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To cite this version:

Robert Voswinckel, Frank Reichenberger, Henning Gall, Thomas Schmehl, Tobias Gessler, et al.. Metered dose inhaler delivery of treprostinil for the treatment of pulmonary hypertension. Pulmonary Pharmacology & Therapeutics, 2009, 22 (1), pp.50. 10.1016/j.pupt.2008.11.009 . hal-00504934

HAL Id: hal-00504934

https://hal.science/hal-00504934

Submitted on 22 Jul 2010

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Accepted Manuscript

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PII: S1094-5539(08)00128-4
DOI: 10.1016/j.pupt.2008.11.009
Reference: YPUPT 885

To appear in: *Pulmonary Pharmacology & Therapeutics*

Received Date: 8 October 2008
Revised Date: 19 November 2008
Accepted Date: 23 November 2008

Please cite this article as: Voswinckel R, Reichenberger F, Gall H, Schmehl T, Gessler T, Schermuly RT, Grimminger F, Rubin LJ, Seeger W, Ghofrani HA, Olschewski H. Metered dose inhaler delivery of treprostinil for the treatment of pulmonary hypertension, Pulmonary Pharmacology & Therapeutics (2008), doi: 10.1016/j.pupt.2008.11.009

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Metered dose inhaler delivery of treprostinil for the treatment of pulmonary hypertension

Voswinckel

Short title: MDI-treprostinil in PHT

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Word count manuscript: 4120

Word count abstract: 245

Support: This study was supported by LungRx Inc. with a research grant.

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Abstract

Background: The stable prostanoid analogue treprostinil is approved as continuous infusion for treatment of pulmonary arterial hypertension. Unique drug characteristics may render this prostanoid feasible for inhalation therapy with a metered dose inhaler.

Methods and Results: Randomised open label investigation of acute haemodynamic effects, safety and tolerability of inhaled treprostinil delivered in seconds by a metered dose inhaler (MDI-TRE). Inhaled nitric oxide (NO) and MDI-TRE were applied once during right heart catheter investigation to 39 consecutive patients with precapillary pulmonary hypertension. Doses of 30µg, 45µg and 60µg MDI-TRE were investigated in separate groups of patients. Haemodynamics and blood gases were measured for two hours following treprostinil application. Acute haemodynamic responses to NO and MDI-TRE were comparable. MDI-TRE significantly improved haemodynamics compared to placebo inhalation. MDI-TRE induced effects were comparable to a historical control group that inhaled treprostinil from an ultrasonic nebuliser. The 120 minutes area under the curve for PVR changes due to placebo, 30µg, 45µg or 60µg MDI-TRE was 1114 ± 998, -870 ± 940, -2450 ± 2070 and -2000 ± 900 min*%. Reduction of systemic vascular resistance and pressure were not clinically relevant. No significant side effects were observed. No impact on ventilation/perfusion matching by treprostinil was demonstrated in 5 patients with pre-existing gas exchange limitations by use of the multiple inert gas elimination technique.

Conclusions: The application of inhaled treprostinil with a metered dose inhaler is feasible and well tolerated. It induced a sustained pulmonary selective vasodilatation.

Key words: prostacyclin; pulmonary hypertension; pulmonary heart disease; treprostinil sodium; metered dose inhaler; aerosol;

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Introduction

Pulmonary arterial hypertension may be treated with prostacyclin or its stable analogues iloprost and treprostinil [1-4]. Prostacyclin, due to its short half life, may only be administered as continuous intravenous infusion. Iloprost treatment provided clinical efficacy by intravenous [3] and inhaled application [5]. Treprostinil has a significantly extended half life [6]. It is approved for i.v. as well as s.c. infusion, the latter avoiding septic events associated with indwelling intravenous catheters. The subcutaneous application however often leads to infusion site pain. We therefore sought for an alternative application route for treprostinil and already demonstrated that the inhalation of treprostinil is safe, well tolerated and evokes acute pulmonary selective vasodilatation without relevant systemic side effects [7]. Continuous treatment with inhaled treprostinil administered four times daily was noted to be effective and without relevant side effects in small open label non randomized trials [8;9]. A clinical phase IIb trial investigating inhaled treprostinil adjunct to sildenafil or bosentan treatment in PAH has just been completed.

In preceding studies we found that quite high doses of inhaled treprostinil could be safely deposited in the lung in as little as a single breath [8]. This suggested for the first time the possibility to deliver a potent vasodilator for pulmonary hypertension treatment with a metered dose inhaler.

In this open label study of acute vasodilator challenge during right heart catheter investigation we addressed the safety, tolerability and pulmonary vasodilator potency of inhaled treprostinil applied in seconds by a metered dose inhaler (MDI-TRE) and compared it to inhaled nitric oxide, which is the standard medication to test pulmonary vasoreaction. We provide evidence for a long lasting acute effect of MDI-TRE on pulmonary haemodynamics in absence of systemic side effects and gas exchange deteriorations.

Methods and Patients

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The protocol was approved by the institutional review board of the University of Giessen. Written informed consent was obtained before enrolment.

A total number of 39 consecutive patients with moderate to severe precapillary pulmonary hypertension were enrolled in an open label, placebo controlled trial. Randomisation to the treatment groups that received either 30µg, 45µg or 60µg treprostinil, which were completed one after the other, relied on the random schedule of patients for routine diagnostic right heart catheter procedures. Patient characteristics were: f/m = 25/14, age 59 ± 2.3 years, mean pulmonary artery pressure (PAP) 45 ± 1.8 mmHg, pulmonary vascular resistance (PVR) 734 ± 52 dynes*s*cm^{-5}, pulmonary capillary wedge pressure (PCWP) 8.6 ± 0.5 mmHg, central venous pressure (CVP) 6.4 ± 0.7 mmHg, cardiac output (CO) 4.5 ± 0.2 l/min, central venous oxygen saturation (SvO2) 62.3 ± 1.2 mmHg (mean ± SEM). Disease aetiologies were idiopathic pulmonary arterial hypertension (iPAH; n=13), PAH of other causes (n=10) and non-operable chronic thromboembolic pulmonary hypertension (CTEPH; n=16). The patient characteristics of the separate groups are shown in table 1.

Baseline values were determined 20 minutes after placement of the catheter (7F Swan Ganz Catheter, Edwards Life Sciences, Irwin, CA, USA). Heart rate, pulmonary and systemic blood pressures and cardiac output were measured and blood gases were taken during each pharmacological intervention at defined time points. Cardiac output (CO) was measured with the thermodilution method by bolus-injection of 10ml cooled sterile saline solution. At least three CO measurements were done at each time point and averaged. Following initial baseline recordings, we applied 20 ppm inhaled nitric oxide (NO) for a duration of 5 minutes to every patient previous to the treprostinil inhalation as a comparative agent. After NO was stopped and PAP and CI had returned back to baseline, patients of the three separate dose groups received a single dose of either 30µg (n=12), 45µg (n=9) or 60µg (n=20) metered dose inhaler -treprostinil sodium (MDI-TRE). Dose escalations in single patients were not performed, each patient received only a single dose and the effect was recorded for 120 minutes. Treprostinil

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was applied with the Respimat® metered dose inhaler (Boehringer, Ingelheim, Germany). Physical aerosol characteristics of the MDI devices were controlled by laser diffractometry as previously reported [10]. The mass median aerodynamic diameter (MMAD) of treprostinil-aerosol was 4-5µm, which was suitable for alveolar deposition. Treprostinil aerosol volume delivered by one puff from the MDI was 15µl. The MDI was either filled with a concentration of 1000µg/ml treprostinil sodium (15µg TRE per puff) or with 2000µg/ml (30µg TRE per puff). The different doses in this study were applied as 2 puffs of 1000µg/ml (30µg), 3 puffs of 1000µg/ml (45µg) or 2 puffs of 2000µg/ml (60µg). Haemodynamics and gas-exchange parameters were recorded for 120 minutes after MDI-TRE inhalation. The Respimat® device was chosen for this study because the implemented "soft mist" technology seemed to be well suited for the peripheral lung deposition of highly active drugs like prostanoids as it generates a rather slow stream of aerosol instead of a sharp pulse that may result in higher oral and pharyngeal deposition.

The impact of MDI-TRE on ventilation-perfusion matching was measured in five patients (30µg TRE, n=2; 45µg TRE, n=1; 60µg TRE, n=2) with pre-existing gas exchange limitations by use of the multiple inert gas elimination technique (MIGET) as it was previously described [11;12].

Statistical analysis

Mean values, standard deviation, standard error of the mean or 95% confidence intervals were calculated. Statistical analysis of areas under the curve was done by use of a paired t-test. For analysis of repeated measurements over time comparing placebo and MDI-TRE or MDI-TRE and ultrasonic nebulisation one way ANOVA for repeated measurements with Bonferroni post test was performed. Statistical analysis was done with the Graph Pad Prism 5 software.

Results

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Safety and tolerability

The inhalation of treprostinil sodium from a metered dose inhaler was well tolerated, only mild and transient cough for a maximum of one minute was reported by some patients. No systemic side effects like headache, flush, nausea or dizziness were observed.

Acute haemodynamic changes due to MDI-TRE

Doses of 30µg, 45µg and 60µg MDI-TRE reduced PVR from 575 ± 104 dynes to 494 ± 109 dynes, from 964 ± 184 dynes to 720 ± 229 dynes and from 667 ± 149 dynes to 530 ± 132 dynes, respectively (mean ± 95% confidence interval). Mean pulmonary artery pressure was reduced by 30µg, 45µg or 60µg MDI-TRE from 40.1 ± 4.9 mmHg to 33.3 ± 4.4 mmHg, from 50.4 ± 6.2 mmHg to 38.1 ± 8.4 mmHg and from 39 ± 4.8 mmHg to 32.2 ± 4.9 mmHg, respectively. Pulmonary vasodilatation surpassed the observation time of 120 minutes in the 45µg and 60µg groups. The lower dose of 30µg TRE induced a somewhat shorter effect on pulmonary vascular resistance; however, the maximal drop in PVR was comparable, arguing for a prolonged effect of higher dose depositions. In contrast, placebo inhalation did not induce pulmonary vasodilatation but lead to a slight increase in PVR over the time of the right heart catheter investigation (figure 1). Because the “negative” effect of placebo inhalation had proven to be very reproducible no new placebo data was derived but taken from a previous study in order not to expose additional patients to prolonged catheter time. The effect of MDI-TRE on systemic vascular resistance and pressure was not clinically significant. Cardiac output was increased over the whole observation period, whereas heart rate was rather unchanged. Arterial oxygen saturation was not influenced by MDI-TRE (figure 2). The maximal changes in haemodynamic and gas-exchange parameters compared to baseline values are depicted in table 2. Statistical analysis of PVR, PAP and cardiac output (one way ANOVA for repeated measurements) showed significant changes for all treprostinil doses compared to placebo. Systemic pressure was significantly affected in the highest dose group

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of 60µg MDI-TRE (figures 1 and 2). In addition, areas under the curve for PVR were calculated for placebo and MDI-TRE doses for the 120 minute observation period (figure 3). Significant effects of 45 and 60µg MDI-TRE compared to placebo were observed.

Comparison of nitric oxide and MDI-TRE effects

We compared the acute effects of NO inhalation and treprostinil inhalation intra-individually. Mean PAP, PVR and CO changes due to nitric oxide inhalation were not significantly different from MDI-TRE induced changes (figure 4). The values for mPAP at NO baseline vs. MDI-TRE baseline in the three dose groups (30, 45, 60µg) were 43.4 ± 2.9 vs. 41.0 ± 2.5 mmHg, 53.0 ± 2.7 vs. 49.1 ± 3.2 mmHg, and 40.1 ± 2.3 vs. 39.0 ± 2.5 mmHg, respectively. The baseline values for PVR in the groups receiving 30, 45 or 60µg MDI-TRE were 603 ± 76 vs. 585 ± 58 dyn*sec*cm^{-5}, 1070 ± 100 vs. 939 ± 102 dyn*sec*cm^{-5}, and 660 ± 72 vs. 667 ± 67 dyn*sec*cm^{-5}. Nitric oxide reduced mPAP to 36.2 ± 2.7 (30µg MDI-TRE group), 43.8 ± 3.4 (45µg MDI-TRE group) and 35.4 ± 2.8 (60µg MDI-TRE group). Nitric oxide reduced PVR to 497 ± 63 dyn*sec*cm^{-5} (30µg MDI-TRE group), 802 ± 100 dyn*sec*cm^{-5} (45µg MDI-TRE group) and 616 ± 81 dyn*sec*cm^{-5} (60µg MDI-TRE group).

Comparison of treprostinil application by MDI or ultrasonic nebuliser

For better judgement, the MDI findings were compared with a historical cohort from our center that was investigated with very similar treprostinil doses (32µg, 48µg, 64µg) inhaled by the ultrasonic nebuliser Optineb (Nebutec, Elsenfeld, Germany) which is also used in the current phase IIb trial. Data from this cohort has been published before [8] but we felt it would be meaningful to present a direct comparison (figure 5). The comparison (which is not an intra-individual comparison) showed quite similar responses in terms of PVR reduction for all respective dose groups. Figure 5 shows only the 45µg/48µg comparison, the two other dose pairs (30µg/32µg and 60µg/64µg) were comparable.

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Ventilation / perfusion distributions

To assess the impact of MDI-TRE on gas exchange and intrapulmonary ventilation-perfusion matching in detail, multiple inert gas elimination technique was used in 5 patients that displayed gas exchange problems already at baseline. These patients were chosen because they are believed to be more prone to gas exchange deterioration induced by pulmonary vasodilators. Characteristics of these patients were: PAP 54.6 ± 3.2 mmHg, PVR 892 ± 88 dynes, SaO2 91.7 ± 0.5 %, SvO2 65.2 ± 1.8 %. Aetiologies were iPAH (n=2), CTEPH (n=3). The maximal relative reduction of SaO2 after inhalation of MDI-TRE in these patients was -3.8 ± 1.5 % compared to baseline values. Shunt flow at baseline, during nitric oxide inhalation and 60 minutes after MDI-TRE inhalation was 6.4 ± 4.3 %, 5.4 ± 3.0 % and 8.3 ±3.4 % (n.s.), respectively (mean ± 95% confidence interval; Figure 6).

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Discussion

Inhaled treprostinil is the most recent development of non- parenteral prostanoid application. It necessitates only four inhalations per day for clinical efficacy and may be applied in approximately one minute by use of an ultrasonic nebulizer [7;8]. The current ultrasonic nebulisers at hand for PAH therapy are highly developed instruments but still are quite cumbersome to handle, to clean and to sterilise and also comprise a substantial size and weight to carry. The Inhalation from a metered dose inhaler would provide several advantages with respect to instrument size, ease of use and minimal exposure of patients who need to take their therapy in public. We provide data on inhaled treprostinil applied by a metered dose inhaler with focus on the safety, feasibility and acute haemodynamic effects. The inhalation of 2 to 3 puffs treprostinil from the MDI induced pulmonary selective vasodilatation with a peak effect after 30-45 minutes and a sustained haemodynamic effect at the end of the observation period of two hours.

Prostacyclin is not feasible for inhalation due to its very short half life of only a few minutes. Iloprost leads to potent and selective pulmonary vasodilatation after a single inhalation of the approved doses of 2.5-5µg. The acute effect of inhaled iloprost may last up to 90 minutes [13]. Long term treatment with repetitive inhalations of iloprost was shown also to reduce pulmonary vascular resistance at trough levels and to improve patient exercise capacity and survival [5]. A dose of more than 5µg iloprost per inhalation or a reduction of inhalation time to less than 3 minutes induces in most patients considerable systemic prostanoid side effects like hypotension, dizziness, headache, jaw pain, nausea or diarrhoea. It was an unanticipated finding that treprostinil, besides the positive consequences of a longer half life for inhalation therapy, was tolerated at single doses up to 60µg without relevant side effects. The inhalation of an effective treprostinil dose in one single breath was achieved with highly concentrated treprostinil sodium solution of 2000µg/ml without side effects [8]. We believe that the absence of systemic side effects despite rapid application of treprostinil in high doses is

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provided by an outstanding pulmonary selectivity of inhaled treprostinil. The reasons for this can be speculated on as being due to storage and slow release of treprostinil in the lung tissue or alveolar lining layer. This phenomenon should be addressed in further studies on pharmacokinetics, tissue distribution and receptor binding and activation. In addition, differential prostanoid-receptor expression in pulmonary and systemic vascular beds could cause preferential pulmonary vasodilatation and less systemic effects [14]. In this respect it has been shown recently in macrophages that treprostinil, in opposite to PGI2 and iloprost, does not only activate the IP receptor but also the EP2 receptor [15]. Another sign for partial pulmonary vascular selectivity of treprostinil is that about two-fold dose of inhaled treprostinil achieves the same acute vasodilation as compared to inhaled iloprost [8]. If given intraveneously up to 10 fold higher doses of treprostinil (20-60 ng/kg/min) are tolerated as compared to iloprost (2-5 ng/kg/min) [3;16].

We show that the effects of metered dose inhaler treprostinil on pulmonary haemodynamics are similar or superior to the acute effects of inhaled nitric oxide. MDI- treprostinil compared to 6 minutes continuous inhalation ultrasonic nebuliser inhalation achieved similar results for 30/32µg, 45/48µg and 60/64µg dose comparisons.

The aerodynamic aerosol diameter of MDI treprostinil of 4-5µm is certainly at the upper limit for alveolar deposition, so reduction of aerodynamic aerosol diameter might improve MDI-TRE deposition.

The inhalation of a highly concentrated aerosol is theoretically prone to disturbances of gas exchange, because the deposition of even small amounts of aerosol may deposit significant drug doses locally and thereby antagonize the hypoxic pulmonary vasoconstriction in poorly ventilated areas. This might lead to increase in shunt flow and low V/Q areas. We addressed this question in selected patients with MIGET, the gold-standard for intrapulmonary V/Q ratio determination. The MIGET patients were selected based on pre-existing gas exchange limitations. We did not find a significant increase in low V/Q areas or shunt fraction after

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inhalation of MDI-TRE, in fact the distribution of perfusion was not different to that at baseline or nitric oxide inhalation. This proves an excellent matching of MDI-TRE induced vasodilatation to local ventilation which is also reflected by unchanged arterial oxygen saturations.

This study had certain limitations: A direct intra-individual comparison of ultrasonic and MDI drug application was not done due to the long lasting drug effect and limited catheter time. The groups that received different treprostinil doses are not very large and heterogeneous with respect to severity of disease and distribution of aetiologies. Therefore direct dose-effect correlations can not be obtained. However, this study was designed to proof the feasibility and safety of MDI treprostinil application and did not primarily address dose effects or clinical efficacy. Safety can only be reported for single drug inhalation in this report, no safety data for long term MDI-TRE application was determined.

Conclusion

Inhaled treprostinil is the first prostacyclin analogue which can be applied in effective doses by a metered dose inhaler in seconds. This may provide a breakthrough for inhaled pulmonary hypertension therapy in terms of device size, ease of handling, patient autonomy and compliance. The long term efficacy of this approach needs to be addressed in a controlled clinical trial.

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Acknowledgements

We would like to thank Melanie Thamm and Burcu Karadas (Department of Internal Medicine, University of Giessen) for technical assistance. We thank Robert Roscigno (LungRX) for proofreading.

Funding Sources

This study was supported by LungRx Inc. with a research grant.

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Conflict of Interest Disclosures

R. Voswinckel, B. Enke, F. Reichenberger, A. Kreckel, S. Krick, R.T. Schermuly, T. Schmehl, T. Gessler and H. Gall have nothing to disclose. H.A. Ghofrani receives grant and contract support by Pfizer Ltd., Altana Pharma AG, Schering AG; in addition, he serves on advisory board of Pfizer Ltd.. F. Grimminger receives grant and contract support by Pfizer Ltd. and Altana Pharma AG. W. Seeger receives grant and contract support by Schering, Altana Pharma, Myogen Inc. Westminster, LungRX and Aventis Pharma. H. Olschewski, is consultant and investigator for Schering AG, LungRX, CoTherix, Encysive and Myogen and received research grants from Schering AG. L.J. Rubin is investigator and consultant for Actelion, Pfizer, Lung Rx, Gilead, MondoBiotech, Encysive and Schering.

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Figure 1

Pulmonary and systemic changes in haemodynamics following the inhalation of placebo (open circles), 30µg treprostinil (triangles), 45µg treprostinil (squares) or 60µg treprostinil (black circles) applied by a metered dose inhaler. Metered dose inhaler application of treprostinil induced sustained reduction of PAP and PVR that outlasted the observation period of 120 minutes at doses of 45 and 60µg. Measurements were performed at baseline (0 min), 5, 15, 30, 45, 60, 90 and 120 minutes. Baseline was set as 100%. PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; SAP = systemic arterial pressure; SVR = systemic vascular resistance. Data are given as mean ± SEM. One way ANOVA for repeated measurements was performed compared placebo and treprostinil: $p<0.01$ for PVR, PAP, and SVR (all doses). SAP was not changed with 30 or 45µg, but significant with 60µg treprostinil ($p<0.01$).

Figure 2

Haemodynamic changes induced by the inhalation of placebo (open circles), 30µg treprostinil (triangles), 45µg treprostinil (squares) or 60µg treprostinil (black circles) applied by a metered dose inhaler. Treprostinil induced sustained elevation of cardiac output. Heart rate was rather unchanged as a sign for low spillover of MDI-TRE to the systemic circulation. Gas exchange was not negatively affected. Measurements were performed at baseline (0 min), 5, 15, 30, 45, 60, 90 and 120 minutes. Baseline was set as 100%. CO = cardiac output; HR = heart rate; SaO2 = arterial oxygen saturation; SvO2 = central venous oxygen saturation. Data are given as mean ± SEM. One way ANOVA for repeated measurements was performed compared placebo and treprostinil: CO ($p<0.01$ for all doses), HR and SaO2 were not significant, SvO2 was significantly changed only by 45µg treprostinil ($p<0.01$).

Figure 3

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Areas under the curve for changes in pulmonary vascular resistance (PVR) were calculated for an observation period of 120 minutes after inhalation metered dose inhaler application of treprostinil. PVR was markedly lowered, the increased pulmonary vasodilation over time with the two highest doses mainly relies on the more sustained effect over time. Data are shown as mean ± 95% confidence intervals. Asterisks mark significant differences compared to placebo ($p<0.05$).

Figure 4

Comparisons of the haemodynamic effects elicited by nitric oxide (bars) and treprostinil (lines). The data on pulmonary vascular resistance (PVR), mean pulmonary arterial pressure (PAP), mean systemic pressure (SAP) and cardiac output (CO) is presented for the three groups receiving either 30µg, 45µg or 60µg treprostinil from the metered dose inhaler. Measurements were performed at baseline (0 min), 5, 15, 30, 45, 60, 90 and 120 minutes. Baseline was set as 100%. Data are shown as mean ± 95% confidence intervals in absolute values.

Figure 5

Comparison of treprostinil inhalation with a metered dose inhaler (closed circles) and ultrasonic nebulisation (open triangles). MDI-treprostinil was applied in seconds as a 45µg dose at the mouthpiece and compared to 48µg (n=6) treprostinil delivered by an ultrasonic nebuliser over 6 minutes of continuous inhalation time, respectively. Measurements were performed at baseline (0 min), 5, 15, 30, 45, 60, 90 and 120 minutes. Baseline was set as 100%. Data are shown as mean ± 95% confidence intervals as percent of baseline (baseline set to 100%). One way ANOVA for repeated measurements was performed compared MDI-TRE and ultrasonic nebulisation. No siginificant differences between devices were observed ($p>0.05$ for all parameters).

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Figure 6

Ventilation/perfusion matching assessed with the multiple inert gas elimination technique. Five patients (30µg TRE, n=2; 45µg TRE, n=1; 60µg TRE, n=2) with pre-existing gas exchange limitations were investigated for changes in ventilation-perfusion ratios. All patients presented with significant shunt flow at baseline. Shunt-flow and low V/Q areas were not significantly changed by nitric oxide (NO) inhalation or treprostinil inhalation from a metered dose inhaler (MDI-TRE; ns = not significant). MDI-TRE applied at high treprostinil concentrations did thus not negatively affect ventilation-perfusion matching and gas-exchange. Data are given as mean ± 95% confidence intervals.

Table 1

Patient characteristics of the investigated groups. Treprostinil was administered by a metered dose inhaler device (MDI-TRE) or in a historical group by an ultrasonic device (US-TRE). PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; CO = cardiac output; SAP = systemic arterial pressure; SaO2 = arterial oxygen saturation; SvO2 = central venous oxygen saturation. Data are mean ± standard error of the mean.

Table 2

Maximal changes of hemodynamic parameters in percent from baseline values following metered dose inhaler delivery of placebo (n=4), 30µg treprostinil (n=12), 45µg treprostinil (n=9) or 60µg treprostinil (n=20). Highest (max) or lowest (min) values observed during the observation period are shown. Data are given mean ± SEM. PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; CO = cardiac output; SAP = systemic arterial pressure; HR = heart rate.

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	Placebo (n=4)	MDI-TRE 30µg (n=11)	MDI-TRE 45µg (n=8)	MDI-TRE 60µg (n=20)	US-TRE 32µg (n=6)	US-TRE 48µg (n=6)	US-TRE 64µg (n=3)
Age [years]	61 ± 8	54 ± 4.2	54 ± 6.5	65.5 ± 3.1	56.8 ± 3.7	51.2 ± 2.4	57.3 ± 9.1
PAP [mmHg]	49.5 ± 10.1	46.5 ± 3.0	53 ± 3.0	39.7 ± 2.0	44.2 ± 2.2	55.5 ± 3.1	45.3 ± 5.2
PVR [dynes]	896 ± 163	608 ± 57.7	1029 ± 119	663 ± 81	856 ± 78	939 ± 69	769 ± 267
CO [l/min]	4.46 ± 0.9	5.3 ± 0.5	4.0 ± 0.4	4.4 ± 0.3	3.8 ± 0.2	3.9 ± 0.2	4.5 ± 1.1
SAP [mmHg]	98 ± 8.1	88.5 ± 3.1	80.5 ± 3.6	86.1 ± 2.0	96.3 ± 2.5	91.2 ± 5.1	99 ± 3.2
SaO2 [%]	85.3 ± 4.5	90.0 ± 1.2	89.5 ± 1.2	90.6 ± 0.5	92.8 ± 1	92 ± 1.2	94.2 ± 1.3
SvO2 [%]	57.5 ±3.9	65.5 ± 1.7	59.0 ± 3.8	62.5 ± 1.6	63.6 ± 1.1	62 ± 3.6	66.3 ± 1.5

Table 1 Patient characteristics

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	Placebo	30µg TRE	45µg TRE	60µg TRE
PAP (min)	-0.6 ± 3.0	-16.6 ± 3.2	-22.4 ± 6.8	-20.5 ± 2.4
PVR (min)	+1.4 ± 1.9	-15.6 ± 4.4	-28.6 ± 8.9	-22.5 ± 3.7
CO (max)	-0.3 ± 1.1	+8.8 ± 3.8	+8.6 ± 5.6	+3.8 ± 2.0
SVR (min)	+4.3 ± 4.3	-2.3 ± 4.2	-8.0 ± 3.9	-8.7 ± 2.1
SAP (min)	+2.7 ± 1.7	-2.7 ± 1.9	-3.9 ± 1.5	-6.4 ± 2.9
HR (max)	+5.0 ± 2.1	+6.1 ± 2.9	-0.9 ± 2.4	+1.1 ± 0.9

Table 2 Maximal changes of hemodynamic parameters following MDI drug delivery

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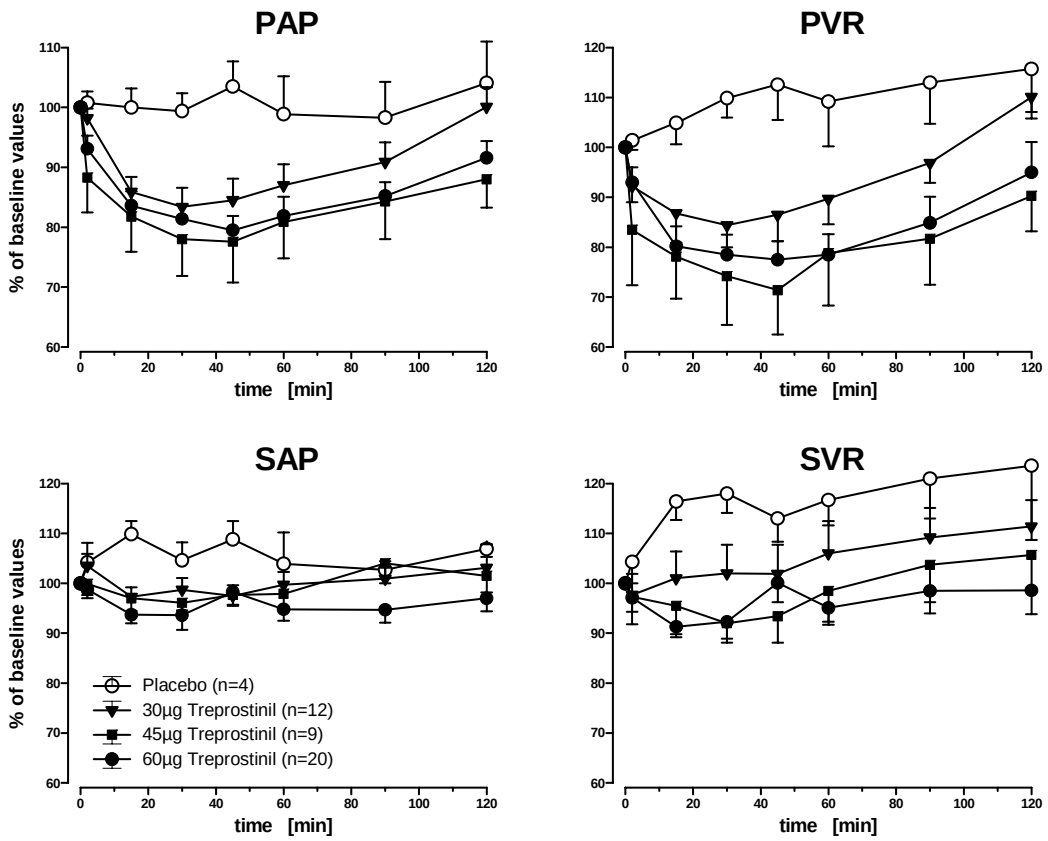

Figure 1

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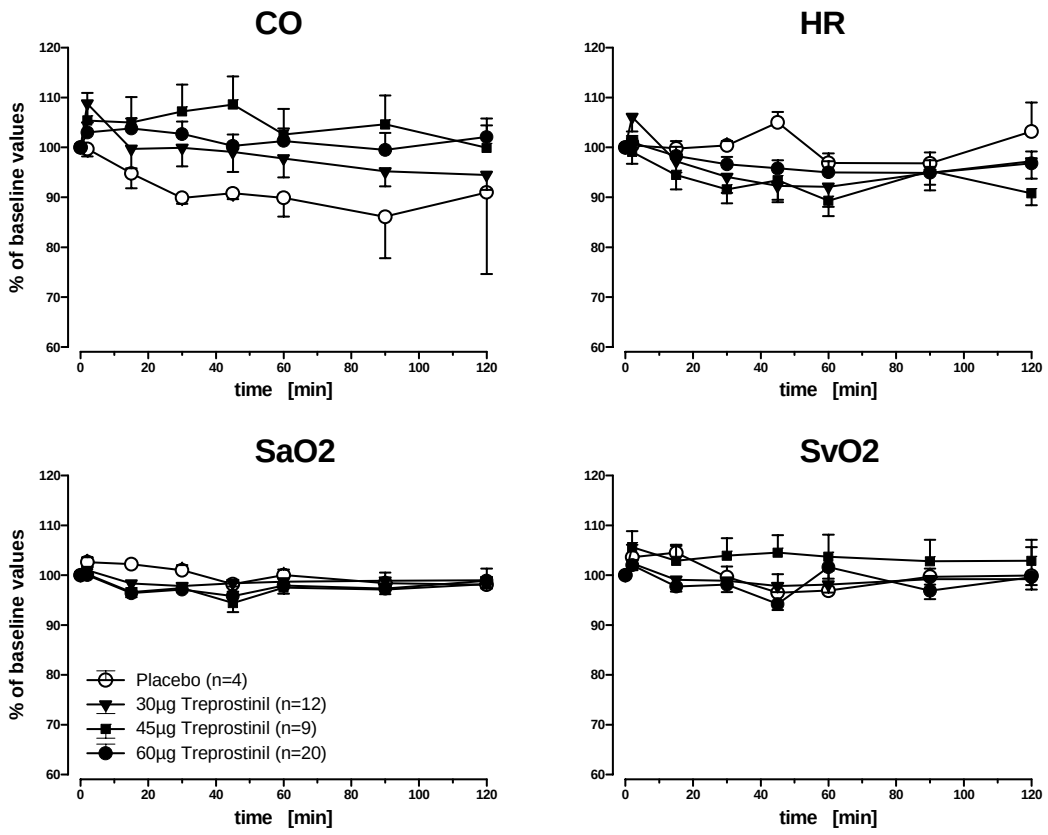

Figure 2

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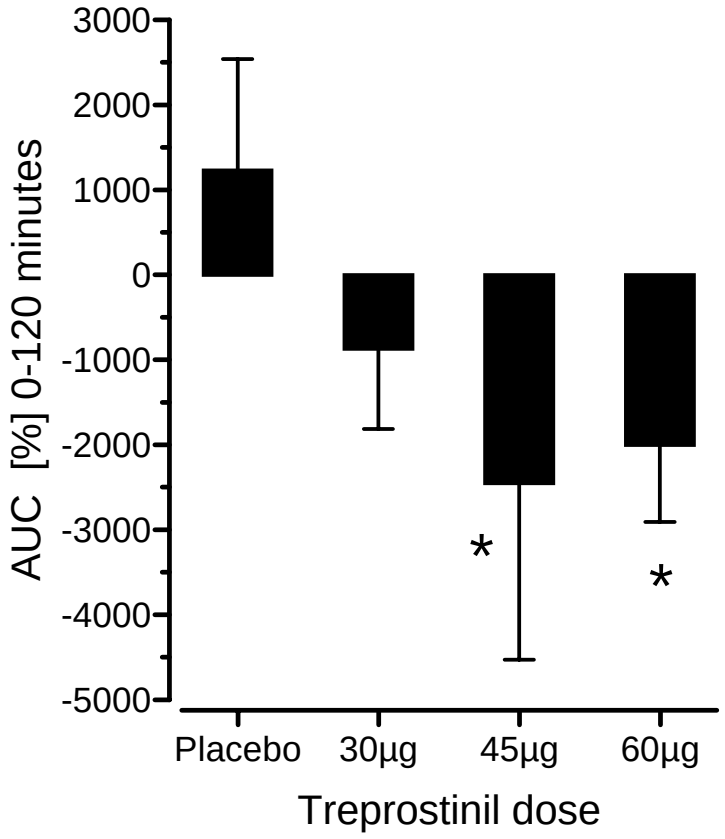

Figure 3

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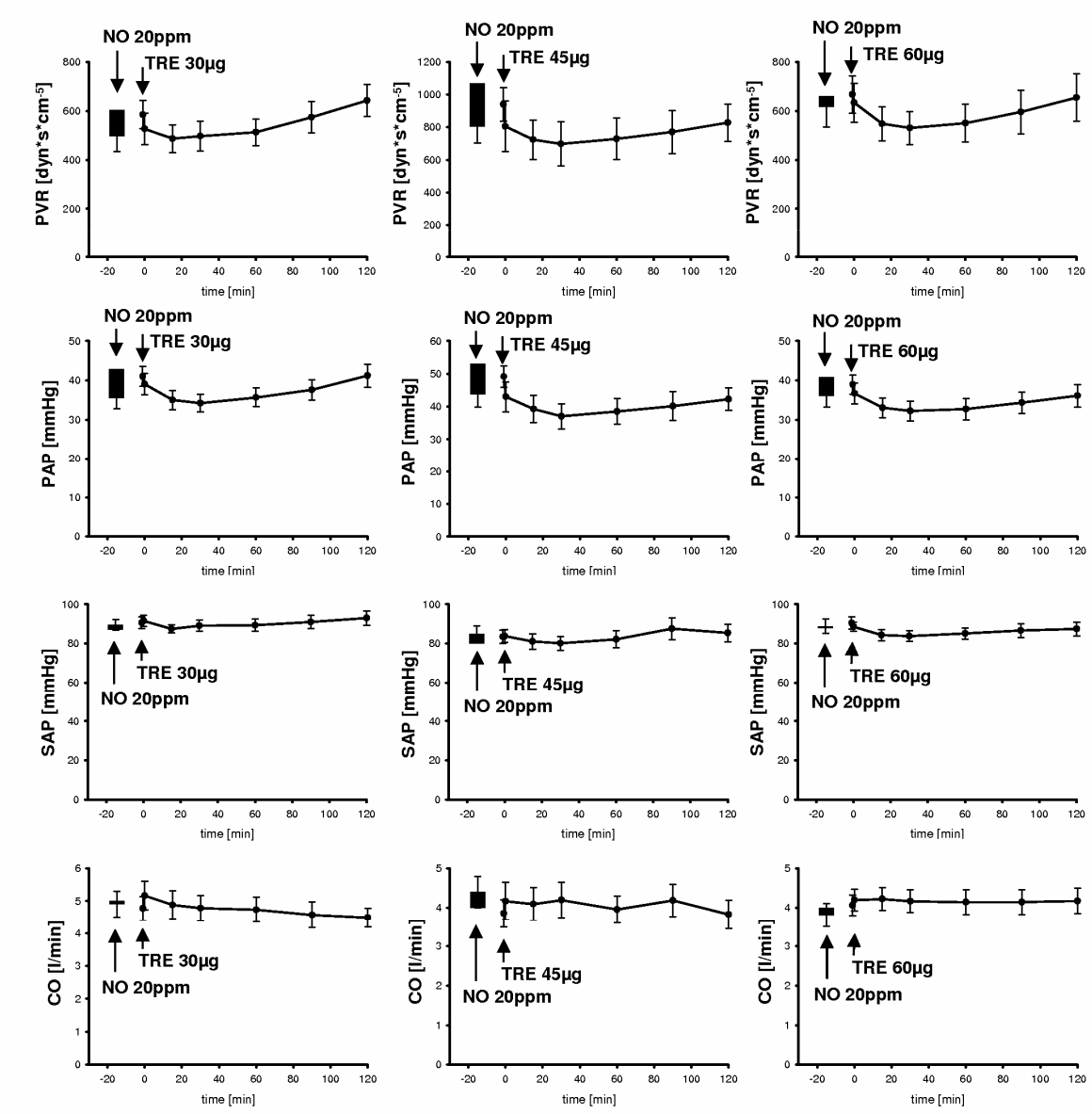
NO 20ppm
TRE 30µg
TRE 45µg
TRE 60µg
PVR [dyn*s*cm-5]
PAP [mmHg]
SAP [mmHg]
CO [l/min]
time [min]

Figure 4

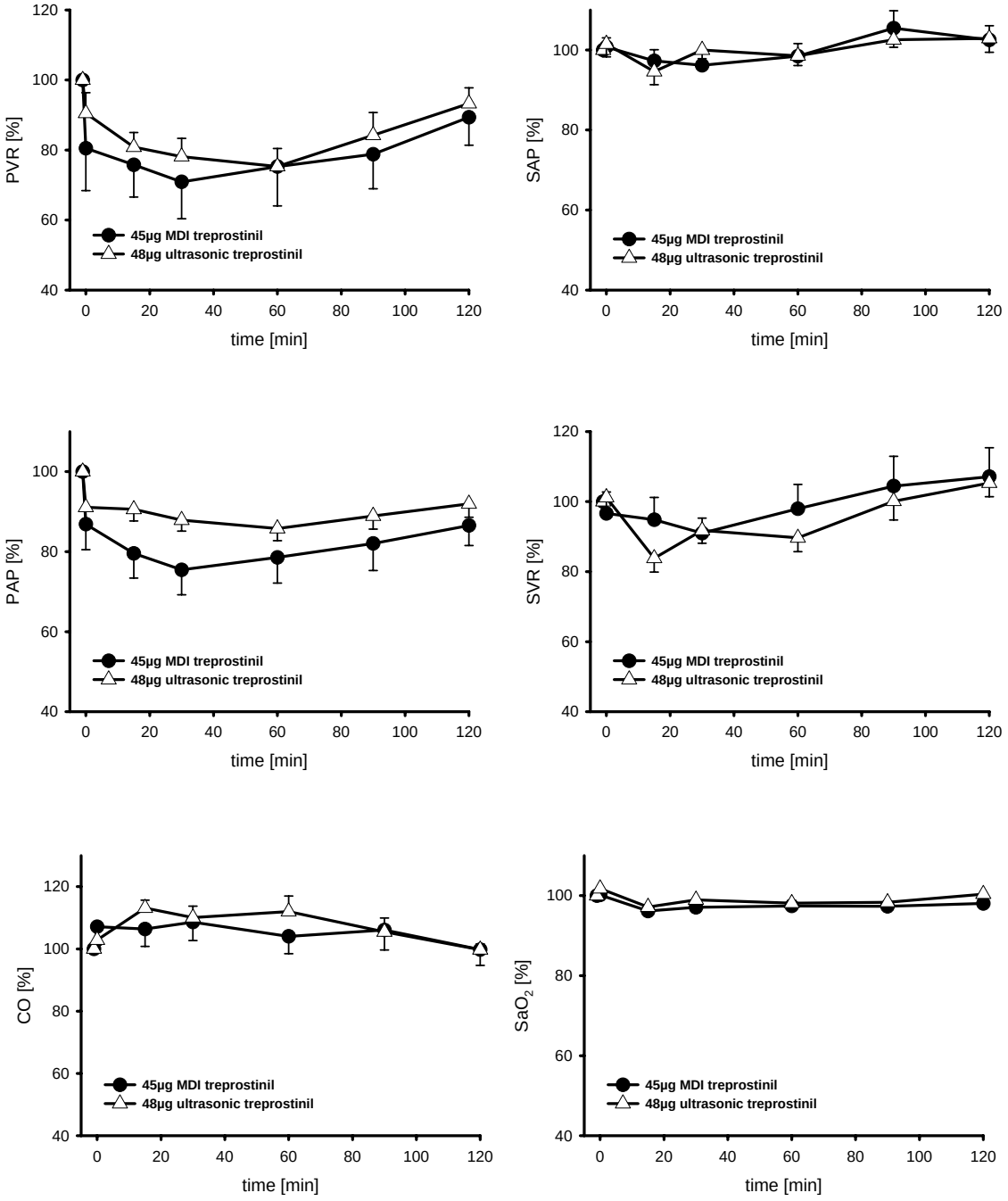
PVR [%]
SAP [%]
PAP [%]
SVR [%]
CO [%]
SaO2 [%]
time [min]
45µg MDI treprostinil
48µg ultrasonic treprostinil

Figure 5

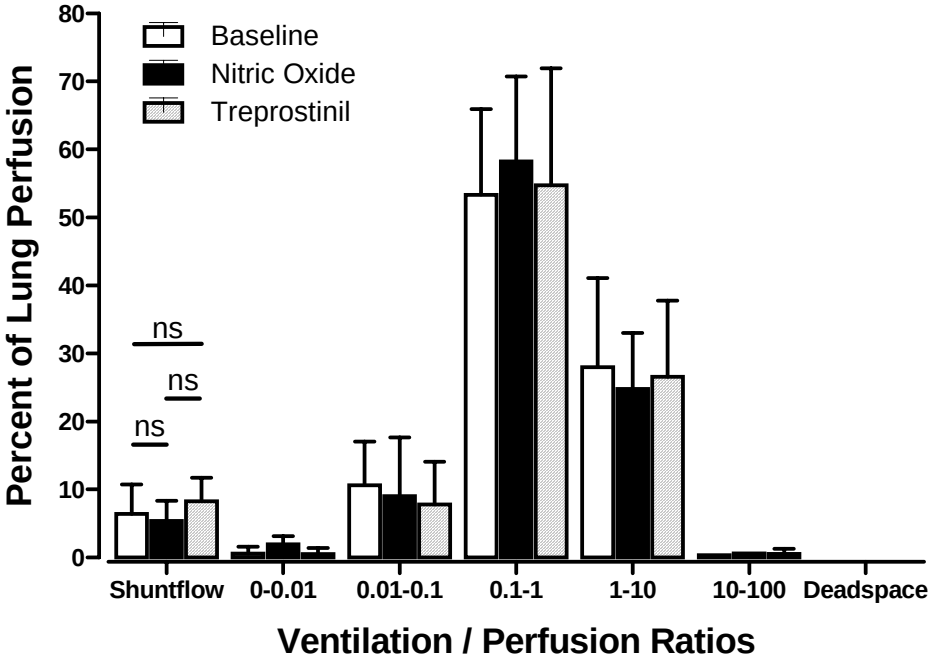

Figure 6

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