Table 1—Results of DMA Inhibition of Hypoxic Pulmonary Hypertension*

<table>
<thead>
<tr>
<th></th>
<th>Hypoxia-</th>
<th>Hypoxia-</th>
<th>Normoxia-</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DMA</td>
<td>Control</td>
<td>Control</td>
</tr>
<tr>
<td>Ppa (mm Hg)</td>
<td>26.0 ± 1.7&lt;sup&gt;11&lt;/sup&gt;</td>
<td>39.0 ± 1.9&lt;sup&gt;1&lt;/sup&gt;</td>
<td>17.0 ± 0.5&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>CI (mL/min/kg)</td>
<td>483 ± 27</td>
<td>453 ± 28</td>
<td>426 ± 39 &lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>TPVRI (mm Hg/mL/min/kg)</td>
<td>0.0541 ± 0.005&lt;sup&gt;11&lt;/sup&gt;</td>
<td>0.0874 ± 0.006&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.0425 ± 0.0275&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>RV/LV+S, %</td>
<td>38.7 ± 1.7&lt;sup&gt;11&lt;/sup&gt;</td>
<td>45.2 ± 2.4&lt;sup&gt;1&lt;/sup&gt;</td>
<td>22.3 ± 1.2&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>58 ± 1&lt;sup&gt;1&lt;/sup&gt;</td>
<td>59 ± 1&lt;sup&gt;1&lt;/sup&gt;</td>
<td>42 ± 1&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Wall thickness, %</td>
<td>5 ± 0.4</td>
<td>6 ± 0.3&lt;sup&gt;1&lt;/sup&gt;</td>
<td>4 ± 0.2&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Thick vessels, %</td>
<td>38 ± 5</td>
<td>48 ± 5&lt;sup&gt;1&lt;/sup&gt;</td>
<td>26 ± 4&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*All data are shown as mean±SE. Ppa=pulmonary-arterial pressure; CI=cardiac index; TPVRI=total pulmonary vascular resistance index (Ppa/CI); RV/LV+S=right ventricle/left ventricle+septum; wall thickness refers to the terminal bronchiule; and thick vessels refers to intra-acinar vessels. 
<sup>1</sup>p<0.05, in comparison with normoxia-control group. 
<sup>1</sup>p<0.05, in comparison with hypoxia-control group.

of hypoxic pulmonary hypertension by interfering with PASMC growth. Sprague-Dawley rats were exposed to 10.5% O₂ for 14 days and were divided into three groups: hypoxia-DMA (n=14, receiving DMA 3 mg/kg/day for 14 days intravenously through osmotic minipump), hypoxia-control (n=10), and normoxia-control (n=6). At the end of the DMA or saline treatment, hemodynamics, blood gas, and hematocrit were measured in anesthetized animals breathing room air to reverse any acute hypoxic vasoconstriction (Table 1).

In conclusion, in spite of the hypertensive effects of polycythemia, DMA can significantly reduce pulmonary hypertension, right ventricular hypertrophy, and vascular remodeling induced by chronic hypoxia.

The Effect of Inhaled Nitric Oxide on 6-Minute Walk Distance in Patients With Pulmonary Hypertension*

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(CHEST 1998; 114:70S-72S)

Both primary pulmonary hypertension (PPH) and secondary pulmonary hypertension (SPH) have been shown to respond to vasodilator therapy.¹⁻³ In selected patients identified by pulmonary vascular reactivity to an oral calcium-channel blocker challenge, treatment of PPH with high-dose calcium-channel blockers has been demonstrated to prolong survival and lead to regression of right ventricular hypertrophy.⁴ Subsequently, drugs more selective for the pulmonary vasculature, including prostacyclin, adenosine, and inhaled nitric oxide (INO) have been used to identify patients with a reactive pulmonary vascular bed,⁵ the presence of which has been shown to be of prognostic significance.⁶However, such identification requires the invasive procedure of pulmonary artery catheterization.

INO may selectively dilate the pulmonary arteries, reduce pulmonary vascular resistance (PVR), and improve exercise capacity in individuals with pulmonary hypertension (PH) where vasoconstriction contributes to elevated pulmonary artery pressure (PAP). We considered the possibility that if exercise in patients with PH was limited by increased PVR, and if INO exerted its effect by reducing PVR, then demonstration of an improvement in exercise capacity while breathing INO would be a simple noninvasive method for detecting patients with reversible pulmonary vasoconstriction. We therefore undertook a pilot study to assess the value of the 6-min walk distance as a sensitive marker of pulmonary vascular reactivity to INO. The 6-min walk distance has been shown previously to increase in patients with PPH treated with long-term continuous IV prostacyclin.⁷ We conducted a randomized double-blind controlled trial of INO in patients with PPH and SPH, and measured the effects on 6-min walk distance, degree of dyspnea, and PAP measured by echo-Doppler.

Materials and Methods

Patients aged 16 to 75 years with known or suspected PH were invited to participate in the study approved by the institutional ethics committee. Direct measurement of PAP at right heart catheterization or indirect measurement of PAP by echo-Doppler assessment of a tricuspid regurgitant (TR) jet was performed prior to the study to confirm PH. Patients with any impairment to walking other than known cardiopulmonary disease were excluded. All patients underwent lung function testing, including flow-volume loops, lung volumes, and the sprint maneuver to determine maximum voluntary ventilation (all tests using a Gould body plethysmograph). Five of the six patients had arterial blood gas analysis.

Patients attended testing on two separate days. Day 1 included lung function testing and three familiarization 6-min walks on the treadmill. Day 2 involved one familiarization walk and the two randomized study walks. Thus, each patient had four familiarization walks to minimize any learning effect and to determine an appropriate initial treadmill speed. The treadmill was operated by the patients, who could increase or decrease the speed, or stop and restart the treadmill if they desired. The patients were instructed "to walk as far as you can in the time given." On the third familiarization walk, maximum ventilation was measured to determine the likelihood of any ventilatory limitation to exercise.

The following measurements were made during the two study walks: distance walked, measured electronically by the treadmill; breathlessness score, recorded every 30 s by the subject on an electronic visual analog scale; pulmonary artery pressure estimation (by echo-Doppler measurement of the TR jet) before commencing on the breathing circuit, at rest on the circuit, and immediately after completion of exercise (peak exercise) while...
### Table 1—Results

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>First Trial Gas</th>
<th>Room Distance Walked, m</th>
<th>Systolic PAP at Peak Exercise, mm Hg</th>
<th>Total VAS Dyspnea Score (Scale=0-120)</th>
<th>SaO₂ at Peak Exercise (SaO₂%)</th>
<th>Rate-Pressure Product, U</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Room Air</td>
<td>INO</td>
<td>Room Air</td>
<td>INO</td>
<td>Room Air</td>
<td>INO</td>
</tr>
<tr>
<td>1</td>
<td>RA</td>
<td>340</td>
<td>350</td>
<td>No TR</td>
<td>No TR</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>INO</td>
<td>850</td>
<td>800</td>
<td>No TR</td>
<td>No TR</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>INO</td>
<td>400</td>
<td>390</td>
<td>95</td>
<td>90</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>INO</td>
<td>550</td>
<td>550</td>
<td>80</td>
<td>90</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>INO</td>
<td>400</td>
<td>400</td>
<td>90</td>
<td>72</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>INO</td>
<td>720</td>
<td>750</td>
<td>No TR</td>
<td>No TR</td>
<td>25</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>543</td>
<td>540</td>
<td>85.3</td>
<td>84</td>
<td>8.7</td>
</tr>
<tr>
<td>SEM</td>
<td></td>
<td>83</td>
<td>79.6</td>
<td>4.4</td>
<td>6.0</td>
<td>4.8</td>
</tr>
</tbody>
</table>

*There are no significant differences between any of the variables measured breathing air and those measured breathing nitric oxide. RA=room air; VAS=visual analog score.

Still on the breathing circuit; pulse, BP, continuous monitoring of arterial oxygen saturation (SaO₂), and continuous ECG recording. Nitric oxide or placebo (room air) was delivered in random order via an unpressurized continuous flow circuit and mouthpiece incorporating a one-way valve.INO concentration was measured by an electrochemical analyzer (Bedfont Scientific Ltd; Kent, UK) and the concentration was maintained at 40 ppm. Nitrogen dioxide (NO₂) concentration was monitored but remained well below toxic levels.

### RESULTS

Six patients (three female; mean age, 47±9 years [range, 21 to 74 years]) completed the protocol. Four patients had PPH and two had SPH (one secondary to idiopathic pulmonary fibrosis and obstructive sleep apnea, the other secondary to cystic fibrosis). Two patients suffered New York Heart Association functional class (FC) I dyspnea, three had FCII dyspnea, and one had FCIII dyspnea. Two patients had a history of syncope with exertion, and two patients demonstrated cor pulmonale. Of four patients who underwent right heart catheterization, the means of the systolic, diastolic, and mean PAPs, respectively, were 75±13, 30±5, and 47±9 mm Hg. Transthoracic echocardiography in all six patients demonstrated right ventricular dilatation, but echocardiographic and/or gated heart pool scanning of left ventricular function was normal in all patients. The FEV₁ was >80% of predicted in four of the six patients, and was lowest at 44% of predicted in the patient with cystic fibrosis. In the five patients in whom arterial blood gas measurements were made, mean PaO₂ was 72±7 mm Hg, and was <60 mm Hg in only one patient (PaO₂=54 mm Hg, corresponding SaO₂=87%).

Mean maximum minute ventilation on the third conditioning walk as a percentage of maximum voluntary ventilation was 49±5%, and was >60% in only two patients, suggesting that ventilation was not the major limiting factor for exercise endurance. Walk distance on familiarization walks increased with each walk, from 393±72 (walk 1), 503±94 (walk 2), and 527±94 (walk 3), to 530±64 (walk 4) (significant [p<0.05] only between walks 1 and 4). Distances walked on the third familiarization walk and on the trial walk on placebo gas were similar.

Mean distance walked on placebo (543±83 m) was not different to that on INO (540±80 m). Only three of the six patients registered any degree of breathlessness in either trial, and in all cases, this was only mild, and did not differ significantly between the two trials. At peak exercise, tricuspid regurgitant jets were detectable by Doppler echocardiography in only three of the six patients. Systolic PAP measured immediately postexercise was not significantly lower after INO in these patients compared with placebo. The rate-pressure product (peak heart-rate/baseline heart-rate × peak systolic BP/baseline systolic BP) was not significantly different between two trials (placebo, 1.9±0.3 vs INO, 1.75±0.1), nor was mean SaO₂ at peak exercise (placebo, 87.2±4.2% vs INO, 89.7±3.3%) (Table 1; all p>0.05).

### DISCUSSION

Six-minute walk distance was not improved by INO in this pilot study. There was neither evidence that a ventilatory limitation to exercise had been reached in any patient nor from rate-pressure product or heart rate alone that patients had exercised to maximal capacity. The limitations imposed by our experimental design in which INO was delivered by a continuous-flow circuit precluded the measurement of maximum oxygen consumption. We consequently could not determine the appropriateness of the cardiac or respiratory responses at any level of exercise or whether exercise ever reached physiologic limitations. The absence in three patients of a tricuspid regurgitant jet from which to calculate the level of peak systolic PAP highlights the limitations of transthoracic echo-Doppler in this setting. It remains possible, therefore, that INO may have produced changes in PAP and PVR that could not be detected by our investigational protocol, and which for other reasons did not result in a greater 6-min walk.
distance. If this were the case, the 6-min walk test must be considered an insensitive measure of pulmonary vascular responsiveness to INO. Alternatively, it is possible that none of the patients had a reactive pulmonary vasculature, in which case our findings were entirely consistent. In conclusion, the results of our study demonstrate that using the 6-min walk test in noninvasive evaluation of pulmonary vascular responsiveness to INO has several limitations that may render it insensitive to possibly significant change.

REFERENCES

Endothelial Dysfunction Providing the Basis for the Treatment of Pulmonary Hypertension*

Giles F. Filley Lecture

Timothy W. Higenbottam, MD, FCCP, and Elizabeth A. Laude, PhD

(CHEST 1998; 114:728-79S)

The past 20 years have seen a revolution in the treatment of pulmonary hypertension. Both clinical interest and scientific interest have increased with the improved prospects of survival.

Lung and heart-lung transplantation for end-stage lung disease, including pulmonary hypertension, initiated the change in clinical attitudes.1,2 This led to careful evalua-
tion of the natural history of chronic lung diseases to allow the selection of patients for this scarce resource. For primary pulmonary hypertension (PPH), the work ofuster et al3 and the National Institutes of Health registry4 provided the understanding that the principal determinant of poor survival was the development of right ventricle failure.

Lung transplantation, where the diseased organ is replaced anew, offers the simplest form of remodeling and restitution of a normal pulmonary vasculature. However, scarcity of donors5 and the problem of fatal and disabling obliterator bronchiolitis6 limit the use of this surgery to the minority of patients.

The first attempts at correcting a cause of pulmonary hypertension occurred in the 1980s. Patients with chronic obstructive lung disease and hypoxemia were treated with continuous oxygen supplements. Two studies of this long-term oxygen therapy demonstrated improved survival of patients.7,8 Other studies also found that long-term oxygen therapy led to reduction of the pulmonary hypertension.9,10

From these experiences arose the notion of replacement therapy for factors impaired by the disease process or therapy that “blocks” or lessens an enhanced production of a factor involved in the pathogenesis.

The Endothelium

The pulmonary endothelium presents a total surface area in excess of 200 m² in an adult. This offers enormous opportunity for interactions between the endothelium and leukocytes, platelets, coagulation factors, and cytokines. In the lung, the endothelium is also subject to the changing partial pressure of alveolar oxygen and oxygen content of the mixed venous blood.

The endothelial cell is not simply a barrier between the blood and airspaces, but it is capable of elaborating powerful vasoactive compounds, cytokines, and regulatory factors that control blood flow, vascular remodeling, and angiogenesis.11 Over the last 25 years, three vasoactive compounds, elaborated by the endothelial cell and implicated in the development of pulmonary hypertension, have been discovered. Each offers an opportunity for new therapies.

This review will consider prostacyclin (PGI2),12 nitric oxide (NO),13 and endothelin-1 (ET-1).14 It will also introduce an important interaction between platelets and the endothelium in lung disease. The aim is first, to provide an indication for treatment based on endothelial dysfunction and second, to identify methods of noninvasive measurement that might be used to assess the extent of the disease or predict those at risk.

Endothelial Dysfunction

Prostacyclin

Prostacyclin: A Treatment for Pulmonary Hypertension:
The discovery of PGI2 or prostaglandin X by Moncada et al15 in 1976 introduced the era of endothelium study. While present in levels in the circulation of <0.05 pmol/ mL,16 it proved to be a potent vasodilator17 and an

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