Effects of Nitric Oxide Inhalation on Periodic Breathing in Awake Patients with Chronic Heart Disease

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Abstract: Background: Periodic breathing, an abnormal pattern of respiration consisting of alternating hyperpnea and hypopnea, has been recognized in patients with heart failure. Although fluctuations in pulmonary blood flow have been considered as a possible cause of this type of breathing, its pathophysiological mechanisms are not fully understood. In this study, we sought to determine whether inhaled nitric oxide (NO), a selective pulmonary vasodilator, attenuates periodic breathing. Methods: Eight cardiac patients who exhibited clear oscillatory ventilation while awake (age: 62±16 years, left ventricular ejection fraction: 48±20%) were enrolled in the study. After breathing room air (RA) for 15 min, the subjects inhaled air containing 30 ppm of NO for 15 min. Respiratory gas variables including minute ventilation (VE) were measured on a breath-by-breath basis throughout the test. Results: There were no differences in VE (10.7±1.5 vs. 11.0±1.7 l/min) or among any of the other hemodynamic or respiratory gas variables studied in the control and NO tests, with the exception of the end-tidal CO2 partial pressure (5.0±0.4 vs. 4.8±0.5%; p=0.018). The % magnitude of oscillation (i.e., the difference between the peak and nadir of oscillating VE, divided by the mean VE) was 40.0±22.4% in RA and not influenced by inhaled NO (43.9±20.8%, p=0.57). Conclusion: Inhaled NO at a concentration of 30 ppm did not attenuate periodic breathing in awake patients with mild heart failure. [Japanese Journal of Physiology, 52, 327–332, 2002]

Key words: heart failure, nitric oxide, oscillatory ventilation.

Periodic breathing alternating between hyperpnea and hypopnea, a phenomenon that resembles Cheyne-Stokes respiration, was already described more than a century ago in patients with heart failure [1]. Periodic breathing is considered as a marker of severe heart failure and as an indication of poor outcome [2–4]. As possible mechanisms of this phenomenon, instability of the ventilatory control system [1], fluctuations in pulmonary blood flow [5, 6], and several other physiological conditions [7–9] have been proposed. However, the origin of this breathing pattern is not fully understood [10].

In this study, we focused on the possibility that fluctuations in pulmonary blood flow act as a mechanism of periodic breathing. If periodic breathing can be attributed to fluctuations in pulmonary blood flow, we speculated that pulmonary vasodilators might attenuate this breathing pattern. To test this hypothesis, we evaluated whether periodic breathing is influenced by inhalation of nitric oxide (NO), a potent pulmonary vasodilator, in cardiac patients who exhibited clear oscillatory ventilation while awake.

METHODS

Study participants. We enrolled 8 patients (7 men, 1 woman, 62.1±16.3 years old) with chronic heart disease who clearly demonstrated periodic breathing,
as determined by respiratory gas analysis while the patients were awake (Table 1). Periodic breathing was defined as occurring when the mean of the differences between the peak and nadir of oscillating ventilation was equal to or greater than 20% of the mean ventilation. Patients were classified as belonging to one of the two following groups: New York Heart Association functional class I \((n = 3)\) or class II \((n = 5)\). No patients with cerebrovascular disease or documented lung disease were included.

The protocol and procedures for the test were approved by the institutional human subjects committee. The nature of the study, its purposes, and its risks were explained to the patients, and each gave his or her informed consent prior to enrollment.

**NO inhalation.** We set the NO gas concentration at 30 ppm, a level which has been shown to sufficiently dilate pulmonary vasculature in humans \([11–13]\). In order to achieve a mixture of 21% O\(_2\) with 30 ppm NO and the remaining N\(_2\), 53 ppm of NO gas balanced with N\(_2\), was mixed with 100% O\(_2\) at a ratio of approximately 4 : 1. After this mixing, NO gas was once stored in a Douglas bag, and several minutes later, the gas was inhaled by the subject through a Hans-Rudolph two-way valve.

The subject initially breathed room air for 15 min, and subsequently NO for 15 min while awake. The inspired air was switched from room air to NO gas by adjusting a 3-way stopcock attached at the outlet of a Douglas bag, without notifying the subject.

The O\(_2\) concentration was monitored both at the inlet of the Douglas bag and at the subject’s face mask by an AE-280 Respiromonitor (Minato Medical Science, Osaka, Japan). The O\(_2\) concentration at the face mask was maintained at 21% by fine tuning the mixing ratio. The concentration of inhaled NO, which was monitored continuously at the subject’s face mask by an NO analyzer (Sievers 270B, Sievers Instruments Inc., Colorado, USA), was 29.0±2.6 ppm during the test with NO.

**Respiratory gas measurements.** ECG was monitored continuously during the test (System ML-5000, Fukuda Denshi Co., Ltd., Tokyo, Japan). Cuff blood pressure was determined each minute with an indirect manometer (STBP-680, Collin Denshi, Aichi, Japan). O\(_2\) saturation \((S_{PO2})\) was measured at the fingertip by a pulse oximeter (DS-5300, Fukuda Denshi Co., Ltd.) during the test. Breath-by-breath O\(_2\) uptake \((\dot{V}O_2)\), CO\(_2\) output \((\dot{V}CO_2)\), end-tidal O\(_2\) partial pressure \((PETO_2)\), end-tidal CO\(_2\) partial pressure \((PETCO_2)\), tidal volume \((VT)\), and minute ventilation \((\dot{V}E)\) were measured throughout the test using an AE 280 Respiromonitor, as previously described \([14, 15]\). Prior to calculating the magnitude and period of periodic breathing, a five-point moving average of the breath-by-breath data was performed. The % magnitude of oscillation was defined as the difference between the peak and nadir of oscillating \(\dot{V}E\), divided by the mean \(\dot{V}E\). The period of the oscillating \(\dot{V}E\) was defined as the mean time from one peak to the subsequent peak of the oscillating \(\dot{V}E\).

**Statistics.** Data are presented as the mean±SD. Differences in the variables between the test with NO and the control test with room air only were analyzed by paired \(t\)-tests. The significance level was set at a \(p\) value of less than 0.05.

**RESULTS**

Figure 1 demonstrates the respiratory gas variables observed during the test with a representative subject. Clear oscillatory changes were noted in \(\dot{V}E\), \(VT\), and
other respiratory gas variables throughout the test.

Table 2 shows the effects of NO inhalation on hemodynamic and respiratory gas variables. Inhaled NO slightly lowered $P_{ET\text{CO}_2}$ (5.0$\pm$0.4 vs. 4.8$\pm$0.5%; $p=0.02$). However, there were no differences in $\dot{V}E$ (10.7$\pm$1.5 vs. 11.0$\pm$1.7 l/min), $\dot{V}O_2$ (214$\pm$50 vs. 210$\pm$46 ml/min), $\dot{V}CO_2$ (180$\pm$44 vs. 184$\pm$39 ml/min), or $P_{ETO_2}$ (15.2$\pm$0.5 vs. 14.9$\pm$0.6%). Also, there were no differences in heart rate or blood pressure between the test with room air and that with NO.

The right panel of Fig. 2 demonstrates the average % magnitude of oscillation in all the subjects. The % magnitude of oscillation was 40.0$\pm$22.4% in the test with room air and 43.9$\pm$20.8% in that with NO, showing no significant difference ($p=0.57$). The period of oscillating $\dot{V}E$ was 94.5$\pm$38.2 s in the test with room air and 79.2$\pm$24.8 s in that with NO, again showing no significant difference ($p=0.14$, Table 2).

\begin{table}
\centering
\caption{Effects of nitric oxide breathing on hemodynamic and respiratory gas variables.}
\begin{tabular}{llll}
\hline
Variable & Room air & Nitric oxide & $p$ value \\
\hline
Magnitude of oscillation (%) & 40.0$\pm$22.4 & 43.9$\pm$20.8 & 0.570 \\
Duration of oscillation (s) & 94.5$\pm$38.2 & 79.2$\pm$24.8 & 0.144 \\
Heart rate (bpm) & 73$\pm$9 & 70$\pm$13 & 0.472 \\
Systolic blood pressure (mmHg) & 131$\pm$18 & 130$\pm$17 & 0.728 \\
Diastolic blood pressure (mmHg) & 77$\pm$9 & 78$\pm$10 & 0.418 \\
Oxygen uptake (ml/min) & 214$\pm$50 & 210$\pm$46 & 0.414 \\
Carbon dioxide output (ml/min) & 180$\pm$44 & 184$\pm$39 & 0.198 \\
Minute ventilation (l/min) & 10.7$\pm$1.5 & 11.0$\pm$1.7 & 0.384 \\
End-tidal $P_{O_2}$ (%) & 15.2$\pm$0.5 & 14.9$\pm$0.6 & 0.074 \\
End-tidal $P_{CO_2}$ (%) & 5.0$\pm$0.4 & 4.8$\pm$0.5 & 0.018 \\
$Sp_{O_2}$ (%)* & 97.6$\pm$0.9 & 97.6$\pm$1.1 & 0.999 \\
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\end{tabular}
\end{table}

* $O_2$ saturation ($Sp_{O_2}$) was measured at a fingertip by a pulse oximeter.
DISCUSSION

In the present study, NO inhalation did not significantly influence periodic breathing in cardiac patients while awake. Previous investigations [11–13] have clearly shown that NO gas at a concentration of 30 ppm dilates the pulmonary vasculature. Thus, the present finding implies that periodic breathing is independent of the tone of the pulmonary vasculature.

Mechanisms of periodic breathing. Heart failure patients often develop a periodic breathing pattern during sleep. Several investigators have noted that approximately 50% of patients with symptomatic congestive heart failure have either sleep apnea or Cheyne-Stokes respiration [16–18]. Although nocturnal Cheyne-Stokes respiration has been considered a sign of poor prognosis [3], this conclusion remains under debate [1, 19].

Investigators have postulated that breathing disorders in patients with heart failure may have a causal relationship with prolonged circulation time [7], impaired systolic and/or diastolic function [9], and left ventricular enlargement [8]. Administration of O2 or theophylline and continuous positive airway pressure therapy have been shown to attenuate periodic breathing [18, 20–22]. However, the origin of oscillatory breathing has not yet been identified [10].

In 1992, Ben-Dov et al. [5] analyzed $\dot{V}O_2$ and $\dot{V}E$ in detail during exercise in patients with periodic breathing. They found a greater amplitude of oscillations in $\dot{V}O_2$ than in $\dot{V}E$. $\dot{V}O_2$ can be determined by Fick’s equation based on pulmonary blood flow, and arterial and mixed venous O2 content. Several lines of evidence also suggest that an abrupt increase in pulmonary blood flow causes hyperpnea, especially during the onset of exercise [23, 24]. Therefore, Ben-Dov et al. [5] suggested that the oscillations in $\dot{V}E$ are secondary to the oscillations in $\dot{V}O_2$ resulting from oscillations in pulmonary blood flow. Oscillatory changes have been noted both in the left ventricular ejection fraction and in $\dot{V}E$ in patients with periodic breathing [6]. Such results further suggest the possible link between periodic breathing and fluctuations in pulmonary blood flow (cardiac output). However, the hypothesis of Ben-Dov et al. has not been substantiated, partly due to the methodological difficulty of detecting the presence of oscillations in pulmonary blood flow.

Increased ventilatory sensitivity to CO2 and the dumping effect of lung and total body gas stores might also prove to be important mechanisms leading to periodic breathing in patients with chronic heart failure. However, measurements of arterial CO2 partial pressure and functional residual capacity, which would be necessary to clarify the role played by these factors in periodic breathing, were not obtained in the present study.

NO inhalation. In 1987, NO was identified as an endothelium-derived relaxing factor [25]. Since then, the inhalation of NO has been used to lower the pulmonary vascular pressure, especially in patients with pulmonary hypertension [11–13, 26–30]. Matsumoto et al. [11] also found that NO inhalation reduces the pulmonary arterial pressure in a dose-dependent manner in patients with congestive heart failure. In their study [11], significant decreases in both pulmonary arterial pressure and pulmonary vascular resistance were observed in subjects who inhaled NO at concentrations as low as 10ppm. They also noted that pulmonary arterial pressure begins to decrease within 2 min after inhalation [11]. These recent findings prompted us to conduct the present investigation. We speculated that the inhalation of NO, a potent pulmonary vasodilator, might attenuate or even eliminate periodic breathing by attenuating oscillations in pulmonary blood flow. However, contrary to our hypothesis, the inhalation of NO did not significantly influence periodic breathing.

Study limitations. We used a respiremonitor, which is a device capable of measuring respiratory gas variables on a breath-by-breath basis. Thus, we believe that the time resolution capacity of this device was sufficient for the detection of oscillatory cycles in respiratory variables, as shown in Fig. 1. In the present study, the magnitude of oscillation ranged from 20 to 87% in the control test. Although the oscillations varied widely, the effects of NO inhalation were similar between those patients with relatively greater oscillations and those with smaller oscillations (Fig. 2). PETCO2 was slightly but significantly decreased by inhaled NO. A similar phenomenon has been noted by other investigators [11]. The decrease in PETCO2 may be attributable to improvements in ventilation/perfusion mismatch by NO inhalation [11], although NO inhalation did not significantly increase SPO2, which was already within the normal range in the test without NO.

We used NO at a concentration of 30 ppm. Previous reports [11–13] have confirmed that this concentration of NO sufficed to dilate the pulmonary vasculature. However, this concentration might not have been sufficient to diminish the oscillatory changes in the pulmonary blood flow, in spite of the dilution of the pulmonary vasculature. The patients in the present study had relatively mild heart failure, with a mean left ventricular ejection fraction of 47.8%. Thus, the cardiac dysfunction of the subjects recruited for the present
study may not have been sufficient to demonstrate the effects of NO inhalation on pulmonary hemodynamics. Moreover, the findings of the present study may not be generalizable to patients with severe heart failure.

NO concentration monitored at the face mask was below the value which would have been expected by our mixing procedure. This unexpected value may in part be attributed to the absorption of NO by the Douglas bag. Another possibility would be the production of nitrogen dioxide (NO$_2$); however, the NO$_2$ concentration was not monitored during our test, because the device used was not capable of measuring NO$_2$. NO$_2$ production is known to increase with a higher inspired O$_2$ fraction ($F_iO_2$), higher NO concentration, and longer contact time with O$_2$ [31, 32]. However, $F_iO_2$ was 21% and the contact time of NO with O$_2$ before inhalation was only several minutes in the present study. Thus, we believe that NO$_2$ production in the present study was negligible from the viewpoint of the health of the subjects.

Evaluation of pulmonary vasculature with right heart catheterization was not performed in the present study. In order to further clarify the mechanisms of periodic breathing, such an evaluation would be necessary.

**Conclusion.** Inhaled NO at a concentration of 30 ppm did not attenuate periodic breathing in awake patients with mild heart failure.

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