Clinical research

Responsiveness to inhaled nitric oxide is a predictor for mid-term survival in adult patients with congenital heart defects and pulmonary arterial hypertension

M.C. Post, S. Janssens, F. Van de Werf, W. Budts*

Department of Cardiology, University Hospital, Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium

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Background

It was previously demonstrated that in adults with congenital heart disease and pulmonary arterial hypertension and/or the Eisenmenger syndrome, the pulmonary circulation remained responsive to inhaled nitric oxide (iNO). We wanted to evaluate whether the responsiveness to iNO was related to mid-term outcome in these patients.

Methods

In 21 consecutive patients, total pulmonary vascular resistance (TPR) was measured at baseline, after 5 min iNO (80 ppm), and after NO withdrawal. Patients were considered responders when TPR was reduced by at least 20% during NO inhalation or when TPR increased by more than 10% after NO withdrawal. Responders and non-responders were followed prospectively and the primary endpoint of the study was cardiopulmonary death, the secondary endpoint the combination of death, need for treatment with prostacyclin or heart–lung transplantation. Kaplan–Meier survival curves for both groups were plotted and compared using log rank testing.

Results

Ten patients were considered responders (four male, median age 25 years, Q1 19 and Q3 66 years), while 11 patients did not respond (two male, median age 27 years, Q1 18 and Q3 40 years). The median follow-up time of the total group was 5.0 years (Q1 3.2 and Q3 5.7 years). Four of the non-responders died a cardiovascular death; none of the responders died. The difference in survival between responders and non-responders was statistically significant. For the secondary endpoint, no significant differences were found between both groups.

Conclusions

The responsiveness to inhaled NO in adult patients with pulmonary arterial hypertension and/or the Eisenmenger syndrome is related to mid-term outcome. These findings might be important for risk stratification and the choice of treatment in this specific patient population.

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* Corresponding author. Tel.: +32 16 344235; fax: +32 16 344240.
E-mail address: werner.budts@uz.kuleuven.ac.be (W. Budts).

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Introduction

Several congenital heart defects are characterized by a left-to-right shunt. If this shunt causes a high flow across the pulmonary vascular bed, it may lead to an increased pulmonary vascular resistance and irreversible pulmonary arterial hypertension. Moreover, when pulmonary artery pressure exceeds systemic pressure, right-to-left shunt evolving into the Eisenmenger syndrome may occur.1

Although the main goal in congenital heart disease is to preserve a low pulmonary vascular resistance, pulmonary arterial hypertension is not uncommon in adult congenital heart disease patients. When irreversible pulmonary arterial hypertension has developed, corrective surgery is no longer a therapeutic option. Therefore, optimal palliation is usually necessary to stabilize the physical status and to bridge heart–lung transplantation.5–8 Selective pulmonary vasodilators, including prostanoids, endothelin receptor antagonists, and sildenafil may be used to prevent further increase in pulmonary vascular resistance.5–8 Accurate survival information of patients with pulmonary arterial hypertension is important for further optimal therapeutic management.

The aim of this study was, therefore, to determine whether residual pulmonary vascular responsiveness to inhaled nitric oxide is predictive of mid-term survival in patients with pulmonary arterial hypertension and/or the Eisenmenger syndrome.

Methods

Patient selection

Between November 1996 and January 2000, 21 consecutive patients with an underlying congenital heart defect and pulmonary arterial hypertension (defined as a mean pressure of more than 25 mmHg at rest) or after a re-existing left-to-right shunt with or without the Eisenmenger syndrome, were included in the study. The patients were selected when they visited the adult congenital heart disease clinic for a routine check-up, or when they were hospitalised for cardiac or non-cardiac reasons. The minimum age for inclusion was 16 years. There were no exclusion criteria, except when an infection was present. Our group previously reported the selection of these patients when we evaluated residual pulmonary vascular responsiveness to inhaled nitric oxide (iNO).9 The institutional ethical committee approved this study and written informed consent was obtained in all patients.

Haemodynamic measurements

The protocols of NO inhalation and the catheterization procedure to obtain the haemodynamic measurements were previously reported.9 Briefly, pulmonary and systemic haemodynamic variables were measured at baseline, at the end of five minutes inhalation of 80 parts per million (ppm) NO and after recovery from 80 ppm NO inhalation. Total pulmonary vascular resistance (TPR) [mean pulmonary artery pressure (mean PAP) divided by cardiac output (CO)], was calculated for each time point. After the procedure the patients were divided into responders and non-responders. A responder was defined as a patient in whom TPR decreased more than 20% after inhalation of 80 ppm NO or increased more than 10% after NO withdrawal compared to baseline TPR.

Cardiac medication was discontinued the day before and immediately restarted after the haemodynamic measurements. Warfarin intake was discontinued for 4–5 days before the heart catheterization.

Outcome

All 21 patients were followed prospectively until April 2003. The clinical outcome data were based on the most recently available medical records. These data and the basic characteristics were compared between responders and non-responders. Cardiovascular death was defined as the primary endpoint of the study. Secondary endpoints were heart–lung transplantation or treatment with any type of a selective pulmonary vascular vasodilator (prostacyclin).

Statistical analysis

An original sample size of 41 subjects was calculated with a power of 80% for a two-sided type I error of 0.05. Follow-up time was scheduled for 10 years. The corresponding survival rates of the non-responder and responder group were estimated at 40% and 90%, respectively. Data analysis was performed halfway through the study (21 patients included, follow-up time of 5 years). Descriptive statistics were used to characterize patients and follow-up characteristics. Continuous variables with normal distribution were presented as mean (standard deviation). Median (first Q1 and third Q3 quartile) was used when normal distribution was absent. Repeated ANOVA was used to evaluate changes in the pulmonary haemodynamic characteristics of the entire study group at different time points (before, during, and after NO inhalation). The baseline characteristics between responders and non-responders were compared using the two-sided Student t-test, the χ² test, and the two-sided Mann–Whitney U test. Bonferroni correction was applied in case of multiple testing. The patients’ outcome was displayed by a Kaplan–Meier survival curve. Log rank testing was performed to evaluate differences in outcome between responders and non-responders. P < 0.05 was considered to be statistically significant. All statistical analyses were performed by using GB Stat software (version 8.0, Dynamic Microsystems, Inc).

Results

Patient characteristics

At the time of inclusion, the median age of the 21 included patients was 27 years (Q1 18 and Q3 51 years). There were six male and 15 female. The underlying congenital heart defects and the type of surgical intervention, if performed, are listed in Table 1. In the same table, medical treatment and changes in medical treatment during follow-up (except initiating prostacyclin therapy) are reported.

Haemodynamic measurements

Pulmonary haemodynamics (mean PAP, CO, TPR, oxygen saturation) at baseline, after 5 min of 80 ppm iNO and
after NO withdrawal are summarized in Table 2. For the global group no significant differences in pulmonary haemodynamics were observed at the different time points.

Ten patients were categorized as responders (four male and six female, median age 25 years, Q1 19 and Q3 66 years) of whom, in six, TPR decreased at least 20% after inhalation of 80 ppm NO. An increase in TPR of at least 10% after NO withdrawal was observed in 6 patients. Eleven patients were non-responders (two male and nine female, median age 27 years, Q1 18 and Q3 40 years). The demographic, haemodynamic, and some biochemical characteristics of both groups are summarized in Table 3. In the group of non-responders, three patients had a history of atrial flutter/fibrillation. One patient suffered from stroke and one patient was known with coronary atherosclerosis. In the group of responders, four patients were characterized by paroxysmal atrial flutter/fibrillation. Also in this group, one patient suffered from stroke and one was known to have diabetes mellitus. The changes in pulmonary haemodynamics of both groups are summarized in Table 4.

### Outcome

For each patient recent follow-up data could be obtained. The median follow-up time for the total group (responders and non-responders) was 5.0 years (Q1 3.2 and Q3 5.7 years) and the overall survival rate was 81.0% (Kaplan–Meier estimate). Four patients died in...
the non-responder group; two patients died because of terminal heart failure, one due to severe and uncontrollable haemoptisis, and one suffered sudden death.

The pre-defined primary endpoint of cardiovascular death occurred in four patients, all non-responders. Treatment with prostacyclin was given in six patients, equally split over both groups: three in the responder and another three in the non-responder group. Two patients, one responder and one non-responder, both initially treated with prostacyclin, underwent a heart–lung transplantation.

The median event-free time interval between the catheterization and the occurrence of the primary endpoint in the non-responder group was 3.9 years (Q1 1.8 and Q3 5.9 years) and in the responders 5.4 years (Q1 3.5 and Q3 5.7 years). Survival rate was 100% for the responders and 63.6% for the non-responders at 76 months of follow-up ($P = 0.04$) (Fig. 1).

The median event-free time interval between the catheterization and the occurrence of death or the need for treatment with prostacyclin or heart–lung transplantation was 2.4 years (Q1 0.2 and Q3 5.0 years), in the non-responder and 5.3 years (Q1 1.5 and Q3 5.7 years).

### Table 3: Demographic, haemodynamic, and biochemical characteristics of the responder and the non-responder group at baseline

<table>
<thead>
<tr>
<th></th>
<th>N-R</th>
<th>R</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>11</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>2/9</td>
<td>4/6</td>
<td>0.27$a$</td>
</tr>
<tr>
<td>Age (year)</td>
<td>27 (19/40)</td>
<td>25 (17/62)</td>
<td>0.81$b$</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>55.0 (10.9)</td>
<td>59.2 (15.2)</td>
<td>0.96$c$</td>
</tr>
<tr>
<td>Pulse rate (/min)</td>
<td>81 (10)</td>
<td>81 (13)</td>
<td>0.98$c$</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>83 (20)</td>
<td>100 (19)</td>
<td>0.11$c$</td>
</tr>
<tr>
<td>Capillary $O_2$ saturation (%)</td>
<td>85 (9)</td>
<td>91 (6)</td>
<td>0.07$c$</td>
</tr>
<tr>
<td>Mean PAP (mmHg)</td>
<td>81 (28)</td>
<td>65 (33)</td>
<td>0.25$c$</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>6.2 (4.4)</td>
<td>6.3 (2.6)</td>
<td>0.95$c$</td>
</tr>
<tr>
<td>TPR (Wood units)</td>
<td>19.2 (12.5)</td>
<td>13.3 (11.7)</td>
<td>0.28$c$</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>52 (3)</td>
<td>49 (4)</td>
<td>0.59$c$</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.0 (0.1)</td>
<td>1.0 (0.1)</td>
<td>0.74$c$</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>6.5 (0.7)</td>
<td>7.5 (0.8)</td>
<td>0.35$c$</td>
</tr>
</tbody>
</table>

Values are mean (standard deviation) and median -Q1/Q3- N-R, non-responder; R, responder; SBP, systemic blood pressure; PAP, pulmonary artery pressure; TPR, total pulmonary vascular resistance.

$a$ $z^2$ test.

$b$ Mann–Whitney $U$ test.

$c$ Unpaired $t$-test.

### Table 4: Pulmonary haemodynamics in the non-responder and responder group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>iNO (80 ppm)</th>
<th>iNO (withdrawal)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N-R N-R R R</td>
<td>N-R N-R R R</td>
</tr>
<tr>
<td>Mean PAP (mmHg)</td>
<td>81 (28)</td>
<td>65 (33)</td>
<td>78 (25) 60 (36)</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>6.2 (4.4)</td>
<td>6.3 (2.6)</td>
<td>4.8 (2.5) 7.0 (2.9)</td>
</tr>
<tr>
<td>TPR (Woods units)</td>
<td>19.2 (12.5)</td>
<td>13.3 (11.7)</td>
<td>21.0 (11.1) 11.4 (11.6)</td>
</tr>
</tbody>
</table>

Values are mean (standard deviation). iNO, inhaled nitric oxide; ppm, parts per million; N-R, non-responder; R, responder; PAP, pulmonary artery pressure; TPR, total pulmonary vascular resistance.
Finally, we wanted to evaluate the outcome of those patients who received only palliative treatment. There were eight non-responders and seven responders after exclusion of all patients who received prostacyclin or underwent heart–lung transplantation. The median survival interval between the catheterization and the occurrence of cardiovascular death was 2.8 years (Q1 0.6 and Q3 5.9 years) for the non-responders and 5.5 years (Q1 5.0 and Q3 6.0 years) for the responders. Survival rates of 50.0% and 100% at 76 months of follow-up for the non-responders and responders, respectively, were recorded ($P = 0.04$).

Discussion

The main finding of this prospective study is that a better mid-term survival is obtained, in adult patients with congenital heart disease and pulmonary arterial hypertension, when pulmonary vascular reactivity, defined as responsiveness to inhaled NO, is preserved. This favorable outcome was observed irrespective of concomitant ongoing therapies.

Pulmonary arterial hypertension is characterized by imbalances between vasoconstricting and vasodilating mediators. Impaired production of NO, a potent endothelium-derived vasodilator, is strongly related to pulmonary arterial hypertension.\textsuperscript{10,11} Despite impaired NO production, residual responsiveness to inhaled NO was documented in children with pulmonary arterial hypertension and simple congenital heart defects.\textsuperscript{12,13} Moreover, the presence of residual pulmonary vasoreactivity has a proven predictive value for subsequent selective vasodilator therapy.\textsuperscript{14–16} Because risk stratification and accurate survival information of patients with pulmonary arterial hypertension are important for optimal therapeutic management, we evaluated pulmonary vascular responsiveness in adult patients with pulmonary arterial hypertension and congenital heart defects of varying complexity.

Several methodological issues need careful consideration in this small patient population when evaluating the prognostic information. First, we needed to reliably and reproducibly detect residual pulmonary vasoreactivity in this group of patients. We used a thermistor probe for continuous cardiac output measurement and could demonstrate residual pulmonary vasoreactivity in 29% and 35% of the patients during and after cessation of 80 ppm NO inhalation, respectively.\textsuperscript{9}

Second, we had to define pulmonary vascular responsiveness to acute vasodilator challenges. There is an ongoing debate on the definition of responsiveness in this context. In the present study a greater than 20% reduction of total pulmonary resistance was defined as responsiveness to NO and this was based on previously reported observations.\textsuperscript{17,18} However, the 10% increase in TPR to describe rebound responsiveness following cessation of inhaled NO was an arbitrarily chosen cut-off point. Unfortunately, there are no "clinical definitions" in the literature that describe rebound responsiveness, although the phenomenon per se reflects residual modulation of pulmonary vascular tone.

Third, the study population was by definition inhomogeneous as both simple and complex defects were included. Yet, in all except one patient the trigger for the development of pulmonary arterial hypertension was the high output across the pulmonary vasculature. In addition, simple and complex heart defects were equally distributed in both responders and non-responders. Therefore, these observations suggest that the responsiveness to inhaled NO, rather than the complexity of the underlying heart defect, was related to mid-term outcome. Moreover, due to the small numbers of patients in each group there was no statistically significant difference in any single characteristic between responders and non-responders. However, responders tended to have a somewhat higher body mass index, a higher systemic blood pressure, and a lower pulmonary artery pressure. Responders also tended to be less hypoxic and have less "heavy" medication at inclusion. Taken together, we therefore suspect that the non-responder group had a more advanced stage of disease with subsequently poorer prognosis, although this was not statistically proven.

Although chronic administration of vasodilators (prostacyclin, endothelin receptor antagonists, sildenafil) has been shown to improve functional status, exercise capacity, pulmonary haemodynamics, and even survival in patients with pulmonary hypertension,\textsuperscript{7,8,19,20} their long-term effect in congenital heart disease remains unknown. The only definitive treatment for patients with irreversible pulmonary hypertension or the Eisenmenger syndrome is lung transplantation with repair of the cardiac defect or combined heart–lung transplantation.\textsuperscript{21,22} The optimal timing for transplantation remains very difficult, as no specific guidelines are available.\textsuperscript{22} Moreover, clinical experience indicates that even in the absence of criteria for poor prognosis, outcome may be limited. The positive correlation between responsiveness to inhaled NO and mid-term survival in the present study may therefore also suggest that this parameter may be helpful in the decision process of transplantation.

As an important caveat, however, we realize that in addition to the heterogeneous study population and the methodological concerns, inclusion in the study was limited to patients who visited the outpatient clinic or who were hospitalized for cardiac or non-cardiac reasons. The latter may represent a selection bias and prohibit generalization of our findings. Prospective larger trials are required to address these important remaining questions.

In summary, responsiveness to inhaled NO in adult patients with pulmonary arterial hypertension and/or the Eisenmenger syndrome is related to mid-term outcome. Residual pulmonary vasoreactivity may be a valuable tool in risk stratification and in choosing specific treatment options for these patients.

References