Timed response to inhaled nitric oxide in pulmonary hypertension

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive, debilitating, and frequently terminal disease of the pulmonary vasculature.[1] Over the past 20 years, the introduction of medications including calcium channel blockers (CCBs), phosphodiesterase-5 inhibitors (PDE5i), endothelin receptor antagonists (ERA), and prostacyclin therapies have significantly improved the treatment and prognosis of PAH.[2] Despite these advancements, however, many patients continue to suffer unacceptably high morbidity and mortality.[3] In light of this fact, it is notable that a subset (~5%–10%) of patients with idiopathic pulmonary arterial hypertension (IPAH) can respond to oral CCBs and have a significantly improved prognosis.[4]

The initiation of CCBs in patients with PAH, however, must be done with caution; unresponsive patients can experience dangerous and even fatal hemodynamic compromise.[5] In order to identify those patients in whom CCBs will be safe and potentially effective, it is essential that an acute vasodilator challenge be performed with a short-acting vasoactive agent such as adenosine, epoprostenol, or inhaled nitric oxide (iNO), iNO being the most common agent.[6-9] During this challenge, the patient's hemodynamic responses are carefully monitored with the aid of right heart catheterization (RHC). Under current recommendations, a patient is considered an acute vasodilator responder and appropriate for CCBs if the mean pulmonary arterial pressure (mPAP) falls by ≥10 mmHg to an absolute value <40 mmHg without a degradation in cardiac output (CO).[3]

Although the use of RHC with an acute vasodilator challenge is an accepted part of the evaluation in patients with PAH, little has been published with regard to its standardization and protocolization.[10] For instance, most investigations have focused on patients categorized into World Health Organization (WHO) group I disease with IPAH. However, recent publications suggest that patients with pulmonary hypertension (PH) diagnoses other than IPAH may benefit from acute vasodilator testing and the use of CCBs.[11,12] Other details regarding the protocolization of acute vasodilator challenge, such as the optimal length of time to adequately observe a patient for an acute vasodilatory response, are likewise unknown or unclear in the literature.

In the timed response to inhaled nitric oxide study, we examined, in patients with diverse PH diagnoses, the effect of iNO administered for acute vasoreactivity testing at 5 and 10 minutes. We performed a single-center, retrospective analysis of patients with suspected PH prospectively enrolled in a quality control initiative entailing RHC with acute vasodilator challenge and hemodynamic measurements recorded at 5 and 10 minutes. Our goal is to better define the length of time necessary for vasoreactivity testing in patients with PH.

METHODS

Patients referred for RHC to a large regional tertiary pulmonary hypertension center (University of Colorado Hospital) were evaluated. The study was approved by the Colorado Multiple Institutional Review Board (COMIRB 07-0018). As part of a previous quality control initiative enacted in the catheterization laboratory, participating physicians prospectively enrolled consecutive patients undergoing RHC for suspected pulmonary hypertension and measured hemodynamic data at 5 and 10 minutes follow-

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ing initiation of vasoreactivity testing. De-identified patient data from March 2005 to February 2006 were reviewed, and patients who had been part of this quality control initiative were identified. All patients with the diagnosis of PAH, who underwent vasoreactivity testing and had hemodynamic data recorded at 5 and 10 minutes during this time period, were included for analysis. Patients were defined as having PH if RHC demonstrated a mPAP >25 mmHg. It should be noted that patients with a resting pulmonary arterial occlusion pressure ≥15 mmHg were excluded from the quality control initiative and consequently this study. Patient demographic data, New York Heart Association (NYHA) class, and medical regimen were obtained from the medical record temporally closest to the RHC. Follow-up data regarding NYHA class, medications, and survival were retrospectively ascertained from the medical records. Patients were considered long-term CCB responders if they continued on CCBs for at least 1 year without additional medical PAH therapy and maintained an NYHA class I or II functional status.

RHC and iNO

All studies were performed at the University of Colorado Hospital in the cardiac catheterization laboratories using standard techniques. After informed consent was obtained, the internal jugular or femoral vein was cannulated and RHC was performed under fluoroscopy. Complete hemodynamic data were recorded using Witt (Philips Medical Systems) and MacLab (GE Medical Systems) hemodynamic recording systems. RHC measurements were obtained at baseline and then repeated at 5 and 10 minutes after initiation of iNO (40 ppm + 0.5 FiO2) via INOvent (INO Therapeutics) and face mask. CO was measured using the thermodilution methodology in all patients except those with structural heart disease, in whom the Fick method was used. In order to account for nonphysiologically relevant variation, a minimum of three measurements of CO were obtained and averaged at each time point. If these three measurements differed by greater than 10%, a total of five measurements were taken, the high and low discarded, and the remaining three averaged. For the purposes of this study, patients were classified as vasoresponsive using modified criteria based on the American College of Chest Physicians 2004 guidelines, which remain unchanged in the latest 2009 update.[13,14] A patient was considered an acute vasoreactive responder if there was a reduction of the mPAP ≥10 mmHg to an absolute value of mPAP <40 mmHg with maintenance of a normal CO or, if CO was below 4 L/min, no more than a 10% reduction in CO at the time the patient's mPAP parameters first became positive for vasoreactivity. This is in contrast to current guidelines, which state that CO must not decrease.[14] This modification was a pragmatic decision based on local clinical practices and sampling errors inherent in the repeat measurement of thermodilution CO.

Patients who met criteria for acute vasoreactivity were started on oral CCB therapy. Patients were defined as long-term responders if their NYHA class improved to or remained at I or II for ≥1 year on CCB monotherapy.[14,16]

Statistical analysis

All statistical analyses, including Student's *t* test, Fisher's exact test, and Bland-Altman analysis, were performed using GraphPad Prism, version 5.00, for Windows (GraphPad software, San Diego, CA; http://www.graphpad.com). *P* values of ≤0.05 were considered significant. A Bland-Altman analysis was used to assess for agreement between patient's mPAP and CO at 5 and 10 minutes of iNO.[16]

RESULTS

Fifty-two patients underwent RHC with iNO with timed acute vasoreactivity testing at 0, 5, and 10 minutes at our institution between March 2005 and February 2006. Mean age, race, sex, and hemodynamics were typical of patients referred for RHC and iNO challenge.[11] A majority of the patients were Caucasian, with a female : male ratio of 3 : 1 and a mean (±SD) patient age at the time of testing of 54.2 ± 14.2 years. A broad mix of PH diagnoses were represented: 6 with IPAH, 15 with associated pulmonary arterial hypertension (APAH), 5 with chronic thromboembolic pulmonary hypertension (CTEPH), 3 due to interstitial lung disease, 5 with underlying structural heart disease (ventricular septal defect, atrial septal defect, mitral valve disease, cardiomyopathy), 4 with multifactorial disease (obstructive sleep apnea/obesity hypoventilation syndrome [OSA/OHS], chronic obstructive pulmonary disease, left heart disease, and/or methamphetamine use), 6 with OSA/OHS, 5 with liver disease, and 3 with other causes of PH (HIV/Castleman's disease, myelodysplastic disorder, fibrosing mediastinitis). The mean (±SD) NYHA functional class of patients in the study was 2.4 (±0.5). The median (25%–75% quartiles) CO of all patients included for analysis was 3.9 L/min (3.1–5.2), mPAP 40 mmHg (34–50), pulmonary arterial occlusion pressure 9 mmHg (5.8–12.3), and pulmonary vascular resistance 7.7 (4.5–12.8) Woods units (Table 1).

A total of 7 patients (13%) were classified as acute vasoresponders (3 IPAH, 3 APAH, and 1 CTEPH). The mean (±SD) age of vasoresponsive patients was 44.3 ± 18.1 years, which was younger than the nonvasoresponsive patients. There were no significant differences in gender, NYHA class, or baseline hemodynamics found between respond-

Table 1. Demographics, diagnosis, New York Heart Association (NYHA) functional class, and baseline right heart catheterization data

Cohort/subjects	Vasoresponders	Nonresponders	*P*	All
n	7	45	. . .	52
Age, years	44.3 ± 18.1	55.8 ± 13.2	0.05	54.2 ± 14.3
Ethnicity			. . .	
Non-Hispanic white	6 (86)	31 (69)	. . .	37 (71)
Hispanic Latino	0	6 (13)	. . .	6 (11)
African American	1 (14)	6 (13)	. . .	7 (14)
Asian, Native American	0	2 (5)	. . .	2 (4)
Male gender	1 (14)	12 (27)	0.49	13 (25)
PH diagnosis				
IPAH	3 (43)	3 (7)	. . .	6 (11)
APAH-CREST/CTD	3 (43)	12 (26)	. . .	15 (29)
ILD	0	3 (7)	. . .	3 (5)
CTEPH	1 (14)	4 (9)	. . .	5 (10)
Structural heart disease	0	5 (11)	. . .	5 (10)
Multifactorial	0	4 (9)	. . .	4 (8)
OSA/OHS	0	6 (13)	. . .	6 (11)
Liver disease	0	5 (11)	. . .	5 (10)
Other	0	3 (7)	. . .	3 (5)
NYHA class				
Class I	0	3 (6)	. . .	3 (5)
Class II	4 (57)	25 (52)	. . .	30 (51)
Class III	3 (43)	15 (31)	. . .	21 (36)
Class IV	0	5 (11)	. . .	5 (8)
Mean NYHA class (+SD)	2.4 (0.5)	2.4 (0.8)	0.96	2.5 (0.7)
Baseline right heart catheterization data				
mPAP, mmHg	47 (45–50)	40 (33–48)	0.41	40 (34–50)
PAOP, mmHg	6 (5–9.5)	9 (6–12)	0.28	9 (5.8–11.3)
PVR, WU	12.8 (8.6–13.6)	7.6 (4.4–12.2)	0.67	7.7 (4.5–12.8)
CO, L/min	4.0 (3.7–4.5)	3.8 (3.0–5.3)	0.86	3.9 (3.1–5.2)

Note: Values are expressed as absolute number with percent of cohort, mean ± standard deviation, or median (25%–75% quartile). *P* values are calculated with Fisher's exact test. APAH: associated pulmonary arterial hypertension; CO: cardiac output; CREST/CTD: calcinosis, Raynaud's syndrome, esophageal dysmotility, sclerodactyly, and telangectasias/connective tissue diseases; CTEPH: chronic thromboembolic pulmonary hypertension; ILD: interstitial lung disease; IPAH: idiopathic pulmonary arterial hypertension; mPAP: mean pulmonary artery pressure; OSA/OHS: obstructive sleep apnea/obesity hypoventilation syndrome; PAOP: pulmonary arterial occlusion pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance.

ers and nonresponders. There did appear to be a higher than expected proportion of IPAH responders (3/6). Bone morphogenetic protein receptor type II genetic status of the patients in each group is unknown.

The RHC hemodynamic data for the 7 acute vasoresponsive patients is presented in its entirety (Table 2). Two patients (4% of all patients, 29% of all acute responders), patients 1 and 5, did not meet vasoresponsive criteria until 10 minutes of iNO. One patient (no. 5) had a drop in CO by 17% at 5 minutes, but the CO remained supranormal, with a cardiac index above 3 L/min/m^2 throughout testing. This patient was treated clinically as an acute vasoresponder and was included for analysis as such. The systemic blood pressure of the acute vasoresponders did not change significantly throughout testing ($P > 0.4$; Table S1; Tables S1, S2 available online).

To evaluate the agreement between hemodynamic measurements at 5 and 10 minutes after iNO institution, a

Table 2. Hemodynamic data of acute vasoresponsive patients

			CO, L/min			mPAP, mmHg			PAOP, mmHg			PVR, Woods units		
Patient	Diagnosis	Sex	Baseline	5 min	10 min	Baseline	5 min	10 min	Baseline	5 min	10 min	Baseline	5 min	10 min
1	IPAH	F	3.5	3.8	3.8	50	42	38	5	ND	5	12.86	ND	8.68
2	APAH	F	3.97	3.63	3.63	53	39	34	6	8	9	12.81	8.54	6.94
3	IPAH	F	4.02	3.67	3.63	47	21	21	8	ND	14	9.7	ND	1.93
4	CTEPH	M	2.93	3	2.77	51	32	33	5	9	5	14.25	7.67	10.12
5	APAH	F	7.27	6.47	6	33	24	23	11	8	8	3.03	2.47	2.5
6	APAH	F	4.23	4.2	4	46	36	34	14	11	11	7.57	5.95	5.75
7	IPAH	F	4.78	4.67	4.57	44	30	31	1	0	1	14.59	6.42	6.56

Note: Underlined mean pulmonary arterial pressures (mPAP) values indicate the time at which criteria were met for acute vasoresponsiveness. APAH: associated pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; CO: cardiac output; F: female; IPAH: idiopathic pulmonary arterial hypertension; M: male; ND: no data; PAOP: pulmonary arterial occlusion pressure; PVR: pulmonary vascular resistance.

Bland-Altman analysis was conducted (Fig. 1). Analysis of mPAP and CO in both the vasoresponsive patients and the nonresponsive patients at 5 and 10 minutes is presented graphically. On average, the mPAP of vasoresponders was 1.4 mmHg less at 10 minutes than at 5 minutes, while the average mPAP of nonresponders was unchanged (data not shown). There is a suggestion that the difference in mPAP at 5 and 10 minutes may become larger in vasoresponders as the mPAP increases; however, our sample size precludes us from drawing definitive conclusions. The

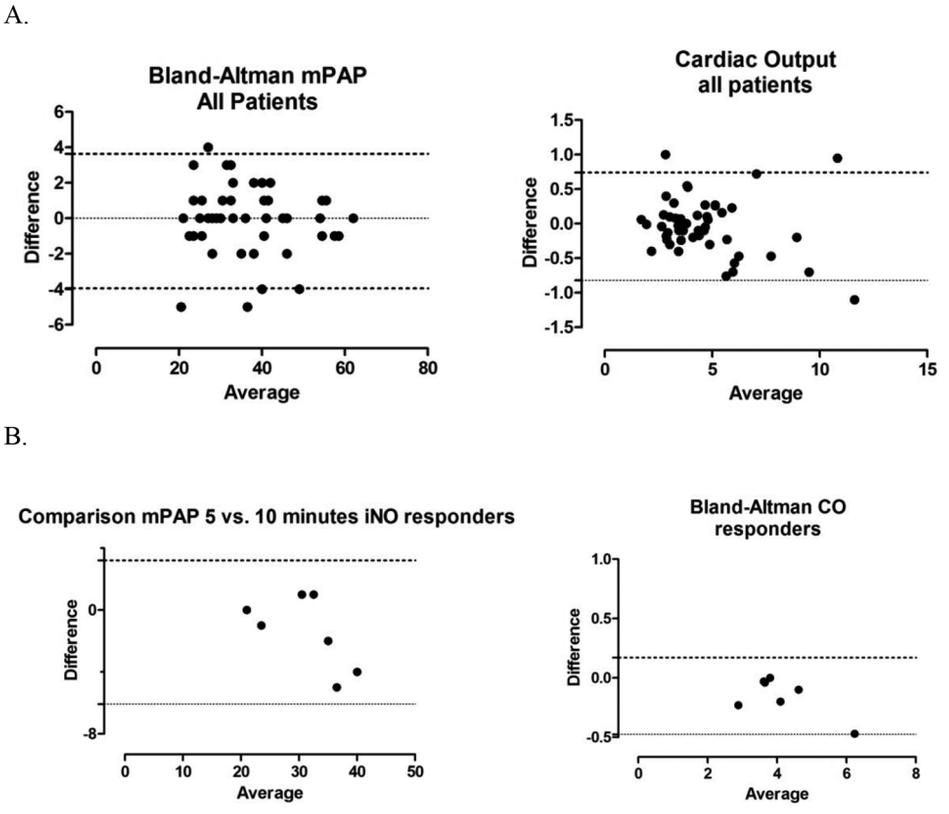

Figure 1. Bland-Altman analysis graphs. The difference between measurements of mean pulmonary arterial pressure (mPAP) and cardiac output (CO) made at 5 and 10 minutes. *A* includes all measurements from the entire cohort studied. *B* includes only those measurements made in acute vasoresponders. iNO: inhaled nitric oxide.

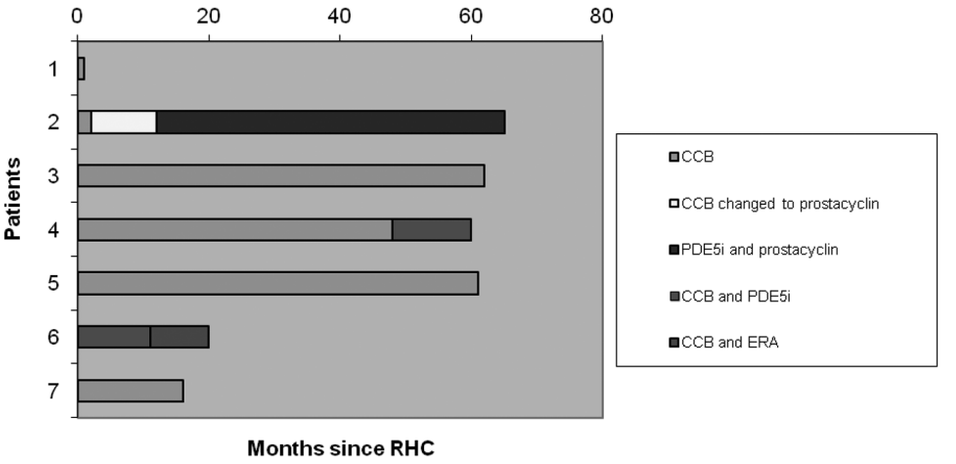

Figure 2. Treatment with pulmonary arterial hypertension (PAH) medications after catheterization. Patient 1 had no further follow-up at our institution after catheterization, patient 6 died of PAH complications 20 months after catheterization, and patient 7 had no further follow-up at our institution 16 months after catheterization. Patients 3, 4, 5, and 7 meet accepted criteria as long-term responders to calcium channel blockers (CCBs; New York Heart Association classes I and II and a CCB without additional therapy for at least 1 year). ERA: endothelin receptor antagonist; PDE5i: phosphodiesterase type 5 inhibitor; RHC: right heart catheterization. A color version of this figure is available online.

CO of vasoresponders was, on average, 0.15 L/min lower at 10 minutes than at 5 minutes. The average CO and mPAP of nonresponders were not significantly changed between 5 and 10 minutes (data not shown).

The medical charts of all 7 acute vasoresponders were reviewed for use of PAH-specific pharmacotherapy. A time line graphing these different therapies is presented in Figure 2. Dosages of PH-specific medications are provided in Table S2. One patient (no. 1) did not have complete data recorded over the time course considered in the study. One patient (no. 6) died of complications related to PAH approximately 20 months after catheterization. Four patients met criteria as long-term responders to CCB therapy, representing 57% of all vasoresponsive patients and 8% of the overall patient sample. One of the long-term responders (patient 5) did not meet acute vasoresponsive criteria until after 10 minutes of iNO. Interestingly, there was a diversity of PAH diagnoses for long-term CCB responders.

DISCUSSION

Diagnostic RHC is a necessary procedure to complete the evaluation and diagnosis of patients with presumed PAH.[14,15,18] To identify patients in whom oral CCBs can safely and effectively be used, assessment with an acute vasodilator challenge is recommended.[3,14] The identification of patients who have an acute vasodilator response is critical as it portends a significantly improved prognosis and represents a potentially large cost savings in their treatment (CCBs vs. PDE5i, ERA, or prostanoids). Despite this, there are no published guidelines outlining the standards by which the vasodilator challenge is administered and performed.[10] This raises concerns both academic and practical in trying to assess and apply findings in the published literature.

For instance, some authors note that although the current acute vasoresponsive criteria are specific in identifying patients who will be long-term CCB responders, they may be insufficiently sensitive and fail to identify some true responders. Indeed, Sitbon et al.,[16] upon whose paper the current vasoresponder criteria are based, found that 5 out of 38 long-term CCB responders (13%) did not meet the current acute vasoresponder criteria. Despite the implementation of current criteria, there is considerable variability in published acute vasoresponder rates, the frequency of which can range from as low as 4.5% to as high as 14%.[6,16,19,20] It is possible that these discrepancies may, in part, be explained by variation of vasodilator testing protocols and the length of time the vasodilator was administered. For example, previous work by Rich et al.[21] demonstrated considerable variability in pulmonary hemodynamics, both spontaneously and in response to vasodilators, over time. Without careful examination of the variables involved in vasodilator testing and a published consensus of protocols and standards, continued discrepancies may persist between institutions and in the published literature. In this study, we sought to determine whether the length of time a vasodilator challenge is performed would have an effect on categorizing patients as acute vasoresponders.

Overall, our study population appears to be similar to other published cohorts of patients with PAH undergoing RHC.[16,17] Thirteen percent of all patients in our study were found to be acute vasoresponders, and 8% went on to be long-term CCB responders. Our observed rates of acute and long-term responders are very similar to those published by Sitbon et al.[16] of 12.6% and 6.8%, respectively. An important difference in our study, however, is that patients with diagnoses other than IPAH were included for analysis. Two of the 4 long-term CCB responders were IPAH, while the other 2 were CTEPH and APAH. Although most prior studies have considered only IPAH,[6,16,19,20] two recent publications have identified acute vasoresponders in patients with nonidiopathic PH, and these patients may have similarly improved survival despite the underlying etiology of their disease. Arunthari et al.[11] published a cohort including 176 PH patients who underwent vasodilator challenge at their institution and found a high prevalence (10%–31%) of acute vasoresponders within most WHO groups of PH. More recently, Krasuski et al.[12] reported on 197 consecutive PH patients from two centers that underwent acute vasodilator testing with iNO. Seventy-seven of these patients were classified as acute vasoresponders, many of whom were not WHO group I patients. Acute response to vasodilator challenge predicted improved survival despite the underlying etiology of PH. In light of these recent publications, it appears that the inclusion of patients with diagnoses other than IPAH in vasodilator studies may be important as it provides data and insights into groups less frequently studied, perhaps identifying nonidiopathic patients with similarly improved prognoses, and may more accurately reflect clinical practice.

Our findings suggest that prolonging hemodynamic observations to at least 10 minutes may identify long-term CCB responders that may otherwise be missed with shorter observation periods. Furthermore, our study suggests that differences in vasodilator challenge protocols, specifically, the length of time observations are made, could potentially influence the sensitivity and specificity of the test. This observation could have important implications to ongoing clinical research and practice and serves to highlight the need for further studies and published guidelines to standardize testing between centers.

There are several limitations of this study that deserve consideration, including its retrospective nature, modest number of subjects, and single-center design. The patients included in this protocol represent a subset of the total patients undergoing acute vasodilator testing at our institution. Patients were consecutively and prospectively enrolled by participating providers into the quality control initiative, however, decreasing the likelihood of a selection bias. In addition, all patients and procedures were performed at a single referral center using only iNO, possibly limiting the generalizability of the findings. This may be especially true when alternative vasodilators are used, such as adenosine or epoprostenol.[6,22] Also, the benefits of further observation beyond 10 minutes of iNO were not addressed by our study. Future prospective studies will be needed to address these limitations and standardize protocols throughout institutions.

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