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Posted Date: 10 April 2025

doi: 10.20944/preprints202504.0860.v1

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Investigation of Individual Variability and Temporal Fluctuations in Exhaled Nitric Oxide (FeNO) for Telemedicine Applications

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Abstract: Measurement of nitric oxide (NO) concentration in exhaled breath (FeNO) is a quantitative, non-invasive, simple, and safe method for assessing airway inflammation. It serves as a complementary tool to other methods for evaluating airway diseases. In recent years, remote monitoring has enabled healthcare providers to support self-management remotely, suggesting that FeNO measurement may also be useful as a tool for telemedicine. However, little is known about the normal NO levels in healthy individuals, including individual differences and variations due to measurement timing. Therefore, this study classified measurement times into four periods and statistically analyzed NO levels in healthy individuals. The mean values among groups were compared using repeated measures ANOVA on eight participants. The analysis showed large individual variations in NO levels, resulting in no significant difference ($P = 0.29$). Notably, greater fluctuations were observed in the morning. These findings align with previous studies suggesting the influence of circadian rhythms and the redundancy of repeated measurements. This study indicates the potential application of FeNO measurement in telemedicine.

Keywords: exhaled nitric oxide (FeNO); airway inflammation; telemedicine; circadian rhythm; repeated measures ANOVA

1. Introduction

Telemedicine offers numerous advantages, including the reduction of regional disparities in healthcare access and improved medical services for patients who have difficulty visiting hospitals or clinics. Furthermore, it contributes to improving the working conditions of physicians and allows for an increase in the number of patients a medical facility can accommodate [1–6]. However, the effective implementation of telemedicine requires appropriate systems and medical devices, along with seamless integration of various diagnostic data in online medical consultations. Since telemedicine does not allow direct physical examinations such as palpation, urine tests, blood tests, or X-ray imaging, its application in remote diagnostics remains limited. Nevertheless, certain physiological measurements, such as electrocardiogram (ECG) monitoring, can be conducted remotely.

Several factors will play a role in the realization of the future of healthcare. First, the evolution of remote monitoring technology will make it possible to grasp the health status of patients in real time. In addition to measuring vital signs using smartwatches and sensors, the introduction of cloud-based health management platforms will allow medical professionals to analyze the patient's condition remotely and take appropriate measures. Second, disease prediction and anomaly detection using AI will promote early intervention. By utilizing machine learning models, it will be possible to compare a patient's past data with real-time data and detect anomalies. Furthermore, more accurate disease management can be achieved by AI proposing optimal treatment plans for

 doi:10.20944/preprints202504.0860.v1

each individual patient. The spread of virtual consultations and online medical care will also contribute to reducing the number of visits to the hospital. By conducting many consultations online, the burden on medical institutions can be reduced and patients can also avoid the trouble of visiting the hospital. In addition, the use of digital prescriptions and online pharmacies will make it possible to complete the prescription and delivery of medicines after consultations remotely. In addition, improving patients' self-management capabilities is also important. By using mobile apps to record symptoms, manage medication, and provide guidance on improving lifestyle habits, patients themselves can easily grasp their health status. In addition, by incorporating biofeedback training, it will be possible to practice appropriate self-care based on real-time biometric data.

One promising candidate for remote diagnostic applications is the measurement of exhaled nitric oxide (FeNO). FeNO testing is a quantitative, non-invasive, simple, and safe method for assessing airway inflammation. It serves as a complementary tool to other diagnostic methods for evaluating airway diseases. Given its ease of use and safety profile, FeNO measurement holds potential as a remote diagnostic tool in the future [7–12]. With advancements in telemedicine, real-time monitoring of FeNO levels could enable healthcare providers to support patient self-management remotely, improving disease control and reducing the need for frequent in-person visits.

Despite its potential, FeNO testing is not commonly included in routine health checkups. As a result, there is limited understanding of FeNO levels in healthy individuals, including interindividual variability and fluctuations over time. Previous studies on FeNO measurements have primarily focused on patients with respiratory conditions such as asthma [13–28], while data on healthy populations remain scarce. Understanding FeNO variations in healthy individuals is crucial for establishing reference values and determining the feasibility of remote FeNO monitoring for broader clinical applications [29,30].

To explore the feasibility of FeNO testing in telemedicine, this study aims to analyze the individual variability and time-dependent differences in FeNO levels among healthy individuals. By categorizing measurement periods into four distinct time frames and conducting statistical analyses, we aim to provide insights into the natural fluctuations of FeNO in healthy subjects. The findings of this study could contribute to the development of remote FeNO monitoring systems, facilitating the early detection and management of airway inflammation in telemedicine settings.

2. Materials and Methods

2.1. Participants

8 healthy participants (mean age: 61.3 ± 14 years, 2 females) were enrolled in this study. The inclusion criteria required all participants to be free from respiratory diseases. The exclusion criteria included individuals diagnosed with respiratory disorders (Table 1). All participants provided informed consent before participation. The study was approved by the Ethics Committee of Faculty of Engineering, Mie University (Approval number 132, Approved February 19, 2025).

Table 1. Medical Exclusion Criteria.

	Conditions
1	Subject with a history of respiratory disease (asthma, COPD, interstitial lung disease, etc.)
2	Subject with acute respiratory tract infections (cold, influenza, pneumonia, etc.)
3	Subject with lung cancer or severe lung disease
4	Subject with recent airway inflammation
5	Subject using bronchodilators (β2 agonists) or steroids
6	Smokers or subject exposed to passive smoking

The measurement times were grouped as shown in the table below (Table 2).

 doi:10.20944/preprints202504.0860.v1

Table 2. Measurement times.

Measurement time	Number of data
9-11	80
11-13	89
13-15	103
15-17	33

2.2. FeNO Measurement Device

Exhaled nitric oxide (FeNO) was measured using the NIOX VERO device (Chest M.I., Inc., Japan; Medical Device Approval Number: 22700BZX00030000, JAN Code: 7350047030229). The device was operated via a PC application, "NIOX Panel," with USB cable communication.

FeNO measurements followed the guidelines established by the American Thoracic Society (ATS) and the European Respiratory Society (ERS), which recommend exhaling at a constant flow rate of 50 ml/sec ± 10% for 10 seconds. The measurement process involved the following steps; participants inhaled NO-free gas through a built-in NO scrubber in the device's respiratory handle. They then exhaled at a constant flow rate (50 ml/sec ± 10%) for 10 seconds following ATS/ERS standards. The last 3 seconds of exhalation were sampled for FeNO analysis to ensure a stable reading. If the exhalation flow rate or duration was insufficient, the measurement was in-erupted and repeated. The total measurement time, from initiation to result display, was approximately 1 minute and 30 seconds. Next, discuss Device Calibration and Environmental Conditions. The NIOX VERO device measures FeNO in parts per billion (ppb) with high precision. To maintain measurement accuracy, the device, sensor, and respiratory handle have predefined expiration and usage limits. During this study, these components were replaced as necessary, eliminating the need for additional calibration. All measurements were conducted in a temperature-controlled environment (24°C ± 2°C). Participants remained seated at rest during the FeNO measurement process.

2.3. Exchange kinetics of exhaled nitric oxide (NO)

For an explanation of the exchange kinetics of NO in exhaled air, Nikolaos M. et al. In this study[31], a model of the lung divided into two compartments, airways and alveoli, was constructed to reproduce the relationship between exhaled NO concentration and expiratory flow rate and to provide an index for assessing the contribution of NO sources in the lung. In this study, a two-compartment mathematical model was developed to analyze the exchange dynamics of NO in exhaled breath, dividing the lungs into two regions: the airways and the alveoli. Each compartment is surrounded by a tissue layer capable of producing and consuming NO, with adjacent blood flow (bronchial circulation for the airways and pulmonary circulation for the alveoli) assumed to be an infinite sink for NO. The NO production rate was estimated based on existing experimental data, and parameters were adjusted to match experimental results by simulating the relationship between the NO elimination rate at end-exhalation (ENO) and the exhalation flow rate ($\dot{V}E$). Additionally, the relationship between ENO and $\dot{V}E$ was used as an index to evaluate the relative contributions of the airways and alveoli to exhaled NO. This model demonstrated that exhaled NO concentration is inversely correlated with exhalation flow rate and that both the airways and alveoli contribute to NO elimination. Unlike previous single-compartment models, which struggled to explain certain experimental findings, this two-compartment model successfully reproduces observed phenomena, providing a more comprehensive framework for understanding NO exchange dynamics [32–38]. The concentration of exhaled NO is known to depend on the $\dot{V}E$, a phenomenon that must be accurately accounted for in mathematical models of NO exchange. As exhalation flow rate increases, the concentration of NO in exhaled breath generally decreases due to the shortened residence time of NO within the airways and the dilution effect of increased airflow. Conversely, at lower flow rates, NO accumulates in the airway compartment, leading to higher concentrations in the exhaled breath.To quantify this relationship, the two-compartment model incorporates flow-dependent NO transport

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dynamics. The parameters governing NO production and uptake in the airway and alveolar compartments were estimated using experimental data, particularly the observed relationship between the NO elimination rate at ENO and V˙E. By fitting the model to experimental results, key physiological parameters such as NO production rates in the airways and alveoli, tissue diffusion coefficients, and airway wall uptake rates were optimized.Through this approach, the model reproduces the characteristic inverse correlation between exhaled NO concentration and exhalation flow rate.

The NO concentration in exhaled breath is described by the following formula,

$$C\ no(t) = C\ alv + \frac{J\ aw}{D\ aw + V\ exp} \quad (1)$$

Cno(t) is the concentration of NO in exhaled air, Calv is the alveolar NO concentration, Jaw is the airway NO flux, and Daw is the airway diffusion parameter.

2.4. Statistical Analysis

We compared FeNO levels at different measurement points using repeated measures analysis of variance (ANOVA). We used SPSS Statistics (IBM SPSS Statistics v29.0.1) for the analysis. We evaluated the temporal variation in FeNO levels, taking into account the within-subject variability. The threshold for statistical significance was set at $P < 0.05$.

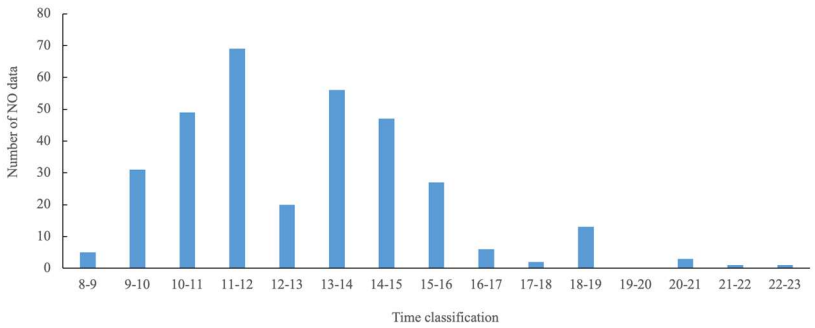
3. Results

The results of statistical analysis using analysis of variance are shown in the table (Table 3). NO levels fluctuated greatly from person to person, so no significant differences were observed (Figure 1). NO levels showed particularly large fluctuations in the morning. Statistical analysis was performed on the three groups of 11am-1pm, 1-3pm, and 3-5pm, there were slight differences in the measured values depending on the measurement time ($P = 0.088$).

Table 3. Analysis results of exhaled NO by time period.

Number of measurements	80	89	103	33
Time classification	9-11	11-13	13-15	15-17
Mean	31.4250	29.8202	33.0194	28.0909
S.D.	19.60933	13.21119	13.77407	8.80470
S.E.	2.19239	1.40038	1.35720	1.53270

S.D. is Standard Deviation and S.E. means Standard Error.



(a)

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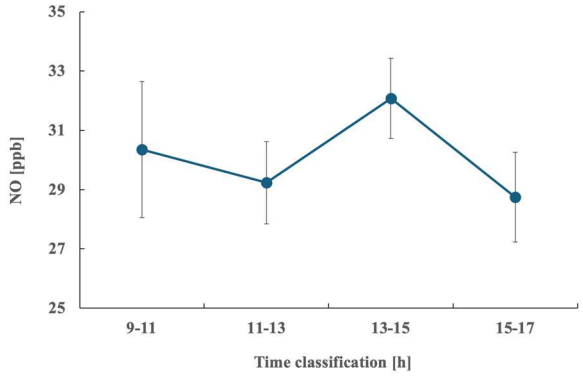

(b)

Figure 1. Number of measurements and variance of measurements. (a) shows the dispersion according to the measurement time period of the data, and (b) shows the results of the variance analysis. The concentration of NO is usually expressed in units of ppb (parts per billion) or ppm (parts per million). This indicates that a substance is present at a rate of one part per billion (ppb) or one part per million (ppm). The vertical axis, ppb (parts per billion), indicates that a substance is present at a rate of one part per billion. For example, if the concentration of NO in exhaled breath is 10 ppb, this means that there are 10 molecules of NO for every 100 million molecules of air.

4. Discussion

In this study, we analyzed exhaled NO values using analysis of variance: 80 cases from 9-11am, 89 cases from 11-1pm, 103 cases from 1-3pm, and 33 cases from 3-5pm. The results showed that there were no significant differences because NO fluctuates greatly from person to person, and that there are large fluctuations in the morning. First, we will consider the effects of circadian rhythms. In a previous study, the possible effects of the important internal variable circadian rhythm on exhaled breath temperature (EBT) were analyzed in a group of 24 healthy adult volunteers [39,40]. EBT was measured repeatedly at different times of day (8am, noon, 4pm, and 8pm), and the correlation with axillary temperature readings at these times was analyzed. The results reported that there were significant differences in some axillary temperature readings. The highest EBT was reported at 4pm, and the lowest EBT was reported at 8am, indicating that circadian rhythms affect EBT. This is the first analysis of circadian rhythms in healthy subjects exhaled NO levels, and it was shown that they are not affected by circadian rhythms compared to EBT.

Next, we will consider repeated measurements. Recent studies have shown excellent reproducibility in FeNO measurements, and in a study that determined whether repeated FeNO measurements were necessary in the same session for asthma screening, the value of repeated measurements was shown to be insignificant [41]. The results of this study are also consistent with the results of previous studies, as although there is a large individual difference in the measured NO values of healthy individuals, the variation within individuals is not that large. However, although previous studies have shown that repeated measurements of exhaled nitric oxide fraction are not essential for asthma screening, and have experimentally demonstrated that recent advances in measuring equipment have demonstrated excellent reproducibility of FeNO measurements, this study retrospectively examined the electronic medical records of adult outpatients who visited a respiratory department for a diagnosis of asthma, and evaluated clinically obtained FeNO measurements (analysis of data from 132 registered patients). This study differs from the previous study in that it was conducted on healthy subjects, and is novel in that similar results were shown in healthy subjects as well. NO analysis in exhaled breath is suitable for telemedicine for several reasons. First, NO is known as a physiological indicator that reflects the inflammatory state of the lungs, and is effective in monitoring respiratory diseases such as asthma and chronic obstructive pulmonary

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disease (COPD). In addition, NO measurement allows for real-time data collection and transmission, allowing medical professionals to remotely monitor the patient's condition and provide appropriate treatment and guidance. However, the problem with measuring NO is that it is costly. Although it can be widely introduced in resource-limited environments, there are some challenges in achieving high-precision health management. Although NO analysis could be a promising tool in telemedicine, it is desirable to continue development such as the development of simplified measurement equipment and the introduction of new sensor technologies.

This study has several limitations. First, the sample size is relatively small, which may affect the generalizability of the results. A limited number of participants can reduce the statistical power required to detect significant differences, potentially impacting the interpretation of the findings. Additionally, there was a wide age range among the participants, which is another limitation. Variations in age can influence the production and fluctuations of FeNO, and age-related physiological differences in the respiratory system may introduce bias in the results. The impact of these age-related variations should be considered, and a more age-homogeneous sample would have been preferable for more precise analysis. Given these constraints, future studies should involve larger sample sizes and aim to balance age groups to obtain more reliable and accurate results. However, despite these limitations, this study holds significant value for several reasons. Firstly, it represents an attempt to analyze diurnal variation using data from healthy individuals, which is a relatively novel approach in the field. By examining how FeNO fluctuates across different times of the day, we have provided insights into the natural variability of FeNO levels. Moreover, the study highlights the individual differences in FeNO measurements, an important factor that has often been overlooked in previous research. Understanding these individual variations can be crucial in interpreting FeNO data, particularly when considering its potential for use in clinical applications such as asthma diagnosis or remote monitoring [42–46]. This focus on individual variability offers valuable insights into how FeNO may behave differently across people, laying the groundwork for future research that could address the challenges and nuances of personalized medicine.

5. Conclusions

In this study, we analyzed NO levels (total 305 cases) of eight subjects measured at four different times in order to clarify the existence of diurnal variations in NO levels in healthy individuals and to examine the applicability of NO measurements to telemedicine. The results of the analysis showed that NO levels varied greatly between individuals, with no significant differences between groups. In addition, it was revealed that NO levels showed particularly large variations in the morning. These results differed from previous studies that showed that exhaled breath temperature showed diurnal variations. Further research is needed to investigate the factors behind individual differences.

Author Contributions: Conceptualization, E.Y.; methodology, E.Y.; software, Y.Y.; validation, E.Y., Y.Y.; formal analysis, Y.Y.; investigation, E.Y.; resources, E.Y.; data curation, T.A., Y.I., H.S.; writing—original draft preparation, E.Y.; writing—review and editing, E.Y.; visualization, Y.Y.; supervision, E.Y.; project administration, E.Y.; funding acquisition, E.Y. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Mie University Faculty of Engineering (No.132, 2/19/2025).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data supporting the reported results in this study are available upon request by contacting the corresponding author via email. Access to the data is restricted to research purposes only.

Conflicts of Interest: The authors declare no conflicts of interest.

 doi:10.20944/preprints202504.0860.v1

Abbreviations

All abbreviations used in this paper are explained within the text.

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