

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 a 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. © 2003 Elsevier Science Ltd. All rights reserved.

doi:10.1053/rmed.2003.1481, available online at <http://www.sciencedirect.com>

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

Received 22 July 2002, accepted in revised form 2 December 2002
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side of the heart to the left. The shunt is closed at the time of transplantation, generally requiring an open cardiac procedure. The most common cause of an extrapulmonary 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 foramen is patent when probed by an instrument in about 30% of all autopsy specimens. A functional shunt can be demonstrated with provocative echocardiographic maneuvers in about 25% of the healthy population (6–8). Patients 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 evaluation 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 breathe 100% oxygen (O_2). The shunt fraction is approximated by the difference between the alveolar and arterial O_2 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 extrapulmonary in origin. Several diagnostic procedures can detect the right to left shunting of blood in the heart (9–15). These techniques include transesophageal echocardiography (TEE), transthoracic echocardiography (TTE), radionuclide angiography (RNA), echo planar magnetic resonance imaging (MRI), and macroaggregated 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 conventional cardiac catheterization to validate the effectiveness 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 candidates 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 evaluation included a comprehensive history and physical examination, 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 candidates 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 measurements 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 independent 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 / or kidneys performed 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 subsequently acquired after the i.v. administration of 100–150 MBq of Tc-99m labeled macroaggregated albumin (Tc-99m-MAA). Standard 6 views of the lungs were obtained 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 kidney activity was identified. The images were assigned a semiquantitative value with a scale referenced to the background activity in the region of interest. Brain activity (which is never normally evident) was referenced to the soft tissue in the neck. The renal activity was referenced to a midabdominal region approximately centrally located between the kidneys and the bladder. Table 2 lists the scintigraphic brain and renal activity grading schedule.

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% O_2 and confirmed by an anatomic study. A right to left shunt was excluded in the other 113 patients. Table 3

TABLE 1. Clinical characteristics of the studied group

Group	Subgroup	Males	Females	Mean age(years)
PH <i>n</i> =21		8	13	38
COPD <i>n</i> =72	57 Emphysema	23	34	55
	4 Cystic fibrosis	3	1	24
	1 Pneumoconiosis	1	0	60
	6 Alpha 1 antitrypsin Deficiency	4	2	46
	2 Bronchiectasis	1	1	52
	1 Bronchiolitis Obliterans	1	0	21
	1 Lymphangiomyomatosis	0	1	46
PF <i>n</i> =22	7 Sarcoidosis	3	4	48
	2 Systemic lupus erethematosi	0	2	36
	5 Pulmonary fibrosis	2	3	55
	2 Pulmonary alveolar microlithiasis	1	1	46
	1 Polymyositis	0	1	54
	1 Cytoxan induced	0	1	42
	1 Scleroderma	1	0	62
	1 Bronchiolitis obliterans	1	0	21
	1 Eosinophilic granuloma	1	0	51
	1 Hodgkin's	1	0	29
	CHD <i>n</i> =11	1 VSD/ASD	0	1
1 Patent ductus arteriosis		1	0	49
1 Tetralogy of falot		0	1	51
6 Atrial septal defect		2	4	36
1 Corrected transposition		0	1	19

TABLE 2. Scintigraphic brain and renal activity parameters.*Semiquantitative 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

Semiquantitative 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

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 1. 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 1. 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 7.2% 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 7.3%. Further classification is demonstrated in Table 4.

TABLE 3. Differentiating features of R-L shunt vs. No R shunt.

Patient set	Observation*	R-L shunt	No shunt	P-value
All Patients <i>n</i> =126		<i>n</i> =13	<i>n</i> =113	
	FEV ₁ /FVC	0.746	0.458	<0.00001
	pO ₂	62.8	90.1	0.003
	pCO ₂	31.7	43.6	0.00006
	A-a gradient	101.6	49.7	0.02
	PA mean	68.7	33.8	0.01
	PCWP	19.5	11.5	NS
	PAD	45.7	23.5	0.0003
	RVEF	33.4	41.8	NS
PPH patients <i>n</i> =21		<i>n</i> =4	<i>n</i> =17	
	FEV ₁ /FVC	0.768	0.705	NS
	pCO ₂	25.3	34.8	0.05
	A-a gradient	86.9	65.8	NS
	PA mean	52.7	56.0	NS
PF patients <i>n</i> =22		<i>n</i> =2	<i>n</i> =20	
	FEV ₁ /FVC	0.775	0.685	NS
	pCO ₂	40.5	43.8	NS
	A-a gradient	189	47.8	NS
	PA mean	57	38	NS
Cardiac disease <i>n</i> =11		<i>n</i> =7	<i>n</i> =4	
	FEV ₁ /FVC	0.726	0.760	NS
	pCO ₂	32.8	34.0	NS
	A-a gradient	84.9	70.8	NS
	PA mean	78.7	73.0	NS
COPD patients <i>n</i> =72		<i>n</i> =0	<i>n</i> =72	
	FEV ₁ /FVC		0.316	
	pCO ₂		46.0	
	A-a gradient		45.3	
	PA mean		25.0	

*Units of pressure in mmHg.

TABLE 4.

	1 (%)	2 (%)	3 (%)
Brain imaging threshold grade for positive			
Sensitivity	100	39	15
Specificity	100	100	100
Kidney imaging threshold grade for positive			
Sensitivity	100	50	33
Specificity	19	76	100

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 <1.1 l, 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. Hypocarbica 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). Echocardiographic 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 9.1% had a shunt and none of the patients with COPD shunted. These data im-

ply 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 a 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 PCO_2 . 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 finding 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.

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