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Inhaled Nitric Oxide Through a Noninvasive Ventilation Device to Assess Reversibility of Pulmonary Hypertension in Selecting Recipients For Heart Transplant

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ABSTRACT

Introduction. Pulmonary hypertension (PHT) is an independent risk factor for right ventricular failure and death after heart transplant. Nitric oxide (NO) is a powerful and selective vasodilator, indicated in this scenario, but its response is unpredictable. Thus, it should be assessed prior to the intervention. However, preoperative assessment has not been widespread due to its difficulties and risks.

Objective. We describe herein a pulmonary vasodilatory test with NO administered through a noninvasive ventilation (NIMV) device. We also assessed the effect of NO in patients with severe PHT owing to cardiac disease. Assessment of the utility of the test to select patients for heart transplant.

Methods. We enrolled 19 patients with severe PHT for a preoperative assessment for heart transplant. Thresholds used were as follows: systolic pulmonary arterial pressure (SPAP) ≥65 mm Hg, transpulmonary gradient (TPG) ≥15 mm Hg, and pulmonary vascular resistance (PVR) ≥4.5 Wood units (WU). NO was administered through a modified noninvasive ventilation device. Cardiac output and pulmonary pressures were measured simultaneously by right heart catheterization.

Results. All patients agreed to be enrolled in the test. No difficulties, interruptions, or severe complications happened in any case. Basal and NO average measured values were SPAP (74.16 and 57.95 mm Hg), PVR (7.5 and 3.7 WU), and TPG (23.25 and 12.58 mm Hg). The differences were significant ($P < .05$) for all three tests. We consider acceptable for heart transplant a response that reduces PHT to a moderate grade. Using these criteria 14 patients were accepted and 11 underwent heart transplant. Two deaths in the postoperative period were both secondary to mediastinal bleeding and not related to right ventricular failure.

Conclusions. A pulmonary vasodilatory test with NO administered through a NIMV device was feasible and useful to select suitable heart transplant recipients with severe pulmonary hypertension.

RIGHT VENTRICULAR failure plays an important role as a complication of heart transplant during the postoperative period. It can occasionally lead to cardiogenic shock and is responsible for a considerable part of the global mortality of the procedure.[1] It has been attributed to a synergistic action of two factors: primary graft failure, to which the right ventricle is particularly prone, and pulmonary hypertension (PHT), which increases the postload of this ventricle.[2]

We tackle the former by reducing ischemia time and improving organ preservation. The latter acts as an important independent risk factor. Consequently, it is considered a relative counterindication. Nevertheless, it is a temporary

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problem; normal heart performance reduces pulmonary congestion and vasoconstriction in a short time, thus improving PHT. It is a matter of surviving a critical period of time, sufficient to allow the graft to assume recipient haemodynamics. Vasodilators can contribute to solving this problem; however, their systemic effects limit their use in these patients, whose hemodynamic status is often critical.[3]

Nitric oxide (NO) is one of the most powerful and selective pulmonary vasodilators. It is physiologic. Its action can be almost limited to the pulmonary vascular tree when inhaled. However the variable response prevents us from knowing beforehand whether achieved pulmonary pressures would be aceptable to the implanted right ventricle.

All patients selection programs include a vasodilatory test selecting those with a better response.[4,5] To date, neither the use of NO nor its vasodilatory test have been widespread due to specific problems and risks related to its performance. Its gaseous nature and narrow therapeutic range (<40 parts per million), makes administration through a mechanical ventilator device mandatory. Because it is desirable to avoid sedation and orotracheal intubation in patients with hemodynamic compromise, we decided to use a noninvasive device specifically adapted to the needs and features of the test.[6,7]

We sought to develop and assess a preoperative vasodilatory test with NO for patients with severe PHT who were eligible to undergo heart transplant. Other targets were assessment of the response to NO in patients with severe PHT owing to heart failure and examination of our experience in heart transplant patients with severe PHT.

METHODS

In 50 months, we enrolled 19 patients with severe PHT from those being preoperatively assessed for heart transplant. Compulsory criteria were two out of three of the following: systolic pulmonary artery pressure (SPAP) ≥65 mm Hg, transpulmonary gradient (TPG) ≥15 mm Hg, and pulmonary vascular resistance (PVR) ≥4.5 Wood units (WU). All patients gave informed consent. They all underwent a test of NO inhalation, inhaling between 5 and 20 parts per million through a modified noninvasive mechanical ventilation (NIMV) device with an occlusive interface made of a mask specifically designed for this test. Patients were properly instructed in advance. Response was monitored by external piezoelectric transducer through a pulmonary artery catheter.

Adjustments in NIMV were those of conventional (invasive) volumetric ventilators with a flat flow profile and an occlusive interphase made of a mask, with a pneumatic bed fit on through headgear specifically developed for this test. Thus, spontaneous breathing modes at low pressure led to minimal leaks. Leaks were measured by the ventilator, getting stable flows and volumes that allowed fine administration of NO.

NO was administered by continuous flow through the inspiratory branch. The gas mixture was checked through a NO and NO_2 analyzer set in the inspiratory branch beyond the mixture chamber. Patients were instructed in advance by breathing air through the device until a stable minute volume with no leaks was achieved and the patient was comfortable to prevent interruption of the test after initiating NO administration.

RESULTS

All patients asked to undergo the test agreed to it. After having been instructed for less than 15 minutes, all patients coped well enough to perform the procedure. The test was well tolerated in all cases.

Patients with severe PHT showed a selective pulmonary vasodilatation that was quantified by the following parameters: average drop in SPAP (mm Hg), basal = 74.16 with NO = 57.95 difference = 16 (22%), 95% confidence interval (CI) 10.84 to 21.58 ($P < .005$); average drop in TPG (mm Hg), basal = 23.25 with NO = 12.58 difference, 11 (46%), 95% CI 7.34 to 13.99 ($P < .003$); and average drop in PVR (WU), basal = 7.5, with NO = 3.7, difference, 3.8 (50%), 95% CI 2.30 to 4.88 ($P < .0001$).

No relevant systemic event was detected, neither hemodynamic nor toxic. No significant changes in either preload or cardiac output were found. No technical problems, changes in dosages, or interruptions were noted during the procedure.

Fourteen patients (74%) improved PHT from severe to moderate during the administration of the drug, in at least two of the three known criteria, so they could be readmitted to the program.

Finally, 11 patients underwent heart transplant. Ischemia time was 201 ± 75 minutes; cardiopulmonary bypass time was 135 ± 30 minutes. ICU stay was (8.2 ± 5.1 days) (range, 4 to 21). Two patients died owing to major bleeding, but none was related to right ventricular failure. NO was administered during the postoperative period while on mechanical ventilation. The adaptative response of the right ventricle was controlled by transesophageal echocardiography. One month later right chamber pressures were: right atrium (RAP), 6.2 ± 3.4 and systolic right ventricular pressure (SRVP) 35 ± 8.6. Six months later were: RAP, 3.5 ± 2.1 mm Hg and SRVP, 24 ± 3.9 mm Hg.

DISCUSSION

A vasodilatory test with NO through a noninvasive ventilation device is feasible. It is well tolerated once the patient has been properly instructed. In the population assessed, the response was limited to the pulmonary vascular tree. Average responses were SPAP, 22%; TPG, 46%; and PVR, 50%. While on NO, 74% of patients improved their PHT from severe to moderate. Patients transplanted using this test had normal pulmonary vascular pressures at 6 months after discharge.

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