Clinical value of vasodilator test with inhaled nitric oxide for predicting long-term response to oral vasodilators in pulmonary hypertension

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Summary Acute vasodilator tests with prostacyclin (PGI2) or inhaled nitric oxide (iNO) are used to select patients with pulmonary arterial hypertension (PAH) who should be treated with oral vasodilators. The haemodynamic effects of PGI2 and iNO are different, and the limits for considering a vasodilator response as significant are controversial. The study was aimed to investigate the diagnostic performance of acute vasodilator testing with iNO and PGI2 in predicting the clinical outcome after 1 year treatment with oral vasodilators. Twenty-seven patients with severe PAH were studied. Nineteen patients were treated with oral vasodilators and their outcome after 1 year was qualified as favourable or unfavourable. The diagnostic performance of vasodilator tests in predicting this outcome was evaluated using receiver operating characteristics (ROC) curves. The acute effects of iNO and PGI2 on pulmonary artery pressure (PAP) were similar. By contrast, PGI2 produced more marked changes on cardiac output and pulmonary vascular resistance than iNO (P <0.05). The evolution at 1 year was favourable in 11 patients and unfavourable in 8. Patients with favourable evolution showed greater decrease of PAP with iNO than with PGI2 (P <0.05). The decrease of PAP with iNO had the greatest predictive value on the clinical outcome (area under ROC curve, 0.83). We conclude that in patients with PAH, acute vasodilator testing with iNO is preferable to PGI2 because it reflects more consistently the changes in pulmonary vascular tone. The acute decrease of PAP with iNO is the best predictor of the long-term response to oral vasodilator treatment.

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Introduction

Patients with pulmonary arterial hypertension (PAH) who show vasodilator responsiveness at the time of diagnosis have better survival than their counterparts when treated chronically with oral vasodilators.1–4 For this reason acute vasoreactivity...
testing is the first step in the current algorithm for the treatment of this condition. However, there is no full agreement on the interpretation of the results of acute vasodilator testing. In addition, vasodilator agents may elicit different patterns of response in terms of the effects on pulmonary artery pressure (PAP), cardiac output and pulmonary vascular resistance (PVR). The clinical significance of these different patterns of response is uncertain and there is no consensus in the criteria used to consider an acute vasodilator response as significant.

Further, different agents have been used for acute vasodilator testing, the most commonly employed of which are intravenous prostacyclin (PGI2), inhaled nitric oxide (iNO) and intravenous adenosin monophosphate. The ability of each of these agents to identify patients who will respond favourably to chronic treatment with oral vasodilators has been assumed to be the same. However, the acute haemodynamic effects of each agent are different, especially with respect to the cardiac function and the calculated PVR. Accordingly, the specific haemodynamic profile of response elicited by each agent might influence the results of the acute vasoreactivity test, and hence their interpretation.

The results of acute vasodilator testing have not been fully validated in terms of their diagnostic accuracy in detecting those patients who will show favourable evolution on the long term with oral vasodilator treatment (i.e. calcium channel blockers). This is important since these patients may obtain clinical benefit from oral vasodilators without the need to undergo other treatments that need permanent intravenous access, are much more expensive or have a less known safety profile. Accordingly, the aims of this study were to compare the acute vasodilator response to iNO and i.v. PGI2 in patients with PAH, and to analyse the diagnostic performance of each agent in predicting the clinical outcome after 1-year treatment with oral vasodilators.

Methods

Subjects

We studied prospectively 27 patients who underwent right heart catheterisation for the diagnosis of pulmonary hypertension. All of them had a previous echocardiography showing increased systolic pulmonary arterial pressure (>40 mmHg). They were diagnosed of PAH, either primary or associated with another condition, using conventional criteria. The patient group consisted of 17 women and 10 men with a mean age of 37 ± 13 years. The majority of patients were in class II or III of the modified New York Heart Association (NYHA) classification. Clinical characteristics of the patients are shown in Table 1.

Study design

A complete initial baseline haemodynamic evaluation was performed in supine position, breathing room air in all but one case, and after all vasodilating agents had been discontinued for at least 48 h before the study. After venous access was achieved through the internal jugular vein, pulmonary artery catheterisation was performed by means of a 7F triple lumen flow-directed thermodilution catheter (Baxter, Irvine, CA, USA), which was advanced by pressure wave monitoring. Transducers were positioned at the anterior axillary line level, zeroed at the atmospheric pressure, and PAP was continuously monitored (M1006A, Hewlett-Packard, Boeblingen, Germany). Cardiac output was determined in triplicate by the thermodilution technique (M1012A, Hewlett-Packard). Because pulmonary capillary wedge pressure could not be recorded in two patients, total pulmonary vascular resistance (TPVR) was considered for the purposes of the present study. An arterial line was inserted in the radial artery (Plastimed, Saint-Leu-La-Fôret, Cedex, France) for continuous systemic arterial pressure monitoring (M1006A, Hewlett-Packard) and arterial blood gas analysis. Trascutaneous arterial oxyhaemoglobin saturation was continuously monitored by pulse oximetry (M1020A, Hewlett-Packard). Arterial and mixed-venous blood samples were collected simultaneously for the determination of pH, CO2 and O2 tensions, oxyhaemoglobin saturation, and haemoglobin and methaemoglobin concentrations (Ciba-Corning 800, Medfield, MA, USA).

Acute vasodilator test

After a duplicate set of baseline measurements, taken more than 20 min apart, the responses to iNO and i.v. PGI2 were studied sequentially. Initially, patients breathed a mixture of NO in air from a Douglas bag using an unidirectional valve (Hans Rudolph, Kansas city, MO, USA) for 20 min, as previously described. Haemodynamic measurements were performed at the end of the inhalation period and the concentration of
NO was increased progressively (10, 20, and 40 parts per million) until a significant response was achieved (see below).

After a washout period of 20 min, and after ensuring return to baseline haemodynamic values, an infusion of PGI2 (Flolan™, Glaxo-Wellcome, Madrid, Spain) was administered. The infusion rate was started at 2 ng/kg/min and increased stepwise by 2 ng/kg/min increments every 15 min up to a maximal dose of 12 ng/kg/min, until a significant response was obtained, or the patient developed symptoms of intolerance.

The vasodilator response to either iNO or PGI2 was considered significant when TPVR decreased by more than 30% and PAP by more than 20% of the respective pre-treatment values. Arterial and mixed-venous bloods were sampled at the highest concentrations of NO and PGI2 for respiratory gas analysis.

### Chronic treatment

Chronic treatment was established according to the acute response to i.v. PGI2. Patients who showed a decrease in TPVR greater than 20% of the baseline value and had a cardiac index greater than 2 l/min/m², were treated with oral vasodilators: calcium channel blockers (nifedipine or diltiazem) or isosorbide mononitrate. The latter was employed in patients with portopulmonary hypertension. In the remaining cases, i.e. those who showed a TPVR decrease with PGI2 lower than 20% from baseline or the cardiac index was always lower than 2 l/min/m², we initiated a continuous infusion of intravenous epoprostenol.

The clinical outcome of chronic treatment with oral vasodilators was analysed after 12 months and qualified as favourable or unfavourable. A favourable outcome was considered when NYHA...
functional class decreased by one or more grades and the echocardiography study showed a reduction in tricuspid jet velocity, as compared with pretreatment values. An unfavourable outcome was considered when the above criteria were not fulfilled, the patient died, or oral vasodilator treatment was discontinued because of the need for lung transplantation or continuous intravenous epoprostenol therapy.

Statistical analysis

All results are expressed as mean ± SD. Changes in the acute vasodilator test were assessed with paired student’s t-test. Comparisons between groups were performed using unpaired student’s t-test. The diagnostic performance of the acute vasodilator test in predicting the outcome of chronic oral vasodilator treatment was evaluated using receiver operating characteristics (ROC) curves.²⁴,²⁵ All tests were performed using the SPSS statistical package and P values <0.05 were considered as significant in all cases.

Results

Study group

Clinical characteristics and baseline haemodynamic results of the 27 patients are shown in Table 1. Overall patients had severe pulmonary hypertension with a mean PAP of 50 ± 11 mmHg and TPVR of 1161 dynes s/cm⁵. At baseline, 11 patients had a cardiac index less than 2 l/min/m². Eight patients were initially treated with continuous epoprostenol infusion. The remaining 19 patients received oral vasodilators.

Acute vasodilator testing

The results of acute vasodilator test with iNO and PG1₂ are shown in Table 2. PAP decreased significantly with the administration of both iNO and PG1₂, being the percent change from baseline the same with both agents (−13%). By contrast, TPVR, which was also reduced by both agents, decreased to a greater extent with PG1₂ (−31 ± 12% from baseline) than with iNO (−21 ± 17%), the difference between them being statistically significant (P < 0.05). This was because the cardiac output increased more markedly when PG1₂ was administered (34 ± 21%) as compared with iNO (12 ± 11%) (P < 0.05). The differences in cardiac output during vasodilator administration resulted mainly from a greater effect of PG1₂ on heart rate (Table 2). As expected, systemic vascular resistance decreased with the administration of PG1₂, whereas it remained essentially unaltered during NO inhalation (−34% and −6% from baseline, PG1₂ and iNO, respectively; P < 0.05). During PG1₂ infusion and NO inhalation there was a moderate decrease in arterial PO₂ that did not reach statistical significance. By contrast, mixed-venous PO₂ increased slightly but significantly with the administration of both agents.

The changes in PAP induced by iNO and PG1₂ correlated significantly (r = 0.57, P < 0.01), although with substantial scatter (Fig. 1). Changes

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Haemodynamic findings during acute vasodilator testing with inhaled NO and prostacyclin.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>50 ± 11</td>
</tr>
<tr>
<td>% change</td>
<td>−13 ± 15</td>
</tr>
<tr>
<td>TPVR (dyn s/cm⁵)</td>
<td>1161 ± 440</td>
</tr>
<tr>
<td>% change</td>
<td>−21 ± 17</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>2.23 ± 0.60</td>
</tr>
<tr>
<td>% change</td>
<td>12 ± 11</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>49 ± 17</td>
</tr>
<tr>
<td>HR (min⁻¹)</td>
<td>79 ± 15</td>
</tr>
<tr>
<td>SVR (dyn s/cm⁵)</td>
<td>1993 ± 661</td>
</tr>
<tr>
<td>% change</td>
<td>−6 ± 10</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>79 ± 35</td>
</tr>
<tr>
<td>PvO₂ (mmHg)</td>
<td>33 ± 5</td>
</tr>
</tbody>
</table>

Results are given as mean ± SD. Definition of abbreviations: see Table 1. iNO, inhaled nitric oxide; HR, heart rate.

*P < 0.05 compared with baseline.

¹P < 0.05 compared with iNO.
in TPVR induced by both agents also correlated significantly \( r = 0.56 \), \( P < 0.01 \), yet the majority of plots lied above the identity line, due to the greater effect of PGI2 on TPVR (Fig. 1). Seven patients reached the initial criteria for a significant vasodilator response (decrease in TPVR > 30% and in PAP > 20%) with iNO, and seven cases with PGI2, these results being significantly associated (Fisher exact test, \( P = 0.03 \)). Nevertheless, only four patients fulfilled the criteria for significant vasodilator response with both agents. Three patients responded only to iNO, and other three responded only to PGI2.

**Long-term response to oral vasodilator treatment**

According to the criteria previously established (decrease in TPVR < 20% or cardiac index < 2 l/min/m²), eight patients (30%) were initially treated with continuous epoprostenol infusion. The remaining 19 patients received oral vasodilator treatment: nifedipine, 12 patients; diltiazem, three patients; and isosorbide mononitrate, four patients. Patients receiving oral vasodilators were followed for a mean of 372 ± 104 days. At the end of this period the mean daily doses of the vasodilator drugs were: nifedipine, 80 ± 26 mg; diltiazem, 330 ± 52 mg; and isosorbide mononitrate, 93 ± 23 mg. The clinical outcome after 1-year treatment was qualified as favourable in 11 patients (41% of the whole group) and unfavourable in eight (Fig. 2). Reasons of unfavourable outcome were death in three cases, need for transplantation in one case, need of prostacyclin therapy in one case, and lack of clinical improvement in three cases. On average, patients with unfavourable outcome were followed during 335 ± 56 days, and those with favourable outcome for 395 ± 56 days.

Baseline haemodynamics and acute responses to iNO and PGI2 in patients grouped according to chronic treatment and clinical outcome are shown in Table 3. Pulmonary haemodynamics at baseline did not differ between patients with favourable and unfavourable outcomes with oral vasodilators. When tested with iNO, patients who had favourable evolution had lower PAP and TPVR, and greater cardiac index, than those with unfavourable evolution (Table 3). The percent change from baseline of PAP was significantly greater in the group with favourable outcome, and there was also a trend for a greater decrease in TPVR in this group (\( r = 0.06 \)). By contrast, when tested with PGI2, patients with favourable and unfavourable outcomes only differed in the cardiac index (Table 3). Patients who underwent continuous epoprostenol treatment had greater impairment in pulmonary haemodynamics at baseline, and the haemodynamic changes elicited by both iNO and PGI2 were significantly lower than in the group who responded favourably to oral vasodilators (Table 3). Interestingly, compared with patients with unfavourable responses to oral vasodilators, those treated with epoprostenol only differed in the magnitude of change in PAP and in the value of TPVR during iNO administration.

The diagnostic accuracy of the results obtained in the acute vasodilator tests with iNO and PGI2 in predicting a favourable outcome after 1-year treatment with oral vasodilators was assessed using ROC curve analysis. Figure 3 shows the ROC curves for the changes in PAP, TPVR and cardiac index.
Figure 2  Clinical outcome after 1-year treatment with oral vasodilators. Panel A. Change in NYHA functional class from baseline (BSL) to follow-up (F.U.) in patients treated with oral vasodilators with favourable and unfavourable outcomes. Panel B. Individual changes in systolic PAP measured by echocardiography.

Table 3  Baseline haemodynamics and acute response to vasodilators according to chronic treatment and clinical outcome at 12 months.

<table>
<thead>
<tr>
<th>Oral vasodilator</th>
<th>Favourable (n = 11)</th>
<th>Unfavourable (n = 8)</th>
<th>Epoprostenol (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline haemodynamics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>45 ± 9</td>
<td>49 ± 15</td>
<td>56 ± 8*</td>
</tr>
<tr>
<td>TPVR (dyn s/cm²)</td>
<td>934 ± 375</td>
<td>1162 ± 470</td>
<td>1472 ± 323*</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>2.51 ± 0.62</td>
<td>2.05 ± 0.50</td>
<td>2.01 ± 0.54</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>56 ± 13</td>
<td>49 ± 19</td>
<td>39 ± 17*</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>5 ± 4</td>
<td>6 ± 4</td>
<td>10 ± 8</td>
</tr>
<tr>
<td>$P_vO_2$ (mmHg)</td>
<td>35 ± 5</td>
<td>32 ± 3</td>
<td>31 ± 6</td>
</tr>
<tr>
<td><strong>Nitric oxide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>34 ± 7</td>
<td>45 ± 16*</td>
<td>58 ± 7*</td>
</tr>
<tr>
<td>$\Delta$PAP (%)</td>
<td>$-23 \pm 15$</td>
<td>$-10 \pm 10^*$</td>
<td>$-1 \pm 5^*,^t$</td>
</tr>
<tr>
<td>TPVR (dyn s/cm²)</td>
<td>592 ± 162</td>
<td>994 ± 342*</td>
<td>1403 ± 347*</td>
</tr>
<tr>
<td>$\Delta$TPVR (%)</td>
<td>$-32 \pm 19$</td>
<td>$-18 \pm 10$</td>
<td>$-7 \pm 11^*$</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>2.82 ± 0.49</td>
<td>2.26 ± 0.50*</td>
<td>2.19 ± 0.72*</td>
</tr>
<tr>
<td>$\Delta$Cl (%)</td>
<td>$15 \pm 13$</td>
<td>$11 \pm 10$</td>
<td>$7 \pm 10$</td>
</tr>
<tr>
<td><strong>Prostacyclin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>39 ± 6</td>
<td>44 ± 14</td>
<td>55 ± 10*</td>
</tr>
<tr>
<td>$\Delta$PAP (%)</td>
<td>$-17 \pm 9$</td>
<td>$-12 \pm 7$</td>
<td>$-7 \pm 10^*$</td>
</tr>
<tr>
<td>TPVR (dyn s/ cm²)</td>
<td>574 ± 174</td>
<td>800 ± 315</td>
<td>1113 ± 310*</td>
</tr>
<tr>
<td>$\Delta$TPVR (%)</td>
<td>$-36 \pm 12$</td>
<td>$-31 \pm 6$</td>
<td>$-25 \pm 13$</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>3.38 ± 0.69</td>
<td>2.64 ± 0.57*</td>
<td>2.62 ± 0.79*</td>
</tr>
<tr>
<td>$\Delta$Cl (%)</td>
<td>$38 \pm 24$</td>
<td>$30 \pm 12$</td>
<td>$32 \pm 23$</td>
</tr>
</tbody>
</table>

Results are given as mean ± s.d.

Definition of abbreviations: see Table 1. $\Delta$ denotes % change from baseline.

*aP < 0.05 compared with the group with favourable evolution (oral vasodilator).

*tP < 0.05 compared with the group with unfavourable evolution (oral vasodilator).
induced by both iNO and PGI2. Statistical analyses of the area under the ROC curve (AUC) showed that the decrease in PAP and TPVR induced by iNO had the greatest diagnostic accuracy in predicting which patients would respond favourably to oral vasodilators on the long term, with an AUC of 0.83 and 0.81, respectively ($P < 0.01$ both compared with a curve with no predictive value, AUC = 0.5) (Fig. 3). The decrease in PAP induced by PGI2 also had an acceptable predictive value, with an AUC of 0.73 ($P < 0.05$ compared with AUC = 0.5). By contrast, the decrease in TPVR induced by PGI2 did not have significant predictive value. Similarly, changes in cardiac index induced by either iNO or PGI2 did not differ from a test with no predictive value (Fig. 3).

**Discussion**

The results of the present study show that in patients with PAH acute vasodilator testing with iNO and PGI2 may elicit different haemodynamic responses, and that the acute response to iNO had the greatest accuracy in detecting patients who showed a favourable outcome with chronic treatment with oral vasodilators after 1 year follow-up.
Inhaled NO and intravenous PGI2 are used indistinctively as screening agents to assess acute vasoreactivity in patients with PAH.5 Intravenous PGI2 has been used for many years due to its potent vasodilator effect and its rapidity of action.12,13 Inhaled NO was first used in PAH by Pepke-Zaba et al.26 and introduced as an acute vasodilating agent more recently by Sitbon et al.14 Compared with PGI2, iNO has the advantage of a selective action on pulmonary circulation due to its inactivation when binded to haemoglobin. Our study confirms the selective action of iNO on pulmonary vascular tone with no effect on systemic vascular resistance (Table 2), in agreement with previous reports in healthy subjects27 and patients with different disease conditions,21,28 including patients with PAH.14,26,29,30 The mean effects of i.v. PGI2 and iNO on PAP were very similar, although there was great interindividual variability (Fig. 1). Regarding TPVR, PGI2 induced a more marked decrease of this measurement than iNO (Fig. 1, Table 2). The distinct effects of both drugs on cardiac output can explain this difference. Whereas cardiac output increased markedly during PGI2 administration, it remained practically unaltered during NO inhalation, even in those patients who showed a significant decrease of PAP. The increase in cardiac output may explain the reduction in TPVR observed in some patients who did not show a reduction in PAP, the so-called “resistance responders”.8,9 The interpretation of this type of response has been always uncertain, since it may not represent true vasodilation of the pulmonary vascular bed.8 In fact, in our study there was a greater number of “resistance responders” when using PGI2 (eight patients) than when using iNO (2 patients). A potential explanation for such different effects on cardiac output could be due to the fact that systemic hypotension induced by PGI2 can activate the baroreceptor reflex and produce sympathetic stimulation of the heart.8 Indeed, in our study differences in cardiac output were essentially due to higher heart rate during PGI2 administration (Table 2). Furthermore, there are some data suggesting that intravenous PGI2 may exert inotropic effect,31 at least when administered for long periods of time.32 We think that in our series this was unlikely because stroke volumes during iNO and PGI2 administration were very similar and did not explain the differences in cardiac output.

These findings are relevant regarding the interpretation of acute vasodilator testing in pulmonary hypertension. The implication is that the agent used for this purpose may influence the pattern of response and consequently its interpretation. According to our findings, the reduction of TPVR elicited by PGI2 appears not to be a reliable marker of pulmonary vasodilation, as it may be influenced by systemic hypotension induced by the drug. Therefore, the use of inhaled NO as screening vasodilator agent appears to be preferable because its selective pulmonary action may reflect more consistently changes in pulmonary vascular tone and because it does not have inotropic effect.

A second question raised in the present study was to what extent the acute responses to vasodilator agents were predictive of the clinical outcome with oral vasodilator treatment. The criteria to indicate chronic treatment with oral vasodilators have not been clearly established and differ among investigators.3,5,10,11,15,22,33 In our study, we indicated chronic treatment with oral vasodilators in patients who showed a decrease in TPVR greater that 20% from baseline when tested with PGI2, as suggested by others.3,22 Only those patients with a clear indication for continuous epoprostenol therapy7 were excluded. Furthermore, we evaluated the clinical evolution after 1 year treatment, a period of time longer than that used in previous studies,3,5,29,34 thus allowing ample margin for detecting patients with unfavourable evolution. Our results indicate that using the criteria of a decrease in TPVR > 20%, 40% of the patients showed clinical improvement after 1-year treatment. Should we have used more restrictive criteria (i.e. decrease in PAP > 20% or > 10 mmHg from baseline5), four of the 11 patients who showed favourable outcomes with oral vasodilators would have been considered “nonresponders” and hence candidates to other treatments (i.e. epoprostenol, bosentan), that entail greater risk of serious adverse effects and are much more expensive than oral vasodilators.

To investigate the accuracy of acute vasodilator test in predicting a favourable outcome we used ROC curves.24,25 These curves are a useful way to display the diagnostic performance of a test by plotting the sensitivity against the false-positive rate (1-specificity) (Fig. 3). The closer the ROC curve is to the upper left corner the more accurate the test is, because the true-positive rate (sensitivity) approximates 1 and the false-positive rate approximates 0. The global accuracy of the test was determined by the area under the ROC curve (AUC). Values of AUC may range from 0.5 (the test does not have predictive value since it may be positive or negative at random) to 1 (the test allows perfect separation of the two groups). Therefore, the closer the AUC to 1, the greater the accuracy of the test.25 Furthermore, ROC curves are also useful to identify “cut-off” values with the best compromise between sensitivity and specificity, as well as to compare the diagnostic performance of two
tests. In the present study, changes in PAP and TPVR induced by iNO had the greatest diagnostic accuracy in predicting which patients would respond favourably to oral vasodilators on the long term, with AUCs greater than 0.8 (Fig. 3). Therefore, changes in PAP or TPVR with iNO can be used indistinctively to assess the reversibility of pulmonary hypertension. The change in PAP induced by PGI₂ also had an acceptable predictive value in detecting patients with favourable response to oral vasodilators, with an AUC of 0.73. Nevertheless, its diagnostic accuracy was lower than that of iNO as shown by a lower AUC. The greater accuracy of iNO, as compared with that of i.v. PGI₂, could be explained by its selective action on pulmonary circulation, which allows better identification of patients with a vasoconstrictive component in their pulmonary hypertension, that are more likely to show a favourable outcome when treated with drugs that reduce vascular tone. Besides, the possibility exists that when using PGI₂, the increase in cardiac output that results from its systemic vasodilator effect, could neutralise the decrease in PAP induced by the drug. Moreover, the change in TPVR induced by PGI₂ did not have significant predictive value on the long-term evolution with oral vasodilators. This finding is consistent with the fact that the change in TPVR induced by PGI₂ is largely influenced by the change in cardiac output. Since the change in cardiac output may result not only from pulmonary vasodilation, but also from systemic vasodilation, as discussed earlier, it is likely that the change in TPVR is a poor indicator of patients with a vasoconstrictive component in their pulmonary hypertension. Furthermore, in the present series changes in cardiac output induced by either NO or PGI₂ did not have predictive value on the long-term evolution with oral vasodilators. This finding is consistent with the fact that the change in TPVR induced by PGI₂ is largely influenced by the change in cardiac output. Since the change in cardiac output may result not only from pulmonary vasodilation, but also from systemic vasodilation, as discussed earlier, it is likely that the change in TPVR is a poor indicator of patients with a vasoconstrictive component in their pulmonary hypertension. Furthermore, in the present series changes in cardiac output induced by either NO or PGI₂ did not have predictive value on the long-term evolution with oral vasodilators. This finding is consistent with the fact that the change in TPVR induced by PGI₂ is largely influenced by the change in cardiac output. Since the change in cardiac output may result not only from pulmonary vasodilation, but also from systemic vasodilation, as discussed earlier, it is likely that the change in TPVR is a poor indicator of patients with a vasoconstrictive component in their pulmonary hypertension. Furthermore, in the present series changes in cardiac output induced by either NO or PGI₂ did not have predictive value on the long-term evolution with oral vasodilators. This finding is consistent with the fact that the change in TPVR induced by PGI₂ is largely influenced by the change in cardiac output. Since the change in cardiac output may result not only from pulmonary vasodilation, but also from systemic vasodilation, as discussed earlier, it is likely that the change in TPVR is a poor indicator of patients with a vasoconstrictive component in their pulmonary hypertension.

From the ROC curve we identified that a decrease in PAP induced by iNO greater than 12% from baseline had a sensitivity of 81% and a specificity of 86% in detecting patients with favourable responses on the long term to oral vasodilator treatment. This “cut-off” point is lower than the value previously proposed by Rich et al.³³ (a decrease greater than 22%) on the basis of the spontaneous variability of pulmonary haemodynamic measurements. In the study by Rich et al.³³ spontaneous variability was assessed during a period of 6 h of observation. As already pointed out by these investigators, measurements carried out in shorter intervals could be less influenced by spontaneous variability.³³ Indeed, in our series the mean individual variation between the two sets of baseline measurements, taken 30 min apart, was 4.5 ± 3.3%. The executive summary of the 1998 World Symposium on Primary Pulmonary Hypertension⁵ suggested that the decrease of PAP should be greater than 10 mmHg from baseline, independent of the vasodilator employed. When using iNO, in our series this threshold value had a lower sensitivity (66%) and a similar specificity (85%) than the threshold of 12%, for detecting patients with favourable response to oral vasodilators. This implicates that using the cut-off of 10 mmHg, we would have missed some patients who responded favourably to oral vasodilators. Accordingly, we think that considering that iNO is a very specific vasodilator of pulmonary circulation, it is likely that a decrease in PAP greater than 12% from baseline, could be considered as suggestive of a good clinical response to oral vasodilators. In this respect, it is of note that a 12% decrease in FEV₁ is currently considered as a significant bronchodilator response in patients with airway obstruction.³⁵ Nevertheless, this suggestion should be tested in a more ample population.

In summary, the present study shows that in patients with PAH acute vasodilator testing with i.v. PGI₂ and inhaled NO elicit different responses on pulmonary haemodynamics, as a result of their distinct effects on systemic circulation. Because iNO is a highly selective vasodilator of pulmonary circulation, its acute haemodynamic effects allow a more accurate identification of those patients who are more likely to respond favourably to chronic treatment with oral vasodilators.

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