Primary research

Atrial natriuretic peptide infusion and nitric oxide inhalation in patients with acute respiratory distress syndrome

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Abstract

Aim: To study the effects of infusion of atrial natriuretic peptide (ANP) versus the inhalation of nitric oxide (NO) in patients with an early acute respiratory distress syndrome (ARDS).
Methods: Ten patients with severe ARDS were studied in a crossover study design, within 72 hours after starting mechanical ventilation. We studied the effects of ANP infusion (10 ng/kg/min for 1 hour) and of inhalation of NO (20 ppm for 1 hour) on hemodynamic and respiratory patient parameters, as well as the effects on plasma levels of ANP, guanosine 3′,5′-cyclic monophosphate, nitrate and endothelin-1.
Results: Despite an approximate 50% increase in mixed venous ANP plasma concentration (from 86 ± 21 to 123 ± 33 ng/l, $P < 0.05$) during ANP infusion, there were no changes in mean pulmonary artery pressure, pulmonary vascular resistance index, extravascular lung water index, or in pulmonary gas exchange. NO inhalation, in contrast, lowered mean pulmonary artery pressure (from 26 ± 1.9 to 23.9 ± 1.7 mmHg, $P < 0.01$), pulmonary vascular resistance index (from 314 ± 37 to 273 ± 32 dyne s/cm^5/m^2, $P < 0.05$) and central venous pressure (from 8.2 ± 1.2 to 7.3 ± 1.1 mmHg, $P < 0.02$). Furthermore, NO inhalation improved pulmonary gas exchange, reflected by a decrease in alveolar–arterial oxygen gradient (from 41.9 ± 3.9 to 40.4 ± 3.6 kPa, $P < 0.05$), a small increase in oxygenation (PaO_2/F_iO_2 from 17.7 ± 1.4 to 19.7 ± 1.1 kPa, $P = 0.07$) and a small decrease in venous admixture (Q_s/Q_t from 35.7 ± 2.0 to 32.8 ± 2.7%, $P = 0.11$).
Conclusion: This study shows that, in contrast to NO inhalation, infusion of ANP neither improves oxygenation nor attenuates pulmonary hypertension or pulmonary edema in patients with severe ARDS.

Keywords: acute respiratory distress syndrome, atrial natriuretic peptide, extravascular lung water, nitric oxide

Introduction

ANP, a peptide mainly secreted in the right atrium, is an important regulator of the sodium and volume homeostasis [1]. Right atrial stretch is the main trigger for the production of ANP. Apart from its natriuretic properties, ANP has vasodilating effects caused by binding to biologically active 'B receptors' [2]. Binding to these B receptors leads to activation of the enzyme particulate guanylate

ANP = atrial natriuretic peptide; ARDS = acute respiratory distress syndrome; cGMP = guanosine 3′,5′-cyclic monophosphate; CI = cardiac index; CO = cardiac output; DST = downslope time; EVLWI = extravascular lung water index; ICG = indocyanin green; ITBVI = intrathoracic blood volume index; MTT = mean transit time; NO = nitric oxide; PBVI = pulmonary blood volume index; RVEDVI = right ventricular end-diastolic volume index.

cyclase, which in turn enhances intracellular production of guanosine 3′,5′-cyclic monophosphate (cGMP). The cGMP leads to relaxation of smooth muscle cells. ANP may, in this way, be an important regulator of pulmonary vascular tone as the lung possesses abundant binding receptors for ANP. Other important triggers for the production of ANP are hypoxia and pulmonary vasoconstriction [3–5]. Finally, another feature of ANP is *in vitro* improvement of the barrier function of pulmonary endothelial cells [6].

These properties suggest that ANP is an attractive agent in the treatment of patients with hypoxia and pulmonary vasoconstriction. ANP infusion improved pulmonary gas exchange under experimental hypoxic conditions in men in a recent study [7]. On the contrary, ANP infusion lowered pulmonary artery pressure but did not improve oxygenation in patients with chronic obstructive pulmonary diseases [8]. In accordance with other vasodilators, the venous admixture was even enhanced in these patients.

ARDS is the extreme clinical example of pulmonary edema and hypoxia induced pulmonary vasoconstriction. Based on our findings in experimental hypoxia, we hypothesized that ANP infusion could be beneficial in ARDS patients. The promising effects of NO inhalation in ARDS [9,10] also supported this hypothesis, because both NO and ANP act through activation of guanylate cyclase. Moreover, in a recent study, ANP infusion was shown to improve oxygenation and to lower pulmonary artery pressure in a hydrochloric acid lung injury model in pigs [11].

In the present paper, we have studied the effects of ANP infusion and NO inhalation in patients with severe ARDS in the early stage of the disease, in a nonblinded crossover design.

Materials and methods

Subjects

Ten patients with severe ARDS were enrolled between October 1994 and January 1996. Only patients with a Lung Injury Score >2.5 were included [12]. To be eligible for the study, the duration of mechanical ventilation for ARDS had to be less than 72 hours. Patients had to be in a stable hemodynamic condition. Patients were excluded if they were younger than age 15, were pregnant, had a known allergy for iodine, or had a known stenosis in a femoral artery. The Local Ethics Committee approved the study protocol, and each patient's next of kin gave informed consent.

Measurements

All patients underwent right-sided heart catheterization with placement of a pulmonary artery catheter (7.5-F Swan–Ganz catheter, Model VS1721; Ohmeda, Swindon, UK). A 4-F fiberoptic catheter (Pulsiocath PV2024; Pulsion, Munich, Germany) was placed in the descending aorta through a 6-F introducer sheath (Model 616150A; Ohmeda) in one of the femoral arteries. Mean arterial pressure was recorded via the side port of the introducer sheath. The pulmonary artery catheter was used for measurements of central venous pressure, mean pulmonary artery pressure, and pulmonary artery wedge pressure, with the midchest level as zero reference. Thermodilution cardiac output (CO) was measured with injection of 10 cm^3 ice-cold saline at random during the respiratory cycle. The mean value of three consecutive measurements was used for analysis. Heart rate was recorded continuously with one of the standard leads of the electrocardiogram. Cardiac index (CI), stroke index, systemic vascular resistance index and pulmonary vascular resistance index were calculated according to standard formulae.

Measurements of extravascular lung water index (EVLWI), intrathoracic blood volume index (ITBVI), pulmonary blood volume index (PBVI), and right ventricular end-diastolic volume index (RVEDVI) were obtained with the thermal-dye dilution technique (COLD Z-021 system; Pulsion). Measurements were carried out with injection of 10 cm^3 ice-cold indocyanin green solution (2 mg/ml). The mean value of two measurements was used for analysis. Refer to the literature for details concerning the thermal-dye dilution technique [13,14]. Briefly, the method uses two indicators: ice-cold water and indocyanin green (ICG). Cold distributes to both intravascular and extravascular volumes, whereas ICG remains intravascular. Both indicators are injected into the right atrium, and concentration changes in time are recorded in the descending aorta. A dilution curve can thus be constructed for both indicators. CO is determined from the thermodilution curve. A mean transit time (MTT) and a downslope time (DST) can be derived from each indicator's dilution curve. The MTT is composed of the appearance time AT_i, which is the time until the first indicator particle has arrived at the point of detection, and the mean time difference between the occurrence of the first particle and all the following particles. The product of CO and MTT is the volume between the site of injection and the site of detection. The DST can be derived from the extrapolated descending limb of a logarithmic transformation of the dilution curve. In a series of mixing chambers, the product of CO and DST represents the volume of the largest mixing chamber in the chain. The volumes already mentioned can be measured using the following formulae.

$$ITTVI\ (ml/m^2) = CI \times MTT_{aorta}(temperature)$$
$$ITBVI\ (ml/m^2) = CI \times MTT_{aorta}(ICG)$$
$$PBVI\ (ml/m^2) = CI \times DST_{aorta}(ICG)$$
$$EVLWI\ (ml/kg) = ITTVI - ITBVI$$

where ITTVI represents the intrathoracic thermal volume index. Because we used the COLD system together with a Swan–Ganz catheter, we were also able to determine RVEDVI by the application of the following formula:

$RVEDVI\ (ml/m^2) = CI \times DST_{pulmonary\ artery}(temperature)$

Together with each hemodynamic measurement, arterial and mixed venous blood samples were drawn for determination of hemoglobin and blood gas analysis (Ciba-Cormig 288 blood gas analyzer; Ciba-Cormig, Medfield, MA, USA). Furthermore, arterial and mixed venous ethylenediamine tetraacetic acid blood samples were taken for determination of plasma levels of ANP, cGMP, nitrate, and endothelin-1. These samples were immediately placed on ice and were centrifuged at 3000 rpm and 0°C, for 10 min. The collected plasma samples were then stored at −70°C until final analysis.

ANP was determined with a sensitive radioimmunoassay, using an immunoextraction with a C-terminal-specific antiserum (Incstar, Stillwater, MN, USA), as described previously [15]. ANP levels vary widely in normal subjects. Generally accepted normal values are 10–70 ng/l in healthy men younger than 65 years [1]. The cGMP was measured with a direct radioimmunoassay (Immuno Biological Laboratories, Hamburg, Germany) according to the method of Steiner *et al* [16]. Normal venous concentrations are 1–6 nmol/l. Nitrate was determined as described previously, the nitrate levels in healthy subjects with no dietary restrictions being 33 ± 3 μmol/l [17].

Mechanical ventilation and NO administration

All patients were ventilated with a Bear 1000 ventilator (Bourns Medical Systems Inc., Riverside, CA, USA) in either a volume-controlled or a pressure-controlled mode, with plateau pressures not exceeding 30 cmH_2O. Positive end-expiratory pressure was guided by the lower inflection point of the pressure–volume curve. Patients were sedated with midazolam and morphine in such a way that they were unable to trigger the ventilator. When necessary, they were also paralysed with pancuronium. The ventilator settings were unchanged during the experiments.

NO (600 ± 30 ppm NO in N_2; Air Products, Waddinxveen, The Netherlands) was added with a continuous flow to the inspiratory limb of the ventilator circuit [18]. Flow was titrated with a high precision flowmeter (Sho-Rate™ Model 1355; Brooks Instrument B.V., Veenendaal, The Netherlands). Inspiratory concentrations of NO and NO_2 were measured between the 'Y' piece of the ventilator and the endotracheal tube, using electrochemical sensors (NO_x-box; Bedfont Scientific Ltd., Upchurch, Kent, UK). The sensors are calibrated every 6 months using a gas mixture containing 55 ppm NO and 5.5 ppm NO_2. The limit of detection is 0.1 ppm for NO and 0.1 ppm for NO_2. The range of detection is 0–200 ppm for both gases. Additional hydrophobic filters were used to protect the sensors from condensed water vapor. The inspired NO_2 concentration was not allowed to exceed 1 ppm.

Study protocol

The effects of ANP infusion and NO inhalation were studied in a crossover design. An entrance number was assigned to each patient before the start of the protocol, according to which patients started with either ANP infusion (odd numbers) or NO inhalation (even numbers).

At the start of the study protocol, two baseline measurements were performed in each patient, 30 min apart. Patients then started with either human ANP infusion (Atriobiss; Clinalfa AG, Läufelfingen, Germany) at a rate of 10 ng/kg/min for 1 hour or NO inhalation of 20 ppm for 1 hour, with a third measurement at the end of this hour. The dosage regimens were based on effective and nontoxic dosages in earlier reports [7,9,19,20]. A fourth measurement was carried out 1 hour after cessation of the first treatment modality. Patients then started with their second treatment modality and a fifth measurement was obtained after 1 hour of treatment. Finally, a sixth measurement was taken 1 hour after cessation of the second treatment modality. No adjustments in inotropic or ventilatory therapy were made during the study protocol.

Statistical analysis

Data are expressed as mean values ± SEM, unless noted otherwise. The mean value of baseline measurements 1 and 2 was used for analysis. Treatment effects were analysed with the Student *t* test for paired samples. When the data did not have a normal distribution, the Wilcoxon signed-rank test was used. $P < 0.05$ was considered to be statistically significant. Statistical analysis was performed with Excel (Version 5.0 for Windows, Microsoft Corporation, Redmond, WA, USA) and SPSS (Version 6.0 for Windows, SPSS Inc, Chicago, IL, USA).

Results

Patient characteristics are presented in Table 1. The mean age was 50.2 years (range, 30–66 years). Duration of mechanical ventilation before starting the study protocol was 26 hours (range, 6–60 hours). The mean Lung Injury Score was 2.8 (range, 2.5–3.25). All patients were hemodynamically stable throughout the study. There were no significant differences in the distinguished baseline measurements (measurements 1, 2, 4 and 6). The values for baseline presented in Tables 2 and 3 are the mean values of measurements 1 and 2. Table 2 presents the various variables measured during ANP infusion. Both the mixed venous and the arterial concentration of ANP increased during infusion of ANP. Statistical significance was only noted for the change in the mixed venous concentration. The same results were obtained for cGMP concentrations. None of the other parameters changed during ANP infusion. Table 3 presents the parameters measured during NO inhalation. Mean pulmonary artery pressure, pulmonary vascular resistance index and central venous pressure decreased during NO inhalation. In contrast to

Table 1

Patient characteristics

Patient number	Diagnosis	Sex	Age (years)	PaO_2/F_iO_2 (kPa)	Q_s/Q_t (%)	Compliance (ml/cmH_2O)	Lung Injury Score	MPAP (mmHg)	PVRI (dyne s/cm^5/m^2)	Inotropic support (μg/kg/min)	Organ failure	Survival
1	Reaction to chemotherapy	M	30	16.1	45	28	3.25	20	167		K	NS
2	Multiple blood transfusion	F	56	15	41	28	3	35	493	Dobutamine 15, Dopamine 8		S
3	Submersion	M	52	23.5	22	45	2.75	22	337	Dobutamine 10		S
4	Pneumonia/sepsis	F	65	13.7	25	24	2.75	28	504	Dobutamine 10	K	S
5	Pneumonia	M	40	17.2	33	40	2.75	19	181			S
6	Aspiration	F	66	24	32	26	2.5	20	225	Dobutamine 5	K	NS
7	Sepsis	F	40	20.1	32	34	2.75	36	327	Dobutamine 20, Norepinephrine 0.3		NS
8	Trauma/aspiration	M	48	15.8	35	42	2.5	25	382	Norepinephrine 0.7	L	S
9	Aspiration	M	55	17.7	34	20	2.75	27	301	Dobutamine 5, Norepinephrine 0.08		S
10	Pneumonia	F	50	16	34	59	2.75	19	224	Dobutamine 5		S

MPAP, Mean pulmonary artery pressure; PVRI, pulmonary vascular resistance index; M, male; F, female; K, kidney (serum creatinine >177 μmol/l); L, liver (serum bilirubin >40 μmol/l); NS, nonsurvivor (hospital mortality); S, survivor.

Table 2

Data of the various substrates and variables measured during atrial natriuretic peptide (ANP) infusion

	Baseline	ANP infusion	*P* value
ANP (ng/l)			
Arterial	97 ± 23	109 ± 27	NS
Mixed venous	86 ± 21	123 ± 33	< 0.05
Nitrate (μmol/l)			
Arterial	33 ± 8	28 ± 6	NS
Mixed venous	30 ± 6	31 ± 6	NS
cGMP (nmol/l)			
Arterial	12 ± 4	16 ± 5	NS
Mixed venous	11 ± 4	15 ± 5	< 0.01
Cardiac index (l/min/m^2)	4.3 ± 0.4	4.2 ± 0.4	0.08
MAP (mmHg)	76 ± 3	78 ± 4	NS
MPAP (mmHg)	25.0 ± 1.9	25.1 ± 2.1	NS
PAWP (mmHg)	9.4 ± 1.2	10.0 ± 1.4	NS
CVP (mmHg)	8.1 ± 1.3	7.5 ± 1.2	NS
PVRI (dyne s/cm^5/m^2)	314 ± 36	305 ± 32	NS
ITBVI (ml/m^2)	882 ± 39	925 ± 66	NS
PBVI (ml/m^2)	184 ± 20	165 ± 27	NS
RVEDVI (ml/m^2)	149 ± 8	150 ± 10	NS
EVLWI (ml/kg)	20.5 ± 1.7	21.3 ± 2.3	NS
PaO_2/F_iO_2 (kPa)	18.0 ± 1.1	18.2 ± 1.5	NS
A–a gradient (kPa)	41.6 ± 3.8	41.8 ± 4.1	NS
Q_s/Q_t (%)	33.1 ± 2.0	34.7 ± 2.1	NS

NS, $P > 0.2$. The exact *P* values were established by a paired *t* test. The other variables were not normally distributed, and these were tested by the Wilcoxon signed-rank test. cGMP, Guanosine 3′,5′-cyclic monophosphate; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; CVP, central venous pressure; PVRI, pulmonary vascular resistance index; ITBVI, intrathoracic blood volume index; PBVI, pulmonary blood volume index; RVEDVI, right ventricular end-diastolic volume index; EVLWI, extravascular lung water index; A–A, alveolar–arterial gradient.

treatment with ANP, both arterial and mixed venous concentrations of cGMP increased significantly during NO inhalation. EVLWI did not change either during ANP infusion or during NO inhalation. In patients who responded to NO inhalation with an increase in $PaO_2/F_iO_2 > 10\%$, EVLWI tended to be lower than in patients who did not show such a response (16.2 ± 1.7 versus 20.6 ± 3.5 ml/kg, $P = 0.29$). The alveolar–arterial oxygen gradient decreased significantly during NO inhalation. The venous admixture also decreased and PaO_2/F_iO_2 increased, but neither change reached statistical significance ($P = 0.11$ and $P = 0.07$, respectively).

Discussion

The present study shows that ANP infusion at 10 ng/kg/min during 1 hour in patients with severe ARDS

Table 3

Data of the various substrates and variables measured during nitric oxide (NO) inhalation

	Baseline	NO inhalation	*P* value
ANP (ng/l)			
Arterial	91 ± 22	86 ± 21	NS
Mixed venous	90 ± 22	85 ± 21	NS
Nitrate (μmol/l)			
Arterial	25 ± 5	29.5 ± 3.1	NS
Mixed venous	30 ± 9	24.4 ± 3.8	NS
cGMP (nmol/l)			
Arterial	13 ± 5	21 ± 7	< 0.05
Mixed venous	12 ± 5	21 ± 7	< 0.02
Cardiac index (l/min/m^2)	4.4 ± 0.4	4.4 ± 0.4	NS
MAP (mmHg)	79 ± 4	80 ± 4	NS
MPAP (mmHg)	26.0 ± 1.9	23.9 ± 1.7	0.003
PAWP (mmHg)	10.3 ± 1.3	10.3 ± 1.3	NS
CVP (mmHg)	8.2 ± 1.2	7.3 ± 1.1	< 0.02
PVRI (dyne s/cm^5/m^2)	314 ± 37	273 ± 32	0.015
ITBVI (ml/m^2)	907 ± 48	915 ± 55	NS
PBVI (ml/m^2)	196 ± 20	186 ± 27	NS
RVEDVI (ml/m^2)	157 ± 11	149 ± 10	NS
EVLWI (ml/kg)			
Total group	18.4 ± 1.9	17.1 ± 1.6	0.14
Nonresponders	20.6 ± 3.5	19.8 ± 3.0	NS
Responders	16.2 ± 1.7	14.5 ± 0.9	0.15
PaO_2/F_iO_2 (kPa)	17.7 ± 1.4	19.7 ± 1.1	0.07
A–a gradient (kPa)	41.9 ± 3.9	40.4 ± 3.6	< 0.05
Q_s/Q_t (%)	35.7 ± 2.0	32.8 ± 2.7	0.11

NS, $P > 0.2$. The exact *P* values were established by a paired *t* test. The other variables were not normally distributed, and these were tested by the Wilcoxon signed-rank test. ANP, Atrial natriuretic peptide; cGMP, guanosine 3′,5′-cyclic monophosphate; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; CVP, central venous pressure; PVRI, pulmonary vascular resistance index; ITBVI, intrathoracic blood volume index; PBVI, pulmonary blood volume index; RVEDVI, right ventricular end-diastolic volume index; EVLWI, extravascular lung water index; A–A, alveolar–arterial gradient.

in the early stage of their disease did not reduce pulmonary hypertension, nor did it improve pulmonary gas exchange. ANP also did not influence the amount of extravascular lung water. In contrast, 20 ppm NO inhalation lowered the pulmonary artery pressure and improved pulmonary gas exchange.

In a previous study, normal subjects were exposed to hypoxia by decreasing barometric pressure, and the effects of ANP infusion were monitored. An improvement in arterial oxygen saturation and a decrease in the alveolar–arterial oxygen difference were noticed under these circumstances [7]. It was then hypothesized that ANP decreased transcapillary filtration in the pulmonary circulation, thereby preventing the development of pulmonary edema under hypoxic conditions and thus improving pulmonary gas exchange. Because extravascular lung water was not measured, it was not possible to prove this hypothesis. Andrivet *et al* studied the effects of ANP infusion in patients with severe chronic obstructive pulmonary diseases. They found a deterioration in the ventilation–perfusion relationship during ANP infusion, with a decrease in arterial oxygenation that was masked by an increased minute ventilation [8]. The present study was designed to elucidate the effects of ANP infusion in ARDS patients during the early phase of the disease. We did not detect a measurable clinical effect of ANP infusion in these patients. Several explanations are possible for this finding.

There was a significant increase in mixed venous concentration of ANP, but only a modest increase in the arterial concentration during the infusion of ANP. Since ANP was infused on the venous side of the circulation, these findings suggest that most of the infused ANP was cleared by the lung. The pulmonary circulation expresses two types of receptors for ANP: the biologically active 'B receptor', and the 'C receptor', which is reported to have a mere clearance function without biological effects [2,21]. We found increased mixed venous concentrations of ANP without measurable clinical effects. This might suggest that the infused ANP was preferentially bound to C receptors. The increase in mixed venous cGMP concentrations indicates that the infused ANP did induce biological effects, although this was not translated into clinical signs.

Another explanation for our results may be that ANP did not produce clinical effects because there was already a maximal vasodilating effect of cGMP at baseline, as the baseline plasma concentrations of cGMP were high in comparison with normal subjects. This hypothesis is refuted by the fact that NO inhalation produced clinical effects with the same baseline plasma levels of cGMP. The increase of cGMP was higher after NO inhalation than after ANP infusion, suggesting that the administered dose of ANP may have been too low. Indeed, we cannot completely exclude too low a dosage. Unfortunately, we did not measure diuresis during ANP; an increase in diuresis might have suggested an adequate dosage. On the contrary, the clinical effects in experimental hypoxia, as seen previously, were achieved with similar doses of ANP.

The different administration routes of ANP and NO may explain the different effects. Pulmonary vascular resistance and pressure are mainly determined by the small resistance vessels. NO is administered near the resistance vessels of the pulmonary circulation and acts primarily on the capillary–venous compartment, as was recently shown

[22]. ANP enters the pulmonary circulation on the arterial side and may bind to receptors at that site. It is imaginable, in this way, that ANP never reaches the 'target vessels', particularly since there is extensive microthrombosis in the capillaries in ARDS [23]. It is also possible that plasma levels of cGMP do not reflect local concentrations. The different clinical effects of NO inhalation and ANP infusion may thus be the result of essential different local cGMP levels in the lung.

The results of the present study do not correspond with the results of ANP infusion in an experimental animal model of lung injury [11]. This indicates that the pathological substrate of ARDS may differ from the experimental models that were used. The shortcomings of experimental models to completely mimic the complex mechanisms involved in ARDS were recently reviewed in extension [24].

Generally, the clinical effects of NO inhalation in our study are in accordance with earlier reports. We did not find a significant improvement of PaO_2/F_iO_2 ($P = 0.07$), possibly because of the small sample size of the study. Furthermore, it is known that approximately 65% of ARDS patients respond to inhaled NO [10]. In our study group, 50% of the patients showed an improvement in PaO_2/F_iO_2 of more than 10%. Finally, we did not construct individual dose–response curves. It is known that patients may vary widely in optimal doses of inhaled NO. Some of our patients may therefore have received a dose that was above their optimum, which is known to deteriorate oxygenation again [25]. Furthermore, NO was administered in a continuous flow to the inspiratory limb of the ventilator circuit. It is now known that this mode of administration with noncontinuous flow modes of mechanical ventilation may produce highly variable and unpredictable concentrations of inhaled NO [26]. This may also have influenced our results in an unknown direction. EVLWI tended to decrease during NO inhalation, somewhat more in responders than in nonresponders, although not significantly. This is in accordance with the recently elucidated primary effect of NO on the venous compartment of the pulmonary capillary circulation [22].

In conclusion, this study shows that short-term ANP infusion in early ARDS does not improve pulmonary gas exchange or pulmonary artery pressure, in contrast to short-term NO inhalation.

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