Iloprost for pulmonary vasodilator testing in idiopathic pulmonary arterial hypertension

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STATEMENT OF INTEREST
None declared.
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**ABSTRACT:** The aim of this study was to confirm the utility of aerosolised iloprost for identifying long-term responders to calcium channel blockers (CCBs) in patients with idiopathic pulmonary arterial hypertension (IPAH).

While undergoing right heart catheterisation, 74 patients with IPAH sequentially received incremental infusions of adenosine and aerosolised iloprost. The effects of the two vasodilators on haemodynamic parameters were recorded. All acute responders identified by aerosolised iloprost were subsequently treated with high doses of a CCB and were re-evaluated after 12 months.

Both adenosine and iloprost produced significant decreases in mean pulmonary arterial pressure and pulmonary vascular resistance, and significant increases in cardiac index. Adverse effects were experienced by 35 of the 74 patients with adenosine, but by only 2 with iloprost. Aerosolised iloprost identified more acute responders than infused adenosine (10 vs 8) according to the criteria recommended in recent consensus guidelines. Nine responders identified by iloprost were followed-up after 12 months of high-dose CCB therapy. Five had normal or near-normal haemodynamics and a WHO functional classification of I or II after 12 months.

Aerosolised iloprost is an appropriate new agent to identify long-term responders to CCBs in patients with IPAH. It is as effective in this regard as infused adenosine but is better tolerated.

**KEYWORDS:** Pulmonary arterial hypertension, iloprost, adenosine, vasoreactivity testing, inhaled therapy, calcium channel blockers
Abbreviations and acronyms

CCB = calcium channel blocker
CI = cardiac index
IPAH = idiopathic pulmonary arterial hypertension
6MWD = six minutes walk distance
mPAP = mean pulmonary arterial pressure
mSAP = mean systemic arterial pressure
PCWP = pulmonary capillary wedge pressure
SvO₂ = mixed-venous oxygen saturation
SVR = systemic vascular resistance
TPR = total pulmonary resistance
WHO = World Health Organization
Idiopathic pulmonary arterial hypertension (IPAH) is characterised by progressive increases in pulmonary vascular resistance without a demonstrable cause that eventually lead to right heart dysfunction or even death. Uncontrolled studies have suggested that extended treatment with calcium channel blockers (CCBs) prolongs survival in rare cases of acutely vasoresponsive patients [1,2].

Recent international consensus statements have recommended vasoreactivity testing as an important component of the evaluation of patients with PAH, especially those with IPAH [3,4]. Currently, three short-acting agents are widely recommended in these guidelines for acute pulmonary vasoreactivity testing: intravenous (IV) epoprostenol [5,6], IV adenosine [4,7], and inhaled nitric oxide (NO) [8,9]. However, both IV epoprostenol and IV adenosine often cause systemic hypotension and other intolerable adverse effects when their dosages are incrementally increased to higher levels [7,10,11]. Inhaled NO has been advocated as an effective way of identifying acute haemodynamic responses, but the use of inhaled NO requires complicated administration and monitoring devices, and its acute withdrawal can lead to dangerous rebound pulmonary hypertension [12,13].

Iloprost is a stable, short-acting carbacyclin analogue of prostacyclin (prostaglandin I2; PGI2) with a plasma half-life of 20 to 30 minutes. There is considerable evidence to show that aerosolised iloprost is a more potent pulmonary vasodilator than inhaled NO [5,14,15], and it has been widely used for pulmonary vasoreactivity testing in many medical centres in the past several years [16]. However, no studies have investigated whether an acute response to iloprost identifies responders to long-term treatment with high doses of calcium channel blockers (CCBs) administered for at least 12 months. Therefore, the principal objective of this study was to determine whether aerosolised iloprost can be used as an alternative to infused adenosine to identify patients who may be long-term responders to CCBs via acute pulmonary vasodilator testing of IPAH patients undergoing right heart catheterisation. Adenosine was used as the comparator as it was the only agent among the three standard short-acting standard pulmonary vasodilators available in China when the study was performed.
MATERIALS AND METHODS

Patient population

Between July 2006 and March 2008, 74 patients with IPAH were enrolled consecutively in the study. Patient selection was based upon the following criteria:

- A diagnosis of IPAH established after exclusion of secondary causes of pulmonary hypertension
- A mean pulmonary artery pressure (mPAP) >30 mmHg
- Symptomatic disease, despite optimised conventional treatment, corresponding to a World Health Organization (WHO) functional classification of II or III
- Cessation of treatment with oral anticoagulants until the international normalised ratio (INR) was lower than 1.5 prior to testing
- Provision of written informed consent by each patient.

To exclude other forms of pulmonary hypertension, patients underwent scintigraphy and/or spiral computed tomography (to exclude chronic thromboembolic pulmonary hypertension), echocardiography (congenital heart disease), high-resolution computed tomography (lung disease), serologic testing (HIV infection; connective tissue disease), and comprehensive pulmonary and liver function studies (lung or liver disease). In addition to clinical features, evaluations undertaken in all patients included an electrocardiogram (ECG), chest radiography, Doppler echocardiography, measurement of the 6-minutes walk distance (6MWD), and measurement of the following specific PAH biochemical indicators: endothelin-1 (ET-1), brain natriuretic peptide (BNP), and serum uric acid (UA).

The study protocol was reviewed and approved by the Ethics Committee of Shanghai Pulmonary Hospital, Tongji University.

Haemodynamic measurements

For this study, all patients were admitted to an intensive therapy room at our hospitals. An 8F (for adults) or 6F (for children) introducer sheet was placed in the right internal jugular vein or the right subclavian vein, and a quadric-lumen 7F (for adults) or 5F (for children) Swan-Ganz
catheter (Edwards Lifesciences World Trade Co., Ltd, USA) was advanced into the pulmonary artery. Correct positioning of the catheter was verified by chest fluoroscopy. Transducers were positioned at the mid-axillary line and zeroed at atmospheric pressure. mPAP, mean systemic arterial pressure (mSAP), right atrial pressure (RAP), and pulmonary capillary wedge pressure (PCWP) were measured at baseline and after vasodilator drug administration. Cardiac output (CO) was measured in triplicate by the thermodilution technique (Cardiac Output Computer; Baxter, Edwards, California) with ice-cold isotonic sodium chloride solution in patients without severe tricuspid insufficiency (40 cases); otherwise, Fick’s method was used to measure CO in patients with severe tricuspid insufficiency (34 cases). The cardiac index (CI) was calculated by dividing CO by body surface area (BSA). Because the PCWP could not be recorded in all patients during the haemodynamic evaluation, total pulmonary resistance (TPR), rather than pulmonary arterial resistance, was determined and calculated as mPAP divided by CO. Systemic vascular resistance (SVR) was calculated as (mSAP – RAP) divided by CO. The heart rate and the transcutaneous arterial oxygen saturation were monitored continuously.

**Vasodilator drug administration**

After baseline haemodynamic parameters had been recorded, adenosine infusions (Ever Bright Pharmaceutical Company, Shenyang, China) were started at a dose of 50 µg/kg/min and increased by 50 µg/kg/min at 2-minute intervals to a maximum dose of 200 µg/kg/min [4,7]. Haemodynamic parameters and blood gases were monitored during adenosine administration. Thirty minutes after discontinuation of adenosine, another set of baseline haemodynamic parameters was recorded, and iloprost (Ventavis®, Bayer-Schering Pharma, Germany) 5 µg was delivered by a PARI LC STAR nebuliser (PARI GmbH, Starnberg, Germany) driven by a PARI TurboBOY-N compressor (PARI GmbH) for about 15 minutes. This combination produces aerosolised particles with a mass median aerodynamic diameter of 2.2 µm and a mass fraction below 5 µm of 89%. Another complete set of haemodynamic measurements and blood gases was obtained at the end of inhalation. Any adverse events that occurred during administration of the vasodilator drugs were recorded.
**Acute vasoreactivity responses**

A positive acute response in this study was defined in accordance with the recent consensus statements of the American College of Chest Physicians (ACCP 2005) and the European Society of Cardiology (ESC 2004) as a fall in mPAP of at least 10 mmHg to ≤40 mmHg, with an increased or unchanged CO.

**Follow-up**

All acute responders identified by iloprost or adenosine were treated with high-dose CCB therapy. Their clinical features were re-evaluated 6-monthly and haemodynamic parameters were measured via repeated right heart catheterisation at 12 months.

**Statistical analysis**

Haemodynamic parameters were expressed as mean values ± standard deviation (SD). SPSS 13.0 software (SPSS Inc, Chicago, Illinois) was used for statistical analysis. A paired t-test was applied to compare the baseline and post-treatment differences for adenosine infusion and iloprost inhalation. Differences in haemodynamic changes between adenosine and iloprost were compared via an independent t-test, and this test was also applied to compare differences in clinical features and haemodynamic parameters between acute responders and non-responders. A chi-square test was used to compare differences in WHO functional class and gender distribution between responders and non-responders. Correlations of haemodynamic changes between adenosine and iloprost were tested via a Spearman correlation test. Significance was set at p < 0.05.

**RESULTS**

**Patient population**

A total of 74 patients, 58 women and 16 men, with IPAH were enrolled in the study. The mean age of the patients was 33 ± 12 years (range, 7 to 66 years); 7 children were among the patients studied (age range, 7 to 17 years). Thirty-five patients had a WHO functional class II assessment and 39 a WHO functional class III assessment. In all patients, the resting mPAP
was abnormally high (mean, 60.1 ± 17.6 mmHg; range, 35 to 103 mmHg) and there was also a marked elevation of TPR (mean, 17.3 ± 9.7 Wood U; range, 3.1 to 54.4 Wood U). The baseline clinical features and haemodynamic variables of the patient population studied are shown in table 1.

**Haemodynamic responses**

The changes of haemodynamic parameters (i.e. maximal changes recorded during administration of the vasodilators) and oxygenation status during adenosine infusion and iloprost inhalation are shown in table 2 and figure 1. During adenosine infusion, mPAP and TPR were both significantly reduced from 61.1 ± 17.6 to 55.2 ± 19.4 mmHg (p < 0.001) and from 17.5 ± 9.8 to 14.4 ± 9.4 Wood U (p < 0.001), respectively. The CI and mixed-venous saturation (SvO2) were significantly increased from 2.7 ± 1.1 to 3.1 ± 1.4 L/min/m² (p < 0.001) and from 60.8 ± 13.4% to 68.5 ± 12.8% (p < 0.01), respectively, while the mSAP and SVR were significantly decreased from 83.8 ± 11.7 to 81.7 ± 10.5 mmHg (p = 0.013) and from 21.5 ± 8.8 to 18.8 ± 8.7 Wood U (p < 0.001), respectively.

Aerosolised iloprost produced a marked decline of both mPAP and TPR from 60.5 ± 18.9 to 54.8 ± 20.9 mmHg (p < 0.001) and from 16.7 ± 9.4 to 13.5 ± 8.2 Wood U (p < 0.001), respectively. Iloprost also significantly increased CI and SvO₂ from 2.8 ± 1.06 to 3.1 ± 1.0 L/min/m² (p < 0.001) and from 62.0 ± 12.3% to 66.0 ± 10.8% (p < 0.001), respectively, and decreased mSAP and SVR from 82.0 ± 10.5 to 79.1 ± 10.9 mmHg (p < 0.005) and from 20.0 ± 7.5 to 17.2 ± 6.5 Wood U (p < 0.001), respectively.

The haemodynamic changes occurring with iloprost inhalation were comparable to those occurring with adenosine infusion and, with the exception of changes in SvO₂, there were no significant differences among any of the measured variables. Strong correlations were found for the changes of mPAP (r = 0.798; p < 0.001) and TPR (r = 0.405; p = 0.004) between iloprost and adenosine.

**Acute vasoreactivity responses**
In accordance with the recommended acute response criteria, 10 of the 74 patients (13.5%) were identified as responders with iloprost and 8 (10.8%) were responders with adenosine. None of the patients who failed to show an acute response with iloprost inhalation (non-responders) showed a positive response to adenosine infusion.

A comparison of the baseline clinical characteristics and haemodynamic variables between acute responders and non-responders to iloprost is shown in table 1. In contrast to non-responders, the acute responders were younger (22.6 ± 9.1 vs 34.5 ± 11.8 years; p = 0.008), had a better WHO functional class (II/III ratio, 9/1 vs 26/38; p = 0.002), a higher SvO₂ (73.5 ± 9.4% vs 60.7 ± 12.0%; p = 0.008), lower mPAP (48.4 ± 10.5 vs 62.6 ± 17.7 mmHg; p = 0.029), lower RAP (3.1 ± 1.9 vs 6.8 ± 5.6 mmHg; p = 0.001), and a lower serum endothelin-1 (ET-1) concentration (0.6 ± 0.2 vs 1.0 ± 0.6 fmol/L; p < 0.001) [table 1].

**Adverse events**

Thirty-five of the 74 patients (47.3%) experienced adverse events during adenosine infusion and only 39 patients were able to tolerate the maximum dosage. In contrast, only 2 patients (2.7%) experienced adverse events during iloprost inhalation (table 3), and none required the test to be discontinued because of intolerable adverse effects.

**Follow-up**

All 10 acute responders to aerosolised iloprost (8 of whom also responded to infused adenosine) were treated with incremental high-dose CCB therapy (diltiazem: mean dosage, 433 ± 119 mg/day; range, 360 to 720 mg/day). One acute responder was lost to follow-up, but the other 9 patients were all re-evaluated for functional class and exercise capacity 6-monthly. In addition, their haemodynamic parameters were also reassessed after 12 months. The long-term follow-up results showed that the WHO functional class and Borg scale score were improved in all 9 responders (table 4). The mean 6-minutes walk distance was also significantly improved from 463 ± 58 meters to 583 ± 61 metres (p < 0.001). Moreover, when re-evaluated by right heart catheterisation, the 9 responders all had a decreased baseline mPAP.
and PVR compared with their first assessment, and 5 had normal or near-normal haemodynamics (mPAP <30 mmHg) [fig. 2].

DISCUSSION

This study is the first to verify the effectiveness and tolerability of aerosolised iloprost for identifying long-term responders to oral CCB therapy in patients with IPAH via acute vasoreactivity testing. Iloprost demonstrated comparable effects on haemodynamic variables to adenosine infusions, and exhibited a similar capacity to identify those who would likely achieve sustained benefit from long-term CCB therapy. However, the safety and tolerability of iloprost during acute vasoreactivity testing were superior to adenosine infusion. After long-term treatment with a CCB for 12 months, all 9 of the 10 iloprost responders (one was lost to follow-up) had significantly improved clinical features and exercise capacity, and 5 had improved heart function (all WHO class I or II) and normal or near-normal haemodynamics (mPAP <30 mmHg).

Adenosine is an endogenous vasodilator with a short half-life [17]. Central venous infusion of adenosine can be used as a ‘selective’ pulmonary vasodilator as it is cleared from the blood in few seconds before it exerts a vasodilating effect in the systemic circulation [18]. Because of these properties, adenosine has become one of the three agents recommended in recent clinical practice guidelines to perform acute vasoreactivity testing [3,4]. As a new treatment option, iloprost has a relatively longer plasma half-life than adenosine (or epoprostenol), and has been shown to have favorable effects on pulmonary haemodynamics. As noted by Palevsky et al. in 1990 [19] and Galiè et al. in 1995 [20], the ideal screening agent should be a short-acting compound that is cleared rapidly from the body. The favourable pulmonary selectivity and improved tolerability of iloprost suggest that it may be a valuable screening agent to identify long-term responders to CCBs. While iloprost has been used for acute vasoreactivity testing in many pulmonary hypertension centres, this is the first study to show that about 50% of acute responders to iloprost vasoreactivity testing may be long-term responders after 12 months. In our study, iloprost inhalation was as effective as adenosine in significantly decreasing mPAP
and TPR, and increasing CI and SvO₂. No patient manifested an acute vasodilator response to adenosine without also responding to iloprost.

Although aerosolised iloprost produced a statistically significant decrease in SVR, the decrease of mSAP was only about 2 mmHg, and only one patient experienced slight hypotension. The numbers of adverse events occurring with aerosolised iloprost during vasoreactivity testing were much less than those occurring with infused adenosine. Whereas 47.3% of patients experienced adverse events (mostly palpitations or shortness of breath) with adenosine, only 2.7% experienced adverse events with iloprost.

The recommended dosage of infused adenosine to acutely assess vasodilator responsiveness is 50 µg/kg/min, increased by 50 µg/kg/min every 2 minutes to a maximum dose of 350-500 µg/kg/min [3,4]. However, in this study, we found that the mean tolerated dose of infused adenosine was just 167 ± 42 µg/kg/min, and only 39 of the 74 patients were able to receive 200 µg/kg/min without experiencing adverse effects. The mean dose of infused adenosine that achieved a maximal reduction of mPAP was 88 ± 40 µg/kg/min, which is significantly lower than the recommended maximal dose. In addition, the dose that achieved a maximal reduction of mPAP was much lower in responders than in non-responders (72 ± 9 µg/kg/min vs 90 ± 42 µg/kg/min, respectively; p = 0.004), and the dose in all responders was less than 100 µg/kg/min. Thus, we believe that the dosage of infused adenosine recommended in recent guidelines is too high to assure its safety and tolerability for acute vasoreactivity testing. At least for Chinese patients, a dose ranging from 50 to 200 µg/kg/min appears high enough to evaluate acute pulmonary responsiveness.

Other than vasoreactivity testing, there are, at present, no valuable clinical or haemodynamic features that can be considered useful predictors for identifying patients who are likely to be acute responders [21-23]. However, in our study, younger patients were more likely to be acute responders. Younger patients may have less severe disease, as demonstrated by a higher proportion in WHO functional class II, a lower mPAP and RAP, and a higher SvO₂. Interestingly, we also found that the ET-1 concentration in acute responders was profoundly
lower than in non-responders. These results may be explained by the strong correlation between ET-1 and the severity of PAH [24,25].

Our study has several limitations. Firstly, adenosine was always given before iloprost, and although we ensured that haemodynamic parameters had returned to baseline before iloprost was administered, we cannot fully exclude a conditioning or priming effect of pretreatment with adenosine. Secondly, adenosine is not the most commonly used agent to perform acute vasoreactivity testing because of its lower selectivity for the pulmonary circulation in comparison with NO or epoprostenol. We were not able to compare iloprost with the latter agents as neither has been available in mainland China up to now. Finally, the duration of follow-up may not have been long enough to fully confirm that those patients who responded acutely in the first evaluation were still long-term responders.

In conclusion, aerosolised iloprost can be effectively and safely used as a screening agent to identify long-term responders to oral CCB therapy in patients with IPAH. In comparison with adenosine infusion, iloprost is much better tolerated, and has the potential to become a valuable new choice for vasoreactivity testing.

ACKNOWLEDGEMENTS
The authors wish to acknowledge Mr Richard Ronald for his editorial assistance in the preparation of this manuscript.
REFERENCES


<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (n = 74)</th>
<th>Responders to iloprost (n = 10)</th>
<th>Non-responders to iloprost (n = 64)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical features:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>33.2 ± 12.1</td>
<td>22.6 ± 9.1</td>
<td>34.5 ± 11.8</td>
<td>0.008</td>
</tr>
<tr>
<td>Male/female, n</td>
<td>16 / 58</td>
<td>3 / 7</td>
<td>13 / 51</td>
<td>0.554</td>
</tr>
<tr>
<td>WHO class II/III, n</td>
<td>35 / 39</td>
<td>9 / 1</td>
<td>26 / 38</td>
<td>0.002</td>
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<td>BSA, m²</td>
<td>1.6 ± 0.2</td>
<td>1.5 ± 0.2</td>
<td>1.7 ± 0.2</td>
<td>0.103</td>
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<tr>
<td>SaO₂, %</td>
<td>91.2 ± 7.9</td>
<td>92.4 ± 11.3</td>
<td>91.0 ± 7.5</td>
<td>0.656</td>
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<tr>
<td>SvO₂, %</td>
<td>62.0 ± 12.3</td>
<td>73.5 ± 9.4</td>
<td>60.7 ± 12.0</td>
<td>0.008</td>
</tr>
<tr>
<td>6MWD, m</td>
<td>390 ± 106</td>
<td>438 ± 80</td>
<td>384 ± 108</td>
<td>0.178</td>
</tr>
<tr>
<td><strong>Biochemical indicators:</strong></td>
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<td></td>
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<tr>
<td>UA, µmol/L</td>
<td>356 ± 110</td>
<td>323 ± 50</td>
<td>359 ± 114</td>
<td>0.419</td>
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<td>ET-1, fmol/L</td>
<td>1.0 ± 0.6</td>
<td>0.6 ± 0.2</td>
<td>1.0 ± 0.6</td>
<td>&lt;0.001</td>
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<tr>
<td>BNP, fmol/L</td>
<td>1273 ± 1137</td>
<td>718 ± 310</td>
<td>1333 ± 1178</td>
<td>0.175</td>
</tr>
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<td><strong>Haemodynamic variables:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>87.3 ± 14.2</td>
<td>80.7 ± 13.9</td>
<td>88.0 ± 14.1</td>
<td>0.196</td>
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<td>PCWP, mmHg</td>
<td>6.7 ± 3.7</td>
<td>6.4 ± 4.6</td>
<td>6.8 ± 3.6</td>
<td>0.772</td>
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<td>mPAP, mmHg</td>
<td>61.1 ± 17.6</td>
<td>48.4 ± 10.5</td>
<td>62.6 ± 17.7</td>
<td>0.029</td>
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<td>mSAP, mmHg</td>
<td>83.8 ± 11.7</td>
<td>77.6 ± 5.2</td>
<td>84.6 ± 12.1</td>
<td>0.115</td>
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<td>RAP, mmHg</td>
<td>5.3 ± 5.1</td>
<td>3.1 ± 1.9</td>
<td>6.8 ± 5.6</td>
<td>0.001</td>
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<tr>
<td>TPR, Wood Units</td>
<td>17.3 ± 9.7</td>
<td>11.4 ± 5.8</td>
<td>18.0 ± 9.9</td>
<td>0.088</td>
</tr>
<tr>
<td>SVR, Wood Units</td>
<td>21.4 ± 8.8</td>
<td>16.7 ± 5.0</td>
<td>21.9 ± 9.0</td>
<td>0.139</td>
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<td>CI, L/min/m²</td>
<td>2.6 ± 1.2</td>
<td>2.9 ± 1.4</td>
<td>2.6 ± 1.2</td>
<td>0.439</td>
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</table>

Values are means ± SD, except for gender and WHO functional class.

* The PCWP could not be successfully measured in 8 patients at the first evaluation because of a markedly enlarged right atrium and severe tricuspid regurgitation, but these 8 patients were identified as having a PCWP <15 mmHg on repeated right heart catheterisation with the aid of a guidewire with a diameter of 0.025 inches (Cordis Co., Ltd, Johnson & Johnson, USA) 6 to 12
months later.

BNP: brain natriuretic peptide; BSA: body surface area; CI: cardiac index; ET-1: endothelin-1; HR: heart rate; m: metres;
6MWD: six minutes walk distance; mPAP: mean pulmonary arterial pressure; mSAP: mean systemic arterial pressure; PCWP: pulmonary capillary wedge pressure; RAP: right atrial pressure; SaO₂: arterial oxygen saturation; SvO₂: mixed-venous oxygen saturation; SVR: systemic vascular resistance; TPR: total pulmonary resistance; UA: uric acid.
# TABLE 2
Haemodynamic variables and blood gases at baseline and in response to infused adenosine and aerosolised iloprost

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adenosine (50-200 µg/kg/min)</th>
<th>Iloprost (5 µg)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline A (before adenosine)</td>
<td>Baseline I (before iloprost)</td>
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<tr>
<td>HR, beats/min</td>
<td>87.3 ± 14.2</td>
<td>87.3 ± 12.6</td>
</tr>
<tr>
<td>mPAP, mmHg</td>
<td>61.1 ± 17.6</td>
<td>55.2 ± 19.4*</td>
</tr>
<tr>
<td>mSAP, mmHg</td>
<td>83.8 ± 11.7</td>
<td>81.7 ± 10.5*</td>
</tr>
<tr>
<td>TPR, Wood Units</td>
<td>17.5 ± 9.8</td>
<td>14.4 ± 9.4*</td>
</tr>
<tr>
<td>SVR, Wood Units</td>
<td>21.5 ± 8.8</td>
<td>18.8 ± 8.7*</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>2.7 ± 1.1</td>
<td>3.1 ± 1.4*</td>
</tr>
<tr>
<td>SvO₂, %</td>
<td>60.8 ± 13.4</td>
<td>68.5 ± 12.8*</td>
</tr>
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</table>

Values are means ± SD.

* p < 0.05 for adenosine vs baseline A, and for iloprost vs baseline I, respectively.

# p < 0.05 for changes of SvO₂ between adenosine infusion and iloprost inhalation.

NS indicates no significant difference in haemodynamic responses between adenosine infusion and iloprost inhalation.

*Abbreviations: refer table 1.*
<table>
<thead>
<tr>
<th>Patients with AEs, n (%)</th>
<th>Adenosine (n = 74)</th>
<th>Iloprost (n = 74)</th>
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<tbody>
<tr>
<td>Increased cough, n (%)</td>
<td>0</td>
<td>1 (1.4)</td>
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<tr>
<td>Hypotension, n (%)</td>
<td>3 (4.1)</td>
<td>1 (1.4)</td>
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<tr>
<td>Flushing, n (%)</td>
<td>2 (2.7)</td>
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<tr>
<td>Palpitations or shortness of breath, n (%)</td>
<td>27 (36.5)</td>
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<tr>
<td>Abdominal pain, n (%)</td>
<td>2 (2.7)</td>
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<tr>
<td>Pharyngeal pain, n (%)</td>
<td>1 (1.4)</td>
<td>0</td>
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<tr>
<td>Other observed AEs, n (%)</td>
<td>0</td>
<td>0</td>
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### TABLE 4
Baseline and long-term follow-up data for 9 responders to aerosolised iloprost* after 12 months of high-dose CCB therapy

<table>
<thead>
<tr>
<th>Responder No.</th>
<th>Sex (F/M)</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Follow-up time (months)</th>
<th>Dose of diltiazem (mg/day)</th>
<th>WHO functional class</th>
<th>6MWD (m)</th>
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* 8 patients were also responders to infused adenosine.

CCB: calcium channel blocker; 6MWD: six minutes walk distance; WHO: World Health Organization.
FIGURE LEGENDS

FIGURE 1. Comparison of the effects of infused adenosine (50-200 µg/kg/min) and aerosolised iloprost (5 µg inhaled for about 10-15 min) on mean pulmonary artery pressure (mPAP) [A], total pulmonary resistance (TPR) [B], and cardiac index (CI) [C] in 74 patients with idiopathic pulmonary arterial hypertension (IPAH). Dots represent individual responses compared with baseline, expressed as a percentage. A location below the line of identity indicates a more pronounced effect of iloprost, while a location above the line of identity reflects a more pronounced effect of adenosine.

FIGURE 2. Changes in mean pulmonary artery pressure (mPAP) between baseline 1 (first evaluation in our centres) and baseline 2 (re-evaluation after 12 months of high-dose CCB therapy) during right heart catheterisation in 9 responders to aerosolised iloprost. After high-dose CCB treatment, haemodynamic parameters at baseline were improved in all 9 patients, and 5 achieved normal or near-normal haemodynamics (mPAP <30 mmHg).
**FIGURE 1 A, B, C**

**Title:** Comparison of the acute effects of infused adenosine and aerosolised iloprost on mPAP, TPR, and CI.

Changes in mPAP with aerosolised iloprost

Changes in TPR with aerosolised iloprost

Changes in CI with aerosolised iloprost
**Figure 2**

**Title:** Changes in mPAP between baseline 1 (first evaluation in our centres) and baseline 2 (re-evaluation after 12 months of high-dose CCB therapy) during right heart catheterisation in 9 responders to aerosolised iloprost