Effects of Inhaled Nitric Oxide Administration on Early Postoperative Mortality in Patients Operated for Correction of Atrioventricular Canal Defects*

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Objective: **Postoperative pulmonary hypertension (POPH) substantially increases mortality after repair of congenital heart diseases. Inhaled nitric oxide (NO) has been reported as an effective and specific means of controlling POPH crisis. No randomized, placebo-controlled study has addressed the ability of NO administration to reduce mortality. Such a trial could raise ethical questions.**

Design: **Observational study with historical control subjects based on multivariate confounder scores.**

Setting: **Surgical pediatric ICU in a university hospital.**

Patients: **Two hundred ninety-four records of patients operated on for atrioventricular (AV) canal between 1984 and 1994 who presented with severe POPH.**

Interventions: **All variables found to be predictive for death by univariate tests were entered in a multivariate forward stepwise logistic regression model. Two paired groups regarding risk factors for death and only differing for POPH treatment (NO or conventional treatment) were constructed on the basis of predicted values obtained from this model. Twenty-five patients received NO, and 39 control patients, operated on between 1984 and 1994, received conventional treatment for POPH.**

Measurements and results: **Postoperative pulmonary pressure, date of operation, and occurrence of an infectious complication were retained in the model. The comparison between the two paired groups showed a significant difference in mortality (24%; 95% confidence interval [CI], 7 to 41%; vs 56%; 95% CI, 37 to 75%, respectively; p = 0.02).**

Conclusions: **This study suggests that there is a high probability for postoperative mortality reduction associated with administration of inhaled NO when severe POPH occurs in children operated for complete repair of AV canal.** ***(CHEST 2005; 128:3537–3544)***

Key words: cardiopulmonary bypass; congenital; Down syndrome complications; heart defects; heart septal defects; hypertension etiology; nitric oxide administration and dosage; pulmonary hypertension; surgery; therapeutic nitric oxide

Abbreviations: AV = atrioventricular; CI = confidence interval; iNO = inhaled nitric oxide; NO = nitric oxide; POPH = postoperative pulmonary hypertension; PRISM = Pediatric Risk of Mortality

Postoperative pulmonary hypertension (POPH) after surgical correction of congenital heart disease, related either to high pulmonary blood flow or to a pulmonary postcapillary obstruction, is associated with important early morbidity and mortality.[1] The effects of conventional treatment of POPH, including deepening of anesthesia, muscle relaxation, and use of drugs such as tolazoline or prostacycline, have not been found to be effective as specific vasodilators for the pulmonary vascular bed.[1] Inhaled nitric oxide (iNO) has been increasingly used as a specific pulmonary artery vasodilator in

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Manuscript received March 21, 2005; revision accepted July 31, 2005.

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acute pulmonary hypertension of the newborn.[2,3] iNO efficacy in controlling POPH in cardiac surgery has been proposed to treat acute right ventricular failure after cardiac transplantation[4] or during the correction of various types of congenital heart diseases.[5–8]

The efficacy of iNO during pediatric cardiac surgery has already been established by several studies, including placebo-controlled trials.[8–10] Nevertheless, evidence has not been shown that administration of iNO reduces the mortality associated with POPH crisis. iNO seems to be well tolerated and appears to be efficient on both clinical experience and published studies. Therefore in 2005, it is difficult, for ethical reasons, to perform a large randomized-placebo controlled study aiming to demonstrate a mortality reduction in pediatric cardiac surgery.

In order to investigate if a correlation exists between treatment by iNO and survival, we compared the perioperative survival rates of two groups of children operated for atrioventricular (AV) canal and presenting with POPH crisis. Although this study has all the drawbacks of a nonprospective study, we selected all the variables associated with mortality in order to compare two groups of children as homogeneous as possible. To limit the potential bias due to surgical techniques advances, only children operated during the period of introduction of iNO have been studied: Twenty-five consecutive patients operated after March 1992 received iNO as standard treatment for severe POPH, while 39 patients operated between 1984 and 1994 received conventional treatment.

Materials and Methods

Patients

Between January 1984 and August 1994, 294 children were operated for various types of AV canal defect at our institution. All the source records were reviewed with regard to the inclusion criteria that we have routinely used for deciding to administer iNO in the postoperative period to treat POPH crisis in the early postoperative period. These inclusion criteria were as follows: pulmonary artery pressure > 70% of systemic arterial pressure in association with a decrease in venous and/or arterial oxygen saturation during mechanical ventilation (in the absence of carbon dioxide retention or hypoxia). Pulmonary artery pressure was measured either with a catheter inserted in the pulmonary artery during operation (125 cases), with echocardiography (149 cases), or both (40 cases). Transpulmonary pressure gradients were calculated when both pulmonary artery pressure and left atrial pressure were available (261 cases). A complete set of data including 98 variables was entered for each patient into a specially designed database by systematic examination of their original medical records.[11] Among these selected variables were those suspected to exert an influence on perioperative mortality according to previous reports.[11,12] Probability of death, based on the Pediatric Risk of Mortality (PRISM) score, was retrospectively measured in all children at ICU admittance.[13,14] Variables that could have induced a bias in patient selection, such as date of operation or method for measuring pulmonary artery pressure, were also included in the analysis.

Recorded Data

AV canal defects were grouped according to the Boston Children's Hospital classification, in complete, intermediate, or associated with other cardiac defects on the basis of operative reports.[11] Hemodynamic preoperative data were provided by cardiac catheterization, echocardiography, or both. As an accurate quantification of AV regurgitation may be difficult or subjective, preoperative and postoperative left AV valve incompetence was classified as present or absent on the basis of all the available data (cineangiography, echocardiography, hemodynamic measurements). All the infectious and postoperative respiratory complications in the ICU were recorded. Infection was defined as any systemic septic syndrome with positive culture findings requiring administration of antibiotics after termination of a 48-h routine prophylaxis. Early postoperative death was defined within 30 days from the operation or before hospital discharge.

Surgical and Postoperative Management

Surgical repair was performed under cardiopulmonary bypass using a double venous cannulation with moderate hypothermia. Deep hypothermic circulatory arrest was used in five patients (8%). Multidose, cold, crystalloid cardioplegia was used before 1989, and multidose (4°C) blood cardioplegia, followed by warm blood reperfusion, was used after this date. Ultrafiltration was systematically performed during rewarming after 1990. A two-patch repair technique was used most of the time. A left atrial catheter was surgically inserted in most patients (Table 1).

Before March 1992, the conventional management of acute POPH crisis consisted of hyperventilation with 100% oxygen, deepening of the level of anesthesia with fentanyl, muscle paralysis, correction of metabolic acidosis, and administration of isoproterenol[15] and/or prostacycline.[16] After March 1992, in all cases of POPH crisis, the same treatment was administered except neuromuscular blocking drugs and vasodilators that were replaced by administration of iNO. During the studied period, dedicated iNO administration systems did not exist.[17] Therefore, iNO was provided by a tank containing 225 ppm of nitric oxide (NO) in N_2 (Kinox°; Air Liquide Santé International; Paris, France) and connected to a specially designed low-flow blender. The mixture of NO and N_2 was continuously delivered in the ventilator inspiratory limb and monitored with a NO/NO_2 analyzer to reach a final administered concentration of 25 ± 8.6 ppm (mean ± SD) [Polytrons NO/NO_2; Dräger; Antony, France].[5] Four patients received both iNO and the conventional treatment. Median duration of iNO administration was 5.2 days (minimum to maximum, 0.25 to 17 days). Methemoglobin concentration, measured twice daily in each patient receiving iNO, was $0.4 \pm 0.11\%$ (laboratory reference value $< 0.5\%$).

Study Design and Statistics

Data were analyzed using statistical software (SPSS version 11; SPSS; Chicago, IL).[18] All continuous data were tested for conforming to a normal distribution using the Kolmogorov-Smirnov test. All normally distributed data are expressed as mean ± SD. The remaining variables are expressed as median (minimum to maximum). Simple contingency tests (χ^2), Fisher exact test, Mann-Whitney *U* test, and univariate logistic regression analyses

Table 1—*Clinical Data of the 64 Patients With Severe POPH

Variables	Data
Patient characteristics	
Median age at operation (range), yr	0.54 (0.2–35)
Low weight for age, U of SD	− 1.6 ± 0.7
Down syndrome	30 (47)
Preoperative evaluation	
AV valve incompetence	43 (67)
Type of AV canal defect	
Complete	48 (75)
Intermediate	14 (22)
Associated with other defects	8 (12.5)
Pulmonary artery hypertension	52 (82)
Atrial septal defect	11 (17)
Additional ventricular septal defect(s)	14 (22)
Operation	
Cardiopulmonary bypass duration (range), min	112 (52–328)
Aortic cross-clamp time (range), min	72 (38–102)
Postoperative data	
Mean pulmonary artery pressure, mm Hg†	54 ± 15/44 (69)
Left atrial pressure, mm Hg†	4 (0–24)
iNO administration, ppm	25 (39)
Mitral valve regurgitation	6 (9.4)
Reoperation during the same hospital admission	6 (9.4)
Median duration of mechanical ventilation (range), d	4.3 (2.5–18)
Infections	20 (31)
Overall mortality	27 (42)

*Data are presented as mean ± SD or No. (%) unless otherwise indicated.

†Data are presented as mean ± SD value/No. (%).

were used when appropriate, to identify associations between mortality and selected variables, or to look and describe trends in the studied population. All comparative tests were two sided. Except for entering multivariate models, statistical significance was chosen at $p < 0.05$.

All baseline variables found to be predictive for death by univariate tests with $p < 0.15$ were entered in a multivariate forward stepwise logistic regression model based on the likelihood ratio statistic with a cutoff value at 0.05.[18] Results are expressed by odds ratios for the occurrence of death; the Mantel-Haenszel method was used to adjust odds ratios for the confounding variable. Finally, two methods were used to address effects of iNO on mortality in the subgroup of children with severe POPH: (1) We identified a historical control group of 39 children with severe POPH but who did not receive iNO. They were paired with the group of 25 children who received iNO. Pairings were based on the logit ln(p/[1-p]) of their predicted probabilities of mortality.[19] Predicted probability was obtained by the stepwise logistic regression described previously. The accuracy of the pairing of the two groups was checked, and the null hypothesis of similar distributions was not rejected ($p = 0.39$, $\beta = 0.13$). (2) iNO administration was forced to enter the stepwise multivariate logistic regression model in association with previously retained variables in order to determine the difference in mortality induced by its administration.

Results

Of the 294 patients, 64 patients (21.8%) met the criteria of POPH defined as above. Clinical data from this group are reported in Table 1. All of these children received either the conventional treatment of POPH or iNO and were received mechanical ventilation with a tidal volume of 16 ± 4 mL leading to a $Paco_2$ of 32 ± 6 mm Hg.

Trends Over Time

No changes were found over time in age at operation ($p = 0.58$) or in the type of AV canal defect ($p = 0.61$). While for the same studied period incidence of infection ($p = 0.0001$), severe POPH ($p = 0.001$), Down syndrome ($p = 0.04$) and duration of aortic cross-clamp ($p = 0.01$) increased over years. Occurrence of associated lesions increased significantly with time ($p = 0.02$), and they were simultaneously repaired in eight patients (12.5%). Conversely, a decrease in the duration of mechanical ventilation was observed over time ($p = 0.01$).

Infection

Postoperative infections were more frequent in patients with complete AV canal defect ($p = 0.04$), in patients reoperated during the same hospital admission (83% vs 25%, $p = 0.009$), in patients with Down syndrome (63.1% vs 17.8%, $p = 0.001$), and in patients with growth retardation ($p = 0.002$). These infections were as follows: pulmonary infections ($n = 12$), septic shock ($n = 3$), catheter-induced bacteremia ($n = 7$), unexplained bacteremia ($n = 1$), and urinary tract infection ($n = 2$). A multiple stepwise regression retained as independent risk factors for sepsis: date of operation (odds ratio, 1.003 ± 0.001 by day from January 1, 1984; $p = 0.002$), reoperation (odds ratio, 8 ± 0.8; $p = 0.002$), and low weight for age (odds ratio, 6 ± 0.3 by unit of SD; $p = 0.001$).

Mortality

Despite a correlation with mortality ($p = 0.02$), the estimation of mortality, based on the PRISM score evaluated at ICU admittance, overestimated the actual mortality (52 ± 7% vs 42%). There were no intraoperative deaths. Variables that appeared significant risk factors for death by univariate analysis are reported in Table 2. Variables not reaching a significance level of 0.15 were as follows: age at operation, Down syndrome, type of AV canal, presence of a single papillary muscle, preoperative cardiac failure, level of preoperative pulmonary artery pressure, surgeon identity, cardiopulmonary bypass length, deep hypothermic circulatory arrest as well as method for measuring pulmonary artery hypertension, and mechanical ventilation duration. Mortality remained unchanged in patients undergoing

Table 2—*Factors Associated With Early Death in Patients With Severe POPH (n = 64)**

Factors	Logistic Parameter†	Risk Ratio	p Value‡
General variables			
Date of procedure (by day from January 1, 1984)	− 0.0002 ± 0.00009	0.9998	0.0354
Low weight for age, U of SD	1.27 ± 0.98	3.56	0.009
Anatomic and operative variables			
Ventricular septal defect	0.91 ± 0.6	2.5	NS (0.12)
Aortic cross-clamp time, /min	0.0098 ± 0.0049	1.01	0.0446
Reoperation for left AV regurgitation	0.49 ± 0.38	1.63	0.007
Postoperative variables			
Postoperative left AV regurgitation	1.25 ± 0.8	3.49	NS (0.118)
Systolic pulmonary artery pressure (> over 25 mm Hg)	0.0145 ± 0.0065	1.015	0.026
Transpulmonary gradient pressure (> over 18 mm Hg)	0.0149 ± 0.008	1.015	0.028
Method of measurement of pulmonary artery hypertension	0.02 ± 0,01	1.02	NS (0.201)
Infections	0.847 ± 0.48	2.33	NS (0.08)
Use of iNO	− 1.153 ± 0.47	0.316	0.012

*NS = not significant.
†Logistic parameter obtained by stepwise multiple logistic regression analysis.
‡Univariate analysis.

the same surgical procedure without POPH. The univariate analysis suggested a decrease of perioperative mortality over time in patients with severe POPH. However, this trend has only reached a significant level only since 1993 (Fig 1).

Results of the multivariate stepwise logistic regression analysis are shown in Table 3. Postoperative pulmonary pressure (or transpulmonary pressure gradient) entered the model first, followed by date of operation and by occurrence of an infection. None of

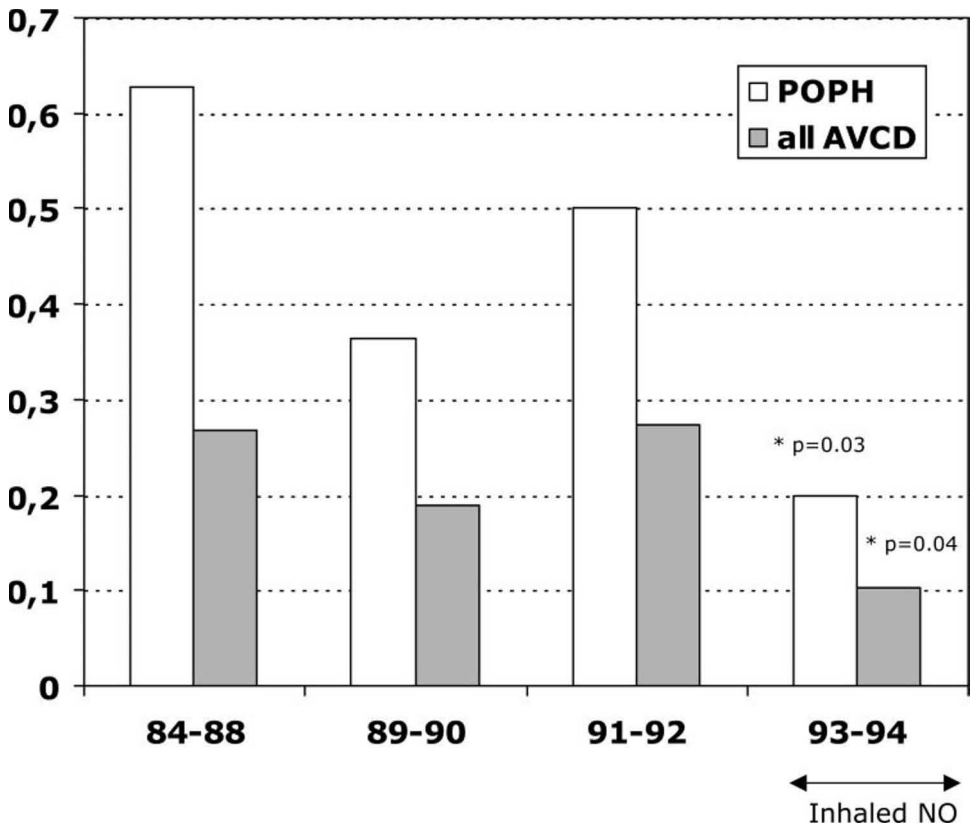

FIGURE 1. Evolution of early postoperative mortality rate between January 1984 and August 1994 in all patients operated from AV canal defect with and without severe pulmonary hypertension. AVCD = atrioventricular canal defect. *$p < 0.05$ vs previous years.

Table 3—*Factors Associated With Early Postoperative Death in Patients With Severe POPH (n = 64)

Factors	β ± SE†	Risk Ratio	p Value
Model with all variables selected by univariate analysis			
Constant	0.443 ± 1.34		NS (0.74)
Date of procedure (by day from January 1, 1984)	− 0.0005 ± 0.0004	0.9995	0.024
Postoperative infections	1.84 ± 1.02	6.3	0.028
Systolic pulmonary artery pressure > 25 mm Hg	0.002 ± 0.001	1.002	0.045
Same model with administration of iNO entered			
Constant	0.541 ± 1.21		NS (0.12)
Administration of iNO	− 1.39 ±0.58	0.25	0.012
Postoperative infections	2.05 ± 1.98	7.8	0.002

*See Table 2 for expansion of abbreviation.
†Logistic parameter obtained by stepwise multiple logistic regression analysis.

the other variables available in the modeling process reached the significance level when these three variables were entered.

A further stepwise multivariate logistic model entering administration of iNO, eliminated date of operation and pulmonary artery pressure (or transpulmonary pressure gradient) as risk factors for death, but retained infection with an increased odds ratio for this variable (odds ratio, 7.8; $p = 0.002$) associated with a significant improvement of the model ($p = 0.003$). The overall significance of the χ^2 of this model was $p = 0.0003$.

Finally, a comparison between the two paired groups of patients, between those who had received iNO and those who had not, confirmed the significant difference in mortality (24%; 95% confidence interval [CI], 7 to 41%; vs 56%; 95% CI, 37 to 75%, respectively; $p = 0.02$). No difference was noticed between groups regarding mortality based on PRISM scores at ICU admittance (50.4% vs 53.7% respectively; $p = 0.32$). Results of a similar multivariate stepwise logistic regression analysis entering all variables selected by univariate analysis and involving the overall population of 294 patients are shown in Table 4.

Discussion

This study suggests that a correlation exists between treatment by iNO and survival in children operated for AV canal complicated by POPH crisis.

Critical Analysis

Several clinical pediatric studies have reported favorable results in the treatment of POPH crisis with iNO[5,6,8,20–23] or in ARDS.[24–26] Nevertheless, prospective randomized trials to substantiate mortality reduction are not available. Since iNO has demonstrated its efficiency on pulmonary hypertension, one may question the ethical value of excluding control patients from iNO in a new randomized study attempting to demonstrate a mortality reduction. For this reason, being aware of the limitations

Table 4—*Factors Associated With Early Postoperative Death in All Patients Operated on for AV Canal (n = 294)

Variables	β ± SE*	Risk Ratio	p Value
Model with all variables selected by univariate analysis			
Constant	− 1.39 ± 0.4771		0.035
Single papillary muscle	1.62 ± 0.45	5.07	0.0003
Date of procedure (by day from January 1, 1984)	− 0.0004 ± 0.0002	0.9996	0.012
Postoperative infections	0.5 ± 0.43	1.65	0.002
Postoperative AV valve regurgitation	1.16 ± 0.64	3.18	0.031
Systolic pulmonary artery pressure > 25 mm Hg	1.3 ± 0.85	3.67	0.0015
Down syndrome	0.002 ± 0.001	1.002	0.011
Variables not reaching significance level in this model			
Age at operation			0.56
iNO administration			0.81
Reoperation during the same hospital admission			0.11
Low weight for age			0.22
AV canal type			0.56
Aortic cross-clamping time			0.84

*Logistic parameter obtained by stepwise multiple logistic regression analysis.

of a retrospective study, we thought that a comparison of homogeneous groups of patients could provide valuable information on the impact on mortality associated with iNO administration. In order to restrain the various factors that could invalidate a comparison between patients having received iNO and a retrospective group of patients that had not received this treatment, we attempted to control the variables that could induce a bias.[27] Therefore, we decided to do the following: (1) to select a single cardiac defect such as AV canal because it is frequently associated with POPH and it is relatively common, therefore providing a substantial population of patients; (2) to use an unequivocal set of criterion to enter the study; (3) to adopt an "intention-to-treat" design avoiding to restrain the analysis to any retrospectively defined subgroup of patient; and (4) to identify mortality risk factors in this population prior to comparing patients having received iNO with those who received conventional treatment.

The accuracy of pulmonary artery pressure measurements was probably not consistent over time. Nevertheless, this limitation is unlikely to have introduce any bias in the analysis for the following reasons: (1) the technique of pulmonary pressure measurement did not exert any effect on the mortality rate; (2) the selected inclusion criteria was based not only on pulmonary artery pressure measurements but also on clinical tolerance of POPH assessed by oxygen blood saturations. Actually, all patients selected with these criteria received a treatment for pulmonary hypertension, suggesting that these criteria appropriately reflected the clinical status of the included children. Moreover the similarity of the probability of mortality, assessed with the PRISM score in the two subgroups, suggests that the retrospective selection of patients is unlikely to have induced a significant bias with regard to mortality.

Finally, before considering administration of iNO, the multivariate analysis took into account several other variables found to be risk factors for mortality. The low significance value of the constant effect of this model ($p = 0.74$) suggests that the entered variables were the actual major determinants of mortality in this population of patients.

Risk Factors for Death

Despite the fact that in our study a trend toward surgical correction of more complex cardiac lesions was associated with an increased incidence of infections, a negative logistic parameter for the date of procedure shows that mortality decreased with time. This trend has already been observed in two studies[11,12] involving patients operated for complete repair of AV canal defect, and is also confirmed in our multivariate analysis involving all patients operated from the AV canal (Table 4). Several factors may explain this phenomenon including more precise preoperative diagnoses or better intraoperative support: improvements in techniques of cardiopulmonary bypass, better myocardial protection using blood cardioplegia, ultrafiltration, and systematic use of aprotinin. Nevertheless, most patients operated for AV canal defect did not experience severe postoperative hypertension, and regarding the subgroup of patients with this complication, the date of operation appeared to be a risk factor for death only before administration of iNO entered the regression model. This suggests that the recent introduction of iNO exerts an important effect on the mortality reduction observed in these children.

As reported by Studer et al[12] and Hanley et al,[11] risk factors for death in the overall population of children operated on for AV canal defect are mainly related to date of operation or to morphologic variables as single papillary muscle or postoperative AV valve regurgitation. The similarity of the results obtained with either pulmonary artery pressure or with transpulmonary pressure gradient in our group of patients suggests that this latter complication exerted a limited role on the outcome and that the most important part of pulmonary artery hypertension was attributable to pulmonary vascular reactivity. Factors responsible for early postoperative death were essentially infection and pulmonary artery pressure. These results were common when conventional treatment of pulmonary hypertension was administered, with approximately 50% of mortality.[1] At this time, the administered vasodilators were probably responsible for an additional morbidity induced by tissue edema and systemic vasodilation.[1,28,29]

Sepsis

The relatively high incidence of sepsis that we have observed has been a noticeable cause of early postoperative death. Hopkins et al,[1] from the Great Ormond Street Hospital group, reported that infection was a frequent cause of death when long stay in the ICU was due to a prolonged mechanical ventilation for treating POPH crises. Infection has also been suspected to be favored by the chronic infections often observed in Down syndrome.[30] However, the infection rate and its effect on mortality that we observed at our center remain notably higher that those reported by other centers.[11,12] One potential reason for this higher sepsis incidence could be precarious nutritional status of many children as reflected by the selection of low weight for age as a

risk factor for infection. This may be due to the fact that numerous children are referred to our institution as a last resort from countries with poor economic conditions.

Effects of iNO

iNO has already been reported to be able to reduce pulmonary artery hypertension,[5,29,31,32] but also to decrease intrapulmonary shunting,[31] to improve arterial blood oxygen saturation,[5,29,31] and to decrease $Paco_2$ slightly.[33] Nevertheless the benefit of iNO administration should be maximal when pulmonary artery hypertension is the main physiopathologic aspect of a disease. A decrease in mortality associated with its administration should therefore have been especially expected in congenital heart defects in which pulmonary hypertension is likely to be responsible for death but usually does not persist more than a few days after surgical correction.[34,35] The efficacy of iNO seems to be markedly higher in this setting than in the adult forms of pulmonary hypertension.[5,29,31,36]

Our results suggest that administration of iNO decreases postoperative mortality rate in children with severe POPH down to a level similar to those observed in patients undergoing A-V canal complete repair without POPH (Fig 1). Despite the fact that $>$ 1,000 patients have been treated with iNO in our institution since March 1992, we chose to confine our study to patients with AV canal defect because this is a fairly common condition. Nevertheless, pulmonary hypertension occurring after AV canal correction is usually not as severe as that observed in some other congenital heart conditions like *truncus arteriosus,* interrupted aortic arch,[5] or anomalous pulmonary venous return.[6] Improvement in survival could therefore prove to be greater when iNO is administered to patients with these underlying heart defects.[6]

Conclusion

This study suggests that there is a strong probability for a reduction of early postoperative mortality associated with administration of iNO when severe pulmonary artery hypertension crisis occurs in children operated for complete repair of AV septal defects. A question to be answered is the theoretical possibility of significant side effects associated with prolonged administration of this agent. At present, we still have had no experience of acute iNO toxicity, and we have monitored the concentration of NO and NO_2 in the airway to avoid any overdosage. A prospective randomized trial would be required if side effects are reported by clinicians to warrant a closer scrutiny of the risk-benefit ratio. At present the potential benefit, the simplicity of administration, and the low cost of this treatment seem to outweigh the risk.

ACKNOWLEDGMENT: The authors thank Francesca Jackson from Ospedale Maggiore della Carità (Novara, Italy), Adeline Boucher and Susan Besnard from B.C.& A. (Brussels, Belgium) for their useful comments, and the entire staff of the Department of Cardiovascular Surgery at Laennec and Necker Hospitals for their active participation in the management of the studied patients during the last 20 years.

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