Quantitative analysis of the effect of fraction of inspired oxygen on peripheral oxygen saturation in healthy volunteers

**CURRENT STATUS:** POSTED

Ji-Yeon Bang  
Asan Medical Center  

Changhun Cho  
Asan Medical Center  

Eun-Kyung Lee  
Ewha Womans University  

Byung-Moon Choi  
Asan Medical Center  

Gyu-Jeong Noh  
Asan Medical Center

**DOi:**  
10.21203/rs.2.20198/v1

**SUBJECT AREAS**  
Anesthesiology & Pain Medicine

**KEYWORDS**  
* mathematical computing, oximetry, pharmacology*
Abstract

Background The international organization for standardization (ISO) 80601-2-61 dictates that the accuracy of a pulse oximeter should be assessed by a controlled desaturation study. We aimed to characterize the relationship between the fraction of inspired oxygen (FiO₂) and peripheral oxygen saturation (SpO₂) using a turnover model by retrospectively analyzing the data obtained from previous controlled desaturation studies. We also measured the changes in biomarkers expected to be related to hypoxia (i.e., lactate, carboxyhemoglobin (COHb), and methemoglobin (MetHb)) in response to short-term exposure to hypoxia.

Methods Volunteers were exposed to various levels of induced hypoxia over 70–100% arterial oxygen saturation (SaO₂). The study period consisted of two rounds of hypoxia and the volunteers were maintained in room air between each round. FiO₂ and SpO₂ were recorded continuously during the study period. A population pharmacodynamic analysis was performed with the NONMEM VII level 4 (ICON Development Solutions, Ellicott City, MD, USA). Lactate, COHb, and MetHb were measured using a CO-oximeter.

Results In total, 2899 SpO₂ data points obtained from 20 volunteers were used to determine the pharmacodynamic characteristics. The pharmacodynamic parameters were as follows: k out = 0.942 1/min, lmax = 0.802, IC 50 = 85.3%, γ = 27.3. The changes in SpO₂ due to decreases in FiO₂ well explained by the turnover model with inhibitory function as a sigmoidal model. As SpO₂ decreased, lactate and COHb increased as a whole, and COHb showed the best correlation (Pearson’s correlation, R² =0.3263, P < 0.0001).

Conclusion The potency of FiO₂ required to reduce SpO₂ from 100% to 70% was 14.7%.

Carboxyhemoglobin has the potential to be a useful biomarker for acute hypoxia.

Background

A pulse oximeter noninvasively measures arterial blood oxygen saturation. In clinical settings, respiratory management of patients is carried out by referring to the value of peripheral oxygen saturation (SpO₂) measured by the pulse oximeter [1, 2]. Therefore, it is important to ensure that pulse oximeters have high accuracy. The accuracy criteria for the pulse oximeter equipment are
provided in the international organization for standardization (ISO) 80601-2-61, and the U.S. Food and Drug Administration (FDA) only permits pulse oximeters that meet these criteria [3, 4]. According to the ISO 80601-2-61, the SpO2 accuracy of a pulse oximeter should be assessed through a controlled desaturation study by comparing to the gold standard measurements of blood arterial oxygen saturation (SaO2) obtained by a CO-oximeter [3]. In controlled desaturation studies, the range of SaO2 is typically 70–100%, and the subjects are temporarily exposed to a fraction of inspired oxygen (FiO2) lower than that in room air. In such situations, SpO2 seems to decrease as FiO2 decreases.

Quantifying the relationship between FiO2 and SpO2 allows us to better explain the two relationships. In general, a turnover model appropriately describes the relationship between drug concentration and response [5]; particularly, the model is able to explain the concentration-response relationship when an endogenous biomarker is the response [5, 6].

During prolonged hypoxia, anaerobic glycolysis increases lactate production [7]. Hypoxia also increases the release of carbon monoxide (CO) from smooth muscle cells [8]. In a previous study, lactate and carboxyhemoglobin (COHb) levels correlated well in patients with CO poisoning [9]. There was a report on a case in which methemoglobinemia was the cause of unexpected hypoxemia [10]. However, more research is needed to identify biomarkers that readily reflect the severity of hypoxia, and it is not known whether lactate, COHb, or methemoglobin (MetHb) could be useful indicators in case of short exposure to hypoxia such as that occurring in a controlled desaturation study.

The aim of this study was to characterize the relationship between FiO2 and SpO2 using a turnover model by retrospectively analysing the data obtained from a controlled desaturation study. In addition, we examined the effects of short-term exposure to hypoxia on the changes in biomarkers (lactate, COHb, and MetHb) that are expected to be related to hypoxia.

**Methods**

In order to evaluate the quantitative relationship between FiO2 and SpO2, we utilized data obtained from previous two controlled desaturation studies. The need for ethical approval for this study was waived by the Asan Medical Center Institutional Review Board. Briefly, the protocol of the controlled
desaturation study is as follows.

**Protocol of the controlled desaturation study.**

The study had a single-center, non-randomized design. The protocol was approved by the Asan Medical Center Institutional Review Board (approval number: 1st study: 2014-1194, 2nd study: 2016-0069). Written informed consent was obtained from all volunteers, whose inclusion criteria included aged 20-50 yr, carboxyhemoglobin < 3%, methemoglobin < 2%, and total hemoglobin concentration > 10 g/dl. Volunteer exclusion criteria included known history of respiratory or cardiovascular disease, smoking habits, evidence of pregnancy, history of syncope, diabetes mellitus, and body mass index ≥ 35 kg/m². The volunteers were fully informed of the study protocols and completed health assessment questionnaires prior to enrollment.

In an operating room equipped for a controlled desaturation study, the volunteers were monitored using electrocardiography, end-tidal carbon dioxide partial pressure, FiO₂, and non-invasive blood pressure by using Carescape® B850 (GE Healthcare, Milwaukee, WI, USA). Throughout the study period, all aforementioned data were continuously downloaded to personal computers. Each volunteer was placed in a semi-Fowler’s position and connected to a breathing circuit to administer the hypoxic gas mixture containing medical air, oxygen, nitrogen, and carbon dioxide. For frequent blood sampling, an arterial cannula was placed in a radial artery of each volunteer, and a reusable finger probe of a pulse oximeter (OxiMax® N-600x, Medtronic, Boulder, CO, USA) was placed on a finger on the cannulated side. In order to prevent hypoperfusion, an air warmer (Bair Hugger™, 3M™, St. Paul, MN, USA) was applied to the hand with the finger probe. Each volunteer was exposed to various levels of induced hypoxia over 70-100% SaO₂. Each plateau of oxygen saturation was maintained for at least 30 s until stabilization, after which 1 ml of arterial blood was drawn into a heparinized syringe. The study period consisted of two rounds of hypoxia and the volunteers were maintained in room air between each round.
Data selection of FiO$_2$ and SpO$_2$

The individual data files of FiO$_2$ and SpO$_2$ were recorded continuously during the study period. The FiO$_2$ and SpO$_2$ values were updated every 10 s and 1 s, respectively. For pharmacodynamic analysis, data points from every 20 s were selected.

Population pharmacodynamic analysis

A population pharmacodynamic analysis was performed with the NONMEM VII level 4 (ICON Development Solutions, Ellicott City, MD, USA). FiO$_2$ values were fitted to a turnover model using the ADVAN 13 subroutines and first-order conditional estimation with interaction. As the turnover model is mainly used to explain the relationship of increasing or decreasing response with increasing concentration, the processed FiO$_2$ was calculated for this application. Processed FiO$_2$ was defined as 100 minus FiO$_2$.

[Please see the supplementary files section to access the formulas.] (1 & 2)

where $k_{in}$ is the turnover rate constant, $k_{out}$ is the fractional turnover rate constant, and $SpO_{2\_baseline}$ is the baseline SpO$_2$. $I(c)$ is an inhibitory function to explain the relationship between the processed FiO$_2$ and SpO$_2$. $I(c)$ was expressed as a linear or a sigmodal model as follows,

[See supp. files] (3 & 4)

where slope is the slope factor in the inhibitory effect of FiO$_2$ on the production of the response (SpO$_2$), $I_{max}$ is the maximum fractional inhibitory ability of processed FiO$_2$ to affect SpO$_2$, $IC_{50}$ is the processed FiO$_2$ producing 50% of $I_{max}$, $g$ is the steepness of the processed FiO$_2$ versus SpO$_2$ relationship. To reduce the number of parameters to be estimated, $SpO_{2\_baseline}$ was set to 100. Inter-individual random variabilities of pharmacodynamic parameters were estimated by assuming a log-normal distribution. Diagonal matrices were estimated for the various distributions of $\eta$, where $\eta$ represents inter-individual random variability with a mean of zero and variance of $\omega^2$. Additive residual error model was evaluated during the model building process. NONMEM computed the
minimum objective function value (OFV), a statistical equivalent to the -2 log-likelihood of the model. An α level of 0.05, which corresponds to a reduction of 3.84 in the OFV (chi-square distribution, degree of freedom = 1, p < 0.05), was used to distinguish between hierarchical models [11]. The covariates analyzed were age, sex (1: male; 0: female), and race (1: Asian, 0: African). Non-parametric bootstrap analysis was used for internal validation of the models (fit4NM 3.3.3, Eun-Kyung Lee and Gyu-Jeong Noh; http://cran.r-project.org/web/packages/fit4NM/index.html; last accessed: March 16, 2011) [6]. Predictive checks were also performed using the fit4NM 3.3.3 [6].

**Biomarker study**

To assess whether there are biomarkers that respond to exposure to short-term hypoxia, we measured lactate, COHb, and MetHb using a CO-oximeter (ABL90 FLEX; Radiometer Medical A/S, Copenhagen, Denmark). These biomarkers were also obtained when arterial blood was collected to measure SaO\textsubscript{2} for the accuracy of the pulse oximeter.

**Statistics**

Statistical analyses were conducted using R (version 3.5.2; R Foundation for Statistical Computing, Vienna, Austria) or SigmaStat version 3.5 for Windows (Systat Software, Inc, Chicago, IL, USA). Data are expressed as mean ± standard deviation for normally distributed continuous variables, median (25-75%) for non-normally distributed continuous variables, or counts for categorical variables.

**Results**

Of the 24 volunteers enrolled, four were excluded from the pharmacodynamic analysis because of a technical error in FiO\textsubscript{2} data file storage. Hence, 20 and 24 volunteers were included in the pharmacodynamic and the biomarker analyses, respectively. The characteristics of these volunteers are summarized in Table 1. In total, 2899 SpO\textsubscript{2} data points from 20 volunteers were used to determine the pharmacodynamic characteristics. Time courses of the processed FiO\textsubscript{2} and SpO\textsubscript{2} are shown in Figure 1. As the FiO\textsubscript{2} decreased, the SpO\textsubscript{2} values tended to decrease as well. The SpO\textsubscript{2}
values were maintained between 65-100% in each round in which hypoxic gas was supplied. The turnover model well described the time course of SpO₂. In particular, expressing the inhibitory function as a sigmoid model rather than a linear model further reduced the objective function value (OFV: 14495.97 for the linear model, 13179.24 for the sigmoidal model). No significant covariates for the pharmacodynamic parameters were observed. Figure 2 shows the plots of the predicted versus observed SpO₂ in the volunteers with the lowest or highest absolute values of the individual mean of weighted residuals. Table 2 shows the population pharmacodynamic parameter estimates, inter-individual variability, and median parameter values (2.5-97.5%) of the non-parametric bootstrap replicates of the final pharmacodynamic model of SpO₂. Predictive checks of the final pharmacodynamic model are presented in Figure 3. In total, 19.5% of the data were distributed outside of the 90% prediction intervals of the predictive check. Each of the 587 values from 24 volunteers were included in the biomarker analysis. Changes in lactate, COHb, and MetHB with the decrease in SpO₂ during the controlled desaturation study period are shown in Figure 4. As SpO₂ decreased, lactate and COHb increased as a whole, and COHb showed the best correlation (Pearson's correlation, $R^2=0.3263$, $P < 0.0001$).

**Discussion**

The changes in SpO₂ due to decrease in FiO₂ under room air was well explained by the turnover model with inhibitory function as a sigmoidal model. In the setting of a controlled desaturation study, the potency of FiO₂ required to reduce SpO₂ from 100% to 70% was 14.7% and COHb increased as SpO₂ decreased. Among lactate, CoHb, and MetHb, COHb showed the best correlation with SpO₂. The pulse oximeter is an essential monitoring medical device across many fields of medicine [12]. The SpO₂ accuracy of a pulse oximeter equipment should be a root-mean-square difference of less than or equal to 4.0% SpO₂ over the range of 70%-100% SaO₂ [3].

[See supp. files] (5)

where $A_{rms}$ describes the combined bias and precision of SpO₂ readings, $SpO_{2j}$ means the $j^{th}$
measured SpO2 value of the ith volunteer, and $S_{Rij}$ refers to the jth measured standard reference value of the ith volunteer. The standard reference value is determined by SaO2, which is measured by using a CO-oximeter for arterial blood collected at the same time when SpO2 is observed. The common manufacturing literature claim for $A_{rms}$ for pulse oximeters is ± 2–3% over the range of 70–100% SpO2 [12]. The total number of acceptable SpO2-SaO2 pairs obtained during clinical trials should be sufficient to statistically validate the specified SpO2 accuracy. Typically, at least 10 volunteers are recruited, and at least 20 arterial blood samples per volunteer are obtained and analyzed with at least 200 data pairs. In addition, the distribution of the SaO2 values should have similar density over the entire required range; for example, the ranges of 70-79%, 80-89%, and 90-100% SaO2 should each have approximately 1/3 of the total data. Particularly, the complexion of the study participants should be specified because the accuracy of SpO2 depends on the complexion, with dark skin pigmentation resulting in an overestimation of arterial oxygen saturation especially at low saturation in some pulse oximeters [13]. With the Nellcor N-595 device (Medtronic, Boulder, CO, USA), there was a significant difference in bias, defined as SpO2 minus SaO2, between light skin and dark skin in the 60-100% SpO2 range [13]. For this reason, the U.S. FDA recommended that controlled desaturation studies should have subjects across a range of skin pigmentation, including at least 2 darkly pigmented subjects or 15% of the subject pool, whichever is larger [4]. However, in Korea, such desaturation study is not required to permit the pulse oximeter equipment.

If equilibrium is quickly established between the concentration of plasma and the response, then the pharmacological effect is immediately apparent; in such case, direct pharmacodynamic models such as the linear model or sigmoid Emax model can be applied. However, several drug responses can be considered as indirect in nature [14]. The turnover model can be appropriate for use when there is a delay between concentration and response [5, 14]; accordingly, the relationship between end-tidal carbon dioxide and regional cerebral oxygen saturation with delay was also quantified by the turnover model [6]. The net baseline effect is the balance between the apparent rate of “production” of the
response and the rate of “removal” of the response [5]. In situations where the production and removal of response are complex, one step is rate-limiting, and these are represented by first-order rate constants $k_{in}$ and $k_{out}$, respectively [5]. The turnover model is divided into four basic models depending on whether the response increases or decreases with increasing concentration [14]. The structural formulas of the four models are as follows [14].

[See supp. files for model formulas.]

Model 1: inhibition of production

Model 2: inhibition of loss

Model 3: stimulation of production

Model 4: stimulation of loss

, where $k_{in}$ is the turnover rate constant, $k_{out}$ is the fractional turnover rate constant, and $I_{max}$ and $E_{max}$ are maximal inhibitory and stimulatory effects attributed to drugs, respectively. $IC_{50}$ and $EC_{50}$ are drug concentration producing 50% of maximum stimulation and inhibition at effect site, respectively. $R$ is a response variable and $g$ is the sigmoidicity factor. In the current study, basic model 1 was applied. Also, the sigmoidal model was more suitable than the linear model for use as an inhibition function. Graphically, the predicted value estimated by the sigmoidal model was also closer to the observed value. Physiologically, it is difficult to interpret a linear decrease in SpO$_2$ as FiO$_2$ decreases. The oxygen–hemoglobin dissociation curve that plots the proportion of hemoglobin in its saturated form on the vertical axis against the prevailing oxygen tension on the horizontal axis has a sigmoid shape; therefore, it is also desirable to apply the sigmoidal model for inhibitory function.

Hypoxia induces changes in the expression of several genes including vascular endothelial growth factor [15]. Specifically, hypoxia increases the expression of the heme oxygenase (HO)-1 gene, thereby resulting in corresponding increases of HO enzymatic activity [8]. Activated HO increases the production of CO in smooth muscle cells [8], and the resulting CO quickly binds with hemoglobin and displaces oxygen to generate COHb [9]. Patients with chronic obstructive pulmonary diseases have a lower partial pressure of oxygen (PaO$_2$) and higher COHb than control subjects of similar age [16] In
our current study, we found that COHb is a sensitive biomarker of acute hypoxia even when exposed to short-term hypoxia, as COHb correlated well with the degree of hypoxia. In general, in cases of CO poisoning, COHb levels measured by CO-oximetry strongly correlates with clinical severity [17]. If the COHb level was less than 5%, there were no symptoms, and none of the volunteers who participated in the controlled desaturation study complained of inconvenience. Although our results showed that lactate had a significant correlation with the degree of hypoxia, previous studies suggested that lactate was not suitable as a reliable biomarker of tissue hypoxia in situations such as sepsis [18, 19]. MetHb is associated with anaemia-induced tissue hypoxia rather than FiO₂ reduction-associated hypoxia [20].

The following issues should be considered as limitations of this study. First, the observed FiO₂ may be somewhat inaccurate as intubation was not used and the volunteers breathed the mixed hypoxic gas through their mouth while their noses were blocked with a clothespin. Therefore, the volunteers’ exhalation may have affected the FiO₂. However, a desaturation study involving volunteers does not generally require endotracheal intubation; also, as shown in Figure 1, the changes in FiO₂ during the study period were generally acceptable. Second, interindividual variability (IIV) in pharmacodynamic parameters could not be explained by covariates. As depicted in Table 2, Imax had approximately 45% IIV. However, in volunteer-based studies, the covariates are often not included because the demographic characteristics are homogenous. Covariates may explain the IIV in pharmacokinetic and/or pharmacodynamic parameters in studies involving patients with varying characteristics [6, 21].

Conclusion
In conclusion, by using the data obtained in previous controlled desaturation studies, we observed that the SpO₂ value tended to decrease as the FiO₂ decreased. The relationship between FiO₂ and SpO₂ was well described by the turnover model with inhibitory function as a sigmoidal model. The potency of FiO₂ required to reduce SpO₂ from 100% to 70% was 14.7%. Lactate and COHb were significantly correlated with the degree of hypoxia. Among lactate, COHb, and MetHb, COHb showed the potential for use as a biomarker for acute hypoxia.

Declarations
Ethics approval and consent to participate
The need for ethical approval for this study was waived by the Asan Medical Center Institutional Review Board

Consent to publish
Not applicable

Availability of data and materials
All data generated or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests
None.

Funding
This study was supported by a grant (MFDS2015-20766) from the Ministry of Food and Drug Safety, Cheongju-si, Republic of Korea.

Author contributions
B. J., C. B. and N. G. designed the study; B. J., C. C., and C. B. collected the data; B. J., L. Y., C. B., and N. G. performed the data analysis and interpretation. All authors contributed to the writing of the manuscript, provided critical revisions and approved the final version.

Acknowledgments
We thank Joon Seo Lim, PhD, ELS from the Scientific Publications Team at Asan Medical Center for his editorial assistance in preparing this manuscript.
Abbreviations

CO  carbon monoxide
COHb  carboxyhemoglobin
FDA  Food and Drug Administration
FiO₂  fraction of inspired oxygen
ISO  international organization for standardization
OFV  objective function value
MetHb  methemoglobin
SaO₂  arterial oxygen saturation
SpO₂  peripheral oxygen saturation

References

1. O'Driscoll BR, Howard LS, Earis J, Mak V. British Thoracic Society Guideline for oxygen use in adults in healthcare and emergency settings. BMJ Open Respir Res. 2017;4:e000170.

2. Castillo A, Sola A, Baquero H, Neira F, Alvis R, Deulofeut R, Critz A. Pulse oxygen saturation levels and arterial oxygen tension values in newborns receiving oxygen therapy in the neonatal intensive care unit: is 85% to 93% an acceptable range? Pediatrics. 2008;121:882-9.

3. International Standard. ISO 80601-2-61:2011. Medical electrical equipment – Part 2-61: Particular requirements for basic safety and essential performance of pulse oximeter equipment. 2011. https://www.iso.org/standard/51847.html. Accessed Oct 17 2019.

4. U.S. Department of Health and Human Services, Food and Drug Administration. Pulse Oximeters - Premarket Notification Submissions [510(k)s]: Guidance for Industry and Food and Drug Administration Staff. 2013. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pulse-oximeters-premarket-notification-submissions-510ks-guidance-industry-and-food-and-drug. Accessed;

5. Upton RN, Mould DR. Basic concepts in population modeling, simulation, and model-based drug development: part 3-introduction to pharmacodynamic modeling methods. CPT Pharmacometrics Syst Pharmacol. 2014;3:e88.

6. Ki SH, Rhim JH, Park JH, Han YJ, Cho YP, Kwon TW, Choi BM, Noh GJ. Quantitative
analysis of the effect of end-tidal carbon dioxide on regional cerebral oxygen
saturation in patients undergoing carotid endarterectomy under general anaesthesia.
Br J Clin Pharmacol. 2018;84:292-300.

7. Rogatzki MJ, Ferguson BS, Goodwin ML, Gladden LB. Lactate is always the end
product of glycolysis. Front Neurosci. 2015;9:22.

8. Morita T, Perrella MA, Lee ME, Kourembanas S. Smooth muscle cell-derived carbon
monoxide is a regulator of vascular cGMP. Proc Natl Acad Sci U S A. 1995;92:1475-9.

9. İcme F, Kozaci N, Ay MO, Avci A, Gumusay U, Yilmaz M, Satar S. The relationship
between blood lactate, carboxy-hemoglobin and clinical status in CO poisoning. Eur
Rev Med Pharmacol Sci. 2014;18:393-7.

10. Spoon KC, Ramar K. Unexplained hypoxemia. J Clin Sleep Med. 2011;7:679-80.

11. Boeckmann AJ, Sheiner LB, Beal SL. NONMEM Users Guides - Part V Introductory
Guide. San Francisco: NONMEM Project Group and University of California; 1994.

12. Milner QJ, Mathews GR. An assessment of the accuracy of pulse oximeters.
Anaesthesia. 2012;67:396-401.

13. Bickler PE, Feiner JR, Severinghaus JW. Effects of skin pigmentation on pulse
oximeter accuracy at low saturation. Anesthesiology. 2005;102:715-9.

14. Dayneka NL, Garg V, Jusko WJ. Comparison of four basic models of indirect
pharmacodynamic responses. J Pharmacokinet Biopharm. 1993;21:457-78.

15. Shweiki D, Itin A, Soffer D, Keshet E. Vascular endothelial growth factor induced by
hypoxia may mediate hypoxia-initiated angiogenesis. Nature. 1992;359:843-5.

16. Yasuda H, Yamaya M, Nakayama K, Ebihara S, Sasaki T, Okinaga S, Inoue D, Asada M,
Nemoto M, Sasaki H. Increased arterial carboxyhemoglobin concentrations in chronic
obstructive pulmonary disease. Am J Respir Crit Care Med. 2005;171:1246-51.

17. Hullin T, Aboab J, Desseaux K, Chevret S, Annane D. Correlation between clinical
severity and different non-invasive measurements of carbon monoxide concentration:
A population study. PLoS One. 2017;12:e0174672.

18. James JH, Luchette FA, McCarter FD, Fischer JE. Lactate is an unreliable indicator of
tissue hypoxia in injury or sepsis. Lancet. 1999;354:505-8.

19. Liu ZJ, Liu JL, Qu HP. Could lactate become a biomarker of hypoxia and a target of
resuscitation in sepsis? Crit Care Med. 2016;44:e178.

20. Hare GM, Tsui AK, Crawford JH, Patel RP. Is methemoglobin an inert bystander,
biomarker or a mediator of oxidative stress--The example of anemia? Redox Biol.
2013;1:65-9.

21. Park JH, Choi SM, Park JH, Lee KH, Yun HJ, Lee EK, Choi BM, Noh GJ. Population
pharmacokinetic analysis of propofol in underweight patients under general
anaesthesia. Br J Anaesth. 2018;121:559-66.

Tables
Table 1. Characteristics of the volunteer populations in the pharmacodynamic and biomarker studies

|                         | Pharmacodynamics (n=20) | Biomarker (n=24) |
|-------------------------|------------------------|-----------------|
| Age, yr                 | 23.7 ± 4.2             | 24.4 ± 5.4       |
| Weight, kg              | 66.9 ± 10.8            | 66.4 ± 10.4      |
| Height, cm              | 173.1 ± 7.7            | 173.0 ± 7.5      |
| Male/Female, n          | 15/5                   | 18/6             |
| Complexion              | Light/Medium/Dark, n   | Light/Medium/Dark, n |
| Race                    | Asian/African, n       | Asian/African, n |

Data are presented as mean ± SD or count as appropriate.

Table 2. Population pharmacodynamic parameter estimates, inter-individual variability, and median parameter values (2.5-97.5%) of the non-parametric bootstrap replicates of the final pharmacodynamic model of peripheral oxygen saturation (SpO₂).
| Parameter               | Estimate (RSE, %) | CV (%) | Median (2.5-97.5%) |
|------------------------|------------------|--------|-------------------|
| $k_{out}$ (1/min)      | 0.942 (8.6)      | 48.0   | 0.98 (0.92-1.01)  |
| $SpO_2_{baseline}$     | 100 (-)          |        | -                 |
| $I_{max}$              | 0.802 (4.2)      | 50.8   | 0.68 (0.30-1.06)  |
| $IC_{50}$ (%)          | 85.3 (3.0)       | 44.5   | 85.6 (82.7-99.4)  |
| $g$                    | 27.3 (13.0)      | 29.4   | 29.8 (26.3-69.6)  |
| $\sigma$              | 32.8 (0.2)       |        | 36.1 (25.6-40.1)  |

Log-normal distribution of inter-individual random variability was assumed. Residual random variability was modeled using an additive error model. Non-parametric bootstrap analysis was repeated 1000 times. RSE: relative standard error = SE/mean * 100 (%); CV: coefficient of variation; $k_{out}$: fractional turnover rate constant; $SpO_2_{baseline}$: baseline $SpO_2$. $SpO_2_{baseline}$ was set to 100. $I_{max}$: maximum fractional inhibitory ability of processed $FiO_2$ (fraction of inspired oxygen, %) to affect $SpO_2$. Processed $FiO_2$ was defined as 100 minus $FiO_2$. $IC_{50}$: processed $FiO_2$ producing 50% of $I_{max}$. $g$: steepness of the processed $FiO_2$ versus $SpO_2$ relationship.

Appendix. Example Of The Control Stream Used In The Pharmacodynamic Modeling

**Turnover model**

```plaintext
$PROB RUN# 508 (Turnover model for quantitative relationship between FiO2 and SpO2)
$INPUT ID OID TIME CP DV MDV HT WT AGE SEX RACE
$DATA MIR_HPR_NONMEM_OID.csv IGNORE=@
  ; TIME: min
  ; CP: 100 - FiO2 (%)
  ; DV: SpO2 (%)
  ; SEX: M=1, F=0
  ; AGE: yr, WT: kg, HT: cm
  ; RACE: Asian=1, African=0
$SUBROUTINE ADVAN=13 TRANS=1 TOL=3
$MODEL COMP (EFF)
$PK
  TH1 = THETA(1)
  TH2 = THETA(2)
  TH3 = THETA(3)
  TH4 = THETA(4)
  TH5 = THETA(5)
  KOUT = TH1*EXP(ETA(1))
```
BRSPO = TH2*EXP(ETA(2))
IMAX = TH3*EXP(ETA(3))
IC50 = TH4*EXP(ETA(4))
GAM = TH5*EXP(ETA(5))
KIN = KOUT*BRSPO
IF(A_0FLG.EQ.1) A_0(1)=BRSPO

$DES
FIO2=1 - (IMAX*CP**GAM/(IC50**GAM+CP**GAM))
DADT(1) = KIN*FIO2 - KOUT*A(1)

$ERROR
SPO2 = A(1)
IPRED = SPO2
W = 1
IRES = DV - IPRED
IWRES = IRES / W
Y = IPRED + W*EPS(1)

$THETA;#4
(0.6, 0.98); KOUT
100 FIX; BRSPO
(0, 0.68); IMAX
(70, 85, 100); IC50
(20, 30); GAM

$OMEGA;#4
0.2; IIV_KOUT
0 FIX; IIV_BRSO
0.2; IIV_IMAX
0.2; IIV_IC50
0.2; IIV_GAM

$SIGMA;#1
40; EPS

$ESTIMATION NOTBT NOOBT NOSBT SIGL=3 NSIG=1 MAXEVAL=9999 PRINT=5 METHOD=1 INTER MSFO=508.MSF NOAB
$COVARIANCE PRINT=E

Figures
Figure 1

Time courses of the processed fractions of inspired oxygen (FiO$_2$, A) and peripheral oxygen saturation (SpO$_2$, C) in all volunteers (n = 20). Processed FiO$_2$ was defined as 100 minus FiO$_2$. Changes in the processed FiO$_2$ (B) and SpO$_2$ (D) during the study period in one volunteer (ID4) are shown.
Predicted and observed peripheral oxygen saturation (SpO2) in volunteers with the lowest (A and B) or the highest (C and D) absolute values of the individual mean of weighted residuals (A: ID2, 8.9%; B: ID4, 8.0%, C: ID8, 14.6%; D: ID7, 14.3%). The weighted residual was calculated as (measured - population predicted)/population predicted. The blue solid line and the red dotted line indicate population and individual prediction, respectively. Closed circles represent the observed SpO2 values.
Figure 3
Predictive checks of the final dynamic model of peripheral oxygen saturation (SpO2). The red solid line indicates the 50% prediction line. The blue dashed lines indicate the 5% and 95% prediction lines. +: observed SpO2.

\[ R^2 = 0.0075, \ P = 0.036 \]
B

\((R^2=0.3263, P<0.0001)\)

C

\((R^2=0.0029, P=0.19)\)
Figure 4

Changes in lactate (A), carboxyhemoglobin (COHb; B), and methemoglobin (MetHB; C) during the controlled desaturation study period. Red solid lines represent the locally weighted scatterplot smoothing (LOWESS) curves. In total, 2348 points were calculated with pulse oximeter ranging from 66.2% to 100%, and the number of points in the smoothing window was 5 (Prism 8 for Windows version 8.2.1; GraphPad Software Inc., San Diego, CA, USA).

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.
Formulas.docx