Inhaled nitric oxide as a screening agent for safely identifying responders to oral calcium-channel blockers in primary pulmonary hypertension

O. Sitbon, M. Humbert, J-L. Jagot, O. Taravella, M. Fartoukh, F. Parent, P. Herve, G. Simonneau

Inhaled nitric oxide as a screening agent for safely identifying responders to oral calcium-channel blockers in primary pulmonary hypertension. O. Sitbon, M. Humbert, J-L. Jagot, O. Taravella, M. Fartoukh, F. Parent, P. Herve, G. Simonneau. ©ERS Journals Ltd 1998.
ABSTRACT: In a subset of patients with primary pulmonary hypertension (PPH), high doses of oral calcium-channel blockers (CCB) produce a sustained clinical and haemodynamic improvement. However, significant side-effects have been reported during acute testing with CCB. Therefore, to identify accurately patients who may benefit from long-term CCB therapy, there is a need for a safe, potent and short-acting vasodilator.

The aim of this study was to compare the acute response to inhaled nitric oxide (NO) and oral high doses of CCB in 33 consecutive patients with PPH. A significant acute vasodilator response was defined by a fall in both mean pulmonary artery pressure and total pulmonary resistance by >20%.

Ten patients responded acutely to NO, nine of whom responded acutely to CCB, without any complications. The 23 other patients failed to respond to NO and CCB. In these nonresponders, nine serious adverse events were observed with CCB (38%). There was no clinical or baseline haemodynamic feature predicting acute vasodilator response. Long-term oral treatment with CCB was restricted to the nine acute responders and a sustained clinical and haemodynamic improvement was observed in only six patients.

In primary pulmonary hypertension, the acute response rate to high doses of calcium-channel blockers is low (27%). Serious adverse reactions to high doses of calcium-channel blockers during acute testing are frequently observed in nonresponders. It is concluded that nitric oxide may be used as a screening agent for safely identifying patients with primary pulmonary hypertension who respond acutely to calcium-channel blockers and may benefit from long-term treatment with these agents .
Eur Respir J 1998; 12: 265–270.

Service de Pneumologie et Réanimation Respiratoire, UPRES Maladies Vasculaires Pulmonaires, Hôpital Antoine Béclère, Université Paris XI, Clamart, France.

Correspondence: O. Sitbon
Service de Pneumologie et Réanimation
157, Avenue de la Porte de Trivaux
92141 Clamart Cedex
France
Fax: 33 146303824

Over the past decade, there has been considerable interest in the use of vasodilator agents in the treatment of patients with primary pulmonary hypertension (PPH) [1, 2]. The calcium-channel blockers (CCB) nifedipine and diltiazem are the most widely used drugs for oral long-term treatment in patients with PPH [3]. Recommended doses of CCB in PPH are usually higher than those commonly given in others indications [3]. However, their long-term administration is restricted to a minority of patients who respond acutely to such drugs [4–6]. In addition, a major issue concerns the possible occurrence of severe side-effects during acute vasodilator testing with CCB in patients with PPH, even when conventional doses are used [7–10]. Therefore, there is a need for a safe, potent and short-acting vasodilator with limited side-effects during acute testing to identify accurately those patients who may benefit from long-term CCB therapy [11–15]. For this purpose, inhaled nitric oxide (NO), a selective pulmonary vasodilator, could be one of the most suitable candidates [12, 16]. The aim of the present study was to assess whether inhaled NO testing could identify patients with PPH

who are likely to respond to high doses of CCB. Thus, the efficacy and safety of inhaled NO and high doses of oral CCB were prospectively compared during acute vasodilator testing in 33 consecutive patients with PPH referred to the authors' centre for therapeutic assessment.

Methods

Subjects

Thirty-three consecutive patients with PPH referred to the authors' centre between September 1994 and May 1995 were included in this study. Each patient fulfilled the diagnostic criteria for PPH according to the protocol of the National Institutes of Health Primary Pulmonary Hypertension Registry [17]. Pulmonary hypertension was defined by a mean pulmonary artery pressure (Ppa) >3.3 kPa (25 mmHg) at rest with a mean pulmonary artery occlusion pressure ð1.6 kPa (12 mmHg), during right-side heart catheterization. Secondary causes of pulmonary hypertension, including significant connective tissue disease,

were excluded on the results of history, physical examination, chest radiography, pulmonary function testing, perfusion lung scan or pulmonary angiography or both, two-dimensional echocardiography and absence of left-to-right shunting.

Study design

A complete initial baseline haemodynamic evaluation was performed in supine patients, while they were breathing room air and after all vasodilating or inotropic agents had been discontinued for at least 36–48 h before the study. After venous access was achieved through an antecubital or internal jugular vein, catheterization was performed by means of a 7F triple lumen flow-directed thermodilution catheter (Baxter Edwards, Irvine, CA, USA) which was advanced into a lower lobar pulmonary artery under fluoroscopic guidance. Transducers were positioned at the mid-axillary line and zeroed at atmospheric pressure. Cardiac output (CO) was determined in triplicate with cold dextrose (0–5°C) by the thermodilution technique (Cardiac Output Computer; Baxter Edwards). Cardiac index (CI) was calculated as CO divided by body surface area (m^2). Because the pulmonary artery occlusion pressure could not be consistently recorded in all patients during the entire haemodynamic evaluation, total pulmonary resistance (TPR), instead of pulmonary arterial resistance, was considered and calculated as Ppa divided by CI. Cardiac frequency (fC) was monitored continuously and systemic arterial pressure determined intermittently by an automated blood pressure cuff (Dinamap® 1800; Critikon, Tampa, FL, USA). Transcutaneous arterial oxyhaemoglobin saturation was continuously monitored by pulse oximetry (Biox 3700; Ohmeda, Louisville, CO, USA).

After two or three sets of baseline haemodynamic measurements over 90 min, patients were initially tested with a short-term inhalation of an air-NO (10 parts per million (ppm)) mixture administered through a face mask over 6–10 min, as described previously [12]. After acute testing with NO was completed, patients were transferred to the intensive care unit for further evaluation with CCB. The study was conducted according to guidelines provided previously by RICH and BRUNDAGE [4]. After return to control haemodynamic values, each patient received a conventional dose of a fast-release preparation of either nifedipine (20 mg) or diltiazem (60 mg), depending on the patients' cardiac frequency at rest (more or less than 100 beats·min^{-1}) and haemodynamic measurements were recorded after 1 h. Consecutive oral doses of either nifedipine or diltiazem were then administered hourly to the patients until: 1) a positive response was observed, defined as a >20% fall in both mean pulmonary arterial pressure and pulmonary vascular resistance, with no further decrease after one additional dose; 2) the patient experienced serious adverse effects such as shock, a decrease in systolic blood pressure >30% relative to control value or <90 mmHg, a decrease in fC <50 beats·min^{-1}; 3) the occurrence of intolerable gastrointestinal side-effects such as vomiting, precluding further drug administration; or 4) unchanged haemodynamics after 6–8 consecutive hourly doses.

Only the patients in whom a positive response was achieved during short-term testing were considered for long-term treatment. About half of the cumulative dose of drug deemed effective was administered every 6–8 h over 24 h. Extended-release preparations were not used because of uncertainties in the dosage required to achieve blood levels equivalent to fast-release preparations and to limit the duration of action of the drugs in case of potential adverse effects during long-term treatment. Anticoagulant therapy with acenocoumarol or warfarin was advised in all patients, at doses needed to maintain an international normalized ratio (INR) of around 2. Repeat right-side heart catheterization was planned after at least 3 months of therapy for each patient receiving long-term treatment.

The study design was conducted as described by RICH and BRUNDAGE [4], and each patient gave informed consent before inclusion.

Statistical analysis

All results are expressed as mean±SD (range). One-way analysis of variance (ANOVA) with repeated measures was performed for haemodynamic values obtained at baseline and during testing with NO and CCB. Multiple comparisons were made when the F-value was statistically significant. The Student's unpaired t-test and the Chi-squared test were performed to compare responders and nonresponders at baseline, as appropriate. A p-value <0.05 was taken as statistically significant.

Results

Study group

The clinical characteristics and baseline haemodynamic features of the 33 patients enrolled into the study are listed in table 1. The mean age, sex distribution (female to male ratio 2:1), disease duration and extent of functional impairment were characteristic of PPH [17], as were the severity of haemodynamic features, with marked elevations in mean Ppa (7.9±1.6 kPa (59±12 mmHg)) and TPR (3.5±1.2 kPa·L^{-1}·min^{-1}·m^{-2} (26±9 mmHg·L^{-1}·min^{-1}·m^{-2})).

Table 1. – Patient baseline clinical characteristics and haemodynamic findings

Age yrs	46±15
Female/male ratio	22/11
Risk factors and associated conditions n	
Raynaud's phenomenon	9
Portal hypertension	2
Family history of primary pulmonary hypertension	1
Appetite suppressant use	5
Human immunodeficiency virus infection	0
Functional class New York Heart Association	
I or II/III or IV n	14/19
Baseline haemodynamics	
Right atrial pressure mmHg	10±6
Mean pulmonary artery pressure mmHg	59±12
Pulmonary artery occlusion pressure mmHg	9±2
Cardiac index L·min^{-1}·m^{-2}	2.4±0.6
Total pulmonary resistance mmHg[-1]·L·min^{-1}·m^{-2}	26±9
Cardiac frequency beats·min^{-1}	82±14
Systemic vascular resistance mmHg[-1]·L·min^{-1}·m^{-2}	37±10
Mixed venous oxygen saturation %	64±10

Results are given as mean±SD. 1 mmHg=0.133 kPa.

Table 2. – Haemodynamic findings during acute vasodilator testing

	Responders (n=10)			Nonresponders (n=23)		
	Baseline	NO	CCB	Baseline	NO	CCB
Right atrial pressure mmHg	10±5	7±4*	6±4*	10±6	10±6	11±5
Mean pulmonary artery pressure mmHg	57±11	39±10***	40±8***	59±12	55±14	55±11
Pulmonary artery occlusion pressure mmHg	9±2	ND	ND	10±2	ND	ND
Mean systemic arterial pressure mmHg	90±11	87±10	80±13*	97±16	97±17	81±9***
Cardiac frequency beats·min⁻¹	75±14	66±14*	83±17	85±14	83±13	83±12
Cardiac index L·min⁻¹·m⁻²	2.5±0.6	2.8±0.6	3.2±0.9*	2.4±0.6	2.4 ±0.6	2.3±0.8
Total pulmonary resistance mmHg·L⁻¹·min⁻¹·m⁻²	25±10	15±6***	14±6***	27±9	24±8	26±10
Systemic vascular resistance mmHg·L⁻¹·min⁻¹·m⁻²	34±9	30±6	24±5*	38±9	37±10	32±10*

Results are given as mean±SD. NO: nitric oxide; CCB: calcium-channel blockers; ND: not done. *: p<0.05, ***: p<0.001 (analysis of variance) compared to baseline. 1 mmHg=0.133 kPa.

Acute response to vasodilators

The results of acute vasodilator challenge with NO and high doses of CCB are presented in table 2.

Ten out of the 33 patients responded to NO with a mean decrease in Ppa and TPR of 32±10% (20–48) and 40±7% (28–52), respectively. Among these patients, nine (90%, *i.e.* 27% of the study population) also responded significantly to high doses of CCB, with a mean decrease of 28±7% (22–43) in Ppa and 43±12% (22–61) in TPR. Responses were observed after a mean of 41±1.8 doses (2–7) of either nifedipine (n=7) or diltiazem (n=2). How-

ever, three patients (one-third of responders to calcium antagonists) had a significant decrease in Ppa and TPR as soon as 1 h after receiving a single test-dose of nifedipine. One patient who initially responded to NO failed to respond to diltiazem after six consecutive hourly doses. The consecutive individual changes in Ppa and TPR observed with NO and high doses of CCB in these patients are shown in figures 1a and 2a.

The remaining patients (n=23) failed to respond significantly to NO, with a mean decrease in Ppa and TPR of 7±8% and 9±11%, respectively. These patients also failed
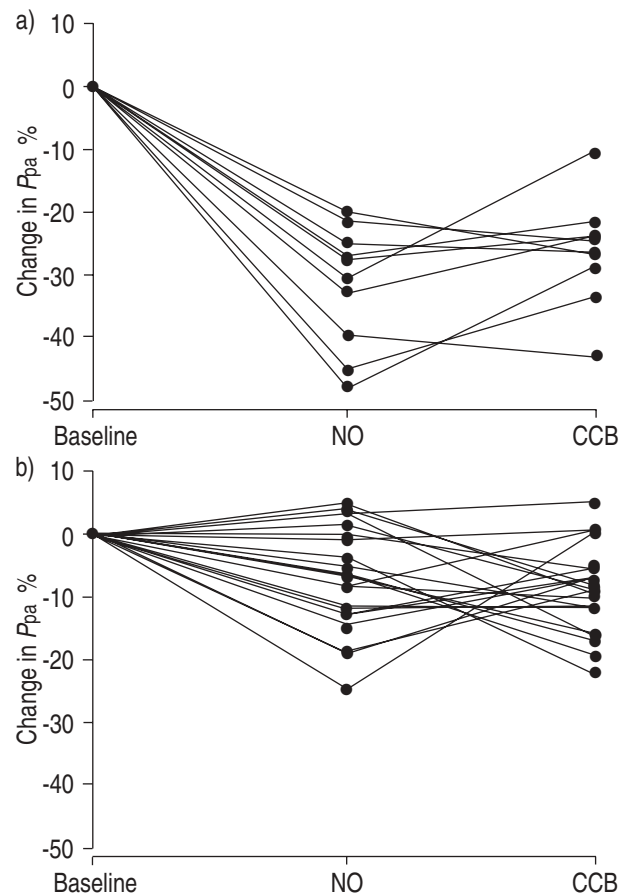

Fig. 1. – Individual change in mean pulmonary artery pressure (Ppa) in a) responders; and b) nonresponders. One patient did not respond to a high dose of diltiazem (360 mg) while responding to nitric oxide (NO). The two apparent responders had no significant change in total pulmonary resistance. CCB: calcium-channel blockers.
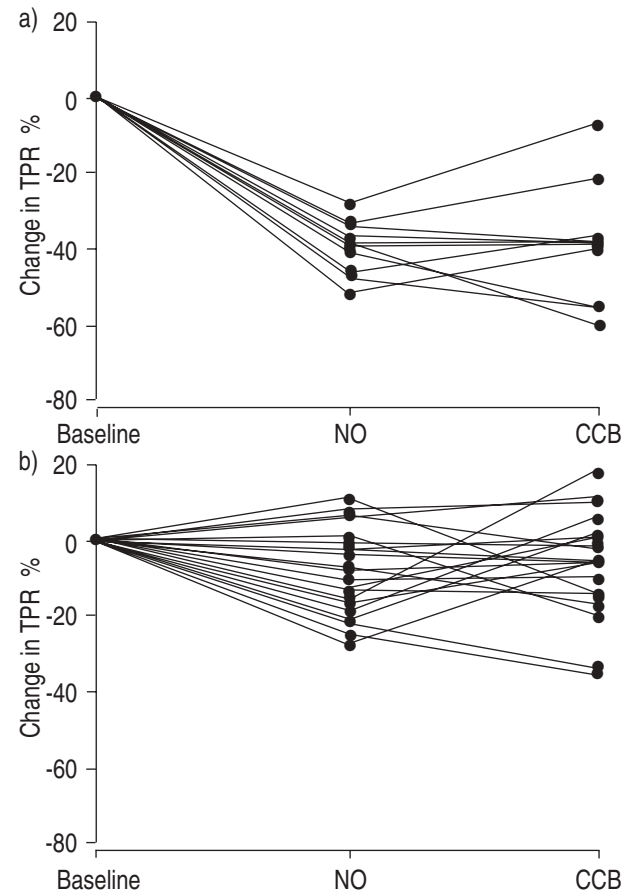
Fig. 2. – Individual change in total pulmonary resistance (TPR) in a) responders; and b) nonresponders. One patient did not respond to a high dose of diltiazem (360 mg) while responding to nitric oxide (NO). The four patients who were apparent responders to either NO or calcium-channel blockers (CCB) had no significant change in mean pulmonary artery pressure.

to respond to CCB. Nine had been tested with nifedipine and 14 with diltiazem. In two of them, severe systemic hypotension occurred after a single test-dose of 20 mg nifedipine, precluding further evaluation. In the 21 remaining patients in whom larger doses (mean 5.6±2.2, range: 2–11) were administered, the mean change in P_{pa} and TPR was -9±7% (-22–+5) and -6±13% (-35–+18), respectively. Individual haemodynamic changes for these patients are presented in figures 1b and 2b. By definition, acute responders had a significant decrease in both P_{pa} and TPR. Therefore, six patients were classified as nonresponders despite an isolated decrease in P_{pa} or TPR (figs. 1b and 2b).

No clinical or baseline haemodynamic feature were found which could have enabled us to predict which patient would have responded to vasodilators (table 3).

Adverse events

Inhalation of the air-NO mixture did not produce any side-effects such as systemic hypotension or cough. Ad-

Table 3. – Patient baseline clinical characteristics and haemodynamic findings in responders (R) and nonresponders (NR)

	R (n=10)	NR (n=23)
Age yrs	38±15	49±14
Female/male ratio	8/2	14/9
Onset of symptoms months	17±13	29±26
Functional class NYHA		
I or II/III or IV n	4/6	10/13
Baseline haemodynamics		
Right atrial pressure mmHg	10±5	10±6
Mean pulmonary artery pressure mmHg	57±11	59±12
Pulmonary artery occlusion pressure mmHg	9±2	10±2
Mean systemic arterial pressure mmHg	90±11	97±16
Cardiac frequency beats·min⁻¹	75±14	85±14
Cardiac index L·min⁻¹·m⁻²	2.5±0.6	2.4±0.6
Total pulmonary resistance mmHg·L⁻¹·min⁻¹·m⁻²	25±10	27±9
Systemic vascular resistance mmHg·L⁻¹·min⁻¹·m⁻²	34±9	38±9
Mixed venous oxygen saturation	67±10	59±10

Results are given as mean±SD. NYHA: New York Heart Association. There were no significant differences between the groups. 1 mmHg=0.133 kPa.

Table 4. – Adverse events with high doses of calcium-channel blockers

Responders (n=9)	Nonresponders (n=24)
No adverse reaction	One death, 12 h after completion of the protocol
	Eight severe adverse events:
	shock (n=1)
	severe systemic hypotension (n=5)
	vomiting (n=2)
	Five major adverse events:
	nausea (n=3)
	headache (n=2)

verse events that occurred during short-term testing with high-dose CCB are listed in table 4. Responders did not complain of any discomfort, nausea, headache or other more severe adverse reactions, whereas one third (eight patients) of the nonresponders presented severe adverse reactions including shock (n=1), prolonged systemic hypotension (n=5) requiring fluid loading and inotropic support with dobutamine for >24 h, and two patients suffered from severe vomiting precluding further drug testing. One patient died suddenly 12 h after completion of the vasodilator challenge, although no adverse event was reported during oral diltiazem challenge (total dose: 360 mg). Five other nonresponders had minor side-effects such as nausea and headache. The high incidence of severe adverse events encountered led us to interrupt the study.

Long-term response to calcium-channel blockers

Long-term therapy with high doses of CCB was restricted to the nine short-term responders, with either nifedipine in seven or diltiazem in two subjects. Eight of these patients returned for haemodynamic evaluation after 13±4 months (range 7–19) of treatment with CCB (table 5). Six patients (18%) had a sustained and major chronic vasodilator effect, but two failed to respond to long-term treatment. The remaining patient died 4 months after the treatment with nifedipine.

Discussion

In patients with PPH, the question of the overall efficacy of administering vasodilators is still of concern, as is

Table 5. – Long-term response to high doses of calcium-channel blockers (CCB) in responders

Patient no.	Baseline		Acute testing			3 months			Last news*		
	P_{pa}	TPR	CCB mg	P_{pa}	TPR	CCB mg·day⁻¹	P_{pa}	TPR	CCB mg·day⁻¹	P_{pa}	TPR
1	57	24.4	DTZ 360	43	14.4	DTZ 720	41	9.4	DTZ 720	28	8.1
2	68	23.1	NIF 140	48	10.1	-	ND	ND	NIF 120	30	10.9
3	42	12.8	NIF 80	28	8.0	NIF 120	27	7.0	DTZ 360⁺	27	7.9
4	62	23.5	NIF 40	35	10.3	NIF 60	46	15.6	DTZ 360⁺	47	17.8
5	45	18.6	NIF 80	34	11.6	NIF 60	47	17.3	DTZ 360⁺	56	21.1
6	70	44.8	NIF 60	51	17.5	NIF 160	44	12.9	NIF 160	46	12.0
7	59	30.0	NIF 60	43	18.2	-	ND	ND	NIF 180	54	19.7
8	39	13.0	NIF 40	30	8.0	NIF 90	41	13.2	DTZ 360⁺	48	14.2
9	60	32.4	DTZ 360	45	25.4	-	ND	ND	-	ND	ND

P_{pa}: mean pulmonary artery pressure (mmHg); TPR: total pulmonary resistance (mmHg·L⁻¹·min⁻¹·m⁻²); DTZ: diltiazem; NIF: nifedipine; ND: not done. 1 mmHg=0.133 kPa. *: At 13±4 months (range 7–19). ⁺: In all patients, adverse events such as lower limbs oedema occurred with nifedipine, leading to the substitution with diltiazem.
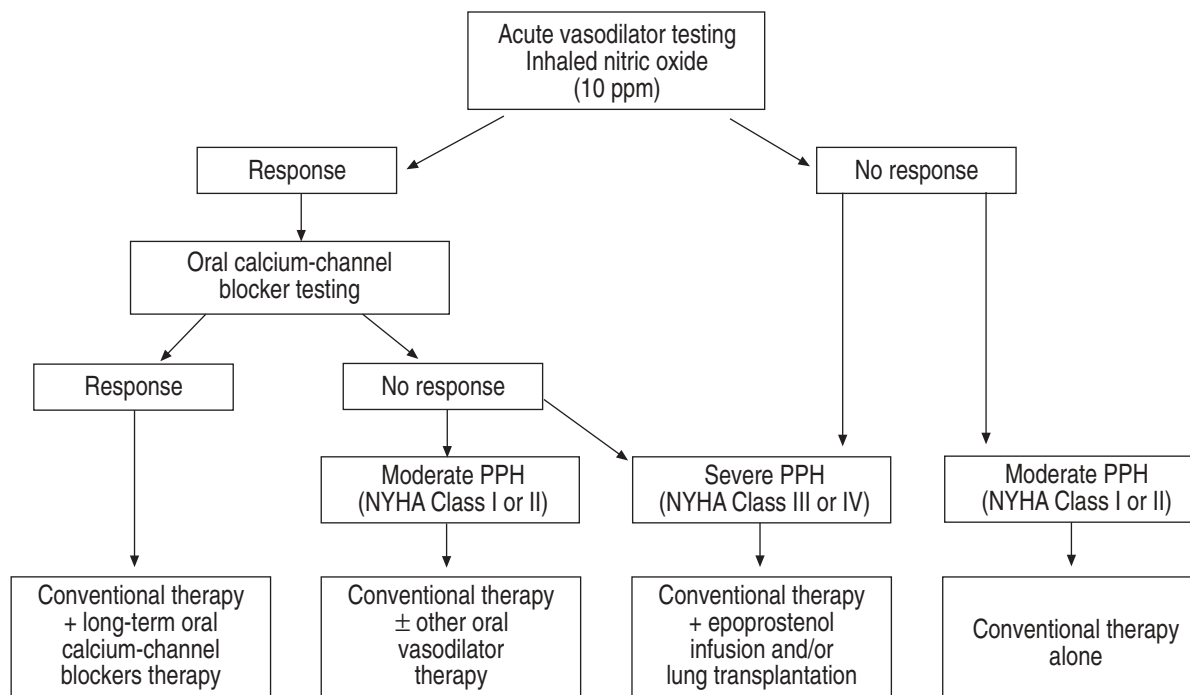
Fig. 3. – Current protocol for the therapeutic approach to primary pulmonary hypertension (PPH) (South-Paris University). Vasodilator response is defined by a fall in both mean pulmonary pressure and total pulmonary resistance by >20%. Conventional therapy includes oral anticoagulation with diuretics and supplemental oxygen if necessary. Epoprostenol infusion is used as an alternative or a bridge to transplantation. Other oral vasodilators include nitroglycerine, phentolamine and hydralazine. NYHA: New York Heart Association; ppm: parts per million.

the method of safely identifying those patients who may benefit from long-term treatment [18, 19]. It is generally accepted that the initial response to acute vasodilator testing accurately identifies patients with PPH who are likely to respond to chronic oral treatment [3]. Currently, the most widely used drugs for long-term therapy are the CCB nifedipine and diltiazem [3, 6].

The main result of our study was to demonstrate that serious adverse events were frequently observed during acute vasodilator challenge with oral CCB (38%). Interestingly, these adverse events, such as vomiting, hypotension, or shock, were only observed in nonresponders to CCB. The importance of these adverse reactions, which may be life-threatening, led us to interrupt the study. Significant side-effects during acute testing with CCB have been previously described by other investigators [9, 10], including a case of sudden death following the administration of a single dose of nifedipine in a patient with PPH [8]. This contrasted with the absence of severe side-effects reported in the main study published by Rich et al. [6] on acute testing with high-doses of CCB. There is no clear explanation for these distinct results. Indeed, the study design for acute vasodilator testing was identical in the present study and the report by Rich et al. [6]. The patients enrolled in the present study had severe pulmonary hypertension (table 1) with comparable clinical and haemodynamic characteristics to the patients reported by Rich et al. [6]. The average dose of CCB given to achieve the maximal pulmonary vasodilatation was the same in the two studies. The proportion of responders was identical in both studies (27%), with a similar magnitude in the pulmonary vasodilator response.

Another important finding of the present study was the demonstration that during the initial evaluation of a large number of consecutive patients with PPH, NO inhalation induced a comparable individual pulmonary vasodilatation to that achieved with high doses of oral CCB. Acute vasodilator testing with inhaled NO had a sensitivity of 90% and a specificity of 100% in detecting a short-term pulmonary vasodilator response to oral CCB. The acute pulmonary vasodilation with inhaled NO, a selective pulmonary vasodilator, was obtained without any adverse event, as we reported previously [12]. Thus, NO can accurately and safely detect those patients with PPH who may benefit from long-term treatment with oral CCB (fig. 3).

In conclusion, in patients with primary pulmonary hypertension, acute testing with oral calcium channel blockers can induce significant adverse reactions, especially in patients who fail to respond to these agents. Therefore, during initial acute haemodynamic evaluation, inhaled nitric oxide, or another short-acting agent, should be used as a first-line vasodilator agent in screening pulmonary vascular responsiveness. Oral calcium-channel blockers should not be used as a screening agent for pulmonary vascular responsiveness in patients with primary pulmonary hypertension. The chronic use of calcium-channel blockers should be restricted to primary pulmonary hypertension patients who respond acutely to inhaled nitric oxide.

References

1.   Weir EK, Rubin LJ, Ayres SM, *et al*. The acute administration of vasodilators in primary pulmonary hypertension: experience from the National Institutes of Health

Registry on Primary Pulmonary Hypertension. *Am Rev Respir Dis* 1989; 140: 1623–1630.

2. Weir EK. Acute vasodilator testing and pharmacological treatment of primary pulmonary hypertension. *In*: Fishman AP, ed. The pulmonary circulation: normal and abnormal. Mechanisms, management and the national registry. Philadelphia, PA, University of Pennsylvania Press 1990; pp. 485–499.

3. Rubin LJ. Primary pulmonary hypertension. *N Engl J Med* 1997; 336: 111–117.

4. Rich S, Brundage BH. High-dose calcium channel-blocking therapy for primary pulmonary hypertension: evidence for long-term reduction in pulmonary arterial pressure and regression of right ventricular hypertrophy. *Circulation* 1987; 76: 135–141.

5. Rich S, Kaufmann E. High dose titration of calcium channel blocking agents for primary pulmonary hypertension: guidelines for short-term drug testing. *J Am Coll Cardiol* 1991; 18: 1323–1327.

6. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992; 327: 76–81.

7. Hoeper MM, Wilke T, Welte T, Breuer HWM, Wagner TOF. How effective is the treatment with high-dose nifedipine for primary pulmonary hypertension? *Semin Respir Crit Care Med* 1994; 15: 490–494.

8. Partanen J, Nieminen MS, Luomanmaki K. Death in a patient with primary pulmonary hypertension after 20 mg of nifedipine. *N Engl J Med* 1993; 329: 812.

9. Farber HW, Karlinskz JB, Faling LJ. Fatal outcome following nifedipine for primary pulmonary hypertension. *Chest* 1983; 83: 708–709.

10. Aromatorio GJ, Uretsky BF, Reddy PS. Hypotension and sinus arrest with nifedipine in pulmonary hypertension. *Chest* 1985; 87: 265–267.

11. Raffy O, Azarian R, Brenot F, *et al*. Clinical significance of the pulmonary vasodilator response during short-term testing with prostacyclin in primary pulmonary hypertension. *Circulation* 1996; 93: 484–488.

12. Sitbon O, Brenot F, Denjean A, *et al*. Inhaled nitric oxide as a screening vasodilator agent in primary pulmonary hypertension. A dose-response study and comparison with prostacyclin. *Am J Respir Crit Care Med* 1995; 151: 384–389.

13. Simonneau G, Herve P, Petitpretz P, *et al*. Detection of a reversible component in primary pulmonary hypertension: value of prostacyclin acute infusion. *Am Rev Respir Dis* 1986; 133: A223.

14. Palevsky HI, Long W, Crow J, Fishman AP. Prostacyclin and acetylcholine as screening agents for acute pulmonary vasodilator responsiveness in primary pulmonary hypertension. *Circulation* 1990; 82: 2018–2026.

15. Rubin LJ, Groves BM, Reeves JT, Frosolono M, Handel F, Cato AE. Prostacyclin-induced acute pulmonary vasodilation in primary pulmonary hypertension. *Circulation* 1982; 66: 334–338.

16. Pepke-Zaba J, Higenbottam TW, Dinh-Xuan AT, Stone D, Wallwork J. Inhaled nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension. *Lancet* 1991; 338: 1173–1174.

17. Rich S, Dantzker DR, Ayres SM, *et al*. Primary pulmonary hypertension: a national prospective study. *Ann Intern Med* 1987; 107: 216–223.

18. Packer M. Is it ethical to administer vasodilator drugs in patients with primary pulmonary hypertension? *Chest* 1989; 95: 1173–1175.

19. Reeves JT, Groves BM, Turkevich D. The case for treatment of selected patients with primary pulmonary hypertension. *Am Rev Respir Dis* 1986; 134: 342–346.