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Inhaled nitric oxide in newborn and paediatric patients with pulmonary hypertension and moderate to severe impaired oxygenation: effects of doses of 3–100 parts per million*

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Abstract *Objective:* To assess the effects of inhaled nitric oxide (INO) 3–100 ppm on oxygenation in both newborn and paediatric patients with pulmonary hypertension and impaired gas exchange.
Design: Open, prospective, multicentre study.
Setting: Tertiary neonatal and paediatric intensive care units in university referral centres.
Patients: Newborn (age $\leq$ 7 days; n = 26) and paediatric (age 8 days–7 years; n = 16) patients with pulmonary hypertension verified by echocardiography and an oxygenation index of (OI) 15–40 were included in the study.
Interventions: The patients were subjected to stepwise increases in doses of INO (0, 3, 10, 30, 60, 100 ppm).
Measurements and results: The effect on oxygenation was measured by repeated blood gas analysis. A positive response to INO was defined as a reduction in OI of $\geq$ 25 % compared to baseline (0 ppm). INO was found to improve oxygenation in both newborn ($p < 0.0001$) and paediatric ($p = 0.015$) patients and the response rate was 77 and 50 %, respectively. A marked interindividual difference in the magnitude of the response was found between patients (change in OI compared to baseline: – 90 to 15 %). Only 2 of 28 responding patients required doses in excess of 30 ppm in order to show a positive response.
Conclusions: INO is capable of improving oxygenation in both newborn and paediatric patients with pulmonary hypertension and impaired gas exchange, although the magnitude of the individual response can vary greatly. Doses in excess of 30 ppm are only rarely required in order to achieve a reduction in the oxygenation index of $\geq$ 25 %.

Key words Children · Infants · Inhaled nitric oxide · Pulmonary hypertension

* This study was carried out by the European Neonatal and Paediatric Nitric Oxide Study Group (ENPNOSG), see appendix for further details

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Introduction

The identification of inhaled nitric oxide (INO) as a selective pulmonary vasodilator [1, 2] together with the first report of the successful clinical use of INO in the treatment of persistent pulmonary hypertension of the newborn (PPHN) [3] have led to the widespread use and popularity of this therapy which is still experimental in neonatal and paediatric intensive care. The present Phase II clinical study was performed by the European Neonatal and Paediatric Nitric Oxide Study Group in order to elucidate the dosing relationship of INO in newborn and paediatric patients with pulmonary hypertension and impaired oxygenation. A second objective of the study was to evaluate the short-term safety of INO.

Materials and methods

Appropriate approval from ethical and drug regulatory authorities and written parental informed consent were obtained before the patients were enrolled in the study. The study was conducted in accordance with the Good Clinical Practice (GCP) guidelines of the European Union [4].

In an open, prospective, multicentre trial, two separate groups of patients with pulmonary hypertension and impaired oxygenation [oxygenation index 15–40; OI = mean airway pressure (cmH_2O) × fractional inspired oxygen (FIO_2) × 100/partial pressure of oxygen in arterial blood (PaO_2) (mm Hg)] were studied: newborn (age ≤ 7 days) and paediatric (age 8 days–7 years) patients, respectively. This stratification is in accordance with previously published classifications for similar types of patients [5]. Before being considered for inclusion in the study, the patients were not responding to "maximal conventional treatment" of pulmonary hypertension including analgesia-sedation-muscle relaxation, acid-base correction, attempted hyperventilation, volume loading and inotropic support. For complete inclusion and exclusion criteria see Table 1.

If no exclusion criteria were identified the patient was then subjected to stepwise increasing concentrations of INO (0, 3, 10, 30, 60 and 100 ppm; duration at each concentration 10 min). At the end of each test period an arterial blood gas sample was collected. All samples were taken from the same sampling site in each patient and samples in the newborn group were all post-ductal. During the dose testing procedure no additional medications were given, no patient handling was allowed and the ventilator settings were fixed. The inspired oxygen concentration was allowed to change, either as a passive event secondary to increasing concentrations of nitric oxide stock gas being blended into the fresh gas flow of the breathing circuit or as a result of changes of inspired oxygen concentration deemed necessary by the attending clinician. With both delivery devices, FIO_2 was measured after the mixing point in the inspiratory limb. None of the patients were treated with intravenous vasodilators either before or during the dosing sequence. A positive response to INO was defined as a reduction of ≥ 25 % in the OI value compared to that recorded at the end of the initial 0 ppm NO test period. At 0 ppm and again at 100 ppm NO, blood samples were taken for the determination of methaemoglobin, activated partial thromboplastin time (APTT), prothrombin complex or simplastin (PC), platelets and ionised calcium.

Any adverse events during the dosing sequence or during subsequent continuation of treatment with INO were registered according to GCP standard.

Medical grade nitric oxide (1000 ppm NO in nitrogen, containing < 10 ppm nitrogen dioxide; AGA, Lidingö, Sweden) was used as stock gas. The stock gas was blended into the air-oxygen fresh gas flow of either a Siemens 300 ventilator equipped with a computerised prototype NO module with a digital controlled NO valve or via a precision rotameter device (Rota, Yokogawa, Japan), carefully calibrated for delivery of the stock gas, which was attached to a conventional constant flow ventilator. The delivery equipment was calibrated at monthly intervals. NO and NO_2 levels were continuously monitored by electrochemical cells (City Technology, Portsmouth, UK-Siemens system; Dräger Pac II, Lübeck, Germany-Constant flow system). NO_2 scavengers were not included in the delivery systems.

Any continuation of treatment after the end of the dosing study was performed outside of the study protocol and left entirely to the discretion of the attending physician. Follow-up of all patients exposed to INO was performed 30 days after the dosing sequence as dictated by GCP.

Table 1 Inclusion and exclusion criteria for the study ($PaCO_2$ partial pressure of carbon dioxide in arterial blood, PaO_2 partial pressure of oxygen in arterial blood, *PDA* patent ductus arteriosus, *ASD, VSD* atrial, ventricular septal defect, *CAVH* continuous arterio-venous haemofiltration, *ECMO* extracorporeal membrane oxygenation)

Inclusion criteria (all criteria to be met before inclusion)

1. Newborn patients ≤ 7 days or paediatric patients 8 days–7 years of age.
2. Acute or subacute pulmonary hypertension of any cause needing vasodilation treatment.
3. The presence of signs consistent with pulmonary hypertension verified by echocardiography < 12 h prior to inclusion (e.g. tricuspid valve insufficiency, complete or partial right-to-left shunting at the atrial or ductal level, "notched" flow signal in the pulmonary artery).
4. $PaCO_2$ < 50 mm Hg (< 6.6 kPa). The mean of two arterial blood gas samples, measured 15 min apart.
5. Base excess more alkaline than – 5.0 mmol/l. The mean of two arterial blood gas samples, measured 15 min apart.
6. Oxygenation index of 15–40 at inclusion. The mean of two arterial blood gas samples, measured 15 min apart.
7. Body temperature 36.5–39.0 °C.

Exclusion criteria

1. Gestational age < 36 weeks.
2. Oxygenation index outside the range 15–40 at inclusion.
3. Underlying disease or injury that was clearly irreversible and expected to be rapidly fatal.
4. Severe uncorrected cardiac malformation. Patients with PDA, ASD or VSD could be included in the study.
5. Systemic hypotension that did not respond to volume or inotropic support with a mean arterial pressure < 35 mm Hg in patients less than 28 days of age and < 50 mm Hg in older patients.
6. The patient had been on intravenous vasodilation treatment < 1 h prior to inclusion.
7. The patient suffered from intracranial haemorrhage grade I–IV.
8. Significant untreated pneumothorax.
9. Previous exposure to INO.
10. Any type of extracorporeal support (e.g. CAVH, haemodialysis, ECMO).
11. Methaemoglobin levels > 5 % prior to inclusion.
12. The patient had never had a normal arterial blood gas after birth, defined as PaO_2 > 45 mm Hg (> 6.0 kPa) and $PaCO_2$ < 55 mm Hg (< 7.3 kPa).
13. The patient had received surfactant therapy < 6 h prior to inclusion.
14. The patient was already participating in another clinical study.

The following statistical methods were used: analysis of variance for repeated measures (OI and tidal volumes), chi-square analysis (response rate between subgroups) and Student's *t*-test (coagulation parameters). A p value of < 0.05 was considered statistically significant.

The study was sponsored by AGA, Lidingö, Sweden and Siemens-Elema, Solna, Sweden. However, analysis of the results and the preparation of this manuscript was carried out independently of the sponsoring organisations by the Study Director and the Study Committee (Appendix). The study is part of an effort to fulfil current regulatory demands for registration of INO as a drug

Table 2 Demographic details of the 42 patients studied (*ARDS* acute respiratory distress syndrome, *CDH* congenital diaphragmatic hernia, *CHD* congenital heart disease, *MAS* meconium aspiration syndrome)

Patient category (age)	Sex (M/F)	Median age (range)	Median weight (kg) (range)	Primary diagnosis causing pulmonary hypertension	
Newborn (0–7 days)	21/5	2 days (0–7)	3.3 (2.6–4.9)	Pneumonia and/or septicaemia	7
				Idiopathic/primary	6
				MAS	6
				CDH	3
				Other	4
Paediatric (8 days–7 years)	11/5	$6^1/_2$ months (9 days–82 months)	6.2 (2.0–24.5)	Paediatric ARDS	9
				Pneumonia and/or septicaemia	6
				CHD	1
				Idiopathic	1

and, thus, in a more formal way proving the efficacy and safety of INO in the patient population described.

Results

A total of 43 patients were included in the study (newborn: $n = 26$, paediatric: $n = 17$; for demographic data see Table 2). One paediatric patient was excluded from the analysis since pulmonary hypertension had not been correctly verified by echocardiography. During the time period between the inclusion of the patient and the start of the dosing sequence the OI had changed in 8 patients (4 newborn, 4 paediatric) to values slightly lower than 15 ($n = 2$) or greater than 40 ($n = 6$). In accordance with "intention to treat", these patients were included in the final analysis. A male predominance was seen in both groups and, as reported in other studies, the underlying aetiologies for PPHN and the paediatric acute respiratory distress syndrome (ARDS) were very diverse (Table 2).

NO inhalation produced a statistically significant improvement in oxygenation in both study groups, as indicated by a decrease in OI ($p < 0.0001$ and $p = 0.015$, respectively) (Fig. 1). Altogether, 77 % of the newborns and 50 % of the paediatric group were found to respond to INO (NS). From 0 to 100 ppm NO the OI decreased from (mean ± SEM) 30.0 ± 3.0 to 19.6 ± 2.0 in the newborn group and from 29.0 ± 3.8 to 21.9 ± 8.6 in the paediatric group. The maximum response to INO (change in OI compared to baseline) varied between − 89 and 17 % and − 91 and 13 % in the newborn and paediatric groups, respectively. The NO concentration associated with maximum improvement in oxygenation varied between patients (Fig. 2). However, 8 of the 10 patients with a maximum improvement in oxygenation at 60 or 100 ppm NO had a positive response at lower dose levels. Thus, in only 2 newborn patients were NO concentrations above 30 ppm necessary in order to consider the patient to be a responder (Fig. 2). A deterioration in oxygenation (increase in OI ≥ 25 %) occurred during the dose testing period in 5 patients (3 newborn, 2 paediatric).

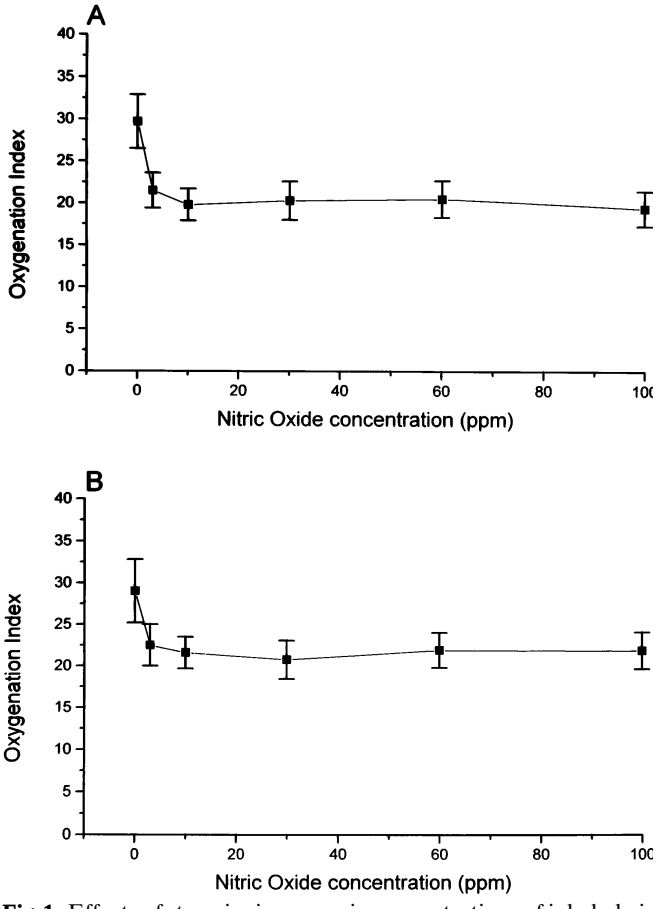

Fig. 1 Effects of stepwise increases in concentrations of inhaled nitric oxide on the oxygenation index in newborn **A** and paediatric **B** patients with echocardiographically verified pulmonary hypertension and impaired gas exchange (mean ± SEM)

In newborn patients, all of whom had been treated with pressure controlled ventilation, a small increase in tidal volume 0 ppm: 40.2 ml (SEM 3.6); 100 ppm:

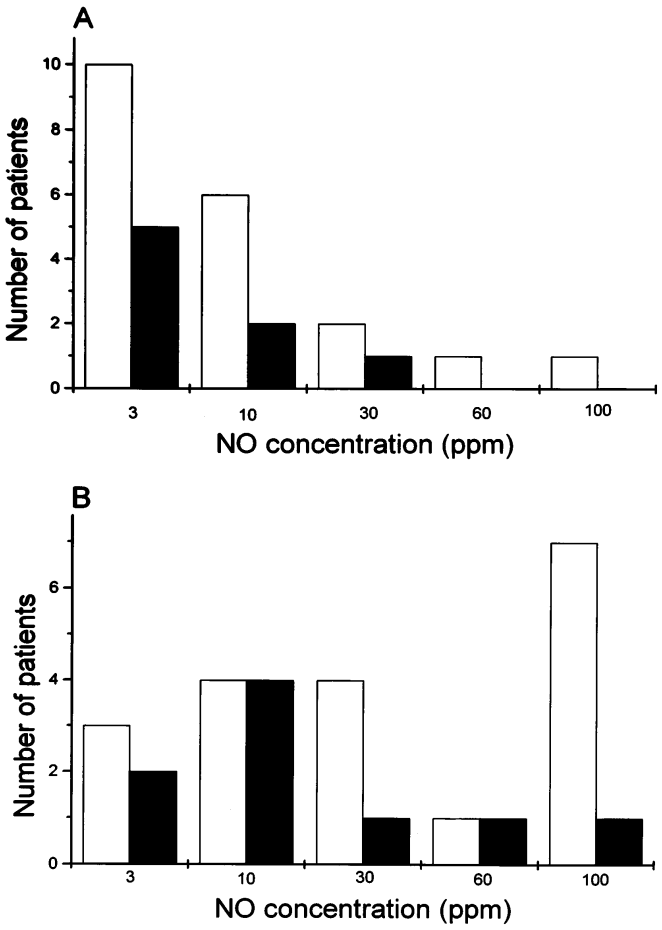

Fig. 2 Concentrations of inhaled nitric oxide first causing a reduction in the oxygenation index by $\geq 25\%$ compared to baseline (= positive response) **A** and concentrations associated with maximum improvement of oxygenation **B**; *open columns* newborns, *filled columns* paediatric patients

41.4 ml (SEM 3.8) was found during the NO exposure, but this was not statistically significant ($p = 0.086$). No other changes in ventilatory parameters were noted during the study.

INO did not result in any statistically significant changes in pH, partial pressure of carbon dioxide (PCO_2) or base excess for the group as a whole. In responding patients, no correlation could be found between the individual maximum reduction in OI and the maximum reduction in PCO_2. No elevations of methaemoglobin or any significant changes in the other measured laboratory parameters were observed during the dosing procedure (median relative change between 0 and 100 ppm; values are given for the newborn and paediatric groups, respectively: metHb: 0.0 and 0.0%, APTT: –3.2 and 7.3%, PC: –0.8 and 0.0%, platelets: 5.6 and –11.5%, ionized Ca^{2+}: –1.6 and –0.4%).

Only one adverse event that possibly could be linked to the NO exposure was reported. In this patient (a 7-day-old caucasian boy with meconium aspiration syndrome) the attending physician chose to continue treatment with 60 ppm NO following the dosing sequence. Almost immediately following the start of compassionate NO treatment, the patient experienced a sudden deterioration associated with hypotension and desaturation. After a brief period of resuscitation, the patient recovered and INO treatment was continued with 4 ppm.

At the day 30 follow-up the investigators stated that, following the end of the dosing study, 17 newborn and 13 paediatric patients had received treatment with INO on compassionate grounds for more than 4 h. The median duration of the treatment was 73 h (range 11–288 h) and 59 h (range 6–480 h) for the newborn and paediatric groups, respectively. Methaemoglobin values > 2.5% were observed in two patients, but values in excess of 5% were not observed in any of the patients exposed to compassionate treatment with INO. The overall mortality was 33% (8/26 and 6/16 in the newborn and paediatric groups, respectively).

Discussion

The major findings of this study were that both newborns and older children with pulmonary hypertension and moderate to severe impaired gas exchange react with improved oxygen exchange when exposed to INO. We also observed a tendency to a higher response rate at between 3 and 100 ppm NO in newborns (77%) compared to paediatric patients (50%). In addition, the dose of INO giving the maximum decrease in OI varied over the whole dose range studied in both groups, although doses ≤ 30 ppm were sufficient to decrease the OI by $\geq 25\%$ compared to baseline in the vast majority of the responding patients.

To our knowledge, this is the most comprehensive paediatric dosing study with INO performed to date. The participants in this study represented seven European countries in a total of 11 neonatal and paediatric intensive care units (ICUs). They were all tertiary referral centres, pioneering the clinical use of INO in their respective areas. In spite of this interest, it took over a year to recruit 43 patients, with some ICUs contributing patients only occasionally. From this we conclude that the clinical syndromes of PPHN and paediatric ARDS were less common than expected from clinical impression.

Both low (< 10 ppm) and high doses (80 ppm) of INO have been observed to bring about an improvement in oxygenation in both adult and paediatric patients [6–8], and lasting improvements from a single, short exposure to INO [9], as well as severe rebound re-

actions upon acute discontinuation of INO [8, 10], have been reported. In addition, the introduction of 10-min 0 ppm points between each new dose would have doubled the time of the dosing sequence. Severely ill patients are known to be unstable and a study duration of 2 h would thus have made comparisons less reliable between early and late doses. Based on the above, we saw the need to study several doses from 3 to 100 ppm INO and chose not to include 0 ppm INO control points before each new dose of INO and, instead, used a stepwise increase in dosage design.

We saw two reasons to focus on patient groups with less severe gas exchange disturbance (OI 15–40, which is below generally accepted criteria for extracorporeal membrane oxygenation): (1) a less unstable population would allow for better controlled study conditions, which would be preferable for both ethical reasons and generalisation of data; (2) based on our own preliminary results with INO [11], early administration of INO might improve the chances of a positive response.

Finer et al., in an initial neonatal dosing study, have reported a variable oxygenation response between 5 and 80 ppm INO, with a considerably lower response rate in neonates without signs of pulmonary hypertension on echocardiography [12]. We studied a larger group of infants, all of whom had verified pulmonary hypertension at inclusion in the study. In addition, we also studied the response to INO in paediatric patients and the study was conducted in accordance with GCP, which includes careful monitoring of participating centres and source data verification.

Response rate

Although not statistically significant, we observed a higher response rate in the newborn group (77 %) compared to the paediatric group (50 %). The higher response rate in newborns suggests a pathophysiology which, to a large extent, is due to vascular spasm and extrapulmonary shunting. The syndrome in paediatric patients is more complex with predominantly intrapulmonary shunting as seen in adult ARDS, which might account for the 50 % response rate seen in the older patient group. In both newborn and paediatric patients, oxygenation can be improved by a microselective vasodilatation in ventilated lung regions [6, 8], resulting in improved ventilation-perfusion matching. However, in newborns with PPHN and severe hypoxaemia, another potential mechanism for improvement in oxygenation is present. A minor reduction in pulmonary arterial pressure (PAP), leading to a more favourable PAP/SAP (systemic arterial pressure) ratio will result in partial or total reversal of right-to-left extrapulmonary shunting (at the atrial or ductal level). The selective action on the pulmonary circulation of inhaled vasodilators such as INO and prostacyclin [13, 14] have a unique potential for improving the PAP/SAP ratio compared to intravenous vasodilators. The general vasodilatation in both the pulmonary and the systemic circulation caused by vasodilators administered intravenously carries a substantial risk for detrimental deterioration of the PAP/SAP ratio, further aggravating hypoxaemia.

Size of response

The relative change in OI varied considerably between patients, from approximately − 90 to 15 % in both groups. We can at present only speculate upon the reasons for this additional variation. Mercier et al. [15] and Karamanoukian et al. [16] claim a reduced response to INO in babies with meconium aspiration syndrome (MAS) and congenital diaphragmatic hernia (CDH). This has recently been further supported by preliminary data presented by Kinsella et al. [17]. Our study numbers were too small to allow for subgrouping, but in our few patients with MAS and CDH we observed only a slightly lower response rate (6/9) compared to the remaining patients (14/17) in the newborn group.

Dose for maximum response

The dose associated with the maximum response varied in our study. There was, additionally, a discrepancy between the dose turning a patient into a responder and the dose giving maximum effect, in both newborns and in paediatric patients. This is clinically important, as patients showing a maximum response at 60 or 100 ppm INO already had meaningful improvements at much lower doses. In other words, limiting the maximum dose of INO to 30 ppm would mean defining 10 % of the potential responders (2/20) as non-responders in the newborn group. However, with the same limitation in dose, no potential responders would be missed in the paediatric group.

Administering higher doses of INO (60–100 ppm) exponentially increases the amount of NO_2 formed in inspired oxygen-enriched gas [18]. In such gas mixtures the correct measurement of NO_2 concentration is very problematic [19, 20], which makes clinical monitoring unreliable. In the Siemens 300 prototype system, NO and NO_2 concentrations were measured on expired gas after the mixing chamber. This system allowed a bypass flow trigger to operate unhampered by inspiratory limb sampling of gas for monitoring. In subsequent laboratory testing it has become clear that NO_2 measurements are extremely time dependent in nitric oxide and

oxygen-rich mixtures (Dr. U. Schedin, personal communication), and the type of monitoring provided by such a research prototype NO delivery system is no longer recommended. We recorded artefactually elevated values of ≤ 7.9 ppm NO_2 at the maximum dose of 100 ppm NO. Intermittent inspiratory measurements during treatment with INO and extensive laboratory testing have shown that the actual NO_2 concentrations present in the inspiratory limb of the 300 prototype is within the 2–3-ppm range at 100 ppm NO at an FIO_2 of 0.90 [21]. However, the NO concentrations for the neonatal and paediatric ventilatory modes remain adequate due to a significant by-pass flow. In the constant flow delivery device sampling was performed on inspiratory gas and the measured NO_2 values should thus be representative in this set-up.

Since the majority of patients display a clinically meaningful response at doses ≤ 30 ppm INO, only the exceptional patient should be treated with higher doses of INO and the exposure time should be as short as possible. Prolonged exposure to more moderate doses of INO has recently also been found to cause functional impairment of neutrophils [22]. INO is not a registered drug and randomised studies have been called for specifically to address the risk/benefit relationship [23].

In summary, this study found improved oxygenation in both newborns and older children with pulmonary hypertension and moderate to severe impaired oxygenation during exposure to short-term, low doses of INO. We also observed a higher frequency of response in newborns than in paediatric patients. In addition, the dose of nitric oxide achieving the maximum decrease in the oxygenation index varied over the dose range studied in both groups, although only a little additional benefit on oxygenation could be achieved from using doses in excess of 30 ppm.

Appendix

European Neonatal and Paediatric Nitric Oxide Study Group
Study Director & Chairman of Study Committee: P. A. Lönnqvist, Stockholm, Sweden. *Study Committee:* Prof. H. L. Halliday, Belfast, UK; Prof. W. Kachel, Mannheim, Germany; C. G. Frostell, Danderyd, Sweden; G. L. Olsson, Stockholm, Sweden. *Principal Investigators:* S. Renolleau, Paris, France; Prof. H. Hartmann, Hannover, Germany; Prof. B. Roth, Cologne, Germany; N. Gullberg, Stockholm, Sweden; J. McKnight, Belfast, UK; J. A. Hazelzet, Rotterdam, The Netherlands; J. Klinge, Erlangen, Germany; S. Michelsen, Oslo, Norway; J. Mulier, Leuven, Belgium; V. Varnholt, Mannheim, Germany. *Monitoring, data handling, and statistical analysis:* M. Jountsenvirta, Norrköping, Sweden; O. Luhr, Danderyd, Sweden; K. Uthne, Södertälje, Sweden; M. Ålenius, Stockholm, Sweden.

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