Downregulation of hypoxic vasoconstriction by chronic hypoxia in rabbits: effects of nitric oxide

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Hypoxic pulmonary vasoconstriction (HPV) is suggested to contribute to the development of hypoxia-induced pulmonary hypertension and right heart hypertrophy. Previous studies, mostly performed in rats, have given conflicting results concerning the effect of chronic alveolar hypoxia on pulmonary vasoactivity, especially HPV. Whereas various investigations found a reduction in HPV (2, 10, 21, 22, 27, 36), others reported increased or unchanged responses to an acute hypoxic challenge after chronic alveolar hypoxia (2, 5, 14; for a review, see Ref. 13). Concerning the rat, it is striking that an unchanged or increased response was found only in Wistar rats, whereas downregulation was mostly evident in Sprague-Dawley rats. The observation that the response to chronic hypoxia varies in different rat strains is also supported by the findings of Ou and colleagues (24, 25). The study of Zhao et al. (36) demonstrated that HPV was unaltered after 1 wk but reduced after 15 h or 2 days of chronic hypoxia. Moreover, the role of lung nitric oxide (NO) synthesis in the effect of chronic hypoxia on pulmonary vasoactivity is not fully clarified. Again, most of the investigations addressing NO were performed in rats, with the few studies performed in other species suggesting different effects of NO in different species including humans (3, 7, 12, 16, 23, 29; for a review, see Ref. 15). Thus the varying results concerning vasoactivity after chronic hypoxia and the contribution of NO to those changes are at least in part related to species and even strain differences. This also has to be kept in mind when trying to transfer findings from animals to humans.

To address these conflicting results in a detailed fashion, we studied the effects of chronic hypoxia in rabbits, a species that has heretofore not been investigated concerning these issues. The animals were exposed to normobaric alveolar hypoxia (10% O₂) for 1–70 days, and pulmonary hemodynamics as well as vascular responsivenessto an acute hypoxic challenge were investigated during this time at small intervals.
Ex vivo characterization of the hypoxia-exposed lungs was undertaken in isolated buffer-perfused organ experiments to exclude any interference with the remainder of the body and blood circulation (34). The vasoconstrictor responses to acute hypoxia were compared with those provoked by the thromboxone mimetic U-46619. To elucidate the role of NO synthesis for the observed effects, we 1) measured NO exhalation in the ex vivo perfused lungs, 2) undertook pharmacological blockade of NO, and 3) performed studies with continuous delivery of NO (15 ppb) into the inspired air during the period of hypoxia.

**MATERIALS AND METHODS**

Reagents. Krebs-Henseleit buffer was provided by Serag-Wiessner (Naila, Germany). U-46619 was from Paesel and Lorei (Frankfurt, Germany), and Nω-monomethyl-l-arginine (L-NMMA) was purchased from Sigma (Deisenhofen, Germany). All other biochemicals were obtained from Merck (Munich, Germany). Gases were from Messer-Griesheim (Siegen, Germany).

Chronic hypoxia and NO treatment. All animal experiments were approved by the local authorities (Regierungsspräsidium Giessen, numbers 17a-10c 20-15(1)-Gi20/10-3/95 and 25.3-19c 20/15(1)-Gi20/10-20/99). Rabbits of either sex (2.5–3.2 kg) were exposed to normobaric hypoxia [inspiratory O2 fraction (FiO2) = 0.10] in a ventilated chamber. The level of hypoxia was held constant by an autoregulatory control unit (model 4010, O2 controller, Labotect; Göttingen, Germany) supplying either nitrogen or oxygen. Excess humidity in the recirculating system was prevented by condensation in a cooling system. CO2 was continuously removed by soda lime. Cages were opened once per day for cleaning as well as for food and water supply.

For treatment with inhaled NO, this agent was continuously flushed into the system to achieve a concentration of 15 ppm. The NO concentration was controlled twice daily by an NO analyzer (Sievers 280 NOA, Sievers Instruments; Boulder, CO). The NO-treated animals were investigated after 42 days of chronic hypoxia. Rabbits exposed to normobaric normoxia were kept in a similar chamber at an FiO2 of 0.21.

After various time periods with chronic hypoxia, lungs were investigated in an isolated lung preparation, and hearts were exposed to room air (tidal volume, 30 ml; frequency, 30 strokes/min). A positive end-expiratory pressure of 1 cmH2O was chosen (zero referenced at the hilum). The isolated perfused lungs were placed in a temperature-equilibrated housing chamber, freely suspended from a force transducer for continuous monitoring of organ weight. The whole system (perfusate reservoirs, tubing, housing chamber) was heated to 38.5°C. Pressures in the pulmonary artery, left atrium, and trachea were registered with the use of a small-diameter tubing threaded into the perfusion catheters and the trachea and connected to pressure transducers. Lungs included in the study were those that 1) had a homogeneous white appearance with no signs of hemostasis, edema, or atelectasis; 2) revealed constant mean pulmonary artery and peak ventilation pressure in the normal range; and 3) were isogravimetric during the initial steady-state period of at least 20 min. Weight increase ranged <3 g throughout the entire experiment, which was approximately <19% of the average lung wet weight.

Hypoxic maneuvers and pharmacological challenges. The technique of successive hypoxic maneuvers in buffer-perfused rabbit lungs has been described previously (34, 35). Briefly, a gas mixing chamber (KM 60-3/6MESO, Witt; Witten, Germany) was employed for step changes in the ventilator O2 content (from 21% (vol/vol) (alveolar Po2 ~160 mmHg, baseline conditions) to 3% (vol/vol) (alveolar Po2 ~23 mmHg, hypoxic conditions)); 5.3% (vol/vol) CO2 was used throughout, and the percentage of N2 was balanced accordingly. Two hypoxic maneuvers of 10-min duration, interrupted by a 15-min period of normoxia, were performed. Fifteen minutes after the cessation of hypoxia, two bolus applications of the stable thromboxane mimetic U-46619 (addition at an interval of 15 min to the perfusate at 0.5 nM) were undertaken as described previously for investigation of lung vascular reactivity to this agent (9, 33). Fifteen minutes after the second U-46619 challenge, the lung vasculature was flushed with 1 liter of fresh buffer, and, after 10 min, 400 µM L-NMMA was added to the perfusate. After another 10 min, an identical sequence of hypoxic and U-46619 challenges as performed before the perfusate exchange was started. The sequence of hypoxic and U-46619 challenges was started 70–90 min after removal of the animals from the hypoxic chambers. For analysis, the maximum strength of each second hypoxic challenge and each first U-46619 challenge was selected. Normoxic vascular tone was assessed after the initial steady-state period as well as 35 min after the L-NMMA addition.

In one set of experiments, the animals were strictly kept at 10% O2 during the entire preparation process until the steady-state period of the isolated lung preparation was finished. Thereafter, the ventilator gas supply was switched to 21% O2 to determine the effect of an immediate increase in alveolar Po2 after long-term hypoxia. These investigations were done in rabbits exposed to 14 days of chronic hypoxia.

**Statistics.** For calculation of statistical differences, ANOVA with the Student-Newman-Keuls post hoc test was
 performed for comparison of more than two groups or a Dunnett multiple-comparison test was done when multiple groups were compared with the control. Statistical significance was assumed when \( P \) ranged < 0.05. Data are given as means ± SE.

**RESULTS**

For detailed characterization of the effects of chronic normobaric hypoxia (10\% O\(_2\)) over a period of 10 wk, analysis was performed after 7, 14, 21, 28, 42, and 70 days. A significant increase in the RV wall-to-LV wall plus septum ratio was already noted after 7 days, and right heart hypertrophy was highest after 70 days (Fig. 1A). Baseline pulmonary arterial pressure (PAP), measured in the ex vivo perfused lungs during normoxia, showed some increase already within the first days and was significantly increased after 42 and 70 days of chronic hypoxia (Fig. 1B). Performance of acute hypoxic ventilation or pharmacological vasoconstrictor challenges in the ex vivo perfused lung resulted in very well reproducible PAP increases as previously described (33, 34). An acute hypoxic ventilation of 10 min duration increased PAP in the perfused lungs, with a maximum reached within 4–6 min. This maximum vasoconstrictor response to an acute hypoxic ventilation was inhibited after chronic hypoxia (Fig. 2A). This inhibition was obvious even after 1 day of chronic hypoxia and was at maximum after 7 days, with no further change in the strength of HPV up to 70 days. In contrast, the vasoconstrictor response to U-46619 was not significantly reduced over the entire period of 70 days of chronic hypoxia (Fig. 2B). In animals exposed for 14 days to chronic hypoxia and not reexposed to 21\% O\(_2\) until the steady-state period of the isolated lung preparation was finished, reoxygenation with 21\% O\(_2\) resulted in a PAP decrease of 0.3 ± 0.1 mmHg, with the maximum reduction observed after 12.6 ± 1.5 min (\( n = 5 \)). Inhibition of lung NO synthesis by 400 \( \mu \)M \( L\)-NMMA only slightly increased the baseline vascular tone (at most ~25% within 35 min). In this respect, lungs undergoing chronic hypoxia did not differ from normoxic controls (data not given in detail).

In contrast, lung vascular reactivity was markedly amplified after NO blockade. This amplification was more prominent for HPV compared with U-46619-induced vasoconstriction (Fig. 3). The difference between the hypoxia- and U-46619-elicited pressor responses was, however, lost after 42 and 70 days of chronic hypoxia.

No changes were detected between the exhaled NO concentrations of lungs from normoxic and chronically hypoxic animals (Fig. 4). An acute hypoxic challenge rapidly decreased lung NO exhalation, as previously shown by investigations from our laboratory (8). The maximum decrease was 20.1 ± 1.4\% (\( n = 7 \), 0 days of hypoxia; Fig. 4) when referenced to the level of normoxic ventilation (= 100\%). This reduction in lung NO exhalation was not altered after chronic hypoxia over the entire period of 70 days (Fig. 4). U-46619-induced vasoconstriction did not decrease NO exhalation.

In a separate set of experiments, rabbits were treated with continuous admixture of NO into the inhaled gas in a concentration of 15 ppm for a 42-day period of chronic hypoxia. As depicted in Fig. 5A, right heart hypertrophy was significantly reduced by inhaled NO. The lung vascular constrictor response to an acute hypoxic challenge, which was prominently reduced after 42 days of chronic hypoxia, was partially restored by treatment with inhaled NO (Fig. 5B). As already evident from the time course of lung vascular reactivity after chronic hypoxia, the strength of
U-46619-induced vasoconstriction was only slightly reduced during hypoxia, and this slight reduction was lost in rabbits chronically coexposed to hypoxia and NO (Fig. 5C). However, chronic NO inhalation did not alter the amplification of vasoconstrictor responses to acute hypoxia and U-46619 challenges (Fig. 5D). Moreover, no differences were found in the exhaled NO concentration and decrease of exhaled NO during an acute hypoxic challenge (3% O₂) between normoxic controls, animals with 42 days of chronic hypoxia, and animals coexposed to hypoxia and NO inhalation for 42 days (Fig. 5E).

**DISCUSSION**

The present study investigated the effects of chronic alveolar hypoxia on the vasoconstrictor response of rabbit lungs to an acute hypoxic challenge and U-46619-induced vasoconstriction. Assessment of vasoreactivity in isolated perfused and ventilated lungs allows investigation of the pulmonary vasculature without any interference with the remainder of the body and impact of blood (34). The latter is important especially with respect to the measurement of exhaled NO, which was shown to represent largely alveolar and vascular NO generation during blood-free perfusion (8, 31).

**Early downregulation of HPV during chronic hypoxia is a specific event independent from lung NO synthesis.** Previous studies in rats have reported conflicting results with respect to the vasoconstrictor re-

**Fig. 2.** Strength of vasoconstrictor response to acute hypoxic challenge (A) or U-46619 bolus application (B). The lung vasoconstrictor response was measured after the indicated time spans of chronic normobaric hypoxia (1–70 days, 10% O₂). Controls (0 days) are from normoxic animals. For hypoxic challenges, 3% O₂ was employed. U-46619 responses were elicited by bolus application of this agent, resulting in a concentration of 0.5 nM in the recirculating buffer fluid. Data are means ± SE (at least 4 animals/group). ΔPAP, magnitude of hypoxia or U-46619-induced increase in PAP. *Significant difference compared with normoxic control.

**Fig. 3.** Amplification of vasoconstrictor responses to acute hypoxic or U-46619 challenges by inhibition of lung nitric oxide (NO) synthesis. Lung NO synthesis was blocked by perfusion of lungs with 400 μM N⁶-monomethyl-L-arginine (L-NMMA). The amplification of vasoconstrictor responses is given as a percentage, related to each individual control before blockage of lung NO synthesis (100%). The lungs originated from rabbits exposed to hypoxia for different time periods. Data are means ± SE; n = 4–5 for days 0–6 and 42. *Significant differences between amplification of hypoxia and U-46619 responses.

**Fig. 4.** Exhaled NO in isolated lungs. Levels of NO measured in the exhaled gas of isolated perfused rabbit lungs are given in absolute values (left ordinate). On the right ordinate, the maximum decrease in exhaled NO during an acute hypoxic ventilation period (3% O₂, 10 min) is given as percent, related to the value directly before the hypoxic ventilation maneuver. Lungs originated from control rabbits (0 days) or from control rabbits exposed to chronic hypoxia over 7–70 days. Data are given as means ± SE (n = 3–7 per group) for normoxic controls (0 days hypoxia) as well as for several time spans of chronic normobaric hypoxia (10% O₂).
Fig. 5. Effects of treatment of rabbits with inhaled NO (15 ppm) during chronic hypoxia for 42 days. A: RV/LV + septum. B and C: strength of the pulmonary vasoconstrictor response, measured in ex vivo perfused lungs, to an acute hypoxic challenge (3% O₂) or bolus application of the thromboxane mimetic U-46619. Lungs originated from normoxic controls or from animals exposed to chronic hypoxia or hypoxia + NO for 42 days. D: amplification of vasoconstrictor responses to acute hypoxic or U-46619 challenges after inhibition of lung NO synthesis. NO synthesis was blocked by perfusion of the lungs with 400 μM L-NMMA. The amplification of vasoconstrictor responses is given as a percent, related to each preceding individual control before blockage of NO (=100%). E: exhaled NO in isolated lungs. Levels of exhaled NO during normoxic ventilation are given in absolute values (left ordinate). On the right ordinate, the maximum decrease in exhaled NO during an acute hypoxic ventilation period (3% O₂, 10 min) is given as a percent, related to the value directly before the hypoxic ventilation period. Data are given as means ± SE; n = number of isolated lung or heart preparations. *Significant difference to the corresponding normoxic control (normoxia) except in D, where *significant difference between the response to an acute hypoxic challenge and U-46619-induced vasoconstriction; + significant difference between the animals treated with 15 ppb NO for 42 days during chronic hypoxia [hypoxia (42 days) + NO] and those not being NO treated [hypoxia (42 days)].
sponse to an acute hypoxic challenge after chronic hypoxia. Whereas a variety of investigations have found a reduced HPV response after long-term exposure to low PO₂ (e.g., Refs. 2, 10, 21, 22, 27, and 36), other groups have reported an enhanced or no change in HPV after exposure to chronic hypoxia (2, 5, 36). Interestingly, an enhanced or unaltered HPV was only observed in studies that investigated Wistar rats, whereas in most of the studies that found decreased HPV Sprague-Dawley rats were investigated. Thus strain differences seem to contribute to the conflicting results. The observation that the response to chronic hypoxia is different in different rat strains is also supported by the findings of Ou and colleagues (24, 25). Karamsetty and colleagues (14) showed a reduced HPV when the lungs were ventilated with 0% O₂ but an unchanged HPV when ventilated with 2% O₂. Zhao et al. (36) demonstrated that HPV was reduced after 15 h and 2 days of chronic hypoxia but unchanged after 7 days. Thus changes in vasoreactivity as well as the ages of the animals investigated may also underlie the partly contradictory results. However, the use of isolated lungs or intact animals does not seem to play a role (2, 13). The present investigation was performed in isolated lungs or intact animals does not seem to play a role (2, 13). The present investigation was performed in isolated lungs or intact animals and a species that heretofore not been characterized with respect to changes in vasoreactivity after chronic hypoxia.

There are also conflicting results concerning changes in lung vasoreactivity after chronic hypoxia to nonhypoxia-induced vasoconstrictor responses, even though most studies gave evidence for increased sensitivity (5, 10, 13, 18–22, 28, 32). To settle this issue for rabbit lungs in a detailed fashion, pulmonary vascular reactivity to hypoxia and the stable thromboxane analog U-46619 was investigated in ex vivo perfused lungs, originating from rabbits undergoing chronic hypoxia for various time intervals. As anticipated, the chronic exposure to hypoxia provoked development of pulmonary hypertension in these animals, confirmed by a progressive RV hypertrophy and increase in baseline PAP (normoxic artificial ventilation of ex vivo perfused lungs) over the 10-wk maximum observation period. The increase in baseline PAP after increasing the duration of chronic hypoxia is rather small compared with measurements in intact animals or isolated lungs perfused with oncotic agents (36). This is anticipated because blood-free perfusion was used in our setup without an oncotic agent, which allows only moderate flow rates.

Most interestingly, as obvious from the various analyses within the first week, only ~5 days of chronic hypoxia sufficed to cause far-reaching loss of the vasoconstrictor response to acute hypoxia, and this feature then remained unchanged up to the end of the 10-wk observation period. This inhibition of HPV was specific for the hypoxia response because the strength of vasoconstrictions elicited by bolus applications of U-46619 was not significantly changed over the entire period of 10 wk of chronic hypoxia. This is in line with the investigations of Eddahibi et al. (4) in isolated rat lungs, in which maintenance of a pharmacological vasoconstrictor response was demonstrated after a period of 28 days of chronic hypoxia in rats; Hampl et al. (10) even noted some increase in the U-46619-elicted vasoconstrictor response under these conditions. To the best of our knowledge, the present study is the first to demonstrate the rapid kinetics and specificity of HPV suppression within several days of chronic hypoxia.

The fact that only a negligible decrease in PAP occurred when the animals were continuously exposed to 10% O₂ until the steady-state period of the isolated lung perfusion was finished and the ventilator gas supply was changed to 21% O₂ suggests that it is not a permanent activation of acute HPV that might mask an additional increase in PAP during an acute hypoxic challenge in the isolated lung preparation. Teleologically, the downregulation of HPV after chronic hypoxia may be interpreted as a protective mechanism against right heart failure that may occur after the increase in baseline PAP is further enhanced by a strong hypoxic vasoconstrictor response.

Previous investigations in isolated rabbit lungs have demonstrated that lung NO generation specifically affects HPV compared with nonhypoxia-induced vasoconstriction (8, 35). Moreover, NO is the only known dilator that specifically suppresses HPV (8, 35) and to which the vascular responses to chronic hypoxia have partially been attributed (13). Thus we focused on the question of whether changes in lung NO generation might underlie the specific loss of HPV during chronic hypoxia. The addition of 400 μM L-NMMA, which has been shown to block lung NO synthesis virtually completely (8, 31), only moderately increased baseline vascular tone, with no differences found between the normoxic control and chronically hypoxic animals. The unchanged L-NMMA-induced increase in baseline PAP during chronic hypoxia is in contrast to investigations in isolated rat lungs (1) and isolated rat pulmonary arteries (19), where the increase in baseline pulmonary artery tone upon NO inhibition was higher after chronic hypoxia than in our investigation, but is in line with the investigation of Zhao et al. (36), where L-NMMA only caused slight increases in baseline PAP. In contrast to our investigation, the study of Liu et al. (17) found an increase in PAP and development of massive edema after NO blockade in normoxic rabbits, which could be inhibited by cyclooxygenase blockade. Their data thus demonstrate a cross-talk between NO and cyclooxygenase pathways. The differences compared with our study may be explained by species differences or by the fact that an in situ blood-perfused lung model or a different NO synthase inhibitor were applied. When blocking lung NO synthesis in our study, the acute hypoxic vasoconstrictor response was significantly more highly amplified than the strength of U-46619-induced vasoconstriction, as previously demonstrated (8). This feature was maintained for up to 14 days of chronic hypoxia but was largely lost after 42 and 70 days, with the L-NMMA-related enhancement of the acute hypoxic vasoconstrictor response then corresponding to the U-46619-induced response. This loss of response to L-NMMA may be related to an...
interaction with lung arachidonic acid metabolism (17, 26), because over the entire observation period of chronic hypoxia, the quantities of NO being exhaled during ex vivo lung perfusion did not change. Moreover, the rapid initial decrease of exhaled NO during an acute hypoxic challenge was not affected by the duration of preceding chronic hypoxia. We have previously provided evidence that the sharp drop in the exhaled NO levels during an acute hypoxic challenge is directly involved in the regulation of HPV, because this NO response occurs before the hypoxia-induced increase in PAP is detectable, and it is fully reversible after cessation of hypoxic ventilation, again with the NO changes preceding the changes in PAP (8).

The unchanged NO release in the chronic hypoxic rabbit lung differs from investigations in rats (12, 23, 29), which found an increase in NO release or an increased expression of NO synthases in chronic hypoxia (6, 16; for a review, see Ref. 15). Such differences may be species dependent because investigations in newborn pigs found decreased NO synthesis during chronic hypoxia (7).

Thus, summarizing the data on the downregulation of HPV, this event was found to occur within a few days of chronic hypoxia and to be specific for hypoxic challenge, because the U-46619-elicted response was maintained. This downregulation is apparently not linked to changes in lung NO synthesis represented by exhaled NO, because the quantities of exhaled NO, the sharp NO drop at onset of hypoxia, and the strong amplification of the hypoxic vasoconstrictor response upon blockage of the NO system remained unchanged. This, however, cannot exclude the possibility that changes in downstream pathways of NO (e.g., cGMP) or an interaction of cyclooxygenase and NO synthase products may be responsible for the observed effects (26). Both NO and cyclooxygenase products contribute to the physiologically low PAP, with a different extent of contribution in different species (17). Thus the differences in the strength of HPV after chronic hypoxia may reflect different levels or different expression profiles of vasodilator or constrictor substances, which may include also cytochome P-450-derived metabolites of arachidonic acid (37). The molecular mechanisms underlying the rapid loss of HPV during chronic hypoxia, occurring before any major increase in baseline PAP is detectable, thus remain to be elucidated.

Impact of long-term NO inhalation on vascular remodeling and HPV during chronic hypoxia. When performing long-term treatment of the lungs with inhaled NO (15 ppb) over the period of chronic hypoxia, development of pulmonary hypertension was significantly reduced, but not normalized, as assessed by right heart hypertrophy. The corresponding efficacy of long-term inhaled NO has been previously observed in rats (11). Interestingly, NO treatment partially restored the response to an acute hypoxic challenge; however, vasoreactivity to U-46619 was also enhanced, suggesting a nonspecific increase in vasoreactivity induced by NO therapy. These effects of inhaled NO were not attributable to changes in exhaled lung NO release, because no significant differences could be observed between the control animals, the chronic hypoxic animals, and the chronic hypoxic animals with NO application when assessing levels of exhaled NO during ex vivo lung perfusion. Moreover, long-term NO did not influence the rapid decline in NO exhalation when performing an acute hypoxic challenge in the perfused lungs. Finally, the significantly higher amplification of HPV under L-NMMA compared with U-46619-induced vasoconstriction, which was lost after >14 days of chronic hypoxia, was not restored by NO treatment. Thus long-term inhaled NO partially antagonizes the development of chronic hypoxia-induced pulmonary hypertension, and some maintenance of the reactivity to acute challenges was also noted. However, this was not specific for HPV compared with U-46619-induced vasoconstriction, and no significant impact on NO-related mechanisms involved in the hypoxia-induced vasoconstrictor response was observed by the parameters investigated. The increase in vasoreactivity after NO treatment may be an advantage with respect to ventilation perfusion distribution by enhancement of HPV and, if humans behave like rabbits, may be of interest for NO therapy in humans.

In conclusion, chronic hypoxia has been shown to cause early downregulation of the acute HPV response, which is a specific event, and is independent of the lung vascular NO system, and as well precedes the development of major pulmonary hypertension. Long-term NO inhalation partially antagonizes the chronic hypoxia-induced pulmonary hypertension, with some maintenance of the reactivity to acute hypoxic challenge.

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