Haemodynamic effects and potential clinical implications of inhaled nitric oxide during right heart catheterization in heart transplant candidates

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Abstract

Aims Right heart catheterization (RHC) is indicated in all candidates for heart transplantation (HT). An acute vasodilator challenge is recommended for those with pulmonary hypertension (PH) to assess its reversibility. The effects of inhaled nitric oxide (iNO) on pulmonary and systemic haemodynamics have been reported only in small series. Our purpose was to describe the response to iNO in a larger population and its potential clinical implications.

Methods and results From 210 RHC procedures performed between 2010 and 2019, vasodilator challenge with iNO was used in 108 patients, of which 66 had advanced heart failure undergoing assessment for HT (55±11 years old; 74.2% male gender; 43.9% ischaemic cardiomyopathy; left ventricular ejection fraction 28.4 ± 11.4%; and peak VO\textsubscript{2} 12.1 ± 3.0 mL/kg/min). iNO was administered through a tight-fitting facial mask regardless of baseline pulmonary pressures. Clinical endpoints (all-cause mortality and acute right heart failure) were assessed according to baseline haemodynamic findings over the available follow-up period. There were no side effects from iNO administration. Typical response consisted of a reduction in pulmonary vascular resistance, consequent to an increase in left ventricular filling pressures, no significant change in mean pulmonary artery pressure (resulting in a lower mean transpulmonary gradient) and a mild increase in cardiac output. Pulmonary arterial compliance increased significantly, whereas systemic vascular resistance was only mildly affected. In five cases (7.6%), pulmonary vascular resistance increased paradoxically. All-cause mortality and post-HT right heart failure events were overall low and similar in patients without PH or reversible PH.

Conclusions Vasodilator challenge with iNO is safe in advanced heart failure patients undergoing RHC prior to HT listing. It produces a reasonably predictable haemodynamic response, which occurs predominantly at the pulmonary circulation level. Clinical implications of iNO-induced reversibility may be relevant, but further systematic validation is warranted in larger cohorts.

Keywords Heart failure; Right heart catheterization; Heart transplantation; Pulmonary hypertension; Vasodilator challenge; Nitric oxide

Introduction

Severe pulmonary hypertension (PH) and elevated pulmonary vascular resistance (PVR) have been considered independent risk factors for post-operative right heart failure (RHF) and early death after heart transplantation (HT).\textsuperscript{1–5} Therefore, right heart catheterization (RHC) should be performed on all patients being considered for HT. Also, the extent of PVR reversibility with pulmonary vasodilators predicts better outcomes in candidates for HT, provided that systemic
hypotension is not induced.\textsuperscript{6} Thus an acute vasodilator challenge should be administered during RHC when the systolic pulmonary artery pressure (sPAP) is $\geq 50$ mmHg and either the transpulmonary gradient (TPG) is $\geq 15$ mmHg or the PVR is $>3$ Wood units (WU), while maintaining a systolic arterial pressure $>85$ mmHg.\textsuperscript{7,8} PH can then be distinguished into vasoreactive PH if the TPG can be reduced to $\leq 12$ to 15 mmHg and the PVR to $\leq 2.5$ to 3 WU; or persistent PH if, despite medical therapy, TPG and PVR fail to meet these targets.\textsuperscript{9} Several drugs have been used to evaluate the reversibility of PH, and none have shown superiority based on clinical outcomes. The effect of inhaled nitric oxide (iNO) during RHC in this specific population has been described solely in small cohorts.

The main purpose of the present study was to evaluate the haemodynamic response to iNO during RHC in a larger cohort of patients with advanced HF under consideration for HT. Also, as a secondary objective, we evaluated its potential implications in hard clinical outcomes—all-cause mortality and RHF after HT.

**Methods**

**Patient selection and inclusion criteria**

In this single-centre retrospective study, all patients referred for haemodynamic assessment with RHC, as part of HT evaluation, and undergoing an acute vasodilator challenge with iNO, between March 2010 and March 2019, were eligible. In patients with more than one RHC procedure over the study period, only the first study was included for the purpose of the present analysis. Patients were considered potential candidates for HT on the basis of severe HF symptoms (New York Heart Association functional class III or IV), episodes of fluid retention requiring high-dose intravenous diuretics, and/or low output requiring inotropes causing more than one unplanned visit or hospitalization in the last 12 months, objective evidence of severe cardiac dysfunction by transthoracic echocardiography, and severe impairment of functional capacity shown by cardiopulmonary exercise testing, despite optimal guideline-directed medical treatment.\textsuperscript{10} All patients provided written informed consent both for the procedure and data collection. The study conforms with the principles outlined in the *Declaration of Helsinki*, and approval by the institutional ethics committee was obtained.

**Right heart catheterization protocol and definition of haemodynamic parameters**

Clinically stable patients underwent RHC and left heart catheterization under local anaesthesia in a supine position, at rest. No premedication was administered other than intravenous heparin at a standard dose of 2500–5000 units. According to patient-specific characteristics and operator preference, venous access could be transfemoral or through an upper limb large vein. An aterial puncture (transradial or transfemoral) was obtained for measurement of central aortic and left ventricular (LV) pressure, as well as collection of a systemic arterial blood sample. Haemodynamic measurements were made at baseline—while breathing room air—and after breathing NO gas through a tight-fitting facial mask at a concentration of 20–40 parts per million (ppm), for at least 10 min. The iNO vasodilator challenge was performed during RHC regardless of the presence of elevated PAPs in the baseline study.

Heart rate, systemic arterial pressures, right atrial pressure (RAP), PAPs, pulmonary capillary wedge pressure (PCWP), and LV end diastolic pressure (LVEDP) were obtained. Measurements were made using standard fluid-filled catheters at end expiration, unless patients were unable to cooperate. The mean of three to five valid measurements was calculated for each parameter.

Cardiac output (CO) was calculated using the indirect Fick method, with oxygen consumption estimated through a nomogram based upon age, sex, age, and height. Systemic arterial and mixed venous oxygen saturations were measured at baseline and during steady-state iNO administration; at least two blood samples were collected at each site to minimize error. In all cases, an additional blood sample was collected to determine the haemoglobin level.

Mean PCWP was used as a surrogate of left atrial pressure. Systemic vascular resistance (SVR), mean TPG, PVR, pulmonary arterial compliance (PAC), pulmonary artery pulsatility index, and pulmonary arterial elastance were calculated using standard formulas, which are further detailed in the Supporting Information (*Table S1*).

**Definition of study clinical endpoints**

All-cause mortality was defined as death from any cause during the observation period. RHF after HT caused by PH was defined by haemodynamic variables (all of the following: RAP $>15$ mmHg, PCWP $<15$ mmHg, cardiac index $<2$ L/min/m$^2$, TPG $>15$ mmHg, and sPAP $>50$ mmHg) and need for right ventricular assist device during the 72-h post-HT.

**Statistical analysis**

Continuous variables are presented as means and standard deviations for data with normal distribution and as median and interquartile range for non-normally distributed data. Normal distribution of continuous data was assessed with the Kolmogorov–Smirnov test. Categorical variables are expressed as frequencies and percentages. Fisher’s exact test.
and paired t-test were used to compare categorical and normally distributed continuous data, respectively.

Survival curves were computed using the Kaplan–Meier method, and comparisons between groups were performed using the log-rank test.

All analyses were performed using IBM SPSS software version 23. Two-tailed P values < 0.05 were considered statistically significant.

Results

Study population

From the 209 patients who underwent RHC during this 9-year period, 66 fulfilled eligibility criteria for inclusion in the study (Figure 1).

Baseline characteristics are presented in Table 1. Most patients were of male gender (74.2%), and all were on New York Heart Association III/IV functional class. The most frequent causes of advanced HF, comprising 88% of all cases, were ischaemic, non-ischaemic dilated, and hypertrophic cardiomyopathy. A high proportion of patients (84.3%) was under optimal guideline-directed medical treatment, and most (92.5%) had a defibrillator device implanted, either alone or as part of ressincornization therapy. Only a small minority of the study population had an LV ejection fraction > 40%, and these were mainly patients with hypertrophic cardiomyopathy (70%). The mean values for the peak VO₂ and VE/VCO₂ slope were compatible with a Weber class C and a ventilatory class IV, respectively.

Procedural characteristics

The median duration of the RHC procedure was 59 [interquartile range (IQR) 45–83] min. Venous access was obtained through an antecubital vein in the majority of cases (64%), mostly with a 6 French introducer sheath (78.8%). The arterial access was mostly transradial (71.2%), using a 4 French introducer sheath in 57.5% of the patients. There were no significant vascular, bleeding, arrhythmic, or embolic events resulting from the RHC procedure.

Inhaled NO was administered at a mean dose of 35 ± 9 ppm for an average of 15 min. There were no complications during the vasodilator challenge, namely acute pulmonary oedema.

Haemodynamic profile and response to inhaled Nitric Oxide

The haemodynamic profile of the study population at baseline and after the acute vasodilator challenge with INO is
presented in Table 2 and Figure 2. Using a mean PAP (mPAP) cut-off of 20 mmHg, 98.5% of patients had PH at baseline. Mean baseline PCWP and LVEDP were similarly elevated (26.4 ± 7.6 and 25.5 ± 7.4 mmHg, respectively), PCWP being slightly higher. Baseline CO was low (2.9 ± 0.9 L/min), as expected in this population, and mean PVR was 4.9 ± 3.3 WU.

With the administration of iNO, the average haemodynamic response at the level of the left heart and the systemic circulation was characterized by a significant increase in both PCWP and LVEDP, a small increase in systemic and mean arterial pressures, and an unchanged SVR; altogether, these changes resulted in an mild increase in CO. In the right heart and pulmonary circulation, the haemodynamic response consisted of small reductions in RAP and sPAP and a largely unchanged mPAP. The net result was a significantly lower TPG, which, coupled with a marginally higher CO, lead to a relevant 43% reduction in PVR and an 18% increase in PAC (Table 2). In summary, the main overall haemodynamic effect was observed on the pulmonary vascular bed.

All but five patients displayed the haemodynamic response described previously. These patients showed a paradoxical response to the iNO vasodilator challenge, with an increase in PVR from 3.0 ± 1.5 to 4.1 ± 1.2 WU (P = 0.07). No baseline clinical features could reliably identify these patients. However, they had lower ejection fraction (23.6 ± 3.5% vs. 28.8 ± 11.7%; P = 0.03) and numerically lower baseline PVR (3.0 ± 1.5 vs. 5.0 ± 3.4 WU; P = 0.20). Interestingly, baseline PAC was higher in patients with a paradoxical response to iNO than in those with a standard response (1.9 ± 0.5 vs. 1.4 ± 0.7 mL/mmHg; P = 0.06), and the relative increase with iNO was much lower (5% vs. 19%, respectively). Clinical and haemodynamic characteristics of patients with standard vs. paradoxical response to iNO are represented in Table S2 in the Supporting Information.

Using a cut-off value for PVR of 3 WU, 68.2% (n = 45) of the patients in our study would have been classified as having elevated PVR (PVR of 6.2 ± 3.2 WU, TPG of 15.8 ± 6.9 mmHg, mPAP of 42.4 ± 10.1 mmHg, and sPAP of 63.6 ± 16.7 mmHg). Of these, 55.6% (n = 25) had significant residual vasoreactivity, with PVR lowered to <3 WU (mean 1.8 ± 0.8 WU) under iNO challenge, while maintaining a SAP > 85 mmHg. Patients who were unresponsive to iNO had higher baseline TPG and PVR. Haemodynamic and clinical features of patients with elevated baseline PVR, with and without response to iNO, are represented in Table S3.

Patients with hypertrophic cardiomyopathy (n = 13) had higher baseline PVR than non-hypertrophic cardiomyopathy patients (7.2 ± 5.4 vs. 4.3 ± 2.3 WU) but responded similarly to iNO.

Table 2: Haemodynamic profile at baseline and after inhaled Nitric Oxide in the study population (n = 66)

| Variable (mean ± SD) (n = 66) | Baseline | iNO | P value |
|-------------------------------|----------|-----|--------|
| SAP (mmHg)                    | 100.5 ± 15.1 | 103.3 ± 14.4 | <0.01 |
| MAP (mmHg)                    | 79.0 ± 10.6  | 80.9 ± 10.0  | <0.01 |
| RAP (mmHg)                    | 14.7 ± 6.5   | 13.4 ± 6.7   | <0.01 |
| sPAP (mmHg)                   | 58.5 ± 17.6  | 56.2 ± 16.0  | <0.01 |
| dPAP (mmHg)                   | 26.5 ± 7.5   | 26.5 ± 7.4   | 0.97  |
| mPAP (mmHg)                   | 39.4 ± 10.7  | 38.5 ± 10.1  | 0.11  |
| PAPp (mmHg)                   | 32.0 ± 12.7  | 29.9 ± 11.5  | <0.01 |
| Papi (mmHg)                   | 2.6 ± 1.8    | 2.7 ± 1.8    | 0.49  |
| PCWP (mmHg)                   | 26.4 ± 7.3   | 30.7 ± 9.1   | <0.01 |
| LVEDP (mmHg)                  | 25.4 ± 7.3   | 28.0 ± 8.3   | <0.01 |
| TPG (mmHg)                    | 12.9 ± 7.2   | 8.0 ± 5.8    | <0.01 |
| CO (L/min)                    | 2.9 ± 0.9    | 3.1 ± 1.1    | <0.01 |
| SV (mL)                       | 41.9 ± 15.0  | 45.4 ± 18.1  | <0.01 |
| CI (L/min/m²)                 | 1.6 ± 0.4    | 1.7 ± 0.6    | <0.01 |
| PAC (mL/mmHg)                 | 1.4 ± 0.7    | 1.7 ± 1.0    | <0.01 |
| PAE (mmHg/mL)                 | 1.6 ± 0.7    | 1.5 ± 0.9    | 0.17  |
| PVR (Wood units)              | 4.9 ± 3.3    | 2.8 ± 2.4    | <0.01 |
| Pulmonary R-C product         | 5.9 ± 2.6    | 4.0 ± 2.7    | <0.01 |
| SVR (dyn·seg·cm⁻⁵)            | 1861.9 ± 800.3 | 1964.6 ± 812.5 | 0.07  |

Cl, cardiac index; CO, cardiac output; dPAP, diastolic pulmonary arterial pressure; LVEDP, left ventricular end-diastolic pressure; MAP, mean arterial pressure; mPAP, mean pulmonary arterial pressure; NO, nitric oxide; PAC, pulmonary arterial compliance; PAE, pulmonary arterial elastance; PApi, pulmonary artery pulsatility index; PAPp, pulmonary arterial pulse pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SAP, systolic arterial pressure; sPAP, systolic pulmonary arterial pressure; SVR, systemic vascular resistance; TPG, transpulmonary gradient.

Relationship between haemodynamic findings, inhaled NO response, and clinical outcomes

From the 66 patients included in our analysis, 21 underwent HT. The median time between RHC and HT was 8.8 months (IQR 2.7–15.4). Baseline characteristics of patients who underwent HT vs. those who stayed listed are represented in Table S4. PVR, TPG, and sPAP in patients undergoing HT were 4.6 ± 3.4 WU, 11.4 ± 5.1 mmHg, and 60.3 ± 17.0 mmHg, respectively. Over a median follow-up of 25.9 months (IQR 16.1–42.4) after HT, all-cause mortality in patients with baseline PVR ≤ 3 WU or with baseline PVR > 3 WU but responsive to iNO (PVR < 3 WU under iNO challenge) was 13.3%, as compared with 33.3% in those without reversibility (P = 0.29) (Figure 3). All-cause mortality in the group with high baseline PVR (>3 WU) that responded favourably to iNO challenge was 14.3%. Incidence of RHF after HT was numerically lower in those with reversible high PVR (6.7% vs. 33.3%; P = NS)—further detailed in the Supporting Information (Table S5). From all relevant baseline haemodynamic parameters, we were unable to identify independent predictors of all-cause mortality or RHF.

In the 45 patients who remained listed, all-cause mortality was 42.2% (n = 19) at a median follow-up of 8.7 months (IQR 3.7–19.7).
Discussion

PH due to left heart disease (LHD) is believed to be the most common cause of PH and is invariably associated with greater disability and decreased survival in patients with LHD.\textsuperscript{11-14} Its definition has been recently revised, combining an mPAP $>20$ mmHg plus a PCWP $>15$ mmHg. This haemodynamic definition further distinguishes isolated post-capillary PH and combined pre-capillary and post-capillary PH.\textsuperscript{15}

As previously stated, elevated PVR and TPG (i.e. combined pre-capillary and post-capillary PH) prior to HT have been associated with marked increases in post-transplant mortality rates.\textsuperscript{1-5} Previous studies, however, have shown that patients with LHD and concomitant PH that can be reversed with pulmonary vasodilators during RHC may have post-HT outcomes...
similar to those without PH at baseline. Therefore, RHC is recommended before HT, and a vasodilator challenge is generally recommended in patients with sPAP ≥ 50 mmHg and TPG ≥ 15 mmHg or PVR > 3 WU. If the PVR can be reduced to ≤2.5 WU during a vasodilator test but the systolic arterial pressure (SAP) falls to ≤85 mmHg, the patient remains at high risk of RHF and mortality after HT.6

There is no consensus as to which is the pharmacologic challenge of choice to assess vasoreactivity during the RHC of HT candidates. Multiple drugs have been used in clinical practice for this purpose, namely sodium nitroprusside, nitroglycerin, nitric oxide, iloprost, prostacyclin, prostaglandin E, sildenafil, milrinone, dobutamine, and niseritide. Also, both the extent to which haemodynamic effects occur as well as the most affected parameters actually differ between agents. Published reports on this subject consist mainly of single centre studies, usually with a small number of patients. As such, the choice of a specific agent will generally depend on local experience, availability, and, sometimes, also its cost.

Broadly speaking, the basic purpose of any testing in this setting is to obtain some type of assessment of the degree of afterload to which the right ventricle will be subjected after HT, when normalization of left heart-dependent haemodynamics is expected to occur. Conceptually, this could be better simulated by an increase in CO and a decrease in left atrial pressure. This haemodynamic condition can be theoretically simulated by systemic vasodilatation and enhanced cardiac performance, such as that obtained with dobutamine for example. However, the extent of the response would necessarily be dependent on the residual LV contractile reserve, which can be somewhat unpredictable, and thus render the estimation of the optimal response of the pulmonary vascular bed less reliable.

To the best of our knowledge, the present study represents the largest report on the acute haemodynamic effects of iNO in a cohort of HT candidates undergoing RHC. Furthermore, we provide information on clinical outcomes that may be linked to the haemodynamic findings.

Overall, our results mirror the findings of prior studies using iNO in this setting. During the vasodilator test, patients experienced significant reductions of the mean TPG and PVR. Mean PCWP and LVEDP both increased significantly with iNO, and no major effect was seen on SVR. These effects can largely be explained by a proeminent reduction in the resistive component of right ventricular afterload, resulting in an increased filling to a non-compliant LV and decompression of the right atrium. The high selectivity of iNO for the pulmonary vascular bed, with little effect on systemic arterial pressure or SVR, might explain why LV filling pressures rise with iNO as opposed to other agents. A previous meta-analysis that included 20 studies addressing this issue compared the effects of the most commonly used drugs on pulmonary haemodynamics. It was found that, when compared with all other drugs (which decreased PCWP), iNO had an opposite effect producing a very significant increase on PCWP. A previous report actually described the occurrence of acute pulmonary oedema in three patients resulting from this effect. In the present cohort, however, none of the patients developed clinically apparent pulmonary congestion or any other relevant side effects.

PVR only reflects the steady/fixed component of right ventricular afterload. It has been shown that, in patients with high filling pressures, the parabolic relationship of PVR and PAC (the so called R-C product) is shifted downward and to the left. Also, as shown in our data, PAC increased by a significant 18% with iNO (from 1.4 ± 0.7 to 1.7 ± 1.0 mL/mmHg), allowing mPAP to remain remarkably stable (Table 2 and Figure 2). The ability to increase compliance has important clinical implications. First, it can explain (at least in part) why these patients were able to accommodate a larger volume of blood in the pulmonary vascular bed without clinical congestion. Second, it may represent a haemodynamic correlate of the severity of structural remodelling of the pulmonary vasculature, and as such, this finding may be an important reason why patients in whom PVR decreases (and PAC increases) have a better clinical outcome. In fact, PAC has been shown to be more strongly associated with outcome than other traditional haemodynamic variables in a population with HF, regardless of the degree of PH.

Finally, considering baseline haemodynamics, 68.2% (n = 45) of our patients had a formal indication to perform a vasoreactivity test. Of these, 56.5% showed reversibility with iNO, achieving a PVR ≤ 3 WU (as per study definition).
while maintaining a SAP > 85 mmHg. These patients had a long-term all-cause mortality rate that was lower than in those without reversibility. Despite no definite conclusions that can be safely drawn because of low statistical power, these findings seem to suggest that iNO-induced reversibility of PVR can safely be integrated into decision algorithms to further refine the eligibility for HT of patients with PH and baseline PVR above the usual thresholds for proceeding with HT.

**Paradoxical response to inhaled NO**

A paradoxical increase in PVR with iNO occurred in 7.3% \( n = 5 \) of our cases. This finding has been previously reported in three published studies, in up to 31% of patients, but the mechanisms ultimately responsible for this unforeseen effect as well as its potential clinical implications remain unclear.\(^{23,35,36}\) The authors speculate that the paradoxical increase in PVR may actually provide a protective mechanism against very high filling pressures and overfilling of the pulmonary circulation, which result from the combination of extensive pulmonary bed vasodilatation and a failing LV working on the upper limit of the Frank–Starling curve. This would mean that, as preload increases during pulmonary vasodilation, the LV would be unable to further increase contractility and CO (as SVR stays remarkably stable with iNO), and PVR would then paradoxically increase at steady state to prevent pulmonary congestion. The fact that these patients had significantly lower LV ejection fraction, lower PVR, and higher PAC at baseline may support these observations (**Table S2**). Concomitantly, reduced left atrial compliance, mitral regurgitation, and pulmonary endotelial dysfunction could also play a role. As none of the patients with paradoxical iNO response underwent HT, we are unable to assess its potential clinical impact.

**Study strenghts and limitations**

Our study was conducted in a single centre and despite including a larger cohort than prior reports, it specifically reflects our experience and patient selection criteria both for HT listing and for performance of RHC. As such, our results may not be directly applicable to other populations.

In most cases, a high dose of iNO was used, and our data cannot inform on the effects of lower doses (10–20 ppm, as recommended in the guidelines\(^12\)), as well as shorter duration of administration protocols.

Only the indirect Fick method was used for CO calculation, with the inherent limitations of using a nomogram to estimate oxygen consumption and not real-time measurements of \( O_2 \) consumption.

Finally, the fact the we provide clinical outcomes as a function of invasive haemodynamics may be considered an important upside of our study. However, estimates should be interpreted with caution, as the small sample size and low number of events hinder definitive conclusions because of lack of statistical power. Still, numerical differences are consistent and may at least be regarded as reassuring.

**Conclusions**

Inhaled NO is a selective pulmonary vasodilator, which yields a reasonably predictable haemodynamic response in patients undergoing acute vasodilator challenge prior to HT listing. It can be used safely to identify those with residual pulmonary vascular reactivity (and reversible PH) who may still be eligible for HT with an acceptable clinical outcome.

**Conflict of interest**

None declared.

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No funding was provided.

**Supporting information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** Correlation between pulmonary capillary wedge pressure and left ventricular end-diastolic pressure at baseline and after inhaled nitric oxide.

**Table S1.** Formulas used for calculation of haemodynamic variables.

**Table S2.** Comparison of baseline clinical characteristics between patients with a standard and those with a paradoxical response to inhaled nitric oxide.

**Table S3.** Comparison of baseline clinical characteristics between patients with reversible pulmonary hypertension (pulmonary vascular resistance \( \leq 3 \) Wood units after inhaled nitric oxide) versus those with irreversible pulmonary hypertension (pulmonary vascular resistance \( > 3 \) Wood units after inhaled nitric oxide).

**Table S4.** Comparison of baseline clinical characteristics between transplanted patients and those on the waiting list.

**Table S5.** Relationship between haemodynamic findings and clinical outcomes.
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