Nitric oxide in ARDS

109

INHALED NITRIC OXIDE IN SEVERE ARDS

R Rossaint, KJ Falke, M Keitel, F Lopez, U Pison, K Slama, T Grüning, K Lewandowski, WM Zapol

Pulmonary hypertension (PH) as a result of an increased pulmonary vascular resistance and hypoxemia because of an elevated intrapulmonary shunt are important pathophysiological features of the adult respiratory distress syndrome (ARDS). Systemically infused vasodilators can reduce PH, but due to their general vasodilator effects on the systemic and pulmonary circulation this may decrease mean systemic arterial pressure (MAP) and impair pulmonary gas exchange. Recently, inhaling low concentrations of nitric oxide (NO) gas, an important endothelium derived relaxing factor, which is rapidly inactivated by hemoglobin, has been reported to cause selective pulmonary vasodilation. We hypothesized that in severe ARDS inhaling low concentrations of NO would cause selective vasodilation of ventilated lung regions, thereby reducing PH and improving gas exchange.
Methods: Nine of ten consecutive patients with severe ARDS inhaled 18 and 36 ppm of NO for 30 minutes. The effects on hemodynamics and pulmonary gas exchange were analysed using the multiple inert gas elimination technique and were compared to those induced by intravenously infused 4 ng/kg/min prostacyclin (PGI_2). To examine the long term effects of inhaling NO, seven of the ten patients were treated with continuous inhalation of 5 to 20 ppm NO for 3 to 53 days. NO inhalation was discontinued for 30 min daily and pulmonary gas exchange and hemodynamics were studied before, during, and after this period.
Results: Inhaling 18ppm NO reduced the mean pulmonary artery pressure (PAP) from 37±9 mm Hg to 30±7 mm Hg (P=0.006) and decreased intrapulmonary shunt from 36±15 % to 31±14 % (P=0.008). The PaO_2/F_iO_2 ratio was increased by NO from 152±45 mm Hg to 199±70 mm Hg (P=0.002) while MAP and cardiac output did not change. In contrast, PGI_2 infusion also reduced the PAP but increased the intrapulmonary shunt and reduced the PaO_2/F_iO_2 ratio and MAP. Continuous NO inhalation consistently lowered the PAP and augmented PaO_2/F_iO_2 ratio in patients receiving the gas for 3 to 53 days.
Conclusions: In severe ARDS, inhalation of low concentrations of NO, in contrast to intravenous PGI_2, causes selective vasodilation of ventilated lung regions, thereby reducing the PAP and improving arterial oxygenation as a result of redistribution of blood flow from shunting towards ventilated regions. Inhaling NO during ARDS improves the matching of ventilation with perfusion. Long term NO inhalation in all seven patients reduced reproducible the PAP and improved arterial oxygenation for periods of 3 to 53 days. Eight of the ten ARDS patients survived including six of the seven who received long term NO inhalation without evidence of toxic side effects. These data suggest that low dose inhaled NO may be an effective supportive measure in severe ARDS.
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Klinik für Anaesthesiologie und operative Intensivmedizin, UKRV, Freie Universität Berlin, Augustenburger Platz 1, 1000 Berlin 65, FRG

110

EFFECTS OF INHALED NITRIC OXIDE AND I.V. PROSTACYCLIN ON RI VENTRICULAR FUNCTION IN PATIENTS WITH SEVERE ARDS

K Slama, R Rossaint, M Keitel, K.Lewandowski, W.Steudel and K Falke

The adult respiratory distress syndrome (ARDS) is associated with pulmonary vascular constriction and occlusion leading to pulmonary hypertension which can result in right ventricular dysfunction. In ARDS inhaling nitric oxide (NO) has been shown to lower pulmonary artery pressure by dilating the vasculature of ventilated parts of the lung withc impairment of gas exchange and systemic arterial pressure, side effects known to occur in association with intravenously given vasodilators. He the short term effects of inhaled NO on RV-function was studied in comparison to those of i.v. prostacyclin (PGI_2).
Methods: In six patients with severe ARDS we measured routine hemodynamic parameters as well as right ventricular enddiastolic volum (RVEDV) and ejection fraction (RVEF) using thermodilution. The inhalatic of 18 and 36 parts per million (ppm) NO and the i.v. administration of P (4ng/kg BW) for 30 minutes inbetween baseline measurements were studied in randomized order (Student T-test, $^{**}p<0,05$, $^{*}p<0,1$).
Results: (mean±se) are shown in the table below:

	control	18ppmNO	36ppmNO	control	PGI2
PAP	35±5	28±3**	30±2	34±3	33±3
RAP	8±1	7±1*	9±1	8±1	9±1
CO	7±3	7±3	8±4	8±4	6±2
SV	65±14	69±14	75±17	71±14	42±11
RVEDV	205±16	188±22	191±22	250±42	189±35
RVEF	31±5	35±4	36±5*	33±4	30±3*
PVR	354±101	258±69**	241±53**	291±59	283±53

Conclusions: The severity of ARDS could be recognized by the PVR, PAF and EF-values. Inhalation of NO resulted in a significant decrease of PAP and PVR. RVEF and EDV were not affected to a statistically significant degree. However, RVEF showed an increasing trend. In these patients PC had no beneficial effect on the pulmonary circulation and the measured right ventricular function parameters. Supported by DFG Fa 139/1-3
Ref:Rossaint et al.:Succesful Treatment of severe adult respiratory distre syndrome with inhaled nitric oxide Am. Rev.Resp.Dis.145/1992/A80p

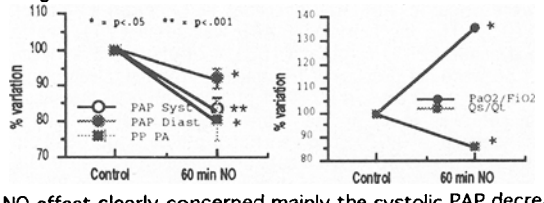
Klinik für Anaesthesiologie und operative Intensivmedizin, UKRV, Freie Universität Berlin, Augustenburger Platz 1, 1000 Berlin 65, FRG

111

INHALATION OF LOW DOSE OF NO AND IV L-ARG IN ARDS: EFFECT ON PULMONARY HEMODYNAMIC AND GAZ EXCHANGE.

PAYEN D, GATECEL C, GUINARD N.

Pulmonary vasodilatation or cardiac output increase usually worsen gas exchange. Inhaled NO (10 to 40 ppm)has proved to decrease mean pulmonary artery pressure (PAP) and to increase PaO2 in various situations. 12 to 18 ppm NO were continuously inhaled via a catheter placed 1 cm above the carena in 10 severe ARDS patients (Murray Score> 2.5): 7 pts conventionally treated and 3 treated with ECCO2R. Measurements before (C) and after 60 min of inhalation have consisted in: systolic (PAPs), diastolic (PAPd), pulse (PAPP) pulmonary pressures, cardiac output (CO; TD), mean arterial pressure(MAP), PaO_2/FiO_2, Qs/Qt, PaO_2, $PaCO_2$, PvO_2, VO_2. L-ARG (NO precursor) was IV infused in 3 pts (30 mg/kg). Mean PAP decreased from 38±5.6 to 33.6±5 mmHg; -11 %) and PaO2 increased about 35%. Results in %: MAP, CO, VO2, PaCO2 did not change.



NO effect clearly concerned mainly the systolic PAP decrease (16%) which did not correlate with PaO2 increase. L-ARG infusion had no effect.

Critical care unit, Dept of Anesth. Lariboisière University Hosp. 2, rue A. Paré 75011 Paris-FRANCE

112

DOES NITRIC OXIDE INFLUENCE PULMONARY VASCULAR TONE AND GAS EXCHANGE IN DOGS WITH LUNG INJURY ?

V. Zegers de Beyl, M. Leeman, E. Gilbert, C. Mélot, R. Naeije.

Introduction : nitric oxide (NO) has been shown to inhibit hypoxic pulmonary vasoconstriction. We hypothetized that inhibitors of NO synthesis or action would increase pulmonary vascular tone and improve gas exchange in oleic acid (OA) lung injury.
Methods : pulmonary artery pressure (Ppa)-flow (Q) relationships (generated by a manipulation of venous return, which was increased by the opening of a femoral arterio-venous bypass or decreased by the inflation of an inferior vena cava balloon catheter), and gas exchange (evaluated by arterial blood gases and SF6 intrapulmonary shunt) were investigated before and after OA (0.06 ml/kg iv) and again after solvent (n = 8), methylene blue, a guanylate cyclase inhibitor (8 mg/kg iv, n = 10) or N(G)-nitro-L-arginine, a NO synthase inhibitor (40 mg/kg iv, n = 8), in anesthetized (pentobarbital) and ventilated (FiO2 0.4) dogs.
Results : OA induced pulmonary hypertension and deteriorated gas exchange. After OA, solvent had no effect on pulmonary hemodynamics and gas exchange. Both methylene blue and N(G)-nitro-L-arginine further increased Ppa at all levels of Q. Only methylene blue, however, improved arterial PO2 (from 71 ± 6 to 89 ± 12 mmHg, P < 0.02) and decreased SF6 intrapulmonary shunt (from 44 ± 6 to 34 ± 6 %, P < 0.02) after OA.
Conclusion : the results suggest that the release of NO modulates the pulmonary hypertension secondary to OA lung injury. However, the effects of NO on the regulation of gas exchange cannot be concluded from our data.

Laboratory of Cardiovascular and Respiratory Physiology, Erasme University Hospital, 808 route de Lennik, B-1070-Brussels, Belgium.

113

COMBINING INHALED NITRIC OXIDE (NO) AND IV NITRIC OXIDE SYNTHASE (NOS) INHIBITION IN AN OVINE LAVAGE MODEL OF ARDS

I. Rovira, T.Y. Chen, E. Greene, W.M. Zapol.

NO is synthesized by endothelial cells from L-arginine and increases cyclic GMP in vascular smooth muscle cells causing vasodilation. Inhibition of endogenous NOS increases vascular tone and enhances hypoxic pulmonary vasoconstriction (HPV). Inhaled NO produces selective pulmonary vasodilation of ventilated lung regions. We hypothesized that combining selective pulmonary vasodilation by NO inhalation, with HPV enhancement by infusing the NOS inhibitor N^G-nitro-L-arginine methyl ester (LNA) might reduce $\dot{V}_A/\dot{Q}$ mismatch and improve gas exchange and pulmonary hemodynamics in a lavage model of ARDS.

Six anesthetized and mechanically ventilated (FiO_2 0.90) lambs (25-35 kg) underwent bilateral lung lavage with Tween 80 in saline at 37°C. Pulmonary artery pressure (PA) and cardiac output (CO) were measured and intrapulmonary shunt ($\dot{Q}s/\dot{Q}t$) was calculated at baseline (BL), lung lavage (LL), 60 ppm NO inhalation (NO), 30mg/kg iv LNA (LNA) and again 60 ppm NO inhalation (LNA+NO). With each treatment 3 levels of CO, low (L), medium (M) and high (H) were obtained by using an A-V fistula and IVC balloon. Mean±SE. A paired t test and linear regression were used, * $p< 0.01$ H vs L CO, # $p<0.05$ vs preceding column.

		BL	LL	NO	LNA	LNA+NO
CO	L	1.7±0.2	2.0±0.2#	2.1±0.1	1.6±0.1#	1.8±0.2
(l/min)	M	3.2±0.5*	3.9±0.3*	3.6±0.1*	2.6±0.3*#	2.7±0.2*
	H	6.2±0.8*	5.9±0.5*	5.3±0.4*	3.8±0.3*#	4.2±0.4*
PA	L	13±0.3	15±0.9#	14±0.6	28±3.2#	19±1.9#
(mmHg)	M	17±0.6*	19±0.7*	16±0.8*#	29±2.1#	22±0.9#
	H	21±0.7*	22±1.1*	20±1.0*	34±1.8*#	26±1.8*#
$\dot{Q}s/\dot{Q}t$	L	7.9±1	34.6±5#	20.7±1#	31.2±4#	16.3±2#
(%)	M	10±2	50.4±4#	32.0±2*#	35.2±3	25.9±2*#
	H	14.5±2*	51.1±2#	42.3±3*#	45.7±6	36.5±4*#

The relationship between PA and $\dot{Q}s/\dot{Q}t$ was linear at all levels of CO (mean $r=0.92$). Inhaled NO either alone or combined with iv LNA improved $\dot{V}_A/\dot{Q}$ matching and decreased $\dot{Q}s/\dot{Q}t$ in this ovine experimental ARDS model. We conclude that inhaled NO combined with iv LNA may provide a useful therapy to reduce $\dot{Q}s/\dot{Q}t$ during ARDS. Supported by USPHS grant HL42397.

Department of Anaesthesia, Harvard Medical School at Massachusetts General Hospital, Boston MA, 02114.

114

PRODUCTION OF NO2 DURING NITRIC OXIDE (NO) INHALATION

Law-koune JD, Moutafis M, Fischler M.

The risk of production of toxic metabolites following NO oxidation have been underlined. We studied the kinetics of NO_2 emergence in two different models: 1) simultaneously mixing air/NO or O_2/NO in a close box; 2) insufflating a mixture of air/NO or of O_2/NO in a Douglas bag. A suction catheter was placed in the close box or in the Douglas bag and analysis of the NO/NO_2 concentrations was perfomed using an electrochemical method (Polytron Dräger^R).

14 litres of air or O_2 and 2 litres of NO (225 ppm/l) were mixed in the close box. NO/NO_2 concentrations (ppm) were measured after ten minutes. NO_2 is over 2.2 ppm in presence of air and 3.2 ppm in presence of O_2.

6 litres/minute of air or O_2 and 2 litres/minute of NO (225 ppm/l) were insufflated in the Douglas bag during 4 minutes. NO/NO_2 concentrations (ppm) were measured after ten minutes. NO_2 reaches 2.2 ppm in presence of air and 11.6 ppm in presence of O_2.

These data confirm that NO_2 production is fast and is particularly important in presence of a high O_2 concentration. Consequently, it appears mandatory to measure NO/NO_2 concentrations during NO inhalation.

Anesthesiology Dept, CMC Foch, 92151 Suresnes, France.

Diagnosis of pneumonia I

115

PULMONARY INFILTRATES IN LIVER TRANSPLANT PATIENTS . DIAGNOSTIC VALUE OF PROTECTED SPECIMEN BRUSHING AND BRONCHOALVEOLAR LAVAGE.

J.M.Guergué *, J.Insausti *, A.Torres **, A. Xaubet **, J. Gonzalez **, C. Agustí **, J. Ramirez **, J.M. Salmerón **, R. Rodriguez-Roisin **.

Liver Transplantation (LT) is often followed by a variety of respiratory complications that may cause significant morbidity and mortality.

We performed 51 fiberoptic bronchoscopic examinations on 41 liver transplant patients with pulmonary infiltrates. Protected specimen brushing (PSB) and bronchoalveolar lavage (BAL) via fiberoptic bronchoscopy were performed in each case. Samples were cultured in aerobic, anaerobic, mycobacterial, and legionella media. Cytologic examination of BAL fluid was also performed. In 39 of 51 (76,5%) cases pneumonia was considered the final diagnosis of the pulmonary infiltrates. By means of PSB and BAL examination a microbiologic identification was obtained in 25 of these 39 (64%) cases. The predominant pathogens isolated were Pseudomona aeruginosa (7 cases), Cytomegalovirus (7 cases) and Pneumocystis carinii (5 cases). The overall diagnostic yield of PSB + BAL was 58,8% (30 cases). The overall mortality was 26,8% (11 cases).

Our results indicate that combined PSB and BAL are valid tools for diagnosing pulmonary infiltrates in LT patients, resulting in a beneficial effect in clinical course.

* I.C.U. Hospital de Navarra- Nafarroako Ospitalea (Osasunbidea). Pamplona- Iruña. Spain.
** Departments of Pneumology, Microbiology, Pathology and Hepatology. Hospital Clinic. Facultat de Medicina. Barcelona. Spain.

116

IS PROTECTED SPECIMEN BRUSH A REPRODUCIBLE METHOD TO DIAGNOSE ICU ACQUIRED PNEUMONIA (IAP)? JF TIMSIT, S FRANCOUAL, B MISSET, FW GOLDSTEIN, E BAVIERA, J CARLET. Hôpital Saint Joseph, Paris, FRANCE.

Protected specimen brush is considered as the gold standard for the diagnosis of ventilator associated pneumonia but intraindividual variability had not been previously studied.

PURPOSE: To compare the results of 2 protected specimen brushes (PSB) performed in the same subsegment on patients with suspected IAP.

STUDY DESIGN: Between October 1991 and April 1992, each mechanically ventilated patients with suspected IAP underwent bronchoscopy with 2 successive PSB in the lung segment identified radiographically. Results of the 2 PSB cultures were compared considering 10^3 cfu/ml cut off, bacterial index, log10 of each microorganisms found. Four definite diagnoses were established: **definite pneumonia** (DP):if patients fulfilled positive pleural culture or rapid cavitation of the lung infiltrate or histopathologic evidence of pneumonia at autopsy performed within 8 days after diagnostic procedure **Probable pneumonia** (PRP):complete resolution after adapted antimicrobial therapy without other treated septic site **Excluded pneumonia** (EP): Full recovery without antibiotic therapy or no sign of pneumonia on postmortem examination and **Uncertain status** (US).

POPULATION: 42 episodes in 21 patients were studied. 60% patients received prior antibiotherapy always innefective on microorganisms found. 32 microorganisms were isolated from 24 pairs of PSB. Definite diagnosis was DP in 7, PRP in 8, EP in 17, and US in 10 cases.

RESULTS: Considering the 10^3 cut off, PSB1 and 2 gave discordant results in 24% microorganisms recovered and in 19% of episodes of suspected IAP. For 6 isolated microorganisms the 2 PSB specimen culture varied of a factor greater than 10^2. Discordance was independent from definite diagnosis. Considering log10 of each microorganism concentration the correlation between the 2 PSB was very significant ($p\leq10^{-5}$) but not very strong: $r=0.63$ signify that the knowledge of the first PSB culture explain only 40% of the variance of the second PSB.

There were no statistical effects of the order of samples between the two specimens for bacterial index and microorganism concentrations.

CONCLUSION: These findings argue for a poor reproducibility of PSB in suspected IAP and challenge the 10^3 cfu/ml threshold routinely used. Results of PSB must be interpreted with caution considering the intraindividual variability for diagnosis of IAP.