

# Pulmonary sequelae in survivors of congenital diaphragmatic hernia

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## Abstract

**Nineteen survivors of congenital diaphragmatic hernia repair were compared with age and sex matched control children six to 11 years after repair. All subjects were examined clinically and underwent lung function testing. The patients also had individual lung volumes assessed radiographically and had radionuclide (krypton-81m, technetium-99m macroaggregates) ventilation-perfusion ( $\dot{V}/Q$ ) lung scans. Four patients had pectus excavatum and two had mild scoliosis. Spirometric measurements were lower in the patients than in the control subjects but only the differences in peak expiratory flow and flow at 50% of expired vital capacity were significant. The radiographic left lung volumes in patients surviving left diaphragmatic repair were larger than expected at 49.3% (SD 2%), suggesting alveolar overdistension.  $\dot{V}/Q$  scans showed a mismatch in the ipsilateral lung, mean  $\dot{Q}$  (40% (7%)) being significantly lower than mean  $\dot{V}$  (47% (6%)). In seven patients who had required ventilation for four days or more perfusion to the ipsilateral lung was significantly lower (34% (6%)) than values for the 12 patients ventilated for less than four days (43% (6%)). Survivors of right diaphragmatic repair had a better outcome in terms of relative radiographic lung volumes and  $\dot{V}/Q$  distribution. More severely affected children are now surviving repair of congenital diaphragmatic herniation, with residual pulmonary abnormalities that could produce functional impairment in adult life.**

Congenital diaphragmatic hernia has an estimated incidence of 1:2500 live births.<sup>1</sup> At the Hospital for Sick Children mortality has increased from 15% in 1946-57<sup>2</sup> to 32% in the most recent series,<sup>3</sup> a change ascribed to referral of more severely ill children more recently. Previous follow up studies<sup>4-7</sup> have included patients born before the recent advances in medical and surgical management and the consequent increase in survival of more severely affected infants, and they may therefore contain few children who were severely affected. We therefore sought to identify the intermediate term respiratory sequelae in survivors from the more recent past, in whom more severe long term effects might be expected.

## Methods

We approached patients who had been operated on in this hospital during 1976-81. Sixty such patients, aged 6-11 years, were identified. A letter explaining the study and asking if they would take part was sent to their parents or guardians. Of the 60 families contacted, only 22 agreed to take part; 16 had moved house with no forwarding address, three refused to take part, and no reply was obtained from 19. Of those agreeing to take part, three were subsequently excluded because of neurodevelopmental delay (two) and because the child was unable to attend on the allotted day (one). The children who attended were compared with non-attenders for age at presentation, length of postoperative ventilation, and side of hernia (to determine whether they were typical of the whole group). There was little difference between those studied and those not studied for presentation before 24 hours of age (72% versus 77%), requirement for more than four days' ventilation (37% versus 36%), and percentage with a left sided hernia (84% versus 82%). The study was approved by the hospital ethical committee and written parental consent was obtained. The parents were asked to approach a friend of the patient, of the same sex and similar age and height, to act as a control for the physical examination and lung function tests. The median age of the patients was seven years and eight months (range six years one month-11 years one month) and of the controls seven years four months (range five years six months-11 years). The height of patients and control subjects did not differ significantly, mean (SD) values being 125.8 (11.4) cm and 128.5 (10.3) cm.

A brief questionnaire on previous and present respiratory symptoms was given to patients and control subjects and all underwent a physical examination by one of the authors (AF). Patients and control subjects produced forced maximum expiratory flow-volume (MEFV) curves with a heated Fleisch 3 pneumotachograph; volume was obtained by electronic integration of flow and displayed on a high performance X-Y recorder (Hewlett Packard 7045B).

Quantitative radiographic estimation of relative lung volumes were performed by a modification of the method described by Barnhard *et al.*<sup>8</sup> The degree of magnification of the images was calculated by attaching a 10 p coin to the chest in both the posteroanterior and the right lateral view and comparing actual with measured coin diameter. All calculations

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were performed on a programmable calculator (Hewlett Packard 97S).

Lung scans were obtained with gamma ray emitting radionuclides, krypton-81m for ventilation and technetium-99m macroaggregates for perfusion.<sup>9</sup> Posterior views were recorded using a Scintronix LFOV gamma camera and a total of  $200 \times 10^3$  counts were recorded for each image. Absolute counts from each lung were calculated with programs resident on an Informatec Simis III computer; the percentage of total  $\dot{V}$  and  $\dot{Q}$  going to each lung was derived from these relative activities. Patients were divided into those who had required post-operative ventilatory support for less than four days and for four days or more as a measure of severity of the initial hernia.

Relative radiographic lung volumes and  $\dot{V}/\dot{Q}$  distribution were compared with relative wet lung weights,<sup>10</sup> and fractional  $\dot{V}/\dot{Q}$  scan data from unpublished data from this hospital obtained from children with normal chest radiographs (H Davies, personal communication).

Power calculations suggested that 30 patients and control subjects would be required to show a significant difference in lung function at the 5% level at a power of 80%.<sup>11</sup> Wilcoxon rank sum tests were used to compare lung function data and Student's paired and unpaired *t* tests as appropriate to analyse the radionuclide lung scans.

## Results

The patients had an increased prevalence of chest symptoms, 10 of the 19 children complaining of episodes of cough occurring more often than six monthly. Six of the patients had subjective exercise intolerance, four had pectus excavatum, two had expiratory wheeze on auscultation, and two had mild thoracic scoliosis on the chest radiograph (both concave to the side of the hernia repair and with Cobb angles of less than 10 degrees and no underlying bony abnormalities). None of the control children had any of these abnormalities. One patient was found to have a recurrence of herniation, which was not suspected clinically; this was subsequently repaired.

Of the 19 pairs of patient and control children 15 were able to complete reproducible ( $\pm 10\%$ ) MEFV curves. The median values for all measurements were lower in the patients than in the control subjects (fig 1), though the differences were significant only for forced expiratory flow at 50% of vital capacity ( $FEF_{50}$ ) (patients 1.6 (range 0.5–2.65) l/s, controls 2.25 (range 1.55–3.15) l/s;  $p < 0.01$ ) and peak expiratory flow (PEF) (patients 220 (range 130–300) l/min, controls 265 (range 210–340) l/min;  $p < 0.01$ ).

Radiographic lung volumes were measured in 17 patients. In the three who had presented with a right sided hernia the percentage volumes of the ipsilateral lung (52%, 53%, and 53%) were close to those expected from data on wet lung weight (mean (SD) 54.4% (1.8%)).<sup>10</sup> For the 14 patients with a left sided hernia ipsilateral volumes were greater than expected

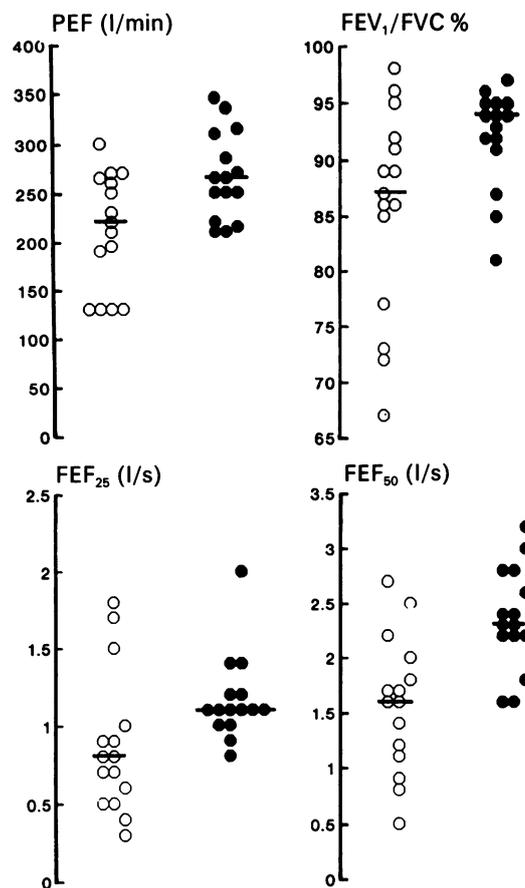


Figure 1 Forced expiratory flows, taken from maximum expiratory flow-volume (MEFV) curves, with median values for 15 pairs of patients and control subjects. Closed circles: controls; open circles: patients.

(mean 49.3% (95% confidence interval 45.3–53.3%); the mean wet weight of the left lung is 45.6% (95% CI 43.7–47.5%).<sup>10</sup>

Perfusion to the ipsilateral lung (40%, CI 26–54%) was lower than ventilation (47%, CI 35–59%);  $p < 0.001$ : fig 2). In survivors of left sided hernia repair mean perfusion to the ipsilateral lung was lower than our normal values from children with no pulmonary disease or abnormality (39%, CI 25–53%, versus 46%, CI 42–50%;  $p < 0.01$ ), whereas no

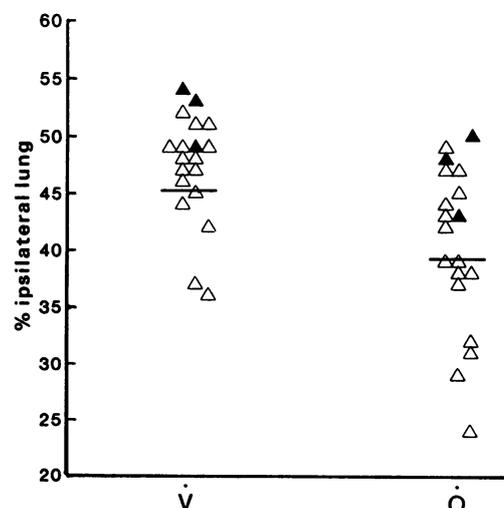
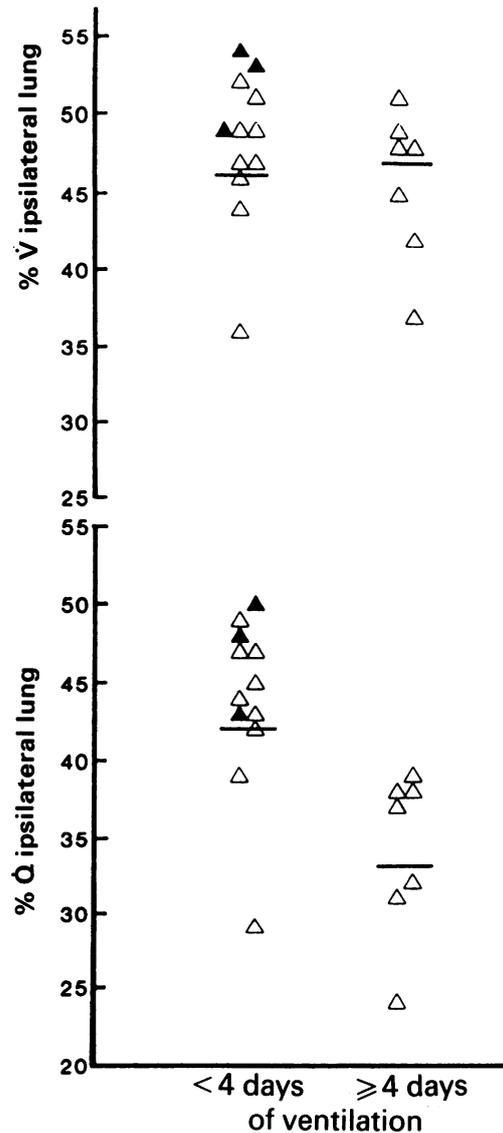


Figure 2 Percentage ventilation ( $\dot{V}$ ) and perfusion ( $\dot{Q}$ ) to the ipsilateral lung on radionuclide scans for 19 patients with means. Closed triangles: right congenital diaphragmatic hernia; open triangles: left hernia.

Figure 3 Percentage ventilation ( $\dot{V}$ ) and perfusion ( $\dot{Q}$ ) to the ipsilateral lung on radionuclide scans in patients ventilated for less than four days and for four days or more. Closed triangles: right congenital diaphragmatic hernia; open triangles: left hernia.



significant difference was found for ventilation (patients 46%, CI 36–56%; normal value 46%, CI 42–50%). Patients who had had a left sided hernia and who had been ventilated for more than four days had less perfusion to the ipsilateral lung (mean 34%, CI 22–46%) than those ventilated for a shorter period (mean 43%, CI 31–35%;  $p < 0.01$ ; fig 3). There was no significant difference in ventilation to the ipsilateral lung between those having short and those having long duration ventilatory support (mean 47%, CI 37–57%, versus 46%, CI 36–56%).

### Discussion

The small number of patients we were able to contact was not unexpected, as these children are not followed up routinely for a long period. The patients studied were, however, representative of the whole group with regard to side of hernia, age at presentation, and length of postoperative ventilation, all of which reflect the severity of diaphragmatic herniation.

The finding of  $\dot{V}/\dot{Q}$  abnormalities on radionuclide scans in patients with a greater reduction in perfusion is in agreement with previous findings,<sup>6,7</sup> though our group contained children with more severe abnormalities

than either of the earlier reports. This is likely to be due to improved survival of more severely affected infants in recent years.<sup>3</sup> At birth the number of divisions and the size of the airways and the pulmonary arterial tree are reduced in the ipsilateral lung and to a lesser extent in the contralateral lung in babies with congenital diaphragmatic hernia.<sup>12</sup> After repair the ipsilateral lung expands to fill the available space in the hemithorax. Alveolar multiplication continues after repair but normal numbers are not achieved<sup>12</sup> and the alveoli thus reduced in number become distended to fill the hemithorax. These alveoli have sometimes been described as “emphysematous.”<sup>4,5,12</sup> The pulmonary arterial supply to the ipsilateral lung is also reduced, though multiplication of its branches takes place to maintain a numerically appropriate relation between pulmonary arterioles and alveoli.<sup>12</sup> Thus the vascular supply per unit surface area of alveolus would be expected to be reduced. If, despite the alveolar distension, gas flow to and from the respiratory region of the lung is maintained, this would result in the  $\dot{V}/\dot{Q}$  mismatch we observed.

Within our group of patients some had near normal ventilation and perfusion, whereas others had very abnormal values (fig 2). The patients with near normal values had required little ventilatory support (less than four days); patients ventilated for four days or more had poorer perfusion. The fact that perfusion was disturbed to a greater extent than ventilation in this group implies that the abnormalities were related to the prenatal insult rather than to barotrauma from prolonged ventilation. Studies of lung morphology suggest that prolonged ventilation might retard alveolar development.<sup>13</sup> None of the three children with right sided hernia required ventilatory support for as much as four days and none had severe lung scan abnormalities. This is likely to be due to the protective action of the liver in shielding the right lung from the herniating bowel during intrauterine lung development.

Previous studies of lung function in children surviving congenital diaphragmatic hernia<sup>4,7</sup> have used reference values derived from other laboratories, and subtle errors may have been introduced from the use of different equipment and demographically different reference populations. For these reasons we compared our patients with age and sex matched control subjects studied on the same occasion with identical equipment maintained by the same operator. Four of our patients had evidence of airways obstruction (fig 1), though some also had normal or near normal function. There are several possible reasons for the finding of airways obstruction in survivors of surgical repair. Reduced lung tissue and consequent alveolar distension may result in early airway closure, as found in the aging emphysematous lung.<sup>14</sup> Alternatively, airway calibre might be reduced, particularly if the herniation occurred before complete development of the conducting airways—that is, before the 16th week of gestation.<sup>15</sup>

Radiographic measurement of lung volumes

showed that when the right lung had been affected lung volume was normal in relation to the volume of the left lung, which is consistent with the lesser severity of right sided hernias. In patients who had had left sided herniation the ipsilateral lung tended to be overdistended, suggesting alveolar overdistension. The mean ipsilateral percentage lung volume on chest radiographs was 49% in the children who had had left sided herniation, though the mean percentage ventilation on radionuclide scans was lower at 46%, a difference that could be accounted for by reduced ventilation in overdistended lung.

Patients at presentation with congenital diaphragmatic hernia have a wide range of clinical severity, from being asymptomatic to having respiratory insufficiency incompatible with life. This has been attributed both to the size of the diaphragmatic defect and to the speed of diagnosis.<sup>3</sup> Follow up studies of survivors need to take this heterogeneity into account, as failure to do so may introduce a bias. Consideration should also be given to the period during which the children were born. Children born since the mid 1960s will include those with more severely affected lungs, as more advanced resuscitative and supportive techniques are likely to have increased the number of more severely affected survivors.<sup>3</sup> Three of our patients had additional abnormalities, including scoliosis in two (albeit of a mild degree) and recurrence of herniation in one, which may otherwise have gone undetected. Some surveillance through early childhood to identify those at risk of developing pulmonary sequelae would seem to be appropriate, particularly for patients with severe herniation who required prolonged postoperative ventilatory support. In the longer term, alveolar overdistension after diaphragmatic repair<sup>4 5 12</sup>

could exaggerate the changes due to aging and smoking<sup>16</sup> and should be viewed as an additional risk factor in the development of chronic obstructive lung disease.

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