The Prevalence and Significance of a Patent Foramen Ovale in Pulmonary Hypertension

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In order to determine the prevalence and significance of a patent foramen ovale (PFO) in pulmonary hypertension, 58 patients were studied with transesophageal echocardiography, right-sided heart catheterization, and exercise testing. In order to examine if a PFO might be associated with a better outcome, survival was estimated, based on a formula derived from the National Institutes of Health Primary Pulmonary Hypertension Registry, for the patients with primary pulmonary hypertension (PPH). A PFO was found in 26 percent (15 of 58) of all patients studied, 25 percent (10 of 40) of those with PPH, and 28 percent (5 of 18) of those with secondary pulmonary hypertension. We found no significant difference in any hemodynamic variable or exercise tolerance between the patients with and without a PFO, or for subsets of patients with primary and secondary pulmonary hypertension. We also found no significant difference in the 1-, 2-, 3-, 4-, or 5-year estimated survival, for the patients with PPH between those with and without a PFO. The prevalence of a PFO in pulmonary hypertension appears similar to the normal population. A PFO provides no detectable influence on resting hemodynamics or exercise tolerance in patients with pulmonary hypertension and is not clearly associated with patients expected to survive longer. (Chest 1993; 104:1673-75)

| PFO | patent foramen ovale; PPH | primary pulmonary hypertension |

It has been reported that patients with pulmonary hypertension commonly have a patent foramen ovale (PFO), and that the PFO may protect against right ventricular failure and even improve survival. The actual prevalence of a PFO in pulmonary hypertension has never been assessed prospectively, nor have its physiologic effects in pulmonary hypertension ever been studied. In order to determine the prevalence and significance of a PFO in pulmonary hypertension, 58 patients were evaluated for the presence of a PFO, with subsequent hemodynamic and exercise evaluations.

METHODS

Patients

Fifty-eight consecutive patients with pulmonary hypertension (44 female, 14 male), with a mean age of 42 ± 11 (range, 15 to 69) years, were studied. All patients were evaluated for the etiology of their pulmonary hypertension based on the protocol used in the National Institutes of Health Registry on Primary Pulmonary Hypertension. Pulmonary hypertension was diagnosed as primary in 40 patients (69 percent) and secondary in 18 (31 percent).

Patent Foramen Ovale Detection

Transesophageal echocardiography was performed using a 5-MHz transducer (Aculs corporation, Mountain View, Cal). A four-chamber view was obtained to provide the best view of the fossa ovales. Contrast consisted of an agitated 5 percent glucose solution, which was injected via an 18-gauge angiocatheter into the right antecubital vein, both during normal breathing and during a Valsalva maneuver. A right-to-left shunt was considered present if at least five microbubbles were clearly seen in the left atrium immediately after opacification of the right side of the heart. All studies were interpreted by at least two physicians experienced in contrast echocardiography.

Hemodynamic Studies

All patients underwent right-sided heart catheterization within 48 h of the transesophageal echocardiogram. A flow-directed, thermodilution catheter was advanced into the pulmonary artery via the right femoral or internal jugular veins, and a small cannula was placed in the right femoral artery. Systemic arterial, right atrial, pulmonary artery, and pulmonary capillary wedge pressures were obtained. Cardiac output was determined (in triplicate) using the thermodilution technique. Pulmonary and systemic vascular resistance values were calculated using standard formulas. Systemic oxygen saturation levels were determined by drawing blood from the arterial line.

Exercise Study

Fifty-two patients (90 percent) underwent a symptom-limited exercise treadmill within 48 h of the catheterization using a standard Naughton protocol.

Survival Estimates

In order to examine if a PFO might be associated with a better outcome, survival was estimated for the 40 patients with primary pulmonary hypertension (PPH), based on a formula derived from the database of the National Institutes of Health PPH Registry, which utilizes the cardiac index, mean pulmonary artery pressure, and mean right atrial pressure. The 1-, 2-, 3-, 4-, and 5-year survivals were estimated for each patient, and the mean survival at each year was calculated for those patients with and without a PFO.
Table 1—Hemodynamic Measurements, Exercise Time, and Arterial Saturation in 58 Patients With Pulmonary Hypertension*

<table>
<thead>
<tr>
<th></th>
<th>Mean Arterial Pressure, mm Hg</th>
<th>Mean Right Atrial Pressure, mm Hg</th>
<th>Mean Pulmonary Artery Pressure, mm Hg</th>
<th>Mean Pulmonary Capillary Wedge Pressure, mm Hg</th>
<th>Cardiac Output, L/min</th>
<th>Vascular Resistance, U</th>
<th>Arterial Oxygen Saturation at Rest</th>
<th>Exercise Time, s</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 58)</td>
<td></td>
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<tr>
<td>PFO</td>
<td>97 ± 17</td>
<td>9 ± 6</td>
<td>54 ± 11</td>
<td>6 ± 2</td>
<td>4.0 ± 1.3</td>
<td>13.6 ± 6.8</td>
<td>25 ± 10</td>
<td>311 ± 211</td>
</tr>
<tr>
<td>No PFO</td>
<td>95 ± 14</td>
<td>10 ± 6</td>
<td>55 ± 18</td>
<td>9 ± 4</td>
<td>4.5 ± 1.6</td>
<td>11.2 ± 6.5</td>
<td>21 ± 8</td>
<td>367 ± 246</td>
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<td>PPH patients (n = 40)</td>
<td></td>
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<tr>
<td>PFO</td>
<td>97 ± 19</td>
<td>9 ± 6</td>
<td>57 ± 8</td>
<td>6 ± 2</td>
<td>4.0 ± 1.1</td>
<td>14.0 ± 4.4</td>
<td>24 ± 9</td>
<td>318 ± 210</td>
</tr>
<tr>
<td>No PFO</td>
<td>96 ± 12</td>
<td>10 ± 7</td>
<td>57 ± 16</td>
<td>8 ± 3</td>
<td>3.9 ± 1.4</td>
<td>14.0 ± 6.6</td>
<td>24 ± 7</td>
<td>380 ± 258</td>
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<tr>
<td>Secondary pulmonary hypertension patients (n = 18)</td>
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<td></td>
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<tr>
<td>PFO</td>
<td>93 ± 5</td>
<td>12 ± 6</td>
<td>48 ± 10</td>
<td>8 ± 2</td>
<td>4.0 ± 1.3</td>
<td>13.0 ± 8.5</td>
<td>24 ± 11</td>
<td>178 ± 765</td>
</tr>
<tr>
<td>No PFO</td>
<td>90 ± 14</td>
<td>10 ± 6</td>
<td>50 ± 14</td>
<td>11 ± 5</td>
<td>5.0 ± 1.7</td>
<td>9.0 ± 4.5</td>
<td>18 ± 7</td>
<td>310 ± 134</td>
</tr>
</tbody>
</table>

*All values are mean ± SD.

Statistical Analysis

Mean ± SD was calculated for all variables measured. Hemodynamic parameters and exercise times were compared using the Student's t test for nonpaired data. Separate evaluations were made for the total group, the PPH patients, the secondary pulmonary hypertension patients, and the subsets with and without a PFO. Mean estimated survival was also compared, using the nonpaired Student's t test, in the patients with PPH.

RESULTS

A PFO was present in 26 percent (15 of 58) of all patients studied, 25 percent (10 of 40) of the patients with PPH, and in 28 percent (5 of 18) of the patients with secondary pulmonary hypertension.

Hemodynamics, resting arterial oxygen saturation levels with patients breathing room air, and exercise times for the groups with and without a PFO are given in Table 1. The patients studied had severe pulmonary hypertension with a mean pulmonary artery pressure of 55 ± 15 mm Hg, pulmonary vascular resistance of 13 ± 7 units, and right atrial pressure of 10 ± 6 mm Hg. Pulmonary capillary wedge pressure, mean systemic arterial pressure, systemic vascular resistance, and cardiac output values were in the normal range. Arterial oxygen saturation values were mildly decreased (88 ± 8 percent), while exercise times were reduced (335 ± 227 s). There was no statistically significant difference in any hemodynamic variable between the patients with and without a PFO or for subsets of patients with primary and secondary pulmonary hypertension.

No significant difference was found in the 1-, 2-, 3-, 4-, or 5-year mean survival estimates, for the 40 patients with PPH, between the patients with and without a PFO (Table 2).

DISCUSSION

A PFO has been reported in 25 to 35 percent of normal patients at autopsy. Several retrospective studies have reported a prevalence from 12 to 31 percent in patients with PPH, 1,6,7 The methods of detection, however, include right-sided heart catheterization and transthoracic echocardiography which, due to technical limitations, tend to underreport the actual prevalence. Recently, contrast transesophageal echocardiography was reported to be possibly the most sensitive and specific test for detecting a PFO in patients with cardiovascular disease. In the current study, this method was used to document the prevalence of a PFO of 26 percent for all patients with pulmonary hypertension, 25 percent for the group with PPH, and 28 percent for the group with secondary pulmonary hypertension. These findings suggest that the prevalence of a PFO, even in the face of severe pulmonary hypertension, is no greater than that found in normal patients at autopsy. The presence of a PFO and the existence of pulmonary hypertension, therefore, appear to be unrelated.

It has been observed early in the surgical literature that patients with congenital heart defects and Eisenmenger's syndrome often deteriorate following surgical repair of the intracardiac shunt. This led to the perception that a right-to-left intracardiac shunt may be protective, or beneficial, in patients with pulmonary hypertension. This was further supported by Austin et al who showed that the creation of a right-to-left intracardiac shunt with an atrial septal defect.
in dogs with experimental right ventricular hypertension resulted in an increase in systemic blood flow and improvement in exercise tolerance. Clinical benefit from right-to-left intracardiac shunting also has been suggested by observations that patients with Eisenmenger’s syndrome may live longer than similar patients with PPH.8 Most recently, the creation of a right-to-left intracardiac shunt by atrial septostomy in patients with severe pulmonary hypertension has been described to provide symptomatic improvement in these patients.9-13

Whether or not right-to-left intracardiac shunting is of benefit in patients with pulmonary hypertension, however, has not been tested in a controlled, prospective trial. Although a PFO has been reported to be associated with a longer survival in one study of patients with PPH,1 the two other studies found no difference in survival in patients with and without a PFO.6-7 In the current study, we found no significant difference in baseline hemodynamics, including cardiac output or exercise tolerance in the patients with a PFO. This suggests that a PFO does not provide substantial right-to-left intracardiac shunting in these patients. Although we were unable to evaluate the significance of a PFO on survival directly, we used a mathematical model of survival estimates for patients with PPH6 to test whether or not any impact on survival might be expected. However, we found no significant difference in estimated survival between the patients with and without a PFO.

In summary, the prevalence of a PFO in pulmonary hypertension is similar to that in normal subjects. A PFO does not appear to influence resting hemodynamics or exercise tolerance in these patients and should not be considered equivalent to an underlying congenital shunt or atrial septostomy. A PFO is also not clearly associated with patients expected to survive longer. Whether right-to-left intracardiac shunting through an atrial septostomy will improve survival in patients with pulmonary hypertension needs to be tested in a prospective fashion.

**APPENDIX**

A proportional hazards model is used to predict survival of primary pulmonary hypertension (PPH) patients. The probability of a given PPH patient surviving past t years, given hemodynamic variables collected at baseline, is

\[ P_0(t;x,y,z) = [H(t)]^{A(x,y,z)}, \]

where

\[ H(t) = 0.88 - 0.14t + 0.01t^2, \]

\[ A(x,y,z) = e^{0.0072x} \cdot 0.608y \cdot 0.0275z, \]

t ranges from one to five years, and the hemodynamic variables are x = mean pulmonary artery pressure, y = mean right atrial pressure, and z = cardiac index.

**REFERENCES**

8 Young D, Mark H. Fate of the patient with the Eisenmenger syndrome. Am J Cardiol 1971; 28:658-69