Right Ventricular Ischemia in Patients With Primary Pulmonary Hypertension

Arturo Gómez, MD,* David Bialostozky, MD,† Alan Zajarias, MD,* Efrén Santos, MD,* Andrés Palomar, MD,* María Luisa Martínez, MD,* Julio Sandoval, MD*

Mexico City, Mexico

OBJECTIVES
The goal of this study was to determine whether right ventricular (RV) ischemia is a contributory factor in the development of RV dysfunction in patients with primary pulmonary hypertension (PPH).

BACKGROUND
Patients with advanced PPH develop RV dysfunction, characterized by a decreased cardiac output, increased right atrial pressure (RAP) and/or elevated RV end-diastolic pressure, which progresses to heart failure and death. The cause of this dysfunction is unknown. Right ventricular ischemia may play a role in its development.

METHODS
From 1992 to 1999, a prospective study involving 23 patients with PPH at the Instituto Nacional de Cardiología “Ignacio Chávez” (Mexico City, Mexico) was undertaken. These patients were evaluated clinically and further studied by echocardiography, right heart catheterization and stress myocardial scintigraphy using technetium 99m sestamibi.

RESULTS
Nine patients of 23 were found to have scintigraphic images consistent with RV ischemia. Significant correlation was found between RV ischemia obtained through myocardial perfusion scintigraphy and elevation of RV end-diastolic pressure (p < 0.001), elevation of RAP (p < 0.037) and a decrease in mixed venous oxygen saturation (p < 0.0001). No other clinical or hemodynamic variables showed a significant correlation with RV ischemia.

CONCLUSIONS
A direct correlation exists between RV ischemia, as determined by myocardial scintigraphy, and hemodynamic alterations suggestive of RV dysfunction in patients with PPH. (J Am Coll Cardiol 2001;38:1137–42) © 2001 by the American College of Cardiology

Primary pulmonary hypertension (PPH) is a disease of unknown etiology and poor prognosis. Platelet (1), endothelial (2) and K⁺ channel (3) dysfunction, as well as alterations in the prostaglandin metabolism (4) have been suggested as probable causes of this disease, but there is still no consensus on its etiology. Patients with end stage PPH develop progressive right ventricular (RV) dysfunction, characterized by a hemodynamic pattern of decreased cardiac output and increased right atrial pressure (RAP) and/or RV end-diastolic pressure (RVEDP) (5,6) leading to heart failure and death. These hemodynamic parameters can be used to predict the probability of survival after diagnosis (6,7).

Attempts to explain the cause of RV dysfunction have yielded at least three hypotheses. First, a genetic predisposition based on angiotensin-converting enzyme isotypes may play a permissive role in the development of RV hypertrophy or failure as a result of pulmonary hypertension (8). Second, excessive adrenergic stimulation, as seen in heart failure, downregulates beta-adrenergic receptor expression and may impair RV function (9–13). Third, myocardial ischemia, a known cause of ventricular dysfunction, may also be involved in this process.

Myocardial scintigraphy utilizing thallium 201 (²⁰¹TI) or technetium 99m (⁹⁹ᵐTc) sestamibi is an instrument readily available for the evaluation of myocardial perfusion. Detection of RV ischemia using nuclear imaging has recently been validated (14,15). In the general population, the size and width of the RV walls limit this technique’s usefulness. In patients with PPH, chronic exposure to pressure overload induces RV hypertrophy, increases radiotracer uptake and enhances its visualization when using myocardial scintigraphy (16). This study’s objectives are: 1) to evaluate the presence of RV ischemia using myocardial scintigraphy in patients with PPH; and 2) to analyze the association between ischemia and RV dysfunction in this patient population.

METHODS
A prospective study starting in September 1992 and ending in September 1999 in the Cardiopulmonary and Nuclear Cardiology Departments of the Instituto Nacional de Cardiología “Ignacio Chávez” (Mexico City, Mexico) was undertaken. Twenty-three incident cases of PPH, with a median age of 23 years, were included. Patients were Hispanic in origin and predominantly women, with a female-to-male ratio of 3.6:1. The diagnosis of PPH was considered for all patients that fulfilled the diagnostic criteria (5) consisting of: elevation of the mean resting pulmonary arterial pressure >22 mm Hg, pulmonary capillary wedge pressure within normal limits (when measurable) and absence of any concomitant disease known to cause or be associated with elevation of the mean pulmonary arterial pressure. These patients were scrutinized with a
diagnostic evaluation, which included a clinical history and physical examination, chest X-ray, 12-lead electrocardiogram with leads v3r and v4r, complete blood count, erythrocyte sedimentation rate, immunological workup, pulmonary function tests, ventilation/perfusion lung scan, right heart catheterization, myocardial scintigraphy and two-dimensional echocardiography. Patients over 40 years of age underwent coronary angiography to rule out the presence of epicardial coronary artery disease. All the procedures were approved by the ethics committee at our institution and were practiced after receiving their written consent.

Patients were excluded if they presented: an abnormal coronary angiography; congenital, acquired valvular or myocardial disease; chronic thromboembolic pulmonary hypertension; obstructive or restrictive lung disease; parasitic involvement of the lungs; cirrhosis; collagen vascular disease; or antiphospholipid syndrome.

**Echocardiography.** Patients underwent transthoracic echocardiographic evaluation using Hewlett Packard Sonos 1000, 1500 and 5500 machines and 3.5 MHz transducers to obtain conventional measurements of left atrial, aortic and left ventricular (LV) dimensions; atrial and ventricular septum integrity; and LV ejection fraction. Right ventricular diastolic free wall width, diastolic RV dimensions and RV wall motion were measured and graded (17). Doppler interrogation was used to quantify the pulmonary arterial pressure determined by the grade of tricuspid insufficiency and tricuspid pressure gradient (18). If the integrity of the interventricular or interatrial septum was in doubt, the study was complemented with a contrast transesophageal echocardiogram.

**Hemodynamic measurements.** The RAP, RV and pulmonary variables were measured by right heart catheterization (19,20). Brachial artery cannulation was performed for blood sampling and systemic pressure measurement. Cardiac output was calculated in triplicate by thermodilution. The data was interpreted independent of knowledge of the myocardial scintigraphy and echocardiographic findings.

**Nuclear cardiology.** Myocardial scintigraphy was performed on each patient. Single photon emission computed tomography (SPECT) or gated SPECT (GSPECT) myocardial perfusion imaging studies were obtained from 1992 to 1996 and 1997 to 1999, respectively. Stress was induced by a symptom-limited exercise test using the multistage modified Bruce (21) or Balke (22) protocol aimed to achieve ≥85% of the maximal predicted heart rate. Exercise end points included physical exhaustion, severe angina, sustained ventricular tachycardia, hemodynamically significant supraventricular arrhythmias or significant exertional hypotension. In patients with decreased exertional capacity, a 0.5 mg/kg intravenous dipyridamole 5 min infusion was used to induce pharmacologic stress.

**SPECT.** Single photon emission computed tomography images using $^{99}$Tc sestamibi were gathered in 23 patients (including 13 GSPECT) with a Siemens Orbiter 2000 gamma camera and an Icon A/P processing system utilizing the Cedars-Sinai Quantitative Gated SPECT program (23). A one-day protocol with $^{99}$Tc sestamibi was used (24). Single photon emission computed tomography acquisitions employed a large field gamma camera view and a low-energy, high-resolution collimator to obtain 32 projections at 30 s per projection over a semicircular arc.

Right ventricular SPECT was independently studied after a modification of De Puey’s technique (14,25) and included post-stress GSPECT imaging (23). A classical short-axis reconstruction of the LV was performed in each patient. From this view, the RV was isolated and manually delineated to define the lateral, anterior and inferior RV wall at the middle and basal third of the short axis (Fig. 1). When subdiaphragmatic radiotracer activity did not permit adequate definition of the inferior wall, the patient was not included in the analysis. The LV, left hemithorax and abdominal background activity were masked, and the radioisotope counts were maximized over the RV walls at rest and during stress.

Right ventricular perfusion was scored by the consensus of three observers (D.B., A.G., E.S.) using a 5 point scoring system: 0 = normal uptake, 1 = equivocal, 2 = moderate reduction of radioisotope uptake, 3 = severe reduction of radioisotope uptake, 4 = absence of detectable radiotracer in a segment. The comparison of the RV perfusion images at rest and during stress was the basis of the diagnosis of ischemia, infarct and reverse-reversibility using the same criteria as images of the LV. No attenuation program was used. Patients were defined as having RV ischemia if all three observers concurred on the visualization of perfusion defects. The physicians interpreting the scintigraphy did not have access to the results of the right heart catheterization, echocardiographic findings and medical history.

To evaluate the RV size confidently, an RV size index was developed by measuring the maximal RV diameter × 100/maximal heart diameter (Fig. 1). The dimensions were taken from the short-axis view of the scintigraphy. It was scored as the following: “0” (size index <10%); mild dilation, “1” (size index 11% to 20%); moderate dilation, “2” (size index 21% to 30%); severe dilation, “3” (size index >30%).
Statistical analysis. The data were analyzed with descriptive statistics (median [50th percentile], 25th and 75th percentiles) and univariate analysis using Mann-Whitney U test because the sample did not have a normal distribution. Dichotomous nominal variables were analyzed with chi-square test. Statistical analysis was performed using the computer packages SPSS (SPSS, Inc., Chicago, Illinois). All clinical and hemodynamic variables were considered to be statistically significant with a $p < 0.05$.

Intra-observer variability was measured by the Kappa test. Interpreters re-evaluated the SPECT images three days after the original reading, unaware of their initial impression, obtaining a kappa of 0.95. Inter-observer variability was calculated as: 1 versus 2 = 0.90, 2 versus 3 = 0.80 and 1 versus 3 = 0.84.

RESULTS

Cardiac perfusion imaging. All patients had a myocardial scintigraphy with $^{99m}$Tc sestamibi. All of the patients had SPECT, and GSPECT was used to evaluate 13 of them. Stress was induced by exercise in four patients and by dipyridamole in 19 patients. The RV walls of all patients were adequately delineated. Patients were characterized into two groups based on the results of the scans. Group 1 (nonischemic) consisted of 14 patients, and group 2 (ischemic) consisted of nine patients (Fig. 1 and 2).

In group 2, dipyridamole was used to cause stress in all the patients. Ischemia was found in the lateral (four patients), inferior (seven patients) and anterior (two patients) RV walls. Simultaneous ischemia in two RV walls was evident in four patients. No fixed perfusion defects were detected in our patients.

Findings common to both groups included leftward septal deviation, a relatively small LV and moderate-to-severe RV dilation (size index from 23% to 69%). Right ventricular hypertrophy was evident in all of the patients, regardless of the presence of ischemia. Hypokinesis of the RV walls was found in all patients in group 2 and two of the patients in group 1.

Correlations between RV ischemia and other clinical parameters. The most common presenting symptom was dyspnea (93% vs. 95% in groups 1 and 2, respectively), followed by the presence of palpitations (71% vs. 78%). Forty-three percent of the patients complained of angina or its equivalent (29% vs. 67% in groups 1 and 2, respectively [$p = 0.07$]). Clinical signs of right heart failure (edema, hepatomegaly and elevated jugular pressure) were present in both groups. There was a greater tendency for patients with New York Heart Association (NYHA) class III/IV to be found in group 2 (21.4% vs. 44.4% [$p = 0.23$]).

None of the changes noted in the electrocardiogram or pulmonary function tests correlated with the presence or absence of RV ischemia.

Hemodynamic parameters. The right side cardiac catheterization results are presented in Table 1. Median RAP (4.8 mm Hg vs. 8 mm Hg [$p < 0.037$]) and RVEDP (6.95 mm Hg vs. 12.6 mm Hg [$p < 0.001$]) in group 2 were elevated when compared with group 1. Patients with RV ischemia had lower mixed venous oxygen saturation when compared with those obtained in the nonischemic group (65% vs. 48% [$p = 0.001$]). No significant differences were found while analyzing the systolic RV pressure, cardiac index, mean pulmonary arterial pressure and arterial $O_2$ saturation.

Echocardiography. There were no differences noted between the RV free wall widths and RV diastolic diameters between the groups (Table 1).

DISCUSSION

The natural history of PPH is characterized by a relatively silent progression until RV dysfunction develops. This is clinically manifested by dyspnea of increasing severity and other physiologic effects resulting from low cardiac output such as syncope and seizures (6,7,26). From this stage on,
patients progressively deteriorate until death ensues. The cause of RV dysfunction in these patients has not been clearly established, and its detection relies on indirect methods limited to invasive hemodynamic measurements or exercise tolerance. This study shows that ischemia is associated with the presence of RV dysfunction.

Myocardial scintigraphy. Radiotracers such as $^{210}$Tl and $^{99m}$Tc sestamibi have a myocardial distribution proportional to coronary blood flow. Right ventricular visualization has a direct correlation with systolic pulmonary arterial pressure (27). Chronic pressure overload, as occurs in patients with PPH, generates compensatory RV wall hypertrophy and an

### Table 1. Hemodynamic and Echocardiographic Parameters of Patients With PPH

<table>
<thead>
<tr>
<th>Category</th>
<th>No Ischemia (14 Patients)</th>
<th>Ischemia (9 Patients)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate ($\times$ min)</td>
<td>80</td>
<td>81</td>
<td>NS</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>4.8 (3, 7.5)</td>
<td>8 (7.05, 12.85)</td>
<td>0.037*</td>
</tr>
<tr>
<td>RV systolic pressure (mm Hg)</td>
<td>95.4</td>
<td>90</td>
<td>NS</td>
</tr>
<tr>
<td>RVEDP (mm Hg)</td>
<td>6.95 (4, 10.7)</td>
<td>12.6 (11, 20)</td>
<td>0.001*</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
<td>64</td>
<td>56</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>2.5</td>
<td>2.14</td>
<td>NS</td>
</tr>
<tr>
<td>Venous $O_2$ saturation (%)</td>
<td>65 (59, 65)</td>
<td>48 (40, 56)</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Arterial $O_2$ saturation (%)</td>
<td>92.6</td>
<td>88.6</td>
<td>NS</td>
</tr>
<tr>
<td>$PaCO_2$ (mm Hg)</td>
<td>27</td>
<td>26.9</td>
<td>NS</td>
</tr>
<tr>
<td>PASP (mm Hg)</td>
<td>80.5</td>
<td>95</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>63.5</td>
<td>62</td>
<td>NS</td>
</tr>
<tr>
<td>RV free wall width (cm)</td>
<td>0.878</td>
<td>1.01</td>
<td>NS</td>
</tr>
<tr>
<td>RV diastolic diameter (cm)</td>
<td>5.25</td>
<td>5.23</td>
<td>NS</td>
</tr>
</tbody>
</table>

*pStatistically significant results. Results are expressed as medians, 25th and 75th percentiles and are added in parenthesis only if the results were statistically significant.

LVEF = left ventricle ejection fraction; MPAP = mean pulmonary artery pressure; $PaCO_2$ = arterial carbon dioxide partial pressure; PASP = pulmonary artery systolic pressure; RVEDP = right ventricle end-diastolic pressure.
increase in coronary blood flow. This augments the uptake of the radiotracer permitting a complete visualization of this region of the heart. In our series, the median pulmonary artery systolic pressure was 99.25 mm Hg, which permitted an adequate observation of the RV perfusion in all of our patients.

We observed myocardial uptake defects in nine patients using SPECT. These findings suggest that there is a point in the natural history of PPH when some patients develop RV ischemia that may be detected by myocardial scintigraphy. It is conceivable that the alteration in RV perfusion modifies the relaxation capacity of the heart, which may be manifested as an elevation of the RVEDP (6.95 mm Hg [group 1] vs. 12.6 mm Hg [group 2] \( p < 0.001 \)). However, the converse may also be true: elevation of the RVEDP produces RV ischemia. Further impairment of RV function will progressively elevate the RAP as shown in our data (4.8 mm Hg [group 1] vs. 8 mm Hg [group 2] \( p < 0.037 \)) and may be manifested clinically by a worsening NYHA classification. This hemodynamic pattern of RAP \( \approx 5 \) mm Hg (odds ratio [OR]: 8.75, confidence interval [CI]: 95% 1.24 to 61) and RVEDP \( \approx 9 \) mm Hg (OR: 12.83 [CI: 95% 1.69 to 97]) may be used to predict the presence of RV ischemia.

**Postulated origin of ischemia.** Hypoxemia or myocardial hypertrophy cannot explain the cause of RVEDP elevation, because no differences were noted in the groups observed. The possibility that cardiac ischemia resulting from coronary artery disease leads to an increase in the RVEDP exists. Major coronary artery anomalies were excluded by the presence of a normal coronary angiography, but do not discard anomalies in the RV microcirculation. Chronic pressure overload generates myocardial wall hypertrophy in order to overcome the systolic pressure in the outgoing vessel. In the presence of severe RV systolic hypertension, transmural and coronary perfusion pressures increase accordingly. This phenomenon limits RV coronary blood flow to diastole only. Compensatory epicardial arterial enlargement occurs but is not proportional to wall hypertrophy (28) nor is it observed at a capillary level (29), making the muscle fibers more susceptible to ischemia. In animal models, Murray and Vanter (30) have demonstrated that the subendocardial to subepicardial blood flow ratio is diminished at rest and after the injection of adenosine. This generates a loss of coronary reserve due to an increase in the basal blood flow, making the RV more susceptible to ischemia.

Although subendocardial ischemia secondary to wall hypertrophy may not be the principal cause, we cannot exclude its possible role, because the hypertrophied heart increases its metabolic demands and ventricular dilatation increases wall stress (Law of Laplace). Other studies are needed to clarify the mechanism responsible for the production of RV ischemia.

**Decrease in mixed venous oxygen saturation.** The decrease in the mixed venous oxygen saturation may reflect a low cardiac output found in the patients with ischemia. Cardiac output was measured by thermodilution allowing erroneous determinations intrinsic to the method and secondary to severe tricuspid regurgitation. Resting oxygen uptake was determined at a time different from the right heart catheterization, permitting differences in the results obtained in oxygen uptake and other hemodynamic measurements. Thus, it may be possible that the mixed venous oxygen saturation was the only measurement that detected a low cardiac output.

**Conclusions.** The presence of RV perfusion abnormalities in patients with severe PPH can be identified by myocardial scintigraphy. A direct correlation exists between the presence of images suggestive of RV ischemia obtained by myocardial scintigraphy and RV dysfunction in patients with PPH. Right ventricular ischemia is a factor associated with RV dysfunction in patients with this disease.

**Reprint requests and correspondence:** Dr. Alan Zajarias, Medicine Clinic South, 90-21-342, 4950 Children’s Place, St. Louis, Missouri 63110.

**REFERENCES**

1. Rubin L. Pathology and pathophysiology of primary pulmonary hypertension. Am J Cardiol 1995;75:51A–4A.