

observation provides potential mechanisms for reverse triggering that were previously unknown, such as the role of thoracic or diaphragmatic stretch receptors, a spinal reflex phenomenon, or the existence of a more complex spinal pattern generator. ■

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## Electric Plasma-generated Nitric Oxide: Hemodynamic Effects in Patients with Pulmonary Hypertension

To the Editor:

Inhaled nitric oxide (NO) is a selective pulmonary vasodilator (1) that is commonly used to perform diagnostic procedures and to treat a spectrum of cardiopulmonary conditions, including pulmonary hypertension (PH) (1–4). The high price of providing NO and its complex delivery system limit access to inhaled NO therapy to in-hospital use at well-equipped medical centers in economically advantaged countries.

We recently developed a novel method of synthesizing NO from air or oxygen (O<sub>2</sub>)-rich gas mixtures by electric plasma generation (5). Two NO generators were built: an offline device, which continuously produces the gas and maintains a constant concentration of NO throughout the respiratory cycle, and an inline generator, which produces NO for 800 milliseconds beginning 20 milliseconds after the onset of inspiration. Both generators can produce more than 100 parts per million (ppm) NO in air for at least a week. The NO delivery systems include a scavenger to remove nitrogen dioxide (NO<sub>2</sub>) and a high-efficiency particulate arresting filter. We previously demonstrated that NO produced by an electric plasma generator caused pulmonary vasorelaxation in lambs with pulmonary vasoconstriction induced by infusing U46619, a thromboxane analog. Both the offline and inline plasma NO generators reliably reduced the lamb's pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP) (5).

In this exploratory study, we tested both NO generators on human subjects. Each subject received 25 ppm of NO for 10 minutes from each of the two generators. This was a two-part study in adult subjects with predefined objectives. The first objective was to optimize the devices for human use and confirm safety in healthy volunteers (part 1). The second objective was to determine whether electrically generated NO could produce selective pulmonary vasodilation and reduce PAP in adults with chronic PH (part 2). The

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**Table 1.** Characteristics of Patients with PH (n=6) Enrolled in Part 2 of the Study

Subject	Diagnosis	PH Diagnostic Group (WHO)	Oxygen Therapy (L/min)	PAH Medications
1	Interstitial lung disease of uncertain etiology	3	5	Sildenafil
2	Scleroderma, type CREST and suspected PVOD	1	5	Sildenafil, macitentan
3	Suspected pulmonary capillary hypertension/PVOD	1	6	Sildenafil
4	Idiopathic PH	1	4	Sildenafil, macitentan, inhaled iloprost
5	Mixed restrictive and obstructive lung disease	3	5	—
6	Sarcoidosis	5	0	Sildenafil

*Definition of abbreviations:* CREST = calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; PVOD = pulmonary veno-occlusive disease; WHO = World Health Organization. Diagnosis, PH diagnostic group, oxygen requirement at rest, and PAH medications are listed.

study was approved by the Massachusetts General Hospital institutional review board and performed at the hospital.

### Study: Part 1

Six healthy subjects (four females and two males) completed the study. Vital signs were unchanged and remained stable during both continuous and inspiratory NO delivery. Methemoglobin did not increase after breathing 25 ppm NO for 10 minutes and remained below 1.1%. No adverse events occurred during or after breathing NO.

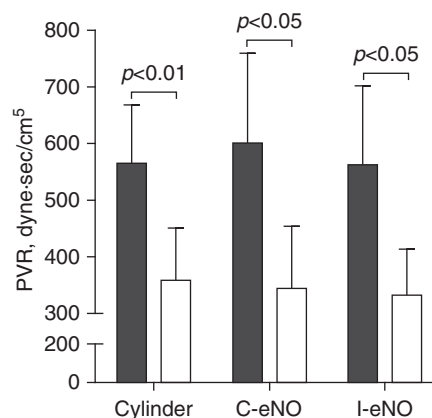
### Study: Part 2

Six patients (two females and four males, aged  $59 \pm 7$  years; all data are mean  $\pm$  SD) with chronic PH were enrolled in the study. As part of the inclusion criteria, each patient had a positive acute pulmonary vasodilator test to 25 ppm NO diluted from NO/N<sub>2</sub> cylinders. Patient characteristics are reported in Table 1. Five of the six subjects were taking one or more medications for pulmonary arterial hypertension (including sildenafil, macitentan, and iloprost). Five of the six subjects required supplemental O<sub>2</sub> at rest (range, 4–6 L/min O<sub>2</sub>); the average peripheral oxygen saturation before the NO test procedure was 95%.

The two generators were safely tested in the cardiac catheterization laboratory. The generators did not cause electrical interference with other electronic equipment (including fluoroscope, electrocardiogram, and invasive and noninvasive vital signs monitoring). There were no adverse effects of administering electric plasma-generated NO to subjects with PH, and there were no instances of shocks or burns. The inspiratory NO<sub>2</sub> levels did not exceed 0.2 ppm in any subject, and the maximum measured blood methemoglobin was 1.2%. The NO concentrations ranged from a minimum of 20 ppm to a maximum of 25 ppm NO during the 10-minute test period with both the inline and offline devices.

Mean systemic arterial pressure was unchanged while breathing NO generated by each method, confirming that inhaled NO does not alter systemic vascular resistance, as previously reported (1). The fraction of inspired oxygen was maintained at the same concentration as during baseline breathing before testing. Peripheral oxygen saturation increased during 25 ppm NO breathing delivered from a standard NO cylinder ( $95 \pm 2\%$  to  $99 \pm 1\%$ ;  $P < 0.01$ ) and showed a trend toward increasing during NO breathing with either the continuous, offline ( $95 \pm 2\%$  to  $98 \pm 1\%$ ;  $P = 0.056$ ), or inspiratory, inline ( $94 \pm 2\%$  to  $98 \pm 2\%$ ;  $P = 0.053$ ), electrical NO generator. Electric plasma NO generation

by the offline generator reduced mean PAP (mPAP) from  $46 \pm 5$  to  $32 \pm 5$  mm Hg ( $P < 0.01$ ); NO produced by the inline generator reduced mPAP from  $43 \pm 4$  to  $32 \pm 4$  mm Hg ( $P < 0.01$ ). Standard cylinder-derived 25 ppm NO decreased mPAP from  $48 \pm 4$  to  $35 \pm 5$  mm Hg ( $P < 0.01$ ). Pulmonary capillary wedge pressure and cardiac index did not change with any of the treatments. As a result of the mPAP decrease and unchanged pulmonary capillary wedge pressure and cardiac index, PVR markedly decreased during NO breathing when delivered via each of the three NO delivery systems (Figure 1). There was a similar percentage reduction in PVR from the resting pretreatment PVR when subjects breathed 25 ppm NO, irrespective of the method used to produce NO. The offline NO generator reduced PVR by  $41 \pm 9\%$  compared with the PVR before breathing NO, the inline generator reduced PVR by  $40 \pm 3\%$ , and cylinder-derived NO reduced PVR by  $39 \pm 7\%$ . The acute pulmonary vasodilator response to NO occurred despite the fact that five of six patients were receiving other pulmonary arterial hypertension therapies, including Sildenafil, a type 5 phosphodiesterase inhibitor. Inadequate endothelial NO production may limit the effect of type 5 phosphodiesterase inhibitors in these patients; providing chronic, supplemental inhaled NO might therefore be clinically useful in patients with pulmonary arterial hypertension.



**Figure 1.** Pulmonary vascular resistance (PVR) of six patients with pulmonary hypertension before (solid bars) and during 25 parts per million of nitric oxide (NO) breathing (open bars) produced by cylinder-derived NO (Cylinder), or continuous offline (C-eNO) and inspiratory inline (I-eNO) electric plasma-generated NO.

In conclusion, the synthesis and testing of electric generation of NO in a hospital setting was safe and led to acute pulmonary hemodynamic effects equivalent to NO obtained from commercially available cylinders. Electric generation of NO from air offers the potential for delivering NO gas for inhalation for prolonged periods and may augment the effects of other chronic therapies. The devices could also expand the delivery of NO to hospitals and clinics around the world because electric plasma generation is economical, easy to use, and safe. ■

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## Preventing Acquired Resistance to Bedaquiline and Delamanid in Multidrug-Resistant Tuberculosis Treatment Requires Optimal Management

To the Editor:

We have read with interest the article by Hoffmann and colleagues (1), which reports the sequential acquisition of drug resistance to bedaquiline and delamanid during the treatment of multidrug-resistant tuberculosis. The authors highlight the rapid development of bacterial resistance and advocate for careful surveillance of resistance to new antituberculosis compounds. Although we agree on the importance of this statement, we note that equal, if not greater, attention should be paid to the optimal use of the new drugs through individualized clinical management.

In this case, bedaquiline and delamanid were both added after substantial delay (8 and 7 mo, respectively) to an ineffective treatment regimen (2). Although this delay could be partly explained by the necessity of acquiring the drugs through compassionate use, the consequence was sequential selection of resistant mutants to these drugs as well as to capreomycin.

Access to bedaquiline and delamanid was granted through compassionate use, which by European Medical Agency definition constitutes “a treatment option that allows the use of an unauthorized medicine. Under strict conditions, products in development can be made available to groups of patients who have a disease with no satisfactory authorized therapies and who cannot enter clinical trials” (3). Yet, bedaquiline under compassionate use was administered according to the package insert and current World Health Organization guidance (4)—that is, for only 24 weeks. Moreover, in accordance with World Health Organization guidance (4), delamanid was added to the regimen only after relapse on the bedaquiline-containing regimen. It is unclear why marketing guidance or guidance for their routine use should define the administration of drugs under compassionate use, which is explicitly outside the purview of routine use of marketed products.

The consequence of these decisions was likely the converse of what was intended: It restricted administration of optimal treatment to a patient with limited therapeutic options, in this case, resulting in a weak treatment regimen and a shorter-than-optimal duration of exposure. It is not surprising that sequential, rather than concurrent, use of the drugs increases the risk of acquired resistance, which may lead to a worrying reversal of response to treatment, and, ultimately, treatment failure (5). Yet, prolongation of bedaquiline treatment beyond 24 weeks and/or concomitant use of bedaquiline and delamanid were justified by a lack of treatment options. Coadministration of these agents in a patient with extensively drug-resistant tuberculosis who experienced no severe adverse events has recently been described (6).

After more than 50 years, new antituberculosis drugs are finally available. Their use could benefit a substantial proportion of patients with multidrug-resistant tuberculosis in many settings. Their responsible stewardship depends on complementary elements: individualized clinical management that favors using the strongest regimens possible to induce cure, reduce transmission, and decrease selection for resistance, as well as ongoing surveillance for resistance to antituberculosis drugs, which will be enhanced by the findings reported by Hoffmann and colleagues (1). These should inform the development of bold policies by regulatory authorities and pharmaceutical companies to facilitate access of effective, lifesaving treatment to those who require it. ■

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