine on D_L and V_c have certain implications concerning

over-all pulmonary capillary function. In 1915, Krogh (12) observed an increase in D_L during exercise. The increase during exercise has not been explained (24). It is known that hyperventilation does not increase breath-holding D_L (24) and that neither breath-holding nor steady-state D_L are increased by acute increases in pulmonary blood flow in man (24, 30). In fact, as was pointed out by Hatch (31), consideration of the CO capacity of blood and the rate of CO diffusion suggests that increased pulmonary blood flow should not affect D_{Lco} at low alveolar CO tensions, unless there is an associated increase in the volume of blood actually involved in gas exchange at any instant in time. In other words, for an increased pulmonary blood flow to increase D_{Lco}, either the area for diffusion, or the volume of blood into which gas is diffusing at any instant must increase, and these two are geometrically related factors. Observations thus far available demonstrate only two naturally occurring situations of increased blood flow that are associated with increased V_c and D_L: the increased flow associated with atrial septal defect (32) and the increased flow with exercise. It is not understood how either increases the instantaneous volume of capillary blood available for diffusion. In man, two other situations have been shown to increase D_L acutely, and these alter pulmonary vascular pressure and volume, but produce little if any change in cardiac output. Ross, Lord, and Ley (4) found an abrupt increase in D_L during acute central vascular engorgement, and Lewis, Lin, Noe, and Komisaruk (33) found an increase in D_L when subjects change from the erect to the supine position. Lewis, McElroy, Hayford-Welsing, and Samberg (34) also found a decrease in D_L during infusion of trimethapan (Arfonad), a procedure designed to decrease pulmonary vascular transmural pressure. Our observations on the effects of atropine in man are in agreement with those of Rosenberg and Forster (35), who, working with isolated cat lungs, concluded that D_L is primarily dependent upon pulmonary vascular transmural pressure. No independent effect of flow was observed.

These observations with atropine tend to separate the factors of pressure and flow as determinants of D_L in man and suggest that D_L is more dependent on pulmonary transmural pressure. This does not imply that pulmonary vascular pressure is the sole hemodynamic determinant of acute changes in D_L. The instantaneous pulmonary capillary blood volume certainly increases with moderate exercise, whereas in normal man there is little or no increase in pulmonary arterial pressure with moderate exercise (36, 37). Such factors as the evenness of distribution of perfusion with regard to ventilation, the compliance of the pulmonary vascular bed, and the effect of systemic venous activity may be of prime importance, but are as yet unresolved problems.

It is uncertain from the present data whether the events occurring in the pulmonary vascular bed after atropine administration are specific direct effects of atropine, or reflect pressure responses to actions of atropine elsewhere. The observed association of decreased D_L, V_c, and pulmonary blood volume with decreased pulmonary arterial pressure and increased cardiac output suggests that the changes in the pulmonary vascular bed are in response to pooling of blood elsewhere.

Severinghaus and Stupfel (38) found an increase in anatomical dead space in man after atropine and interpreted this change as evidence of bronchomotor tone and an effect of atropine on this tone. Our finding of decreased airway resistance after atropine is in general agreement with this concept. The observed increase in $V_{D(phys)}$ could reflect an enlargement of anatomic airway volume. The possibility of increased alveolar dead space associated with uneven distribution of perfusion and ventilation after atropine is not excluded, although the small increase in $V_{D(phys)}$ suggests that total closure of pulmonary capillaries must not contribute greatly to the decreased D_L and V_c observed. This implies a more evenly distributed decrease in pulmonary capillary volume without actual capillary closure.

The dependence in man of dynamic C_L upon pulmonary vascular pressure, or volume, or both, was shown by Bondurant and co-workers (7, 39, 40), who produced acute central vascular engorgement by G-suit inflation and decreased C_L by this maneuver. The effects of atropine on C_L suggest that, just as increased pulmonary vascular pressures decrease C_L, decreased pulmonary vascular pressures and volume increase C_L.

The observed association of an increase in dynamic C_L and a decrease in airway resistance after atropine suggests that the change in C_L might be the consequence of more even distribution of the inspired air, but the absence of change in the slowly ventilated component of the FRC after atropine suggests that the change in C_L is not caused by altered distribution of ventilation. Furthermore, a change in C_L caused by decreased airway resistance would suggest that C_L, in normal men, is affected by breathing frequency and that C_L should increase at decreased breathing frequencies; however, Otis and co-workers (41) found that C_L is not frequency dependent in normal men. It would seem, therefore, that the observed increase in C_L after atropine is not the result of the decreased airway resistance. Since atropine produced no change in FRC, the change in C_L after atropine cannot be attributed to a change in lung volume.

The possibility cannot be denied that the observed change in C_L after atropine is not real, but is the result of a change in esophageal compliance. If atropine increased the rigidity of the esophagus, similar changes in C_L measured by this method would be observed. The information available concerning the effects of atropine on alimentary smooth muscle, however, suggests that the esophagus should become more relaxed after atropine (42). Consequently, subject to the inherent reservations associated with the use of the esophagus as a site for pressure measurement in respiratory mechanics, it would seem that the observed increase in C_L after atropine is dependent upon the decreased pulmonary vascular pressure and volume after atropine.

These observations of the effects of atropine on C_L, D_L, V_c, and pulmonary blood volume seem to substantiate the thought that atropine, despite its associated increase in cardiac output, reduces the actual volume of blood in the lung and certainly reduces the volume available for gas exchange. These observations do not define the site to which blood has been translocated after atropine, nor the mechanisms involved. The plethysmographic observations of Horsley and Eckstein (3), who found an increased extremity venomotor tone and decreased extremity venous volume after atropine, suggest that blood is also shifted away from the extremities, so by exclusion, a shift to the splanchnic region seems likely.

It is tempting to consider this effect of atropine the result of its parasympatholytic action. There is evidence, however, that the effects of atropine are more complex and that atropine may, in large doses, have actions similar to sympathetic ganglionic blocking agents (43–45).

SUMMARY

In normal supine subjects, atropine increases cardiac index and decreases right atrial pressure and pulmonary artery pressure. Changes in pulmonary blood volume, estimated by an external I^{131}-counting technique, suggest that atropine causes a redistribution of the blood volume away from the lung.

With the decrease in pulmonary vascular pressures and volume, pulmonary diffusing capacity (D_L) and pulmonary capillary volume (V_c) decrease, whereas lung compliance (C_L) increases. These changes are not the result of altered distribution of ventilation or changes in lung volume.

Acute pulmonary vascular engorgement produced by G-suit inflation increases right atrial pressure, pulmonary artery pressure, D_L, and V_c and decreases C_L. Similar, though smaller, changes are produced by G-suit inflation after atropine.

Continuous positive-pressure breathing, a procedure known to move blood out of the chest, decreases D_L and V_c.

These findings suggest that atropine causes a shift of blood out of the lungs into an area where it is not effectively mobilized by G-suit inflation. A specific effect of atropine on the pulmonary vasculature cannot be excluded.

This study demonstrates, in man, the dependence of D_L and V_c on pulmonary vascular pressures, or volume, or both, and their relative independence of cardiac output.

The decrease in C_L after atropine is independent of change in lung volume or distribution of ventilation and probably is a further manifestation of the dependence of C_L on pulmonary vascular pressure.

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