

# Reliability of body-weight scalars on the assessment of propofol induction dose in obese patients

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## Conflicts of interest

None.

ClinicalTrials.gov Identifier: NCT02713698

Submitted 30 October 2017; accepted 30 October 2017; submission 5 September 2017.

## Citation

Araújo AM, Machado HS, Falcão AC, Soares-da-Silva P. Reliability of body-weight scalars on the assessment of propofol induction dose in obese patients. *Acta Anaesthesiologica Scandinavica* 2017

doi: 10.1111/aas.13039

**Background:** Obese patients require specific perioperative care when compared with non-obese patients. The present study aimed to analyse the ability of size descriptors to estimate propofol induction dose in class II and III obese patients.

**Methods:** A cross-sectional study on adult patients with body mass index (BMI) equal to or greater than 35 kg/m<sup>2</sup> and on adult patients with BMI lower than 35 kg/m<sup>2</sup> was carried out. General anaesthesia was induced with remifentanyl, propofol and rocuronium. Propofol infusion was started at 2000 mg/h until loss of consciousness. Bioelectrical impedance analysis and Brice modified interview was completed during pre- and post-operative evaluation, respectively. Measurements of propofol plasma concentration were performed using gas chromatography/ion trap-mass spectrometry.

**Results:** Forty patients were enrolled in the study. The median values of fat free mass (FFM) in BMI < 35 kg/m<sup>2</sup> and BMI ≥ 35 kg/m<sup>2</sup> groups were 70% and 55% of total body weight, respectively. Our results did not demonstrate a strong correlation level between the studied size descriptors and propofol induction dose in both groups. Nevertheless, when propofol doses were normalized by FFM, an apparent convergence of the empirical cumulative distribution functions was observed.

**Conclusion:** None of the size descriptors was seen to be an effective predictor of the propofol induction dose in class II and III obese patients when a fixed infusion rate was used. Due to the observed variability between patients, guiding propofol induction dose against a clinical endpoint of unconsciousness appears more appropriate in order to avoid side effects related both with under or overdosing of propofol.

## Editorial comment

There is not a perfect guide today for pre-operatively choosing the propofol dose needed to induce sleep in obese patients. This study assessed propofol induction dose effects related to total body weight and fat-free mass. These factors were not observed to be strongly predictive of propofol dose for hypnosis in extremely obese groups.

Worldwide, obesity has more than doubled since 1980.<sup>1</sup> For adults, World Health Organization defines obesity as a body mass index (BMI) greater than or equal to 30.<sup>1</sup> Obese patients present a different set of challenges and require specific perioperative care compared with non-obese patients.<sup>2</sup>

Among these challenges is the different drug pharmacokinetics associated to physiological and anthropometric changes. Obese patients have an increased amount of fat and lean body weight (LBW), an increased blood volume, cardiac output, splanchnic blood flow and hepatic blood flow which possibly affect the apparent volume of distribution, peak plasma concentration, clearance and elimination half-life of many agents.<sup>2,3</sup> However, there is still limited evidence on the effect of obesity on the pharmacology of commonly used anaesthetic drugs.

Propofol is presently the most frequently used induction agent for obese patients.<sup>4</sup> Propofol is highly lipophilic and it distributes rapidly from the plasma to the peripheral tissues. Redistribution from the effect site accounts for its short duration of action after a single bolus dose. Therefore, at the present, it is recommended to calculate the induction dose of propofol considering LBW.<sup>2,4,5</sup> However, it has been reported that LBW-based induction dose of propofol is not adequate to achieve loss of consciousness (LOC)<sup>6</sup> and TBW has also been suggested as a more appropriate scalar for propofol dosing in obese patients.<sup>7</sup>

Computed tomography, magnetic resonance imaging and dual absorptiometry x-ray are used to estimate LBW, but it may be difficult to have access to these methods in clinical practice. Bioelectrical impedance, anthropometry and hydrostatic weighting can also be used to measure LBW; however, these methods still require the acquisition of special equipment.<sup>8–10</sup> Therefore, numerous predictive equations have been developed as an alternative in measuring LBW when the access to more accurate methods is limited, but they are specific to the population they are developed in and have limited general application.<sup>10</sup>

Accordingly, although LBW seems to be the preferred size descriptor to be used in pharmacokinetic studies in obese patients, this

recommendation is not yet a clear cut. The problem is even more complex in obese children and in obese patients with organ failure. Furthermore, recent publications proposed to titrate drug doses in obese patients to direct measure effects.<sup>2,11,12</sup>

In this study, we planned to assess propofol induction dose in class II and III obese patients using a fix propofol infusion rate and to analyse the ability of size descriptors, measured by bioelectrical impedance, to estimate propofol dose in these patients. We also measured propofol plasma concentration after LOC and conducted a questionnaire to assess the incidence of awareness in order to evaluate the effect of obesity on the relationship among propofol dose, plasma concentration and effect.

## Material and methods

The study was performed at Centro Hospitalar do Porto, Porto, Portugal after Hospital Review Board and Ethical Committee approvals (IRB: N/REF.<sup>a</sup> 2015.221(183-DEFI/165-CES). This study trial contains secondary analyses of clinical trial data registered at [clinicaltrials.gov](http://clinicaltrials.gov) under the reference NCT02713698 on 23 February 2016. Written, informed consent was obtained from all study patients.

This manuscript adheres to the applicable STROBE (Strengthening the reporting of Observational studies in epidemiology) guidelines.

## Patients

Adult patients (18–68 years) with ASA physical status II to III and BMI equal to or greater than 35 kg/m<sup>2</sup> scheduled to undergo laparoscopic gastric bypass surgery and adult patients (18–68 years) with ASA physical status I to II and BMI lower than 35 kg/m<sup>2</sup> scheduled for nose or ear surgery were included in the study. BMI between 35 and 39.9 kg/m<sup>2</sup> defines class II obesity and BMI equal to or greater than 40 kg/m<sup>2</sup> defines class III obesity.<sup>13</sup>

Exclusion criteria included severe hepatic or renal insufficiency, significant haemodynamic instability prior to the surgery or a known allergy to propofol at the time of enrolment. Patients with predictive criteria for difficult

airway management, patients with a pacemaker and pregnant woman were also excluded.

### Analysis of body composition by bioelectrical impedance

The body composition of each patient was assessed by BCM (Fresenius Medical Care, Germany) during pre-operative evaluation.<sup>14</sup>

The values of resistance and reactance obtained at 50 kHz were used to estimate fat free mass (FFM) or fat mass (FM) according to bioelectrical impedance analysis equations.<sup>15</sup>

The equation proposed by Kyle et al.<sup>16</sup> was used for the assessment of FFM in patients with BMI < 35 kg/m<sup>2</sup> and the equation proposed by Horie et al.<sup>17</sup> was used in patients with BMI ≥ 35 kg/m<sup>2</sup> for the assessment of FM.

### Study design and anaesthetic procedure

The proposed study is a cross-sectional study. The whole anaesthetic procedure was standard except for additional body composition assessment with body composition monitor (BCM, Fresenius Medical Care, Germany) and arterial blood sample after LOC.

All patients received standardized anaesthesia without pre-medication. In the operative room, continuous pulse oximetry, electrocardiography, invasive blood pressure and neuromuscular blockade were established. The bispectral index was monitored using a BIS VISTA™ Bilateral Monitoring System (Covidien, Colorado, US) with a bilateral sensor on the forehead of the patient.

General anaesthesia was induced with remifentanil, propofol (using Orchestra™ Mobile stand, Fresenius Vial, Brézins, France) and rocuronium. Remifentanil effect-site concentration was set at 3 ng/ml, according to pharmacokinetic model of Minto et al.<sup>18</sup> and a continuous infusion of propofol was started at 2000 mg/h until LOC, defined by 'loss of eyelash reflex' and 'loss of response to name calling'. Total dose of propofol at LOC was recorded in all patients. After LOC, rocuronium (0.6 mg/kg) was administered and propofol infusion rate was reduced to 6 mg/kg/h (LBW in BMI ≥ 35 kg/m<sup>2</sup> group) and then guided by BIS.

### Awareness interview

The Brice interview was used to detect awareness. The interview comprised of five questions, based on the study of Brice et al.<sup>19</sup>, and was addressed to the patients after post-anaesthesia care unit admission and in the first 24–48 h after surgery. The patient's reports were classified as definitive awareness, possible awareness and no awareness according to commonly used classifications described in the literature.<sup>20–22</sup>

### Quantification of propofol plasma concentration

The quantification of propofol in serum was performed using gas chromatography/ion trap-mass spectrometry (GC/IT-MS).<sup>23</sup>

Arterial blood samples were collected into serum tubes after LOC, and at the end of surgery they were centrifuged at 2862 ×g for 5 min. Serum was preserved at –80°C until analysis.

The detection of thymol and propofol was conducted in Fullscan mode and the quantification performed by reprocessing the Fullscan chromatogram with the characteristic m/z fragments of each molecule. For propofol, the m/z ions used were 163 and 178 and for thymol m/z 135 and 150. Seven-point calibration curves<sup>24</sup> for propofol were constructed regularly by plotting the ratio of propofol/internal standard areas vs. propofol concentration. The concentration range for the calibration curve was defined according to the expected serum concentrations (0.25, 0.5, 1, 2, 4, 5 and 10 µg/ml). Considering propofol and internal standard areas of each serum sample, final propofol concentration was then calculated using the calibration curve.

### Sample size

Literature shows a strong correlation ( $r^2 = 0.74$ ) between propofol induction dose and LBW in obese patients.<sup>5</sup> As a result, sample size considerations were based on association analyses using the Pearson correlation test.

To detect a correlation of at least 0.6 between propofol induction dose and LBW a sample of 19 subjects was calculated to provide 80% power and a 0.05 level of significance.

## Statistical methodology

The Shapiro–Wilk test was used to test for the normality of data. Categorical variables are presented as frequency. Continuous data are presented as mean (standard deviation).

For comparison between groups, the Student's *t*-test and Mann–Whitney–Wilcoxon test were used for continuous variables and the Chi-square test was used for categorical variables.

The correlation between propofol dose at LOC and body composition parameters was measured using Pearson's coefficient and the coefficient of determination ( $r^2$ ).

A *P*-value < 0.05 was considered to be statistically significant.

## Results

Twenty adult patients with BMI equal to or greater than 35 (BMI  $\geq$  35 kg/m<sup>2</sup> group) and 20 adult patients with BMI lower than 35 (BMI < 35 kg/m<sup>2</sup> group) were enrolled for participation in the study from April 2016 to March 2017.

Patient's demographics and comorbidity indexes are presented in Table 1. There are no statistical significant differences between groups for age and Charlson comorbidity index.<sup>25</sup>

**Table 1** Patient demographic characteristics and comorbidity indexes.

Variables	BMI < 35 group	BMI $\geq$ 35 group	<i>P</i> -value
Age (years)	43.7 (12.5)*	47.9 (9.5)*	0.236
Gender			
Female	13 (65)†	18 (90)†	0.018
Male	7 (35)†	2 (10)†	
ASA			
I	7 (35)†	0	< 0.001
II	13 (65)†	0	
III	0	20 (100)†	
Charlson Comorbidity index			
0–1	19 (95)†	14 (70)†	0.058
2–3	1 (5)†	5 (25)†	
4–5	0	1 (5)†	
BMI	25.4 (3.4)*	42.6 (4.8)*	< 0.001

\*Data present as mean (SD). †Data present as frequency (%). ASA, American society of anaesthesiology; BMI, body mass index (kg/m<sup>2</sup>).

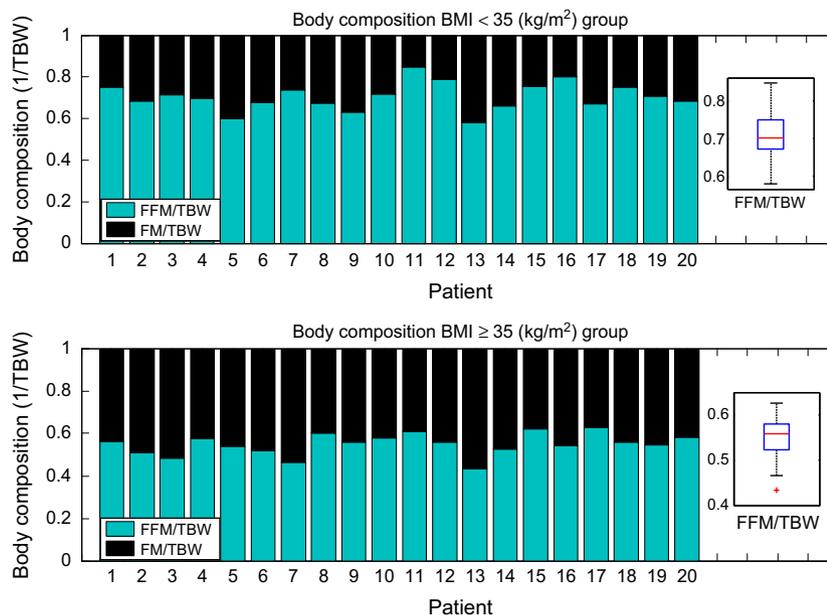
However, all patients in BMI  $\geq$  35 kg/m<sup>2</sup> group were classified as ASA class III, while all patients in the other group were classified as ASA class I or II.

The body composition of each patient evaluated by bioelectrical impedance analysis is illustrated in Fig. 1. The median values of FFM in BMI < 35 kg/m<sup>2</sup> and BMI  $\geq$  35 kg/m<sup>2</sup> groups are 70% and 55% of TBW, respectively. There is a good agreement between the LBW values obtained by the Janmahasatian equation<sup>26</sup> and FFM values measured by the BCM in both groups (Fig. 2).

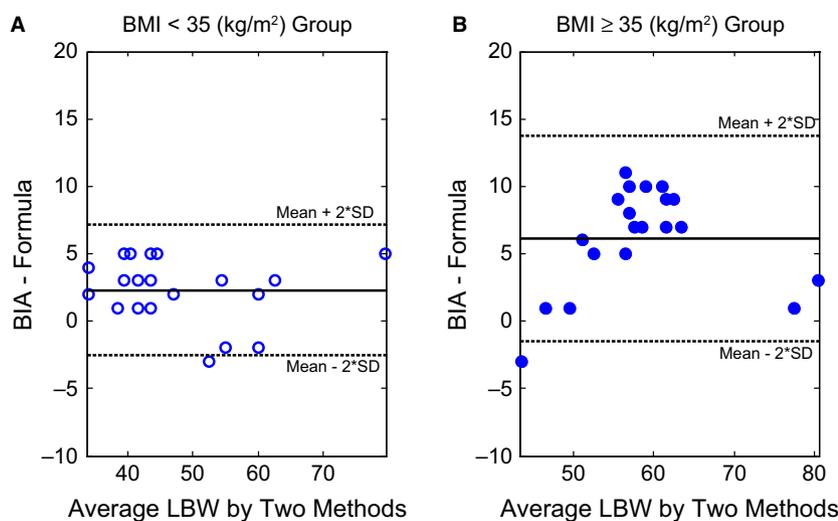
Table 2 shows that there are statistically significant differences in propofol induction dose ( $P < 0.001$ ) and BIS values ( $P < 0.001$ ) between groups. However, with respect to BIS values at LOC, both groups registered a mean value higher than 60. Table 2 also shows that the measured plasma propofol concentration after LOC was  $3.77 \pm 1.49$   $\mu$ g/ml and  $4.87 \pm 1.03$   $\mu$ g/ml for BMI < 35 kg/m<sup>2</sup> and BMI  $\geq$  35 kg/m<sup>2</sup> groups, respectively ( $P = 0.012$ ). Furthermore, at the time of arterial blood sample collection, BIS values indicated an appropriate level of general anaesthesia in both groups.

Figure 3 shows that none of the size descriptors was seen to be an effective predictor of the propofol dose at LOC in both groups. The higher correlation level ( $r^2 = 0.43$ ) was observed for BMI < 35 kg/m<sup>2</sup> group when TBW was used as the dependent variable. Nevertheless, even in this case the significance of the correlation is limited due to the effect of one isolated point. Figure 3 also indicates that the use of a standard propofol induction dose (2 mg/kg) based on TBW will result in very high doses in the BMI  $\geq$  35 kg/m<sup>2</sup> group. Conversely, the use of FFM in the calculation of propofol induction dose results in inappropriately low doses in some patients of both studied groups.

The empirical cumulative distribution functions (ECDFs) of propofol dose at LOC (Fig. 4) show that the median propofol dose based on TBW is 1.24 and 0.91 mg/kg, for BMI < 35 kg/m<sup>2</sup> group and BMI  $\geq$  35 kg/m<sup>2</sup> groups, respectively. In comparison, when propofol dose at LOC is normalized by FFM, the median propofol dose is similar in both groups (1.84 vs. 1.73 mg/kg).



**Fig. 1.** Body composition according to bioelectrical impedance analysis. Upper and lower panels represent, respectively, body composition of patients with BMI < 35 kg/m<sup>2</sup> and BMI ≥ 35 kg/m<sup>2</sup>. Box plots in both panels display the degree of dispersion of FFM in relation to TBW. BMI, body mass index; FFM, fat free mass; FM, fat mass; TBW, total body weight.



**Fig. 2.** Bland–Altman plots - Janmahasatian formula vs. body impedance analysis in BMI < 35 kg/m<sup>2</sup> group (A) and BMI ≥ 35 kg/m<sup>2</sup> group (B). BMI, body mass index.

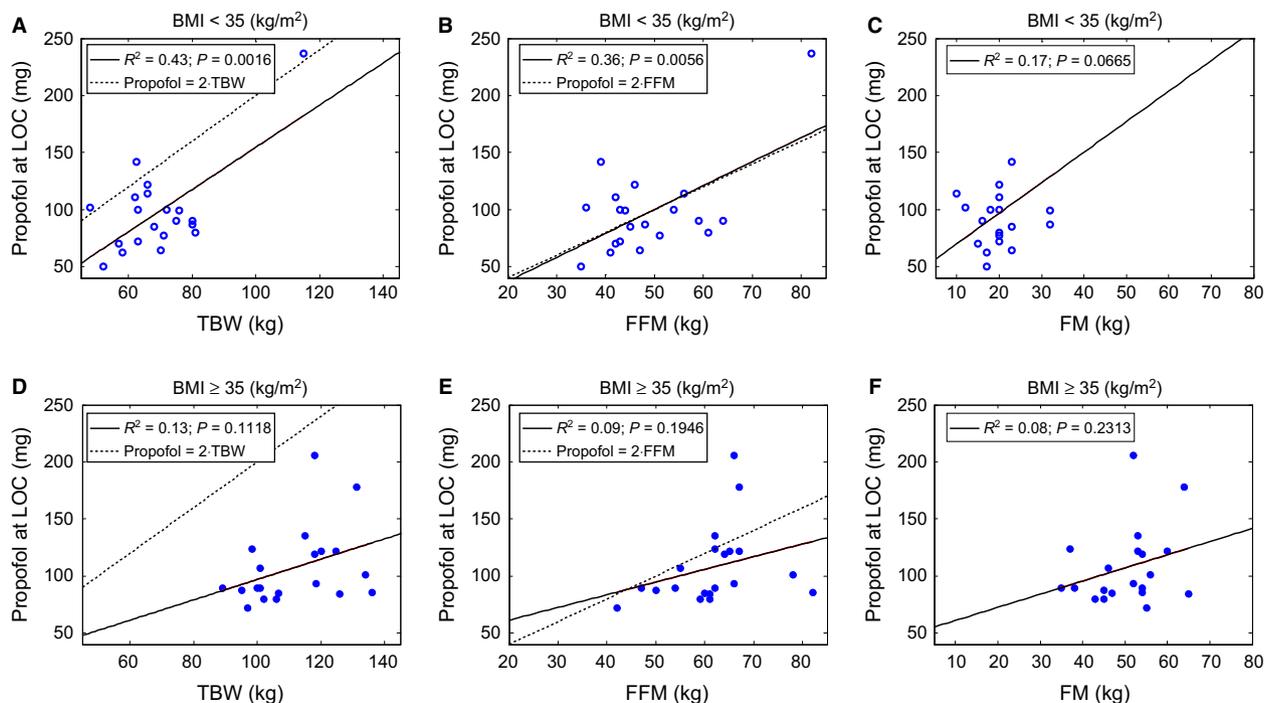
With respect to haemodynamic variables (Table 3), hypotension after induction of general anaesthesia was defined as a decrease in baseline mean arterial pressure (MAP) higher than 40%, within 5 min of propofol infusion.

These results show a statistically significant difference between MAP values before and after propofol dose in both groups for BMI ≥ 35 kg/m<sup>2</sup> and BMI < 35 kg/m<sup>2</sup> groups, respectively. However, only one morbidly

**Table 2** Propofol dose until loss of consciousness.

Variables	BMI < 35 group	BMI ≥ 35 group	P-value
Propofol at LOC (mg)	97.7 (39.5)*	107.5 (34.2)*	0.239
Time to LOC (s)	175.8 (71.2)*	193.5 (61.5)*	0.408
Propofol at LOC (mg/kg of TBW)	1.4 (0.4)*	0.96 (0.3)*	< 0.001
BIS at LOC	63.8 (10.3)*	75.8 (10)*	< 0.001
Plasma [Propofol] (µg/ml)	3.8 (1.5)*	4.9 (1)*	0.012
Propofol† after LOC (mg)	12.69 (12.25)*	28.24 (16.57)*	0.002
Time‡ after LOC (s)	88 (82.3)*	121.5 (34.7)*	0.114
BIS§ after LOC	53.8 (12.1)*	48.1 (10.1)*	0.050

\*Data presented as mean (SD). †Propofol after LOC is the propofol dose administered between LOC and arterial blood sample. ‡Time after LOC is the time when arterial blood sample was obtained after LOC. §BIS after LOC is the numeric BIS value at the time of blood sample collection. BIS, bispectral index; BMI, body mass index (kg/m<sup>2</sup>); LOC, loss of consciousness; TBW, total body weight.



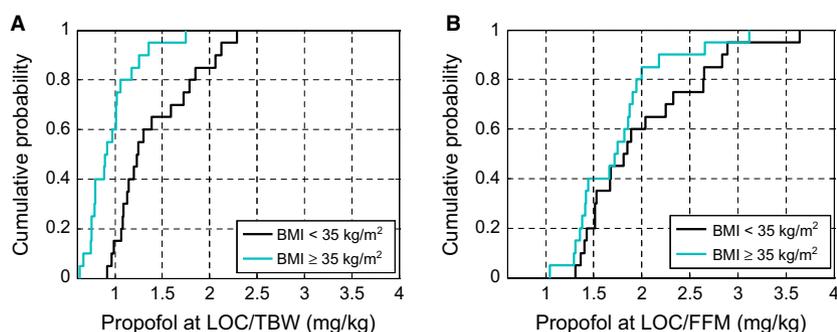
**Fig. 3.** Correlation between propofol induction dose and body weight-scalars. A, B and C show, respectively, the correlations of propofol induction dose with TBW, FFM and FM of BMI < 35 kg/m<sup>2</sup> group. D, E and F illustrate, respectively, the correlations of propofol induction dose with TBW, FFM and FM of BMI ≥ 35 kg/m<sup>2</sup> group. Dashed line in A, B, D and E represents the function equivalent to the standard propofol dose (2 mg\*TBW in A and D and 2 mg\*FFM in B and E). BMI, body mass index; FFM, fat free mass; FM, fat mass; LOC, loss of consciousness; TBW, total body weight.

obese patient has shown a variation higher than 40% in MAP values. This patient was treated with ephedrine and fluid boluses to return MAP to baseline levels.

There were no other side effects during anaesthetic induction and none of the patients' interviews indicated awareness during induction of general anaesthesia.

## Discussion

Notwithstanding the apparent convergence of the ECDFs when doses of propofol are normalized by FFM, none of the size descriptors were seen to be an effective predictor of the propofol dose at LOC.



**Fig. 4.** Empirical cumulative distribution function of propofol dose at LOC. A and B show, respectively, empirical distribution functions of propofol dose at LOC relative to TBW and FFM. Continuous black vertical lines characterize the standard adult propofol induction doses. BMI, body mass index; FFM, fat free mass; FM, fat mass; LOC, loss of consciousness; TBW, total body weight.

**Table 3** Mean arterial pressure during induction of general anaesthesia.

Variables	BMI < 35 group	BMI ≥ 35 group	P-value
MAP before propofol (mmHg)	87.4 (8.7)*	99 (14.1)*	0.004
MAP after propofol (mmHg)	69.2 (12.7)*	82.5 (22.9)*	0.031
MAP variation† (%)	20.4 (13.8)*	16.3 (22.3)*	0.483

\*Data presented as mean (SD). †Variation = [(MAP before propofol – MAP after propofol)/MAP before propofol]\*100. BMI, body mass index (kg/m<sup>2</sup>); MAP, mean arterial pressure.

Previously, Ingrande et al.<sup>5</sup> have used an infusion rate (100 mg/kg/h) based on TBW or LBW to characterize the differences in dose requirements and LOC in morbidly obese patients. These authors concluded that, when compared with control subjects receiving a propofol induction dose based on TBW, morbidly obese subjects receiving propofol based on LBW required similar doses of propofol and similar times to reach LOC, suggesting the relevance of LBW as a more accurate dose scalar in these patients.

For the fixed infusion rate used in this study (2000 mg/h), the average amount of propofol required to LOC was lower and the time to reach LOC was higher than those observed by Ingrande et al.<sup>5</sup> The strong correlation levels observed in<sup>5</sup> were also not verified in this study. Since propofol administration rate has a critical impact on the dose and time required to induction of general anaesthesia,<sup>27–29</sup> the use of multiple rates of propofol infusion calculated

according to different body size scalars appear alone to result in different dosing regimens and correlation levels. In this study, remifentanyl infusion was started before propofol for arterial line placement. Nevertheless, it has been shown by Milne et al.<sup>30</sup> that low target remifentanyl concentrations (< 4 ng/ml) have poor hypnotic potency and therefore a limited contribution to propofol requirements in the early induction phases, in the absence of painful stimulation.

Additionally, Subramani et al.<sup>6</sup> verified that the induction dose of propofol based on the BIS index (100 mg/kg/h to an initial target endpoint of a BIS of 50) was different from the induction dose based on LBW in morbidly obese patients. The LBW dose of propofol was based on the results obtained in the study conducted by Ingrand et al.<sup>5</sup>, but their findings suggest that the LBW-based dose of propofol may be inadequate for induction of anaesthesia in morbidly obese patients. The LBW group required additional propofol to achieve LOC, which was evaluated using the observer's assessment alertness/sedation scale score of 0 (lack of response to a painful stimulus). Notwithstanding BIS monitoring has been shown to be an effective guide for dosing anaesthetic drugs, the delay between clinical recognition of LOC and the decrease in BIS values observed in the present study may lead to propofol overdosing when BIS values are used to monitor propofol induction dose. Furthermore, the delay between processed electroencephalogram and drug effect during induction of general anaesthesia and the subsequent

administration of excess propofol dose have already been reported elsewhere.<sup>31</sup>

According to the results of NAP5 (5th National Audit Project of the Royal College of Anaesthesiologists and the Association of Anaesthetists of Great Britain and Ireland), induction is a high-risk phase of anaesthesia for awareness, particularly in obese patients. They concluded that dosing propofol based on TBW might be a better strategy to reduce the risk of awareness in these patients. Nevertheless, with propofol dose used in this study, none of the patient's interviews indicated awareness or possible awareness during the induction of general anaesthesia and the propofol plasma concentrations obtained in both groups were in accordance to previous published literature to ensure an adequate level of anaesthesia.<sup>32,33</sup>

With respect to propofol plasma concentrations, it was additionally noted that they were lower in the BMI < 35 kg/m<sup>2</sup> group. These results suggest that the volume of distribution of the central compartment of propofol is not increased in the BMI ≥ 35 kg/m<sup>2</sup> group despite its lipophilicity. Consequently the use of TBW as a weight scalar to calculate propofol induction dose should result in an inappropriately high dose level. As previously described, obesity is not only associated with an increase in tissue mass but also with different lean body mass to fat mass ratios, which will have a significant impact on drug distribution.<sup>34</sup> Additionally, previously literature demonstrates that the increased body size in obese patients result in an increase in total blood volume and cardiac output, which is important in the first minutes after propofol administration.<sup>34</sup> However, some studies also mention that cardiac output correlates with BMI in a nonlinear manner and the hyperdynamic circulation caused by obesity is observed only at early stages of the disease; adiposity increases vascular resistance and over time leads to structural heart changes.<sup>11,35</sup>

Regarding haemodynamic effects of propofol, it was observed that slower rates of propofol infusion could allow for a more suitable haemodynamic control during induction of general anaesthesia, since for the same haemodynamic endpoint that has been previously reported (40% decrease in baseline MAP within 5 min of propofol infusion),<sup>5</sup> post-induction hypotension

was only identified in one patient in the BMI ≥ 35 kg/m<sup>2</sup> group.

There are potential limitations associated to this study concerning cardiac output evaluation and group composition. Firstly, cardiac output was not measured and cardiac output is an important factor for early propofol distribution. However, it has already been published that cardiac output is more strongly related to lean tissue than to adipose mass.<sup>5,36</sup> Additionally, there was a delay between clinical LOC and blood sample collection. Nevertheless, the main reason for the presentation of these results consisted in showing that the strategy adopted (2000 mg/h) was efficient given the adequate range of plasma concentrations measured. With respect to group composition, significant differences were verified concerning gender and ASA scores. Body composition is a known difference between genders. However, as the authors used a direct characterization of the size of each patient, the focus was put on the ability of different body size descriptors to estimate propofol dose to LOC. With respect to ASA score, as BMI is a direct measure that is related with ASA score and both groups were nominated according to selected BMI, BMI alone contributed to the increasing of the ASA score of a given patient of BMI ≥ 35 kg/m<sup>2</sup> group. The age range of patients was also heterogeneous in both groups since patients between 18 and 68 years were included. Nevertheless, the average age of patients was not significantly different between groups.

In conclusion, none of the size descriptors was seen to be an effective predictor of the propofol induction dose in class II and III obese patients when a fixed infusion rate was used (2000 mg/h). Due to the observed variability between patients, guiding propofol induction dose against a clinical endpoint of unconsciousness appears more appropriate in order to avoid side effects related both with under or overdosing of propofol.

### Acknowledgements

Financial support from the 'Fundo para a Investigação e Desenvolvimento do Centro Hospitalar do Porto' is gratefully acknowledged. BIS brain monitoring sensors were provided by MedtronicTM. The BCM monitor was made available

by Fresenius Medical Care Portugal™. The authors thank Toxicological Laboratory, Department of Biological Sciences, Faculty of Pharmacy, University of Porto for technical cooperation in propofol plasma dosing. The assistance provided by Food and Nutrition Department of Centro Hospitalar do Porto, in the critical analysis of bio-electrical impedance results is also gratefully acknowledged.

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