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EDITORIAL

Inhaled Nitric Oxide for Acute Right Heart Failure in Pulmonary Hypertension

— Bridging the Evidence-to-Practice Gap —

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Decompensated acute right heart failure (RHF) is one of the most severe complications of pulmonary hypertension (PH).[1] Despite recent progress in disease-specific treatment, such as selective pulmonary vasodilators and balloon pulmonary angioplasty,[2–4] patients with acute RHF due to PH have high morbidity and mortality rates. Most of these patients require intensive care, but therapeutic options remain limited. Supportive therapy, including inotropes, vasopressors, diuretics, and oxygen administration, is being used to optimize preload, afterload, and cardiac contractility (**Figure**).[1,5] However, there is a lack of high-quality evidence regarding pharmacological strategy during the acute phase for pulmonary vasodilators

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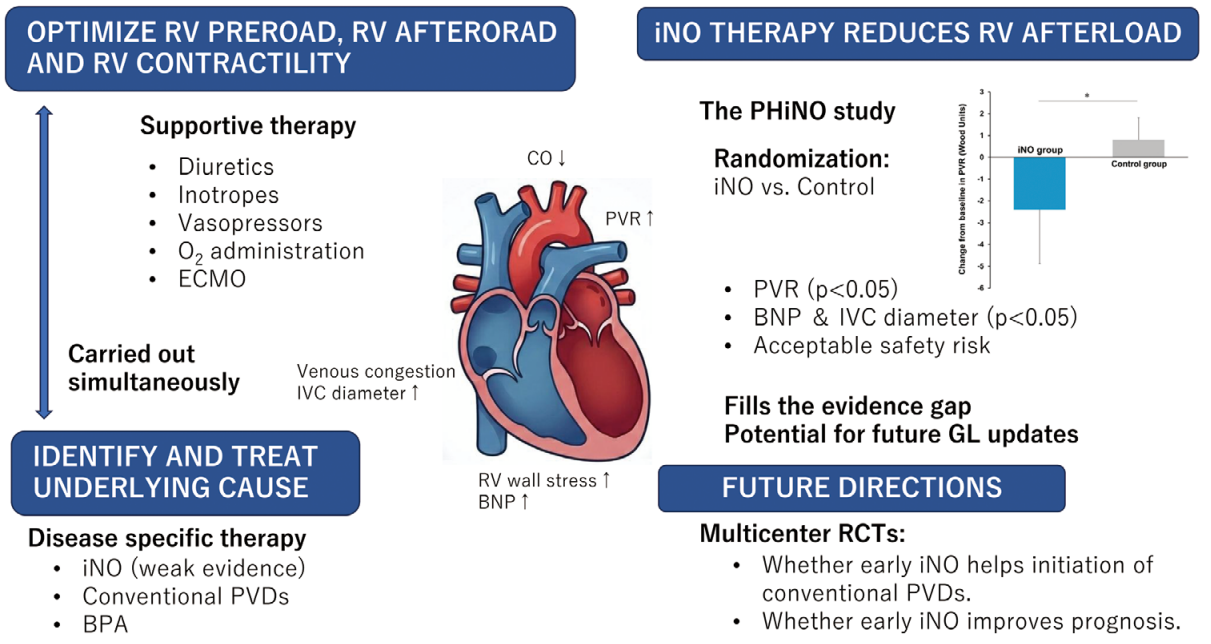

Figure. Role of iNO in the treatment of acute RHF associated with PH. BNP, B-type natriuretic peptide; BPA, balloon pulmonary angioplasty; CO, cardiac output; ECMO, extracorporeal membrane oxygenation; GL, guideline; iNO, inhaled nitric oxide; IVC, inferior vena cava; PH, pulmonary hypertension; PVD, pulmonary vasodilator; PVR, pulmonary vascular resistance; RCT, randomized controlled trial; RHF, right heart failure; RV, right ventricular.

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in patients with PH complicated by acute RHF.[3]

Inhaled nitric oxide (iNO) is used in the critical care setting to reduce right ventricular (RV) afterload and improve oxygenation. Diseases for which iNO is indicated include PH, acute pulmonary embolism, perioperative PH in cardiac surgery, acute respiratory distress syndrome, and persistent PH of the newborn.[6] NO dilates blood vessels by increasing cyclic guanosine monophosphate through activation of soluble guanylate cyclase in vascular smooth muscle cells. When administered by inhalation, it distributes only to ventilated lung areas and improves ventilation-perfusion mismatch and oxygenation. In addition, NO is rapidly inactivated by hemoglobin, and iNO has little effect on systemic vascular resistance and systemic blood pressure.[7] These characteristics of iNO are beneficial for hemodynamically unstable patients with PH compared to pulmonary vasodilator therapy via oral or intravenous administration. However, current clinical evidence supporting its use in this population is limited.[3]

In this issue of the Journal, Ogo et al. report their results from the PHiNO study, a Phase 2, randomized, clinical trial evaluating the efficacy and safety of iNO in patients with acute severe RHF associated with PH.[8] The study was designed to address the evidence gap in the acute management strategy for this population.[9] A total of 30 PH patients with acute RHF were randomized in a 1:1 ratio to receive either iNO in addition to conventional PH therapy or conventional PH therapy alone. They clearly demonstrate a significant reduction in the primary endpoint of change in pulmonary vascular resistance (PVR) from baseline to 30 min after the initiation of iNO in the iNO group compared with the control group (**Figure**). The iNO group also showed a significant improvement in the secondary endpoints of B-type natriuretic peptide (BNP) levels and inferior vena cava (IVC) diameter during the 7-day study period. Importantly, neither severe adverse events nor significant methemoglobinemia was observed in either group.

These results have much clinical importance. First, there have been very few randomized studies of patients with severe RHF due to PH because these patients are a challenging population in which to conduct randomized controlled trials. The PHiNO study holds significant value in filling a long-standing evidence gap by conducting research in the framework of an investigator-initiated trial. Second, the improvement in various markers observed in this study is consistent with the pathophysiology of RHF caused by PH.[10] Increase in RV afterload by elevated PVR results in a decrease in RV contractility and cardiac output, leading to RHF. The improvement in the primary endpoint of PVR demonstrates that iNO selectively exerts its effect on pulmonary resistive vessels. Furthermore, an improvement in the secondary endpoints (BNP levels and IVC diameter) suggest that the early RV afterload reduction achieved by iNO is also effective in improving subsequent RV wall stress and systemic congestion. Third, in Phase 2 trials targeting high-risk patients, safety is as important as efficacy. The PHiNO study provided robust evidence that iNO can be safely administered as an acute treatment for patients with acute RHF associated with PH. Finally, these findings have important implications for clinical practice. In patients with de novo PH, diagnosis and treatment typically proceed simultaneously. The PhiNO study suggests that iNO thepapy may be useful as a bridging therapy until hemodynamic stabilization is achieved, or disease-specific treatments are optimized.

Nonetheless, it is imperative to acknowledge the limitations of the PHiNO study. First, the sample size was very small, and the study population was restricted to patients with pulmonary arterial hypertension and chronic thromboembolic PH. Thus, the findings should be interpreted as exploratory and cannot be extrapolated to the other PH groups. Second, the open-label design introduces the possibility of performance and assessment bias, potentially influencing clinical management and outcome evaluation. Third, iNO was administered at a single fixed dose. The study was not designed to investigate optimal dose of iNO, treatment duration, or tapering strategy. Fourth, the primary endpoint was assessed at 30 min after iNO initiation, and the study did not evaluate sustained clinical benefits or long-term outcomes such as survival or rehospitalization. Although improvements were observed in the secondary endpoints of BNP levels and IVC diameter, these are surrogate markers. The association between iNO and hard clinical endpoints such as death or need for mechanical circulatory support remains unclear. Finally, safety assessments were limited to the short study period. The long-term effects of iNO on safety profiles require further investigation.

Future research should expand the present trial to encompass larger multicenter studies. Increasing the sample size will reveal whether iNO therapy aids in the early initiation of conventional pulmonary vasodilators in patients with acute RHF caused by PH, and whether it improves long-term clinical outcomes. Moreover, it may be possible to identify the patient subgroups most likely to benefit from iNO by comprehensive risk assessment.[11]

In conclusion, the PHiNO study represents a significant advance in managing acute RHF associated with PH. iNO has been used for many years based mainly on physiological rationale and clinical experience. The results of the PHiNO study fill a long-standing evidence gap by demonstrating improvements in clinically relevant endpoints. This may help guide future clinical practice and change guideline recommendations for the management of decompensated RHF in PH patients.

Disclosures

S.Y. is member of *Circulation Journal*'s Editorial Team. The remaining author has no conflicts of interest to disclose.

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