

# Some aspects of respiratory function in three siblings with Morquio-Brailsford disease

E. O. S. HOPE, M. J. B. FAREBROTHER<sup>1</sup>, and D. BAINBRIDGE

*The Chest Unit and the Department of Respiratory Diseases, City Hospital, Edinburgh*

Morquio-Brailsford disease is a rare genetic disorder of mucopolysaccharide metabolism, and its features include dwarfism and thoracic deformity. A boy aged 15 with this condition developed respiratory failure and later died. This boy and his two affected female siblings were studied and the results are presented. The height of the lungs was less than the anteroposterior diameter on standard chest radiographs. All had small lungs without evidence of airways obstruction. Measurements of dependent airway closure were made in the erect and supine positions. These showed some abnormalities which could cause ventilation-perfusion imbalance. Possible mechanisms leading to the development of respiratory failure in this condition are discussed, including nasopharyngeal obstruction, thoracic deformity, and disturbed ventilation-perfusion relationships. The importance of respiratory failure as a cause of death in Morquio's disease is emphasized.

Cases of this rare genetic disorder were described independently by Morquio (1929) and Brailsford (1929). The disease has now been classified as a disorder of mucopolysaccharide metabolism and is inherited as an autosomal recessive. The genetic mucopolysaccharidoses have been reviewed and classified by McKusick *et al.* (1965). These and other investigators (Pedrini, Lenzini, and Zambotti, 1962; Robins, Stevens, and Linker, 1963; Maroteaux, Lamy, and Foucher, 1963) have found that those affected by Morquio's disease excrete abnormal amounts of keratosulphate in their urine. This mucopolysaccharide is normally found in cornea, cartilage, and nucleus pulposus.

Typical features of Morquio's disease include dwarfing, a short trunk and neck, a barrel-shaped chest, and pectus carinatum. Osteogenesis is disturbed and radiographs show deficient and irregular endochondral ossification. The vertebrae have a characteristic flattened shape. Intelligence is not impaired. Extraskelatal manifestations may occur, especially in older patients, including corneal opacities and cardiac murmurs. The average age at death is less than 20 years and is often attributed to neurological sequelae of the vertebral abnormalities or to respiratory failure.

We have recently seen a patient with this disease who presented to us in respiratory failure and later died. This paper presents a clinical report

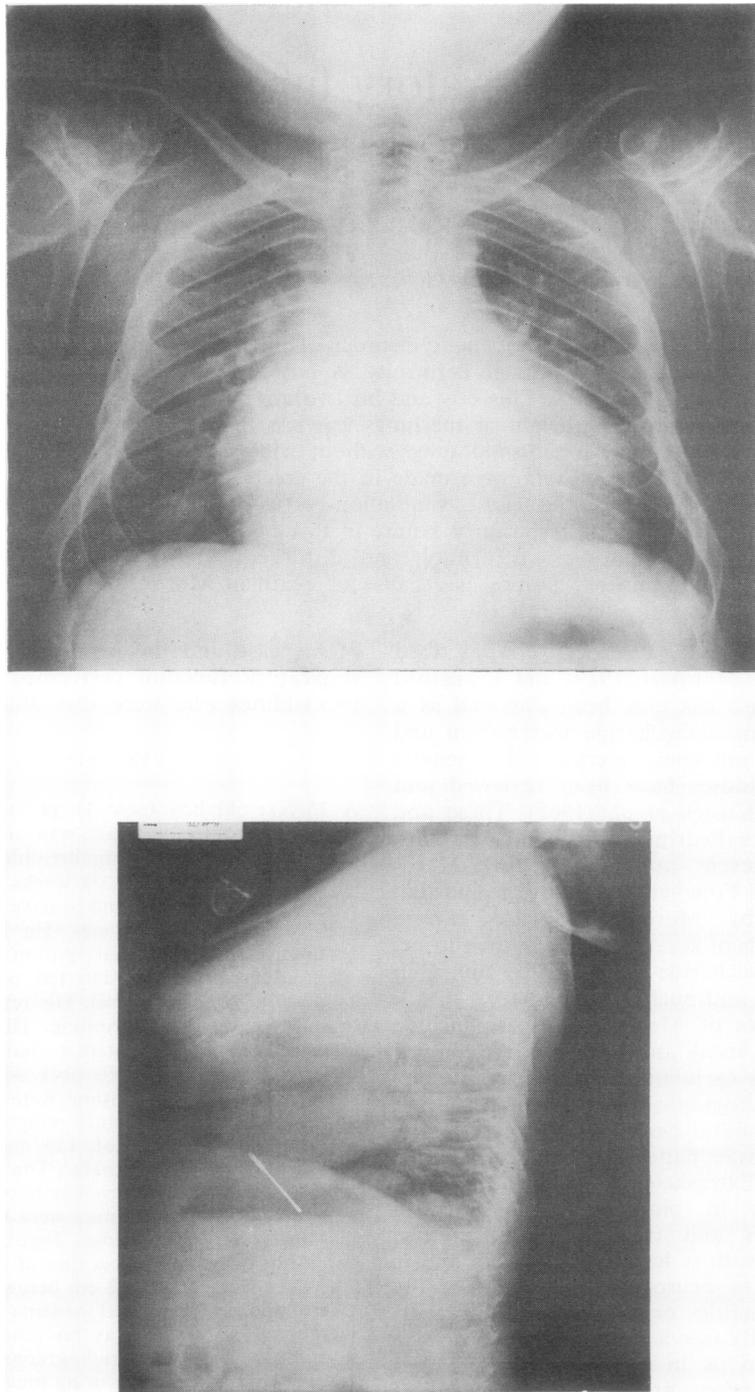
of his case and the results of measurements of respiratory function performed on him and his two siblings who were also affected.

## CASE HISTORY

A 15-year-old boy (case 1), previously diagnosed as having Morquio's disease, was admitted to hospital complaining of increasing breathlessness on exertion for several months. For six weeks he had been noted to be breathless at rest and to have attacks of sweating and cyanosis while asleep. He had had a cough productive of a little clear sputum.

On admission he was dwarfed, plump, and centrally cyanosed sitting up in bed. His respirations were 35/minute, shallow and grunting. His chest was short, increased in anteroposterior diameter, and moved little with respiration. His neck was short, the accessory muscles of respiration were poorly developed, and breathing was mainly diaphragmatic. He was afebrile with a pulse of 130/minute and a blood pressure of 120/80 mmHg. The heart seemed enlarged, with a right ventricular heave, and soft systolic and early diastolic murmurs were heard maximally at the lower left sternal edge. Jugular venous pressure could not be estimated because of the neck deformity. The liver was palpable 2 cm below the costal margin. There was no peripheral oedema. Bilateral deafness was noted but there was no other neurological abnormality. His chest radiographs (Fig. 1) showed cardiac enlargement obscuring much of the lung fields, large main pulmonary vascular shadows, and the flattened vertebrae typical of the disease. The electrocardiogram showed sinus rhythm, right atrial and right ventricular hypertrophy with clockwise rotation,

<sup>1</sup>Correspondence to: Dr. M. J. B. Farebrother, Department of Respiratory Diseases, City Hospital, Greenbank Drive, Edinburgh EH10 5SB



**FIG. 1.** *Posteroanterior and lateral chest radiographs in case 1, a 15-year-old boy with Morquio-Brailsford disease.*

and a right ventricular strain pattern. His haemoglobin was 16.8 g/100 ml and white blood count 12,500/mm<sup>3</sup> (neutrophils 73%). Plasma urea, sodium, potassium, and chloride were normal. The venous plasma bicarbonate was 37 mEq/litre. Arterial blood was taken when he was fully awake, lying at 45° in bed and breathing oxygen at 1 l/min through an Edinburgh mask (approximately 25% oxygen). Analysis showed Po<sub>2</sub> 76 mmHg, PCO<sub>2</sub> 66 mmHg, and pH 7.35.

During sleep he was deeply cyanosed, sweating, and difficult to rouse. When fully awake he was less cyanosed and breathed through the mouth with the tongue protruding. Examination of the nose and throat showed a severe degree of posterior nasal obstruction, but inspection of the nasopharynx was difficult because depression of his large tongue caused choking and asphyxia.

Treatment with antibiotics, digoxin, diuretics, and controlled oxygen produced a slight improvement in his general condition but subsequent measurements of his mixed venous PCO<sub>2</sub> (by the rebreathing technique) were all above 66 mmHg and he continued to sweat and be more cyanosed during sleep. These findings indicated chronic respiratory failure and cor pulmonale, thought to be a result of his thoracic deformity and probably aggravated by upper airways obstruction. He died five months later in another hospital. Necropsy was not performed.

The results of respiration function tests are discussed below, with those of his siblings (cases 2 and 3).

#### METHODS

**SPIROMETRY** Forced expiratory volume in one second (FEV<sub>1</sub>) and forced vital capacity (FVC) were the best of three satisfactory recordings on a Poulton timed vital capacity spirometer. Total lung capacity (TLC) and residual volume (RV) were measured standing and supine by helium dilution.

**CLOSING VOLUMES** The effect of gravity acting along the vertical axis of the lung in any position creates a gradient of pleural pressure so that it is less negative in the lowermost parts. At RV it may even be positive. Because of this pressure gradient, during expiration progressive airway closure may occur in the dependent parts of the lung, starting at a volume point above RV. If this occurs the first gas inspired at RV goes to the uppermost part of the lung and hence a bolus of tracer gas injected at the mouth at RV will preferentially label these uppermost parts. During subsequent expiration the alveolar plateau of tracer gas is followed by a terminal rise in concentration due to the emptying of the already preferentially labelled upper regions. In our studies argon was used as the tracer gas, and following the injection of a bolus of argon into the mouth at RV a slow and even inspiration was made to TLC (flow rate <0.5 l/sec). A similar slow and even expiration was then made from TLC to RV, and during this the expired argon concentration at the mouth was measured with a respira-

tory mass spectrometer together with the expiratory flow rate and expired volume. The record for a normal subject is shown (Fig. 2a) and the onset of the terminal rise (arrow, Fig. 2a) is thought to mark the beginning of closure of the dependent airways. The volume point at which this occurs may be expressed as a division of vital capacity (VC), or TLC if RV is already known, and is known as the closing volume (CV), as described by Dollfuss, Milic-Emili, and Bates (1967). The use of argon rather than radioactive xenon as the tracer gas was described by Jones and Clarke (1969).

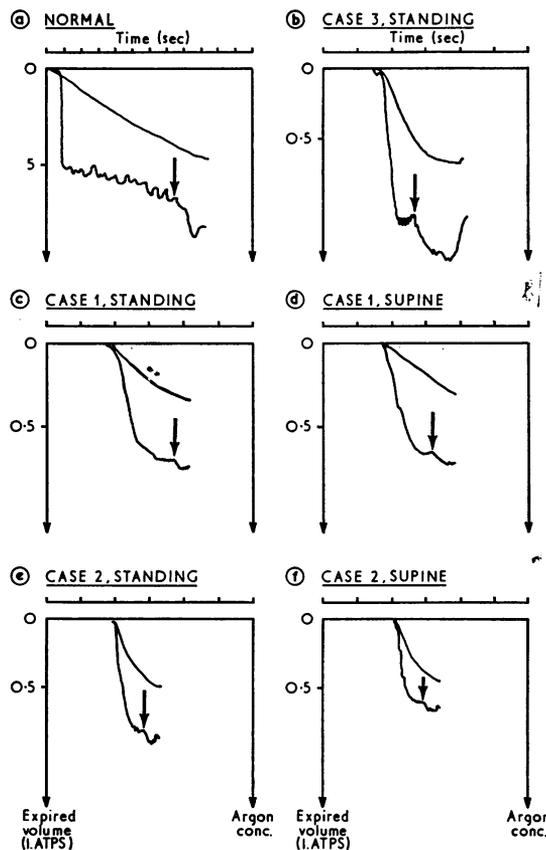


FIG. 2. Representative records of expired volume (upper trace) and argon concentration (lower trace) in three subjects with Morquio-Brailsford disease, standing and supine (b-f). No satisfactory record was obtained for case 3 supine. A normal record (a) is also shown for comparison. In each record expired argon and volume concentration are plotted on the ordinate against time (seconds) on the abscissa, but the individual scales differ. The onset of the terminal rise, which may represent the onset of airway closure, is marked by an arrow in each record.

All values for closing volumes are the mean of at least two satisfactory recordings. In our subjects satisfactory flow rates not exceeding 0.5 l/sec during the

TABLE

1 Personal Data		2 Spirometry		3 Lung Volumes by Helium Dilution		4 From CV Traces			5 FRC TLC		6		7 Ventilation		8 Chest Radiograph Measurements									
Case	Age (yr)	Sex	Height (m)	Weight (kg)	FEV <sub>1</sub>	FVC	TLC	RV	VC	VC ERV	V <sub>T</sub>	CV as a division of VC	CV as a division of TLC	Best ERV + RV (ml ATPS)	Best VC + RV (ml ATPS)	RV TLC %	CV TLC %	FRC TLC %	V <sub>E</sub> fr VT (l/min ATPS)	Lung Apex (R)	Height to AP Dome (L)	Max Diameter (L)		
1	15	M	1·03	29·5	350	400	850	400	450	410	40	230	35	435	440	850	47	51	52	18	4·1	12	12·5	17·5
							850	400	450	320	30	260	100	500	430	850	47	59	51	20	5·2			
2	22	F	0·97	22·7	300	400	690	290	400	470	60	280	75	365	350	760	38	49	46	17	4·8	9	9·5	15
							570	190	380	440	20	280	55	245	210	630	30	39	33	20	5·6			
3	24	F	1·04	25·4	730	850	990	340	650	760	50	220	155	495	390	1100	31	45	35	17	3·7	11·5	13	17
							1030	410	620	620	100	320												

For explanation see text

manoeuvre represented much shorter times than normal because of the small vital capacities involved.

**RADIOGRAPHS** Standing chest radiographs were taken from 6 feet in the posteroanterior and lateral projections. The vertical height from the lower border of the neck of the first rib to the dome of the diaphragm for each lung, and the maximum anteroposterior diameter of the lungs, were measured. The configuration of all radiographs was similar to that of Figure 1.

## RESULTS

Age, height, weight, and the results of measurements of forced expiratory spirometry, lung volumes, closing volumes, ventilation, and chest radiographs are presented in the Table.

The expiratory reserve volume (ERV) and VC used to determine the functional residual capacity (FRC) and TLC in section 5 of the Table were the greatest values recorded on either the lung volume or the closing volume tracings, and these values of FRC and TLC were used to calculate the percentages in section 6. This was done so that any error would minimize the abnormalities demonstrated. Frequency of respiration ( $f_r$ ), tidal volume ( $V_T$ ), and minute volume ( $\dot{V}_E$ ) were determined from the spirometric tracings.

All three subjects were deformed and we have not attempted to compare the lung volumes with predicted values for either age or height. All lung volumes are small. The  $FEV_1/FVC$  ratios do not suggest intrathoracic airways obstruction.

The lung volumes and closing volumes and their relative relationships, standing and supine, are presented diagrammatically (Fig. 3). All the values are

small. Minute ventilation increased in all three subjects on changing from the standing to the supine position, by increase in tidal volume in case 3, by increase in frequency of respiration in case 2, and by increase in both frequency and tidal volume in case 1. Expiratory reserve volume decreased on changing from the standing to the supine position in cases 1 and 2. Closing volume is greater than FRC in cases 2 and 3 standing and in cases 1 and 2 supine. One expired argon and volume record is shown for each subject in each position (Fig. 2b-f) but no satisfactory records were obtained in case 3 in the supine position.

The anteroposterior diameter of the lungs was greater than the height of the lungs in all three subjects.

## DISCUSSION

Our patient (case 1) died in respiratory failure. He and his two siblings showed abnormalities of pulmonary function. All had small lung volumes and severe thoracic deformity. None of them showed evidence of airways obstruction. In the presenting patient (case 1) in the standing position, the expired argon concentration following the inhalation of an argon bolus at residual volume showed an uneven alveolar plateau (Fig. 2c), suggesting abnormal distribution of ventilation. Despite the small vital capacity and thoracic deformity the expired argon pattern was normal in this patient in the lying position and in his two siblings (cases 2 and 3) (Fig. 2b, d-f). Because of the small vital capacity the alveolar plateau is short and the terminal rise in argon concentration is not as high relative to the alveolar plateau as in normals (Fig. 2).

Dollfuss *et al.* (1967) demonstrated that in normal subjects a bolus of xenon-133 ( $^{133}\text{Xe}$ ) injected at residual volume is preferentially distributed to the lung apices, and that therefore the onset of the terminal rise of expired  $^{133}\text{Xe}$  concentration marked the point where the bases began to contribute less to the expired gas. They attributed this to dependent airway closure, thought to be due to the gradient of pleural pressure. Using a bolus of argon, which is not radioactive and therefore cannot be detected within the chest, we have no definite evidence that the terminal rise in expired argon concentration indicates a falling contribution of dependent areas late in expiration, but it does indicate a lung region similarly contributing less to total ventilation close to residual volume. The explanation of this phenomenon is almost certainly the same whatever the tracer gas, and for this reason we also have called the volume

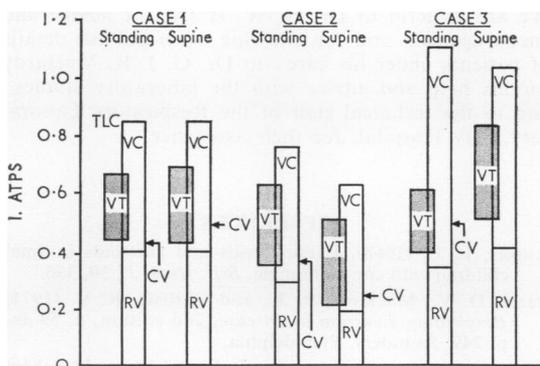


FIG. 3. Relationship of lung volumes and closing volumes, standing and lying, in the three subjects with Morquio-Brailsford disease: TLC=total lung capacity; VC=vital capacity; VT=tidal volume; FRC=functional residual capacity; RV=residual volume; CV=closing volume.

point at the onset of the terminal rise of expired argon concentration the closing volume. It is interesting to note that all three subjects had antero-posterior chest diameters greater than the lung height; this would be expected to increase the gradient of pleural pressure due to gravity in the supine position. In cases 1 and 2 the closing volume increased on lying down, which would be expected if the height of the lung were a significant factor.

In our three cases closing volume exceeds FRC in case 1 supine, in case 2 standing and supine, and in case 3 standing. When closing volume exceeds FRC, part of tidal breathing occurs in the range in which some of the airways are thought to be closed, leading to underventilation of perfused areas of lung and hence arterial hypoxaemia. This has been shown to occur in normal subjects with ageing—in the upright position at a mean age of 65, and in the supine position at a mean age of 44 (Leblanc, Ruff, and Milic-Emili, 1970). This is due to a fall in FRC in the supine position. Craig *et al.* (1971) have shown that when the closing volume falls within or above the range of tidal breathing arterial hypoxaemia may occur. The mechanism for this change of relationship between closing volume and FRC in the subjects with Morquio's disease is not clear, but it could be due to altered mechanics of the deformed thoracic cage or to changes of the airways secondary to recurrent infection. The relatively normal slope of the short alveolar plateaux, except in case 1 standing, suggests that in this part of the vital capacity the distribution of ventilation is relatively homogeneous.

A prominent feature in case 1 was central cyanosis, worse on lying supine, and especially during sleep. On lying down the increase of closing volume relative to FRC suggests one possible mechanism for the worsening of hypoxaemia in this position. All three subjects showed increased minute ventilation on lying down, and this might be due to increased dead space ventilation or to increased hypoxaemia in this position. Normally, minute ventilation falls slightly on changing from the standing to the supine position (McGregor, Adam, and Sekelj, 1961; Bates, Macklem, and Christie, 1971).

Clinical examination in case 1 had shown a severe degree of nasal obstruction, and depression of his large tongue caused choking. When fully awake he breathed through the mouth with the tongue protruding. He was fully awake on all occasions when  $Paco_2$  was estimated in the semi-recumbent or upright positions. The values obtained were all greater than 60 mmHg, indicating

alveolar hypoventilation. When asleep, partial obstruction of the nasopharynx by his large tongue may have contributed to his hypoxaemia. We were unable to measure the extent of this obstruction but it may have been an important factor. Upper airways obstruction due to enlarged tonsils and adenoids has been shown to cause hypoventilation in children, and these children often have worsening of hypoxaemia and even apnoeic attacks when recumbent or asleep (Ainger, 1968), features similar to those here reported. Ventilatory failure and cor pulmonale have also been reported in Crouzon's disease, in which there is deformity of the facial bones leading to upper airways narrowing (Don and Siggers, 1971).

Some of the abnormalities we have described in these respiratory function tests are similar to those in patients with advanced kyphoscoliosis (Bates *et al.*, 1971). The closing volume is increased in erect patients with kyphoscoliosis and may partially explain the hypoxaemia in this condition (Bjure *et al.*, 1970).

In Morquio-Brailsford disease death has often been attributed to respiratory failure. Much of the literature is concerned with the morphological and biochemical details and there is scant detail of pulmonary function. The evidence presented here suggests that alveolar hypoventilation, possibly contributed to by upper airways narrowing, underventilation of perfused lung regions, possibly in dependent areas, and a more generalized inhomogeneity of ventilation may be some of the important factors contributing to the development of respiratory failure in this disease.

We are grateful to Dr. N. W. Horne for advice and encouragement and for allowing us to publish details of patients under his care; to Dr. G. J. R. McHardy for his help and advice with the laboratory studies; and to the technical staff of the Respiratory Laboratory, City Hospital, for their assistance.

#### REFERENCES

- Ainger, L. E. (1968). Large tonsils and adenoids in small children with cor pulmonale. *Brit. Heart J.*, **30**, 356.
- Bates, D. V., Macklem, P. T., and Christie, R. V. (1971). *Respiratory Function in Disease*, 2nd edition, p. 59 and p. 249. Saunders, Philadelphia.
- Bjure, J., Grimby, G., Kasalicky, J., Lindh, M., and Nachanson, A. (1970). Respiratory impairment and airway closure in patients with untreated idiopathic scoliosis. *Thorax*, **25**, 451.
- Brailsford, J. F. (1929). Chondro-osteo-dystrophy. Roentgenographic and clinical features of a child with mallocation of vertebrae. *Amer. J. Surg.*, **7**, 404.

- Craig, D. B., Wahba, W. M., Don, H. F., Couture, J. G., and Becklake, M. R. (1971). "Closing volume" and its relationship to gas exchange in seated and supine positions. *J. appl. Physiol.*, **31**, 717.
- Dollfuss, R. E., Milic-Emili, J., and Bates, D. V. (1967). Regional ventilation of the lung, studied with boluses of <sup>133</sup>Xenon. *Resp. Physiol.*, **2**, 234.
- Don, N., and Siggers, D. C. (1971). Cor pulmonale in Crouzon's disease. *Arch. Dis. Childh.*, **46**, 394.
- Jones, J. G., and Clarke, S. W. (1969). The effect of expiratory flow rate on regional lung emptying. *Clin. Sci.*, **37**, 343.
- Leblanc, P., Ruff, F., and Milic-Emili, J. (1970). Effects of age and body position on "airway closure" in man. *J. appl. Physiol.*, **28**, 448.
- McGregor, M., Adam, W., and Sekelj, P. (1961). Influence of posture on cardiac output and minute ventilation during exercise. *Circulat. Res.*, **9**, 1089.
- McKusick, V. A., Kaplan, D., Wise, D., Hanley, W. B., Suddarth, S. B., Sevcik, M. E., and Maumanee, A. E. (1965). The genetic mucopolysaccharidoses. *Medicine (Baltimore)*, **44**, 445.
- Maroteaux, P., Lamy, M., and Foucher, M. (1963). La maladie de Morquio. Etude clinique, radiologique et biologique. *Presse méd.*, **71**, 2091.
- Morquio, L. (1929). Sur une forme de dystrophie osseuse familiale. *Arch. Méd. Enf.*, **32**, 129.
- Pedrini, V., Lenzi, L., and Zambotti, V. (1962). Isolation and identification of keratosulphate in urine of patients affected by Morquio-Ullrich disease. *Proc. Soc. exp. Biol. (N.Y.)*, **110**, 847.
- Robins, M. M., Stevens, H. F., and Linker, A. (1963). Morquio's disease: an abnormality of mucopolysaccharide metabolism. *J. Pediat.*, **62**, 881.