Evaluating the effects of air quality improvements on lung function trajectories will address an important policy-relevant question: are the harmful effects of early-life traffic pollution exposure on lung function reversible if air quality is subsequently improved? ■

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Mary B. Rice, M.D., M.P.H.
Stephen A. Mein, M.D.
Department of Medicine
Beth Israel Deaconess Medical Center
Boston, Massachusetts

ORCID IDs: 0000-0003-2538-391X (M.B.R.); 0000-0002-6567-1564 (S.A.M.).

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Home Nitric Oxide Therapy for COVID-19

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a range of cardiopulmonary and vascular complications, ranging from upper respiratory tract symptoms to severe acute respiratory distress syndrome (ARDS), as well as shock, acute kidney injury, and thromboembolic complications (1, 2). Although SARS-CoV-2 initially infects the upper respiratory tract epithelia, some of the most serious complications of the disease appear to arise through vascular inflammation and injury.

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Although further mechanistic and epidemiological studies are needed, case reports, imaging studies, and autopsy series have suggested the possibility that the SARS-CoV-2 virus, once in the lower respiratory tract, may directly infect endothelial cells, leading to a cascade of consequences including vasoplegia, vascular thromboses, pulmonary edema, endothelial sloughing, and abnormal regulation of pulmonary perfusion (2, 3). Regardless of the mechanisms, it is clear that patients often develop severe respiratory failure with hypoxemia that may be refractory to oxygen supplementation and often requires invasive mechanical ventilation. Because of the rapidity with which the virus spread, many healthcare systems were stressed by the sudden increase in coronavirus disease (COVID-19) cases, with the accompanying increased need for hospital beds, ICU beds, ventilators, and even oxygen. A high percentage of mechanically ventilated patients develop multi-organ failure syndrome, characterized by pressor-dependent shock and a high associated mortality. Even those who survive with the assistance of mechanical ventilation may require prolonged hospitalizations (4). These concerted adverse sequalae of SARS-CoV-2 infection create major strains on health care system resources.

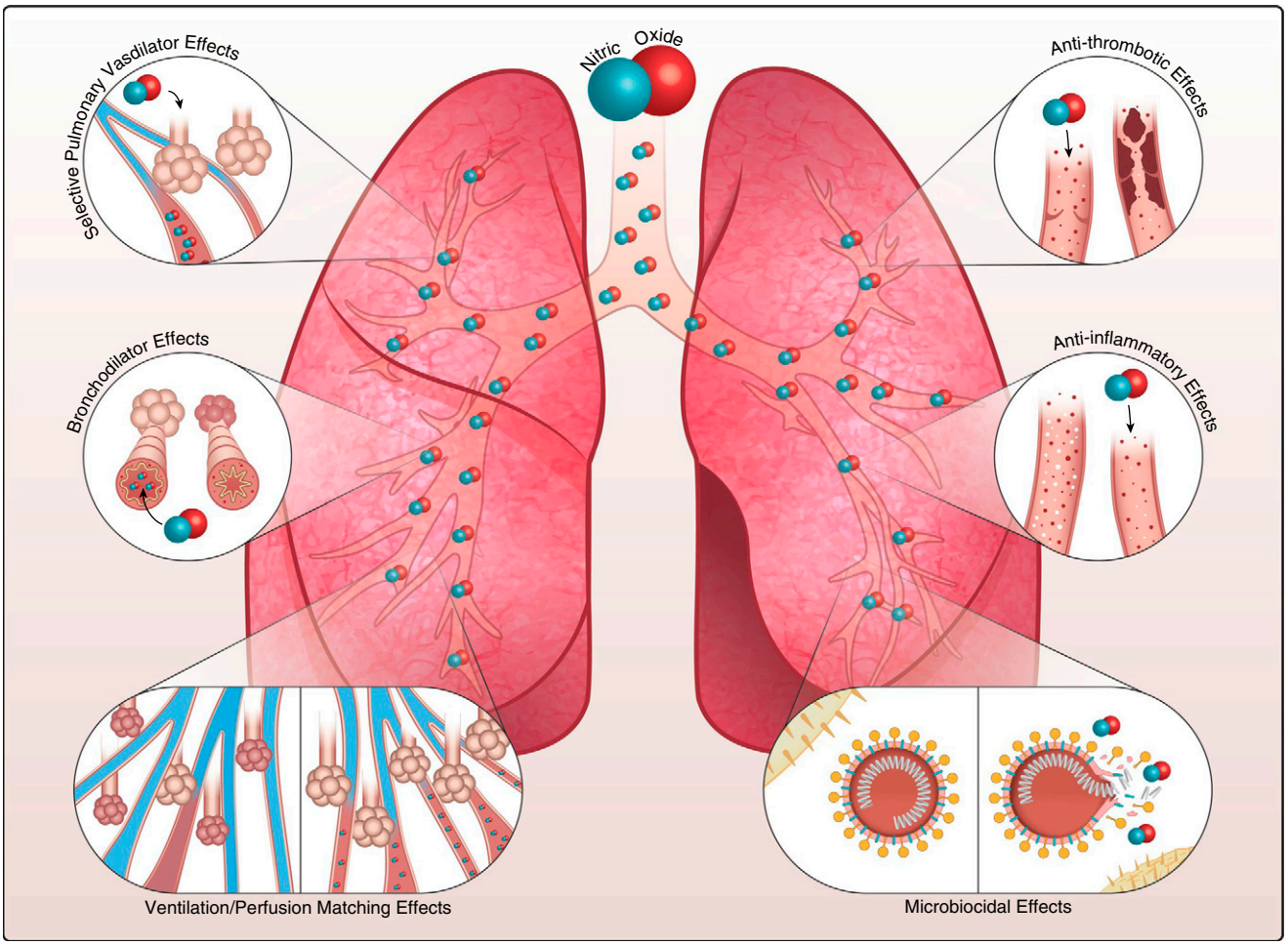

Figure 1. Summary of major therapeutic properties of inhaled nitric oxide gas (NO). From top left: inhaled NO gas is known to be a selective pulmonary vasodilator. NO can improve right heart function and decrease pulmonary vasoconstriction in subjects with acute and chronic pulmonary hypertension. Middle left vignette: breathing NO gas is shown to improve ventilation and provide bronchodilation in mild asthmatic subjects. Bottom left vignette: NO gas in the alveolar space improves oxygenation by increasing blood flow to ventilated lung units (i.e., improvement of ventilation perfusion matching). Top and middle right vignettes: *in vitro* and *in vivo* data showed that NO gas can act as an antiinflammatory and antithrombotic agent. Bottom right vignette: NO donors and NO gas showed antibacterial and antiviral properties in *in vitro* studies and early clinical investigations. The extent of benefits of these six therapeutic pathways of NO gas in coronavirus disease (COVID-19) infection are now under investigation. Some of those studies testing NO therapeutic properties are highlighted in Table 1.

It is with this backdrop that, in this issue of the *Journal*, Zamanian and colleagues (pp. 130–132) present an interesting and compelling case of a patient with pulmonary arterial hypertension (PAH) who was treated remotely in an ambulatory setting with inhaled nitric oxide (iNO) (5). This patient with well-controlled vasoreactive PAH lived in a remote area more than 300 miles away from their center and experienced symptoms of worsening breathlessness after being diagnosed with COVID-19. Considering her concerns about traveling the long distance to their center to receive care, and with recognition of her prior confirmed responsiveness to iNO, they established a plan to support her with an ambulatory iNO system while monitoring her symptoms, vital signs, and functional capacity remotely. The patient had rapid and sustained improvement in her 6-minute-walk distance, as assessed by her caregiver, and symptom score, and she recovered over several days without having to engage emergency department or hospital care.

This case report raises many questions. How might iNO have benefited this patient? Would we expect the benefit to be unique to iNO, or could other therapies that increase signaling along the NO axis also be helpful, such as NO donors, NO precursors, or phosphodiesterase 5 inhibitors? Can NO be safely administered to a patient in their own home, potentially helping to unburden overwhelmed healthcare systems?

NO is a free radial gas that functions as an important signaling molecule in human physiology. Its canonical receptor, guanylate cyclase, is highly expressed vascular smooth muscle cells, where it becomes activated once NO binds to its heme moiety, significantly increasing its enzymatic conversion of guanosine-5′-triphosphate to cyclic guanosine monophosphate, which subsequently promotes vasorelaxation. As a gas, it has unique pharmacological properties including its delivery into well-ventilated lung units where it promotes local vasodilatation. When NO enters the blood stream,

Table 1. Ongoing Clinical Trials Registered on clinicaltrials.gov Testing NO Gas in COVID-19 Infection

Short Title	PI	Coordinating Center	Study Design	Drug	Dose (*ppm*)	Duration	Subjects (*n*)	Study Status	Follow-up (*d*)	Detailed Protocol	Primary Endpoint	Secondary Endpoint	NCT Number
NO Therapy: Healthcare Providers	Lorenzo Berra	MGH, Boston	Multicenter, open-label RCT	NO gas	160	15 min twice daily	470	Recruiting	14	https://www.medrxiv.org/content/10.1101/2020.04.05.20054544v1	Prevention of COVID-19 in healthcare providers	(I) Prevention to become positive (II) Number of quarantine days	NCT04312243
NO Therapy: COVID-19 Infection in ED	Stuart Harris	MGH, Boston	RCT	NO gas	250	30 min, single dose	260	Recruiting	28	Not available	Rates of return visits to the ED	(I) Inpatient hospitalization (II) Rates of intubation (III) Mortality	NCT04338828
NO Therapy: Spontaneous Breathing COVID-19 Infection	Lorenzo Berra	MGH, Boston	Multicenter, open-label RCT	NO gas	160	30 min twice daily	240	Recruiting	28	https://www.medrxiv.org/content/10.1101/2020.03.10.20033522v1	Prevention of progression of the disease	(I) Antimicrobial effect (II) Other clinical outcomes	NCT04305457
NO Therapy: Ventilated Patients with COVID-19	Lorenzo Berra	MGH, Boston	Multicenter, open-label RCT	NO gas	Initial dose 80	Continuous until extubation	200	Recruiting	90	https://www.medrxiv.org/content/10.1101/2020.03.09.20033530v1	Sustained improved oxygenation	(I) Time to reach normoxia (II) Other clinical outcome	NCT04306393
High-Dose NO for COVID-19 (ICU Patients)	Jennifer Lister	University Health Network, Toronto	Multicenter, open-label RCT	NO gas	160	6 h for 2 d	20	Not yet recruiting	3	Not available	Rate of PCR positivity	Not available	NCT04383002
The NO-COVID-19 Study	Marvin Kostam	Tufts Medical Center, Boston	Open-label RCT	NO gas	20	Not available	42	Not yet recruiting	28	Not available	Prevention of progression of the disease	(I) Prevention of progression (II) Clinical improvement	NCT04388683
Pulsed NO in Mild or Moderate COVID-19	Hunter Gilles	Not available	Expanded access	NO gas	20	14 d	Not available	Recruiting	28	Not available	Prevention of progression of the disease	Not available	NCT04358588
Randomized Trial of INOpulse for COVID-19	Roger Alvarez	Miller School of Medicine, Miami	Placebo-controlled RCT	NO gas	40	To resolution of acute hypoxemia	30	Not yet recruiting	2	Not available	Safety and tolerability	(I) Prevention of progression (II) Clinical improvement	NCT04398290
NO Releasing Solutions to Prevent and Treat COVID-19	Jeremy Road	BC Diabetes Vancouver	Multicenter RCT	NORS	Not available	14	200	Recruiting	21	Not available	Prevention of COVID-19 and progression of the disease	(I) Prevention of progression (II) Antimicrobial effect	NCT04337918
NO Treatment for Lung Infections	Jeremy Road	Diamond Centre Vancouver	Sequential assignment	NO gas	160	Not available	20	Active, not recruiting	26	Not available	Safety	(I) Lung function (II) Antimicrobial effect (III) Quality of life	NCT03331445

Definition of abbreviations: BC = British Columbia; COVID-19 = coronavirus disease; ED = emergency department; MGH = Massachusetts General Hospital; NO = nitric oxide; NORS = NO-releasing solution; PI = principal investigator; RCT = randomized controlled trial.

it rapidly reacts with intraerythrocytic Hb, thus inactivating the NO, resulting in an extremely short half-life, which limits its systemic effects. By preferentially vasodilating pulmonary arterioles in well-ventilated lung units, it decreases the relative blood flow to poorly ventilated lung units and enhances $\dot{V}/\dot{Q}$ matching, increasing oxygenation (6). NO also induces mild bronchodilation, and inhibits neutrophil-mediated oxidative burst (6). These properties have been well known for decades and have led to U.S. Food and Drug Administration approval for the treatment of persistent pulmonary hypertension of the newborn, as well as various trials of iNO for patients with myriad conditions including ARDS, right ventricular failure after cardiac surgery, acute pulmonary embolism, and more recently pulmonary fibrosis in patients requiring long-term oxygen therapy (6–10). In patients with SARS, iNO was associated with improvements in oxygenation in a severity-matched observational cohort (11). Both endogenous and exogenous NO were shown to inhibit SARS-CoV viral replication (12). While iNO has not been shown to reduce the time on mechanical ventilation or mortality in adults with ARDS, iNO does significantly improve oxygenation in ARDS patients and leads to reduction in pulmonary vascular resistance (6) (Figure 1). These therapeutic responses suggest that iNO could be used early in the course of COVID-19 infection to reduce the need for invasive mechanical ventilation. Studies of prone positioning and neuromuscular blockers in ARDS both provide a historical reminder of that potential, as clinical trials of early delivery of those therapies demonstrated benefits where prior studies had not (13, 14).

Zamanian's case also highlights the feasibility of portable iNO delivery systems to treat patients at home, an option not previously available. While GENOSYL DS (VERO Biotech) is designed for the hospital intensive care setting, it has features, such as a tankless delivery system, that make it feasible to deliver at home, as demonstrated in this case. Other systems, such as INOpulse (Bellerophon Therapeutics), Nu-Med Plus (UT), and an iridium electric NO generator (Third Pole Therapeutics), have been designed with at least some degree of portability. Although there would be concerns in treating patients with a therapy like iNO at home, there is precedent. In a randomized and placebo-controlled trial of ambulatory patients with fibrotic lung disease requiring long-term oxygen, INOpulse therapy was associated with greater physical activity than placebo, and in an acute dose escalation study of patients with pulmonary hypertension associated with pulmonary fibrosis, iNO delivered through the INOpulse system lead to a 30% reduction in pulmonary vascular resistance, with improvements in Q and pulmonary artery compliance (15).

It is important to recognize that the experience of Dr. Zamanian's patient is unlikely to be representative of all patients with COVID-19, or even those with PAH complicated by COVID-19. This patient had an established diagnosis of vasoreactive PAH, and as a physician herself, was uniquely qualified to engage in a complex treatment regimen. But the example serves as an interesting proof-of-concept study that supports the rationale of studying iNO therapy in patients with COVID-19 to establish if this intervention can improve oxygenation and reduce need for mechanical ventilation. In Table 1, we have summarized planned and ongoing clinical trials available that are testing NO gas therapy in COVID-19 patients. Dr. Zamanian and colleagues are to be commended for their innovative approach and important contribution to this field. ■

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Roger A. Alvarez, D.O., M.P.H., M.S.
Department of Medicine
University of Miami Miller School of Medicine
Miami, Florida

Lorenzo Berra, M.D.
Department of Anesthesia
Massachusetts General Hospital and Harvard Medical School
Boston, Massachusetts

Mark T. Gladwin, M.D.*
Department of Medicine
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania
and
Pittsburgh Heart, Lung, Blood and Vascular Medicine Institute
Pittsburgh, Pennsylvania

ORCID IDs: 0000-0001-7819-6486 (R.A.A.); 0000-0003-2702-2093 (L.B.).

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Listen to Your Heart (but DON'T Look at Theirs): Risk Assessment for Home Treatment of Pulmonary Embolism

Outpatient therapy of pulmonary embolism (PE) has gained greater acceptance in the current era of risk stratification and direct oral anticoagulant (DOAC)-based treatment regimens. A growing experience in the medical literature has documented the safety and improved patient satisfaction with outpatient treatment of low-risk PE (1–4). Furthermore, the opportunity to decongest emergency departments and inpatient units, and reduce the overall cost burden of PE on healthcare systems, compels clinicians to select this strategy when feasible (5). The 2019 European Society of Cardiology guidelines for diagnosis and management of acute PE recommend risk stratification to identify low-risk patients who may be considered for home treatment if outpatient care can be arranged and adequate anticoagulation initiated (6). The 2016 American College of Chest Physicians guidelines suggest early discharge or home treatment of PE over hospitalization in low-risk patients whose home circumstances are adequate (7). However, despite tools for identification of appropriate patients, options for safe and effective outpatient treatment, and endorsement by guidelines, patients with low-risk PE are still frequently hospitalized (4).

Current risk stratification strategies for acute PE rely on synthesis of clinical decision rules; cardiac biomarkers, such as troponin and BNP (brain-type natriuretic peptide); and imaging of right ventricular (RV) function (8). Although these tools have been most widely endorsed for prognostication of adverse outcomes, they are also used for identification of low-risk patients who may avoid hospitalization for acute PE. Specific criteria for eligibility for home therapy were assessed by the Hestia investigators in a prospective cohort study of 297 patients with PE (9). The Hestia criteria identified a cohort of patients with acute PE who completed outpatient therapy with a low risk of adverse events, including recurrent venous thromboembolism (2%), all-cause mortality (1%), and major bleeding (0.7%).

Further contributing to a low adverse event rate with outpatient therapy for acute PE is the widespread integration of DOACs into treatment algorithms. Compared with vitamin K antagonists, DOACs provide similar efficacy but enhanced safety with a 40% reduction in major bleeding and 60% reduction in intracranial hemorrhage (10). The relative ease with which the DOACs are initiated and the promise of consistent, safe, and effective anticoagulation without the need for dose adjustment make them preferred for PE treatment and a major advance in the movement toward outpatient therapy (6, 7).

In this issue of the *Journal*, Hendriks and colleagues (pp. 138–141) provide an important perspective on risk stratification in patients with PE who are eligible for outpatient therapy (11). The investigators report a *post hoc* analysis of combined data from the prospective Hestia and Vesta studies to assess the incremental prognostic value of increased computed tomographic–measured right ventricular–to–left ventricular (RV-to-LV) diameter ratio on recurrent venous thromboembolism and mortality. In the analysis of 752 patients with PE treated at home, 30% had RV enlargement (RV-to-LV diameter ratio > 1). Adverse events were infrequent in these otherwise low-risk patients with RV enlargement compared with those without (2.7% vs. 2.3%; odds ratio, 1.2; 95% confidence interval, 0.44–3.2). The investigators concluded that RV enlargement would have excluded a large proportion of their cohort from outpatient therapy without impacting prognosis.

Despite the main limitation of its *post hoc* design, the study findings support previous observations demonstrating that routine assessment of RV function and cardiac biomarkers in low-risk patients identified using clinical criteria provides little prognostic value and may come at the cost of hospitalizing patients who could otherwise be treated at home (Table 1). A previous analysis from the study investigators demonstrated that 35% of patients who were treated at home according to the Hestia criteria had RV dysfunction and were classified as intermediate risk according to the European Society of Cardiology criteria (12). Similarly, other studies from the investigators have shown that increased high-sensitivity cardiac troponin T (13) and N-terminal pro-BNP (14) were associated with a low rate of adverse events in patients with PE determined to be low-risk by the Hestia criteria. One potential explanation for infrequent adverse events in clinically

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