ORIGINAL ARTICLE

Residual pulmonary vasodilative reserve predicts outcome in idiopathic pulmonary hypertension

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ABSTRACT

Objective Idiopathic pulmonary arterial hypertension (IPAH) remains a devastating and incurable, albeit treatable condition. Treatment response is not uniform and parameters that help to anticipate a rather benign or a malignant course of the disease are warranted. Acute pulmonary vasoreactivity testing during right heart catheterisation is recommended to identify a minority of patients with IPAH with sustained response to calcium channel blocker therapy. This study aimed to evaluate the prognostic significance of a residual pulmonary vasodilative reserve in patients with IPAH not meeting current vasoresponder criteria.

Design Observational right heart catheter study in 66 (n=66) patients with IPAH not meeting current vasoresponse criteria. Pulmonary vasodilative reserve was assessed by inhalation of 5 μg iloprost-aerosol.

Results Sixty-six (n=66) of 72 (n=72) patients with IPAH did not meet current definition criteria assessed during vasodilator testing to assess pulmonary vasodilatory reserve. In those, iloprost-aerosol caused a reduction of mean pulmonary artery pressure (Δ pulmonary artery pressure—11.4%; p<0.001) and increased cardiac output (Δ cardiac output +16.7%; p<0.001), resulting in a reduction of pulmonary vascular resistance (Δ pulmonary vascular resistance—25%; p<0.001). The magnitude of this response was pronounced in surviving patients. A pulmonary vascular resistance reduction of ≥30% turned out to predict outcome in patients with IPAH.

Conclusions Residual pulmonary vasodilative reserve during acute vasodilator testing is of prognostic relevance in patients with IPAH not meeting current definitions of acute vasoreactivity. Therefore vasoreactivity testing holds more information than currently used.

BACKGROUND

Idiopathic pulmonary arterial hypertension (IPAH) is a devastating, progressive and still not curable condition. Complex pathophysiological mechanisms, including variable pulmonary vasoconstriction and remodelling processes of pulmonary arteries, result in an increased pulmonary vascular resistance (PVR) with a subsequent reduction of cardiac output (CO) and, eventually, right heart failure.[1] Current approved therapies for the treatment of PAH have been shown to successfully target the predominance of vasoconstrictive and proproliferative mediators, resulting in an increased exercise capacity and clinical outcome.[2] However, treatment response is not uniform and a more benign as well as a rapidly progressive course of the disease may develop. Therefore, parameters that help to anticipate the natural course of a disease are warranted. This is especially true during first diagnosis of IPAH.

In this context, acute vasoreactivity testing during right heart catheterisation (RHC) is recommended to identify a small subgroup of patients with IPAH with favourable long-term response to treatment with high dose calcium channel blockers (CCBs). Acute vasoresponse criteria include a reduction of mean pulmonary arterial pressure (PAP) of at least 10 mm Hg to an absolute value below 40 mm Hg, accompanied by a normalisation of CO.[3] Since this applies to less than 10% of patients with an otherwise progressive and deadly disease, it is still important to identify this phenotype. Pulmonary vasodilators as inhaled nitric oxide (iNO) or iloprost, or an infusion of epoprostenol are recommended to quantify the vasodilative reserve of the pulmonary circulation.[4] Consequently, patients with an extensive pulmonary vasodilative response, meeting the strict criteria of pulmonary vasoresponse, should undergo treatment with solely vasodilating substances, that is, high dose CCB.[4] However, as stated above, this applies only for a minority of patients with IPAH and therefore it is implicated that relevant information from acute vasodilator testing can only be drawn for a very small number of patients with IPAH.

OBJECTIVE

The objective of this study was to evaluate the prognostic significance of a residual pulmonary vasodilative reserve during acute testing with iloprost-aerosol in a cohort of patients with IPAH not meeting current vasoresponder criteria.

DESIGN AND METHODS

Seventy-two (n=72) consecutive and clinically stable patients underwent vasoreactivity testing during RHC mainly during the initial workup of IPAH.

The diagnosis of IPAH was based on current recommendations[4] after exclusion of significant left heart and lung disease or other associated conditions. Exclusion of chronic thromboembolic pulmonary hypertension included a ventilation/perfusion scan.

Six individuals (n=6) met the current definition of acute vasoresponse[4] during RHC testing and were excluded from this analysis. RHC

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examinations were mainly done during the process of the first diagnosis of IPAH (incident cases) and therefore comprised patients who were therapy naïve for PAH therapies (n=49).

An informed consent was obtained from all patients; the study was approved by the institutional ethics committee.

Right heart catheterisation and haemodynamic testing

Patients were either naïve for PAH treatments (n=49; 74%) or PAH treatment was paused 12 h before the RHC.

Our modifications of RHC including a vasodilator test have been reported before.[5] Swan-Ganz Catheterisation (Criti-Cath; Becton Dickinson; Temse, Belgium) was done over the femoral vein access. Systemic blood pressure was measured non-invasively. All measurements were performed in recumbent position. Pressures were taken from right atrium and pulmonary artery (PAP, including pulmonary artery wedge pressure, PAWP). The mean value of triplicate measures using the thermodilution method was taken as CO (Cardiac Output Computer; Edwards Laboratories; Data Ana, USA). In addition, arterial blood gases and mixed venous oxygen saturation were measured. The PVR, systemic vascular resistance and cardiac index were calculated using standard formulas.

After a stable baseline period of at least 20 min (baseline) each patient inhaled 5 µg of iloprost (Ventavis, BayerVital, Germany) at mouthpiece over a time period of approximately 15 min.

Haemodynamic variables were taken immediately after stopping the iloprost inhalation and 15 min after the end of the aerosolisation period and the maximal response was recorded.

Definition of residual pulmonary vasoreactivity

A residual pulmonary vasoresponse was defined as a PVR reduction (Δ PVR) of ≥30%.[6] Additionally, patients were classified into four categories with regard to the achieved PVR reduction (ΔPVR ≤−10%, >−10≤−20%, >−20<−30% and ≥−30%).

Survival estimates

The observation period started with the day of the RHC and ended when the patient died or received lung transplantation (n=2). These patients were included as 'alive' until the day of transplantation and censored thereafter. All non-survivors died of cardiorespiratory failure. No patient was lost to follow-up.

Treatment approach

Six patients meeting the definition of positive vasoreactivity testing were excluded. In the remaining patients, the results of the vasoreactivity testing did not influence the therapeutic strategy.

In general, PAH therapy-naive patients were started on either an endothelin receptor antagonist (ERA) or phosphodiesterase 5 inhibitor (PDE5 I). Since this study was initiated before the approval of macitentan and riociguat, treatment included bosentan or ambrisentan (ERA) and sildenafil or tadalafil (PDE 5I). According to Hoeper *et al*[7] and current recommendations[2] we followed a goal oriented escalation of therapies, that is, combining of two oral drugs before initiating parenteral prostanoid therapy when individual therapy goals were not met.

Statistical analysis

Values are given as mean, median, SEM and/or minimum/maximum, respectively. The effect of iloprost-aerosol on haemodynamic parameters and blood gases was calculated in a paired fashion of the t test. A one factorial analysis of variance (ANOVA) with Bonferroni correction for multiple testing was performed when more than two groups were compared. The prognostic value of each variable was tested by univariate Cox proportional hazards regression analysis. Survival was derived from Kaplan-Meier curves. A p value <0.05 was considered statically significant. The statistical software used was SPSS V.15.0 for Windows.

RESULTS

Patient characteristics

Forty-six female and 20 male patients with IPAH with a mean age of 52.4±2 years were included. Pulmonary haemodynamics revealed severe precapillary PH with already reduced CO (table 1).

Haemodynamic effects of iloprost-aerosol

Inhalation of 5 µg of iloprost-aerosol was well tolerated and only minor side effects (coughing at beginning of the procedure, flushing, slight headache and feeling of warmth) occurred (table 1). None of these was judged as clinically significant or led to an early termination of the procedure.

The observed acute haemodynamic response was similar in pretreated and therapy-naive patients. After the inhalation, a reduction of mPAP (overall: Δ—11.3%; pretreated Δ—12.7%; treatment-naive: 10.9%; all p<0.001) paralleled by an increase of CO (overall: Δ+15%; pretreated: Δ+16%; treatment-naive Δ+14%; all p<0.001) and mixed venous saturation (overall: SvO_2+6.7 relative%; pretreated: SvO_2+7 relative% and treatment-naive:+6.6 relative%; all p<0.001) was observed. PAWP was unchanged and the achieved overall PVR reduction was Δ PVR—24.6% overall, Δ PVR—25.3% in the pretreated and Δ PVR—24.2% in the treatment-naive patients; (all p<0.001). While heart rate and oxygenation were not significantly affected, a mild reduction of systemic blood pressure was noted (overall: mean systemic arterial pressure from 92.4±2 mm Hg to 85±2 mm Hg, p<0.001, pretreated: 90±1.7 mm Hg

Table 1 Patient characteristics and haemodynamic response to a single dose of 5 µg iloprost-aerosol in idiopathic pulmonary arterial hypertension, IPAH (n=66)

Patient characteristics	
Gender (male/female)	20/46
Age (years)	52.4±2.0
6 MWD (m)	390±15

Haemodynamic data during vasoreactivity testing		
	Baseline	**Iloprost (5µg)**
HR (bpm)	77.4±1.8	79.1±2.1
CO (l/min)	4.0±0.13	4.6±0.2***
CI (l/min/m^2)	2.2±0.6	2.6±0.9***
RAP (mm Hg)	6.4±0.7	6.8±0.7
PAPmean (mm Hg)	50.6±1.9	44.9±2.0***
PAWPmean (mm Hg)	9.2±0.9	9.5±1
PVR (WU)	11.4±0.6	8.6±0.6***
SAPmean (mm Hg)	92.4±2.0	85.0±2.0***
SaO2 (%)	88.3±1.2	88.1±1.3
SvO2 (%)	56.3±1.3	60.1±1.3***
paO_2 (mm Hg)	64.4±2.6	66.0±2.3
$paCO_2$ (mm Hg)	36.3±1.3	35.1±1.4

*p<0.05; **p<0.01; ***p<0.001 compared with baseline.
6MWD, 6 min walking distance; CI, cardiac index; CO, cardiac output; HR, heart rate; paO_2, arterial partial pressure oxygen; $paCO_2$, arterial partial pressure carbon dioxide; PAP, pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SAP, systemic arterial pressure; SaO_2, arterial oxygenation; SvO_2, mixed venous oxygenation; WU, Wood units.

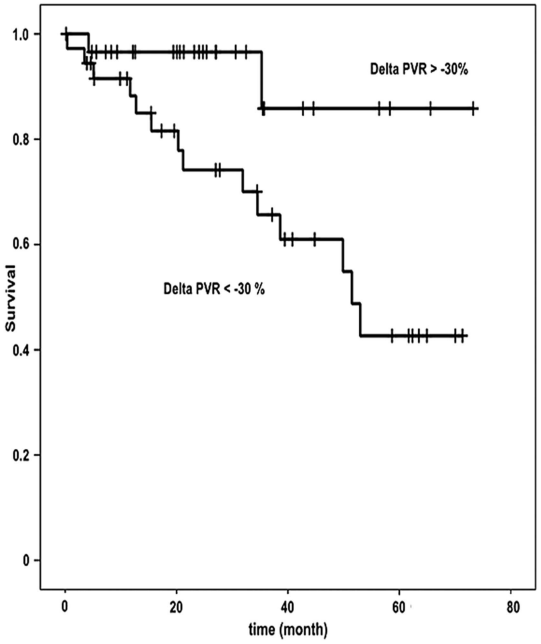
to 85.5±2 mm Hg p<0.01, treatment-naive 93.4±2.7 mm Hg to 84.8±2, p<0.001).

In terms of categorised PVR reduction, 10 (2 pretreated and 8 treatment naive) patients (15%) had Δ PVR of ≤−10%, 17 (3 pretreated and 14 treatment naive) (26%) had a Δ PVR of >−10≤−20%. In 9 patients (2 pretreated and 7 treatment naive) (14%) ΔPVR was >−20<−30% and 30 (10 pretreated and 20 treatment naive) (45%) patients had a ΔPVR of ≥−30%.

Prognostic implication of vasodilator testing

At the end of the observation period (mean observational time 30 months), 50 patients were alive or had undergone lung transplantation, while 16 (n=16; 24.2%) patients had died (table 2). The observed (transplant free) survival after 1 year, 3 years and 5 years was 91%, 65% and 38%, respectively. Comparing survivors and patients who died during follow-up revealed no significant differences with regard to baseline haemodynamics. However, the haemodynamic response to iloprost-aerosol was pronounced in the surviving patients. More precisely, the magnitude of CO increase and the associated reduction of PVR were significantly higher in patients who survived despite comparable baseline haemodynamics.

In addition, the failure to decrease PVR ≥30% was the only haemodynamic parameter at baseline and during vasoreactivity testing predictive of mortality (HR 4.6; CI 1 to 20.6, p<0.05) during univariate analysis. Moreover, patients with preserved pulmonary vascular reserve (ie, PVR reduction ≥30%) had a better observed outcome (figure 1). In detail, 2 out of 30 (7%) patients with a PVR reduction ≥30% died during an estimated mean survival time of 66.8±4.4 (CI 95% 58.1 to 75.5) months, while 14 of 36 patients (39%) with less PVR reduction died during a mean survival time of 47.6±3.7 (CI 95% 38.4 to 56.8) months (p<0.05).



T0	12 mo	24 mo	36 mo	48 mo	60 mo	72 mo	
30	23	16	6	4	2	1	DeltaPVR > -30%
36	27	20	15	10	6	0	DeltaPVR < -30%
66	50	36	21	14	8	1	Σ

Figure 1 Observed survival (Kaplan-Meier) in pulmonary arterial hypertension with or without pulmonary vascular resistance (PVR) reduction ≥30% during vasodilator test with iloprost-aerosol.

DISCUSSION

Although significant advances have been made in the diagnosis and treatment, IPAH remains a devastating and incurable, albeit treatable condition. However, since treatment response is not uniform and a more benign as well as a rapidly progressive course of the disease may develop, parameters that help to anticipate the natural course of a disease could help to improve IPAH management. This seems to be especially true for newly

Table 2 Comparing baseline haemodynamics and vasoreactivity (single dose of 5 μg iloprost-aerosol) in surviving and non-surviving patients

	Baseline		Iloprost-aerosol Max response	
	Non-survivors (n=16)	Survivors (n=50)	Non-survivors (n=16)	Survivors (n=50)
HR (bpm)	80.0±4.2	76.5±2.0	80.3±4.3	78.8±2.4
ΔHR (bpm)			0.3±1.3	2.2±1.2
CO (L/min)	4.0±0.3	4.0±0.1	4.4±0.3	4.7±0.2
ΔCO (L/min)			0.35±0.1	0.73±0.1*
PAPmean (mm Hg)	47.6±3.2	51.5±2.3	43.6±3.3	45.4±2.3
ΔPAPmean (mm Hg)			−4.2±1.4	−6.14±0.85
PAWPmean (mm Hg)	8.8±0.8	9.2±1	8.9±0.7	9.3±1.2
PVR (WU)	10.2±1.0	11.8±0.8	8.6±0.9	8.5±0.7
ΔPVR (WU)			1.6±0.5	−3.2±0.3*
SAPmean (mm Hg)	92.8±4.9	92.3±2.2	83.2±6.1	85.8±4.3
RAP (mm Hg)	7.6±1.4	7.3±0.8	7.8±1	7.2±1.2
SaO2 (%)	87.7±2.2	88.9±1.2	87.7±2.2	88.9±1.2
SvO2 (%)	53.8±2.6	57.3±1.3	57.4±3.3	61.7±1.3
paO_2 (mm Hg)	67.4±5.0	64.6±3.1	62.3±4.1	70.5±4
$paCO_2$ (mm Hg)	36.8±1.7	35.9±1.7	34.4±2.3	35.7±1.5

Statistical significances between survivors and non-survivors are given as *p<0.05; **p<0.01; ***p<0.001.
Values are given as absolute and changes (Δ) during vasodilator testing.
6MWD, 6 min walking distance; CO, cardiac output; HR, heart rate; paCO2, arterial partial pressure carbon dioxide; paO_2, arterial partial pressure oxygen; PAP, pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SaO_2, arterial oxygenation; SAP, systemic arterial pressure; SvO_2, mixed venous oxygenation; WU, Wood units.

diagnosed (incident) patients.[8] Since the care of patients with IPAH is very complex already, it would be attractive to retrieve prognostic parameters from already established methods, such as vasodilator testing during RHC.

This study demonstrates that the acute haemodynamic response to iloprost-aerosol burrows more information for the majority of patients with IPAH than currently used to identify a minority of patients with IPAH who can successfully be treated with CCB. The key finding of our study is that the extent of a residual but significant vasodilative reserve, defined as a decrease of PVR of at least 30% in response to inhalation of 5 μg iloprost, translates into a survival benefit in patients with IPAH.

During acute haemodynamic testing iloprost-aerosol caused pulmonary vasodilation paralleled by an increase of CO and SvO_2, resulting in a PVR reduction of about 25%. This part of the study confirms previous data.[9] However, this current study excluded patients meeting current vasoresponder criteria, in contrast to all previous studies. Therefore acute haemodynamics were not driven by a small number of patients with a superb vasoreactivity in this study.

The definition of a positive pulmonary vasodilator test in IPAH has changed over time. Historically, a significant pulmonary vasoreactivity was defined by an acute reduction of the mean PAP and PVR by at least 20% in response to oral CCB by Rich *et al*.[10] Due to the occurrence of severe side effects during acute vasodilator testing with CCB, short acting pulmonary selective vasodilators such as iNO and intravenous epoprostenol have been introduced to safely identify patients with a preserved ability to acutely reduce PVR. Sitbon *et al* defined a positive vasodilator response as a decline of the PVR by at least 30% in response to iNO or infusion of epoprostenol.[6] Later, the same authors described the iNO challenge as a safe method to identify patients with IPAH who would respond acutely[11] and chronically to CCB therapy.[3] Meanwhile, comparable results have been achieved with inhaled iloprost, a stable prostacyclin analogue predicting clinical response to CCB treatment.[12] Of note, it is not known whether the long-term survival of classical acute vasoresponders is restricted to CCB treatment, or if any other PAH medication would be equally effective. However, established PAH drugs (ERA, PDE 5I and Riociguat, prostanoids and their analogues) have positive effects that may be attributed to pure pulmonary vasodilation. Therefore these drugs are also beneficial in so-called patients with non-vasoreactive PAH.[2] One of the explanations for this observation is that these drugs affect chronic remodelling processes that seem to play a major role in the development and progression of the disease. However, IPAH is not a uniform disease and different pathophysiological aspects may be present to a variable extent in single patients. Therefore it seems comprehensive to describe an IPAH phenotype with pulmonary vasodilative reserve, not meeting the current criteria for CCB treatment.

Since the results of the acute haemodynamic response did not influence treatment algorithm in this study, it is unclear why this phenotype translates into survival benefit.

Almost 75% of the study population were patients with newly diagnosed (incident) IPAH and overall survival was comparable to previous studies.[8] However, only 2 out of 30 patients (7%) with a PVR reduction ≥30% as compared with 14 out of 36 (39%) died during follow-up. Considering that pulmonary vasoreactivity and progressive remodelling are different features (besides others) of PAH this could lead to either a more benign or a malignant course of the disease, depending on the extent of each feature.

Current data has led to treatment strategies that favour (early) combination of available substances, regardless of the initial haemodynamic status.[13 14] Therefore, it is not clear how our findings could influence these strategies. However, it may offer an explanation why patients with very comparable characteristics have different outcomes during treatment. Nevertheless, treatment strategy should be based on large-scale outcome trials, irrespective of the residual vasodilative reserve. This is also because pathophysiologically both groups could benefit from aggressive therapy strategies, for example, addressing the vasodilative reserve as a therapeutic target in the respective patient group and combining PAH drugs in those without vasodilative reserve in terms of a diminishing progress of the disease.

There are several limitations of this study. First, we could have missed vasoresponders by not using different substances or higher doses of iloprost-aerosol during vasoreactivity testing. For instance, we could have used inhaled NO for pulmonary vasoreactivity testing. However, as compared with iNO, iloprost-aerosol seems to have pronounced haemodynamic effects in patients with PAH.[14] In addition, the 5 μg iloprost-aerosol approach has been used in several settings before, especially by Jing *et al* in order to identify classical vasoresponders.[12] Therefore we are confident of having chosen a comprehensible approach for the vasodilator test. Also, since our population is small, and especially in terms of the observational part of the study, conclusions can only be drawn with caution. However, IPAH is a rare disease and this size of the study seems to be comparable to other single-centre trials. Third, vasoresponse trials especially by Sitbon *et al*[3] have been published before and have already suggested a better outcome for patients with pronounced vasoreactivity. However, this study tested different substances for vasoreactivity, namely intravenous epoprostenol and inhaled NO which per se exert very different haemodynamic profiles as compared with iloprost-aerosol.[15] Finally, pretreatment of PAH with per se vasoactive substances could have influenced vasoreactivity. However, only a fourth of the patients were pretreated and medication was paused 12 h before the RHC. In addition, we did not observe any difference between these groups.

CONCLUSION

These data underline that vasoreactivity testing in IPAH is still timely and that it holds more information for the majority of patients than currently used. In addition, we identified residual pulmonary vasodilative reserve as a prognostic factor in this devastating disease.

Key messages

What is already known about this subject?
Pronounced vasoreactivity is rare (<10%) in idiopathic pulmonary arterial hypertension (IPAH). However such (rare) patients can successfully be treated with high dose calcium channel blockers. Therefore vasoreactivity testing is required for every patient with IPAH.

What might this study add?
Vasoreactivity testing also carries prognostic information for the majority of patients with (IPAH), since the lack of a residual pulmonary vasodilative reserve seems to be a feature of a malignant curse of the disease.

How might this impact on clinical practice?
Patients with a missing residual pulmonary vasodilative reserve have to be identified and very early treatment escalation may be necessary.

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Competing interests None declared.

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Heart

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