COR PULMONALE IN MUSCULOSKELETAL ABNORMALITIES OF THE THORAX*

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IN this symposium thus far, only cor pulmonale which occurs as a consequence of intrinsic disease of the lungs has been considered. However, in recent years a form of cor pulmonale has been observed in which primary lung disease is absent. In this form, musculoskeletal deformities of the thorax or disturbed regulation of the muscles of ventilation lead to abnormalities in the composition of alveolar gas.[1-3] The abnormal pattern of alveolar gas is characteristically that of alveolar hypoventilation, i.e., hypercapnia and hypoxia and, though different mechanisms may lead to alveolar hypoventilation, the effects on the pulmonary circulation are the same.

Since alveolar hypoventilation is the common feature in the development of pulmonary hypertension and cor pulmonale in this group of diseases, we should like to begin by defining this state.

One of the most constant values in mammalian physiology is the pressure of carbon dioxide in the arterial blood (P_{CO_2}). This value, which is maintained close to 40 mm. Hg despite marked variations in body metabolism, is virtually the same as the alveolar P_{CO_2}. The alveolar ventilation, which determines the alveolar P_{CO_2}, is the ultimate determinant of the arterial P_{CO_2}. To maintain a normal and constant value of alveolar CO_2 tension, the alveolar ventilation must be regulated precisely with respect to the carbon dioxide produced by tissue metabolism. These relationships are depicted in Figure 1, in which the alveolar ventilation is plotted against alveolar CO_2 and O_2 tensions at three different rates of tissue metabolism. In this figure the perpendicular line

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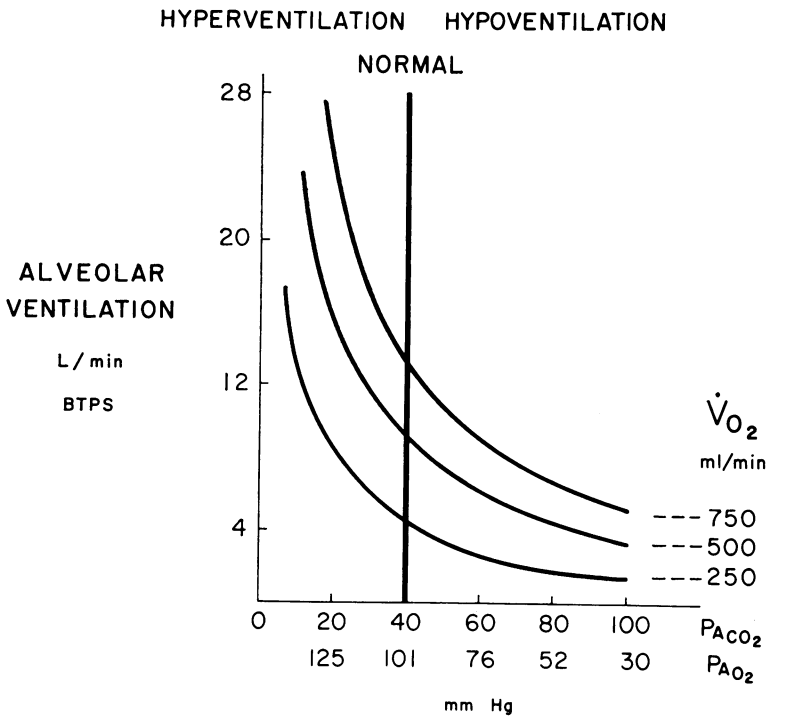

Fig. 1. The relationship between alveolar ventilation and the alveolar oxygen and carbon dioxide tensions at three different metabolic rates. Alveolar P_{O_2} and P_{CO_2} were calculated on the basis of a respiratory quotient of 0.8, assuming steady-state relationships between expired gas, alveolar gas, and tissue metabolism.

depicts the normal increase in alveolar ventilation required for a given rise in metabolic CO_2 production to maintain an alveolar P_{CO_2} of 40. If alveolar ventilation is too low, the state of alveolar hypoventilation will ensue and alveolar CO_2 tension rises while alveolar P_{O_2} falls below normal. Similarly, a lowering of alveolar P_{CO_2} indicates alveolar hyperventilation. While the increased alveolar or arterial P_{CO_2} is the critical manifestation of alveolar hypoventilation, it is important to recognize that alveolar hypoxia is a necessary concomitant and that the two cannot be dissociated. However, in clinical states of alveolar hypoventilation, the degree of hypoxemia for the level of hypercapnia may be accentuated by superimposed uneven alveolar ventilation and perfusion secondary to regional differences in distensibility of the lung or localized atelectasis. This stands in contrast to the alveolar hypoventilation of obstructive lung disease, which results predominantly from uneven alveolar ventilation and perfusion.

TABLE I—ALVEOLAR HYPOVENTILATION AND COR PULMONALE IN MUSCULOSKELETAL ABNORMALITIES OF THE THORAX

Pectus excavatum	*Not associated* with alveolar hypoventilation or cor pulmonale
Rheumatoid spondylitis	Associated with alveolar hypoventilation but *without* cor pulmonale
Fibrothorax Muscular dystrophy Kyphoscoliosis Poliomyelitis Obesity	Associated with alveolar hypoventilation and cor pulmonale

It should be noted also that once the syndrome of alveolar hypoventilation is established chronic hypercapnia itself leads to a functional depression of the respiratory center, which reduces the ventilatory response to further increases in arterial P_{CO_2} regardless of the initiating cause of the alveolar hypoventilation.[4]

A review of the types of abnormality of the thoracic cage indicates that cor pulmonale develops only when alveolar hypoventilation is also present. This is shown in Table I. Pectus excavatum has not been a cause of either alveolar hypoventilation or cor pulmonale.[5,6] Ankylosing spondylitis causes at most only mild alveolar hypoventilation.[7,8] The levels of hypercapnia and hypoxemia have been slight and no cases of pulmonary hypertension have been reported. On the other hand, fibrothorax,[1] muscular dystrophy,[3] kyphoscoliosis,[9] poliomyelitis,[10] and obesity[11-13] have all been associated with alveolar hypoventilation, pulmonary hypertension, and cor pulmonale.

The critical role of the alveolar hypoventilation per se in causing cor pulmonale in this group of disorders is given further emphasis by the occurrence of marked pulmonary hypertension during the clinical course of patients whose alveolar hypoventilation stems from a primary disorder of the respiratory center in the presence of a normal thorax and muscles of ventilation.[14]

Obesity has been included in this group of musculoskeletal deformities because of associated alveolar hypoventilation. However, there is a pre-existing circulatory abnormality in obesity that differentiates it from the other states under discussion in two aspects: 1) an abnormally high resting cardiac output that imposes an increased volume load on the right and left heart and 2) a high pulmonary capillary "wedge" pres-

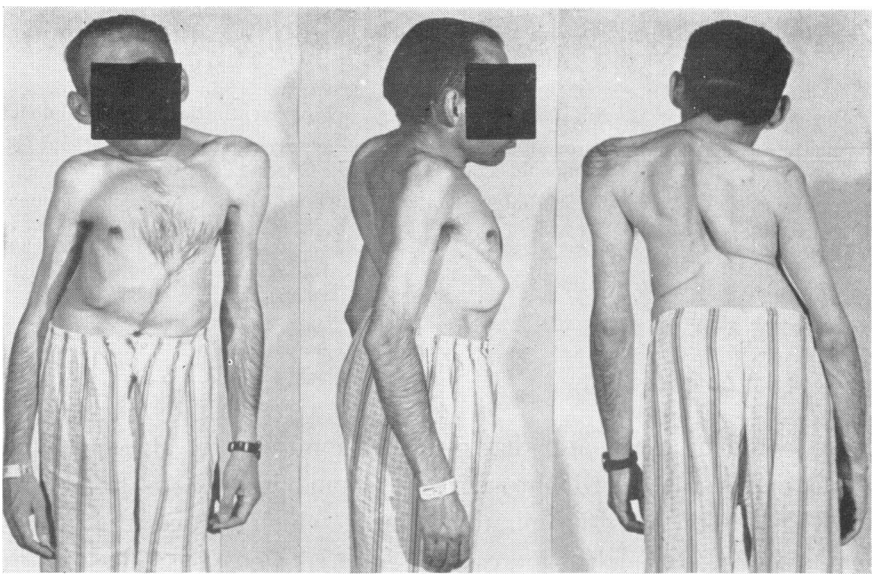

Fig. 2. Thoracic contour in a 38-year-old man with severe thoracic spine kyphoscoliosis and alveolar hypoventilation (see text).

sure that probably results from abnormally high left ventricular filling pressures and contributes to the pulmonary hypertension.[15] Nonetheless when the obese state is complicated by alveolar hypoventilation, hypoxemia and hypercapnia may affect the pulmonary vascular resistance and contribute substantially to the volume and pressure load on the right heart.

For the remainder of this discussion let us consider the cor pulmonale of kyphoscoliosis and poliomyelitis and the cardiorespiratory failure of obesity.

Kyphoscoliosis

It had long been recognized that a severe kyphoscoliotic deformity of the thoracic spine was associated with heart failure[16] although the underlying mechanisms remained unknown. However, more recently, studies relating the respiratory failure of kyphoscoliosis to the disturbances in the pulmonary circulation have clarified some of the mechanisms leading to cor pulmonale.[9, 17, 18]

Kyphoscoliosis (see Figure 2) arises from a lateral bending and rotation of the vertebral column. If the deformity is in the thoracic vertebral column, the thoracic cage is shortened and the rib cage is distorted

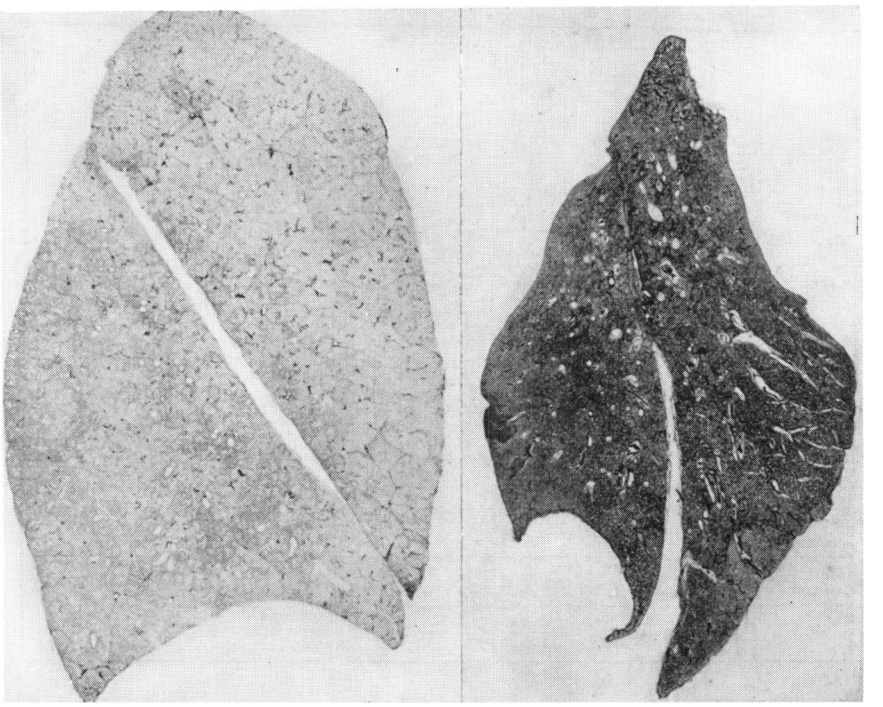

Fig. 3. Whole lung sections prepared according to the technique of Gough.[19] *Left:* normal lung. *Right:* compressed lung of a patient with severe kyphoscoliosis of the thoracic spine.

to produce rib concavity on one side and convexity on the other. The hump in rotatory kyphoscoliosis is largely composed of the deformed ribs, whereas in severe kyphosis from destructive lesions such as Potts disease, the hump is composed of the protruding vertebral bodies.

This shortening and distortion of the thoracic cage results in compression of the lungs, as demonstrated in Figure 3. In this figure a whole lung section prepared according to the method of Gough[19] from the lungs of a patient with kyphoscoliosis is compared with a normal lung. The lung from the deranged thorax shows a marked reduction in size and an altered external contour. Microscopically, focal atelectasis occurs in various parts of the parenchyma but there is no evidence of destruction of lung tissue or bronchitis. Pulmonary emphysema is therefore not a feature.

The thoracic deformity in kyphoscoliosis leads to alveolar hypoventilation by two mechanisms: 1) absolute reductions in ventilatory

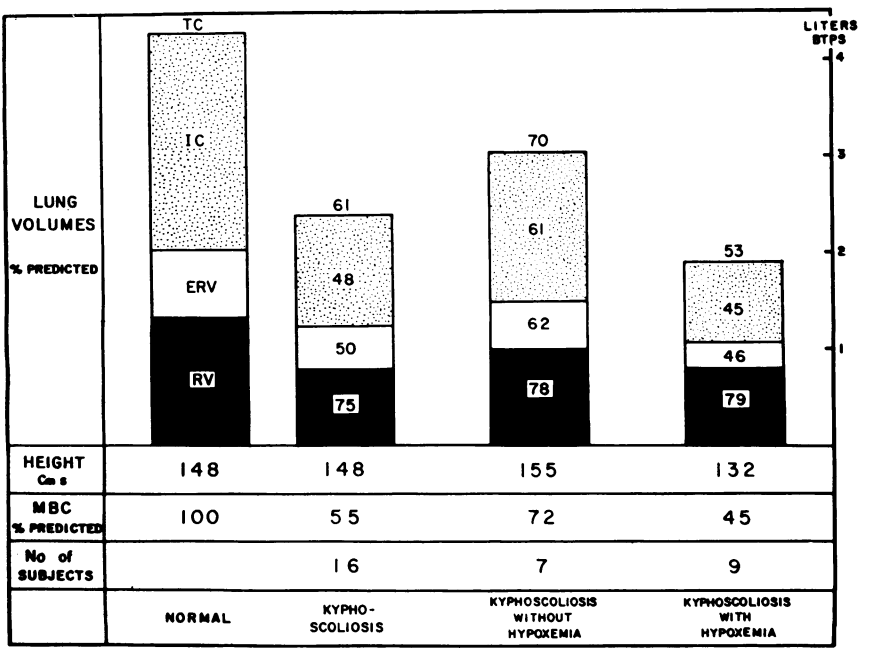

Fig. 4. The relationship between hypoxemia and the reduction in lung volumes and maximum breathing capacity in patients with kyphoscoliosis.

capacity imposed by reduced lung volume and the mechanical disadvantage of the thoracic muscles, and 2) a breathing pattern of rapid frequency and small tidal volume that is associated with a less compliant chest wall and increased mechanical work of breathing.

The abnormality in the volume of the lungs is shown in Figure 4 for 16 subjects with kyphoscoliosis. The vital capacity is reduced sharply and the residual volume less so. As shown in this figure, hypoxemia and hypercapnia occur in those patients with the lowest lung volumes, the severest restriction of the maximum breathing capacity and, in general, the severest deformity. This direct correlation between blood-gas abnormalities and the reduction of the vital capacity and maximum breathing capacity makes these tests useful in detecting patients prone to the development of alveolar hypoventilation.

Measurements of the pressure volume characteristics of the lung and thorax while being mechanically ventilated by a body respirator permit an estimate of the compliance of the chest cage and of the lung separately. In the normal subject, the compliance of the chest cage is approximately

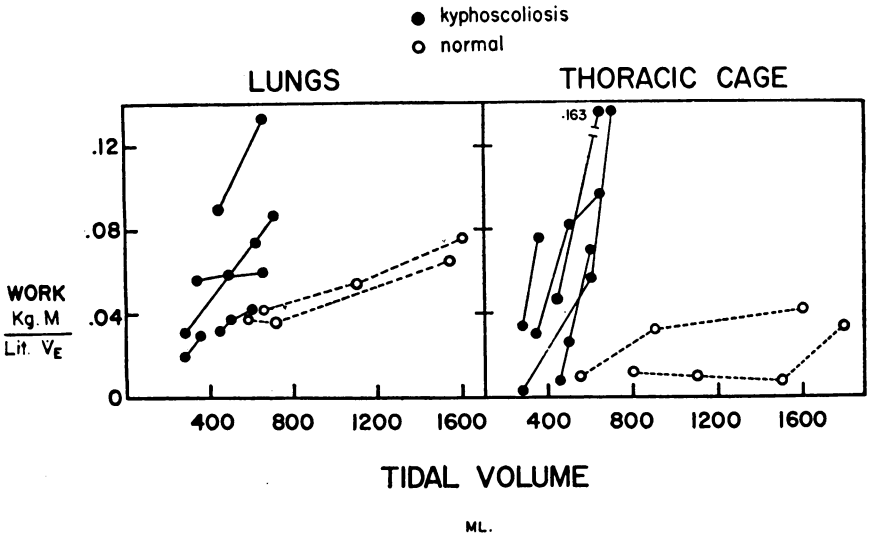

Fig. 5. The partition of the work of breathing done on the lungs and on the thoracic cage in kyphoscoliosis (see text).

equal to the compliance of the lung. However, in kyphoscoliosis the compliance of the chest is reduced and may be as low as 25 per cent of normal. The compliance of the lung is slightly reduced but commensurate with the decrease in lung volume. The mechanical work of breathing therefore is increased in kyphoscoliosis largely as a result of an increased elastic resistance of the chest wall. The relationship between tidal volume and the mechanical work performed per liter of ventilation is shown in Figure 5. This figure shows that any increase in tidal volume requires inordinate increments in mechanical work done on the less compliant chest wall as compared to the normal. These relationships are not as marked for the work of breathing done on the lung, where the reduction in compliance is less. A breathing pattern utilizing small tidal breaths and a rapid frequency is therefore a more economical pattern in this form of mechanical disturbance.[20] However, due to the necessity of ventilating the dead space, the alveolar ventilation is reduced even though total ventilatory volume may be at the normal level. Thus the reduction in alveolar ventilation occurs as a consequence of the pattern of rapid frequency and small tidal volume that is characteristic of kyphoscoliosis.[9, 17] Disturbances in ventilation-perfusion relationships that result from atelectasis or uneven ventilation from re-

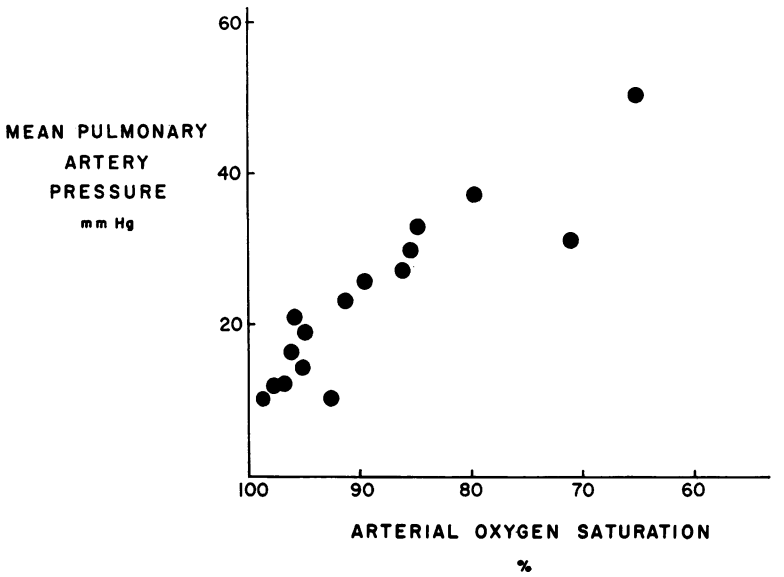

Fig. 6. The relationship between mean pulmonary artery pressure and arterial oxygen saturation in kyphoscoliosis.

gional changes in distensibility are additional mechanisms contributing to the alveolar hypoventilation.

Study of the pulmonary circulation in patients with kyphoscoliosis before alveolar hypoventilation occurs gives some insight into the role of the blood-gas disturbances per se in the evolution of cor pulmonale. Figure 6 shows the correlation between mean pressure in the pulmonary artery and arterial blood oxygen saturation in 15 patients with kyphoscoliosis. There is an excellent linear correlation as shown. Individuals with normal or near-normal oxygen saturations have normal resting pulmonary artery pressures. Conversely, the group with the lowest arterial oxygen saturation has the highest mean pulmonary artery pressures and comprises the patients who develop cor pulmonale. However, even subjects with normal pulmonary artery pressures at rest and normal arterial oxygen saturations have an abnormal pulmonary vascular bed as indicated by the abnormally high increment in pulmonary artery pressure, which accompanies a rise in cardiac output during exercise. This is shown in Figure 7. Patients with the highest resting pulmonary arterial pressure and the lowest arterial oxygen saturation also have the largest increments in mean pulmonary artery pressure in response to increases in pulmonary blood flow.

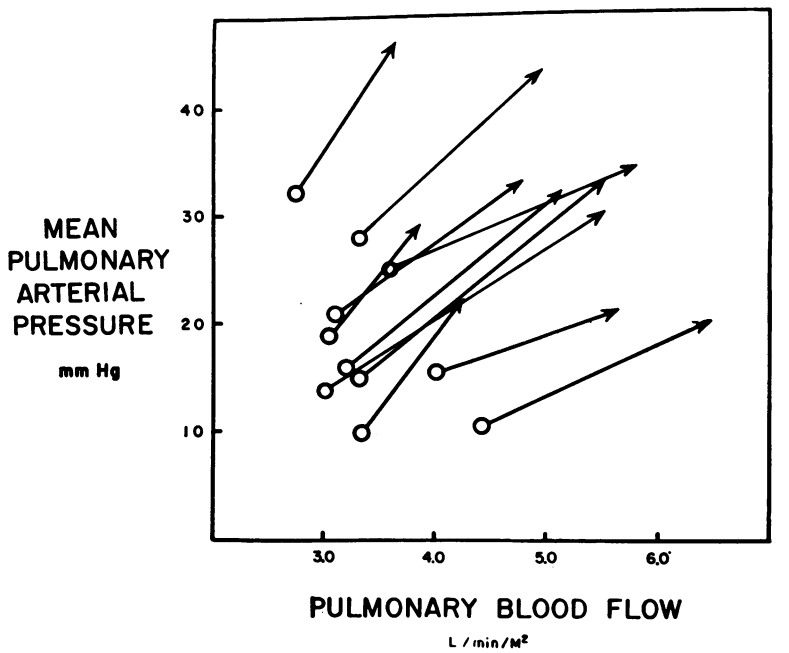

Fig. 7. The effect of increases in pulmonary blood flow during exercise on the mean pulmonary artery pressure in kyphoscoliosis. Open circles are values at rest; the arrow heads are values during exercise. Patients with normal pulmonary artery pressure at rest demonstrate inordinate rises in pulmonary artery pressure with increases in pulmonary blood flow.

In kyphoscoliosis, as in chronic obstructive lung disease, several lines of evidence suggest a major role for alveolar hypoxia as the basis of severe pulmonary hypertension leading to cor pulmonale: 1) the excellent correlation between hypoxemia, reflecting alveolar hypoxia, and mean pulmonary artery pressure in kyphoscoliosis, 2) the presence of anatomic hypertrophy of the pulmonary arterioles in kyphoscoliosis similar to that observed in the lungs of individuals chronically exposed to the hypoxia of altitude,[21] and 3) the reduction of pulmonary hypertension in kyphoscoliosis that occurs with the administration of oxygen acutely or with improvement of alveolar hypoxia over weeks or months.

The effects of oxygen administration on pulmonary hypertension have been evaluated by the administration of oxygen acutely and by repeated studies in the same subjects with kyphoscoliosis and cor pulmonale in different stages of clinical severity.

In Figure 8 are shown the data in a 28-year-old kyphoscoliotic man who was studied during an episode of right heart failure not associated

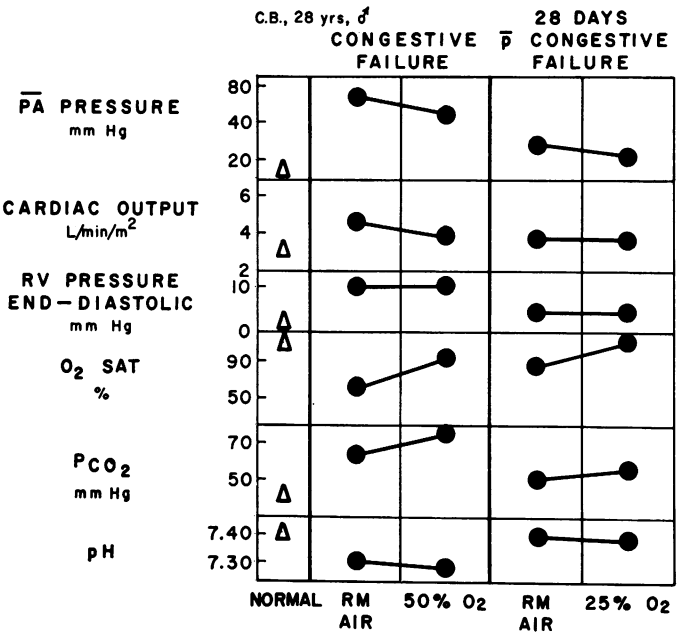

Fig. 8. Right heart pressures and arterial blood gas composition during the breathing of enriched oxygen in a patient with kyphoscoliosis and cor pulmonale (see text).

with evidence of pulmonary infection. When seen initially he had a markedly elevated pulmonary artery pressure at rest while breathing room air. Cardiac output was higher than normal as was the right ventricular end-diastolic pressure. Arterial hypoxemia and hypercapnia were marked and acidosis was moderate. The breathing of 50 per cent oxygen for a period of 30 minutes resulted in a decrease in pulmonary artery pressure associated with a decrease in cardiac output. As shown in this figure, the relief of hypoxemia was accompanied by a decrease in ventilation. This resulted in a rise in P_{CO_2} and further acidosis which did not prevent the decrease in pulmonary artery pressure.

The patient was treated with a body respirator to assist ventilation and prevent further hypercapnia while receiving nasal oxygen at a flow of 5 to 6 l. per minute. Digitalis and diuretics were also administered. After 28 days of therapy and a 10-lb. weight loss, arterial CO_2 tension and arterial oxygen saturation were close to normal, and pulmonary artery pressure was markedly reduced. At this stage, further improvement in the alveolar tension of oxygen by breathing high oxygen mixtures acutely, resulted in a further decrease in pulmonary artery

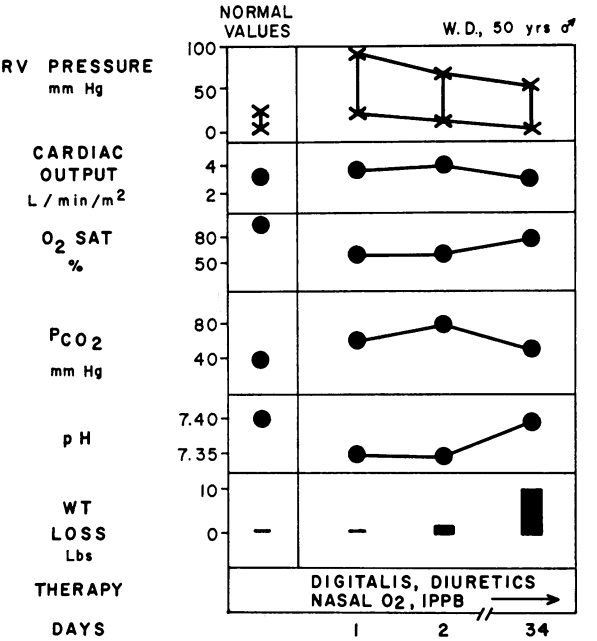

Fig. 9. The changes in right heart pressures, cardiac output, arterial blood gases, and body weight 24 hours and 34 days after institution of therapy in a patient with kyphoscoliosis and cor pulmonale.

pressure to normal without a decrease in cardiac output, the latter response suggesting a direct effect of a high inspired oxygen tension on pulmonary vascular resistance.

The clinical course of this patient illustrates the marked reversibility of pulmonary hypertension associated with the correction of the abnormal composition of alveolar and blood gases.

The sequence of the change in pulmonary artery and right heart pressure in the cor pulmonale of kyphoscoliosis can be examined more closely by repeated studies within the early phases of therapy. In Figure 9 are shown data from a 50-year-old man with severe kyphoscoliosis also obtained during an episode of severe right heart failure that was not associated with pulmonary infection. Right ventricular end-diastolic pressure was markedly elevated to 25 mm. Hg, indicating advanced right heart failure. Arterial hypoxemia, hypercapnia, and acidosis were severe. The patient refused to use a tank-type body respirator because of pain in his gibbus when lying flat. Therefore, over the next 24 hours, he was given nasal oxygen at low flows of 1 to 2 l. per minute and intermit-

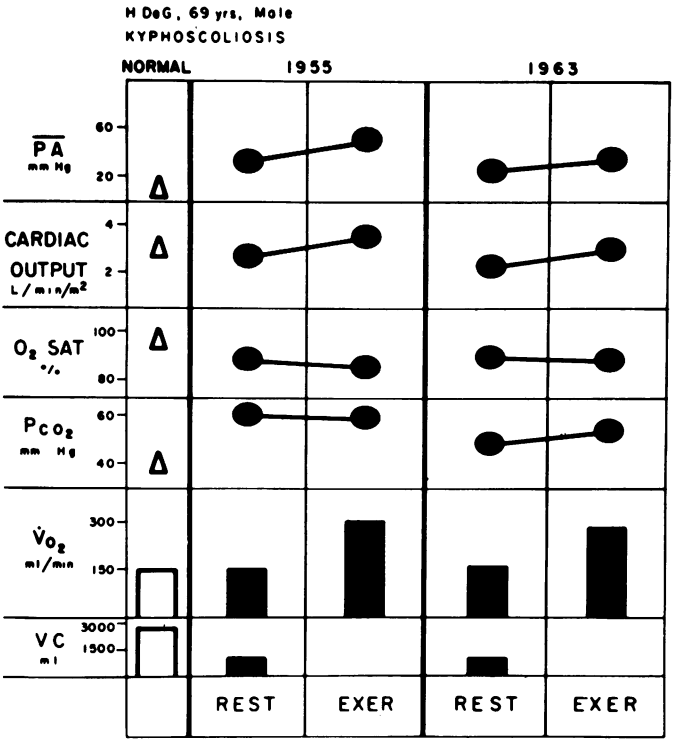

Fig. 10. Pulmonary artery pressures, cardiac output, and arterial blood-gas composition after an 8-year interval in a patient with kyphoscoliosis. Vo_2 refers to the oxygen consumption and is an index of the severity of exercise performed during the study. VC is the vital capacity.

tent positive pressure breathing through a mouthpiece 10 minutes of each hour.

Twenty-four hours later, though weight had decreased by only 1½ lb., there was a substantial drop in both right ventricular systolic and end-diastolic pressures with no change in either the cardiac output or the level of oxygen saturation while breathing room air. At this time, as may be seen in Figure 9, the arterial *p*H is more acidotic because of the further rise in CO_2 tension that accompanied the improved arterial oxygenation and decreased alveolar ventilation. Finally, 34 days after admission and after a 10-lb. weight loss, there was a decrease of right ventricular end-diastolic pressure to normal, a further decrease in right ventricular systolic pressure, and improvement in arterial oxygen saturation, *p*H, and Pco_2.

This patient demonstrates the rapidity with which changes in right

heart pressures may occur without changes in cardiac output or an improvement in arterial oxygen saturation. The possible role of shifts in central blood volume as the basis for this type of early change in pulmonary vascular resistance deserves further study. Unfortunately it was not possible to obtain a pulmonary capillary "wedge" pressure with these studies; however, wedge-pressure elevations have not occurred in the cor pulmonale of kyphoscoliosis[9] and pulmonary congestion was not evident, so that a role for left heart hypertension is unlikely in this instance. The characteristics of these more rapid adjustments of the pulmonary circulation in cor pulmonale with failure is currently under study in our laboratory.

What is the long-term view with regard to cor pulmonale in individuals with kyphoscoliosis who have pulmonary hypertension? Is it progressive, stable, or regressive? Data pertaining to the long-term follow-up of patients with kyphoscoliosis are limited. We have studied one such patient over an interval of eight years. He had severe kyphoscoliosis from Pott's disease for over 40 years and was 61 years old when first seen. His data are shown in Figure 10. In 1955, the pulmonary artery pressure, cardiac output, oxygen saturation, and P_{CO_2} were measured after treatment for an episode of severe right heart failure and CO_2 narcosis. At rest he had moderate elevation of his pulmonary artery pressure. Cardiac output was normal. Arterial oxygen saturation was 88 per cent at rest and 82 per cent during supine, steady-state exercise. Arterial P_{CO_2} was 60 mm. Hg at rest and 59 mm. Hg during exercise. Eight years later, during which time he had been treated at home with intermittent positive pressure breathing for 10 minutes 4 times per day, digitalis, diuretics, salt restriction, and the administration of antibiotics with infections of the upper respiratory tract, his pulmonary pressure at rest and during exercise were approximately the same. Arterial oxygen saturation was slightly higher and the P_{CO_2} slightly lower both at rest and during exercise. The clinical course of this patient illustrates that pulmonary hypertension need not be progressive if the underlying anatomic deformity and blood-gas abnormalities are stable.

Poliomyelitis

There are several reports of the occurrence of alveolar hypoventilation in anterior poliomyelitis, usually with bulbar involvement.[10, 22] The

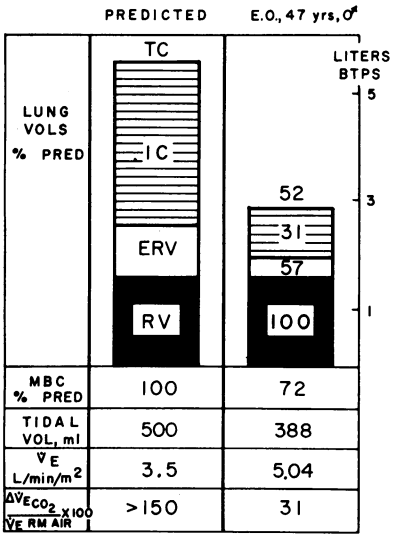

Fig. 11

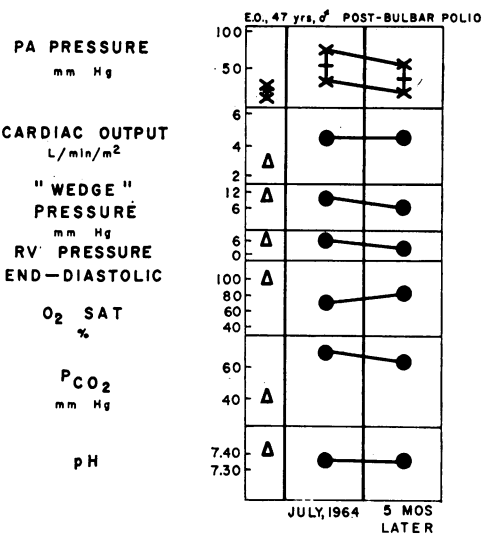

Fig. 12

Fig. 11. Lung volumes and ventilation in a patient with alveolar hypoventilation 11 years following anterior poliomyelitis. MBC=maximum breathing capacity as per cent of the predicted value. $\dot{V}_E$ is the resting minute ventilation while breathing room air. $\dot{V}_{ECO_2}$ is the minute ventilation while breathing 5 per cent CO_2 (see text).

Fig. 12. Right heart pressures, cardiac output, and arterial blood gases in patient E.O. with alveolar hypoventilation 11 years following anterior poliomyelitis (see text).

presence of right heart hypertrophy at postmortem examination in patients dying from respiratory failure in poliomyelitis has indicated the coexistence of cor pulmonale.[23]

Recently we have studied a 47-year-old man who had bulbar poliomyelitis 11 years ago with residual weakness of the intercostal muscles and diaphragm. Beginning three years ago, or eight years after his attack of poliomyelitis, he noted increasing shortness of breath and ankle edema.

The lung volumes in this patient are shown in Figure 11. The total lung capacity was reduced because of a reduction in inspiratory capacity. However, he could muster enough strength from his abdominal, sternocleidomastoid, and intercostal muscles to ventilate to 75 per cent of his maximum ventilatory capacity for the short test period of 12 seconds.

Small tidal volumes resulted in a low alveolar ventilation despite a higher-than-predicted total minute ventilation. Arterial P_{CO_2} was ele-

vated, arterial oxygen saturation was reduced and his *p*H was mildly acidotic. It was known only that these blood gas abnormalities had been present 2 years before. Also shown in Figure 11 is the response of ventilation to the breathing of 5 per cent carbon dioxide in which the increment in minute ventilation was profoundly reduced.

The outstanding disturbances in the circulation were pulmonary hypertension with a pulmonary artery pressure of 71/33 mm. Hg and a high cardiac output (Figure 12). The pulmonary "wedge" pressure was normal at 9 mm. Hg.

In this patient, a major problem concerned the exacerbation of alveolar hypoventilation that accompanied sleep. While asleep, breathing room air, he was observed to be markedly cyanotic with periods of Cheyne-Stokes breathing. He would often awaken confused and disoriented. It is likely that the mild alveolar hypoventilation that accompanies sleep in the normal individual[24, 25] accentuates the blood-gas abnormalities in the patient with existing alveolar hypoventilation. Attempts to assist breathing during sleep with an intermittent positive-pressure breathing apparatus and a mask were unsuccessful because of the discomfort of the mask. He was hospitalized and taught to sleep in an Emerson U-cyclit chest respirator. At a setting of −20 cm. H_2O and cycled automatically he could achieve oxygen saturations of over 91 per cent while inhaling room air. When studied 5 months later (Figure 12), he was observed to have an improved arterial blood-gas composition and a decrease in pulmonary artery pressure. The decrease in pulmonary artery pressure with the same cardiac output and a normal "wedge" pressure suggests a decrease in pulmonary vascular resistance.

The observations in this patient demonstrate the insidious onset of alveolar hypoventilation and the long interval preceding clinical evidence of right heart failure. The absence of spinal deformity or pulmonary compression is further evidence of the causative relationship between the alveolar and blood-gas abnormalities of alveolar hypoventilation and cor pulmonale.

Obesity

Up to this point in this discussion we have considered forms of alveolar hypoventilation and cor pulmonale in which the underlying thoracic deformity is irreversible. The alveolar hypoventilation of obesity is potentially reversible if weight loss can be induced. This is

TABLE II—ARTERIAL BLOOD GASES AND RIGHT HEART PRESSURES AT REST AND DURING EXERCISE IN PATIENT E.W.

	1956						*1961*					
	Rest			*Exercise*			*Rest*			*Exercise*		
	S	D	M	S	D	M	S	D	M	S	D	M
Pulmonary artery pressure mm. Hg	27	12	20	56	31	38	56	30	40	68	40	53
Cardiac output l/min./M^2	3.30			4.71			3.23			3.62		
Pulmonary capillary "wedge" pressure mm. Hg	—			—			18			23		
Arterial Blood												
O_2 saturation %		88			99			68			82	
Pco_2 mm. Hg		52			56			70			62	
*p*H		7.29			7.27			7.28			7.31	
O_2 consumption STPD ml./min.		152			430			106			222	

S, D, and M refer to systolic, diastolic, and mean pressures.

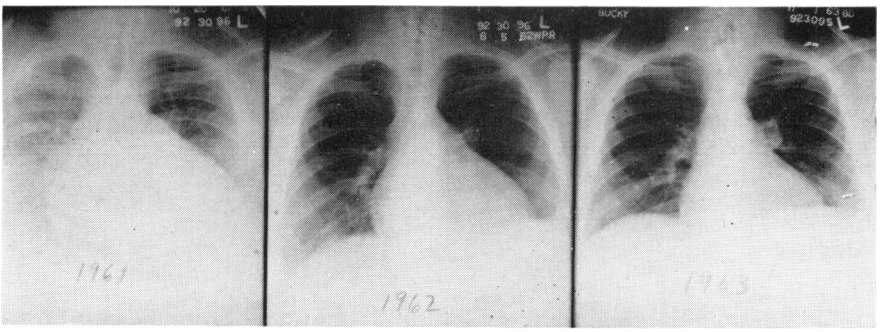

Fig. 13. The chest roentgenograms in patient E.W. with obesity and alveolar hypoventilation. The film in 1961 was taken before weight loss during an episode of heart failure. The films in 1962 and 1963 were taken after weight loss; clinical evidence of heart failure was absent.

illustrated by the study of a massively obese patient in whom the disturbances in ventilation and circulation were reversed when weight loss was successfully induced.

The patient was seen first at the age of 19 years when he weighed 425 pounds. He presented with marked right heart failure, weakness, and shortness of breath.

Treatment with digitalis, diuretics, and bed rest resulted in a 45-lb. loss of edema fluid in 2 weeks. His first study is shown in Table II and was carried out in 1956 after cardiac compensation had been restored.

Pulmonary artery pressure was slightly increased at rest but increased to 56 over 31 with the increased pulmonary blood flow of exercise. Right ventricular end-diastolic pressure was normal. Hypoxemia and hypercapnia were present. In 1961, after 5 years of unsuccessful attempts at weight loss through dieting, he was again in heart failure. His cardiorespiratory data at this time appear in the second half of Table II. Pulmonary artery pressure was much higher at rest and during exercise. The pulmonary capillary "wedge" pressure was also above normal, indicating a contribution of left atrial hypertension to the pulmonary hypertension. Hypoxemia and hypercapnia were more marked in 1961 than in 1956.

In view of his desperate clinical state and the total failure of conventional measures to cause weight loss, it was elected to perform an intestinal bypass by anastomosing the jejunum to the ileum as described by Payne.[26] Following this treatment he lost 125 pounds in one year.

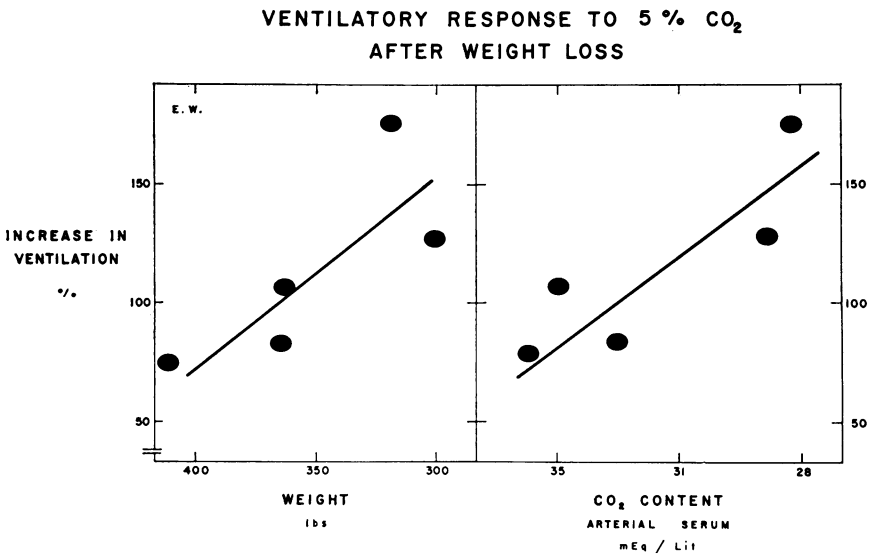

Fig. 14. The increase in the ventilatory response to the breathing of 5 per cent carbon dioxide and the decrease in serum bicarbonate content after weight loss, in patient E.W. with obesity and alveolar hypoventilation.

His progressive reduction in heart size with weight loss is shown in Figure 13. With loss of weight, his arterial oxygen saturation and P_{CO_2} became normal. Unfortunately he refused repeat cardiac catheterization, so that physiological confirmation of his clinical improvement could not be obtained. However, further study of his ventilatory response to CO_2 revealed a normal increment in ventilatory volume on breathing 5 per cent CO_2 as compared with the low response when he was obese (Figure 14),* indicating the reversibility of the abnormality in the regulation of ventilation.

Acid-Base Derangements in Alveolar Hypoventilation

We should like now to turn to another aspect of cor pulmonale that concerns the effects of treatment with diuretics and salt restriction on the electrolyte composition of the blood and tissues, the arterial blood-gas content, and the regulation of ventilation. It has been shown that normal individuals with induced metabolic alkalosis have a measurable reduction in ventilatory response to the breathing of carbon dioxide.[27]

*In January 1965 this patient died of acute renal shutdown as a result of an acute urinary tract infection with pseudomonas aeruginosa that was superimposed on subacute glomerulonephritis diagnosed anatomically at postmortem examination. No gross or microscopic anatomic abnormalities of the lungs, medulla, or hypothalamus were present. The walls of the right and left ventricular myocardium were hypertrophied.

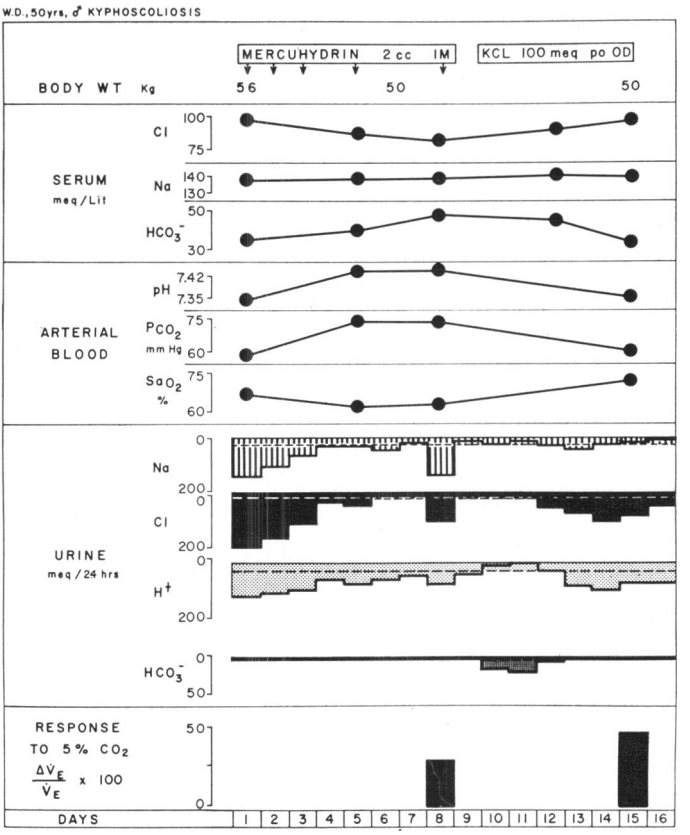

Fig. 15. The effect of chloride depletion on arterial blood gas composition and ventilatory responsiveness in chronic hypercapnia (see text).

It has been shown also that reductions in serum chloride and potassium secondary to conventional diuretic therapy are capable of inducing metabolic alkalosis with increases in serum bicarbonate.[28-30] In addition, Schwartz *et al.*[31] have shown that chloride deficiency interferes with the return of serum bicarbonate concentration to normal in dogs recovering from chronic exposure to high carbon dioxide environments.

In Figure 15 are shown the data of patient W. D. with kyphoscoliosis and cor pulmonale, who was studied in collaboration with Dr. Henry O. Heinemann. While on a fixed caloric and electrolyte intake, observations were made during a period of severe chloride depletion and repletion. Mercuhydrin was administered repeatedly during the first days of treatment, resulting in a decreased serum chloride concen-

tration and an increasing serum bicarbonate concentration. Serum *p*H increased from the acidotic to the alkalotic range. Also, as shown in this figure, the P_{CO_2} of the arterial blood increased from 60 to 73 mm. Hg and the oxygen saturation decreased from 70 to 62 per cent.

The administration of potassium chloride orally in a dose of 100 mEq. per day resulted in a rise in serum chloride concentration and a decrease in serum bicarbonate concentration, which was in part the result of increased bicarbonate excretion in the urine. Associated with the decrease in bicarbonate, there was an increased ventilatory response to breathing 5 per cent carbon dioxide. The rise in ventilatory responsiveness was reflected in the lowering of arterial P_{CO_2} and the increase in arterial oxygen saturation.

In patients with alveolar hypoventilation and reduced ventilatory responsiveness, the superimposition of chloride depletion and further lowering of ventilatory responsiveness may contribute to the blood-gas derangements of alveolar hypoventilation and prevent recovery from states of severe hypercapnia.

Summary and Conclusions

In summary, then, it has been shown that musculoskeletal abnormalities of the thorax taken as a group induce cor pulmonale when alveolar hypoventilation is superimposed. Also it has been shown that the relief of alveolar hypoxia and hypercapnia is associated with relief of pulmonary hypertension. The treatment of the blood-gas abnormalities of alveolar hypoventilation is, then, a crucial therapeutic objective in the treatment of cor pulmonale in this category of disease. In the association of pulmonary hypertension with alveolar hypoxia the patients presented here, with alveolar hypoventilation and normal lungs, resemble native residents of areas of high altitude in whom reversible pulmonary hypertension and right heart hypertrophy have also been demonstrated.[32]

The precise site of action of alveolar hypoxia in the genesis of pulmonary hypertension is still unclear. However, the demonstration that alveolar gas tensions are sensed by precapillary arterioles in man at least provides a mechanism for the direct effect of alveolar hypoxia on precapillary vascular resistance.[33, 34] Conversely, there is little evidence that alveolar hypoxia affects the pulmonary capillary or pulmonary venous resistance in man.[35] As in patients with pulmonary

emphysema,[36] in normal man, and in dogs[37] it is likely that increases in hydrogen ion concentration contribute to pulmonary vascular resistance in this form of cor pulmonale. However, the magnitude of the effect of acidosis, when coupled with hypoxia and existing increases in pulmonary vascular resistance from thoracic deformities, remains to be explored.

The alveolar hypoventilation and pulmonary hypertension associated with obesity appear to be reversible with weight loss.

Observations on the interaction between blood and tissue buffers and the stimuli to ventilation suggest that metabolic alkalosis from induced hypochloremia may accentuate alveolar hypoventilation and diminish ventilatory responsiveness.

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