Original Article

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

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**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 ($FiO_2$) and peripheral oxygen saturation ($SpO_2$) using a turnover model by retrospectively analyzing the data obtained from previous controlled desaturation studies.

**Materials and Methods:** 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. Volunteers were exposed to various levels of induced hypoxia over 70-100% arterial oxygen saturation ($SaO_2$). The study period consisted of two rounds of hypoxia and the volunteers were maintained in room air between each round. $FiO_2$ and $SpO_2$ 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).

**Results:** In total, 2899 $SpO_2$ 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, $Imax$ = 0.802, $IC_{50}$ = 85.3%, $\gamma$ = 27.3.

**Conclusion:** The changes in $SpO_2$ due to decreases in $FiO_2$ well explained by the turnover model with inhibitory function as a sigmoidal model.

**Keywords:** Mathematical Computing; Oximetry; Pharmacology.



## INTRODUCTION

A pulse oximeter noninvasively measures arterial blood oxygen saturation in dental care area. Respiratory management of patients is carried out by referring to the value of peripheral oxygen saturation ($SpO_2$) 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 Standard 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 $SpO_2$ accuracy of a pulse oximeter should be assessed through a controlled desaturation study by comparing to the gold standard

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measurements of blood arterial oxygen saturation ($SaO_2$) obtained by a CO-oximeter [3]. In controlled desaturation studies, the range of $SaO_2$ is typically 70–100%, and the subjects are temporarily exposed to a fraction of inspired oxygen ($FiO_2$) lower than that in room air. In such situations, $SpO_2$ seems to decrease as $FiO_2$ decreases. Quantifying the relationship between $FiO_2$ and $SpO_2$ 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].

The aim of this study was to characterize the relationship between $FiO_2$ and $SpO_2$ using a turnover model by retrospectively analyzing the data obtained from a controlled desaturation study.

## METHODS

In order to evaluate the quantitative relationship between $FiO_2$ and $SpO_2$, we utilized data obtained from a previous controlled desaturation study. Briefly, the protocol of the controlled desaturation study is as follows.

### 1. 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/m$^2$. 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, $FiO_2$, 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% $SaO_2$. 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.

### 2. 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.

### 3. Population pharmacodynamic analysis

A population pharmacodynamic analysis was performed with the NONMEM VII level 4 (ICON Development Solutions, Ellicott City, MD, USA). A turnover model using the ADVAN 13 subroutines and first-order conditional estimation with interaction was fitted to $FiO_2$-$SpO_2$ pair data. 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 $FiO_2$.

$$\frac{d(SpO_2)}{dt} = k_{in} \cdot I(c) - k_{out} \cdot SpO_2 \qquad (1)$$

$$SpO_{2\_baseline} = \frac{k_{in}}{k_{out}} \qquad (2)$$

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,

$$I(c) = 1 - slope \times FiO_2 \qquad (3)$$

$$I(c) = 1 - I_{\max} \times \left( \frac{C_p^{\gamma}}{IC_{50}^{\gamma} + C_p^{\gamma}} \right) \qquad (4)$$

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 $I_{max}$, $\gamma$ 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 $\alpha$ 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 [7]. 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].

### 4. 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 because of a technical error in $FiO_2$ data file storage. Hence, 20 volunteers were included in the pharmacodynamic analysis. The characteristics of these volunteers are summarized in Table 1. In total, 2899 $SpO_2$ data points from 20 volunteers were used to determine the pharmacodynamic characteristics. Time courses of the processed $FiO_2$ and $SpO_2$ are shown in Figure 1. As the $FiO_2$ decreased, the $SpO_2$ values tended to decrease as well. The $SpO_2$ values were maintained between 65-100% in each round in which hypoxic gas was supplied.

The turnover model well described the time course of $SpO_2$ (Appendix). 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

Table 1. Volunteer characteristics (n = 20)

| | |
|---|---|
| Age, yr | 23.7 ± 4.2 |
| Weight, kg | 66.9 ± 10.8 |
| Height, cm | 173.1 ± 7.7 |
| Male/Female, n | 15/5 |
| Complexion | |
| Light/Medium/Dark, n | 2/16/2 |
| Ethnicity | |
| Asian/African, n | 18/2 |

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

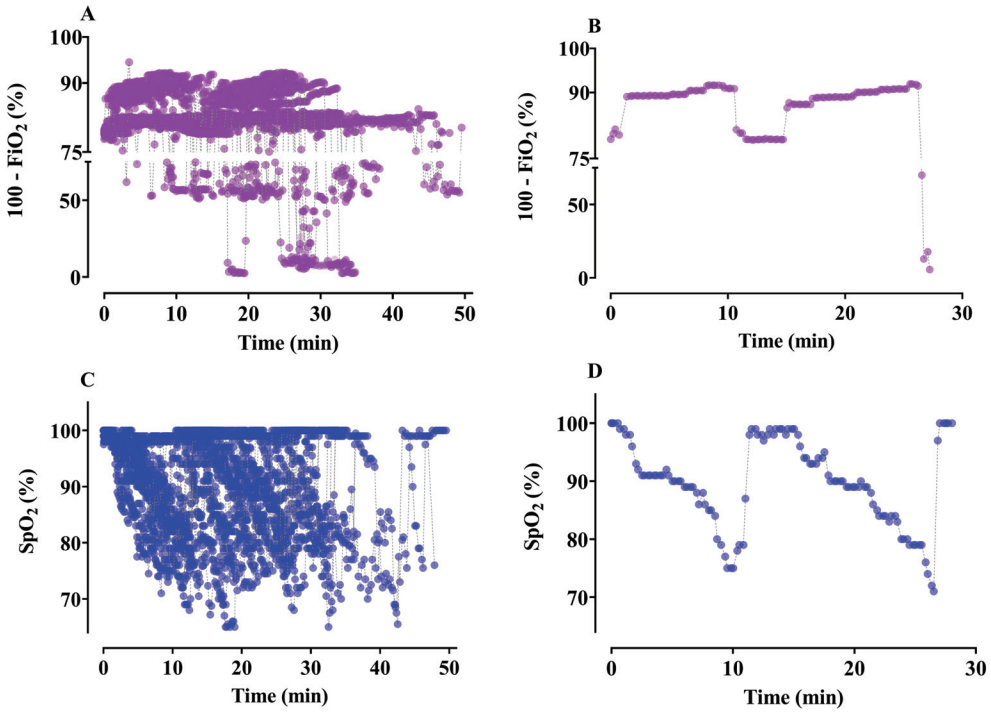


Fig. 1. Time courses of the processed fractions of inspired oxygen ($FiO_2$, A) and peripheral oxygen saturation ($SpO_2$, C) in all volunteers (n = 20). Processed $FiO_2$ was defined as 100 minus $FiO_2$. Changes in the processed $FiO_2$ (B) and $SpO_2$ (D) during the study period in one volunteer (ID4) are shown.

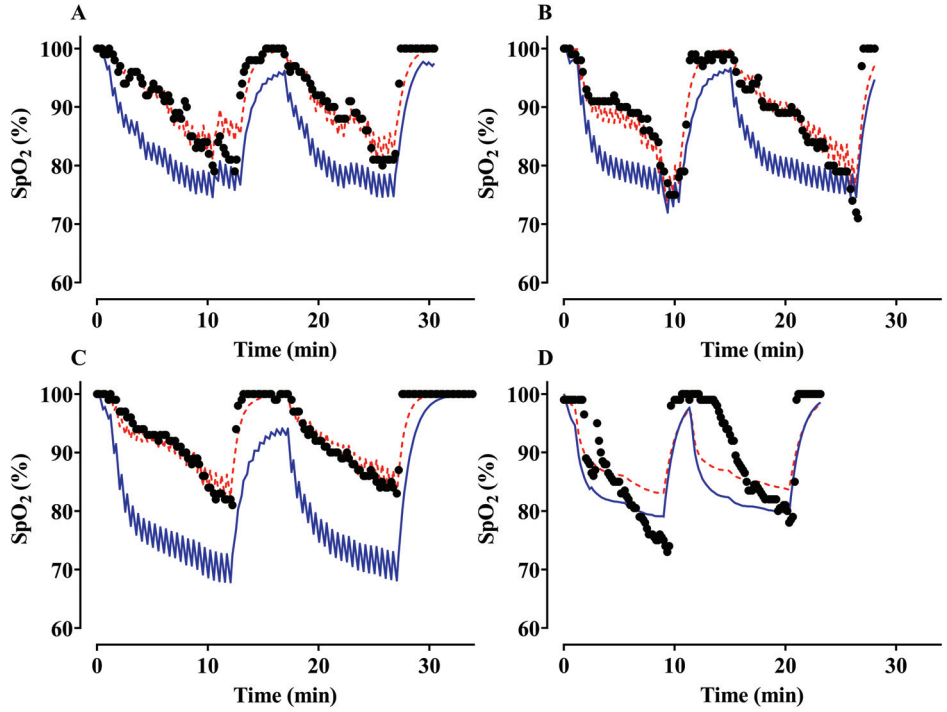


Fig. 2. Predicted and observed peripheral oxygen saturation ($SpO_2$) in volunteers with the lowest (A and B) or the highest (C and D) absolute values of the individual mean of weighted residuals (A: ID2, 8.9%; B: ID4, 8.0%, C: ID8, 14.6%; D: ID7, 14.3%). The weighted residual was calculated as (measured - population predicted)/population predicted. The blue solid line and the red dotted line indicate population and individual prediction, respectively. Closed circles represent the observed $SpO_2$ values.

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 ($SpO_2$)

| 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) |
| $\gamma$ | 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 $I_{max}$. $\gamma$: steepness of the processed $FiO_2$ *versus* $SpO_2$ relationship.

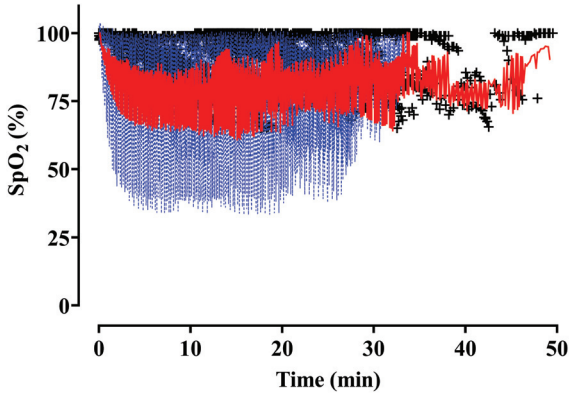


Fig. 3. Predictive checks of the final dynamic model of peripheral oxygen saturation ($SpO_2$). The red solid line indicates the 50% prediction line. The blue dashed lines indicate the 5% and 95% prediction lines. +: observed $SpO_2$.

significant covariates for the pharmacodynamic parameters were observed. Figure 2 shows the plots of the predicted versus observed $SpO_2$ 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 $SpO_2$. 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.

## DISCUSSION

The changes in $SpO_2$ due to decrease in $FiO_2$ 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 $FiO_2$ required to reduce $SpO_2$ from 100% to 70% was 14.7%.

The pulse oximeter is an essential monitoring medical device across many fields of medicine [8]. The $SpO_2$ accuracy of a pulse oximeter equipment should be a root-mean-square difference of less than or equal to 4.0% $SpO_2$ over the range of 70%–100% $SaO_2$ [3],

$$A_{rms} = \sqrt{\frac{\sum_{i=1}^{n}\left(SpO_{2ij} - S_{Rij}\right)^2}{n}} \qquad (5)$$

where $A_{rms}$ describes the combined bias and precision of $SpO_2$ readings, $SpO_{2ij}$ means the $j^{th}$ measured $SpO_2$ value of the $i^{th}$ volunteer, and $S_{Rij}$ refers to the $j^{th}$ measured standard reference value of the $i^{th}$ volunteer. The standard reference value is determined by $SaO_2$, which is measured by using a CO-oximeter for arterial blood collected at the same time when $SpO_2$ is observed. The common manufacturing literature claim for $A_{rms}$ for pulse oximeters is ± 2–3% over the range of 70–100% $SpO_2$ [8]. The total number of acceptable $SpO_2$-$SaO_2$ pairs obtained during clinical trials should be sufficient to statistically validate the specified $SpO_2$ 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 $SaO_2$ values should have similar density over the entire required range; for example, the ranges of 70-79%, 80-89%,

and 90-100% $SaO_2$ should each have approximately 1/3 of the total data. Particularly, the complexion of the study participants should be specified because the accuracy of $SpO_2$ depends on the complexion, with dark skin pigmentation resulting in an overestimation of arterial oxygen saturation especially at low saturation in some pulse oximeters [9]. With the Nellcor N-595 device (Medtronic, Boulder, CO, USA), there was a significant difference in bias, defined as $SpO_2$ minus $SaO_2$, between light skin and dark skin in the 60-100% $SpO_2$ range [9]. For this reason, the U.S. FDA recommended that controlled desaturation studies should have subjects across a range of skin pigmentations, 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 [10]. The turnover model can be appropriate for use when there is a delay between concentration and response [5,10]; 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 [10]. The structural formulas of the four models are as follows [10].

Model 1: inhibition of production

$$\frac{dR}{dt} = k_{in} \times \left(1 - I_{\max} \times \frac{C_p^{\gamma}}{IC_{50} + C_p^{\gamma}}\right) - k_{out} \times R$$

Model 2: inhibition of loss

$$\frac{dR}{dt} = k_{in} - k_{out} \times R \times \left(1 - I_{\max} \times \frac{C_p^{\gamma}}{IC_{50} + C_p^{\gamma}}\right)$$

Model 3: stimulation of production

$$\frac{dR}{dt} = k_{in} \times \left(1 + E_{\max} \times \frac{C_p^{\gamma}}{EC_{50} + C_p^{\gamma}}\right) - k_{out} \times R$$

Model 4: stimulation of loss

$$\frac{dR}{dt} = k_{in} - k_{out} \times R \times \left(1 + E_{\max} \times \frac{C_p^{\gamma}}{EC_{50} + C_p^{\gamma}}\right)$$

, 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 $\gamma$ 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.

The following issues should be considered as limitations of this study. First, the observed $FiO_2$ 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 $FiO_2$. However, a desaturation study involving volunteers does not generally require endotracheal intubation; also, as shown in Figure 1, the changes in $FiO_2$ 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, $IC_{50}$ 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 [6,11]. Importantly, the number of volunteers in this study was too small to include covariates.

In conclusion, by using the data obtained in previous controlled desaturation studies, we observed that the $SpO_2$ value tended to decrease as the $FiO_2$ decreased. The relationship between $FiO_2$ and $SpO_2$ was well described by the turnover model with inhibitory function as a sigmoidal model. The potency of $FiO_2$ required to reduce $SpO_2$ from 100% to 70% was 14.7%.


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## AUTHOR CONTRIBUTIONS

**Bong Jin Kang:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Visualization, Writing - original draft.
**Myojung Kim:** Data curation, Methodology, Visualization, Writing - original draft, Writing - review & editing
**Ji-Yeon Bang:** Conceptualization, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.
**Eun-Kyung Lee:** Methodology, Formal analysis, Writing - review & editing.
**Byung-Moon Choi:** Conceptualization, Data curation, Formal analysis, Methodology, Investigation, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.
**Gyu-Jeong Noh:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing


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Appendix. Example of the control stream used in the pharmacodynamic modeling

*Turnover model*

```
$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 NOABORT
$COVARIANCE PRINT=E
```