Acute response to rapid iloprost inhalation using the Breelib™ nebulizer in pulmonary arterial hypertension: the Breelib™ acute study

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Abstract
The Breelib™ nebulizer was designed to reduce iloprost inhalation times for patients with pulmonary arterial hypertension (PAH). In 30 patients with PAH, rapid inhalation of iloprost 2.5 μg using Breelib™ caused significant improvements in invasively measured afterload and cardiac index but not echocardiographic right ventricular strain during 30 min post-inhalation.

Keywords
pulmonary hypertension, prostanoid, aerosol drug therapy, hemodynamics, right ventricular function

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To the Editor:
Inhaled iloprost is an established part of pulmonary arterial hypertension (PAH) therapy.1,2 With the standard I-neb nebulizer (Philips Respironics, Chichester, UK), each inhalation session is estimated to last up to 10 min, but some patients experience even longer inhalation times.3,4 There has been much interest in approaches to reduce inhalation times and thus improve treatment convenience and adherence, with examples including a change in the iloprost formulation5 and unapproved modification of the I-neb device.6 The Breelib™ nebulizer (Vectura Group plc, Chippenham, UK) was approved in the EU in 2016.7 Compared with I-neb, Breelib™ resulted in substantially reduced median inhalation times.4 Nevertheless, the acute hemodynamic and right ventricular (RV) response of rapid iloprost inhalation with the Breelib™ is currently unknown. We therefore conducted a prospective, single-arm, open-label, proof-of-concept study. The study was conducted between May 2017 and July 2018 (ClinicalTrials.gov Identifier: NCT03365479). All participating patients gave written informed consent and the study was approved by the ethics committee of the Faculty of Medicine at the University of Giessen (approval number: 111/16). Pulmonary hemodynamics, RV strain (measured by echocardiography in a subset of the patients) and adverse events were evaluated at baseline and at 5, 10, 15, and 30 min post-inhalation.

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15, and 30 min after the end of iloprost inhalation in prostanoid naïve PAH patients. The primary outcome measure was the change from baseline in pulmonary vascular resistance (PVR) assessed by RHC. Thirty patients with PAH (idiopathic (n = 17) or associated with connective tissue disease (n = 7), portal hypertension (n = 4) or congenital heart disease (n = 2)) were enrolled. The median length of time required to inhale iloprost 2.5 µg via the Breelib™ nebulizer was 0.40 min (interquartile range: 2.8–5.0 min). PVR decreased rapidly and significantly following iloprost inhalation. Cardiac index showed a rapid and significant increase response to iloprost inhalation. Significant decreases from baseline were observed in median oxygen saturation and partial pressure of oxygen (Table 1). In the 21 patients with available RV strain measurements, RV longitudinal strain and mid-RV free wall strain showed no improvement after iloprost inhalation (data not shown).

Our study shows a substantial decrease in afterload (PVR) after rapid inhalation of iloprost 2.5 µg via the Breelib™ nebulizer in PAH patients. The observed concomitant increase in cardiac index was previously attributed to indirect positive inotropic effects (due to systemic vasodilatation and activation of the arterial baroreflex) in PAH. Without causing a clinical relevant adverse event blood oxygenation (also observed in previous studies) was worsening after inhalation. Therefore, use of the Breelib™ nebulizer in patients with respiratory insufficiency and concomitant high long-term oxygen therapy might not be feasible. Surprisingly, we saw no acute effect of rapid iloprost inhalation on RV strain, although RV strain was recently described as mirroring afterload and RV diastolic function. Therefore, the acute effects of inhaled iloprost or other pulmonary vasoactive drugs on RV function, which have been previously been proposed, merit further investigation. The clinical need to shorten iloprost inhalation times is unquestionable. Our study supports this concept as rapid inhalation of iloprost 2.5 µg via the Breelib™ nebulizer resulted in a substantial improvement from baseline in PVR and cardiac index.

**Table 1.** Parameters in PAH patients before and after inhalation of a single dose of iloprost 2.5 µg via the Breelib™ nebulizer. Data are shown as mean ± standard deviation or median [interquartile range].

| Time after end of inhalation, min | Baseline | 5 | 10 | 15 | 30 | p   |
|----------------------------------|----------|---|----|----|----|-----|
| PVR, dyne*s/cm⁵                  | 619 [427–972] | 430 [284–680] | 464 [305–706] | 489 [314–698] | 495 [385–689] | <0.001 |
| Cardiac index, L/min/m²           | 2.5 ± 0.6 | 3.0 ± 0.8 | 2.9 ± 0.8 | 2.8 ± 0.8 | 2.8 ± 0.8 | <0.001 |
| mPAP, mmHg                       | 41.5 [34.8–55.3] | 37.5 [29.0–48.3] | 38.0 [28.0–50.0] | 39.0 [28.8–50.8] | 40.0 [28.8–47.3] | <0.001 |
| PAWP, mmHg                       | 9.5 ± 3.1 | 9.4 ± 3.5 | 9.6 ± 3.3 | 9.8 ± 3.8 | 9.3 ± 3.7 | 0.688 |
| pO₂, mmHg                        | 69.5 [61.9–82.0] | 64.0 [57.5–70.3] | 64.6 [57.2–70.3] | 67.8 [57.0–73.7] | 65.9 [57.0–73.1] | 0.008 |
| SpO₂, %                          | 94.0 [91.8–95.7] | 91.9 [89.9–94.0] | 91.7 [88.6–94.0] | 92.5 [89.4–95.0] | 92.1 [87.6–94.9] | 0.004 |
| SAP, mmHg                        | 81.5 [71.8–91.5] | 80.0 [72.0–92.3] | 83.0 [72.0–91.0] | 85.5 [73.8–96.3] | 85.0 [74.8–93.3] | 0.208 |

Measurements were compared across time points by related-samples Friedman’s two-way analysis of variance by ranks, with P < 0.05 considered statistically significant. Statistical analyses were performed using SPSS software version 22 (IBM, Armonk, NY).

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**Authors’ contribution**

Richter had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. He contributed as the principal investigator for this study to project oversight, organization, data collection, and writing of the manuscript. Wan contributed to data collection, critical reviewing of the manuscript, and final approval of the version to be published. Ghofrani contributed to the conceptual study design, data collection, writing and critical reviewing of the manuscript, and final approval of the version to be published. Seeger contributed to the conceptual study design, data collection, writing and critical reviewing of the manuscript, and final approval of the version to be published. Gall contributed to the conceptual study design, data collection, statistical analysis, writing and critical reviewing of the manuscript, and final approval of the version to be published. Rieth contributed to the conceptual study design, data collection, writing and critical reviewing of the manuscript, and final approval of the version to be published. Tello contributed to the conceptual study design, data collection, writing and critical reviewing of the manuscript, and final approval of the version to be published.

**Conflict of interest**

The author(s) declare the following conflicts of interest: Richter has received support from United Therapeutics and Bayer; speaker fees from Actelion, Bayer, MSD and OMT; and consultancy fees from Bayer. Wan has nothing to disclose. Ghofrani has received consultancy fees from Bayer, Actelion, Pfizer, Merck, GSK, and Novartis; fees for participation in advisory boards from Bayer, Pfizer, GSK, Actelion, and Takeda; lecture fees from Bayer HealthCare, GSK, Actelion, and Encysive/Pfizer;
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**Ethical approval**
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