Nitric Oxide and Milrinone: Combined Effect on Pulmonary Circulation After Fontan-Type Procedure: A Prospective, Randomized Study

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Background. **Early morbidity and mortality after Fontan operations are related to the elevation of postoperative pulmonary vascular resistance. Inhalation of nitric oxide (iNO) and intravenous milrinone are two options capable of reducing pulmonary vascular resistance. We hypothesized that their combined use could maximally stabilize the pulmonary circulation after Fontan operation.**

Methods. **Forty-six patients with high pulmonary vascular resistance (transpulmonary pressure gradient >10 mm Hg or central venous pressure >15 mm Hg) and impaired oxygenation after Fontan operation were prospectively randomized into three groups: group Mil (n = 15, milrinone at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$), group iNO (n = 15, iNO at <20 ppm), and group iNO + Mil (n = 16, iNO plus Mil). Pulmonary hemodynamic and oxygenation changes were compared among the three groups.**

Results. **Inhalation of nitric oxide with milrinone led to (1) the most significant reduction of pulmonary vascular resistance (transpulmonary pressure gradient from 11.26 ± 1.40 mm Hg [baseline] to 7.93 ± 0.90 mm Hg [24-hour use] in group iNO + Mil versus from 11.10 ± 1.38 to 8.69 ± 0.86 mm Hg; $p = 0.048$ in group iNO and from 11.17 ± 1.41 mm Hg to 9.72 ± 1.32 mm Hg; $p < 0.001$ in group Mil); (2) the most significant improvement of arterial blood oxygenation (ratio of arterial oxygen partial pressure to inspired fraction of oxygen from 68.88 ± 14.09 to 131.25 ± 15.92 in group iNO + Mil versus from 70.07 ±14.24 to 120.20 ± 15.92; $p = 0.047$ in group iNO and from 72.60 ± 12.92 to 95.20 ± 13.49; $p < 0.001$ in group Mil). Time on mechanical ventilation was shortest in group iNO + Mil ($p = 0.043$).**

Conclusions. **Combined use of iNO and milrinone optimally stabilized pulmonary hemodynamics after Fontan operation.**

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The natural history of patients with complex cardiac lesions characterized by single-ventricle physiology is poor. For example, the 1-year mortality is greater than 50% for patients with heterotaxy syndrome (asplenia or polysplenia) [1]. The Fontan procedure (creation of a total cavopulmonary anastomosis thereby exposing the pulmonary vascular bed to flow without a hydraulic pump as the driving force) is a definitive palliation for single-ventricle physiology. Based on original development for treatment of children with tricuspid atresia, current indications for Fontan operation have been extended to basically all types of complex cardiac lesions not amenable for biventricular repair [2, 3]. In the absence or severe attenuation of pulsatile pulmonary blood flow within the Fontan circuit, elevation of pulmonary vascular resistance (PVR) has been widely recognized as one of the most important risk factors contributing to hemodynamic compromise and early mortality after surgery [4, 5]. As a result, maintenance of a low PVR becomes a major priority during the period of intensive care immediately after Fontan operation.

To meet this objective, inhalation of nitric oxide (iNO) has become the most preferred option [6], if available, as it can selectively reduce PVR by relaxing the smooth muscle without major negative impact on the systemic circulation because of its high affinity for hemoglobin after diffusion into the blood. However, clinical practices have also implied that its efficiency might not be sustainable during or after its withdrawal, which sometimes could lead to severe PVR rebound requiring its prolonged use [7–9].

Milrinone has long been proven to be an efficient medication for patients with preexisting pulmonary hypertension or depressed postoperative cardiac function as it can (1) relax vascular smooth muscle and (2) improve both systolic and diastolic cardiac function. Its usage has become a first-line choice for patients with various extents of pulmonary hypertension. Its efficiency as an adjunct to iNO for treatment of high PVR after a Fontan operation, however, has not been reported before.

The purpose of this study was to determine the early hemodynamic and oxygenation responses to iNO, milri-

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none (intravenous use), or both in patients with marked elevation of PVR after a Fontan operation.

Patients and Methods

The ethics committee of the hospital approved this study. Informed consents for the study were obtained from children's parents before initiation.

Patient Selection

Pediatric patients, who underwent modified fenestrated Fontan operation and suffered marked elevation of PVR (1) with no explainable causes (eg, low cardiac output, arrhythmia, and atrial-ventricular valve regurgitation) and (2) without response to conventional managements (ie, sedation, analgesia, and respiration adjustment so as to establish normal arterial carbon dioxide tension of about 40 mm Hg and an arterial pH of about 7.40) were enrolled in this study. The inclusion criteria for elevated PVR included patients whose transpulmonary pressure gradient (TPG, ie, the difference between central venous pressure [CVP] and left atrial pressure) was higher than 10 mm Hg or CVP was higher than 15 mm Hg with concomitant deterioration of arterial blood oxygen saturation (Sao_2 <85%) despite increased inspiratory oxygen fraction. Patients were assigned with random number allocation to iNO group (inhalation of NO), milrinone group (intravenous administration of milrinone), or iNO in conjunction with milrinone group (inhalation of NO and intravenous milrinone), immediately after they were determined to be a suitable candidate. The exclusion criteria of enrolled patients during the study were complications of major organ dysfunction, pulmonary infection, and conduit thrombosis.

Study Design

The following protocol was used for all patients: (1) baseline measurements of all variables (detailed in the following section), (2) administration of iNO (group iNO), milrinone (group Mil), or both (group iNO + Mil), (3) repeated measurements of variables at 4, 12, and 24 hours after initiation of respective medication strategies. To prevent confounding results, normal ventilation, stable oxygen inspiration fraction (60%), and one intravenous positive inotropic agent, ie, dopamine (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$), were continued throughout the study.

Drug Administration

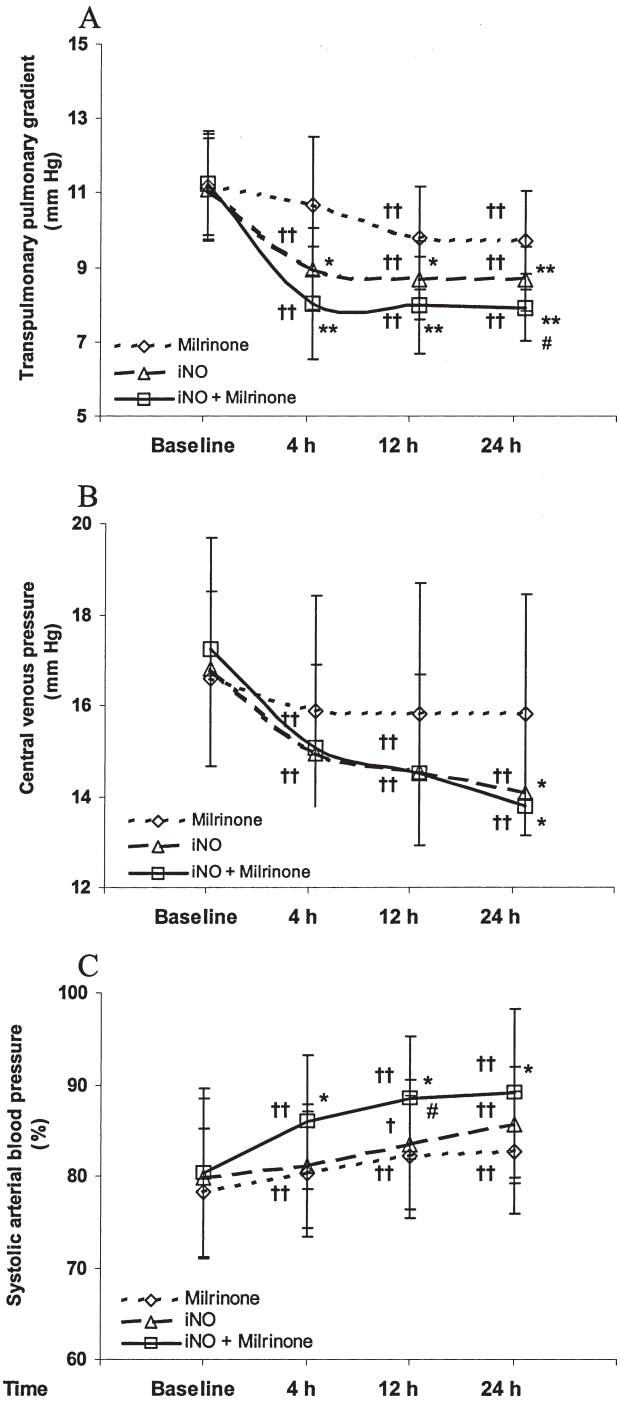
Patients assigned to groups iNO and iNO + Mil would inhale NO, which was stored as a mixture with nitrogen at 800 ppm NO (Shanghai Jiliang Gas Reference Co Ltd, Shanghai, China) in a cylinder. The gas was added into the part of the inspiratory circuit of the prototype Servo ventilator 300 NO-A (Siemens, Germany). Inhalation of NO began from 10 ppm with subsequent adjustment aimed at achieving greater than 20% improvement in TPG or greater than 10% Sao_2 with the lowest possible dose of iNO (1 to 20 ppm) within 2 hours after initiation. Peak nitrite and nitrate concentrations were continuously monitored during NO administration. Methemoglobin concentration in the blood was measured with a radiometer ABL 700 blood gas analyzer (Copenhagen, Denmark) at baseline and every 4 hours after the first exposure to iNO. Gradual weaning from iNO was attempted 24 hours after its use. If the patient's hemodynamics or Sao_2 deteriorated during iNO withdrawal, the weaning attempt was postponed until their recovery. Milrinone (Lunan Pharmaceutical Inc, Shandong, China), which would be used for patients in group Mil and iNO + Mil, was prepared from a vial of 5 mg/5 mL and infused continuously into the circulation at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$

Table 1. Preoperative and Operative Data of Patients Undergoing Modified Fontan Procedure

Variable	Milrinone (n = 15)	iNO (n = 15)	iNO + Milrinone (n = 16)	*p* Value
Demographic characteristics				
Age (y)	5.8 ± 2.1	5.5 ± 2.6	5.7 ± 2.8	0.97
Weight (kg)	19.1 ± 5.9	18.4 ± 6.5	20.0 ± 7.7	0.86
Sex (male/female)	8/7	6/9	9/7	0.63
Preoperative oxygen saturation (%)	77.2 ± 5.4	80.5 ± 5.2	78.5 ± 4.6	0.229
Preoperative diagnosis				
Tricuspid atresia	3/15	4/15	1/16	
Heterotaxy syndrome (asplenia or polysplenia)	5/15	6/15	8/16	
Double-outlet right ventricle	3/15	4/15	4/16	
Pulmonary atresia with intact ventricular septum	4/15	1/15	3/16	
Prior staging with Glenn	4/15	6/15	6/16	
Preoperative mPAP (mm Hg)	13.8 ± 2.9	14.4 ± 2.1	13.5 ± 4.1	0.786
Operative feature				
Lateral tunnel/extracardiac conduit	10/5	7/8	6/10	
Cardiopulmonary bypass time (min)	143 ± 69	138 ± 44	134 ± 55	0.929
Aortic cross-clamp time (min)	67.9 ± 36.1	61.1 ± 32.8	63.1 ± 29.6	0.871

iNO = inhalational nitric oxide; mPAP = mean pulmonary arterial pressure.

with an infusion pump. If there was no significant improvement in TPG (>10%) and Sao_2 (>5%) within 6 hours after its use, iNO was added to the therapeutic regimen and the patient was excluded from final statistical analysis. Milrinone would be gradually weaned from patients after uneventful extubation with consistently stable hemodynamic condition. The total intake and output volume was strictly balanced every day to exclude any other factors influencing results.



Measurements

PRIMARY OUTCOME. Primary outcomes to be measured included both pulmonary (TPG and CVP) and systemic hemodynamics as well as arterial blood oxygenation (oxygenation index, ie, ratio of arterial oxygen partial pressure to inspiratory oxygen fraction, and Sao_2). To achieve these measurements, catheters were placed inside the superior vena cava through the right internal jugular vein, the left atrium through the right superior pulmonary vein, and a peripheral systemic artery to allow their simultaneous measurements. Intravascular pressures were measured with fluid-filled transducers. Blood gas was sampled from the systemic arterial blood. Inspiratory oxygen fraction was acquired from the ventilator.

SECONDARY OUTCOME. To further evaluate the short-term effect of iNO or milrinone use, total time on mechanical ventilation and amount of chest drainage, as well as time in the intensive care unit and hospital, were evaluated.

Statistical Analysis

The data are expressed as the mean ± standard deviation for continuous variables. Statistical analysis was performed using statistical software (Statistica 6.0, Statsoft Inc, Tulsa, OK). Two-way analysis of variance for repeated measurements was used to test null hypotheses regarding the effects of between-subject factor (medication group), the within-subjects factor (time), and the interaction between them. If a statistically significant interaction between group and time was found, subsequent comparison among the groups at respective time points was performed by one-way analysis of variance followed by Duncan's multiple range test. Nominal variables were analyzed by nonparametric test. A difference was considered significant if the probability value was less than 0.05.

Results

During the study period, 1 patient in group iNO, 2 patients in group Mil, and 2 patients in group iNO + Mil were excluded based on the aforementioned exclusion

*Fig 1. Absolute change of transpulmonary pressure gradient (A) and central venous pressure (B) and percent change of systolic arterial blood pressure (C) after the use of intravenous milrinone (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, group Mil), inhalational nitric oxide (<20 ppm, group iNO), or both (group iNO + Mil). Data are expressed as mean ± standard deviation. Significant interactions existed between group and time in every variable ($p < 0.001$ for transpulmonary pressure gradient, $p = 0.021$ for central venous pressure and 0.008 for systolic arterial blood pressure; two-way analysis of variance for repeated measurements). Subsequent comparison was carried out with Duncan's multiple range test. Baseline is before administration of milrinone, inhalation of nitric oxide, or both, 4 h is 4 hours after medication, 12 h is 12 hours after medication, 24 h is 24 hours after medication. *$p < 0.05$; **$p < 0.01$ as compared with group Mil at respective time points. #$p < 0.05$ as compared with group iNO at respective time points. †$p < 0.05$; ††$p < 0.01$ as compared with respective baseline value in each group.*

criteria. Three patients in group Mil, who had to be shifted to combined therapy of iNO and milrinone because of severe hypoxemia and abnormally high TPG within 6 hours of the use of milrinone, were also excluded during the study period. In addition, 1 patient each in group Mil and group iNO + Mil were excluded because of severe thrombocytopenia. In total, 46 patients finished this study and were included for final statistical analysis. The three groups did not differ statistically with regard to demographic features and intraoperative maneuvering strategies including the time on cardiopulmonary bypass and aortic cross-clamp (Table 1). For patients receiving iNO (ie, group iNO and group iNO + Mil), methemoglobin concentration in the blood remained less than 2.5% and the expiratory nitrate concentration measured at an iNO dose of 20 ppm in 80% O_2 was 0.9 ppm. No patient had clinical signs of toxicity.

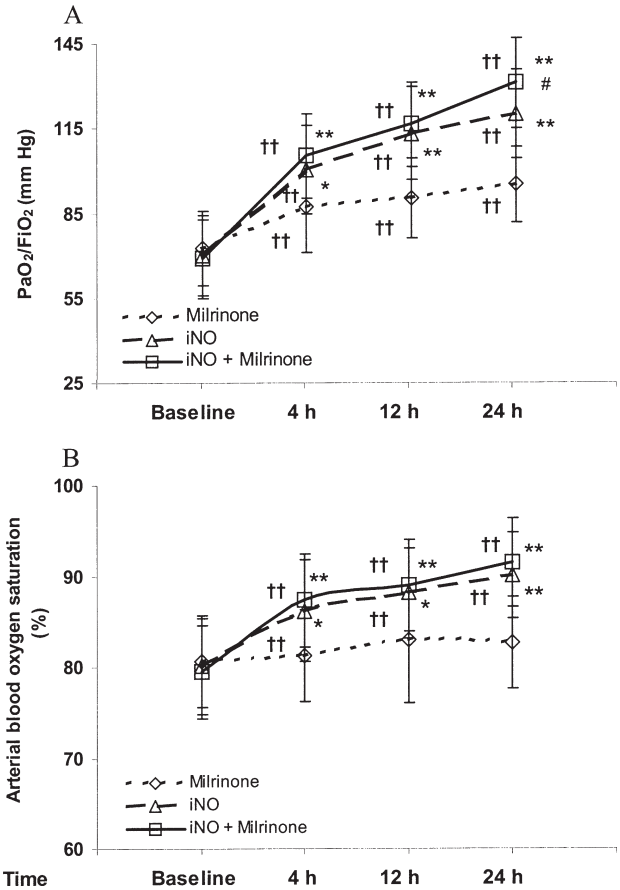


*Fig 2. Change of oxygenation index (PaO_2/FiO_2, A) and arterial blood oxygen saturation (B) after the use of intravenous milrinone (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, group Mil), inhalational nitric oxide (<20 ppm, group iNO), or both (group iNO + Mil). Data are expressed as mean ± standard deviation. Significant interactions existed between group and time in each variable ($p < 0.001$ in both variables; two-way analysis of variance for repeated measurements). Subsequent comparison was carried out with Duncan's multiple range test. Baseline is before administration of milrinone, inhalation of nitric oxide, or both, 4 h is 4 hours after medication, 12 h is 12 hours after medication, 24 h is 24 hours after medication. *$p < 0.05$; **$p < 0.01$ as compared with group Mil at respective time points. #$p < 0.05$ as compared with group iNO at respective time points. †$p < 0.05$; ††$p < 0.01$ as compared with respective baseline value in each group.*

Pulmonary and Systemic Hemodynamic Change

The change of TPG and CVP, variables reflecting PVR, is detailed in Figure 1. There was no significant difference among the three groups in baseline levels of either variable. Use of iNO alone (group iNO) or in conjunction with milrinone (group iNO + Mil) quickly reduced the PVR as both TPG and CVP decreased below 15 mm Hg and 10 mm Hg, respectively, within 4 hours after their use. However, use of milrinone alone (group Mil) led to the least and slowest decrement of PVR (though still significant in TPG). The maximal reduction of PVR usually appeared between 12 and 24 hours after administration of milrinone, iNO, or both. Beginning from 4 hours until 24 hours after administration of respective medications, the difference in CVP and TPG between group Mil and the other two groups achieved statistical significance. In addition, the difference in TPG between group iNO and group iNO + Mil at 24 hours also achieved statistical difference.

Simultaneously, the systemic circulation significantly improved with the use of milrinone, iNO, or both (Fig 1C). Similar to changes of TPG and CVP, such improvement was fastest and most significant in group iNO + Mil.

Arterial Blood Oxygenation

The change of oxygen index (ratio of arterial oxygen partial pressure to fraction of inspired oxygen) and Sao_2 is detailed in Figure 2. There was no significant difference among the three groups in baseline values of either variable. Use of iNO alone (group iNO) or in conjunction with milrinone (group iNO + Mil) quickly increased both variables within 4 hours after their use, which was in contrast to much slower improvement in patients receiving milrinone exclusively. Beginning from 4 hours until 24 hours after administration of respective medication, the difference in both variables between group Mil and the other two groups was statistically significant. Additionally, the difference in the ratio of arterial oxygen partial pressure to fraction of inspired oxygen between group iNO and group iNO + Mil at the 24th-hour measuring point also achieved statistical difference.

Mechanical Ventilation

Patients receiving both iNO and milrinone had the least time on mechanical ventilation (101.7 ± 36.5 hours in group iNO + Mil versus 129.2 ± 47.8 hours in group iNO and 133.6 ± 23.3 in group Mil; $p = 0.043$). One patient in group iNO + Mil and 3 patients in group iNO suffered CVP and TPG rebound during the process of iNO withdrawal ($p = 0.138$). In addition, 1 patient in each group iNO and iNO + Mil as well as 2 patients in group Mil had to be reintubated after weaning from the ventilator because of compromised blood oxygenation ($p = 0.739$).

Table 2. Other Secondary Outcomes Related to Inhalational Nitric Oxide or Milrinone

Variable	Group iNO	Group Mil	Group iNO + Mil	*p* Value
Chest drainage (mL)	282 ± 246	227 ± 95	191 ± 120	0.316
Time in ICU (days)	15.3 ± 9.5	13.7 ± 12.3	11.5 ± 10.8	0.619
Time in hospital (days)	24.7 ± 10.1	20.1 ± 14.2	18.6 ± 9.7	0.321

ICU = intensive care unit; iNO = inhalational nitric oxide; iNO + Mil = inhalational nitric oxide and milrinone; Mil = milrinone.

Other Secondary Outcomes

Other outcomes are detailed in Table 2. The total amount of chest drainage was not different among the three groups. Although the time in the intensive care unit and hospital tended to be shorter in group iNO + Mil, the difference was not statistically significant.

Comment

Because pulmonary blood flow becomes passive rather than driven by a ventricular pump with Fontan-type hemodynamics, pulmonary perfusion and, consequently, cardiac output are critically dependent on low PVR. However, PVR is most unstable in the early postoperative period mainly because of pulmonary edema and endothelial dysfunction. These pulmonary pathophysiologic changes are related to cardiopulmonary bypass–induced (1) systemic inflammation response syndrome resulting from activation of the alternate complement pathway, leukocytes, and endothelial cells releasing cytokines, proteases, and oxygen free radicals, and (2) lung reperfusion injury after temporary ischemia during cardiopulmonary bypass as it shunts the majority of blood flow away from the pulmonary arterial tree [10–12]. Pulmonary endothelial dysfunction is characterized by a shortage of endothelium-derived relaxation factor, ie, intrinsic NO, which helps relax the pulmonary vascular smooth muscle [13]. Furthermore, an interatrial fenestration was used to offset the negative effect of high PVR, but if the shunt had become excessive, the resulting hypoxemia may have further exacerbated elevated PVR as a result of hypoxemia-induced acid-base disturbance causing pulmonary vasoconstriction and caused low cardiac output syndrome.

Inhaled NO could induce selective pulmonary vasodilation in ventilated lung regions by increasing the levels of the vasodilator cyclic-guanosine 5′-monophosphate (cGMP) within the pulmonary vascular smooth muscle. As a result, iNO has been proposed as a therapeutic choice for patients with acutely elevated TPG and impaired arterial blood oxygenation after Fontan-type operation [14, 15]. However, clinical practices indicate that the response to iNO remains inconsistent in respective patients and may require higher dosage or prolonged exposure. The reasons for various individual responses to iNO exposure may involve (1) varied extent of preoperative pulmonary arteriole abnormalities that are not detectable based on current hemodynamic measurements [5]; (2) impaired preoperative ventricular mechanical property, especially, relaxation in patients with single-ventricular pathophysiology [2, 16]; and (3) varied extent of body response to cardiopulmonary bypass–induced inflammation and endothelial sensitivity to reperfusion after temporary ischemia. However, prolonged use or high dosage of iNO may easily incur various toxic side effects in human beings [17] and withdrawal rebound [7] owing to various mechanisms [8, 18]. As a result, every effort is made to minimize the length and dosage of iNO exposure for individual patients.

In most reported studies, the strategy aimed at minimizing iNO exposure and achieving early uneventful withdrawal focused on maintaining cGMP level inside the pulmonary vascular smooth muscle as several studies have found that exogenous NO exposure would inhibit the endogenous NO-cGMP cascades. For example, Black and colleagues [19] found that iNO use for 6 hours at 40 ppm in neonatal lambs could reduce endogenous NO synthase activity by approximately 40%, although twice the increment in plasma cGMP level was observed during the period of NO inhalation owing to stimulation of guanylate cyclase by exogenous NO. As a result, after acute withdrawal of NO, PVR bounced back with simultaneous significant decrement of plasma cGMP concentration, both of which did not return to normal levels until 60 minutes later with concomitant partial recovery of endogenous NO synthase [19]. Furthermore, Thelitz and associates [20] found that iNO use also reduced soluble guanylate cyclase level in pulmonary vascular smooth muscle and thus, decreased intracellular cGMP concentration immediately after its withdrawal. As a result, phosphodiesterase-5 inhibitors such as dipyridamole [21] and sildenafil [22] have been proposed as a method of choice to facilitate earlier withdrawal from iNO by inhibiting cGMP degradation.

Nevertheless, recent studies also indicated that iNO could also induce other important biochemical changes inside the pulmonary tissue related to its later withdrawal rebound. For example, Thelitz and coworkers [23] found that although iNO could lead to a decrement of lung tissue cyclic adenosine monophosphate concentrations by 25.3%, PVR remained stable after acute iNO withdrawal and lung tissue cyclic adenosine monophosphate concentrations were preserved during NO therapy in milrinone-treated lambs [23]. The first reported clinical study comparing the effects of iNO or milrinone for postoperative patients with congenital heart diseases causing pulmonary hypertension also appeared recently. In that report, Khazin and colleagues [24] found that combined use of both drugs could maximally lower PVR. In our study, we also observed that their combination could provide fastest and maximal effects in reducing PVR and, thus, ameliorate arterial blood oxygenation. Of course, use of milrinone did not only benefit the pulmo-

nary circulation as it also provided important lusitropic effects on the heart, which has extreme importance for the heart with single-ventricle pathophysiology. Penny and associates [25] used Doppler echocardiography and micromanometer pressure during steady states before bypass and after bypass to assess the effects of Fontan surgery. The perioperative increase in mass to volume ratio of the single ventricle was described as an "acute hypertrophic cardiomyopathy" with inherent diastolic dysfunction, quantified as prolongation of the time constant of isovolumic pressure decay. Garofalo and colleagues [2] further reported the ventricle had significantly higher stiffness immediately after Fontan operation as a result of cardiopulmonary bypass use. As such, milrinone could further improve the pulmonary circulation by increasing myocardial relaxation. Simultaneously, milrinone also helped improve myocardial contractility without further exhaustion of oxygen. Of course, the influence of milrinone on the systemic circulation was still a major concern in carrying out this study. As a result, we carefully initiated its intravenous administration using a maintenance dosage. The results indicated that this strategy provided a satisfactory outcome as indicated by a minor increment in systemic arterial blood pressure.

However, use of milrinone alone may not be enough to address severely elevated PVR as its effect appeared slower and weaker than iNO use. Three potential explanations are proposed here. Firstly, a limited amount of milrinone could enter the pulmonary circulation at the initial stage as a result of a significant shunt to the systemic circulation through the fenestration secondary to high PVR. As a result, its concentration in the pulmonary vascular wall would be low and fail to provide an immediate influence. Second, the pharmacodynamic potency within its therapeutic window in reducing PVR was less than NO. Third, the effective concentration in the blood was gradually increased as the maintenance dosage was directly used in our study.

Our study had several limitations. Perioperative histologic and immunohistochemical analyses of lung and cardiac tissue were not performed. Also, we did not measure both cGMP and cyclic adenosine monophosphate levels in both tissue and blood. Finally, we did not continuously monitor cardiac systolic and diastolic function, which may have revealed the cardiac influence of both drugs.

In summary, this study demonstrated the benefits of the association of iNO and milrinone for patients exhibiting high PVR after the Fontan procedure. This association produced better and longer-lasting hemodynamic effects than iNO alone. By reducing iNO administration time, the association strategy might help minimize the risk of iNO-induced side effects in clinical practice. The hemodynamic improvement related to this pharmacologic approach might be of particular value in the management of patients with associated cardiac insufficiency.

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DISCUSSION

DR FRANK A. PIGULA (Boston, MA): I have one question. You documented an improvement in oxygenation. And maybe you presented it, but did you measure and report your mixed venous saturations, or is this all presumably an improvement in pulmonary function, pulmonary oxygenation, or did you see increases in your mixed venous saturations as well?

DR YANG: As we did not see significant difference regarding the venous oxygen saturation among the three groups, we didn't put the data into the report.

DR PIGULA: Because I'm just wondering if that is one way to look at cardiac output as a contributor with improved mixed venous saturations versus the pulmonary effect of the milrinone and nitric oxide?

DR YANG: We didn't find significant difference in this variable among the three groups.

DR CHRISTOPHER A. CALDARONE (Toronto, Canada): The dosage of milrinone is given as an infusion, but there wasn't any loading dose. I'm sure that you considered that. What were your considerations and why did you make the choice you did?

DR YANG: During our initial study, we found that a loading dose of milrinone before its subsequent continuous infusion led to severe hypotension in some patients. As a result, a maintenance dose was applied in this study. We suspected that milrinone (administered via a loading dose) was immediately shunted, to some extent, to the systemic circulation from the fenestration, a reason leading to severe hypotension. Inhalation of milrinone, instead of intravenous loading dose, might be helpful to prevent hypotension.