Respiratory failure and pulmonary hypertension associated with Klippel-Feil syndrome

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A 28-year-old woman with a deformed thorax and kyphoscoliosis associated with Klippel-Feil syndrome developed respiratory failure with pulmonary hypertension. Pulmonary ^{133}Xe ventilation and ^{99m}Tc-MAA perfusion scintigraphies showed maldistributions of lung ventilation and perfusion, and noticeably delayed ^{133}Xe washout from the lungs. Dynamic breathing MR imaging showed poor and/or asynchronous respiratory movements of the chest wall and diaphragm. These findings indicate that the perfusion-ventilation imbalance, the decreased ventilatory turnover, and expiratory flow from the alveolar space partly derived from the impaired respiratory mechanics may be responsible for the respiratory complications in this patient.

Key words: radionuclide study, Klippel-Feil syndrome, chest deformity, scoliosis, respiratory mechanics, ventilation

INTRODUCTION

This paper describes the findings of pulmonary ventilation and perfusion scintigraphies and dynamic magnetic resonance (MR) imaging in a patient with severe thoracic deformity associated with Klippel-Feil syndrome, who developed respiratory failure and pulmonary hypertension (PH),[1,2] and discusses the possible mechanisms of the respiratory compromises and the associations between the impaired lung function and respiratory mechanics.

CASE REPORT

A 28-year-old woman (height: 140 cm, body weight: 42 kg), who had been diagnosed with Klippel-Feil syndrome in early childhood based on the typical triad of low hairline, short neck and webbing of the neck, was hospitalized with progressive dyspnea and moderate cyanosis after common cold-like symptoms for several days. She also had severe chest deformities associated with kypho-

scoliosis and agenesis of the left kidney. She had never smoked and there was no history of any chronic pleuropulmonary disease, but she had complained of slight dyspnea on exertion from her childhood. Her respiratory rate was 40–46/min, pulse rate 90–96/min, and ausculation of the chest was normal. The arterial gas analysis showed severe hypoxemia (PaO$_2$ ranging from 40 mmHg to 68 mmHg) with hypercapnia (PaCO$_2$ ranging from 66.2 mmHg to 80.0 mmHg) in room air. She required assisted mechanical ventilation support with oxygen. Her leukocyte count was increased to 12,300/mm^3 but without a shift to the left, with a slightly increased in CRP of 0.44 mg/dl (normal < 0.25 mg/dl). Chest radiograph showed a small, deformed thorax with a backward protuberance and abnormal spacing of the ribs and rib fusion, and kyphoscoliosis with convexity to the left (Fig. 1). There was no pneumonic opacity in the lungs, and the heart was relatively large with a cardiothoracic ratio of approximately 64% in the small thorax. Radiography of the spine showed a fusion of the C$_3$–C$_5$ cervical spine, along with marked shortening and kyphoscoliosis of the thoracolumbar area due to multiple fused vertebrae and deformed costovertebral joints. Electrocardiogram showed P pulmonale and right axis deviation. Echocardiography showed right ventricular dilatation with hypertrophy and severe PH with an estimated systolic pressure of 120 mmHg, but
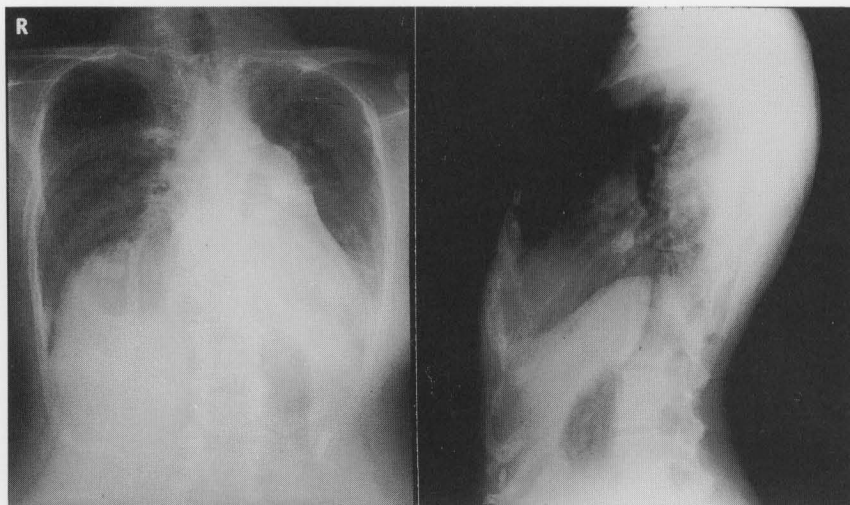
Fig. 1-A Posterior-anterior and left lateral views of chest radiograph on admission, showing the small, deformed thorax with a backward protuberance and abnormal spacing of the ribs and rib fusion.
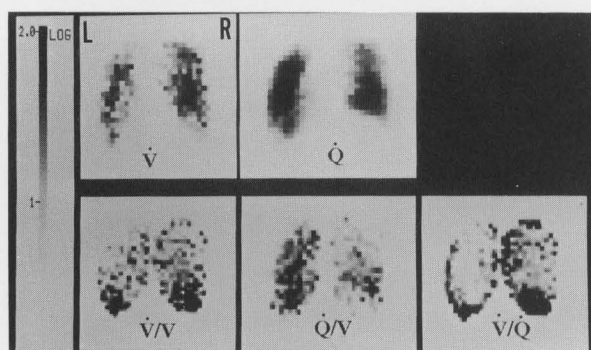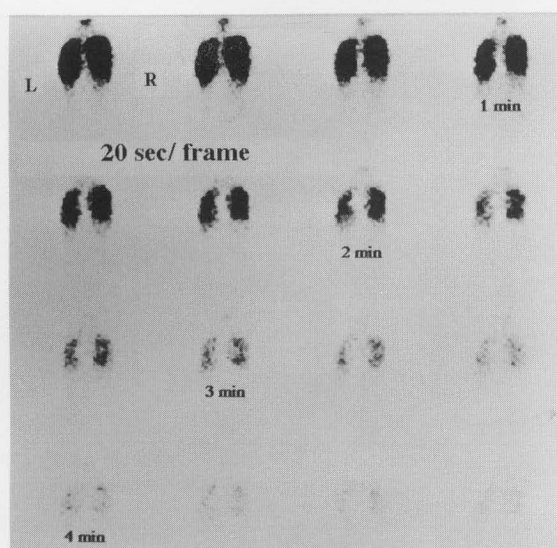

Fig. 1-B ^{133}Xe washout images (bottom; left) and functional map imaging of lung ventilation and perfusion (bottom; right) on a pixel-by-pixel basis in 64×64 matrix image (V: ventilation distribution after a single inhalation of ^{133}Xe, V; volume distribution, Q, perfusion distribution, V/V, Q/V, and V/Q, the ratios by point-by-point division of normalized image of V, V and Q, respectively). The ^{133}Xe washout images show heterogeneously delayed ^{133}Xe washout. The functional map images show maldistributions of ventilation and perfusion with focal mismatches.

there was no associated congenital cardiac anomaly or intracardiac shunting. Catheterization on the second day of hospitalization revealed severe PH with systolic pressure ranging from 93 to 111 mmHg; which was improved to 67 mmHg on average by test administration of prostaglandin E1 and calcium antagonists. At this time, PaO_2 ranged from 86 to 91 mmHg with nasal inhalation of oxygen (1.5 l/min) and was not significantly changed after administration of these drugs. Spirometry was not measurable due to severe dyspnea (NYHA IV), but previous spirometric data obtained 5 years before had shown typical restrictive respiratory dysfunction with mean values for vital capacity (%VC) of 26.3% and predicted forced expiratory volume in 1 second (%FEV$_1$) of 100%.

Under the suspicion of upper respiratory tract infection, she was medicated with antibiotics for five days, which quickly improved the increased leukocyte count and CRP value. To reduce pulmonary arterial pressure, she was also orally given prostaglandin E1 and calcium antagonist. On the tenth day of hospitalization, the mechanical ventilator was replaced with nasal inhalation of oxygen, since her dyspnea had improved to NYHA II, and PaO_2 and $PaCO_2$ to 97 mmHg and 54.2 mmHg, respectively, with nasal inhalation of oxygen (1.5 l/min). A spirometric test at this time showed %VC of 27.2% and %FEV$_1$ of 65%. Chest CT scan, obtained on the thirteenth day of hospitalization, showed increased vascular markings throughout the lungs and a slight increase in lung attenuation probably due to compression in both dorsal lung areas at the level of the heart, but the scan did not show pneumonic infiltrate or pulmonary developmental anomalies. Radionuclide ventilation and perfusion scintigraphies were then requested to rule out pulmonary thromboembolism as the cause of her severe PH. After the inhalation of 370 MBq of ^{133}Xe gas in the sitting position, ventilation images of the first-breath (wash-in), equilibrium, and washout phases were obtained from a posterior view, and subsequently perfusion imaging was obtained
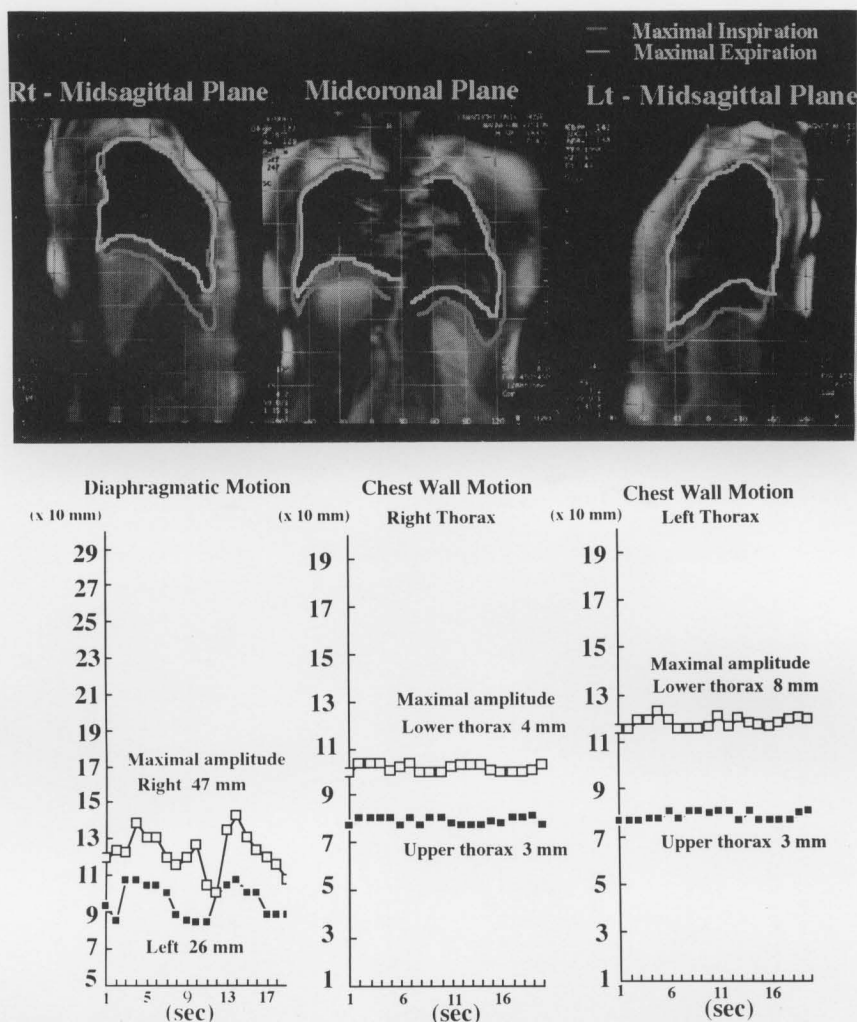
Fig. 2-A Fusion MR displays (top) at the same mid-coronal and mid-sagittal planes, coregistered with two different image sets of the maximal inspiration and expiration MR images (the interface between the lung and the diaphragm and chest wall are manually traced) and time-distance curves (bottom) representing respiratory changes of vertical length from the top of the lung to the right and left hemidiaphragms on the mid-coronal plane and those of the transvertical antero-posterior dimension of the chest 10 cm below the lung apex and 5 cm above the diaphragm on the mid-sagittal planes (the maximal amplitude of diaphragmatic and chest wall motions during respiration are measured). The poor and/or asynchronous motions of the diaphragm and chest wall are noted compared to those in a normal subject (Fig. 2-B).

after intravenous injection of 185 MBq of technetium-99m-macroaggregated albumin (^{99m}Tc-MAA) at the same position. During these scans, this patient showed rapid and shallow breathing with a mean respiratory rate of 43/min. Thereafter, standard multiple views of the perfusion image were obtained. ^{133}Xe ventilation scan showed mild heterogeneity in the first-breath (wash-in) phase and heterogeneously delayed ^{133}Xe washout from the lungs (Fig. 1). The mean transit time (MTT) in the upper, middle and lower lung fields, acquired by the height-over-area method, ranged from 126.5 sec to 163.1 sec (5 normal subjects aged 25–29 years old similar in age to this patient had an MTT of 47.3 sec ± 5.2 in our institute). The perfusion scan

also showed moderately non-uniform distribution of the radiotracer in the lungs. The functional map of ventilation and perfusion showed maldistribution of ventilation and perfusion with focal mismatches (Fig. 1). Dynamic breathing magnetic resonance imaging (MRI) was performed in the same mid-coronal and midsagittal planes by means of a HASTE (half-Fourier single-shot turbo SE) technique to evaluate respiratory motions of the chest wall and diaphragm (CW/D) during two or three deep respiratory cycles. A fusion MR image, coregistered with two different image sets of the maximal inspiration and expiration MR images, showed poor and/or asynchronous respiratory motions of the CW/D (Fig. 2). The maximal ampli-
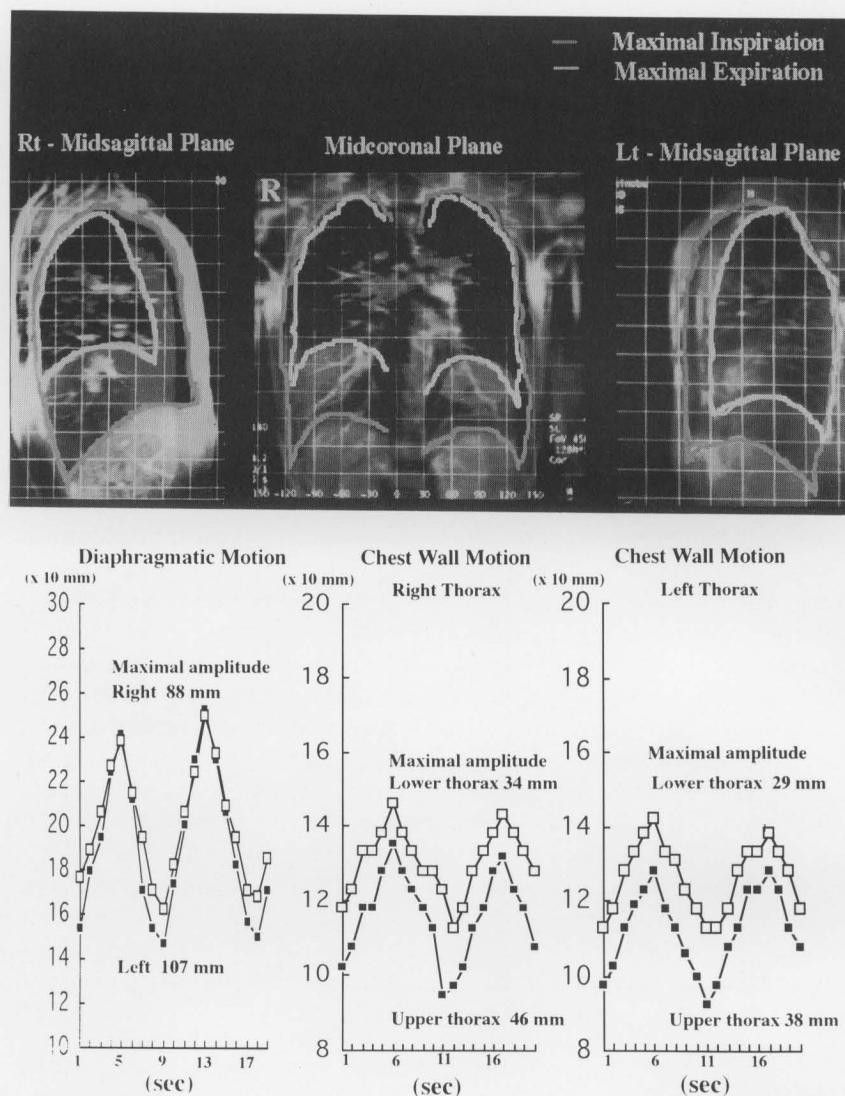
Fig. 2-B Fusion MR displays (top) and time-distance curves in a healthy subject, showing regular, synchronous motions with a good mobility of the diaphragm and chest wall.

tude of the CW/D motions was noticeably reduced compared to normal subjects. After an approximately one-month hospitalization with treatment by oxygen inhalation and administration of the drugs to reduce pulmonary arterial pressure, the patient gradually recovered to walk unassisted without oxygen inhalation as previously.

DISCUSSION

Patients with thoracic deformity typically exhibit a restrictive type of respiratory dysfunction, as seen in our patient before developing respiratory failure. Restrictive dysfunction in these patients can be explained by reductions in lung compliance and alveolar size and number in the compressed lungs due to the reduced thoracic space,[1,3] but on this admission our patient also showed signs of an obstructive type of respiratory dysfunction, as indicated

by the reduced %FEV_1 and delayed ^{133}Xe washout. The obstructive dysfunction and maldistributions of ventilation and perfusion in the lungs seem responsible for the respiratory failure in our patient.

Klippel-Feil syndrome, well known for the triad of short neck, low dorsal hair line, and restricted neck mobility, is also frequently associated with congenital kyphoscoliosis and thoracic deformity, with a wide variety of other associated anomalies in the urogenital, neurological, cardiovascular, and musculoskeletal systems.[1,2] Respiratory failure, pulmonary hypertension and cor pulmonale have been reported to be associated with other thoracic deformities such as pectus excavatum, severe kyphoscoliosis, neuromuscular disorders, rheumatoid spondylitis, Hurler syndrome and obesity,[1] although review of the literature has revealed only two case reports of respiratory failure in patients with Klippel-Feil syndrome

complicated by focal pneumonia or pulmonary hypoplasia.[1,4] The association of PH has not previously been reported in this syndrome. This patient is therefore the first to develop respiratory failure and PH without coexistent pneumonia and developmental anomalies in the lungs. This is also, to our knowledge, the first description of the findings of ventilation and perfusion scintigraphies in a patient with respiratory disability associated with this syndrome.

In patients with severe chest deformity, abnormal thoracic geometry reduces the strength of the respiratory muscles (RMs) and disrupts efficient respiratory motion of the chest wall and diaphragm (CW/D).[3–5] Thoracic stiffness with other mechanical abnormalities such as abnormal spacing/configurations of the ribs and the deformed costovertebral joints extrinsically disturbs pulmonary ventilation, since thoracic pump function operated by well-cordinated CW/D motions is indispensable for generating efficient respiratory intrathoracic pressure.[5] Alveolar ventilatory turnover and expiratory flow should be interrupted by reduced alveolar inflation capacity due to abnormal thoracic pump function.[6,7] Increased central airway resistance can be induced by thoracic deformity, as a recent bronchoscopic study showed evidence of torsion or secondary obstruction of the central airways during breathing due to a distortion and rotation of lung parenchyma or bronchial compression by vertebral bodies in patients with severe kyphoscoliosis.[8] In our patient, bronchospasms due to the precipitating upper respiratory tract infection may further increase airway resistance. A rapid and shallow breathing pattern, which is often seen in kyphoscoliotic patients, can reduce the work of RMs,[3] but it also interrupts efficient ventilatory turnover in the lungs.[1] Focal emphysematous overdistention or small airway obstruction due to changes in lung growth also may occur in the congenitally deformed thorax.[1] The noticeably delayed ^{133}Xe washout in our patient may be explained by these multifactorial mechanisms associated with severe chest deformity. An obstructive type of respiratory dysfunction certainly develops in association with chest deformity; several studies in a large numbers of kyphoscoliotic patients documented decrease in %$FEV_{1.0}$ as well as in %VC even in patients with no apparent obstructive lung disease.[3]

As seen in our patient, the finding of maldistributions of ventilation and perfusion with mismatches has been demonstrated in patients with severe chest deformity.[8] Nonuniform distribution of ventilation may be partly related to compression and/or reduced lung inflation due to abnormal respiratory CW/D motions.[8] The compressed lung tissue secondary to thoracic deformity and immobility may heterogeneously increase vascular resistances.[8] Chronic hypoxemia due to hypoventilation leads to hypertrophy of the pulmonary arterial muscle and to pulmonary hypertension (PH), which also cause heterogeneous distribution of pulmonary perfusion.[3] Regional changes in lung growth due to the deformed thorax also cause ventilation-perfusion imbalance; autopsy of the lungs in kyphoscoliosis has demonstrated non-uniform distributions of alveolar volume with areas of compression and areas of decreased vascularity.[4] The relatively large heart in the reduced thoracic space further degrades ventilation-perfusion imbalance.

PH in our patient may be explained by reactive pulmonary arterial vasoconstriction resulting from hypoventialtion and restriction of the pulmonary vascular bed due to thoracic deformity.[5] Severe hypoxemia enhanced by bronchospasms due to the precipitating respiratory tract infection should further enhance reactive vasoconstriction and exaggerate PH in this patient. Reduction of PH by the vasodilator agents was effective in alleviating respiratory difficulty in our patient. The vasodilator agents may partly improve the maldistribution of lung perfusion by improving the enhanced reactive vasoconstriction.

Respiratory infection can trigger respiratory failure in patients with thoracic deformity, as seen in this patient.[1] Acute respiratory infection with reactive bronchospasm should further degrade preexisting lung dysfunction and thoracic mechanical impairments by increasing airway resistance and/or reducing regional blood flow and by increasing the mechanical load of RMs.[1,3] There is evidence that patients with mild scoliosis and minimal impairment of resting pulmonary function easily exhibit abnormal ventilatory responses even to mild hypoxemia or hypercapnia.[3] After improvement of respiratory infection, mechanical ventilation and oxygen inhalation facilitated alleviation of respiratory difficulty in our patient. These treatments may help reduce mechanical loads and fatigue of the RMs.

Ventilation/perfusion scintigraphies and dynamic MRI are helpful for noninvasively assessing abnormal lung function and respiratory mechanics in patients with thoracic deformity. Asymmetric volumes and expiratory flow of the lung in these patients may cause underestimation of lung function when assessed with spirometry. The MR technique has the advantages of no irradiation and accurate quantification of D/CW motion by using digital data. Because Klippel-Feil syndrome can be a progressive disease which may lead to severe cardiopulmonary impairment, serial assessments of lung function and thoracic mechanics by these methods may be highly useful.

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