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Short Communication

Morbid Obesity Alters both Pharmacokinetics and Pharmacodynamics of Propofol:

Dosing Recommendation for Anesthesia Induction

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Running Title: Effects of morbid obesity on propofol PK/PD

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Non-standard abbreviations

BIS, bispectral index; BMI, body mass index; EEG, electroencephalographic; GABA, gamma amino butyric acid; HPLC, high performance liquid chromatography; LBW, lean body weight; MO, morbidly obese; PK/PD, pharmacokinetics and pharmacodynamics; TBW, total body weight, VPC, visual predictive check.
Abstract

The prevalence of obesity has markedly increased worldwide. Obese patients pose significant challenges to anaesthesiologists with regard to accurate dosing of anesthetics due to potentially altered pharmacokinetics (PK). Here we determined the PK and pharmacodynamics (PD) of propofol for anesthesia induction in morbidly obese (MO) subjects (BMI > 35 kg/m²) at two dosing regimens [i.e., dosing based on TBW (total body weight) and LBW (lean body weight), respectively]. The propofol pharmacokinetic profile was well fitted with a two-compartment model. It was found that both elimination clearance [CL; 223-243% of control group (BMI < 25 kg/m²), p < 0.01] and peripheral compartment volume (V₂; 156-180% of control, p < 0.01) were significantly increased in MO subjects, resulting in an equal or decreased propofol level in the plasma (TBW-based dosing). Further, the propofol pharmacodynamics (measured by bispectral index) were adequately described by a PK/PD model that linked an effect compartment to the two-compartment PK model through a sigmoidal Eₘ₅₀ model. All PD parameters except EC₅₀ (the half maximal effect concentration) were similar (p > 0.05) between MO and the control subjects. MO led to a significant decrease (37.9-38.6%, p < 0.01) in the EC₅₀ value, suggestive of increased brain sensitivity to propofol in MO population. Moreover, dose reduction (i.e., dosing based on LBW) generated identical anesthetic effects in MO as compared to the control subjects. In conclusion, morbid obesity significantly altered both pharmacokinetics and pharmacodynamics of propofol. LBW was a better weight-based dosing scalar for anesthesia induction with propofol in MO subjects.
Introduction

Propofol is a commonly used drug for the induction and maintenance of general anesthesia. Basic pharmacokinetic properties of propofol in humans are well documented (Campbell et al., 1988; Morgan et al., 1990). In line with its highly lipophilic feature, propofol shows a very large volume of distribution (Shafer, 1993). Despite that propofol undergoes extensive metabolism (mainly glucuronidation and oxidation) in the liver, it has a very long apparent elimination half-life (Campbell et al., 1988; Favetta et al., 2002). The relatively long elimination is accounted for by the multi-compartment PK of the drug wherein the elimination process is primarily governed by the inter-compartment distribution (Morgan et al., 1990). Propofol PK is generally described by the two-compartment (Peeters et al., 2008a; Bienert et al., 2010; Wiczling et al., 2012) or three-compartment model (Schnider et al., 1998; van Kralingen et al., 2011). The selection of best model appears to depend on the duration of blood collection, sampling frequency, and the manner of administration (e.g., bolus or infusion) (Wiczling et al., 2012).

Propofol PK and pharmacodynamics (PD) are subjected to a high inter-individual variability. The factors contributing to the variability include the age, body weight and disease state (Peeters et al., 2008a; van Kralingen et al., 2011). Of note, obesity (the individuals with BMI values of > 30 kg/m² are defined as obese, whereas those with BMI values of > 35 kg/m² are defined as morbidly obese) is shown to significantly affect propofol PK (van Kralingen et al., 2011). The prevalence of adult obesity has been reported to be 34.9% in the United States (Ogden, 2014). Therefore, it remains a major task to determine the dosing regimen for propofol use in obese...
patients. Mistakes are often made in drug administration using the same recommended dose as that for the individuals with normal weights (De Baerdemaeker and Margarson, 2016).

It has been reported that morbid obesity significantly influences propofol PK, possibly resulting in altered drug responses (van Kralingen et al., 2011; Ingrande et al., 2011). However, there is still no consensus on correct dosing regimen of propofol for morbidly obese (MO) patients (Friesen, 2016). The present study aimed to evaluate the PK/PD of propofol (dosed based on TBW and LBW, respectively) in MO subjects, and to explore the correct dosing regimen of propofol in this population. A clinical trial study was performed to determine and compare the propofol PK/PD in MO versus the control subjects. Concentrations of propofol in the plasma were quantified by HPLC analyses. The bispectral index (BIS) values were collected to define the PD effects. Population PK/PD modeling were performed using the MONOLIX software.

**Materials and Methods**

**Materials**

Propofol (reference standard) was obtained from Sigma–Aldrich (St Louis, MO).

**Study design**

This clinical trial study of propofol was approved by the Ethic Committee of the First Affiliated Hospital of Jinan University and was conducted in the First Affiliated Hospital of Jinan University (Guangzhou, China). A total of 29 patients were enrolled in this clinical trial (see Supplemental Figure1 for the approval form). All 29 patients were ASA (American Society of Anaesthesiologists) physical status I or II, and were scheduled for gastrointestinal operations under general
anesthesia (Supplemental Table 1). Of these 29 subjects, 23 were MO (BMI > 35 kg/m2). These 23 subjects were randomized into 2 groups to receive a bolus injection of propofol (2 mg/kg) for anesthesia induction based on either TBW \((n = 12)\) or LBW \((n = 11)\). All MO subjects underwent laparoscopic gastric bypass surgery. Six patients in the control group (BMI < 25 kg/m2) received a bolus injection of propofol (2 mg/kg) based on TBW. All subjects in the control group underwent laparoscopically assisted gastrectomy due to stomach cancer or gastric bleeding.

**Anesthesia**

A catheter was introduced into the cephalic vein for drug administration. All patients breathed oxygen for 3 minutes via the facemask (to maintain SpO2 of > 95%) prior to anesthesia execution. Anesthesia was induced with intravenous administration of 0.05 mg/kg midazolam, 2 μg/kg fentanyl, 0.6 mg/kg rocuronium, and 2 mg/kg propofol (Diprivan, Corden Pharma, Caponago, Italy). All patients received midazolam, fentanyl and rocuronium at the doses based on LBW (Janmahasatian et al., 2005). MO patients were randomized to receive propofol basing on TBW \((n = 12)\) or LBW \((n = 11)\), whereas all control patients received propofol based on TBW \((n = 6)\). Anesthesia was maintained by continuous infusion of propofol (4 mg/kg/h), tracrium (8 μg/kg/min), and remifentanil (0.2 μg/kg/min) based on LBW.

**BIS monitoring**

The depth of anesthesia was determined with a BIS® Vista monitor (Aspect Medical Systems, Newton, MA). BIS, an electroencephalographic measure of anaesthetic depth, was selected as the PD endpoint quantifying the effects of propofol on CNS. The BIS values were obtained before anesthesia (time 0) and at 1, 2, 4, 6, 8, 10, 15, 20 min after anesthesia (propofol administration).

**Blood sampling**

About 3-ml of blood samples were collected via radial artery catheterization before (time 0) and at 1, 2, 4, 6, 8, 10, 15, 20 min after administration of propofol. The samples were subsequently transferred to heparin-pretreated EP tubes. This was followed by 9,000 g centrifugation at 4°C.
for 3 mins. The supernatant was collected and the samples were stored at -80 °C until analysis.

**Quantification of plasma propofol by HPLC**

Plasma propofol was quantified using Dionex U3000 HPLC system (Dionex, Sunnyvale, CA) equipped with an Acclaim 120 C18 column (4.6 × 250 mm, 5 μm, Thermo). A gradient elution was performed using water (A) and acetonitrile (B). The gradient program consisted of 30-80% B at 0-5 min, 80% B at 5-9 min, and 80-30% B at 9-12 min. The detection wavelength was 220 nm and the flow rate was set at 1 ml/min. The quantitation method was validated with regard to the linearity (0.12–7.5 μg/ml), intra-day/inter-day precision (RSD <15%), and recovery (within 90–110%) etc. (Supplemental Figure 2).

**Pharmacokinetic modeling**

Nonlinear mixed-effect modeling approach was used to analyze the pharmacokinetic data of propofol. The population analysis was performed using the MONOLIX software version 2016R1 (LIXOFT, Paris, France). The Stochastic Approximation Expectation-Maximization (SAEM) algorithm coupled with the Markov Chain Monte Carlo procedure for likelihood maximization was used for estimation of population parameters (Chan et al., 2011). The inter-individual variability in mixed-effect model parameters was described using an exponential model:

\[ P_{\text{ind}} = P_{\text{pop}} \cdot \text{Exp}(\eta) \quad \eta \sim N(0, \omega) \]

where \( P_{\text{ind}} \) represents the individual parameter; \( P_{\text{pop}} \) is the fixed effect (population mean) and \( \eta \) denotes the random effect (normally distributed) accounting for the individual deviations from the population mean.

Conventional two-compartment and three-compartment models (the mass balance equations can be found in Supplementary Materials) were used to fit the pharmacokinetic data (Figure 1A). The Goodness of fit was evaluated by Akaike information criterion (AIC), Bayesian information criterion (BIC), and the diagnostic plots such as VPCs.
Pharmacokinetic/pharmacodynamic (PK/PD) modeling

A PK/PD model was built by linking an effect (biophase) compartment to the two-compartment pharmacokinetic model (Figure 1B). The rate constant $k_{e0}$ describes the drug distribution to the effect compartment from the central compartment, accounting for the delay in the PD (anesthetic) effect. The anesthetic effect (BIS) was linked to the drug concentrations in the effect compartment through a sigmoidal $E_{max}$ model.

$$BIS(t) = BIS_0(1 - \frac{E_{max} C_e^\gamma}{EC_{50}^\gamma + C_e^\gamma})$$

where $BIS_0$ is the baseline BIS score, $E_{max}$ is the maximal effect (fixed at 1), and $EC_{50}$ is the drug concentration associated with 50% of the maximal effect (or half maximal effect concentration). The slope factor ($\gamma$) is a PD parameter relating to the steepness of the response curve. The $C_e$ denotes the effect compartment concentration. The change in $C_e$ was defined by the following equation:

$$\frac{dC_e}{dt} = k_{e0}C_e - k_{e0}C_e$$

Nonlinear mixed-effect modeling approach was used to analyze the PK/PD data. The population analysis was performed using the MONOLIX software version 2016R1 (LIXOFT, Paris, France). The inter-individual variability for the PK/PD parameters was modelled assuming log-normal distribution:

$$P_{ind} = P_{pop}Exp(\eta) \quad \eta \in N(0, \omega)$$

where $P_{ind}$ represents the individual parameter; $P_{pop}$ is the fixed effect (population mean) and $\eta$ denotes the random effect (normally distributed) accounting for the individual deviations from the population mean.

A sequential approach was applied in PK/PD modeling (Zhang et al., 2003). In the sequential approach, a PK model was firstly developed and the parameter estimates were derived. In the second step, the individual estimates of PK parameters derived from the PK
analysis were used to drive the PD modeling.

Statistical Analysis

Data are presented as mean ± standard deviation (SD). Statistically significant differences were analyzed by one-way ANOVA or Student’s t-test (the significance level was fixed at \( p < 0.05 \) or \( p < 0.01 \) or \( p < 0.001 \)).

Results and Discussion

Altered propofol pharmacokinetics in MO patients

The plasma levels of propofol at later time points (≥ 6 mins) were significantly lower (\( p < 0.05 \)) in MO-TBW than in the control subjects (Figure 1C). This suggested that the pharmacokinetics of propofol was significantly altered in MO subjects. We also compared the plasma levels versus time profiles for the control and MO-LBW subjects (Figure 1C). It was not surprising that plasma levels of propofol (≥ 2 min) were markedly lower (\( p < 0.001 \)) in MO-LBW than in the control subjects (Figure 1C).

The conventional two-compartment model was a more appropriate model for describing the PK data on the basis of the AIC and BIC values (Supplemental Table 2). The predicted concentrations based on individual parameters were close to the observed ones (Supplemental Figure 3), suggestive of adequate model fitting. The CL value was significantly higher (9.15-10.0 vs 4.11 L/min, \( p < 0.01 \)) in MO than in the control subjects (Figure 1D & Table 1). Further, morbid obesity led to a significant increase (73.2-84.2 vs 46.9 L, \( p < 0.01 \)) in the volume of peripheral compartment (\( V_2 \)). It was interesting to note that TBW-normalized CL and \( V_2 \) values were not
changed (p > 0.05) in MO subjects (Figure 1E). Consistently, CL and V₂ were positively correlated with the body weight according to the covariate models generated using both obese and non-obese data (Figure 1D & Supplemental Table 3). Taken together, the results suggested that morbid obesity altered the pharmacokinetics of propofol by increasing the systemic clearance and the peripheral compartment volume, resulting in an equal or decreased propofol level in the plasma.

Our finding that morbid obesity increased the elimination clearance of propofol and the peripheral volume of distribution was consistent with the previous studies in which the authors showed that total body clearance and the volume of distribution at steady state were positively correlated to body weight (Servin et al., 1993; Cortinez et al., 2010). An increase in the volume of distribution most likely resulted from the increased fat and lean masses of obese individuals (Casati and Putzu, 2005). Propofol clearance is blood flow dependent (Peeters et al., 2008b). Obesity is usually associated with a higher cardiac output due to increased stroke volume and heart rate (Alexander, 1993; Adams and Murphy, 2000). An increase in the cardiac output can result in an enhanced drug elimination. This helped to explain why the body clearance of propofol was increased in MO subjects.

**Altered propofol pharmacodynamics in MO patients**

The BIS values were significantly lower (p < 0.05) at and after 2 mins in MO-TBW than in the control group (Figure 2A). This indicated that the anesthetic effects were greatly enhanced in MO
subjects when propofol was dosed using the weight scalar of TBW (i.e., the regular dosing regimen). Interestingly, dose reduction (i.e., dosing based on LBW) generated identical anesthetic effects in MO compared to the control subjects (Figure 2A).

TBW-based dosing of propofol produced an aggravated anesthetic effect (i.e., an overdose effect) in MO subjects (Figure 2A). In particular, the BIS values at 2-6 min were below 40 (Figure 2A). The BIS values ranging from 40 to 60 indicate a proper level for general anesthesia (Kissin, 2000), whereas a BIS value below a threshold of 40 is an indicator of burst suppression and of deep anesthesia that may be harmful to the patients (e.g., deleterious hemodynamic and cardiovascular effects may result) (Drexler and Grasshoff, 2012). It was also suggested previously that propofol may be overdosed in clinical practices wherein TBW is usually used as the dosing scalar (Chidambaran et al., 2013). Therefore, dose reduction appeared to be necessary for anesthesia induction in MO subjects. It was noteworthy that propofol maintenance infusion can be based on TBW in obese patients, as in lean subjects (Servin et al., 1993; Cortinez et al., 2010).

The proposed PK/PD model (Figures 1B) was well fitted to the data. The predicted BIS values based on individual parameters were close to the observed ones (Supplemental Figures 4-6). Further, majority of the observed values were well predicted by the model as revealed by the VPC plots (Figure 2B). All estimated PD parameters except EC50 were similar (p > 0.05) between MO and the control subjects (Table 1). Morbid obesity led to a significant decrease
(0.94-0.95 vs 1.53 μg/mL, p < 0.01) in the EC₅₀ value (Figure 2C). Consistently, the covariate model demonstrated that EC₅₀ was inversely related to the total body weight (Figure 2C). The results suggested that MO subjects showed an enhanced brain sensitivity to propofol.

MO subjects dosed basing on LBW had a similar pharmacodynamic profile (i.e., BIS versus time curve) as compared to the control subjects (TBW-based dosing) (Figure 2A). This clearly indicated that LBW was a better dosing scalar in MO population. By using the time to loss of consciousness (syringe drop as the marker) as the pharmacodynamic endpoint, Ingrande et al (2011) proposed that LBW was the best scalar for anesthesia induction with propofol in MO subjects. Therefore, this study and the previous one consistently indicated that propofol should be given to MO subjects using LBW as the scalar for anesthesia induction (Ingrande et al., 2011).

More importantly, our study for the first time provided the explanations as to why LBW-based dosing of propofol (i.e., a dose reduction strategy) was more appropriate for MO subjects (see the following discussion).

It was a novel finding that morbid obesity significantly decreased the EC₅₀ value, the half maximal effective concentration (Figure 2C). This indicated that MO subjects had a greater CNS sensitivity to propofol. Decreased EC₅₀ value for propofol was also noted in patients undergoing abdominal aortic surgery (Wiczling et al., 2012). However, the exact reasons remain unknown as to why MO subjects were more sensitive to the anesthetic effects. Nevertheless, it was speculated that the increased sensitivity to propofol was associated with the changes in
cardiovascular and respiratory functions (Casati and Putzu, 2005; Ingrande and Lemmens, 2010).

The increased CNS sensitivity (i.e., a decreased EC<sub>50</sub> value) to propofol was probably responsible for the aggravated anesthetic effects (Figure 2A). This was because equal or lower propofol concentrations were observed in MO patients (TBW-based dosing of propofol) due to enhanced elimination clearance and increased volume of distribution. A lower systemic exposure of drug would translate to diminished drug response. However, the pharmacokinetic change did not predict the alterations in the pharmacodynamics. This was because the pharmacodynamic property was also altered by morbid obesity, namely, the drug potency was enhanced. Therefore, our study provided a mechanistic PK/PD explanation as to why dose reduction was required in MO subjects. In addition, our study and the previous one highlighted that determination of the pharmacodynamic parameters was essential to fully assess the effects of diseases on clinical responses of propofol (Wiczling et al., 2012).

In summary, the pharmacokinetics and pharmacodynamics of propofol were characterized in MO subjects. Both elimination clearance (CL) and peripheral compartment volume (<i>V</i><sub>2</sub>) were significantly increased in MO subjects, resulting in an equal or decreased plasma propofol level. Further, the PD parameter EC<sub>50</sub> was significantly decreased in MO subjects, suggestive of enhanced brain sensitivity to propofol in this population. Moreover, LBW was a better weight-based dosing scalar for anesthesia induction with propofol in MO subjects.
Authorship Contributions

Participated in research design: Dong, Peng, Liu and Wu.

Conducted experiments: Dong, Qian and Li.

Contributed new reagents or analytic tools: Peng and Liu.

Performed data analysis: Dong, Peng, Qian, Li and Wu.

Wrote or contributed to the writing of the manuscript: Dong, Peng and Wu.
References


Ingrande J, Brodsky JB, Lemmens HJ. (2011) Lean body weight scalar for the anesthetic induction dose of propofol in...


Footnotes

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DD and XP contributed equally to this work.
Legends for Figures

Figure 1  Altered propofol pharmacokinetics in MO patients. A: Schematic representation of the PK models used for data analysis. For two compartment (2-compt) model: V\textsubscript{1}, volume of central compartment; V\textsubscript{2}, volume of peripheral compartment; CL, elimination clearance; Q, distribution clearance. For three compartment (3-compt) model: V\textsubscript{1}, volume of central compartment; V\textsubscript{2}, volume of first peripheral compartment; V\textsubscript{3}, volume of second peripheral compartment; CL, elimination clearance; Q\textsubscript{2}, distribution clearance between central and first peripheral compartment; Q\textsubscript{3}, distribution clearance between central and second peripheral compartment.  
B: Schematic representation of the PK/PD model used for data analysis. K\textsubscript{e0}, distribution rate constant to effect compartment from central compartment.  
C: The propofol plasma levels versus time profiles for control and MO subjects. MO patients received propofol (2 mg/kg) based on TBW (n = 12) or LBW (n = 11), whereas all control patients received propofol based on TBW (n = 6). The plasma levels of propofol at later time points (≥ 6 min) were significantly lower (p < 0.05) in MO-TBW than in control subjects. The plasma levels of propofol (≥ 2 min) were markedly lower (p < 0.001) in MO-LBW than in control subjects.  
D: Comparisons of CL and V\textsubscript{2} values in three groups of patients. The equations show the covariate models for CL and V\textsubscript{2}. **P < 0.01 versus the control.  
E: Comparisons of TBW-normalized CL and V\textsubscript{2} values in three groups of patients.

Figure 2  Altered propofol pharmacodynamics in MO patients. A: The PD effect (i.e., BIS) versus time profiles for control and MO subjects. MO patients received propofol (2 mg/kg) based on TBW (n = 12) or LBW (n = 11), whereas all control patients received propofol based on TBW (n = 6). The BIS values were significantly lower (p < 0.05) at and after 2 min in MO-TBW group than in control group.  
B: The visual predictive checks (VPCs) for BIS values versus time. The green lines show the 10\textsuperscript{th}, 50\textsuperscript{th} and 90\textsuperscript{th} percentiles of observed data; the areas represent the 90% confidence interval around the simulated percentiles.  
C: A comparison of EC\textsubscript{50} values in three groups of patients. **P < 0.01; ***P < 0.001 versus the control. The equation shows the covariate model for EC\textsubscript{50}.  

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Table 1

Pharmacokinetic and pharmacodynamic parameters derived from population fitting of the PK/PD model to the individual data of three patient groups. The data are expressed as population mean (inter-individual variability) or θ (ω).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Control</th>
<th>MO (TBW)</th>
<th>MO (LBW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL</td>
<td>L/min</td>
<td>4.11 (0.13)</td>
<td>10.0 (0.36)</td>
<td>9.15 (0.39)</td>
</tr>
<tr>
<td>V₁</td>
<td>L</td>
<td>25.7 (0.32)</td>
<td>25.5 (0.57)</td>
<td>27.0 (0.60)</td>
</tr>
<tr>
<td>Q</td>
<td>L/min</td>
<td>9.50 (0.42)</td>
<td>11.9 (0.50)</td>
<td>14.8 (0.36)</td>
</tr>
<tr>
<td>V₂</td>
<td>L</td>
<td>46.9 (0.27)</td>
<td>73.2 (0.20)</td>
<td>84.2 (0.34)</td>
</tr>
<tr>
<td>Kₑ₀</td>
<td>min⁻¹</td>
<td>0.36 (0.39)</td>
<td>0.31 (0.28)</td>
<td>0.34 (0.23)</td>
</tr>
<tr>
<td>BIS₀</td>
<td>/</td>
<td>92.8 (0.03)</td>
<td>90.1 (0.03)</td>
<td>87.3 (0.07)</td>
</tr>
<tr>
<td>EC₅₀</td>
<td>μg/mL</td>
<td>1.53 (0.20)</td>
<td>0.95 (0.27)</td>
<td>0.94 (0.37)</td>
</tr>
<tr>
<td>γ</td>
<td>/</td>
<td>0.66 (0.06)</td>
<td>0.63 (0.07)</td>
<td>0.64 (0.08)</td>
</tr>
</tbody>
</table>

CL= clearance from the central compartment; V₁ = volume of distribution of the central compartment; V₂ = volume of distribution of the peripheral compartment; Q = inter-compartmental clearance from the central compartment to the peripheral compartment; Kₑ₀ = the drug distribution from the central to the effect compartment; BIS₀ = baseline BIS score; EC₅₀ = half maximal effect concentration; γ = steepness of the pharmacodynamic response curve.
**Figure 1**

**A PK models**

- **2-Compt**
  - Peripheral $\rightarrow$ Q $\rightarrow$ V1 $\rightarrow$ Central
  - CL

- **3-Compt**
  - Peripheral $\rightarrow$ Q$_2$ $\rightarrow$ V1 $\rightarrow$ Q$_3$ $\rightarrow$ V3 $\rightarrow$ Peripheral
  - CL

**B PK/PD model**

- Peripheral $\rightarrow$ Q $\rightarrow$ V1 $\rightarrow$ Effect $\rightarrow$ K$_{e0}$ $\rightarrow$ Central
- Effect = BIS$_0$\left(1 - \frac{E_{max}C_e^\gamma}{EC_{50}^\gamma + C_e^\gamma}\right)

**C**

- Graph showing Plasma Conc (μg/ml) vs. Time (min)
- Control, MO (TBW), MO (LBW)

**D**

- CL = 4.09 × (\frac{TBW}{70})^{1.33} L/min
- V$_2$ = 51 × (\frac{TBW}{70})^{0.7} L

**E**

- Bar charts showing Normalized CL L/min and Normalized V$_2$ L for Control, MO (TBW), MO (LBW)
Figure 2

A

Control
MO (TBW)
MO (LBW)

BIS

Time (min)

0 5 10 15 20

B

Control
MO (TBW)
MO (LBW)

BIS

Time (min)

0 5 10 15 20

C

EC_{50} = 1.55 \times \left(\frac{TBW}{70}\right)^{-0.8} \mu g/ml

EC_{50}, \mu g/ml

Control
MO (TBW)
MO (LBW)

**

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