Review Article

Pulmonary involvements caused by changes in peripheral perfusion in collagen–vascular diseases

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ABSTRACT

Collagen–vascular diseases (CVD) involve many organs. Among organ involvements, pulmonary disorders may determine the prognosis of CVD. Because the vasculature and blood perfusion are commonly altered in CVD, we have attempted to analyze pulmonary disorders from the viewpoint of pulmonary vessels and perfusion. Based on routine pulmonary function tests, many patients were observed to have a decreased diffusion capacity (DLco) isolated from or comparative to lung volumes. In these patients, matched ventilation/perfusion scintigraphy revealed a decrease in pulmonary peripheral perfusion. These findings may be an early sign of pulmonary hypertension, which develops as a result of several pathophysiological causes in CVD. When a remedy for each pathogenesis of pulmonary hypertension was applied, more than half the patients recovered, at least initially; therefore, early diagnosis, including the methods described above, and treatment are important. With regard to pneumonitis in amyopathic dermatomyositis, which has been considered to develop acutely, we observed its progression to be subacute in its early stage. Along with this disease, pneumomediastinum characteristically develops simultaneously with vasculopathy. Disease-modifying antirheumatic drugs, which must be perfused into the blood stream, sometimes induce lymphocyte alveolitis or pneumonitis in good responders, with a decrease in the peripheral blood lymphocyte count and immunoglobulin levels. Examinations, differential diagnoses, therapies and studies from the viewpoint of the blood circulation and vessels may be important and useful for clinical studies and for the further investigation of pulmonary involvement in CVD.

Key words: collagen–vascular diseases, diffusion capacity (DLco), drug-induced, perfusion, pulmonary hypertension, pulmonary involvement, vasculopathy.

INTRODUCTION

Collagen–vascular diseases (CVD) are chronic inflammatory illnesses associated with immune system disorders, involving many organs. Of these organs, the lung is important and its involvement may diminish the quality of life or the activities of daily living, as well as indicating a poor prognosis (Table 1). Approximately half the 34 CVD patients who were admitted to our department in the past 5 years died of pulmonary diseases, including interstitial pneumonitis in three cases and pulmonary hypertension in two.

All parts of the lung may be involved, along the same line that all organs are potentially injured in CVD. However, until recently, pulmonary diseases were mostly studied in terms of their alveolar aspect, with analysis of bronchoalveolar lavage fluid as a representative of that point of view. In contrast, we have attempted to investigate lung involvement in CVD from the viewpoint of pulmonary vessels, because vascular changes are very common manifestations of CVD.

DECREASED DIFFUSION CAPACITY ISOLATED FROM OR COMPARATIVE TO LUNG VOLUMES

We treated a girl with systemic lupus erythematosus (SLE) complicated with severe Raynaud’s phenomenon, whose
routine pulmonary function tests (PFT) revealed a decreased diffusion capacity (DLco), as low as one-half of the predicted value, despite normal lung volumes (Fig. 1). Repeated PFT revealed the same results in subsequent years, but there was no abnormality on chest X-ray and no rales could be heard on auscultation. Since then, a substantial number of patients, including those with Raynaud’s phenomenon, have been found to show a decreased DLco despite almost normal lung volumes.

If ventilation from the mouth to the alveoli is normal, alveolar wall thickening unlikely and peripheral blood hemoglobin levels normal, then the isolated decrease in DLco is probably due to decreased perfusion in the alveolar capillary bed around the alveoli.

We used matched ventilation/perfusion (V/Q) scintigraphy to reveal a decrease in perfusion relative to ventilation in a matched area (Fig. 2). When a pixel or a range of interest (ROI) in the scintigram showed decreased peripheral perfusion compared with ventilation, the (V/Q) ratio of a pixel or ROI increased (Fig. 3). The (V/Q) scintigram of the patient described above revealed a dense area in the pulmonary periphery with an increased (V/Q) ratio, which indicated decreased pulmonary peripheral perfusion. Using this methodology, many patients with an isolated decrease in DLco have been confirmed to have an area with a high (V/Q) ratio, mostly in the periphery. Most of these patients were also found to have vascular impairments in the extremities.

### The V/Q Ratio in Pulmonary Hypertension

A probable outcome of decreased pulmonary peripheral perfusion may be pulmonary hypertension. Our cases of CVD with pulmonary hypertension showed both an isolated decrease in DLco, or decreased DLco comparative to lung volumes (Fig. 4), as well as a dense peripheral shadow on the (V/Q) scintigram (Fig. 5).

In CVD, several underlying disorders may be considered to cause disturbances in peripheral perfusion, including vasoconstriction, thickening of the endothelial intima, thrombi, vasculitides, hypergammaglobulinemia, veno-occlusion and parenchymal diseases. Among these, vasoconstriction, endothelial thickening and lung fibrosis are the three major underlying disorders, although more than one pathogenesis frequently overlap. Our patients with pulmonary hypertension were treated on a case-by-case basis by first determining how peripheral perfusion was disturbed in each patient. As a result, two-thirds of 24 patients improved at least initially and more than one-half survived for more than 3 years.

### Vascularopathy in Amyopathic Dermatomyositis

Interstitial pneumonitis complicated with amyopathic dermatomyositis (amyo-DM) is known to be acutely progressive and occasionally severe with a poor prognosis.

Recently, we have treated five patients with amyo-DM associated with pneumonitis. All had typical skin lesions and, in addition, persistent ulcerations in the skin or mucous membrane lesions were noted, suggesting an underlying vasculopathy. During the course of their therapy, pneumomediastinum developed in all five patients.
Fig. 2 Matched ventilation ($^{133}$Xe gas)/perfusion ($^{99m}$Tc-macroaggregated albumin) scintigraphy. Images are obtained sequentially in the same position and the ventilation/perfusion ($V/Q$) ratio for each pixel is calculated and drawn; a high density indicates a high ratio.

Fig. 3 Ventilation/perfusion ($V/Q$) image of a 39-year-old female patient with dermatomyositis with diffusion capacity of 48% and a vital capacity of 108% of predicted values.

Fig. 4 Ventilation/perfusion ($V/Q$) image of a 60-year-old female patient with systemic sclerosis and pulmonary hypertension. Scant perfusion was indicated in the lower fields of both lungs.
Bronchoscopy performed on a 30-year-old male patient revealed a necrotic lesion in the bronchial mucosa, which was confirmed by biopsy (Fig. 6). Pneumomediastinum in amyo-DM may be caused by bronchial mucosal ulceration that is related to the underlying vasculopathy. Among our patients with myopathic DM, only one patient developed pneumomediastinum, who had old tuberculosis. Cutaneous vasculopathy was significantly more frequent in five patients with pneumomediastinum than in 44 DM/polymyositis patients without it. Examination of previous reports of 13 patients with polymyositis or DM complicated by pneumomediastinum revealed that 10 of 13 patients had pneumonitis, and five had cutaneous vasculopathy.

When the pulmonary findings of our five patients were analyzed retrospectively, we found that the changes had already started a few months before, although hardly any symptoms had been noted subjectively. We may suppose that interstitial pneumonitis complicated by amyo-DM does not progress acutely, but subacutely.
Although one of the five patients, a 25-year-old man, had a poor prognosis, four survived and the pulmonary findings in these four patients, including radiographic findings, were gradually improved with steroid treatment, alone or in combination with cyclophosphamide.

**DISEASE-MODIFYING ANTIRHEUMATIC DRUG-INDUCED LUNG INJURY**

A number of pulmonary diseases having a vascular pathogenesis are probably drug induced. Today, disease-modifying antirheumatic drugs (DMARD) are among those drugs that potentially cause adverse reactions in the lung.

Principally, reversible drug-induced lung injuries are observable radiographically as diffuse bilateral infiltrations that usually appear acutely or subacutely and disappear following cessation of the drug. When we treated rheumatoid arthritis patients with bucillamine, an occasional lung injury developed exclusively after the drug had taken effect; the radiographic findings were mottled dense infiltrates around the bronchovascular bundles, distributed in the upper and middle lung fields and sparing the periphery, which contrasted with the radiographic findings in usual interstitial pneumonitis or fibrosis complicated by rheumatoid arthritis (Fig. 7). These radiographic findings are similar to those reported for gold-induced lung injury. On auscultation, no rale was audible. We found that our patients had decreased serum immunoglobulin levels at the onset of bucillamine-induced lung injury, that re-increased to the levels at rheumatoid arthritis remission. Until recently, two major types of drug-induced adverse reactions have been considered: (i) allergic hypersensitivity; and (ii) cell toxicity. Because bucillamine could be reintroduced successfully and because adverse events did not appear to be dose dependent in patients treated by bucillamine, neither hypersensitivity nor toxicity was likely.

Methotrexate-induced lung injuries that we treated in nine rheumatoid patients were much more severe; radiographic infiltrates were intensely diffused predominantly in the upper and middle lung fields, sparing the lung base. Respiratory distress was severe, in that \( P_aO_2 \) decreased to as low as below 30 mmHg and C-reactive protein increased up to 30 mg/dL with high fever. All patients responded to methotrexate treatment for arthritis. Immunoglobulin levels decreased at the onset of lung injury, then increased to levels measured at arthritis remission. The peripheral blood lymphocyte count, which had remained unchanged during arthritis remission, decreased at the onset of lung injury and returned to normal levels after its improvement. After our study, two new patients were diagnosed as having early stage methotrexate-induced lung injury with slight fever and cough. Computed tomography images revealed patchily distributed thin infiltrates and the lymphocyte count and immunoglobulin level decreased. Bronchovascular lavage fluid from four patients revealed many CD3-positive cells, the majority of which were also CD4 positive, as was noted in the earlier studies. A DMARD that circulates via the blood to the joints and lungs may remit arthritis in a responder, but may also induce lymphocytic alveolitis.

**REFERENCES**