HYPOVENTILATION IN OBESITY*

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Recently, numerous reports have noted that marked obesity may be associated with hypoxia, hypercapnia, polycythemia and right heart failure in the absence of apparent intrinsic pulmonary disease. Weight loss has been followed by alleviation of the derangements in some cases (1–4) and this syndrome has been called the "Pickwickian Syndrome" by Burwell, Robin, Whaley and Bickelmann (5).

Fairly general agreement exists that the basic physiological defect in this syndrome is alveolar hypoventilation which leads to hypoxia and hypercapnia followed by polycythemia and eventual cor pulmonale. It has been suggested that the alveolar hypoventilation in obesity is due to an increased resistance to respiratory movements, thus necessitating an increase in work per unit ventilation (2, 6–8), although little evidence to support this has been advanced. In addition, there is little information in the literature regarding pulmonary function and blood volume in obese individuals.

The purposes of this paper are *1*) to report studies of pulmonary function and blood volume in a group of obese subjects, *2*) to attempt to correlate arterial blood gases with the blood volume measurements, *3*) to report measurements of the oxygen cost of breathing in these individuals, and *4*) to attempt to correlate the oxygen cost of breathing with the occurrence of alveolar hypoventilation.

METHODS

Twenty-six obese individuals, whose physical characteristics are shown in Table I, were studied. The mean age was 46 years; the mean weight, 113 Kg.; and mean heights and body surface areas, 168 cm. and 2.18 $M.^2$, respectively.

Any patient giving a history of lung disease such as chronic cough and sputum, cardiac disease or neuromuscular disease was excluded from the series. Some patients had complaints of somnolence and exertional dyspnea but all were primarily referred because of their obesity.

Ventilatory function was assessed in 21 subjects. Vital capacities, timed vital capacities and maximum breathing capacities were measured using a Collins respirometer with the valves and CO_2 absorber removed and a high speed rotating drum incorporated. The maximum of at least three trials was recorded. Predicted values were determined from the data of Baldwin, Cournand and Richards (9).

The intrapulmonary distribution of inspired gas was assessed by determining the breath-to-breath washout of nitrogen from the lungs while breathing oxygen and by measurement of the concentration of nitrogen in alveolar gas after seven minutes of the oxygen breathing, using an instantaneously-recording nitrogen meter (10).

Simultaneous samples of arterial blood and expired air were obtained in 15 subjects and arterial blood alone in another three. Collections were made after the individuals had been in the semirecumbent position for 20 to 30 minutes. Arterial carbon dioxide and oxygen tensions were determined by a modification (11) of the technique of Riley, Proemmel and Franke (12). Expired air was collected over a three minute period in a Tissot spirometer and analyzed with the micro-Scholander apparatus (13). From these data tidal volume and physiological dead space, calculated by the Bohr method (14), were obtained.

Blood volumes were determined in 16 subjects using the slightly modified (15) T-1824 dye dilution technique of Gibson and Evans (16). These studies were done after the subjects had fasted for 12 hours and just before the collection of arterial bloods and expired gas. All samples of blood were drawn from an indwelling arterial needle.

The oxygen cost of the respiratory mechanism was determined in 25 subjects using the method of Campbell, Westlake and Cherniack (17) as modified by Cherniack (18). The oxygen consumption at rest and at increased ventilation was measured, using a closed-circuit spirometer in which a carbon dioxide absorber was incorporated. A cam on the pulley of the spirometer activated a micro-switch, which in turn controlled a solenoid valve, through which oxygen was delivered from a second spirometer. It was thus possible to keep a level, nonsloping baseline on the records of ventilation while the second spirometer recorded the oxygen consumed.

In order to obtain oxygen consumption at different levels of ventilation, the ventilation was altered by the

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interposition of thick-walled rubber tubing, 2.5 cm. internal diameter, between the subject and the spirometer circuit. Tubes of different lengths were chosen in random order and the individuals were allowed to increase their ventilation spontaneously with no external control of rate or depth of breathing.

Before studies were begun, the subjects, who had fasted for at least nine hours, rested in a comfortable chair for one hour in the case of out-patients and for 20 minutes in the case of hospitalized patients.

Resting oxygen consumption and ventilations were recorded at the beginning and at the end of each study and the mean was used for calculation. Before each measurement, whether resting or at increased ventilation, the subjects breathed oxygen from a meteorological balloon for 10 minutes and then into and out of the oxygen-filled spirometer circuit for five minutes in order to allow the attainment of a steady state. Recordings were then taken over a 5 to 10 minute period. Oxygen consumption was corrected to S.T.P.D. and ventilation to B.T.P.S. Ten to 20 minutes rest was allowed between each measurement.

In each subject, oxygen consumptions at the resting ventilation and at at least two increased ventilations were obtained, one of the increased ventilations being 7 to 13 L. per minute above the resting. The difference between the oxygen consumption at the increased ventilation and at rest, divided by the difference in ventilation, has been used as the oxygen cost of increased ventilation and expressed in milliliters of oxygen per liter of ventilation.

In three subjects the oxygen cost of increased ventilation, as calculated above, was determined on several occasions and in each did not vary by more than 0.3 ml. O_2 per L.

RESULTS

1. Ventilatory function

The results of the ventilatory function studies are listed in Table I. It will be seen that some subjects had fairly marked reduction in vital capacity and maximum breathing capacity. However, timed vital capacities and maximum mid-expiratory flow rates performed before and after nebulized bronchodilator revealed no evidence of bronchiolar obstruction.

The index of intrapulmonary mixing was normal in all subjects but the washout of N_2 from the lungs was somewhat slower than normal in Subjects 18, 20, 23 and 25.

TABLE I

Physical data and pulmonary function in obese subjects

Subject no., sex	Age	Height	Weight	Body surface area	Vital capacity		Maximum breathing capacity		I.I.P.M.*	D.S./T.A.†	O.C.I.V.‡
	yrs.	*cm.*	*Kg.*	*M.²*	*ml.*	*% of pred.*	*L./min.*	*% of pred.*	*% N_2*	*%*	*ml./L.*
1, F	46	163	100	2.04							5.76
2, F	46	162	111	2.13							4.45
3, F	53	165	90	1.97							2.5
4, F	31	174	114	2.26							2.57
5, F	47	160	97	1.98	3,420	129	93	113	0.4		9.73
6, F	53	163	99	2.03	2,355	86	74	75	0.4		1.75
7, F	35	162	101	2.02	3,810	131	154	174	0.4		0.82
8, M	37	180	131	2.47	4,500	107	124	103	0.4		5.24
9, F	38	151	115	2.07	2,095	82	69	88	0.4		1.75
10, F	69	155	101	1.94	1,875	88	56	84	0.4		1.75
11, M	56	166	86	1.95	3,920	114	127	140	0.4	23	1.86
12, F	51	170	127	2.33	3,260	111	79	89	0.4	22	3.47
13, F	47	156	103	2.00	2,650	104	71	92	0.4	32	2.57
14, M	43	175	123	2.44	4,650	119	166	151		32	1.80
15, F	28	178	124	2.40	3,670	109	110	108	0.4	26	2.77
16, M	36	185	135	2.55	6,030	136	129	98	0.4	37	2.70
17, M	64	174	114	2.26	3,380	98	82	90	0.4	42	2.01
18, M	61	182	111	2.36	4,120	112	122	123	2.0	61	3.93
19, F	52	155	122	2.14	2,930	122	101	120	0.4	43	2.3
20, F	44	163	98	2.02	2,900	104	72	88	0.4	33	1.6
21, M	41	175	120	2.31	3,820	93	104	90		44	2.76
22, M	45	173	121	2.31						43	3.85
23, F	49	155	88	1.87	2,260	70	73	83	0.4	52	4.77
24, M	33	173	167	2.65	2,970	75	65	55	0.7	53	6.46
25, F	57	153	125	2.12	1,277	56	52	59	0.4	35	7.04
26, M	34	180	99	2.19	5,260	122	185	145	1.0		

* Index of intra-pulmonary mixing.
† Physiological dead space-tidal air ratio.
‡ Oxygen cost of increased ventilation.

TABLE II

Blood studies in obese subjects

Subject	pO_2	pCO_2	Ht.*	R.C.M./M.²†	P.V./M.²‡	T.B.V./M.²§
	mm. Hg	*mm. Hg*	%	*ml.*	*ml.*	*ml.*
9	94	39	43	1,053	1,378	2,431
10	74	40	44	1,177	1,544	2,721
11	90	31	46			
12	93	40	42	1,105	1,550	2,655
13	116	41	45	1,202	1,463	2,665
14	99	38	51			
15	102	36	38	1,271	1,940	3,210
16	79	39	47	1,269	1,460	2,729
17	64	39	48	1,612	1,780	3,392
18	65	45	45	1,529	1,530	3,059
19	76	44	43	1,178	1,586	2,764
20	83	40	37	926	1,555	2,481
21	67	44	49	1,330	1,385	2,715
22	65	47	44	1,595	1,935	3,530
23	75	53	42	1,110	1,616	2,726
24	51	77	53	1,966	1,715	3,681
25	44	57	44	1,588	2,038	3,626
26	71	40	60	1,545	1,195	2,740

* Hematocrit.
† Red cell mass per square meter body surface area.
‡ Plasma volume per square meter body surface area.
§ Total blood volume per square meter body surface area.

2. *Physiological dead space-tidal air ratios*

Dead space-tidal air ratios are also listed in Table I. This ratio was greater than the normal upper limit of 30 per cent (19) in 12 of the 15 obese subjects in whom it was measured.

3. *Arterial blood studies*

Table II lists the arterial blood gas tensions in 18 obese subjects. The subjects can be divided into three groups. In six subjects pO_2 was greater than 90 mm. Hg and pCO_2 was less than 45 mm. Hg; in eight subjects pO_2 was less than 90 mm. Hg and pCO_2 less than 45 mm. Hg; while four subjects had pO_2 less than 90 mm. Hg and pCO_2 greater than 45 mm. Hg.

The tidal volumes, respiratory rates and physiological dead spaces of the 15 subjects on whom these measurements were obtained are shown in Figure 1. Except for one patient with hypoxia, all physiological dead spaces are within normal limits as defined by Comroe and co-workers (19). It will be noted that there was a tendency for the tidal volume to be less in those patients with hypoxia than in those with normal gas tensions and this is more pronounced in those subjects with both hypoxia and hypercapnia. In addition, it will be seen that there was a tendency for the respiratory rate to increase as the tidal volume decreased.

4. *Blood volume studies*

Table II also lists the partitions of blood volume in 16 obese subjects. The mean blood volume in the male subjects was 3,122 ml. per M.² (S.D., ± 412), the mean plasma volume was 1,571 ml.

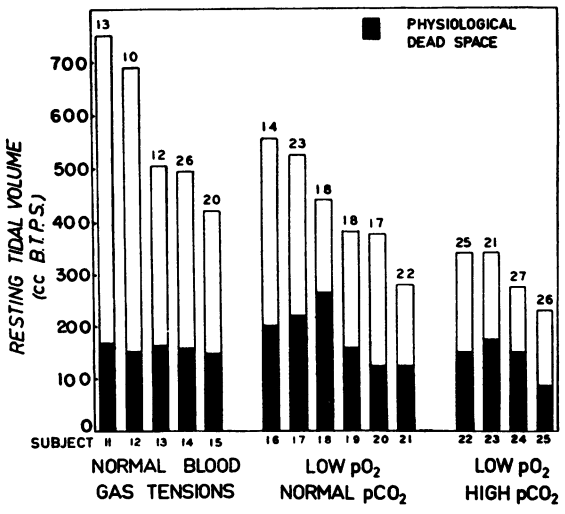

FIG. 1. TIDAL VOLUMES AND PHYSIOLOGICAL DEAD SPACES IN THE THREE GROUPS OF OBESE SUBJECTS
Respiratory rates are also shown for each subject.

TABLE III

The partitions of blood volume in normal and obese individuals

Investigator	Method	Males			Females		
		No. of subjects	P.V.*	R.C.M.†	No. of subjects	P.V.*	R.C.M.†
			ml.	*ml.*		*ml.*	*ml.*
Present study	T-1824	7	1,571 ± 253	1,549 ± 225	9	1,630 ± 217	1,179 ± 182
Doupe, Ferguson and Hildes (15)	T-1824	72	1,645 ± 130				
Gibson and Evans (16)	T-1824	49	1,619 ± 182		39	1,467 ± 160	
Hedlund (20)	P^{32}	35		1,131 ± 131	7		868 ± 115
Samet, Fritts, Fishman and Cournand (21)	T-1824	30	1,527 ± 156		30	1,463 ± 162	
	P^{32}	30		1,039 ± 123	30		782 ± 80

* Mean plasma volume per square meter body surface area plus or minus standard deviation.
† Mean red cell mass per square meter body surface area plus or minus standard deviation.

per M.^{2} (S.D., ± 253) and the mean red cell mass was 1,549 ml. per M.^{2} (S.D., ± 225). The mean blood volume in the females was 2,810 ml. per M.^{2} (S.D., ± 375), the mean plasma volume was 1,630 ml. per M.^{2} (S.D., ± 217) and the mean red cell mass was 1,179 ml. per M.^{2} (S.D., ± 182).

In Table III these results are compared with other reported measurements on subjects with predominantly normal weights (15, 20, 21). It can be seen that in the male subjects the mean plasma volume per M.^{2} apparently was not different from the rest, while in the females it was slightly higher. Red cell mass per M.^{2} was higher than that reported in the literature in both sexes. It should be noted, however, that the red cell masses reported by Hedlund (20) and by Samet, Fritts, Fishman and Cournand (21) were determined using the tagged red cell method, while in this series it was estimated indirectly by measuring the plasma volume and hematocrit.

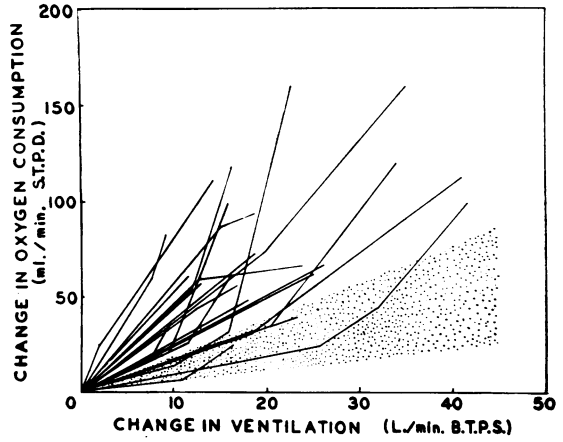

FIG. 2. THE CHANGES IN OXYGEN CONSUMPTION ASSOCIATED WITH CHANGES IN VENTILATION IN 25 OBESE SUBJECTS

The stippled area represents the range found in normal subjects (17).

When an attempt was made to correlate the partitions of blood volume and the resting arterial blood gas tensions, it was found that in the seven male subjects there was a significant correlation between red cell mass and pO_2 ($p < 0.01$) and pCO_2 ($p < 0.05$), and between total blood volume and pO_2 ($p < 0.05$). In the nine female subjects the only significant correlation was between red cell mass and pCO_2 ($p < 0.05$).

5. *Oxygen cost of breathing*

The oxygen cost of increased ventilation for each subject is given in Table I. These values are to be compared with values ranging from 0.5 to 1.8 ml. O_2 per L. obtained in 16 normal subjects (18). Thus, 18 of the 25 obese subjects had values higher than the upper limit of normal. This can also be seen in Figure 2 which shows the increments in oxygen consumption associated with increases in ventilation. In addition, it can be seen that in most obese subjects there was a disproportionate increase in the oxygen cost of breathing with further increases in ventilation.

The relationship between the oxygen cost of increased ventilation and the resting arterial oxygen and carbon dioxide tensions in the 17 obese subjects who had arterial blood estimations is shown in Figures 3 and 4. It can be seen that there was a tendency for the highest costs of increased ven-

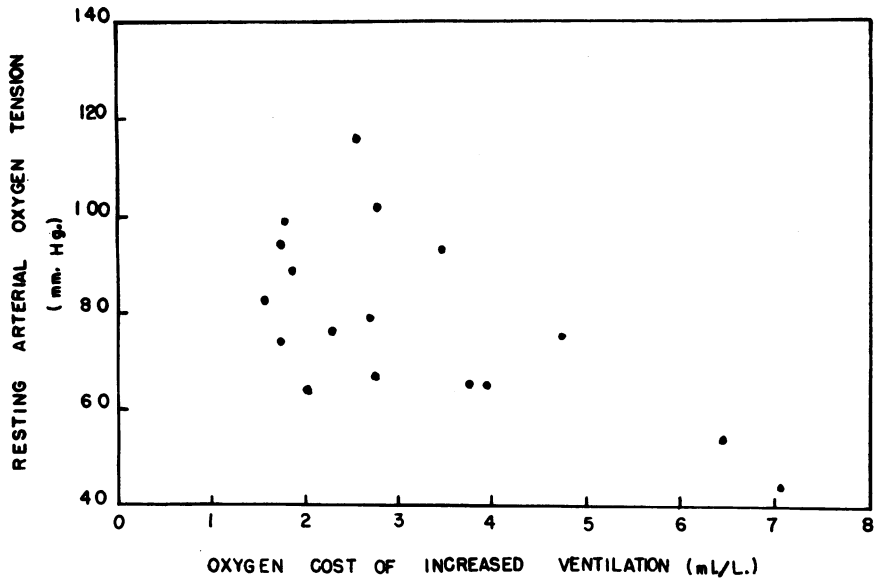

FIG. 3. THE RELATIONSHIP BETWEEN THE RESTING ARTERIAL OXYGEN TENSION AND THE OXYGEN COST OF INCREASED VENTILATION IN 17 OBESE SUBJECTS

tilation to be asociated with the lowest arterial oxygen tensions and the highest arterial carbon dioxide tensions.

In two of the patients with highest carbon dioxide tensions and costs of breathing the physical properties of the lungs were studied. The lung compliance was 0.220 in Subject 24 and 0.300 in Subject 25. The viscous resistance, as expressed by the pressure required to cause a flow of 60 L. per minute, was 1.8 cm. H_2O in Subject 24 and 2.4 cm. H_2O in Subject 25 on expiration, with similar values for inspiration. These measurements are within the normal range (22, 23).

No correlation between the oxygen cost of in-

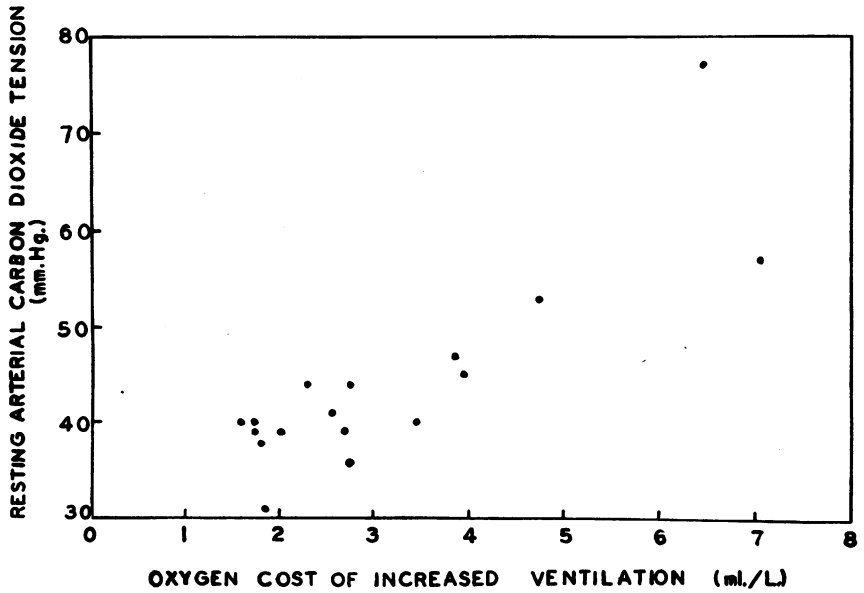

FIG. 4. THE RELATIONSHIP BETWEEN THE RESTING ARTERIAL CARBON DIOXIDE TENSION AND THE OXYGEN COST OF INCREASED VENTILATION IN 17 OBESE SUBJECTS

creased ventilation, measurements of pulmonary function, partitions of blood volume and the degree of obesity could be found in these subjects.

DISCUSSION

It is of some interest to note that, of 18 supposedly normal obese subjects, only 32 per cent had normal resting blood gas tensions. Hypoxia of varying degrees was present in 42 per cent and was associated with hypercapnia in an additional 26 per cent.

Only three of the 12 subjects with hypoxia had hematocrits above 50 per cent but the red cell mass was increased in the majority of the subjects. Although red cell mass was measured indirectly and no correction for body hematocrit was made, it nevertheless appears to be significantly increased. While hypoxia was probably acting as an erythropoietic stimulus in these subjects, its effect is not readily apparent in the hematocrit determination, presumably because of an increase in the plasma volume, particularly in the female subjects.

The correlation between red cell mass and pCO_2 in both sexes may be due to the fact that fairly marked hypoxia always accompanied hypercapnia. No explanation for the increased plasma volume in the obese females studied is readily apparent.

The data presented indicate that the oxygen cost of breathing is increased in obese individuals. If the assumption is made that the oxygen cost of breathing obtained from measurements of small increments in ventilation can be extrapolated back to the resting level, then obese individuals have increased costs of breathing even at rest.

A high oxygen cost of breathing could be due to increased muscular work being done on the lungs or on the thorax or a reduced efficiency of the respiratory apparatus. No measurements of efficiency were made in this study. While slight impairment of distribution of gas may have been present in some of the subjects studied, this could not account for the changes in arterial gases and oxygen cost of breathing. In addition, the absence of bronchiolar obstruction and the lack of clinical history of lung disease suggest that no intrinsic lung pathology was responsible for an increased work of breathing. Also, measurement of the physical properties of the lungs in two of the subjects with high costs of breathing and hypercapnia revealed normal lung compliance and nonelastic resistance. Hence it is postulated that the high cost of breathing is due to increased mechanical work necessary to move thoracic cage, diaphragm and abdominal wall and contents—presumably due to obesity.

The individuals who had the highest oxygen costs of breathing tended to breathe with the lowest tidal volumes and highest respiratory rates at rest. Since Liljestrand (24) and Cournand and associates (25) have demonstrated that the oxygen cost of breathing is less for a given ventilation when the tidal volume is small, the findings in the obese subjects may be an example of the selection of an optimum rate and depth of breathing where the least work is done.

The rapid, shallow breathing observed in the obese subjects is the type of breathing pattern found when the elastic resistance is increased (26), in contra-distinction to the slow, deep breathing encountered when air flow resistance is high (27). This suggests that the increased mechanical work necessary to move "the thorax" in these obese subjects was elastic in nature.

In addition, there appears to be a relationship between the oxygen cost of breathing and the arterial carbon dioxide tension in the obese subjects. This is in accordance with the hypothesis advanced by Cain and Otis (27) and by Riley (28) who viewed respiratory acidosis as an adaptive mechanism sparing oxygen for nonventilatory work, a rise in CO_2 tension being tolerated when the work of breathing is increased "in preference to expending the effort that would be required to keep it at the original level."

The data also indicate that in the obese individual, who may already have an increased cost of breathing at rest, further small increments in ventilation could result in a disproportionate increase in metabolic work of breathing. This would probably be even more exaggerated if an obese person developed bronchitis or other lung disease.

Conversely, in individuals with chronic lung disease and increased work of breathing, the development of obesity would lead to a further rise in the oxygen cost of breathing and possible alveolar hypoventilation. The therapeutic implications of obesity in chronic lung disease thus become apparent.

SUMMARY AND CONCLUSIONS

1. Twenty-six obese subjects were studied. Ventilatory function was assessed in 21, arterial blood gas tensions in 18, blood volume estimations in 16 and the oxygen cost of breathing in 25.

2. Clinical history and ventilatory function revealed no evidence of gross lung disease aside from a slight impairment in distribution in four patients.

3. Twelve of the subjects who had measurements of arterial blood gas tensions had hypoxia. Four had associated hypercapnia which apparently was due to reduced tidal volumes.

4. Red cell masses per M.^{2} body surface area were increased in both male and female subjects. Plasma volume was increased in the female subjects.

5. The oxygen cost of breathing was increased in the obese subjects.

6. A suggestion has been made that the increased oxygen cost of breathing in the obese subjects was due to an increase in elastic resistance of the thorax.

7. A relationship between the oxygen cost of breathing and the arterial blood tensions of carbon dioxide and oxygen has been indicated.

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