CENTRAL RESPIRATORY FAILURE REVERSED BY TREATMENT

BY

J. M. B. HUGHES

(*Formerly House Physician, Department of Medicine Hammersmith Hospital, London*)

RESPIRATORY failure in neurological disease is usually caused by respiratory muscle paralysis; common examples are polyneuritis, poliomyelitis and myasthenia. This report describes a patient with a cerebral tumour who had respiratory failure, shown by carbon dioxide retention, but who did not have respiratory muscle paralysis. His respiratory status was monitored by frequent estimations of mixed venous P_{CO_2}. These measurements are easily performed by the house physician at the bedside without distress to the patient.

There are three especial points of interest in this case. First, mixed venous P_{CO_2} was a more sensitive index of respiratory status than minute volume, respiratory frequency or ventilatory capacity. Secondly, measurements of P_{CO_2} showed that the patient's respiratory failure waxed and waned as his clinical state worsened and then improved after radiotherapy. Lastly, observations were made which suggest a possible mechanism of respiratory failure when the lungs are normal and respiratory muscles adequate.

Case History.—J. C. Male. Age 18. Educationally subnormal. In August 1965 he was seen by his general practitioner because of diplopia and was noticed to have a right external rectus palsy. Four weeks later his speech became slurred and nasal in quality and he had difficulty in swallowing. On September 25th he was admitted to Hammersmith Hospital having had, in addition, a staggering gait and progressive cough for three days. He had had no sensory symptoms in the face or limbs.

Examination.—Alert and co-operative. No papillœdema. Complete bilateral external rectus palsy. Coarse horizontal nystagmus on conjugate gaze to right and left and vertical nystagmus on conjugate upward gaze. Right masseter palsy. Gross bilateral facial palsy of lower motor neurone type. Palatal palsy. Pharyngeal anæsthesia with absent gag reflex. Difficulty in swallowing and accumulation of secretions in pharynx. Weak tongue movements. Moderate right hemiparesis with hyper-reflexia and equivocal extensor plantar response. Cerebellar type ataxia in all four limbs. No sensory loss in the limbs. Sphincters functioned normally. Pulse irregular due to ventricular ectopic beats. Good equal chest expansion. Rhonchi in the lungs.

A provisional diagnosis of brain-stem tumour was made. A nasogastric tube was passed and tracheostomy was performed in view of the danger of aspiration. The inspired air was humidified and oxygen at 3 litres a minute was added.

Investigations.—The CSF was normal. Blood count, serum electrolytes and urea normal. Chest X-ray normal. Lumbar air-encephalogram showed slight posterior displacement of the fourth ventricle with smooth indentation of the floor, suggestive of a pontine tumour; there was no filling of the pontine cistern. On vertebral angiography the only abnormality was slight stretching of the superior cerebellar arteries on the Towne projection.

Weekly summaries of his neurological and respiratory progress are shown below. Measurements of Pco_2 and FEV_1 are discussed in the section on methods and results, and are charted more fully in fig. 1. As his neurological status deteriorated over the first few weeks, so Pco_2 rose. After the start of radiotherapy neurological improvement was accompanied by a gradual fall of Pco_2 to normal. Throughout this time, ventilatory capacity, as judged by FEV_1, was unchanged.

1st week: Progressive weakness of both upper limbs. Mixed venous Pco_2 ($P\bar{v}co_2$) 54 mm.Hg.; forced expiratory volume in one second (FEV_1) 1·2 litres.

3rd week: Drowsy; unable to turn over in bed. $P\bar{v}co_2$ 55; FEV_1 1·5.

4th week: Painful spasms in right hand and leg. Progressive spasticity of right arm. Left masseter palsy. $P\bar{v}co_2$ 58.

5th week: More drowsy. Both arms spastic. Increasing weakness of limbs; now unable to raise right arm from the bed. $P\bar{v}co_2$ 61; FEV_1 1·5. Deep X-ray therapy to the brain-stem started with supervoltage radiation on the linear accelerator.

7th week: Right arm and left masseter stronger; return of normal tone to upper limbs. $P\bar{v}co_2$ 55; FEV_1 1·6.

8th week: Sat out of bed and walked down the ward for the first time. $P\bar{v}co_2$ 52.

10th week: Swallowing well. Nasogastric tube removed. $P\bar{v}co_2$ 47; FEV_1 1·5.

12th week: Tracheostomy tube removed. Dressed and fed himself.

13th week: Discharged.

Complete bilateral external rectus palsy unchanged. Slight impairment only of facial, palatal, tongue and jaw movements. Power in limbs and gait were normal.

Three months later his condition relapsed and he was readmitted partially conscious, unable to swallow, and with severe weakness of all his limbs. Gross papillœdema was now present. Carbon dioxide retention was again a feature with arterial Pco_2 at 58 mm.Hg. Two weeks later he died and at necropsy a tumour was seen diffusely involving the brain-stem and medulla and the surfaces of the third, fourth and lateral ventricles. Histological examination showed that this tumour was a glioblastoma multiforme.

Methods and Results

(*1*) *Estimation of mixed venous* Pco_2 ($P\bar{v}co_2$)

The rebreathing method of Campbell and Howell (1962) was used to measure mixed venous Pco_2; measured in this way Pco_2 at rest is about 6 mm.Hg. greater than arterial. The normal range is 40–50 mm.Hg. The principle of the method is that rebreathing from a rubber bag filled with oxygen causes co_2 to pass from the mixed venous blood to the lungs and bag until equilibrium is obtained between the bag,

the lungs and blood. P_{CO_2} of the gas in the bag at this time will equal the P_{CO_2} of mixed venous blood. Details of the theory and method are given in Campbell and Howell's paper. As an additional check the gas in the bag at the end of each rebreathing period was analysed as described by Godfrey (1965). At the bedside the procedure took about five minutes including analysis of the gas on a simplified Haldane gas analysis machine, mounted on a small tray. A small attachment on the rebreathing bag fitted into the tracheostomy and the procedure is actually easier for operator and patient than if a mouthpiece is being used.

On two occasions arterial blood was sampled from the brachial artery; the values obtained were raised and agreed well with the predictions made from $P\bar{v}CO_2$. CO_2 production was measured at the same time by collecting expired air over a five minute period in a Douglas bag. On both occasions we found CO_2 production normal but ventilation much reduced. The results on one occasion with approximate normal values are shown in Table I. The reduction of ventilation was sufficient to explain the CO_2 retention, and in this case there was no reason to suppose ventilation perfusion inequality was a significant factor.

TABLE I

22.10.65	*Patient*	*Normal*
4th week of illness; breathing air		
Ventilation (L/min. BTPS)	4·8	6–7
Tidal volume (ml.)	300	400–600
Arterial P_{CO_2} (mm.Hg.)	51	40
Mixed venous P_{CO_2} (mm.Hg.) ..	57	46
CO_2 production (STPD) ml./min. ..	176	150–280

Fig. 1 shows the rise and subsequent fall of $P\bar{v}CO_2$ to normal values after radiotherapy. It can also be seen that $P\bar{v}CO_2$ is a much better index of reduced ventilation

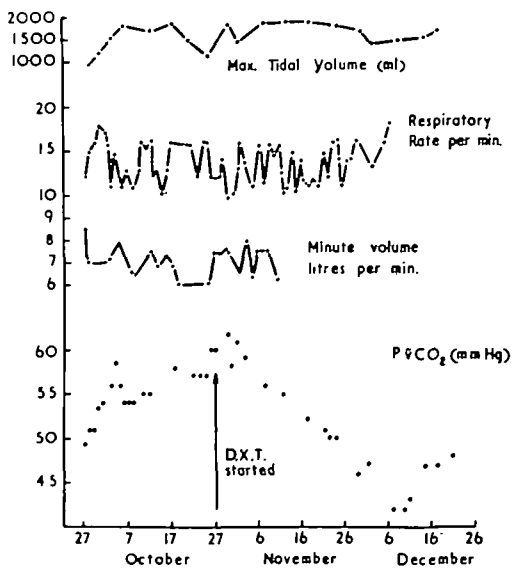

FIG. 1.—Mixed venous P_{CO_2} is shown rising to values of 60 mm.Hg. and then falling to normal after radiotherapy. Measurements of total ventilation (minute volume), respiratory rate and ventilatory capacity or FEV_1 (expressed as maximum tidal volume) are unchanged during this time.

than respiratory rate (while sleeping) or minute volume measured with a Wright anemometer.

(2) *Estimation of ventilatory capacity*

In respiratory muscle paralysis ventilatory capacity is impaired. This means that the maximum minute volume of ventilation that can be voluntarily achieved is reduced. For clinical purposes this is usually estimated from the forced expiratory volume in one second (or FEV_1). The FEV_1 is the volume of air that can be forced out of the chest in the first second of a maximal expiration after a maximal inspiration.

While the patient was ill, and breathing through a tracheostomy, he was unable to perform respiratory movements to command sufficiently well for FEV_1 to be measured on a spirometer. Instead, tidal volume was stimulated by rebreathing from a bag of oxygen; during the second minute his tidal volume and respiratory rate increased markedly due to the stimulus of the accumulating CO_2; as soon as this became uncomfortable for him the bag was taken off and the next two or three inspiratory excursions were recorded with a Wright anemometer. We never went to the limit of tolerance and our readings varied from 1 litre (30 per cent of the predicted FEV_1) to 1·9 litres. These measurements of tidal volume would be a minimum estimate of FEV_1. Most of the time (*see* fig. 1) the tidal volume under CO_2 stimulation was 1·5 litres. After the tracheostomy tube had been removed we obtained the same value on a dry spirometer for the formal FEV_1 measurement. For this patient 1·5 litres is 45 per cent of predicted normal for FEV_1. Experience shows that FEV_1 must be reduced to less than 25 per cent of predicted before the ability to maintain a normal P_{CO_2} is lost (Burrows *et al.*, 1965). We conclude that ventilatory capacity in this case was more than adequate.

Discussion

Reduction of ventilation can cause CO_2 retention in the presence of normal lungs and ventilatory capacity. Intracranial causes of this are either non-specific cerebral depressants such as barbiturates, morphine, or general anæsthesia, or else lesions of the brain-stem and medulla such as tumours (Comroe, 1955), bulbar poliomyelitis, or encephalitis (Garlind and Lindenholm, 1958). Poliomyelitis epidemics from 1947–51 focused attention on respiratory function in cases with bulbar rather than spinal palsy. There are suggestions from cases reported in the literature that the changes seen in our patient may be found more often if specifically looked for. Thus Sarnoff *et al.* described two patients—aged 9 and 11 years—with bulbar poliomyelitis whose arterial P_{CO_2} was raised to 50 and 48 mm.; these values fell to 41 and 38 mm. after a period of hyperventilation rather than muscular paralysis. They also pointed out the irregularity of respiratory rate and rhythm in patients with bulbar poliomyelitis. This is well seen in our patient; fig. 2 shows such episodes alternating with periods of regular breathing. Respiratory muscular inco-ordination is well described too and, as mentioned, our patient was unable to perform the FEV_1 manœuvre until he was much improved. To be more precise, his difficulty was that of being unable to make a deep forced expiration to command and it seemed more like a respiratory apraxia than respiratory paralysis. There was no failure of comprehension.

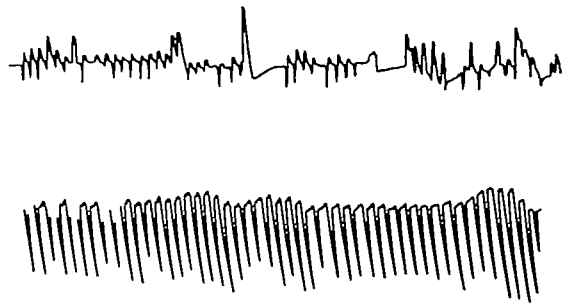

FIG. 2.—Stethograph recording of episodes of irregular and regular breathing (inspiration downwards).

Plum and Swanson (1958) reported further studies of the respiratory centre defect in bulbar poliomyelitis. The first signs of respiratory inequality occurred during sleep, and they noticed marked sensitivity to respiratory depressant drugs and anæsthesia. On return to the ward after a vertebral arteriogram for which a general anæsthetic had been given, our patient's breathing became so slow and irregular that assisted respiration via a bag attached to his tracheostomy was needed for about forty-five minutes. $P\bar{v}CO_2$ had risen to 64 mm. but returned to pre-anæsthesia levels (57 mm.) within a few hours. During this time Cheyne-Stokes respiration was noticed.

The odd thing about this patient is that in spite of under-ventilation and allowing his $P\bar{v}CO_2$ to rise to 60 mm. he always remained extremely sensitive to the CO_2 stimulus of rebreathing from a bag of oxygen (fig. 3). Quantitative measurements of ventilatory response to CO_2 were not made; however, until the tracheostomy was removed, frequent measurements of the extent to which CO_2 stimulated his tidal volume were obtained (*see* Methods—Estimation of Ventilatory Capacity). Since the tidal volume, respiratory frequency and rebreathing time remained remarkably constant in these measurements, it is unlikely that significant changes in CO_2 sensitivity would have occurred. In support of this, Plum and Swanson found that the response to CO_2 in bulbar poliomyelitis was only diminished in those whose ventilatory capacity was reduced below 50 per cent.

The functional defect in this patient can be described by analogy with a chemostat whose threshold level of response has been raised but whose sensitivity is unimpaired. We remain ignorant, however, of the precise mechanisms whereby the respiratory centre controls breathing.

Finally, the practical implications to be drawn from this case are these. If there is any doubt about the breathing in patients with neurological disease, the physician would be well advised to ask the following three questions. First, are the airways safe from aspiration? Secondly, is ventilatory capacity adequate as judged by FEV_1? Finally, is ventilation sufficient for metabolic needs as judged by PCO_2?

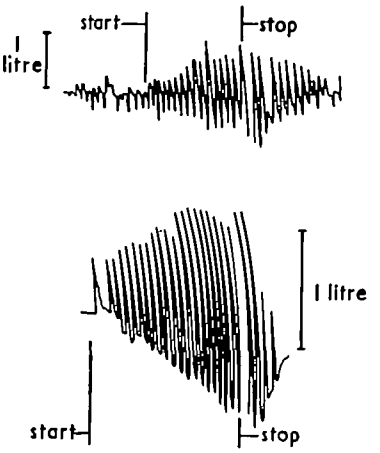

FIG. 3.—Stethograph recordings made during the fourth and sixth weeks after admission showing the response of ventilation to rebreathing from a 2 litre bag of oxygen. As CO_2 accumulates tidal volume increases three to four times. Calibrations are approximate.

SUMMARY

A case of a young man with bulbar palsy, respiratory failure and a brain-stem tumour, is presented.

The respiratory failure was closely monitored by frequent estimation of mixed venous P_{CO_2} by the rebreathing method. Marked improvement in neurological status and carbon dioxide retention occurred after radiotherapy.

The cause of the respiratory failure was reduction of ventilation due to disturbance of respiratory structures in the brain-stem rather than respiratory muscle paralysis.

ACKNOWLEDGMENTS

I am grateful to Dr. E. J. M. Campbell for allowing me to publish this case, and for all his help and constructive criticism. I should also like to thank Dr. A. Breckenridge, Dr. C. Pallis, Dr. M. Rice-Edwards and Dr. J. B. West for helpful suggestions, and Dr. W. I. Carter, the patient's general practitioner, for reading the manuscript. Dr. N. Cooter kindly carried out pathological studies.

REFERENCES

BURROWS, B., NIDEN, A. H., BARCLAY, W. R., and KASIK, J. E. (1965) *Amer. Rev. Resp. Dis.*, **91**, 665.

CAMPBELL, E. J. M., and HOWELL, J. B. L. (1962) *Brit. med. J.*, **2**, 630.

COMROE, J. H., Jr. (1955) "The Lung," Chicago. p. 39.

GARLIND, T., and LINDERHOLM, H. (1958) *Acta med. scand.*, **162**, 333.

GODFREY, S. (1965) *Brit. med. J.*, **1**, 1163.

PLUM, F., and SWANSON, A. G. (1958) *Arch. Neurol. Psychiat., Chicago*, **80**, 267.

SARNOFF, S. J., WHITTENBERGER, J. L., and AFFELDT, J. E. (1951) *J. Amer. med. Ass.*, **147**, 30.