Acute Pulmonary Embolism in Pediatric Patients Awaiting Heart Transplantation

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Acute pulmonary embolism with infarction can delay urgently needed heart transplantation and increase the postoperative pulmonary complications. Few data are available concerning pulmonary embolization in the pediatric patient with end-stage congestive heart failure. Sixty-two consecutive pediatric patients awaiting heart transplantation were monitored for evidence of acute pulmonary embolism. Acute pulmonary infarction was documented by ventilation-perfusion scan, pulmonary angiography or pathologic examination in six patients. The prevalence differed by diagnosis; 5 of 36 patients with dilated cardiomyopathy and 1 of 20 patients with congenital heart disease developed acute pulmonary embolism with infarction.

No significant difference in age at the time of transplantation evaluation, duration of congestive heart failure, presence of cardiac arrhythmias or degree of cardiac dysfunction was seen between patients with and without pulmonary embolism. Two-dimensional echocardiography failed to detect the presence of an intracardiac thrombus in four of the six patients. Two patients who developed acute pulmonary infarction are alive after successful heart transplantation. The remaining four patients died within 6 weeks of initiation of anticoagulant therapy before transplantation could safely be performed.

In summary, pediatric patients with end-stage congestive heart failure are at risk for acute pulmonary embolism. No specific clinical factor identified those patients who developed acute pulmonary infarction. Anticoagulant therapy is strongly recommended in the pediatric patient with poor ventricular function awaiting heart transplantation.

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Cardiac disease is a major risk factor for thromboembolic events in adult patients (1–3). The mortality rate associated with systemic or pulmonary embolism has been reported (4) to be as high as 38% in patients with dilated cardiomyopathy. For the patient with end-stage congestive heart failure, acute pulmonary infarction secondary to embolization can delay urgently needed heart transplantation and increase the postoperative pulmonary complications (5–8). Anticoagulant therapy is currently recommended for the prevention of an embolic event in the adult patient who is at risk (1,9–11).

A few reports (12–15) have characterized the incidence of systemic embolic phenomena in the pediatric patient with poor ventricular function, but no data are published concerning pulmonary embolization. This study 1) describes the occurrence of acute pulmonary embolism with infarction in a group of children evaluated for heart transplantation at our institution, and 2) addresses issues of prevention and management.

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Methods

Study patients. Pediatric patients referred for evaluation for heart transplantation from May 1984 until October 1989 were observed for evidence of acute pulmonary embolism with infarction on admission and while awaiting transplantation. Sixty-two consecutive patients who were referred to our transplantation center because of intractable heart failure or symptomatic inoperable congenital heart disease, or both, were included in the study. Thirty-six patients had dilated cardiomyopathy, 20 had congenital heart disease, 5 had restrictive cardiomyopathy and 1 had a large left ventricular tumor.

The clinical history of all patients referred for evaluation was reviewed for the occurrence of thromboembolic events. Five patients had a history of systemic embolism before evaluation for transplantation; three of the five had a documented cerebrovascular accident and two had evidence of a transient ischemic attack. One patient with a transient ischemic attack also had pulmonary infarction treated by pulmonary resection 2 years before referral for transplantation.

Clinical evaluation. Acute pulmonary embolism with infarction was demonstrated by several means including ventilation-perfusion scan, pulmonary angiography, direct visualization or pathologic examination of the lungs. The clinical course of the patients with and without an embolic event was analyzed with respect to diagnosis, age at the time of

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Table 1. Profile of Patients With Acute Pulmonary Embolism and Infarction

Patient No.	Diagnosis	Age (yr)	Clinical Signs	Location on X-ray Film	V-Q Scan	Pulmonary Angiogram	Pathologic Findings	Outcome
1	Dilated cardiomyopathy	6.5	Asymptomatic	RUL	N/A	N/A	Acute infarction, RUL	Alive, heart transplanted
2	Chronic rejection 4 yr s/p heart transplant	9.0	SOB, hypoxemia	RML	Positive	N/A	N/A	Alive, heart transplanted
3	Dilated cardiomyopathy	18.0	Chest pain, cough, hemoptysis	RLL	Indeterminate	RLL	N/A	Died
4	Dilated cardiomyopathy	14.3	Respiratory failure, hemoptysis	LLL	Indeterminate	LLL	Recurrent infarction, right and left lungs	Died
5	Dilated cardiomyopathy	18.0	SOB, hypoxemia, hemoptysis	RUL, RLL	Positive	N/A	Massive infarction, right and left lungs	Died
6	s/p repair of cTGA, PS and VSD	13.8	SOB, hypoxemia	RML	N/A	N/A	Multiple areas of infarction	Died

cTGA = corrected transposition of the great arteries; LLL = left lower pulmonary lobe; N/A = not available; PS = pulmonary stenosis; RLL = right lower pulmonary lobe; RML = right middle pulmonary lobe; RUL = right upper pulmonary lobe; SOB = shortness of breath; s/p = status post; VSD = ventricular septal defect; V-Q scan = ventilation-perfusion scan.

evaluation, duration of congestive heart failure, cardiac rhythm, cardiac function, anticoagulant therapy and presence of echocardiographically demonstrated intracardiac thrombus. To identify additional patients who might have been at increased risk for an embolic event, autopsy or explanted hearts were examined for the presence of intracardiac thrombus in 41 patients.

Statistics. Statistical analysis was performed with the use of Student's *t* test and chi-square analysis.

Results

Embolic events (Table 1). In five patients the diagnosis of acute pulmonary infarction was suspected on the basis of clinical history and chest roentgenographic findings during the evaluation period or while awaiting heart transplantation. In another patient, the diagnosis was made by direct visualization of a small wedge of pulmonary infarction at the time of transplantation. The cardiac diagnosis, age, mode of presentation, chest X-ray localization of pulmonary infarction, method of documentation and outcome of the six patients are summarized in Table 1.

Four patients had a ventilation-perfusion scan performed; in two, the study was diagnostic of acute pulmonary embolism and in two, the diagnosis was indeterminate because of matched ventilation-perfusion defects. Pulmonary embolism was documented in the latter by selective pulmonary angiography. Patient 6 could not undergo diagnostic studies because of his unstable hemodynamic condition, but multiple areas of pulmonary infarction were demonstrated at autopsy. No episodes of systemic thromboembolism were documented during the study period.

Prevalence. The prevalence of pulmonary infarction differed by diagnosis in the 62 patients referred for evaluation for heart transplantation. Of the 36 patients with the diagnosis of dilated cardiomyopathy, 5 (14%) developed acute pulmonary infarction. One (5%) of the 20 patients with congenital heart disease had documented pulmonary infarction. This patient had undergone repair of corrected transposition of the great arteries, ventricular septal defect and pulmonary stenosis with placement of an artificial conduit to the pulmonary artery and closure of the ventricular septal defect. The five patients with restrictive cardiomyopathy and the one patient with a large left ventricular tumor did not have acute pulmonary embolism.

Age, duration of illness and cardiac rhythm. There was no significant difference in the age of the six patients who developed acute pulmonary infarction (mean ± SD 13.3 ± 4.8 years) and that of the 56 patients who did not (10.3 ± 6.5 years). The median duration of illness was similar for the two groups (13.5 and 12 months, respectively). Two patients had a history of tachyarrhythmias before the development of acute pulmonary embolism; one had recent conversion from atrial fibrillation/flutter and the other had automatic atrial tachycardia controlled by antiarrhythmic therapy for 3 months. The remaining four patients had normal sinus rhythm before acute pulmonary infarction. Eleven of the 56 patients without acute pulmonary embolism also had rhythm disturbances; 2 had atrial tachycardia, 4 had atrial fibrillation/flutter and 5 had complete heart block.

Ventricular function (Table 2). Both groups of patients exhibited markedly decreased left ventricular function. However, no significant difference in cardiac index, M-mode echocardiographically determined percent fractional shortening and ejection fraction determined by gated pool nuclear angiography was seen between the groups with and without pulmonary infarction.

Two of the six patients with pulmonary embolism had clinical signs of right heart failure, including hepatomegaly, peripheral edema and ascites. Four of these patients had

Table 2. Left Ventricular Function in Six Patients

	Patients With Pulmonary Embolism	Patients Without Pulmonary Embolism
Cardiac index (liters/min per m^2)	2.4 ± 1.6	2.7 ± 1.1
Fractional shortening (M-mode echo)	10 ± 8%	14 ± 10%
Ejection fraction (MUGA)	25 ± 12%	23 ± 9%

echo = echocardiography; MUGA = gated pooled nuclear angiography.

right ventricular dilation seen on echocardiography and five had Doppler evidence of tricuspid regurgitation.

Anticoagulant therapy. Three patients were receiving anticoagulant therapy before the onset of acute pulmonary infarction: aspirin in one, aspirin and disopyramide in another and low dose subcutaneous heparin in the third. None of the patients who developed acute pulmonary embolism were treated with anticoagulation with warfarin or intravenous heparin.

Of the patients who did not have pulmonary embolism, 5 were taking aspirin with or without disopyramide, 1 was taking subcutaneous heparin and 20 were taking either warfarin or intravenous heparin for anticoagulation. Eleven of the 20 in the latter group received anticoagulant therapy after intracardiac thrombus was noted on echocardiography. The five patients who had a thromboembolic event before evaluation underwent anticoagulant therapy and none of these developed acute pulmonary embolism while awaiting transplantation. There were no bleeding episodes associated with anticoagulant therapy.

Intracardiac thrombus. All six patients who developed pulmonary embolism underwent two-dimensional echocardiography ≤1 month before clinical acute pulmonary infarction. Intracardiac thrombus was seen on echocardiography in two of these six patients (in the right atrium in one and in the left ventricle in the other); it was not seen in the other four. Thirteen (23%) of the 56 patients without pulmonary infarction had intracardiac thrombus demonstrated on echocardiography. The thrombus was located in the left ventricle in six patients, the left atrium in one patient, the right atrium in three patients and the right ventricle in three. Statistical analysis of these data revealed no significant difference in the incidence of echocardiographically demonstrated intracardiac thrombus between the groups with and without acute pulmonary embolism.

Risk of thromboembolism. Among the 62 patients, 5 had a history of a thromboembolic event, 6 had pulmonary embolism during the study period, 12 had intracardiac thrombus seen on echocardiography and 1 patient had thrombus identified at pathologic examination of the explanted heart. Thus, 39% of the patients in the study were found to have experienced an embolic event or could be considered at risk for such an occurrence on the basis of intracardiac thrombus. This includes 19 (53%) of the 36 patients with dilated cardiomyopathy and 5 (25%) of the 20 patients with congenital heart disease. None of the patients with restrictive cardiomyopathy or the patient with the left ventricular tumor had either intracardiac thrombus or an embolic phenomenon.

Patient outcome. Two of the six patients who developed acute pulmonary infarction are alive after heart transplantation. A small wedge of pulmonary infarction was resected intraoperatively in a 6.5 year old boy in whom the diagnosis was not suspected. The second patient, a 9 year old boy, underwent successful heart transplantation 3 months after the diagnosis of acute pulmonary infarction. He had received anticoagulant therapy with intravenous heparin followed by oral warfarin for a total of 2 months. Normal pulmonary vascular resistance was documented before transplantation. Neither of these two patients had further pulmonary sequelae attributable to their pulmonary embolism.

Four patients with documented pulmonary infarction died while receiving anticoagulant therapy. Each had been placed on the active heart transplant recipient waiting list and were inactivated because of the diagnosis of acute pulmonary infarction. Three of these children died of congestive heart failure at 8, 38 and 39 days, respectively, after the diagnosis of infarction. The fourth child died of sudden ventricular fibrillation 41 days after anticoagulant therapy was instituted.

Discussion

Intracardiac thrombus and dilated cardiomyopathy. Intracardiac thrombus formation among patients with end-stage congestive heart failure is initiated by blood stasis in the poorly functioning ventricle. In a series of 120 adult patients studied at necropsy with idiopathic dilated cardiomyopathy, right- or left-sided thrombus or a mural endocardial plaque was seen in 103 (86%) (16). Using a decision analysis model, Tsevat et al. (4) reported the risk for systemic and pulmonary embolization in dilated cardiomyopathy to be 4% and 5%/year, respectively, with a case-fatality rate of 30% for systemic embolization and 38% for pulmonary embolization.

Prevention of intracardiac thrombus. Although no randomized trials have been conducted, evidence suggests that the incidence of thromboembolic events in dilated cardiomyopathy can be decreased with the use of either warfarin or intravenous heparin. Fuster et al. (1) reported an occurrence of four embolic events/100 patient-years of exposure in patients not treated with an anticoagulant agent and no embolic events in those receiving oral anticoagulant therapy. In another study (9) of 38 patients with dilated cardiomyopathy, oral anticoagulant therapy for a median period of 39 weeks resulted in no thromboembolic events. Seventeen of these patients had systemic or pulmonary embolism before initiation of anticoagulant therapy. According to many workers (1,9–11), standard therapy for the prevention of thromboembolic events includes anticoagulant therapy in the adult patient with dilated cardiomyopathy.

Risk of thromboembolism in pediatric patients. In this study, pediatric patients with dilated cardiomyopathy and low cardiac output were found to be at risk for thromboembolic events. Among patients with congenital heart disease, only one child had pulmonary embolism and this may have been related to the presence of a right ventricular to pulmonary artery porcine valved conduit. However, 4 of the remaining 19 patients had intracardiac thrombus demonstrated echocardiographically or pathologically. Thus, at this time, no conclusion can be made regarding the relative risk of thromboembolism in patients with congenital heart disease and poor ventricular function. No specific clinical risk factor for acute pulmonary embolism was identified. Patient age, duration of illness and left ventricular function were similar for both groups. Two of the six patients with pulmonary embolism had a history of atrial tachyarrhythmia, but a similar percent of nonaffected children also had arrhythmias. This finding does not imply that arrhythmias are not an initiating factor in embolic phenomena. Indeed, such a relation is well documented. Anticoagulation may have prevented the patients with arrhythmias in our study from experiencing thromboembolic events.

Echocardiographic evidence of thrombus did not emerge as a statistically significant risk factor for acute pulmonary embolism. This is possibly a result of the limitations of two-dimensional echocardiography in detecting mural plaque or small thrombi. These findings underscore the importance of measures to prevent embolic events, even in patients without intracardiac thrombus demonstrated echocardiographically.

Pulmonary infarction and heart transplantation. Although most centers consider acute pulmonary infarction to be a contraindication to heart transplantation, successful transplantation has been described in patients with acute pulmonary infarction. Young et al. (7) described eight patients with clinical and roentgenographic evidence of pulmonary infarction who underwent transplantation. These authors do not state whether or how long pretransplantation anticoagulant therapy was administered. All received pulmonary physiotherapy and antibiotic and anticoagulant therapy postoperatively. In four of the eight patients, the infarction resolved without surgical intervention. The remaining four patients developed intrathoracic infection as a result of infarction: one died and three required a late thoracic surgical procedure; prolonged (39 to 99 days) chest drainage was needed. Cavarocchi et al. (8) recently reported on two patients who underwent successful transplantation within 4 days of the development of acute pulmonary embolism. Both patients developed lung abscess, empyema and a bronchopleural fistula after transplantation; these were treated surgically by lobectomy and latissimus dorsi muscle flap placement in addition to prolonged hospitalization for antibiotic therapy. Although these two patients survived, the authors (8) conclude that "preoperative pulmonary emboli should remain a strong relative contraindication for heart transplantation."

The mortality and morbidity associated with acute pulmonary infarction were significant in this series. All six patients with acute infarction had been accepted as candidates for heart transplantation, but surgery was delayed until the acute process could be resolved in five. Four of these five patients died within 6 weeks of the diagnosis of infarction without undergoing transplantation. Although the postoperative management of pulmonary infection can be complicated and prolonged, the reported survival of patients undergoing transplantation during the acute phase of pulmonary embolism may indicate that a more aggressive approach to transplantation could result in a better outcome in these critically ill children. Two patients with acute pulmonary embolism were able to undergo successful transplantation, one with pulmonary wedge resection at the time of diagnosis and one after maintenance on inotropic support during 2 months of anticoagulant therapy.

Conclusions. Anticoagulation is standard therapy in pediatric patients with atrial fibrillation; however, many clinicians are reluctant to initiate anticoagulant therapy in children who do not have this specific indication. The risk and morbidity of thromboembolic events in this series justify extensive measures to prevent the formation of intracardiac thrombus. In addition, although none of the patients in this series had clinical evidence of venous thrombosis, this potential factor in the origin of pulmonary embolism can also be diminished by anticoagulation. Careful monitoring of anticoagulant therapy to maintain the therapeutic prothrombin time between 1.3 to 1.5 times the control value results in minimal risk of bleeding (17). It appears that the potential benefits from anticoagulation far outweigh the risk of complications in the pediatric patient with poor ventricular function awaiting heart transplantation. In our series, 8% of patients referred for transplantation had already experienced a thromboembolic event before referral. On this basis, it seems reasonable to broaden the indications for anticoagulation to include pediatric patients with severe cardiomyopathy early in the course of the disease, even before heart transplantation is considered to be the only recourse.

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