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ORIGINAL ARTICLE

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Increased expired NO and roles of CO_2 and endogenous NO after venous gas embolism in rabbits

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Abstract Venous gas embolism (VGE) is a feared complication in diving, aviation, surgery and trauma. We hypothesized that air emboli in the lung circulation might change expired nitric oxide (FeNO). A single intravenous infusion of air was given (100 µl kg^{-1}) to three groups of anaesthetized mechanically ventilated rabbits: (A) one with intact NO production, (B) one with intact NO production and where end-tidal CO_2 was controlled, and (C) one with endogenous NO synthesis blockade (L-NAME, 30 mg kg^{-1}). Air infusions resulted in increased FeNO of the control group from 20 (4) [mean (SD)] ppb to a peak value of 39 (4) ppb within 5 min ($P < 0.05$), and FeNO was still significantly elevated [27 (2) ppb] after 20 min ($P < 0.05$). Parallel to the NO increase there were significant decreases in end-tidal CO_2 ($ETCO_2$) and mean arterial pressure and an increase in insufflation pressure. In group B, when CO_2 was supplemented after air infusion, NO was suppressed ($P = 0.033$), but was still significantly elevated compared with pre-infusion control ($P < 0.05$). In group C, all animals died within 40 min of air infusion whereas all animals in the other groups were still alive at this time point. We conclude that venous air embolization increases FeNO, and that a part of this effect is due to the concomitant decrease in $ETCO_2$. Furthermore, an intact NO production may be critical for the tolerance to VGE. Finally, FeNO might have a potential in the diagnosis and monitoring of pulmonary gas embolism.

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Introduction

Pulmonary embolism (PE) is a common disorder accompanied by a significant morbidity and mortality (Olin 2002). It is reported to be the main or contributing cause of death in as much as 15% of mortality at hospitals (Lindblad et al. 1991). One special form of PE, pulmonary gas embolism, is a feared complication after decompression in diving and aviation, and in surgery and trauma (Souders 2000). All forms of PE are able to cause severe haemodynamic and gas exchange abnormalities. In the clinical practice, PE represents a true diagnostic challenge because of its many non-specific clinical features, often mimicking those found in other diseases (Olin 2002). For final diagnosis pulmonary angiography is the gold standard, although several other techniques, such as helical computerized tomography, perfusion and ventilation lung scanning, D-dimer measurement and ultrasonography may help to establish the correct diagnosis. Several of these techniques are both expensive and/or time consuming. Therefore, a simple non-invasive and fast test indicating PE should be of great value.

One physiological parameter that could be expected to change rapidly during PE is expired nitric oxide (FeNO), a factor that could easily and non-invasively be measured by using chemiluminescence technique (Adding and Gustafsson 2002; Gustafsson et al. 1991). Several factors coupled to PE would likely contribute to change in FeNO, such as local reduction of nitric oxide (NO) scavenging from blood perfusion (Rimar and Gillis 1993), reduced inhibition of NO formation from blood-borne CO_2 (Adding et al. 1999) and/or release of inflammatory mediators, which might all act to increase FeNO. Furthermore, Wisloff et al. (2003) have shown that endogenous NO attenuates gas bubble formation during and after decompression in a rat model. On the other

hand, decreased pulmonary perfusion in conjunction with pulmonary hypertension has been shown to be associated with a decrease in FeNO (Cremona et al. 1994), and low FeNO is associated with an increased risk for pulmonary hypertension (Archer et al. 1998). NO has been shown to be a molecule of importance in several biological systems (Gustafsson et al. 1991; Nathan 1992) and in the pathogenesis of common diseases, such as asthma, diabetes and arterial hypertension (Anggård 1994). However, the role of endogenous NO during PE remains to be established.

The aims of the present study were: (a) to test the hypothesis that PE causes a change of FeNO, and thus has the potential to be used as a marker of PE, and (b) to address the question whether endogenously produced NO is essential for the survival in an animal model of PE. Furthermore, when we initally obtained the results for point (a) we wanted to assess the role of alveolar CO_2 for FeNO during PE.

In order to accomplish these aims, we studied the changes of FeNO, haemodynamic parameters and arterial blood gases in anaesthetized rabbits subjected to pulmonary gas embolization. Venous gas emboli (VGE) were given both to animals with intact NO production and to animals where the normal endogenous NO production was inhibited, and where end-tidal CO_2 ($ETCO_2$) was controlled.

Methods

Anaesthesia and initial surgical procedures

The experiments were approved by the local animal ethics committee and the experiments were performed in compliance with The Guide for the Care and Use of Laboratory Animals. Male New Zealand white rabbits (2.6 ± 0.3 kg body weight, $n = 14$) were anaesthetised with pentobarbital sodium (40–60 mg kg^{-1} body weight) via an ear vein, and were placed in a supine position, tracheotomized and ventilated by a rodent ventilator (model 683, Harvard Apparatus, South Natick, MA, USA). The ventilator was supplied with NO-free air using a charcoal filter. The respired concentrations of O_2 and CO_2 were recorded by a ventilatory monitor (Oscar-Oxy, Datex, Helsinki, Finland), connected to the tracheal cannula and sampled at 150 ml min^{-1}. Ventilation rate was 40 min^{-1} and the tidal volume was adjusted to keep $ETCO_2$ at 4.5–5.5%, resulting in a minute ventilation of 0.64–0.96 l min^{-1}, and approximately 15–20% of the minute ventilation being sampled by the O_2/CO_2 analyser. A pressure transducer connected to a side arm of the tracheal cannula recorded the insufflation pressure (IP) (Statham; Hato Rey, Puerto Rico, Latin America). The gas from the ventilator outlet was led through a beaker with water creating a positive end expiratory pressure (PEEP) set at 1.5 cm H_2O. Intermittently for 1 min at 10-min intervals, the PEEP was increased to 5 cm H_2O. This was done in order to minimize atelectasis formation, and thus to optimize oxygenation and to stabilize FeNO.

Arterial pressure was determined by means of a catheter in the carotid artery and pressure transducer (Statham; Hato Rey). A catheter was placed in a jugular vein for drug and gas infusions. A continuous infusion containing glucose (24.3 g l^{-1}) dextran 70 (Macrodex 26.5 g l^{-1}), $NaHCO_3$ (6.2 g l^{-1}), sodium pentobarbital (4.1 g l^{-1}) and pancuronium bromide (98 mg l^{-1}) was administered at a rate of 5 ml kg^{-1} h^{-1} during the experiment.

NO measurements

FeNO was continuously monitored in mixed expiratory gas by means of a NIOX prototype chemiluminescence analyzer (Aerocrine, Stockholm, Sweden) using a sample flow rate of 100 ml min^{-1} regulated by a restrictor attached to the ventilator outlet via a mixing chamber. Detection limit was 1.0 ppb and response time ($T_{10–90}$) was 3 s. Calibration was made using certified NO standard gas in nitrogen (AGA Specialgas, Lidingö, Sweden). The NO concentration in inhaled and expired gas was continuously recorded on a Grass model 7 Polygraph (Grass Instruments, Quincy, MA, USA) together with IP, $ETCO_2$ and mean arterial pressure (MAP).

Experimental protocol

After completion of the surgical procedures, the animals were allowed a 30-min intervention-free period to obtain stable circulatory conditions and stable FeNO.

A single dose of 100 µl kg^{-1} of air was infused at a rate of 500 µl min^{-1} as an addition to the fluid infusion into the jugular vein. Three groups of animals were studied: (A) one with intact endogenous NO production ($n = 6$), (B) one with intact NO production where $ETCO_2$ was kept constant ($n = 5$) and (C) one with blockade of NO synthesis (L-NAME, 30 mg kg^{-1}, 10-min infusion) ($n = 4$).

In group B, CO_2 and O_2 were added to the respiratory circuit to yield an $ETCO_2$ of $110 \pm 5\%$ control (control = $ETCO_2$ just prior to the air emboli), but constant O_2 concentration (21%). The content of the gas mixture was controlled by means of precision mass flow controllers (Bronkhorst, Ruurlo, Holland). Thus, CO_2 was continuously added beginning 5 min after the air injection, the FeNO 10 min after the air emboli was recorded and compared with the FeNO in group A, whereafter CO_2 in the inspired air was reduced to zero again.

Blood gas samples were drawn (using the heparinized carotid catheter also used for blood pressure recording) and analyzed in a Radiometer ABL 300 acid–base laboratory blood gas analyzer (Radiometer, Copenhagen, Denmark). Blood gas samples were drawn as control just before the air infusion and 5, 10, 20, 40 and 60 min thereafter. A blood gas sample was also drawn prior to the L-NAME (N^G-nitro-L-arginine methyl ester) infusion.

Drugs

L-NAME was purchased from Sigma Chemical Company, St Louis, MO, USA; heparin from Kabi Vitrum, Stockholm, Sweden; pancuronium bromide (Pavulon) from Organon, Oss, Holland; pentobarbital from Apoteksbolaget, Stockholm, Sweden; and dextran 70 (Macrodex) from Pharmacia Infusion.

Statistics

Statistical data are given as means and standard deviations (SD). Statistical significance was examined by means of one-way analysis of variance (ANOVA with Dunnet's post-hoc analysis) for repeated measures or *t*-test for comparison between groups. Differences were considered statistically significant if $P < 0.05$.

Results

Baseline conditions

After the stabilization period FeNO, MAP and heart rate (HR) stabilized at 20 ppb (SD 4), 80 mmHg (SD 10) and 310 bpm (SD 30), respectively ($n = 15$) and there were no significant differences in the blood gases between the groups (Table 1).

Effects of air embolization

Upon air infusion in group A, FeNO rapidly increased from the basal control level of 20 ppb (SD 4) in expired air. The FeNO value peaked at 39 ppb (SD 4) within 5 min, and then slowly decreased but was still significantly elevated [27ppb (SD 2)] after 20 min (Figs. 1, 2). Parallel to the NO increase there were significant decreases in $ETCO_2$ and MAP (Figs. 1, 2). IP was also significantly increased from 5.4 mmHg (SD 0.7) to 6.1 mmHg (SD 0.6).

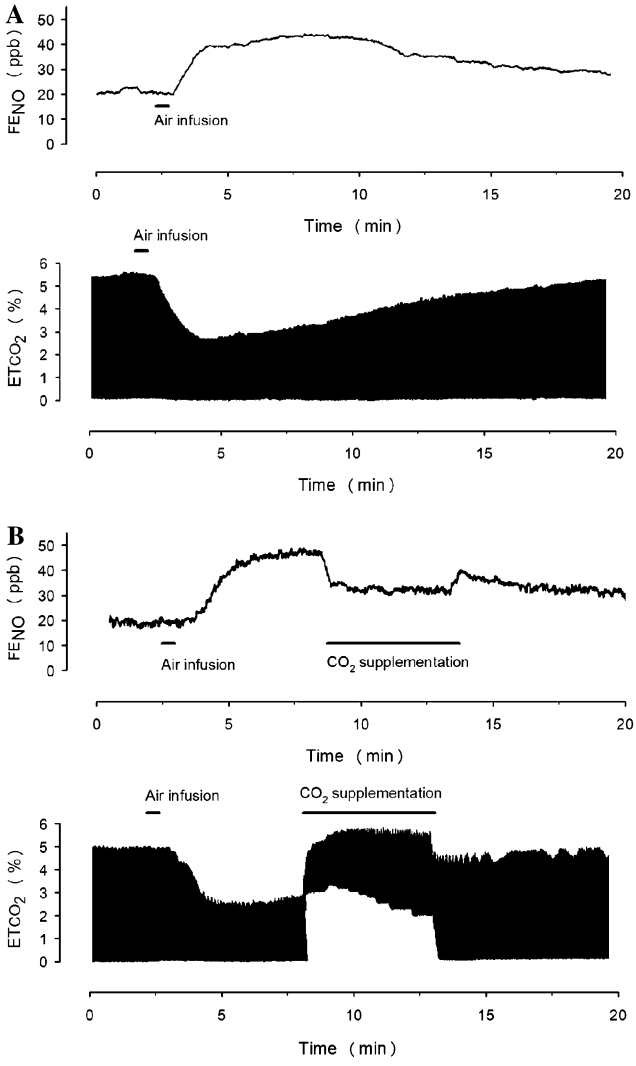

Fig. 1 Artificially ventilated pentobarbital anaesthetized rabbits. Experimental recording of mixed expired NO (*FeNO*) and end-tidal CO_2 (*ETCO*$_2$) following intravenous bolus infusion of air (100 µl g^{-1} at a rate of 500 µl min^{-1}). *Panel A* control animal; *Panel B* animal where CO_2 was added to the inspired gas to yield $ETCO_2$ of 110 ± 5% of pre-infusion levels

Table 1 Blood gases before (control) and 5, 10 and 60 min after intravenous bolus infusion of air (100 µl kg^{-1} at a rate of 500 µl min^{-1})

Group	Parameter	Control	5 min	10 min	60 min
A	pO_2 (kPa)	10.5 (SD 0.4)	4.1 (SD 0.6)	4.7 (SD 1.7)	9.2 (SD 0.5)
	pCO_2 (kPa)	4.5 (SD 0.4)	6.1 (SD 0.3)	5.8 (SD 0.9)	4.9 (SD 0.4)
	pH	7.48 (SD 0.04)	7.40 (SD 0.04)	7.39 (SD 0.03)	7.44 (SD 0.05)
B	pO_2 (kPa)	10.6 (SD 0.04)	6.6 (SD 3.4)	5.2 (SD 0.18)	9.3 (SD 0.52)
	pCO_2 (kPa)	4.5 (SD 0.5)	5.7 (SD 0.3)	7.7 (SD 1.3)	4.9 (SD 0.8)
	pH	7.48 (SD 0.08)	7.38 (SD 0.06)	7.25 (SD 0.16)	7.27 (SD 0.4)
C	pO_2 (kPa)	10.0 (SD 0.8)	5.0 (SD 0.7)	5.7 (SD 1.4)	+
	pCO_2 (kPa)	4.5 (SD 0.3)	6.1 (SD 0.5)	7.8 (SD 0.6)*	+
	pH	7.49 (SD 0.02)	7.38 (SD 0.03)	7.22 (SD 0.04)*	+

Group A intact endogenous nitric oxide (NO) production; *GroupB* intact endogenous NO production and supplementation of CO_2 to inspired air; *Group C* inhibited endogenous NO production (N^G-nitro-L-arginine methyl ester, 30 mg kg^{-1})
*A significant difference compared with group A
+ Indicates that all animals had died

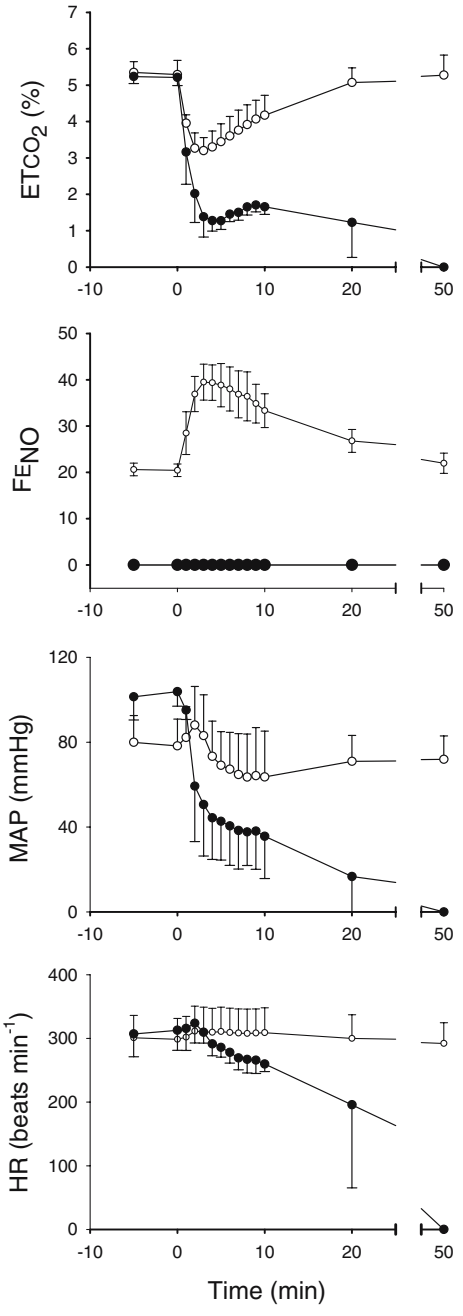

Fig. 2 The effect of intravenous bolus infusion of air (100 µl kg^{-1} at a rate of 500 µl min^{-1}) on end-tidal CO_2 (*ETCO$_2$*), expired NO (*FeNO*), mean arterial pressure (*MAP*) and heart rate (*HR*). *Group A* (*open circles*, $n = 6$) intact endogenous NO production. *Group C* (*filled circles*, $n = 4$) inhibited endogenous NO production (N^G-nitro-L-arginine methyl ester, 30 mg kg^{-1}). Data are group means and *vertical bars* represent ±SD. The responses were significantly different between the groups in all parameters measured. See also Fig. 1 for explanations

When in group B the fall in $ETCO_2$ was reversed by supplying CO_2 in the inspired air, NO fell from 44 ppb (SD 9) (5 min after emboli) to 29 ppb (SD 6) (10 min after VGE), which is a suppression of 34% (SD 8), but still represents an elevated NO level. This reduction was significantly greater than the spontaneous 14% (SD 4) levelling off of NO in group A [38 ppb (SD 5) to 32 ppb (SD 5)] during the same time period.

In group C, L-NAME infusion (30 mg/kg) elicited a significant rapid and sustained decrease in FeNO to levels below detection limit of 1 ppb, and concomitant to this MAP tended to increase [from 85 mmHg (SD 10) to 100 mmHg (SD 10)] and HR tended to decrease [from 320 bpm (SD 25) to 310 bpm (SD 35)]. Upon air emboli injection in group C, the fall in MAP and $ETCO_2$ was significantly greater than in group A, and all animals in group C died within 40 min after the air infusion (Fig. 1). In groups A and B, all animals were alive and in stable haemodynamic condition for an hour after the gas emboli.

In all groups, air infusion reduced PaO_2, increased $PaCO_2$ and reduced pH (Table 1). In groups A and B, the changes in blood gases were most pronounced in samples taken 5 and 10 min after the embolization and were nearly normalized in the 60-min samples (Table 1). In group C, the increase in $PaCO_2$ and decrease in pH was significantly greater after 10 min compared with group A, and in this group no 60-min value was obtained due to the death of the animals (Table 1).

Discussion

The present study demonstrates that pulmonary gas embolization increases FeNO, and that a part of this effect is due to the concomitant decrease in CO_2. Furthermore, an intact endogenous NO production appears critical for the tolerance to VGE.

To our knowledge, this is the first study showing a clear FeNO increase following embolization with gas in amounts comparable with that seen in models of decompression sickness (Vik et al. 1994). Two prior studies have measured NO in association with gas infusions. The first, from our own group, studied the effect of very large (ml) lethal infusions of air or helium, large enough to momentarily stop the blood circulation; in these rabbit and guinea pig experiments FeNO increased (Gustafsson et al. 1991). The second study (Deem et al. 1999) with the primary aim to study the effect of haemodilution during VGE in dogs, used continuous small doses of nitrogen infusions (6 µl kg^{-1} min^{-1}) and observed transiently increased NO in haemodiluted animals; however, the effect was not present in control animals without haemodilution. The lack of effect in their study might be due to species difference or differences in dose regimen, anaesthesia or ventilatory setting (e.g., they used 100% oxygen). These factors might also explain variability between existing studies of gas embolization regarding haemodynamic response and effects on blood gases. Thus, in the present study the effects on MAP, HR and blood gases were relatively profound compared with other studies although a rather low dose of air was infused.

Despite the relative profound effect, we consider the amount of gas infused to be of the same magnitude or

less than that liberated in decompression sickness. For example, Vik et al. (1994) found that a continuous infusion of 50 μl kg^{-1} min^{-1} elicited a similar response in pulmonary artery pressure (PAP) as animals underwent a 30-min compression to 5 bar followed by a rapid decompression (2 bar min^{-1}), although the bubble count was much lower in the decompression group.

In this study, we used air infusion for simplicity as in pilot experiments we found that they gave similar levels of NO increase as infusions of nitrogen (data not shown). Another factor that may affect the response to pulmonary embolization is the size of the emboli. It might be that small emboli induce a shunt and the larger emboli induce areas of higher ventilation–perfusion ratios (Delcroix et al. 1990, 1993). In the present study, we assume that the gas emboli were comparatively small, which has to be taken into account when interpreting the results. It might therefore be necessary in the future to do a similar study with solid emboli of different sizes to further establish the concept that FeNO increases during PE.

Several mechanisms might contribute to the increase in FeNO following VGE. One is that altered blood flow through the lungs alters FeNO by changes in the NO-scavenging effect of the haemoglobin flow through the lung circulation (Persson et al. 1994; Rimar and Gillis 1993).

Another is a decrease of the levels of $ETCO_2$, as CO_2 normally inhibits NO production (Adding et al. 1999; Stromberg et al. 1997). The phenomenon of reciprocal changes in expired CO_2 and NO has been shown both for hypocapnia and hypercapnia in vivo and in isolated lungs (Brogan et al. 2000; Carlin et al. 1997; Yamamoto et al. 2001). The present data show that about 50% of the FeNO increase remained despite normalization of the $ETCO_2$. Thus, reduced inhibition of NO formation by a lowered CO_2 flux to the lung can only account for part of the FeNO increase after VGE.

PE is also known to lead to the release of bioactive substances (Malik 1983), several of which have been shown to modulate FeNO (Adding and Gustafsson 2002). An indication that the latter mechanism also is involved was the significant increase observed in IP. This fits with the assumption that one or several smooth-muscle contracting substances are released.

Little is known about the possible role of NO during PE. As mentioned previously, only two previous studies have attempted NO measurements following PE. Nor has anything hitherto been published to clarify the relationship between PE, NO production in the airways and its role for the haemodynamic effects and changes in blood gases. However, in earlier studies NO-synthase (NOS) inhibition has been shown to augment platelet aggregation induced by adenosine diphosphate, platelet-activating factor or thrombin (May et al. 1991). NOS inhibition reduces the dose of collagen+adrenalin required to induce thromboembolic mortality (Emerson et al. 1999). Also, NOS inhibition has been shown to increase bubble formation after decompression and reduce survival in rats (Wisloff et al. 2003).

It is not due to a general toxic effect on, for example, circulation or respiration as rabbits tolerate several hours of the employed L-NAME dose with periods of marked hypoxic challenge (Persson et al. 1990). It has been shown in rabbits that NOS inhibition slightly increases basal pulmonary vascular resistance (Persson et al. 1990) and severely augments the pulmonary hypertension induced by hypoxia (Persson et al. 1990) and a thromboxane A_2-mimetic (Wall et al. 1999). A contributing factor to the reduced survival rate in the present study and in that of Wisloff et al. (2003) could thus be that NOS inhibition resulted in a pulmonary hypertension that worsened the impact of VGE in the lung circulation.

Inhaled NO has been widely tested as a treatment in PE both in animal models (Bottiger et al. 1996; Melot et al. 1997; Tanus-Santos et al. 1999) and in humans (Capellier et al. 1997; Tulleken et al. 1998), but with conflicting results. Thus, both beneficial effects, like reduced PAP, and negative findings have emerged. In this context, our finding that endogenous NO appears to have a crucial role for the survival of the animals is of importance.

In conclusion, this study demonstrates a rapid and sustained increase in FeNO following acute pulmonary gas embolization with small doses of air comparable to those used in models of decompression sickness.

This finding indicates that measurement of expired NO might have a potential in the diagnosis of and monitoring of cases with suspected lung emboli, although this has to be addressed in future experimental and clinical studies. Furthermore, we show that intact endogenous NO production is crucial for the survival of the animals during PE, thus adding new knowledge regarding the pathogenesis of this disease.

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