Modified INOvent for delivery of inhaled nitric oxide during cardiac MRI[☆]

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Abstract

Background: The aim of this study was to assess the feasibility of delivering NO through a modified system to allow clearance of the magnetic field and thus compatibility with cardiac magnetic resonance (CMR). Nitric oxide (NO) is an inhalational, selective pulmonary vasodilator with a wide range of applications in a variety of disease states, including diseases that affect the right ventricle. Accurate assessment of dynamic changes in right ventricular function necessitates CMR; however, delivery of NO is only possible using equipment that is not magnetic resonance imaging (MRI) compatible (INOvent delivery system, Ohmeda, Inc., Madison, WI, USA).

Methods: The INOvent delivery system was modified by using 35 ft. of standard oxygen tubing to allow NO delivery through an electrical conduit and into the MRI suite. The concentrations of oxygen (O₂), nitrogen dioxide (a harmful byproduct, NO₂) and NO were measured in triplicate using the built-in electrochemical analyzer on the INOvent. After confirmation of safety, the system was used to administer drug to a patient x, and dynamic MRI measurements were performed.

Results: When the standard INOvent was set to administer 40 ppm of NO, the mean/standard deviation of gas delivered was as follows: NO: 42/0 ppm; NO₂: 0.3/0.1 ppm; and O₂: 93/0 ppm. In comparison, the gas delivery of the modified INOvent was follows: NO: 41/0 ppm; NO₂: 0.5/0 ppm; and O₂: 93.7/0.6 ppm. During administration to an index patient with severe pulmonic insufficiency (PI), a measurable reduction in PI was observed by CMR.

Conclusions: Nitric oxide can be administered through 35 ft. of standard oxygen tubing without significantly affecting dose delivery. This technique has potential application in patients with right-sided structural heart disease for determination of dynamic physiological changes. © 2011 Elsevier Inc. All rights reserved.

Keywords: Modified INOvent; Inhaled nitric oxide; Cardiac MRI

1. Introduction

Cardiac magnetic resonance imaging (CMR) has emerged in recent years as the gold standard for detailed evaluation of

the right ventricle (RV) [1–5]. CMR can be used to assess both morphological and functional aspects of the RV and pulmonary vasculature [6], and as such has a wide range of applications in right heart disease. These include, but are not limited to, evaluation of pulmonary hypertension, RV systolic dysfunction, RV diastolic dysfunction and right-sided valvular disease [7–12].

Nitric oxide (NO) is an inhaled selective pulmonary vasodilator that decreases pulmonary vascular resistance and is commonly used for vasodilator challenges in patients with pulmonary hypertension [13–17]. Considering the anatomic specificity of this vasodilator and its ability to reduce RV afterload, acute challenges with NO

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could measurably modify disease states outside of pulmonary hypertension and assess the potential reversibility of pathologic sequelae. In fact, NO has been shown to measurably reduce RV diastolic dysfunction [18] and could theoretically have similar effects on right-sided valve disease. Regardless of the disease state that is being tested, the ideal modality for functional imaging of the right ventricle during such a vasodilator challenge would certainly be CMR. Unfortunately, NO is typically delivered through a specialized delivery system (INOvent delivery system, Ohmeda, Inc., Madison, WI, USA) that has ferromagnetic components and therefore is not compatible with magnetic resonance imaging (MRI). The aim of this study was to determine the feasibility of administering NO in the CMR environment through a modified delivery system.

2. Materials and methods

This study was performed with approval by the local institutional review board, and the patient gave individual, signed informed consent. The study and manuscript are also in compliance with the provisions of the Health Insurance Portability and Accountability Act (HIPAA) of 1996. All data were compiled and analyzed by using the JMP 8.0

software (SAS Institute, Inc., Cary, NC, USA). Means were compared using two-sided *t* tests and a *P* value $\leq .05$ was considered significant.

2.1. Modified NO delivery

The standard method for NO delivery has been previously described [17]. Medical-grade NO gas (INO Therapeutics, Madison, WI, USA) was delivered via the INOvent delivery system (Fig. 1A) from source tanks and flushed through to the patient using supplemental oxygen (O_2) flow at 5 L/min. The dose of NO (ppm) is controlled by the INOvent regulator and confirmed by the electrochemical analyzer incorporated into the INOvent system (Fig. 1C) by connection to the sample port (Fig. 1B). The INOvent's electrochemical analyzer has been previously used to determine drug concentrations in modified iNO delivery methods [19]. Concentrations of NO (ppm), nitrogen dioxide (a harmful byproduct, NO_2 , ppm) and O_2 (%) are continuously reported to the INOvent display from the analyzer (Fig. 1A).

As the INOvent is incompatible with the magnetic field in the MRI suite, we chose to extend the delivery tubing leading from the INOvent to the patient using five pieces of standard 7-ft. AirLife O_2 tubing connected by AirLife O_2 tubing connectors (Cardinal Health, Dublin, OH, USA) (Fig. 1D).

Fig. 1. INOvent delivery system (A), sample port (B), electrochemical analyzer (C) and modified sample port with O_2 tubing (D).

For the purpose of calibration, the tubing was looped back to INOvent and drug concentration was tested using the on-board electrochemical analyzer via factory-issued sampling line. For the purpose of drug administration to a patient, an extended delivery tube was routed through a shielded electrical conduit allowing the INOvent to remain safely outside the MRI suite.

To verify that the doses of delivered gases with the extended delivery tube were similar to the standard INOvent setup, we connected the electrochemical analyzer to the sample port at the end of the extended delivery tube (Fig. 1D). The INOvent regulator was set at standard doses of 10, 20, 40 and 80 ppm with an accompanying O₂ flow of 15 L/min. The higher O₂ flow rate was chosen in order to achieve adequate delivery through the extended tubing. Concentrations of delivered gas at each setting were measured in triplicate with both the standard and modified setups. Comparisons of NO, NO₂ and O₂ at the various dosage settings between the standard and modified INOvent settings were analyzed using two-tailed *t* tests of the means with a *P* < .05 assumed to be significant. For some measurements the range was too small to measure a standard deviation. As such, a *P* value was not reported for all comparisons.

2.2. Nitric oxide administration during CMR

CMR imaging was performed using a 1.5-T unit (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany) with a multi-element phased-array surface coil. The study was performed with the patient in the supine position using a phased-array surface coil as a receiver and electrocardiographic gating. Images were obtained during end-expiratory breath-holds.

Initially, multiplanar scout images were obtained using a steady-state free-precession (SSFP) technique, followed by axial SSFP images encompassing the heart and great vessels. Cine SSFP images were then acquired in two long-axis orientations (vertical long-axis and four-chamber) and subsequently in short-axis orientation encompassing both ventricles. Typically, 12 to 16 contiguous short-axis cine SSFP images were acquired from the atrioventricular valve plane through the cardiac apex to measure ventricular volumes.

The SSFP sequence used for cardiac gated cine imaging had the following acquisition parameters: TR/TE/flip, 2.8 ms/1.4 ms/65°; field of view (FOV), 320 mm; matrix, 160×160; slice thickness, 8 mm; slice gap, 0 mm; acquired voxel size (dimensions along the frequency, phase and slice encoding directions, respectively), 2.0×2.0×8.0 mm, and the reconstructed voxel size in the corresponding directions, 1.3×1.3×8.0 mm; and temporal resolution, 25–40 ms, depending on heart rate.

Following cine imaging phase-contrast, a retrospectively gated, velocity-encoded phase-contrast sequence was performed perpendicular to the long axis of the main pulmonary artery just proximal to the pulmonary artery bifurcation with

velocity-encoding initially set at 100 cm/s. If aliasing was noted, the velocity was progressively raised in 50 cm/s steps until aliasing disappeared.

The sequence had the following acquisition parameters: TR/TE/flip 5.0 ms/3.1 ms/30°; FOV, 300–380×240–360 mm; matrix, 256×128 (typical in-plane resolution, 2.3×1.3 mm); slice thickness, 6 mm; number of signal averages, 1; and temporal resolution, 25–35 ms, depending on heart rate. The typical breath-hold time ranged from 15 to 25 s. Patients were encouraged to hold their breath during the whole acquisition. If obvious breathing artifacts were noted, the acquisition was repeated until artifacts were eliminated.

After completing the initial baseline CMR, the participant received NO at 40 ppm through a non-rebreather mask connected to the modified INOvent with extended delivery tubing. This method of iNO delivery has an established safety record and is commonly used in acute testing with iNO [16,20]. After 4 min of NO administration (to achieve steady-state conditions), repeat cine imaging for ventricular volumes and function, and flow velocity mapping of the pulmonary valve were obtained identical to the baseline imaging.

Postprocessing and data measurements were completed off-line after transferring images to a commercially available workstation (Leonardo, Siemens Medical Solutions). There, RV volumes and function and pulmonary valve insufficiency were determined. Two independent readers made measurements with the average values between readers used.

From the stack of ventricular short-axis SSFP cine images, contours were drawn manually to delineate RV endo- and epicardial boundaries on the end-diastolic and end-systolic phases. From these, the end-diastolic (EDV) and end-systolic volumes (ESV) were computed and the following quantitative metrics derived: Stroke Volume (SV)=EDV–ESV; Ejection Fraction (EF)=SV/EDV; and Cardiac Output (CO)=SV*HR. For flow quantification data, the contours of the main PA were automatically traced on magnitude- and velocity-encoded images simultaneously with manual correction as needed. The following metrics were determined: forward flow volume, reverse (regurgitant) flow volume and regurgitant fraction calculated as [reverse flow volume/forward flow volume].

3. Results

3.1. Nitric oxide delivery with modified INOvent setup

Delivery of O₂ was similar between the standard and modified INOvent setups at each setting (Table 1). At a

Table 1
Mean O₂ delivery (%) for the standard and modified INOvent

	10 ppm	20 ppm	40 ppm	80 ppm
Standard	97±0	96±0	93±0	88.7±0.6
Modified	97±0	96±0	93.7±0.6	89±0
<i>P</i> value	–	–	.18	.42

Table 2

Mean NO₂ delivery (ppm) for the standard and modified INOvent

	10 ppm	20 ppm	40 ppm	80 ppm
Standard	0.2±0.2	0.23±0.1	0.33±0.1	0.73±0.2
Modified	0.27±0.2	0.33±0.1	0.5±0	1.5±0
<i>P</i> value	.69	.1	.04	.02

setting of 10 ppm NO, mean delivered O₂ was 97±0% in both the standard and modified INOvent. Similarly at the 20-ppm setting, mean O₂ was 96±0% with both the standard and modified INOvent setups. At a setting of 40 ppm NO, delivered O₂ in the standard setup yielded 93±0% O₂ and the modified INOvent delivered 93.7±0.6% (*P*=.18). At a setting of 80 ppm NO, the standard INOvent delivered 88.7±0.6% O₂ and the modified INOvent delivered 89±0% (*P*=.42).

NO₂ levels were similar between the standard and modified INOvent setups (Table 2). At a setting of 10 ppm NO, the standard INOvent delivered 0.2±0.2 ppm NO₂, while the modified setup delivered 0.27±0.2 ppm NO₂ (*P*=.69). At the 20-ppm NO setting, the standard INOvent delivered 0.23±0.1 ppm NO₂, while the modified INOvent delivered 0.33±0.1 ppm NO₂ (*P*=.1). At the 40-ppm setting, the standard INOvent delivered 0.33±0.1 ppm NO₂ and the modified INOvent delivered 0.5±0 ppm NO₂ (*P*=.04). At the 80-ppm NO setting, the standard INOvent delivered 0.73±0.2 ppm of NO₂, whereas the modified INOvent delivered 1.5±0 ppm NO₂ (*P*=.02).

Finally, the mean delivery of NO was also similar between the standard and modified setups (Table 3). At the 10-ppm NO setting, the standard INOvent delivered 10.5±0.9 ppm of NO and the modified INOvent delivered 10.1±0.9 ppm (*P*=.62). At the 20-ppm NO setting, the standard INOvent delivered 20.3±0.6 ppm of NO and the modified INOvent delivered 20±0 ppm NO (*P*=.42). At the 40-ppm NO setting, the standard INOvent delivered 42±0 ppm NO and the modified INOvent delivered 41±0 ppm NO. At the 80-ppm NO setting, the unmodified INOvent delivered 86±0 ppm of NO, while the modified INOvent delivered 85±0 ppm.

3.2. Evaluation of pulmonary valve insufficiency

The patient undergoing evaluation was a 21-year-old male with a history of complete tetralogy of Fallot repair at age 5 with resultant severe pulmonary insufficiency (PI), undergoing preoperative evaluation of his right heart. His BMI was 23.6 and baseline blood pressure was 146/71, pulse

Table 3

Mean NO delivery (ppm) for the standard and modified INOvent

	10 ppm	20 ppm	40 ppm	80 ppm
Standard	10.5±0.9	20.3±0.6	42±0	86±0
Modified	10.1±0.9	20±0	41±0	85±0
<i>P</i> value	.62	.42	—	—

Table 4

Cardiac magnetic resonance measurements

	Baseline CMR	CMR with NO	Difference (%)
End systolic volume (ml)	192	231	20
End diastolic volume (ml)	305	343	13
Stroke volume (ml)	113	112	1
Heart rate (bpm)	61	75	23
Cardiac Output (L/min)	6.9	8.4	22
Regurgitant volume (ml)	70	62	−10
Regurgitant fraction (%)	47.7	42.0	−12

was 71 and oxygen saturation was 99% on room air. The patient's NYHA function class was II.

The baseline scan was performed without complications. Right ventricular analysis revealed an end diastolic volume of 305 ml and an end systolic volume of 192 ml for a stroke volume of 113 ml. The patient's heart rate was 61 bpm, yielding a cardiac output of 6.9 L/min. The pulmonary regurgitant volume was 70 ml and the regurgitant fraction was 0.48.

With NO administration, the right ventricular end diastolic volume increased to 343 ml and the end systolic volume increased to 231 ml, giving an almost identical stroke volume of 112 ml. The heart rate modestly increased to 75, yielding a cardiac output of 8.4 L/min. The regurgitant volume decreased to 62 ml and the regurgitant fraction was decreased to 0.42, representing a 12% reduction in PI (Table 4).

There were no complications associated with NO administration or performance of the additional images. The subject also reported no adverse effects when contacted on the day after the procedure.

4. Discussion

We have demonstrated that NO can be safely and efficaciously administered during CMR. We have also shown that selective pulmonary vasodilation can reduce afterload mismatch across a compromised pulmonary valve and in turn reduce the degree of pulmonary valve insufficiency. The importance of our findings is twofold: First, by demonstrating that NO may be delivered in an MRI suite, we have opened the door to dynamic functional assessment of the RV. This technique may also prove useful in other structural and congenital heart lesions, as well as in pulmonary arterial hypertension. Second, this study suggests that selective pulmonary vasodilation may prove to be a novel therapeutic target in pulmonary valve disease. In order to assess the latter we are currently enrolling patients into a larger study designed to more definitively evaluate the effects of NO inhalation on PI after tetralogy of Fallot repair.

Our measurements indicate that the delivery of NO through a standard INOvent and our modified INOvent are virtually identical across a wide range of doses. O₂ delivery was similarly unchanged between the two delivery methods,

although the NO₂ level (a compound with potential pulmonary toxicity) was statistically increased with the modified INOvent setup at NO doses of 40 and 80 ppm. We hypothesize that the extended tubing increases the exposure time of NO (a highly reactive molecule) to O₂ and would thereby facilitate oxidation of NO to NO₂. The increased level of NO₂ exposure during the CMR is well below the occupational exposure limit of 5 ppm averaged over an 8-h period [21] or the 3-ppm threshold suggested by INO Therapeutics and may pose no significant risk to patients. However, the accuracy of the NO₂ measurement at 80 ppm is not certain as levels may be too high to meet the criteria in the FDA guidance document [22]. Due to this issue, potential toxicity and the fact that the sampling port is not proximal to the subject mask in the modified, we would recommend against administering iNO through this method at the 80-ppm setting as the NO₂ increment was substantial. Using a lower dose should not influence the efficacy of this assay as doses as low as 20 or 40 ppm are standard protocol in acute vasodilator assessment [23].

We were able to demonstrate a 12% drop in pulmonary regurgitation with the administration of NO in our index patient. Although this reduction appears modest, the half-life of NO has been estimated between 2 and 6 s [24], while the breath-hold sequence necessary to complete this study was approximately 25 s. The measured reduction in PI may therefore be much greater if continuous pulmonary vasodilation were achieved. These potential shortcomings should be evaluated in the future with a larger study cohort and longer-acting pulmonary vasodilators.

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