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EXPERIMENTAL

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Theoretical and experimental comparison of constant inspired concentration and pulsed delivery in NO therapy

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Abstract Objective: Inhaled NO therapy of artificially ventilated patients has been established as being based on constant inspired concentration of NO. In this study a new volumetrically controlled pulsed NO delivery mode is compared with the established concentration-based concept.
Design: To evaluate the relationship between NO delivery parameters, alveolar NO fraction, and patient uptake, a mathematical lung model was created where NO delivery can be simulated in varying ventilator settings, delivery modes, and lung properties. This model and the efficacy of pulsed delivery in inducing pulmonary capillary vasodilatation were examined experimentally.
Setting: Animal laboratory, Department of Medical Sciences, Clinical Physiology.
Subjects: The experimental study was performed with nine pigs of mixed breed weighing 25–35 kg.
Interventions: The pigs were anaesthetised and artificially ventilated. Pulmonary vasoconstriction was induced by hypoxia. NO was delivered periodically in the various delivery modes.
Measurements and results: In simulation, in all delivery modes the NO uptake was found to be dependent on the ventilator settings and the volume of the dead space. Measured from pulmonary artery pressure, the pulsed delivery was as effective in reducing the induced pulmonary vasoconstriction as the constant inspired concentration delivery. The amount of NO that could reduce the vasoconstriction back to baseline was 105 nmol · min^{-1}. By delivering in the early part of the inspiration, ambient contamination by the exhaust gas is avoided. The expired NO values obtained in the simulation and the experiments were equal. Based on the simulation, the alveolar NO fraction and the NO uptake depend on the ventilator settings and the dead space in both volumetric- and concentration-based delivery.
Conclusions: With pulsed delivery, a therapeutic effect comparable to constant inspired concentration delivery is achieved, NO gas is used more effectively, and environmental exhausts are reduced. The theoretical model shows that the NO delivery does not predict alveolar NO fraction and the NO uptake. However, it still remains an open question if the online measurement of these parameters would provide useful information, having added value in predicting and controlling the efficacy of the NO treatment.

Key words Nitric oxide · Pulmonary vasoconstriction · Pigs · NO delivery · Hypoxia

Introduction

Nitric oxide (NO) was identified as an endothelium-derived relaxation factor in 1987 [1, 2]. The smooth muscle tone of the pulmonary vessels has been shown to be influenced by continuous release of NO from the endothelium, leading to an increase in cGMP that mediates relaxation. The NO administered by inhalation acts as replacement of the locally decreased NO production. Arising from this finding, inhaled NO has been used to reduce pulmonary hypertension [3], improve oxygenation [4, 5], and lessen the right ventricular loading [6] in patients with severe acute lung diseases.

In artificial ventilation NO has mostly been administered by constant inspired NO concentration [7, 8, 9, 10, 11, 12]. The possibility of a delivery concept based on the NO volume has also been discussed [8, 13]. However, the relation between the inspired NO concentration or amount and the alveolar NO partial pressure and the NO uptake in various ventilator settings and patient physiology has not been studied analytically before.

To exert a vasodilatory effect, the NO molecules are transported from the alveolar space into the vascular smooth muscle by diffusion. According to Fick's first law of diffusion the flux is proportional to the partial pressure gradient. Since the NO is rapidly metabolised, the blood concentration is zero. Therefore, alveolar partial pressure of NO, the NO diffusing capacity alveolar partial pressure of NO, and the NO diffusing capacity control the NO transport.

Due to high diffusing capacity, 95–100 % of the NO is taken up from the alveoli [14] meaning that thus almost all the NO exhaust is coming from the dead space. NO delivery in pulses of known amounts synchronously with the inspiration makes it possible to avoid the anatomic dead space administration and reduce the environmental exhausts. Pulsed delivery mode has been used for the treatment of persistent pulmonary hypertension in spontaneously breathing patients [15, 16].

This study presents a model to predict the relationship of the administered NO to alveolar NO fraction, NO uptake and, further, to exhaled NO fraction. In an experimental part of this study a new delivery device for pulsed administration was tested. The efficacy of various pulsing schemes, including one equivalent to the constant concentration mode, was investigated. The differences in the safety aspects, including the rebound effect, between various NO administration modes will also be discussed. To confirm the theoretical model the measured exhaled NO fractions in different delivery settings will be compared to the predicted ones.

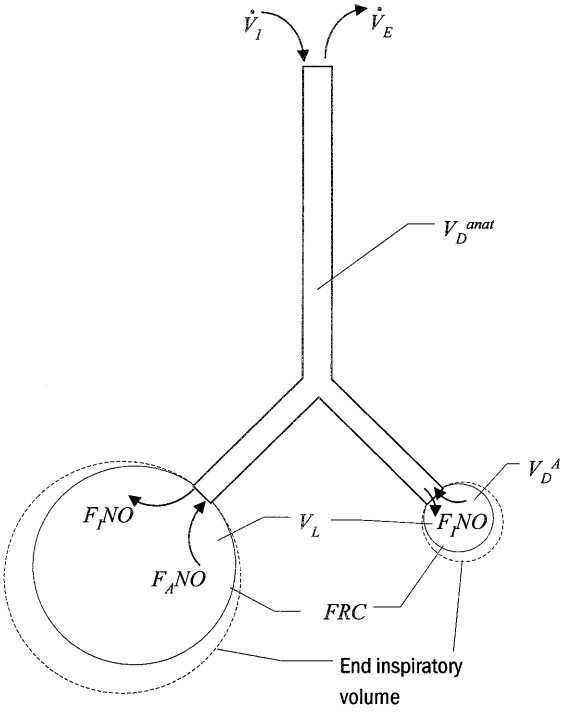

Fig. 1 Lung model used for the simulation of the NO inhalation

Methods

Theoretical study

The theoretical model consists of two elastic compartments representing perfused and non-perfused lung sections (Fig. 1). The lung volume (V_L) is set initially to functional residual capacity (*FRC*). The elasticity is determined by compliance *C*. In simulation, the compliance was selected for the tidal volume to give 10–15 cmH_2O peak inspiratory pressure. The lung is ventilated with inspiratory flow ($\dot{V}_I$)through a channel representing the anatomic dead space volume (V_D^{anat}). NO is administered into the inspired flow at a rate defined by the NO delivery mode and delivery rate. NO is transported through the V_D^{anat} into the lung. The gas entering the elastic compartment is divided to flows into the parallel perfused and non-perfused lung compartments in a ratio ($V_D^A \cdot V_L^{-1}$) determined by the proportion of the alveolar dead space (V_D^A) of the V_L. The gas will be mixed with the gas already existing in the compartments so that the compartment mixture is always homogeneous.

The V_L and lung pressure (P_L) during inspiration are represented by Eqs. (1) and (2). In the perfused compartment, the diffusion of NO is continuous and determined by the lung NO partial pressure, or fraction (F_ANO), and diffusion constant (D_{LNO}). The lungs are provided with NO mixed in the inspired gas in fraction (F_INO). The F_ANO for the compartments is determined by Eq. (3). In the non-perfused compartment the diffusion constant value is zero.

Expiratory gas flow ($\dot{V}_E$) is determined by the P_L and airway resistance (*R*) according to equation (4). The $\dot{V}_E$ is a mixture of parallel flows derived from the perfused and non-perfused compartments in a ratio determined by the $V_D^A \cdot V_L^{-1}$. The corresponding decrement in the lung volume is determined by equation (5). The

R was selected to keep the P_L calculated with equations (2) and (5) typically below 1 cmH_2O at the end of expiration. Equation (6) presents the F_ANO during expiration. For the non-perfused compartment the F_ANO remains unchanged because D_{LNO} is zero. Also, the exhaled gas is transported through the V_D^{anat}. The gas exiting the V_D^{anat} represents expired NO fraction (F_ENO).

$$dV_L = \dot{V}_I \cdot dt \quad (1)$$

$$dP_L = \frac{dV_L}{C} \quad (2)$$

$$dF_ANO = \frac{dV_L \cdot (F_INO - F_ANO) - F_ANO \cdot D_{LNO} \cdot dt}{V_L} \quad (3)$$

$$\dot{V}_E = \frac{P_L}{R} \quad (4)$$

$$dV_L = -\dot{V}_E \cdot dt \quad (5)$$

$$dF_ANO = \frac{-F_ANO \cdot D_{LNO} \cdot dt}{V_L} \quad (6)$$

The model can determine the F_ANO, F_ENO and NO uptake in any ventilation settings of tidal volume (V_T), I:E ratio, respiration rate (RR), FRC, lung mechanics, D_{LNO}, $V_D^A \cdot V_L^{-1}$, V_D^{anat}, and NO administration pattern. The set of derived differential equations are simulated by integration of infinitesimal changes in LabView version 5.0 programming platform (National Instruments, Austin, Tex., USA). The V_D^{anat} is modelled as an array of elements of 1 ml. The array is loaded with NO fraction from the one end and shifted in rate and direction determined by the simulation carrying the NO fraction through the array to be released from the opposite end.

Experimental study

Animals and anaesthesia

Nine healthy pigs of mixed breed (Hampshire, Yorkshire and Swedish landrace)with a body weight of 25–35 kg were used in this study. Premedication was given by an intramuscular (i.m.) injection before transport with the neuroleptic Stresnil (Janssen Pharmaceutical, Beerse, Belgium). Anaesthesia was induced with 0.5 mg atropine and a mixture of Zoletil forte vet. (Virbac Laboratories, Carros, France) diluted in 5 ml Domitor (Orion Corporation, Farmos, Finland); 1 ml per 20 kg body weight i.m. The pigs were intubated with a cuffed endotracheal tube and ventilated mechanically in constant flow volume controlled mode with ZEEP (Siemens Servo 900 C, Siemens-Elema, Solna, Sweden). The I:E ratio was 1:2. The V_T was 10 ml per kg plus compensation for dead space volume and the frequency adjusted to an end tidal CO_2 of 5 %. Anaesthesia was maintained by infusion of 5 $ml \cdot kg^{-1} \cdot h$ of 4 g Ketamin (Veterinaria, Zürich, Switzerland), 1 mg Fentanyl (Antigen Pharmaceuticals, Roscrea, Ireland), and Pavulon 48 mg in 1000 ml Rehydrex with glucose (Pharmacia and Upjohn, Stockholm, Sweden).

NO delivery

A prototype delivery device for pulsatile NO therapy was designed and constructed at the Datex-Ohmeda Research Unit, Helsinki, Finland. The device delivers adjustable volumetric dose at the onset of inspiration. The time-related NO delivery rate is obtained by multiplying this with the respiration rate. The RR and the delivery mode determine the pulse duration. The pulse volume is adjusted by controlling the administered NO/N_2 flow with a proportionally controlled solenoid valve to meet the set pulse volume. The delivered dose is measured with two flow sensors connected in series. One of these sensors is assigned to the delivery control and the other one to the delivery monitoring providing safety against device failures. The breath pattern is measured for the start of inspiration detection and pulse delivery triggering with a patient flow sensor (D-lite, Datex-Ohmeda, Helsinki, Finland).

The delivery device was connected to a NO/N_2 cylinder supply of 1000 µl/l (= ppm) concentration (AGA, Lidingö, Sweden). The NO was delivered into the breathing circuit at the entrance of the endotracheal tube.

NO was delivered in a range of 10–5000 $nmol \cdot min^{-1}$ (0.5–240 nmol/inspiration). This corresponds to a pulse volume of 11 µl–5.4 ml/inspiration. Three different pulse widths were used: the first third of inspiration (= 1/3), two-thirds also starting from the onset of the inspiration (= 2/3), and whole inspiration (= 3/3). With constant flow ventilation the 3/3 pulsation is equivalent to the constant inspired concentration delivery.

Protocol and monitoring

A dose response study comprised of three phases: (a) baseline, b) vasoconstriction induced by hypoxic gas mixture, and c) NO delivery combined with the induced vasoconstriction. During 30-min baseline the mean pulmonary artery pressure (PAP) was 20–30 mmHg at an inspired gas oxygen fraction (F_IO_2) of 0.21. During vasoconstriction the F_IO_2 was decreased to 0.13–0.18 for targeted PAP of 30–40 mmHg. After 15 min of hypoxia, the NO was given in steps of different delivery modes and/or amounts for 5 min each followed by measurements of pulmonary capillary wedge pressure ($PCWP$) and thermodilution cardiac output (CO). As one step the NO delivery was stopped for studying the consequences of an abrupt cessation of the inhaled NO delivery. The maximum PAP value after this cessation was recorded as rebound pressure and assigned with the NO delivery preceding the cessation.

The $MetHb$ was analysed at baseline, vasoconstriction, and at the end of NO delivery. PAP, oxygen saturation (SpO_2), mixed venous oxygen saturation (SvO_2), F_IO_2, end-tidal oxygen fraction ($F_{ET}O_2$), and end-tidal carbon dioxide fraction were monitored continuously. The haemodynamics and respiration were monitored with a CS/3 (Datex-Ohmeda, Helsinki, Finland) patient monitor.

The exhaled NO was sampled for each NO delivery rate with a fast chemiluminescence monitor (Sievers NOA 280, Sievers Instruments, Boulder, Colo.,, USA) having a rise time of 200 ms and a resolution of 1 ppb. The electrochemical NO_2 analyser (Nomius, Dan-Sjö Medical, Stockholm, Sweden) was connected to the expiratory limb of the breathing circuit.

To compile the PAP values of different pigs, response studies, and NO dosage levels, the PAP values measured at baseline and vasoconstriction values were assigned with values 0 and 1, respectively. The monitored values during the NO delivery of the following response study were normalised on this scale. An example of the course of the study is presented in Fig. 2. The normalised values were analysed by one-dimensional ANOVA (Analyse-it, Analyse-It Software) for statistical significance of the NO delivery rate and mode. This software was also used for regression analysis.

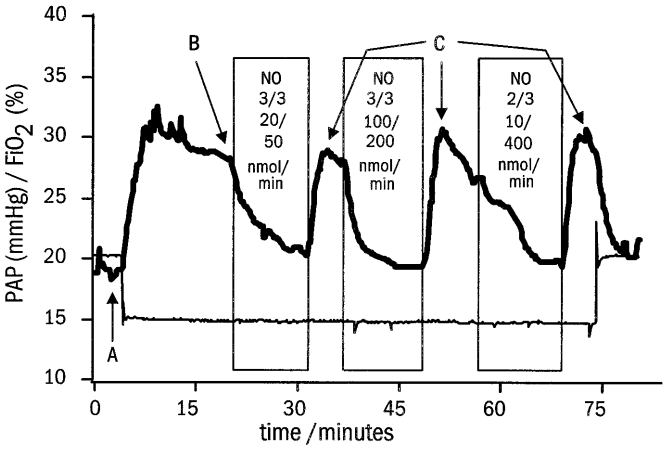

Fig. 2 PAP (*thick line*) and FIO2 (*thin line*) in a typical response study introducing with borders the NO delivery phases and the dosage rates during the delivery phase. *A* baseline, *B* vasoconstriction, *C* rebound

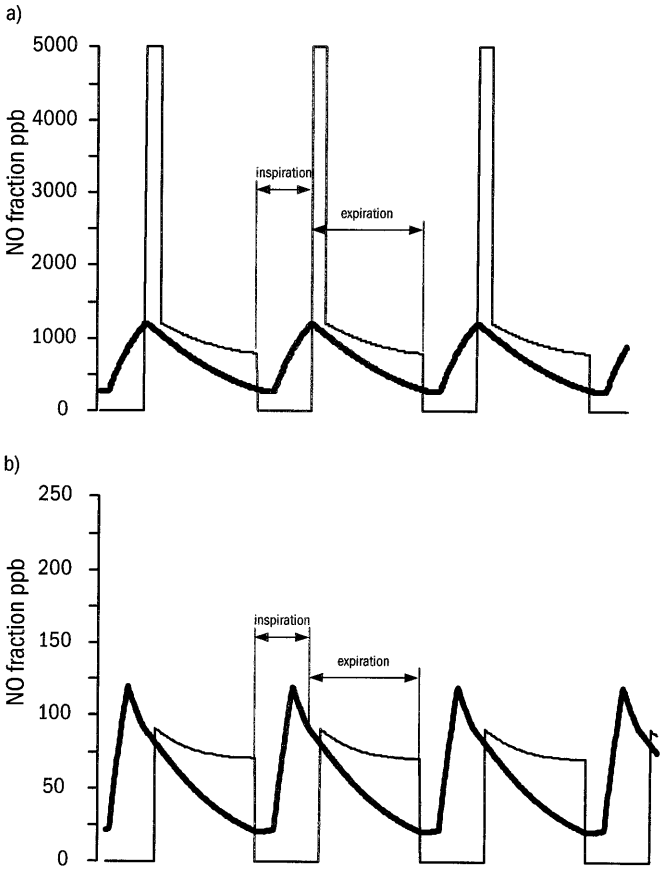

Fig. 3 Simulated alveolar (*thick line*) and expiratory (*thin line*) NO fraction for a) constant 5 ppm inspired concentration representing a typical clinic value and b) pulsed delivery 100 nmol · min^{-1} used in the experiments of this study delivered into the first third of the inspiration period

Results

NO delivery simulation

The simulated F_ANO and F_ENO curves for the 5 ppm constant inspired concentration and the 100 nmol · min^{-1} pulsed in 1/3 mode are presented in Fig. 3 a and Fig. 3 b, respectively. In simulation the $RR = 20$ min^{-1}, V_T = 400 ml, $I{:}E$ = 1:2, FRC = 700 ml, $V_D{}^{anat} = 150$ ml, $V_D{}^{A} \cdot V_L{}^{-1} = 0$, $C = 22$ ml · cmH$_2$O^{-1}, and $R = 12$ kPa · l^{-1} · s^{-1}. The $D_{LNO} = 6$ ml · s^{-1} · kPa^{-1} is estimated from the results of Borland [17]. In the constant inspired delivery mode an exhaust spike from the $V_D{}^{anat}$ is shown. Correspondingly, in pulsed delivery the F_ENO is zero at the beginning of expiration. The differences between the F_ANO and F_ENO resulting from continuous alveolar NO uptake during the transport through $V_D{}^{anat}$ are also clearly demonstrated.

Table 1 presents mean F_ANO, end-tidal NO fraction (F_{ET}NO), and NO uptake/delivery ratio calculated for a representative set of various ventilator settings, lung volumes and mechanics, and delivery modes. Derived from Table 1, the NO uptake equals the NO delivery rate multiplied by 0.86 for the pulsed delivery. For the delivery in constant inspired concentration the relation factor is 0.53 and the correlation between the uptake and delivery is weakened due to variations in administration into $V_D{}^{anat}$.

Experimental study

The *CO* for baseline, vasoconstriction, and NO delivery was 4.6 (with standard error of mean, SEM, of 0.3), 4.7 (0.3), and 4.8 (0.4) l/min. Respectively, *PCWP* was 9.2 (0.6), 8.9 (0.5), and 8.8 (0.5) mmHg. The *PAP* response on the NO delivery in the different delivery modes is presented in Table 2. No significant mode dependent difference in the response was detected. The *PAP* dependency on the NO delivery rate is presented in Fig. 4. The NO delivery produces a significant effect on the *PAP* ($P < 0.001$). All the induced hypoxic vasoconstriction was relieved with 105 nmol · min^{-1} NO delivery ($P < 0.05$). Extracting from Fig. 4, 50 % of the maximum effect was achieved with 50 nmol · min^{-1} delivery, and even the smallest tested dose of 10 nmol · min^{-1} produced significant reduction in the *PAP* ($P < 0.001$). Increasing the delivery from the 105 nmol · min^{-1} did not provide any further advantage.

When the NO delivery was stopped, there was an inevitable consistent increase in *PAP*. The maximum *PAP* was reached within 2–4 min after the interruption of the NO delivery. The magnitude of this rebound effect turned out to depend on the NO delivery rate ($P < 0.001$) as also presented in Fig. 4.

Table 1 Simulated NO delivery, uptake ratio, and mean F_ANO and F_ENO for different NO delivery modes. The selected NO delivery rates represent typical clinical setting and the value providing the total vasodilatation in this study. Due to the linearity of the simulation model, similar results would be obtained with other dose rates also

	Parameter Setting							Constant 5 ppm inspired concentration delivery				The first 1/3 pulsed delivery 5 nmol/inspiration			
	D_{LNO} ml · s^{-1} · kPa^{-1}	$V_D{}^{A.} \cdot V_L{}^{-1}$ %	RR min^{-1}	V_T ml	I : E	$V_D{}^{anat}$	FRC ml	Delivery nmol · min^{-1}	mean F_ANO ppb	$F_{ET}NO$ ppb	NO uptake/ delivery %	Delivery nmol · min^{-1}	mean F_ANO ppb	$F_{ET}NO$ ppb	NO uptake/ delivery %
a	6	0	20	400	0,33	150	700	1786	558	820	51	100	52	67	83
b	6	0	30	267	0,33	150	700	1788	427	617	39	150	81	115	88
c	6	0	20	400	0,67	150	700	1786	572	751	53	100	54	56	88
d	6	0	20	400	0,33	100	700	1786	654	814	60	100	51	53	82
e	8	0	20	400	0,33	150	700	1786	432	670	53	100	40	53	87
f	10	0	20	400	0,33	100	700	1786	354	562	54	100	33	43	88
g	3	0	40	100	0,67	50	300	893	370	515	45	200	218	273	89
h	1	0	20	400	0,33	150	700	1786	2160	2350	33	100	197	208	54
i	6	50	20	400	0,33	150	700	1786	677[a]	2500	31	100	62[a]	220	51
j	18	0	10	700	0,33	250	4000	1563	193	252	60	50	10	11	95
k	18	0	10	700	0,33	250	4000	1563	196	169[b]	61	50	10	8[b]	96

[a] in the perfused compartment
[b] airway resistance fitted for 10 cmH_2O intrinsic PEEP

Table 2 PAP response on NO delivery mode in various delivery rates. Mean (SEM)

NO delivery Rate nmol/min	NO delivery mode		
	1/3	2/3	3/3
21	0.54 (0.04)	0.53 (0.04)	0.47 (0.05)
52.5	0.38 (0.05)	0.56 (0.07)	0.41 (0.11)
105	0.25 (0.12)	0.14 (0.12)	0.32 (0.11)
210	0.25 (0.21)	0.12 (0.11)	0.31 (0.12)

The *MetHb* varied during the NO delivery between 0.6 %–1.4 % compared to the baseline variation of 0.8–1.2 %.

No NO_2 above the baseline noise level of 0.1 ppm could be detected. The relationships between the delivery rate and the resulting expired peak and end-tidal NO fractions for the different delivery modes derived from the chemiluminescence measurements are presented in Fig. 5. The dispersion is the highest in the peak concentration of the 3/3 mode. This might be a reflection of the slow response times of the analyser causing inaccuracy in measuring the fastest expired spikes.

Comparison of the measured NO with simulation

In the sample simulation depicted in the Fig. 3, the expired peak- and end-tidal NO fractions are 5 ppm and 820 ppb for the 5 ppm constant inspired concentration. For the 100 nmol/min pulsed delivery these are 90 ppb and 67 ppb, respectively. Calculated with the experimental regression values (Fig. 5, 3/3 and 1/3 modes), the respective values are 4.7 ppm, 890 ppb, 90 ppb, and 60 ppb.

Discussion

The results of this study show that the therapeutic efficacy of pulsed administration mode of known amounts of NO is comparable to the constant inspired concentration delivery mode. The pulsed administration provides, however, an advantage by reduced environmental exhausts. By optimisation of the delivery to the minimum level, the expected therapeutical effect will result in smaller rebound effect.

The experimental results indicate a good, consistent and robust inhaled dose-therapeutic response on *PAP* as a function of the increasing inhaled NO delivery rate relationship. These changes in *PAP* reflect the changes in the pulmonary capillary resistance since the *PCWP* and the *CO* remained unchanged. The response was strong in all the pigs and the induced hypoxic vasoconstriction could be relieved back to the baseline level preceding the hypoxia. In the experiments there was no significant difference between the different delivery modes in relieving the hypoxia-induced elevation in *PAP*.

The theoretical analysis reveals that a variation in F_ANO and NO uptake may vary even with the delivery kept unchanged. This is caused by the variation in the amount of NO administered to the dead space. This variation is caused by differences in ventilation settings, lung anatomy, and ventilation/perfusion distribution. In

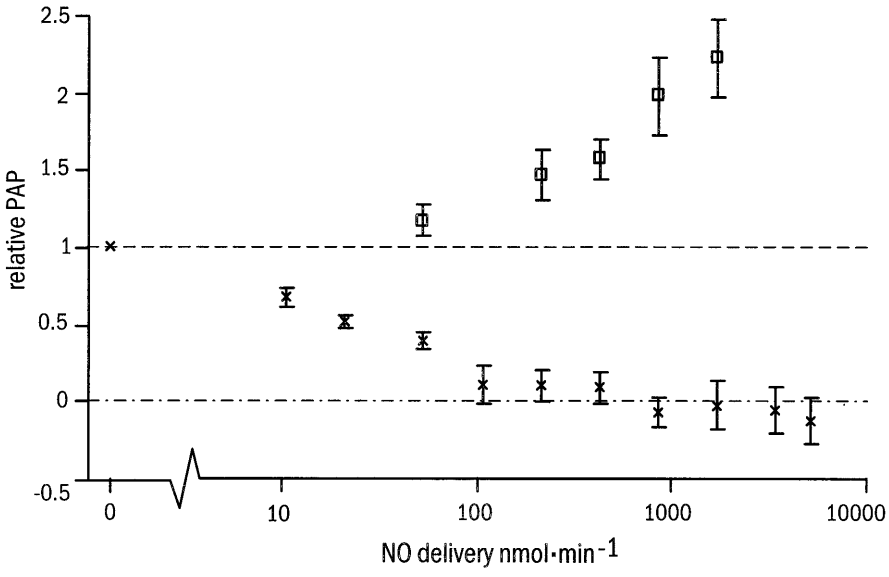

Fig. 4 The NO delivery response on relative *PAP* (×) and rebound effect dose dependency (□) on the normalised scale, mean ± SEM

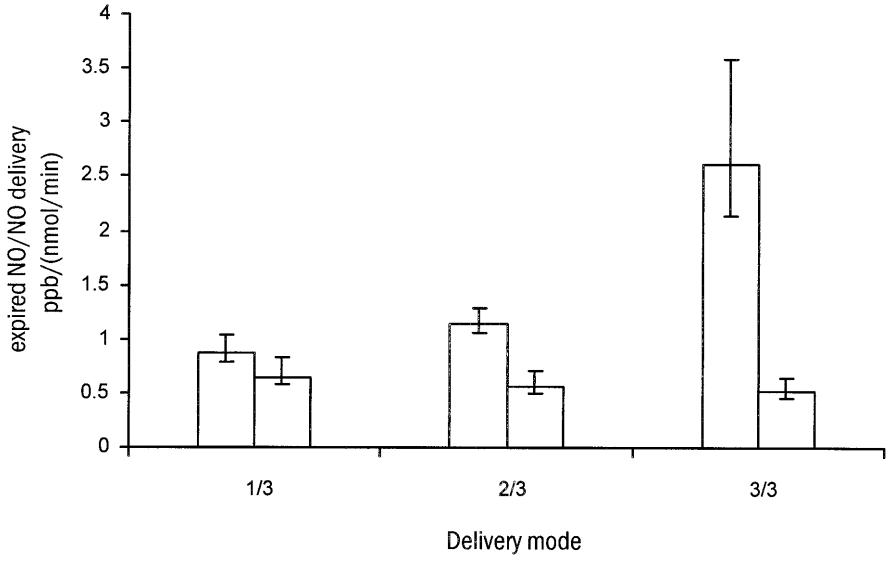

Fig. 5 The experimental regression relationships (mean with 95% confidence interval) between the delivery rate and the resulting expired peak (*left bar*) and end tidal (*right bar*) NO fraction for the different delivery modes

the experimental study the ventilation was kept constant and the lung-related factors most probably did not vary remarkably. In these conditions the F_ANO and NO uptake are both related to the delivery. Whether the therapeutic efficacy depends on the F_ANO or NO uptake cannot be verified from the current results. In any case, it is obvious that F_{ET}NO monitoring is a valuable tool to measure the NO the patient receives. The end-tidal NO is a good indicator of the mixed F_ANO and the NO uptake can be calculated from the F_{ET}NO according to Eq. (7).

$$NOuptake = (\int F_INO \cdot \dot{V}_I \cdot dt - \int F_ENO \cdot \dot{V}_E \cdot dt) \cdot RR \approx (V^I_{NO} - (V_T - V^{anat}_D) \cdot F_{ET}NO) \cdot RR \quad (7)$$

where V^I_{NO} is the delivered NO volume in one inspiration. The approximation in the equation (7) can only be used when the NO delivery into the $V_D{}^{anat}$ is avoided. With constant inspired concentration delivery the uptake can be measured as the difference between the inspired and mixed expired NO concentrations multiplied by V_T. The mixed expiratory concentration monitoring is, however, difficult, especially when using a ventilator having an expiratory bypass flow. Therefore, ease of the NO uptake monitoring is an additional advantage gained when the administration into the $V_D{}^{anat}$ is avoided. In clinical practice the delivery control can naturally also be related to the physiological parameter such as *PAP* or arterial oxygenation for which the NO is used.

The simulated expiratory peak- and end-tidal NO concentration values for healthy lungs were in good agreement with the experimental observations. Furthermore, the simulated 95 % NO uptake/delivery ratios for the pulsed delivery and 60 % for the constant concentration delivery (Table 1, case j) are in line with the published alveolar retention rate of 95–100 % [14] and average 55 % [18] for healthy adult volunteers exposed to constant inspired concentration delivery. The uptake ratio of 31 % calculated for the constant inspired delivery with 50 % of $V_D{}^A \cdot V_L{}^{-1}$ (Table 1, case i) is comparable to the published values of 30–35 % for acute lung injury patients having alveolar dead space of 10 % to 60 % [14].

In the experiments there was no difference between the different delivery modes in relieving the hypoxia-induced elevation in *PAP*. The changes in *PAP* reflected the changes in the pulmonary capillary resistance since the *PCWP* and the *CO* remained unchanged. The response was strong in all the pigs and the induced hypoxic vasoconstriction could be relieved back to the baseline level preceding the hypoxia.

In the case of lung damage the magnitude of the induced vasodilatory NO therapy effect is liable to decrease from the level observed in healthy pigs. According to the findings in humans [19], the smaller the perfusion shunt, the more pronounced is the NO-induced decrease in *PAP-PCWP*. It has been suggested that NO diffusion to unventilated lung sections is suspected to cause the reduction in the oxygenation improvement by increasing the shunt perfusion when the NO delivery is increased [4]. By increasing the NO delivery, the vasodilatation might be extended even to the non-ventilated lung areas. Deterioration of the vasodilatory effect caused by the shunt could possibly be compensated. Because the NO lung diffusion constant, and thus the uptake, depend on the diffusing surface area and the thickness of the diffusion barrier which, in turn, depend on the patient size, it is most likely that the patient size affects the effective dose as well.

It is clear that results obtained with the hypoxic pulmonary vasoconstriction in healthy animal lungs do not justify any predictions concerning diseased human lungs. However, we feel it necessary to give some numbers allowing comparison of ppm's with the delivery rates in nmol/min. As a rule of thumb, each ppm at 1 l/min of alveolar ventilation represents 50 nmol · min^{-1} delivery. For example, in adult ARDS patients 2 ppm has been found to give 50 % effect in relieving *PAP* [4] and in adult PPH 2.5 ppm was reported to be as effective as 10 ppm [20]. One can calculate 2 ppm at $V_T = 700$ ml, $RR = 12$ min^{-1}, $V_D{}^{anat} = 200$ ml corresponds to 600 nmol · min^{-1} alveolar delivery. In the animals of this study the 50 % effect was reached with 50 nmol · min^{-1}.

NO delivery until the end of inspiration will cause a high exhaust spike of NO from the anatomic dead space at the beginning of the expiration, as clearly demonstrated in Fig. 3 a and Fig. 5 for 3/3 mode. In Fig. 3 b and Fig. 5 for 1/3 mode no exhaust spikes can be seen because the dead space delivery is avoided. With the optimal pulsed NO delivery (105 nmol · min^{-1}) the expired NO levels were less than 100 ppb (Fig. 5), and the NO_2 levels unmeasurable. As a consequence, it is evident that scavenging is unnecessary. This was also the conclusion found in an evaluation of pulsed delivery for spontaneously breathing patients [21].

The *PAP* rebound increased significantly with increasing dose (Fig. 4). The rebound dose dependency has been also detected in patient therapy [22]. Whether the dependency also applies to oxygenation can, however, not be concluded from the current results. This rebound is a substantial risk to patients encountering intentional or unintentional termination of the therapy [23]. To reduce this substantial risk the optimising action of the delivery to the minimum to provide the expected therapeutic effect is important. With the smallest effective rate, the magnitude of the rebound in the event of an abruption of the delivery can be minimised. Also, with the optimal delivery the *metHb* generation increment, NO_2 formation in excess of the safety limits [24], and F_IO_2 dilution are avoided with the optimal therapy dosage. However, if the patient suffers degraded *metHb* metabolism, *metHb* may elevate and therefore it should be monitored regularly. The optimised therapy may also ease weaning the patient from the therapy.

An apparent advantage of the constant inspired concentration delivery over pulsed delivery is the automatic scaling of the delivery according to patient size as defined by ventilator settings. However, this scaling defines only the NO delivery, not how much the patient receives. With the pulsed delivery, the user has to determine the amount of drug needed taking into consideration patient characteristics and symptoms, as in the administration of any drug in general.

In conclusion, the results of this study indicate insufficient correlation existing between the NO delivery related parameters and NO uptake. Therefore, for better description of the NO delivery, the NO uptake should be measured, or the therapy should be related to the physiological parameter it is intended to affect.

In conclusion, in respiratory therapy, the pulsed inhaled nitric oxide delivery was shown to be as effective as constant inspired concentration delivery to induce pulmonary vasodilatation. Compared to the constant inspired concentration delivery, the pulsed delivery provides more effective NO usage and reduced environmental exhausts, thereby eliminating the need of scavenging. The relationship between the delivered NO and the NO reaching the alveoli or taken up by the patients is fuzzy. Therefore, uncertainty is involved in

guiding the therapy by the delivery rate alone. Expired NO measurement provides useful information which helps to gain further understanding about efficacy vs. the delivery dose of the inhaled NO therapy and to optimise the delivery.

By optimisation of the delivery to the minimum, the harmful side effects of the rebound vasoconstriction arising from sudden cessation of the delivery is reduced.

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