Enhancement of Hypoxemia by Atrial Shunting in Cystic Fibrosis*

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Patients with CF may develop hypoxemia which seems disproportionate to the degree of pulmonary disease. In a series of patients with CF and advanced pulmonary disease undergoing transesophageal echocardiography for the evaluation of cor pulmonale, eight of 15 patients were found to have atrial shunts through a stretched foramen ovale. To our knowledge, this is the first observation of intracardiac shunting in CF. This phenomenon may account for unexplained levels of cyanosis and worsening of hypoxemia with exercise, vasodilators, or PEEP and poses the threat of paradoxical emboli when central venous lines are used in these patients. (Chest 1990; 98:543-45)

Cor pulmonale and progressive hypoxemia are expected in the advanced stages of CF. On occasion, refractory hypoxemia develops which seems disproportionate to the degree of pulmonary disease.

We report atrial-level shunting in CF, a previously undescribed phenomenon. Atrial shunting may cause significant systemic hypoxemia, worsen it during exercise, cough, or with certain vasodilators, and could facilitate paradoxical emboli when central venous lines are used.

During the course of evaluating a series of patients with CF and cor pulmonale, we used transesophageal echocardiography. This is a new imaging modality in CF, described herein for the first time.

Case Report and Subsequent Series

A 20-year-old white man had been diagnosed with CF at two years of age, presenting with respiratory infections, chronic cough, foul-smelling, oily floating stools, and elevated sweat chloride levels. He did relatively well until the age of 19 years, requiring several hospitalizations for pulmonary rehabilitation of chronic bronchitis and bronchiectasis secondary to Pseudomonas aeruginosa, but attending college and enjoying a reasonably full range of activity.

At 19 years of age, the patient had two separate transthoracic echocardiographic examinations showing an enlarged right ventricle with thickened wall and normal sized atria. At the age of 20 years, he presented with severe hypoxemia which seemed disproportionate to the degree of pulmonary involvement. His arterial blood gas levels on room air showed a pH of 7.40, PaCO₂ of 56 mm Hg, PaO₂ of 26 mm Hg, saturation of 45 percent, and bicarbonate of 34 mEq/L. His pulmonary function tests showed the following: FVC, 39 percent of predicted; FEV₁, 23 percent of predicted; MEF₅₀, 4 percent of predicted; and residual volume, 418 percent of the predicted normal.

Transthoracic echocardiography provided very poor imaging of the heart because of excessive air retention in the chest. Transeso-

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Figure 1. Transesophageal echocardiographic image of atrial shunting through stretched foramen ovale. Shunting appears orange-red on color Doppler (flow towards transducer). Arrowsheads mark edges of atrial septal defect. LA, Left atrium; and RA, right atrium.
Enhancement of Hypoxemia by Atrial Shunting (Davidson et al)

In a subsequent series, 15 patients with CF, aged 19 to 44 years, underwent transesophageal echocardiography. They had advanced pulmonary disease, with a mean FVC of 45.5 ± 11.9 percent of predicted and a mean FEV₁ of 25.3 ± 7.2 percent of the predicted normal. Seven (47 percent) of the 15 patients were found to have right-to-left atrial shunting by bubble contrast injection and color Doppler. The patients had atrial shunting documented at rest or with Valsalva's maneuver. One of the patients had no atrial shunting initially. Six months later, he developed overt right heart failure. At that time, he had severe hypoxemia which was very labile. He underwent a repeat transesophageal echocardiographic examination and was found to have atrial-level shunting. This increased the total incidence of atrial shunting in this series to 53 percent (8/15).

**Discussion**

In 30 to 35 percent of adult hearts, the foramen ovale remains potentially patent.¹ The elevated right atrial pressure in cor pulmonale may stretch the interatrial septum and reopen the foramen ovale. Right-to-left intracardiac shunting would explain a worsening hypoxemia, unaccounted for by the degree of pulmonary disease. For many years, it was believed that only intrapulmonary shunting, via bronchopulmonary anastomoses and perfusion of poorly ventilated lung areas, was responsible for this type of hypoxemia in patients with CF.²

Right-to-left atrial shunting, documented by contrast echocardiography, has previously been described in primary pulmonary hypertension.³ To our knowledge, our observations are the first report of this intracardiac phenomenon in CF. Transthoracic echocardiography often provides a poor image in patients with emphysema.⁴ Echocardiographic studies in CF reported an imaging success rate varying from 50 percent to 90 percent.⁵ These series studied only the ventricles (cavity dimensions, wall thickness, septal motion, ejection fraction, and, occasionally, systolic time intervals).

No information regarding the atra was ever reported in any of these investigations. Our study group consisted of patients with advanced disease and severe air trapping, in whom the conventional transthoracic echocardiography was quite disappointing. We therefore resorted to transesophageal echocardiography, which provided us with much improved imaging of the heart.

Given the posterior location of the atria, they are easier to visualize from the esophagus than from a transthoracic approach. Even in normal subjects, the atria are better seen from a transthoracic approach.¹⁰⁻¹² Transesophageal echocardiography allowed us, for the first time, to observe atrial phenomena in CF.

This initial series documents a significant percentage (53 percent) of patients with CF and advanced pulmonary disease who had shunting at the atrial level. This may explain incidents of systemic desaturation to a degree that cannot be accounted for by the pulmonary disease. One of us (D.S.H.) clinically examined all of the patients without knowledge of the echocardiographic findings.

Based on pulmonary function tests and clinical and radiologic evaluations, six patients were thought to have unusually low or labile PaO₂, or excessive oxygen requirements, for the degree of pulmonary disease. Five of them were among the eight patients documented by echocardiography to have atrial shunts, and only one was among the seven patients without shunting. These early observations indicate that atrial shunting is a clinically significant event in patients with CF, more commonly present than previously suspected.

Although not studied in this series, the elevation of pulmonary pressures during exercise¹³ may increase right atrial pressure and augment a right-to-left shunt. This could result in worsening desaturation during exercise and diminished oxygen supply to the coronary arteries at a time of increased myocardial oxygen demand. The same could occur with the application of PEEP (by nasal cannula or assisted ventilation), which may elevate the right atrial pressure.¹⁴

Vasodilators, in particular calcium antagonists, have been used increasingly in recent years to treat pulmonary hypertension.¹³,¹⁵,¹⁶ Nifedipine has been shown to result in a decrease in PaO₂.¹³,¹⁵,¹⁷ This has been attributed mainly to an increased ventilation-perfusion mismatch secondary to recruitment of poorly ventilated vascular beds;¹³,¹⁶ however, nifedipine is more potent as a systemic vasodilator than as a pulmonary vasodilator.¹⁵,¹⁷ A decrease in systemic resistance to a greater extent than the pulmonary resistance will facilitate right-to-left atrial shunting and could account for part of the hypoxemia observed with nifedipine.

Although not reported in CF, atrial shunting could result in paradoxic emboli, such as previously described in neurosurgical patients¹⁴,¹⁸ and in adult
patients with atrial septal defects. A right-to-left atrial shunting in a patient with an atrial septal defect has been described even with normal pulmonary artery pressures. This is of concern in view of the increasing use of central venous lines in patients with CF. It may be useful to screen patients with CF for the presence of atrial shunts before the placement of such lines. The presence of atrial shunting in CF may be significant because of the documented risk of pulmonary artery thrombosis in patients with atrial septal defects and pulmonary hypertension.

The patient who had no atrial shunting early in the study and later stretched his foramen ovale and developed labile hypoxemia exemplifies the value of serial evaluations over time. Transesophageal echocardiography is a safe procedure which is easy to repeat, even on an outpatient basis, and is therefore suitable for serial assessments of the hemodynamic situation.

The observation of atrial shunting improves our understanding of the pathophysiology of labile hypoxemia in patients with CF. There is no direct therapeutic implication at present, since atrial shunting seems to occur in patients with advanced disease, in whom surgical closure of the atrial septal defect is not a reasonable undertaking. Such surgery would also prohibit later heart-lung transplantation and should therefore be avoided.

Transcatheter closure of atrial septal defects appears to be emerging from the experimental laboratory into the clinical domain. If these devices become practical clinical tools, then closure in the catheterization laboratory may be a reasonable therapy for CF patients with documented atrial shunts.

Transesophageal echocardiography has allowed us to document a stretched foramen ovale and atrial shunting in CF for the first time.

This phenomenon seems to occur in a significant number of CF patients with advanced pulmonary disease. It could account for unexplained levels of cyanosis and worsening of hypoxemia with exercise, vasodilators, or PEEP and poses the threat of paradox emboli when central venous lines are used in these patients.

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