Fatal Lung Scan in a Case of Pulmonary Hypertension due to Obliterative Pulmonary Vascular Disease*

John S. Child, M.D.; James D. Wolfe, M.D.; Donald Tashkin, M.D.; and Frank Nakano, M.D.

A young woman with pulmonary hypertension due to sclerodermatous pulmonary vascular disease died immediately following the injection of macroaggregated albumin labeled with $^{99}$Tc for a perfusion lung scan. Review of the literature suggests that patients with chronic pulmonary hypertension due to an obliterate pulmonary vascular disease are at risk of developing a serious reaction to perfusion lung scanning. Important factors which predispose to an adverse reaction to lung scanning are the size and dose of macroaggregated albumin particles in relation to the total cross-sectional area of the pulmonary vascular bed and a critical arteriolar lumen size.

Perfusion lung scanning with macroaggregated albumin (MAA) and a radionuclide is well accepted as an important diagnostic tool in detecting pulmonary emboli.\(^1\)\(^2\) As this procedure is considered extremely safe, little attention has been given to possible adverse effects. However, serious reactions to lung scanning have been reported in three patients with chronic pulmonary hypertension due to a diffuse obliterate pulmonary vascular disease.\(^3\)\(^4\)

We report a patient with pulmonary hypertension due to sclerodermatous pulmonary vascular disease who died immediately after perfusion lung scan.

**Case Report**

A 20-year-old Japanese girl was admitted to UCLA Medical Center with a one year history of Raynaud's phenomenon, migratory polyarthralgias, stiffness of her fingers, and a six month history of dysphagia and fingertip ulcerations. For the two months preceding her admission, she experienced progressive exertional dyspnea. Two days before entering the hospital, she developed pleuritic anterior chest pain associated with a nonproductive cough and increasing dyspnea at rest. On admission the pulse rate was 120 per minute, the blood pressure was 110/95 without pulsus paradoxicus, and the respiratory rate was 30 per minute. She was afebrile. There was jugular venous distention with no Kussmaul's sign. The lungs were clear. The cardiac examination revealed a prominent right ventricular heave, an increased pulmonic closure sound, a grade 4/6 left parasternal systolic murmur without inspiratory increase, a right-sided S\(_3\) and S\(_4\), and a pericardial rub. There was no hepatosplenomegaly. Scleroderma and partially healed fingertip ulcerations were present.

The hemogram was 47 percent, the white count was 10,500 cells per cu mm with a normal differential, and the sedimentation rate was 27 mm per hour. Urinalysis revealed a normal sediment and 3-plus proteinuria. Twenty-four hour urinary protein excretion was 3.7 grams. The serum creatinine was 0.9 mg percent. Antinuclear antibody was positive at 1:1 dilution. Total hemolytic complement was 42 (8 20-50 hemolytic units) and latex fixation was positive at 1:160. The gamma globulin was elevated (3.3 g percent). Marked right ventricular and main pulmonary arterial enlargement were noted on chest x-ray examination (Fig 1). The lung fields were clear and the peripheral pulmonary arteries were attenuated. An electrocardiogram revealed sinus tachycardia, right axis deviation, right atrial enlargement, and right ventricular hypertrophy. There were no ST-T abnormalities suggesting pericarditis. A small pericardial effusion was detected on the echocardiogram. The arterial blood gases on room air showed a pH of 7.52, a PaO\(_2\) of 22 mm Hg, and a PaCO\(_2\) of 54 mm Hg. Pulmonary function tests disclosed a mildly decreased vital capacity (233 ml, 71 percent predicted), but normal flow rates and a normal single breath diffusing capacity (22 ml/min/mm Hg, 96 percent predicted).

To exclude pulmonary thromboemboli as a cause, in part, for the patient's clinical presentation, a pulmonary perfusion scan was carried out. An abnormality was noted in the right middle lobe perfusion pattern. Review of the perfusion lung scan revealed a nonhomogeneous pattern of perfusion in the right middle lobe with preservation of perfusion in the right lower lobe. The patient died two days later with exacerbation of her dyspnea.

**Figure 1.** Chest x-ray (PA projection): Note the rounded upturned cardiac apex suggesting right ventricular enlargement (confirmed in lateral view). The main pulmonary artery segment is enlarged yet the peripheral pulmonary arteries are small ("pruned") consistent with a pattern of pulmonary arteriolar hypertension on a precapillary basis.

*From the Department of Medicine, University of California Medical Center, Los Angeles.

Manuscript received June 27; accepted August 5.

Reprint requests: Dr. Child, Department of Medicine, UCLA Hospital, Los Angeles 90024

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scan was performed on admission with 4.4 mg of MAA (average particle size 30-40 μ) labeled with 99mTc given by rapid intravenous injection. She was receiving supplementary nasal oxygen. The lung scan revealed multiple areas of decreased perfusion but was not diagnostic of pulmonary embolism. Anticoagulant therapy was withheld because of a pericardial friction rub. After treatment with digoxin and sodium restriction were instituted, the patient initially improved. However, four days after admission she developed an abrupt increase in dyspnea. Repeat lung scan was performed with 4.3 mg of MAA (average particle size 75 μ) labeled with 99mTc, while the patient was not receiving supplemental oxygen. She immediately developed labored respirations and cyanosis followed by apnea and ventricular arrhythmias. Resuscitation attempt, including tracheal intubation, mechanical ventilation with 100 percent O2, intra-cardiac epinephrine, numerous attempts at defibrilation and transvenous ventricular pacing, was unsuccessful.

At postmortem examination, the right ventricle was hypertrophied and dilated and the pulmonary trunk was enlarged. The left heart, coronary arteries, and cardiac valves were normal. No intracardiac septal defects were present and the foramen ovale was closed. A fibrinous pericarditis with a small serous pericardial effusion was seen. No microscopic evidence of pulmonary emboli was found. There was marked fibrous and fibromyxomatous intimal thickening of the arterioles and small muscular arteries throughout the lung (Fig 2). This resulted in generalized severe narrowing and obliteration of the pulmonary vascular bed. No significant interstitial pulmonary fibrosis was present.

**DISCUSSION**

The perfusion lung scan, an indicator of regional distribution of pulmonary arterial blood flow, is primarily used for diagnosis of suspected pulmonary emboli. It is generally assumed that the procedure is not associated with risk to the patient. However, there are three previous reports of fatalities following intravenous injection of radionuclide-labeled MAA for perfusion lung imaging (Table 1).

Dworkin, Smith, and Bull reported the case of a 35-year-old woman with adenocarcinoma of the breast who developed profound dyspnea, cyanosis, and acute cor pulmonale 1 to 2 minutes after the injection of 131I-labeled MAA for a perfusion lung scan. The patient returned to her prescan status within several hours but died the following day. Microscopic examination of the lung revealed extensive narrowing and occlusion of the pulmonary vasculature by tumor emboli.

Vincent, Goldberg, and Desilets reported the case of a seven-year-old child with a ventriculovenous shunt for hydrocephalus who presented with a brief history of pulmonary hypertension and progressive right heart failure. One minute following the injection of 99mTc-MAA for a perfusion lung scan, the child developed acute respiratory distress and died shortly thereafter. Microscopy of the pulmonary arterioles showed marked, generalized, eccentric cellular and fibrous intimal thickening and medial hypertrophy which were felt to be due to recurrent pulmonary emboli. Recurrent pulmonary emboli and pulmonary vascular disease have previously been reported in children with ventriculovenous shunts.

Recently, Williams reported the case of a 23-year-old woman with a collagen vascular disorder, probably sclerodermatous, who presented with the recent development of severe pulmonary hypertension. Within one minute following intravenous injection of 99mTc-MAA for lung scan, the patient developed cyanosis and respiratory distress. She continued to deteriorate and died six hours after injection. Microscopic examination of the lung revealed diffuse medial hypertrophy and concentric intimal thickening of the small muscular pulmonary arteries.

Our young patient, as in the case reported by Williams, presented with rapidly progressive sclerodermatous pulmonary vascular involvement.

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**Table 1—Fatalities Following Radio-nuclide-MAA Perfusion Lung Scanning**

<table>
<thead>
<tr>
<th>Case</th>
<th>Date</th>
<th>Report</th>
<th>Age yrs</th>
<th>Sex</th>
<th>mg/Kg</th>
<th>Underlying disease</th>
<th>Lung pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1966</td>
<td>Dworkin et al</td>
<td>F</td>
<td>35</td>
<td>11(0.22)</td>
<td>Adenocarcinoma breast</td>
<td>Tumor emboli</td>
</tr>
<tr>
<td>2</td>
<td>1968</td>
<td>Vincent et al</td>
<td>M</td>
<td>7</td>
<td>3.8(0.16)</td>
<td>Ventriculo-arterial shunt</td>
<td>Recurrent pulm emboli</td>
</tr>
<tr>
<td>3</td>
<td>1974</td>
<td>Williams</td>
<td>F</td>
<td>23</td>
<td>1.5</td>
<td>Collagen vascular disease</td>
<td>Diffuse pulm vascular thickening</td>
</tr>
<tr>
<td>4</td>
<td>1974</td>
<td>Present case</td>
<td>F</td>
<td>20</td>
<td>4.3(0.07)</td>
<td>Scleroderma</td>
<td>Diffuse pulm vascular thickening</td>
</tr>
</tbody>
</table>

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**Figure 2.** Small pulmonary arteriole. Note the extensive intimal thickening by loose myxomatous material with increased cellularity and strands of collagen (Verhoff and Van Gieson, x 500). This is representative of the histology uniformly found throughout the lung.

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with severe pulmonary hypertension and cor pulmonale. In both of these patients, roentgenographic examination of the chest revealed no evidence of pulmonary fibrosis. Although scleroderma is commonly thought to be a disease of lung parenchyma resulting in pulmonary fibrosis, pulmonary vascular involvement is often noted. Occasionally, severe pulmonary vascular lesions may be present without evidence of parenchymal involvement, and pulmonary function abnormalities may be minimal.

As in the three previously reported cases, our patient had severe pulmonary hypertension due to widespread narrowing and occlusion of the pulmonary vasculature. Clinical deterioration occurred in all of these patients immediately following injection of the radionuclide-tagged MAA. This close temporal relationship makes the possibility of incidental acute deterioration extremely unlikely. The reaction to the injection of MAA was similar in each case and included respiratory distress, cyanosis, and hypotension. A similar reaction is seen in animals given toxic doses of MAA.

Dog studies indicate that the toxic effect of MAA is an abrupt rise in pulmonary artery pressure due to mechanical obstruction to blood flow. As previously discussed, this untoward effect is dependent on the number and size of MAA particles in relation to the total available pulmonary vascular bed. In normal man, it has been estimated that the usual MAA dose of 0.1 mg to 4.0 mg with particle sizes of 10 to 50 μ results in occlusion of only approximately 0.1 percent of the cross-sectional area of the pulmonary vasculature. This degree of occlusion does not result in elevation of the pulmonary artery pressure. However, a significant fraction of the pulmonary vascular bed may become occluded by MAA if an underlying obliterative pulmonary vascular process has reduced the total cross-sectional area of the pulmonary vascular and has produced a generalized decrease in lumen size of the arterial tree.

The fact that our patient tolerated the first lung scan using MAA of normal particle size (30 to 40 μ) but developed a “toxic” reaction following injection of larger average size particles (75 μ) for the second scan, would support the concept of a critical particle size occluding this patient’s markedly narrowed pulmonary vascular bed. As a result of narrowing of the lumen of the small pulmonary blood vessels, MAA particles obstruct at a more proximal point, resulting in greater interruption of pulmonary blood flow. This may lead to potentially disastrous elevation in pulmonary vascular bed resistance, development of acute cor pulmonale, decrease in cardiac output, and shock.

We suggest, therefore, that perfusion lung scanning in patients with suspected diffuse obliterator pulmonary vascular hypertension be approached with caution. If lung scanning is definitely considered necessary, then the following precautionary measures are recommended: (1) slow intravenous injection of radionuclide-tagged MAA; (2) careful monitoring of particle size; and (3) utilization of a high specific activity of radionuclide in order to reduce the required total dose of MAA. The use of 99mTc human serum albumin microspheres (HAM) of high specific activity might be considered in place of macroaggregated albumin (MAA) because of its advantages of increased uniformity of particle size (15 to 30 μ), thereby increasing the margin of safety with respect to the percentage of pulmonary vessels blocked. In addition, supplemental oxygen during the scanning procedure might decrease the likelihood of an adverse reaction by relieving hypoxic pulmonary vasoconstriction.

ACKNOWLEDGMENT: The assistance of Dr. Norman Poe of the Department of Nuclear Medicine (University of California Medical Center) in the preparation of this manuscript, is gratefully acknowledged.

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