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Exaggerated Pulmonary Hypertensive Responses During Chronic Hypoxia in Mice With Gene-Targeted Reductions in Atrial Natriuretic Peptide*

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(CHEST 1998; 114:798-808)

To test the hypothesis that atrial natriuretic peptide (ANP) plays a physiologic role in blunting the development of hypoxic pulmonary hypertension, we measured cardiac hypertrophic and pulmonary hypertensive responses in hypoxia-adapted mice genetically altered to produce normal or decreased ANP expression. Mice were targeted to interrupt exon 2 of the proa'nuclear factor gene. Southern blot analysis of the offspring of heterozygous breeding pairs identified mice that were homozygous for the wild-type ANP gene, heterozygous, or homozygous for the mutated ANP gene in a 1:2:1 ratio, consistent with Mendelian distribution. Mice homozygous for the mutated ANP gene had RA ANP levels that were at least 20-fold lower than the rest of their littermates and were referred to as ANP deficient. Homozygous wild-type and heterozygous mice had similar RA ANP levels and were considered ANP sufficient. After 2 weeks of normoxia or hypobaric (0.5 atm) hypoxia, we measured body weight, hematocrit, right ventricular weight, left ventricle plus septum weight, and right ventricular peak pressure. The results are shown in Table 1.

We conclude that ANP deficient mice have larger hearts and higher right ventricle peak pressure during normoxia and develop more severe pulmonary hypertension during hypoxia than ANP sufficient mice. These findings suggest that ANP plays a physiologic role in modulating pulmonary vascular tone and cardiac hypertrophy under both normoxic and chronically hypoxic conditions.

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Treatment of Severe Pulmonary Hypertension Secondary to Connective Tissue Diseases With Continuous IV Epoprostenol (Prostacyclin)*

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(ECHST 1998; 114:808-828)

Epoprostenol (prostaglandin I₂, prostacyclin) is a potent vasodilator and inhibitor of platelet aggregation produced by vascular endothelium. Epoprostenol reduces pulmonary vascular resistance and increases cardiac output and oxygen delivery when administered acutely to patients with primary pulmonary hypertension (PPH). Moreover continuous IV epoprostenol produces substantial and sustained hemodynamic and symptomatic responses as well as improves survival in severe PPH refractory to conventional medical therapy.1-4 Pulmonary hypertension is an uncommon but well-recognized complication of connective tissue diseases (CTDs), such as scleroderma, mixed connective tissue disease, systemic lupus erythematosus, dermatomyositis, rheumatoid arthritis, and primary Sjögren’s disease.5-10 In CTD, the cause of vascular involvement is unknown, pathologic changes are often those of plexogenic arteriopathy similar to those observed in PPH, exercise capacity is greatly affected, and the prognosis of pulmonary hypertension is poor with a frequent lethal outcome.5 We have therefore attempted to evaluate the effects of the continuous IV infusion of epoprostenol on exercise capacity and hemodynamics in patients with severe pulmonary hypertension secondary to CTD who continued to be in New York Heart Association (NYHA) functional class III or IV despite conventional therapy, which consisted of the administration of oral anticoagulants, diuretics, and supplemental oxygen.

**Materials and Methods**

Twelve patients with severe pulmonary hypertension secondary to systemic lupus erythematosus (n=4), systemic sclerosis (n=4), mixed CTD (n=3), and primary Sjögren’s syndrome (n=1) entered this study. The diagnosis of pulmonary hypertension was established by right heart catheterization. Secondary causes of pulmonary hypertension other than CTD were eliminated by perfusion lung scanning and/or pulmonary angiography, lung function testing, and echocardiography. Patients were in NYHA functional class III or IV despite optimal medical therapy, which consisted of the administration of oral anticoagulants, diuretics, and supplemental oxygen. All patients were referred to our center because they were either unresponsive or could not tolerate the vasodilators commonly used to treat the disease.

All the patients received continuous infusion of epoprostenol (Flolan) at doses based on clinical signs and symptoms of pulmonary hypertension. All the patients also received oral anticoagulants in doses adjusted to achieve an international normalized ratio of approximately 2.0. Adjustments in concomitant medications were allowed during the study on the basis of clinical judgment. Venous access for the infusion of epoprostenol was obtained by the insertion of a permanent catheter into a subclavian vein. Epoprostenol was infused continuously with the use of a portable infusion pump (Graseby Medical Ltd, Watford, UK). Before being discharged from the hospital, patients were trained in sterile technique, catheter care, and drug preparation and administration. Epoprostenol therapy was initiated at a dose ranging from 8 to 16 ng/kg/min (11±1 ng/kg/min). All patients were evaluated 6 weeks after initiation of continuous IV epoprostenol.

Right heart catheterization was done on all patients using standard techniques. Mean right atrial pressure, mean pulmonary artery pressure (mPAP), mean pulmonary capillary wedge pressure, cardiac index (CI), mixed venous oxygen saturation (SvO₂), and pulmonary vascular resistance (PVR) were measured at baseline, and at 6 weeks after initiation of continuous IV epoprostenol in all patients. Exercise capacity was assessed in parallel at baseline and during each scheduled visit with the use of the unencouraged 6-min walk test. Patients who were unable to walk were assigned a value of 0 m.

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**Table 1—Results of Experiment**

<table>
<thead>
<tr>
<th></th>
<th>Normoxic (n=35)</th>
<th>Hyponic (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ANP sufficient</td>
<td>ANP deficient</td>
</tr>
<tr>
<td>Body weight, g</td>
<td>25±1</td>
<td>27±2</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>38±1</td>
<td>38±2</td>
</tr>
<tr>
<td>Right ventricular weight/body weight, mg/g</td>
<td>0.8±0.01</td>
<td>1.2±0.08*</td>
</tr>
<tr>
<td>Left ventricular weight+septum/body weight, mg/g</td>
<td>3.3±0.1</td>
<td>4.7±0.4*</td>
</tr>
<tr>
<td>Right ventricular weight/left ventricular weight+septum, mg/g</td>
<td>0.25±0.01</td>
<td>0.26±0.02*</td>
</tr>
<tr>
<td>Right ventricular peak pressure, mm Hg</td>
<td>17±1</td>
<td>22±2</td>
</tr>
</tbody>
</table>

*All data are given as mean±SE.

†p<0.05, in comparison with ANP sufficient group.

‡p<0.05, in comparison with normoxic control group.