Scintigraphic diagnosis of a right to left shunt in end-stage lung disease

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Abstract

Purpose: The presence of a right to left shunt influences the surgical approach to lung transplantation in patients with end-stage pulmonary disease. The purposes of this study included comparing contemporaneous lung scintigraphy with cardiac catheterization in the detection of intracardiac shunts in patients with end-stage lung disease and the point prevalence of right to left shunting was determined in patients with several different types of end-stage lung disease.

Methods: Hundred and twenty-six patients with end-stage lung disease who were candidates for lung transplantation underwent perfusion images of the lungs with Tc-99m-labeled macro-aggregated albumin (MAA). Planar scans of the brain and the kidneys were performed contemporaneously. Statistical analyses included correlation of the clinical, laboratory and scintigraphic variables. Group means were compared with the students t-test (two-tailed P-value).

Results: There were 21 patients with primary pulmonary hypertension (PPH), 72 with emphysematous lung disease (COPD), 22 with pulmonary fibrotic disease (PF), and 11 with congenital heart disease (CHD) leading to pulmonary hypertension. Only 13 patients (10.3%) were found to have a right to left shunt. Of these, 4 had PPH, 2 had PF, and 7 had CHD. No shunts were found in patients with emphysema. All the positive studies had abnormally increased activity in both the brain and the kidneys. However, there were 25 cases with renal activity and none of these patients had brain activity or clinical evidence of a shunt. Increased pulmonary artery pressure was associated with scintigraphic presence of a shunt. There were no cases of a right to left shunt with a mean pulmonary artery pressure less than 50 mmHg. In the subset of patients with a pulmonary pressure greater than 50 mmHg, approximately 40% of the patients had a right to left shunt. There were no measurable differences in the spirometry results, right ventricular ejection fraction (RVEF) or left ventricular ejection fraction (LVEF) in the subgroup of patients with PPH and right to left shunt in comparison with patients with PPH but without a right to left shunt.

Conclusions: The findings indicate that images of the brain, but not the kidneys, are an effective way to diagnose extrapulmonary right to left shunts in patients with end-stage pulmonary disease. The problem of a right to left shunt is uncommon in patients with emphysematous lung disease and relatively common in patients with primary pulmonary hypertension.

Keywords: VQ scans; end-stage lung disease; lung transplant; vascular shunt.

INTRODUCTION

Chronic lung diseases are common with a high morbidity and mortality rate (1). Approximately 10 million people in the United States have some degree of chronic obstructive pulmonary disease (COPD) (1). Nearly half of these patients can be categorized as having end-stage lung disease (ESLD) with limitations on their daily activity imposed by shortness of breath. There are currently no cures for these diseases, only palliative treatment. Some symptoms improve with medical management, but never resolve, and most pharmacological therapies produce untoward symptoms which also compromise the quality of life. Lung transplantation may significantly prolong life and improve its quality in selected patients. This treatment has become more available as an option for selected patients (2). The immediate post-operative success rate has been improving, with a mean extension of life expectancy of at least 3 years (3). Lung transplantation has been successfully performed in patients with COPD, primary pulmonary hypertension (PPH), pulmonary fibrosis, and several congenital disorders. The operative approach is modified in patients with intracardiac defects which shunt blood from the right...
side of the heart to the left. The shunt is closed at the
time of transplantation, generally requiring an open car-
diac procedure. The most common cause of an extrapul-
monary shunt is the diastolic shunting of blood across a
patent foramen ovale. A potentially patent foramen
ovale is present in a significant minority of the general
population, although it is functionally closed. The fora-
men is patent when probed by an instrument in about
30% of all autopsy specimens. A functional shunt can be
demonstrated with provocative echocardiographic man-
euvers in about 25% of the healthy population (6–8). Pa-
tients who have elevated pulmonary pressures and right
ventricular diastolic dysfunction are at greater risk for
developing a clinically significant right to left shunt. The
incidence of shunting in candidates for lung transplantation
has not been fully characterized. A complete evalua-
tion of this problem may require meta-analyses of data
from many centers. Patients are usually screened for a
shunt by measuring their arterial blood gases while they
breath 100% oxygen (O2). The shunt fraction is approxi-
mated by the difference between the alveolar and arter-
ial O2 divided by 20. A value of less than 5% obviates the
need for further evaluation (9). When the calculated
shunt fraction is greater than 5%, the critical clinical
question is whether the shunt is intrapulmonary or ex-
trapulmonary in origin. Several diagnostic procedures
can detect the right to left shunting of blood in the heart
(9–15). These techniques include transesophageal eco-
chocardiography (TEE), transthoracic echocardiography
(TTE), radionuclide angiography (RNA), echo planar
magnetic resonance imaging (MRI), and macroaggre-
tated albumin scintigraphy (MAA) of the brain after
a V/Q scan. Most of these procedures have been validated
by using cardiac catheterization as the reference
standard.

The study described in this report also utilized con-
ventional cardiac catheterization to validate the effec-
tiveness of MAA scintigraphy in the detection of
right to left shunts in this patient population. The
purpose of the study included a determination of the
spot prevalence of an extrapulmonary shunt in candi-
dates for lung transplantation with several different
diseases.

MATERIAL AND METHODS
The initial population included over 650 candidates for
lung transplantation who presented to an urban teaching
hospital for a duration of 5 years. Candidates for lung
transplantation were evaluated by a pulmonary medicine
and transplant medicine specialist. The screening evalua-
tion included a comprehensive history and physical ex-
amination, a review of outside records, pulmonary
function testing, arterial blood gas measurement (ABG)
on room air and alveolar–arterial (A–a) gradient mea-
surement. Patients who were considered suitable candi-
dates for a lung transplantation underwent a cardiac
catheterization. An evaluation for an intracardiac right
to left shunt was determined by the cardiologist based
on visual analysis of contrast as well as with measure-
ments of intraventricular and intraatrial oxygen
saturation. A lung scan was subsequently performed
prior to enrolling the patient on the transplant list.

The decision to perform a lung scan was independant
of the results of the cardiac catheterization. The final
sample was limited to the 126 patients who also had
scintigraphic images of their brains and kidneys per-
formed at our institution at the time of the lung scan.
(113 patients with both kidney and brain images,
12 patients with brain images alone, one patient with
kidney image alone) The final group consisted of
55 men and 71 women with an average age of 47 years
(range: 18–66). The underlying disorder causing the
end-stage lung disease in these patients was COPD (72),
PPH (21), fibrotic lung disease (22), and CHD (11). The
clinical characteristics of the sample are summarized in
Table 1.

Lung scintigraphy was performed with a protocol that
has already been described (14,15). Ventilation studies
were acquired using 400–700 MBq of Xenon (Xe)-133 in
the posterior projection while perfusion scans were sub-
sequently acquired after the i.v. administration of 100–
150 MBq of Tc-99m labeled macroaggretated albumin
(Tc-99m-MAA). Standard 6 views of the lungs were ob-
tained as well as images of the brain, kidneys and bladder.
Brain and kidney images were acquired for 1 min images
with a 64 × 64 matrix in the posterior projection. All
films were reviewed by two experienced physicians who
were unaware of the clinical circumstances surrounding
each case. A visual analysis of the degree of brain and kid-
ney activity was identified. The images were assigned a
semiquantitative value with a scale referenced to the
background activity in the region of interest. Brain activ-
ity (which is never normally evident) was referenced to
the soft tissue in the neck. The renal activity was refer-
cenced to a midabdominal region approximately centrally
located between the kidneys and the bladder. Table 2 lists
the scintigraphic brain and renal activity grading sched-
ule.

Statistical analyses were used to determine the
significance of differences between group mean values
was determined using a Student’s t-test (2-tailed
P-values).

RESULTS
A significant right to left shunt was demonstrated in 13
patients with an abnormal A–a gradient on 100% O2
and confirmed by an anatomic study. A right to left
shunt was excluded in the other 113 patients. Table 3
summarizes the relevant cardio-pulmonary values for the various patient groups.

In all 13 patients with an identified intracardiac shunt, Tc-99m MAA scintigraphy demonstrated abnormally increased activity in the brain with an intensity that was greater than or equal to grade I. The interpretation of these brain images was very reproducible. The readers were divergent in only two studies. Both of these patients had an intracardiac shunt and there was no change in the determination of shunt when the threshold value for interpretation was a grade I. No clinical or anatomic evidence of extrapulmonary shunting was found in all 113 patients having no intracerebral activity by MAA scintigraphy.

All 12 patients with confirmed intracardiac shunts and renal images had increased renal activity by MAA scintigraphy with a grade of ≥1. One patient with a documented right to left shunt had a brain image but no renal images. Half (6/12) of the patients with a shunt had mild renal activity (grade 1). Eighty three of 102 patients with no evidence of intracardiac shunting also demonstrated Tc-99m MAA renal activity with our grade of ≥1. When a positive study for a shunt was based on a renal activity grade interpreted as a 2 or 3, 6/12 patients with shunt were correctly identified and 25/102 patients without shunting were false positives. Only 6 of the 83 renal scans interpreted at a grade of 1 had a shunt. This provides a positive predictive value of 72% at this grade of interpretation. The interpretation of the renal images as a shunt at a grade of 2 gives a similar positive predictive value of 73%. Further classification is demonstrated in Table 4.

### Table 1. Clinical characteristics of the studied group

<table>
<thead>
<tr>
<th>Group</th>
<th>Subgroup</th>
<th>Males</th>
<th>Females</th>
<th>Mean age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH n=21</td>
<td>57 Emphysema</td>
<td>8</td>
<td>13</td>
<td>38</td>
</tr>
<tr>
<td>COPD n=72</td>
<td>4 Cystic fibrosis</td>
<td>23</td>
<td>34</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>1 Pneumoniosis</td>
<td>3</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>6 Alpha 1 antitrypsin Deficiency</td>
<td>1</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>2 Bronchiectasis</td>
<td>1</td>
<td>0</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>1 Bronchiolitis Obliterans</td>
<td>1</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>1 Lymphangioleiomyomatosis</td>
<td>0</td>
<td>1</td>
<td>46</td>
</tr>
<tr>
<td>PF n=22</td>
<td>7 Sarcoidosis</td>
<td>3</td>
<td>4</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>2 Systemic lupus erythematosus</td>
<td>0</td>
<td>2</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>5 Pulmonary fibrosis</td>
<td>2</td>
<td>3</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>2 Pulmonary alveolar microlithiasis</td>
<td>1</td>
<td>1</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>1 Polymyositis</td>
<td>0</td>
<td>1</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>1 Cytoxan induced</td>
<td>0</td>
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<td>42</td>
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<td></td>
<td>1 Scleroderma</td>
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<td>62</td>
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<td></td>
<td>1 Bronchiolitis obliterans</td>
<td>1</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>1 Eosinophilic granuloma</td>
<td>1</td>
<td>0</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>1 Hodgkin's</td>
<td>1</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>CHD n=11</td>
<td>1 VSD/ASD</td>
<td>0</td>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>1 Patent ductus arteriosis</td>
<td>1</td>
<td>0</td>
<td>49</td>
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<tr>
<td></td>
<td>1 Tetrology of falot</td>
<td>0</td>
<td>1</td>
<td>51</td>
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<tr>
<td></td>
<td>6 Atrial septal defect</td>
<td>2</td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>1 Corrected transposition</td>
<td>0</td>
<td>1</td>
<td>19</td>
</tr>
</tbody>
</table>

### Table 2. Scintigraphic brain and renal activity parameters.

**Semi-quantitative brain activity scale**
posterior image of the head and neck — visual analysis
- 0 — no abnormal activity detected
- 1 — slightly increased activity — quantum mottling present
- 2 — moderately increased activity
- 3 — markedly increased activity — brain activity 300%+ that of the neck

**Semi-quantitative renal activity scale**
posterior image of the kidneys and bladder — visual analysis
- 0 — no significant renal activity
- 1 — mild renal activity — renal activity just detectable
- 2 — moderate renal activity
- 3 — intense renal activity — renal activity 300%+ that of background

These brain images were very reproducible. The readers were divergent in only two studies. Both of these patients had an intracardiac shunt and there was no change in the determination of shunt when the threshold value for interpretation was a grade I. No clinical or anatomic evidence of extrapulmonary shunting was found in all 113 patients having no intracerebral activity by MAA scintigraphy.

All 12 patients with confirmed intracardiac shunts and renal images had increased renal activity by MAA scintigraphy with a grade of ≥1. One patient with a documented right to left shunt had a brain image but no renal images. Half (6/12) of the patients with a shunt had mild renal activity (grade 1). Eighty three of 102 patients with no evidence of intracardiac shunting also demonstrated Tc-99m MAA renal activity with our grade of ≥1. When a positive study for a shunt was based on a renal activity grade interpreted as a 2 or 3, 6/12 patients with shunt were correctly identified and 25/102 patients without shunting were false positives. Only 6 of the 83 renal scans interpreted at a grade of 1 had a shunt. This provides a positive predictive value of 72% at this grade of interpretation. The interpretation of the renal images as a shunt at a grade of 2 gives a similar positive predictive value of 73%. Further classification is demonstrated in Table 4.
Clinical parameters which were predictive of the patients who had a shunt include mean pulmonary artery pressure ≥ 50 mmHg and an elevated A–a gradient. The most significant clinical variable for the presence of shunt is the underlying cause of the ESLD. No shunts were seen in the patients with COPD in contrast with 4/21 PPH patients with an intracardiac shunt. Elevated pulmonary artery pressures and the absence of a decreased FEV₁ were more frequent in patients with a shunt. There were no cases of shunt with an FEV₁ < 1.11, FEV₁/FVC < 0.59 or a RV (expressed as % of normal) > 198%. These same features are of value in differentiating PPH from COPD. Increased A–a gradient was associated with a shunt in both PPH and in the pooled group comprising all patients. Hypocarbia was associated with the presence of a shunt in PPH patients as well as in the pooled group. Pulmonary hypertension was present in a subset of patients in each group; however, the mean pulmonary pressure was higher in the PPH group (mean 55) and the CHD group (mean 76) and lowest in the COPD group (mean 25 mmHg).

**DISCUSSION**

Detecting the presence of an extrapulmonary right to left shunt is important in the preoperative evaluation of candidates for lung transplantation. When intracardiac shunt lesions are present, they are repaired at the time
of transplantation. The identification of a right to left shunt can be performed using anatomic imaging techniques that directly visualize a patent foramen ovale or an atrial septal defect. These techniques can be supplemented with a contrast agent to provide some information on the direction and the size of the shunt. Alternative diagnostic strategies include noninvasive scintigraphic techniques such as radionuclide angiography or perfusion pulmonary imaging with radiolabeled particles (9). Echo-cardiographic techniques are widely available and are the most commonly used procedure for the evaluation of extrapulmonary shunting. TTE does not have adequate sensitivity for detecting intracardiac shunts. TEE is optimal for this purpose but it is not a benign procedure in all patients, especially in those with advanced lung disease. The patients for TEE are typically noted with a contrast agent to provide some information on the direction and the size of the shunt can be performed using anatomic imaging techniques that directly visualize a patent foramen ovale or an atrial septal defect. These techniques can be supplemented with a contrast agent to provide some information on the direction and the size of the shunt. Alternative diagnostic strategies include noninvasive scintigraphic techniques such as radionuclide angiography or perfusion pulmonary imaging with radiolabeled particles (9). Echo-cardiographic techniques are widely available and are the most commonly used procedure for the evaluation of extrapulmonary shunting. TTE does not have adequate sensitivity for detecting intracardiac shunts. TEE is optimal for this purpose but it is not a benign procedure in all patients, especially in those with advanced lung disease. The patients for TEE are typically sedated, resulting in a significant risk of aspiration and pneumonia.

Magnetic resonance imaging, a noninvasive procedure, has been used in the evaluation of right ventricular function. Matsuoka et al. (18) has described the use of this technique to determine right ventricular mass. MRI has the additional advantage of excellent delineation of cardiac anatomy, with the potential ability to directly visualize the intracardiac abnormalities (19). MRI has not been specifically investigated for its role in detecting right to left shunts and is not routinely performed in lung transplant evaluations.

In our study the absence of brain activity on the MAA images virtually excluded a significant intracardiac shunt. The specificity of brain imaging was 100% when the scan was interpreted as positive at any threshold (grade of 1, 2, or 3). In contrast, renal images alone were not specific in defining the absence of shunting: A reference of the kidney activity to bladder activity (as a measure of free pertechnetate) did not add any additional specificity and provided an interpretation that is not clinically acceptable.

Right to left shunt on perfusion lung images is suggested when brain activity is visualized. Dogan et al. (20) has shown that brain images may be interpreted as positive for a right to left shunt with even minimal brain activity. Our retrospective study was undertaken to corroborate these findings as well as to determine the optimal threshold for the interpretation of the images. The bladder activity was utilized as a visual aid to provide a reference in the evaluation of the renal images. Our findings are in agreement with the report by Dogan and demonstrate that brain images are sufficient to determine the presence of the right to left shunt. Patients with a shunt had PPH as the predominant underlying disease. The prevalence of probe-patient foramen ovale in the general population is 29% (21). In our study 19% of the patients with PPH demonstrated right to left shunting, of patients with pulmonary fibrosis 91% had a shunt and none of the patients with COPD shunted. These data imply that patients with PPH may have significant PFO and are at an increased risk for paradoxical emboli.

The most significant clinical parameters associated with an extrapulmonary right to left shunt are elevated pulmonary artery pressure, RV dysfunction and hypoxemia. Lin et al. (22) studied the dynamics of right to left shunt in patients with ASD. They found that the shunt first occurs during early diastole. As right ventricular diastolic abnormalities become more pronounced, the shunt fraction increases and the duration of diastole during which shunting occurs increases. We found a strong correlation between right to left shunt and the presence of increased pulmonary artery pressure. At a mean pulmonary artery pressure of less than 50 mmHg there were no patients with a shunt. In the subset of patients with a pulmonary pressure greater than 50 mmHg, approximately 40% of the patients had a right to left shunt. This incidence is similar to the described prevalence of potentially patent foramen ovale.

PPH represents a disproportionate share of transplant candidates both at this institution and worldwide because of the young age of these patients (PPH mean age=36 years; COPD mean age > 60 years) (2,3,4). Because PPH represents a large share of our patient group as well as the bulk of patients with a right to left shunt, some additional analysis was performed. Our patient group with PPH represents a select group with end-stage lung disease. PPH patients with low pressures and preserved right ventricular function are not considered for lung transplant because they are at an early stage of their illness. Pulmonary pressures, spirometry data and the RVEF did not differ significantly in PPH patients with and without a shunt. The only clinically measurable parameter in the subgroup of patients with PPH that partitions the patients with and without a shunt is the PCO₂. Although in our study the number of patients with PPH is small, the difference with regard to this parameter is large enough to provide a P < 0.05. The explanation for these findings is not clear but may relate to a disturbance in respiratory stimulus or to a manifestation of right ventricular dysfunction.

Opening a patent foramen ovale requires an elevated pulmonary pressure and time to generate right ventricular diastolic dysfunction. These co-related factors are required to develop the right to left shunt pathophysiology. The RV diastolic dysfunction was not directly measured in our study; however a related parameter, the RVEF, was measured. A trend in the pooled patient group comparing the RVEF in patients with and without a shunt was noted (33.4 vs. 41.8; P=NS). The patients with PPH had a higher mean pulmonary pressure, lower RVEF and a higher proportion of right to left shunt than any other subgroup. This subgroup of patients with end-stage lung disease is at significantly increased risk for development of a right to left shunt.
This retrospective study is limited by the nature of retrospective studies and the manner in which the data was acquired. Analog film images were obtained in the routine performance of these studies for transplant candidates. The lack of a digital archive of these clinical images precluded a quantitative measure of the activity present in the brain or the kidneys. Several clinical parameters were also not measured in all the cases. The RVEF was depressed in patients with a right to a left shunt but no significance was achieved due to the small number of measurements.

CONCLUSIONS
Extra pulmonary right to left shunt is not uncommon in patients with end-stage lung disease. We found a prevalence of 10.3% in the total patient group studied and a prevalence of 19.0% in the patients with primary pulmonary hypertension.

Clinical markers may help to identify those patient at most risk for the opening of a potentially patent foramen ovale and subsequent right to left shunt. We found a significant positive correlation of shunt with increased pulmonary pressure, underlying pulmonary vascular disease, and hypocarbia. The addition of a single brain image as part of a routine perfusion lung scan in patients with these clinically identifying features provides valuable information for the managing clinician. In contrast, renal imaging was clinically unreliable. The routine use of brain imaging along with lung perfusion scintigraphy provides a cost-effective method for identifying a right to left shunt.

REFERENCES