European Review for Medical and Pharmacological Sciences 2020; 24: 11900-11908

Should the dosage of propofol be higher and independent of immunosuppressive therapy in adult cystic fibrosis patients undergoing sedation during flexible video bronchoscopy?

B. BRAJER-LUFTMANN[1], M. STELMACH-MARDAS[2], M. MARDAS[3], M. GRABICKI[1], H. BATURA-GABRYEL[1], T. PIORUNEK[1]

[1]Department of Pulmonology, Allergology and Pulmonary Oncology, Poznań University of Medical Sciences, University Hospital of Lord's Transfiguration, Poznań, Poland
[2]Department of Biophysics, Poznań University of Medical Sciences, Poznań, Poland
[3]Department of Oncology, Poznań University of Medical Sciences, University Hospital of Lord's Transfiguration, Poznań, Poland

Abstract. – OBJECTIVE: Flexible video bronchoscopy (FVB) performed under sedation is a useful procedure in adults with cystic fibrosis (CF). Propofol dosage for CF is poorly described, although it is of high importance for professionals. The study aimed to assess whether propofol dosage should be higher in adults CF undergoing sedation during FVB.

PATIENTS AND METHODS: 50 adult CF and non-CF patients undergoing sedation during FVB were included. Clinical features of studied patients were assessed. In CF group spirometry, liver enzymes, inflammatory biomarkers, albumin, protein concentration, WBC were estimated. Propofol and fentanyl dosage was calculated. Multiple regression model was performed.

RESULTS: CF patients were characterized by a lower mean value of body weight and lower mean requirement of total propofol (135 mg in CF *vs.* 145 mg in non-CF). Calculated propofol dose per kg of body weight was significantly higher in CF (2.43 mg/kg *vs.* 2.04 mg/kg) and did not depend on the bronchopulmonary disease stage. Propofol dose per kg of body weight was predicted by CF status (CF *vs.* non-CF), sex, and age.

CONCLUSIONS: Adult CF patients not receiving immunosuppressive therapy require higher propofol dose per kg of body weight compared to non-CF, independently on bronchopulmonary disease stage showing a narrow therapeutic window for propofol in CF group.

Key Words:
CF, Bronchoscopy, Anesthetics, Sedation, Propofol.

Introduction

Cystic fibrosis (CF) is an autosomal recessive disease-causing mutational defect of the CF transmembrane conductance regulator (CFTR) protein leading to multi-organ dysfunction such as bronchiectasis and chronic bronchopulmonary disease, chronic sinusitis, pancreatic insufficiency, and hepatobiliary disease[1,2]. One of the medical procedures useful for microbiological evaluation, collapse, hemoptysis, etc. in CF patients is flexible bronchoscopy (FB)[3]. This procedure may be performed without sedation. However, the use of pharmacological sedatives and anxiolytics improves the tolerance of the procedure and reduces patients' discomfort[4-6]. Sedation with propofol in comparison to midazolam had similar efficacy and safety[7], but the quicker onset of action and patients' recovery leading to early discharge[6]. Propofol is a lipophilic drug that is mainly eliminated by hepatic glucuronidation[6,8-10]. Although liver dysfunction may occur in CF patients[1], there is consistent evidence showing that CF population has intensified hepatic glucuronidation of drugs[11], mainly *via* the propofol metabolic pathway[10,12,13]. Nevertheless, the exact propofol dosage in CF patients undergoing FB is unknown, especially without immunosuppressive therapy. It is of high importance for bronchoscopists and anesthesiologists to know if adult CF patients require higher doses of propofol to achieve the same level of sedation as healthy adults. This knowledge may improve the safety of this procedure and patients' comfort.

Therefore, the aim of this study was to assess whether the propofol dosage should be higher and independent of immunosuppressive therapy in adult cystic fibrosis patients undergoing sedation during flexible video bronchoscopy.

Corresponding Author: Beata Brajer-Luftmann, Ph.D, MD; e-mail: bbrajer@ump.edu.pl

Patients and Methods

Study Design

This is an observational cross-sectional study that was conducted in accordance with Helsinki Declaration. The study protocol was approved by the Bioethical Committee at Poznan University of Medical Science (No: 1077/19). Written informed consent was obtained from all individual participants included in the study. Patients were recruited in 2019 at the Department of Pulmonology, Allergology and Pulmonary Oncology, Poznan University of Medical Sciences (Poland). All enrolled patients underwent routine flexible video bronchoscopy for diagnostic purposes in the Bronchoscopy Laboratory, being the university unit that followed all procedures related to good laboratory and diagnostic practice. All endoscopies were recorded in the institution's endoscopy documentation system (ENDOBASE 13.0, Olympus Corporation. 2013, Hamburg, Germany).

Study Population

Fifty adult CF patients not receiving immunosuppressive therapy were included in the study according to the following inclusion criteria: age over 18, CF diagnosed in childhood in accordance with The *European Cystic Fibrosis Society* guidelines published by Castellani et al[1]. The indication for the FVB in CF group of patients was microbiological evaluation[3]. The control group (non-CF patients) consisted of 50 generally healthy individuals without any pulmonary, liver, kidney, and cardiac disorders, who suffered from prolonged cough as the main indication for FVB. The exclusion criteria were as follows immunosuppressive therapy, bronchial biopsy during FVB due to prolonged procedure and thus a higher dose of anesthetics intake, respiratory failure required oxygen therapy before the FVB. Active drug or alcohol abuse, legal incompetence, and limited legal competence were additional exclusion criteria.

Methods

The body weight was assessed with an approximation of 0.1 kg (Seca digital scale 763; Seca, Hamburg, Germany). This measurement was used to calculate the propofol dosage per unit of body weight (kg).

Flexible video bronchoscopy was performed by a trained pulmonologist/bronchoscopist and assisted by a specially trained health-care professional team consisting of the experienced anesthesiologist, endoscopic and anesthesiologic nurse. The procedures were performed in accordance with the applicable guidelines, including indications and contraindications[4,5,14]. The examination was carried out in the supine position after intravenous premedication with fentanyl followed by sedation with propofol, which was administered as bolus injections until the *Richmond Agitation-Sedation Scale* of 3 was achieved[15]. This means that the patients did not react to the voice and did not open their eyes after physical stimulation, had spontaneous ventilatory ability and maintained cardiac function[15]. The facial expression, pupils, and body movement were observed to achieve adequate sedation. All patients received oxygen 2 l/min (LPM) via a nasal cannula. Patients were monitored throughout the procedure with a continuous electrocardiograph (ECG), oxygen saturation, and repeated noninvasive blood pressure measurements. The selected parameters such as saturation, systolic (SBP) and diastolic blood pressure (DBP) measured 5 minutes before and immediately after bronchoscopy were registered in the database. The time of the procedure and the information about complications such as hypoxemia (SpO_2<90%), hypotension: SBP < 80 mmHg or DBP < 40 mmHg, arrhythmias, hemorrhage, as well as the total propofol and fentanyl dosages, were recorded in the database.

In addition, laboratory tests and spirometry were performed in CF patients due to the possible influence of liver dysfunction, inflammation status and the severity of the disease (represented by forced expiratory volume in one second - FEV_1) on the propofol dosage used during the procedure. Blood samples were taken from patients following overnight fasting. The biochemical assessment was performed in a certified laboratory according to standardized procedures and good laboratory practice[16]. The concentrations of the inflammation markers such as high sensitive C-reactive protein (hsCRP) and white blood cells (WBC), and biochemical liver markers: the activity of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (GGT), concentration of albumin and total protein (TP) were measured with the use of enzymatic methods (Roche Diagnostics Corp., Indianapolis, IN, USA). In addition, an international normalized ratio (INR) was calculated to assess liver function indirectly.

The spirometry was performed according to the current American Thoracic Society/European Respiratory Society guidelines[17]. The FEV1 as % predicted was presented according to the Global

Lung Function Initiative (GLI) references[18]. This parameter was chosen because it is a significant predictor of lung function decline, and both respiratory morbidity and mortality in CF patients[19]. The blood pressure (BP) measurements were performed according to the guidelines of the European Society of Hypertension[20] with the use of a digital electronic tensiometer (Omron Corp., Kyoto, Japan). The continuous ECG and the patient's oxygen saturation (SpO_2) were assessed using a digital electronic tensiometer (IntelliVue X3 patient monitor Philips 2018, Böblingen, Germany).

Statistical Analysis

The data were expressed as mean and standard deviation. The normality of the distribution was checked by the Shapiro-Wilk test. Mann-Whitney test was used to analyze the differences between variables in the control and study group and Wilcoxon test to describe the differences before and after medical intervention. Multiple regression model was performed to predict the propofol dosage based on the value of other variables. A *p*-value <0.05 defined statistically significant differences). All calculations were performed with the use of Statistica 10 software (TIBICO Software INC., Palo Alto, CA, USA).

Results

One hundred patients were enrolled into the study from inpatient and outpatient clinic. The CF group consisted of fifty patients and non-CF group also from fifty patients. The basic characteristics of the study population are presented in Table I.

The CF group of patients was younger and characterized by a lower mean value of body weight and lower mean requirement of propofol dose in total. However, taking into account the propofol dose calculated per kg of body weight, the higher intake was observed in CF group than in non-CF group. The propofol dose in total and calculated per kg of body weight was not associated with FEV_1 % predicted in CF group. The fentanyl dose used in both groups was at a similar level.

The clinical characteristic of CF patients showed a slightly higher WBC count and hsCRP concentration compared to the recommended value of the Clinical and Laboratory Standards Institute (CLSI)[19]. No increase in liver enzymes activity and INR level was observed in CF group of patients. However, an approx. of 44% of CF developed hypoalbuminemia and only 0,01% of CF patients hypoproteinemia. The FEV_1 % predicted results showed that the population of CF differed in the severity of the bronchopulmonary disease. The detailed data are presented in Table II.

The time of procedure was similar for both groups and ranged from 10 to 15 minutes. The statistically significant changes over the FVB were observed in SBP and SpO_2 for both groups, but DBP only in non-CF patients. The changes in saturation and BP in CF and non-CF patients are presented in Table III. There were no complications in the entire study group, both during and after FVB.

To predict the propofol dosage based on the values of other variables, we performed two multiple regression models for the entire study population and only for CF group. In the first model, we identified that propofol dose per kg of body weight is predicted by CF status (CF *vs.* non-CF), sex, and age. In the second model, we identified that propofol dose per kg of body weight in CF group is predicted by age only (Table IV). Both models were well fitted (Figures 1 and 2). Propo-

Table I. Clinical characteristics of cystic fibrosis patients (n=50) and non-cystic fibrosis patients (n=50) undergoing flexible video bronchoscopy.

	CF (n=50)		Non-CF (n=50)		
Analyzed variable	Mean	SD	Mean	SD	*p*-value
Age (years)	28.6	8.33	33.6	8.6	0.0045
Sex (% of men)	40	-	42	-	-
Body weight (kg)	56.6	9.84	72.7	19.7	<0.0001
Propofol dose (mg)	135	38.1	145	48.3	0.3859
Propofol dose per kg body weight (mg/kg)	2.43	0.69	2.04	0.58	0.0014
Fentanyl dose (mg)	0.08	0.03	0.07	0.03	0.7185

Abbreviations: CF, cystic fibrosis; Non-CF, non-cystic fibrosis.

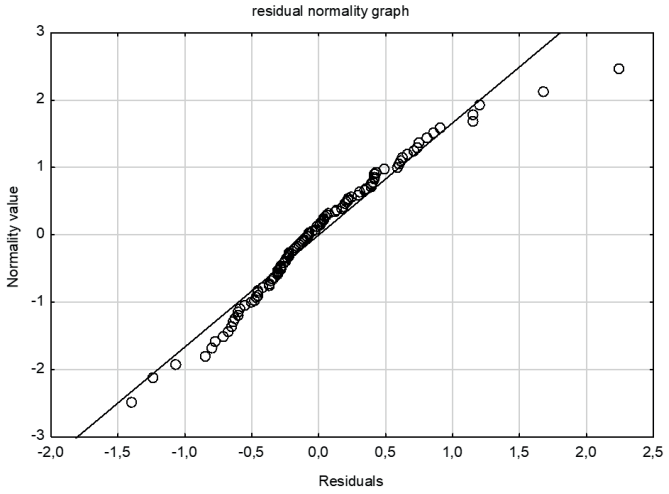

Figure 1. Multiple regression model for propofol dose per kg of body weight in the whole study population.

fol dose per kg of body weight correlations with age both for the whole study population and for CF- group only, were presented in Figures 3 and 4, respectively.

Discussion

The current study is the first to the knowledge of researchers, which presents the sedative drugs (propofol and fentanyl) requirements during flexible video bronchoscopy in adult CF patients with no history of lung transplantation. It was shown that CF patients needed a higher propofol dose per kilogram of body weight compared to non-CF patients, to achieve the same level of sedation during the FVB. Furthermore, the propofol dose was not dependent on FEV1 % pred., liver enzymes activity, protein and albumin concentration, and INR level in the CF group. This may indicate that the intensified hepatic glucuronida-

Table II. Baseline clinical characteristic of cystic fibrosis group of patients (n=50).

	CF (n=50)	
Analyzed variable	**Mean**	**SD**
WBC (billion cells/L)	9.48	3.49
hsCRP (mg/L)	12.02	2.32
ALT (U/L)	27.02	14.97
ASP (U/L)	19.63	6.97
GGT (U/L)	22.59	10.41
INR	1.093	0.076
Total protein (g/L)	75.69	8.52
Albumin (g/L)	34.75	5.13
FEV1 % pred	44.11	21.02

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CF, cystic fibrosis; FEV1, forced expiratory volume in 1 second; GGT, gamma-glutamyl transpeptidase; hsCRP, high sensitive C-reactive protein; INR, international normalised ratio = prothrombintest / prothrombincontrol)ISI; non-CF, non-cystic fibrosis; TP, total protein; WBC, white blood cells.

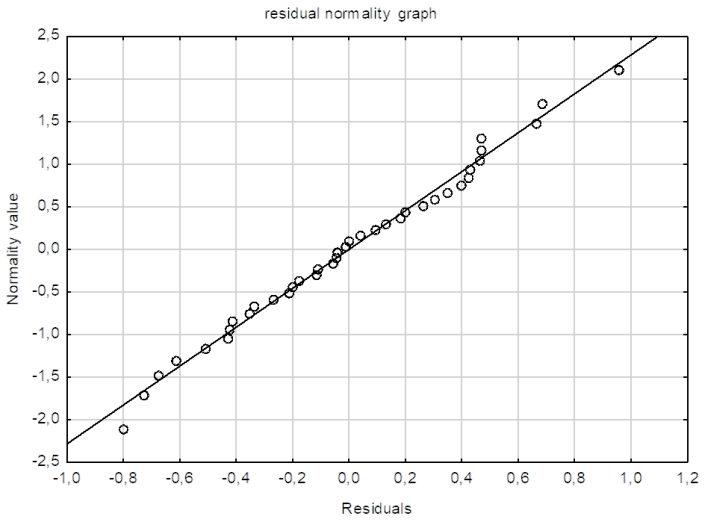

Figure 2. Multiple regression model for propofol dose per kg of body weight in cystic fibrosis (CF) group.

Table III. Changes in saturation and blood pressure in cystic fibrosis patients (n=50) and non-cystic fibrosis patients (n=50) undergoing flexible video bronchoscopy.

Analyzed variable	CF (n=50)			Non-CF (n=50)		
	Mean ± SD before	Mean ± SD after	*p*-value	Mean ± SD before	Mean ± SD after	*p*-value
SBP (mmHg)	122.38±10.72	118.94±9.43	0.0078	126.68±10.72	118.86±10.02	<0.0001
DBP (mmHg)	75.18±9.09	74.44±8.72	0.4892	81.72±12.19	72.48±10.31	<0.0001
SpO_2 (%)	94.44±2.90	96.22±2.74	<0.0001	96.29±2.22	97.22±1.73	0.0031

Abbreviations: DBP, diastolic blood pressure; CF, cystic fibrosis; non-CF, non-cystic fibrosis; SBP, systolic blood pressure; SpO_2, peripheral capillary oxygen saturation.

tion and in this pathway increased drug clearance, is the main factor responsible for this phenomenon in this group. The interesting result of our study is also the fact that the dosage of propofol and thus the length of the FVB did not depend on the severity of the bronchopulmonary disease. The stage of CF bronchopulmonary disease may influence on the shortened time of the procedure and the shallower sedation, and thus limiting the doses of anesthetics used. The clinical magnitude of this study highlights the importance of knowledge regarding the use of anesthetics by anesthesiologists and bronchoscopists caring adult CF patients during FVB with the use of a higher dose of propofol over sedation and on the other hand, showing the use of propofol and fentanyl as a safe in this group of patients.

Flexible fiberoptic bronchoscopy (FFB) and FVB are the gold standard in direct visualization of the airways, allowing many diagnostic and therapeutic interventions, including for CF patients[1,3,6,21,22]. With the widespread use, the evolution of diagnostic options, and longer procedures, more and more sedatives are used. On the other hand, sedation during flexible bronchoscopy (FB) improves patient comfort during this procedure[4-6]. The most common anesthetics used during FB include benzodiazepines like midazolam, opioids like fentanyl, as well as propofol and ketamine[6]. There are only a few reports of the use of anesthetics during the FB in adult CF patients, which affect only lung transplant recipients[23,24]. The obtained data by Chhajed et al[23] and Ho et al[24] groups are in line with the results presented in the current study. The midazolam and fentanyl doses administered to CF lung transplant recipients were higher compared to those with other diseases during the FFB. Nevertheless, the propofol was used during 17 procedures only in 7 CF patients because of the inability to achieve optimal sedation despite high doses of midazolam and fentanyl. Therefore, Chhajed et al[23] were unable to compare the dose of propofol depending on the diagnosis. Ho et al[24] suggested that

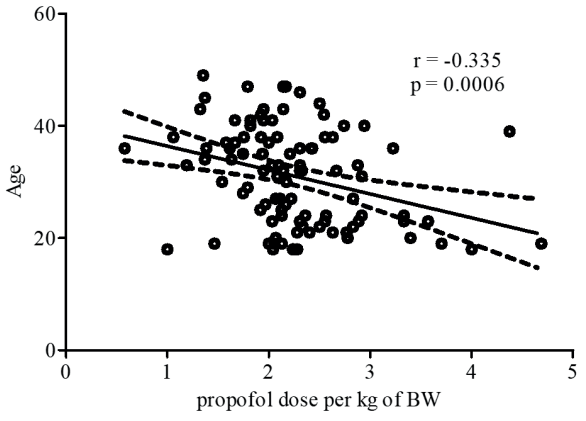

Figure 3. The correlation between propofol dose per kg of body weight (BW) and age in the whole study population.

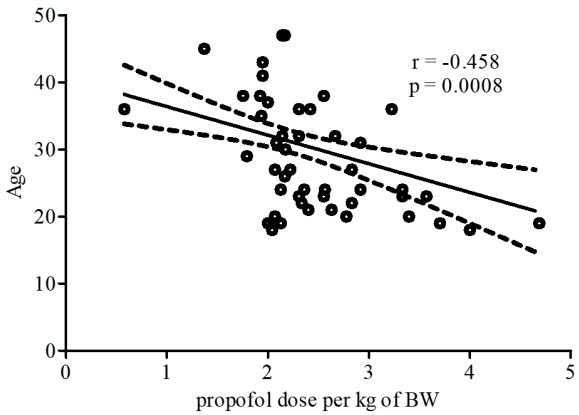

Figure 4. The correlation between propofol dose per kg of body weight (BW) and age in cystic fibrosis (CF) group.

Table IV. Multiple regression models for the whole study population and CF group only.

Study population (n=100)	
Factor	***p*-value**
CF *vs.* non-CF	0.0134
Sex (% of men)	0.0077
Age (years)	0.0202
Procedure time (minutes)	0.5195
SBP before (mmHg)	0.9205
DBP before (mmHg)	0.6897
SpO_2 (%)	0.3577
Fentanyl dose (mg)	0.4066
CF group of patients (n=50)	
FEV_1 % pred	0.7315
Procedure time (minutes)	0.7916
SBP before (mmHg)	0.2374
DBP before (mmHg)	0.2268
SpO_2 (%)	0.1177
WBC (billion cells/L)	0.2812
CRP (mg/L)	0.5237
ALT (U/L)	0.2669
AST (U/L)	0.6554
GGT (U/L)	0.6286
INR	0.5770
Albumin (g/L)	0.7083
Age (years)	0.0199
Fentanyl dose (mg)	0.4511
Sex (% of men)	0.6214

Model statistics: R= 0.4913, R2= 0.2413, F=3.6194, $p<0.0010$.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CF, cystic fibrosis; DBP, diastolic blood pressure; FEV1, forced expiratory volume in 1 second; GGT, gamma-glutamyl transpeptidase; hsCRP, high sensitive C-reactive protein; INR, international normalized ratio = prothrombintest /prothrombincontrol)ISI; non-CF, non-cystic fibrosis; SBP, systolic blood pressure; SpO_2, peripheral capillary oxygen saturation; TP, total protein; WBC, white blood cells.

CF lung transplant recipients required a higher dosage of propofol for sedation during FFB compared to their non-CF counterparts which stays in contrary to the currently obtained data. It has to be mentioned that fentanyl is lipid soluble, has a high first pass metabolism and also has a high volume of distribution and increased demand in this group of patients may also be expected[25]. The mechanism of another result and the same fentanyl dose requirement in adult CF patients is not clear. The difference in the current study was the lack of immunosuppressive treatment in the adult CF group[26]. Propofol has a rapid onset and short duration due to a quick penetration through the blood-brain barrier and distribution to and from the central nervous system, followed by redistribution to inactive tissue depots such as muscles and fat[26,27]. The pharmacokinetic variability is in the order of 70%[27]. Differences in cardiac output, hepatic perfusion, protein binding, and enzyme activity are responsible for these interindividual differences[6,27.] The pharmacodynamic variability is much larger. Some patients may already lose consciousness at a target concentration of 1 mg/L, whereas others need 4-5 mg/L to achieve a similar effect. The factors responsible for this process are not quite clear[13,23,27,28]. The main pathway responsible for propofol elimination is liver glucuronidation and phase I metabolism by cytochrome P450 (CYP-450)[10,12]. Lungs, kidneys and brain have been suspected as possible extrahepatic sites of propofol metabolism[12]. CF is a systemic disease that concerns many organs such as lungs, sinuses, liver, pancreas which are involved in drugs absorption, metabolism and elimination. For this reason, some medications disposition may vary between CF and non-CF group[29].

Based on the current literature, the main route responsible for propofol clearance is the hepatic glucuronidation – phase II drugs metabolism[6,10,28,30]. Furthermore, phase I metabolism by cytochrome P450 may also be involved in propofol elimination, predominantly by CYP2B6, and to a lesser extent by ex. CYP 2C9, 1A2, 2C18, 2C19, 2A6 and 2C8[28,31,32]. Both liver biotransformation phases may be increased in CF patients. In this population, abnormal functions of oxidases and P450, CYP2C8, CYP2C9, and CYP3A4 cytochromes are observed2[4,32]. This data may partially explain our study results. The increased liver glucuronidation process in CF patients may be responsible for the higher propofol dose in comparison to non-CF patients during FB sedation. The clinical features of CF patients enrolled in our study may support this hypothesis. The whole estimated group presented a normal range of liver aminotransferases and normal INR level, which indicates that the study group did not have liver dysfunction and highlights that other factors should be responsible for this phenomenon.

As mentioned above, lungs and kidneys may also be involved in the propofol clearance. The bronchopulmonary disorder in CF patients is one of the essential features responsible for this disease progression and patients' deaths because of respiratory failure[1,2]. On the other hand, lungs are suspected as one of the organs which take part in propofol elimination[33,34]. Dawidowicz et al[35] reported higher propofol concentration in blood from the right atri-

um than from radial and pulmonary artery oxidative metabolism of propofol during propofol infusion. In contrast, He et al[36] presented that the lungs do not seem to be site contributing to propofol extrahepatic metabolism in humans. In the available literature, there is no more data on propofol elimination by lungs, especially depending on FEV1% predicted value. Our study is the first that concerns this aspect. The adult CF patients enrolled in our study presented the various stages of bronchopulmonary disease based on FEV1% predicted, ranging from 19.7 to 88.4%.

Another way to explain the obtained data in the current study is the uridine diphosphate glucuronosyl- transferase (UGT) isoforms that are expressed likewise in the kidneys, which may take part into propofol glucuronidation and its metabolism[12,37-39]. Enhance glomerular filtration rate, reduced tubular reabsorption, extend tubular secretion have been indicated of accelerated kidney drug metabolism in CF patients[29,40]. This mechanism to a lesser extent, however, may affect the need for higher doses of drugs in CF population.

The CF patients enrolled in our study were younger and presented lower body weight compared to non-CF group similar to the study by Chhajed et al[23]. The lower body weight in CF group is frequently associated with bronchopulmonary disease, its exacerbation and pancreatic insufficiency. This status often leads to malnutrition and changes in body composition[1,41,42]. Prandota et al[29] explained the dose of drugs differences between CF population and healthy controls depending on body weight. He emphasized that the differences in total blood volumes between patients with CF and healthy young adults "were less pronounced when indexed by height and compared to the respective values in normal children and adolescents." Furthermore, in CF children, the difference in the blood volume calculated as a percent of the weight in grams was highly significant compared to age-matched non-CF29. There are no studies on the pharmacokinetics of distribution and metabolism of propofol in adult patients with CF. It seems that we can only indirectly explain the higher demand for propofol in this group of patients.

During FB, all undergoing patients have to be monitored. Statistically significant changes regarding SBP, DBP, and SpO_2 during the FVB may be associated with propofol effect[43]. On the other hand, the improvement of oxygenation after the procedure in both groups may be related to good control of oxygen therapy. Additionally, the important information resulting from this study is the lack of significant side effects of propofol sedation and complications during and after FVB, regardless of the bronchopulmonary stage of the CF. It could refer to bronchoscopist's and anesthesiologist's experience in the procedure performing and anesthetic drugs giving in this kind of sedation. These data suggest that FVB performed in sedation with propofol and fentanyl is a safe procedure in CF patients.

This study has several limitations. First, the propofol was administered as bolus injections until the Richmond Agitation-Sedation Scale of 3 was achieved, which could affect our results. We may suspect that the use of intravenous pump with greater precision could allow to determine the dose necessary to achieve the appropriate sedation. Second, we did not measure the fentanyl and propofol concentration in the blood during the procedure, therefore pharmacokinetics of the fentanyl and propofol in the CF group could not be assessed This prospective, observational study performed in the clinical setting in so specific group of patients may contribute to further research that will allow to draw casual conclusions.

.

Conclusions

The findings of this study showed that adult cystic fibrosis patients undergoing flexible video bronchoscopy need higher doses of propofol per kg of body weight. Moreover, it was indicated that the cystic fibrosis diagnosis does not influence the fentanyl dosage during this procedure. Propofol has a very narrow therapeutic window, and an increased dose may lead to excessive sedation. Therefore, current study reveals very important information for the bronchoscopist and anesthesiologist for optimal use of sedative drugs in adult CF-patients.

Conflict of Interest

The Authors declare that they have no conflict of interest.

Author Contributions

Conceptualization, B.B.-L., Data curation, B.B.-L., M.S.-M.; Formal analysis, M.M.; Investigation, B.B.-L., M.G.; Methodology, B.B.-L., M.S.-M.; Project administration, B.B.-L.; Resources, T.P.; Supervision, T.P., H.B-G.; Validation, M.G.; Visualization, M.M., M.G.; Writing-original draft, B.B.-L., M.M.-S..; Writing-review and editing, B.B.-L., M.S.-M. and T.P. All authors have read and agreed to the published version of the manuscript.

Funding Sources
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors received no funding for this work.

Acknowledgments
We would like to thank Irena Narska, MD anesthesiologist working in Bronchoscopy Laboratory for sharing her knowledge and experience with us during this research..

References

1) Castellani C, Duff AJA, Bell SC, Heijerman HGM, Munck A, Ratjen F, Sermet-Gaudelus I, Southern KW, Barben J, Flume PA, Hodková P, Kashirskaya N,. Kirszenbaum MN, Madge S, Oxley H, Plant B, Schwarzenberg SJ, Smyth AR, Taccetti G, Wagner TOF, Wolfe SP, Drevinek P. ECFS best practice guidelines: the 2018 revision. J Cyst Fibros 2018; 17: 153-178.
2) Cystic Fibrosis Foundation Patient Registry 2017 Annual Data Report, (2018). https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2017-Patient-Registry-Annual-Data-Report.pdf.
3) Paul L. Is bronchoscopy an obsolete tool in cystic fibrosis? The role of bronchoscopy in cystic fibrosis and its clinical use. J Thorac Dis 2017; 9: 1139-1145.
4) Gonzalez R, De-La-Rosa-Ramirez I, Maldonado-Hernandez A, DominguezÐCherit G. Should patients undergoing a bronchoscopy be sedated? Acta Anaesthesiol Scand 2003; 47: 411-415.
5) Ni YL, Lo YL, Lin TY, Fang YF, Kuo HP. Conscious sedation reduces patient discomfort and improves satisfaction in flexible bronchoscopy. Chang Gung Med J 2010; 33: 443-452.
6) José RJ, Shaefi S, Navani N. Sedation for flexible bronchoscopy: Current and emerging evidence. Eur Respir Rev 2013; 22: 106-116.
7) Lo YL, Lin TY, Fang YF, Wang TY, Chen HC, Chou CL, Chung FT, Kuo CH, Feng PH, Liu CY, Kuo HP, Feasibility of bispectral index-guided propofol infusion for flexible bronchoscopy sedation: a randomized controlled trial. PLoS One 2011; 6: e27769.
8) LiverTox: Clinical and Research Information on Drug- Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Propofol. [Updated 2014 Jan 25]. Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/.
9) Rigouzzo A, Servin F, Constant I. Pharmacokinetic-pharmacodynamic modeling of propofol in children. Anesthesiology 2010; 113: 343-352.
10) Favetta P, Degoute CS, Perdrix JP, Dufresne C, Boulieu R, Guitton J. Propofol metabolites in man following propofol induction and maintenance. Br J Anaesth 2002; 88: 653-658.
11) Kearns GL, Mallory GB, Crom WR, Evans W. Enhanced hepatic drug clearance in patients with cystic fibrosis J Pediatr 1990; 117: 972-979.
12) Hiraoka H, Yamamoto K, Miyoshi S, Morita T, Nakamura K, Kadoi Y, Kunimoto F, Horiuchi R. Kidneys contribute to the extrahepatic clearance of propofol in humans, but not lungs and brain. Br J Clin Pharmacol 2005; 60: 176-182.
13) Rathore VS, Singh S, Taank P, Khandelwal A, Kaushal. Clinical analysis of propofol, etomidate and an admixture of etomidate and propofol for induction of general anaesthesia. Turkish J Anaesthesiol Reanim 2019; 47: 382-386.
14) Saklad M. Grading of patients for surgucal procedures. Anesthesiol J Am Soc Anesthesiol 1941; 2: 281-284.
15) Sessler CN,. Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, Elswick RK. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002; 166: 1338-1344.
16) Horowitz GL, Altaie S, Boyd JC, Ceriotti F, Garg U, Horn P, Pesce A, Sine HE, zakowski J. EP28-A3c: Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition. CLSI document C28-A3c. Clinical and Laboratory Standards Institute, Wayne, PA, USA
17) Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CPM, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. Eur Respir J 2005; 26: 319-338.
18) Langhammer A, Johannessen A, Holmen TL, Melbye H, Stanojevic S, Lund MB, Melsom MN, Bakke P, Quanjer PH. Global lung function initiative 2012 reference equations for spirometry in the Norwegian population. Eur Respir J 2016; 48: 1602-1611.
19) Kerem E, Reisman J, Corey M, Canny GJ, Levison H. Prediction of mortality in patient with cystic fibrosis. N Engl J Med 1992; 326: 1187-1191.
20) Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Klejdson SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirns PA, Sleight P, Viigimaa M, Waeber B, Zannad F. ESH/ESC Practice guidelines for the management of arterial hypertension. Blood Press 2017; 23: 3-16.
21) British Thoracic Society, Quality standards for diagnostic flexible bronchoscopy in adults. BTS Rep 2014: 1-37.
22) Jain K, Wainwright C, Smyth AR. Bronchoscopy-guided antimicrobial therapy for cystic fibrosis. Cochrane Database Syst Rev 2018; 9: CD009530.
23) Chhajed PN, Aboyoun C, Chhajed TP, Malouf MA, Harrison GA, TammM, Leuppi JD, Glanville AR. Sedative drug requirements during bronchoscopy are higher in cystic fibrosis after lung transplantation. Transplantation 2005; 80: 1081-1085.

24) Ho C, Hayes D, Khosravi M, Splaingard ML, Tumin D, Lloyd EA. Sedation with propofol for bronchoscopy in cystic fibrosis lung transplant recipients. Lung 2018; 196: 435-439.

25) Labroo RB, Paine MF, Thummel KE, Kharasch ED. Fentanyl metabolism by human hepatic and intestinal cytochrome P450 3A4: implications for Interindividual variability in disposition, efficacy, and drug interactions. Drug Metab Dispos 1997; 25: 1072-1080.

26) Kanto J, Gepts E. Pharmacokinetic implications for the clinical use of propofol. Clin Pharmacokinet 1989; 17: 308-326.

27) Lichtenbelt BJ, Mertens M, Vuyk J. Strategies to optimise propofol-opioid anaesthesia. Clin Pharmacokinet 2004; 43: 577-593.

28) Biswal P, Singh S, Taank P. Application of ' Priming Principle ' on the induction dose requirements of propofol - A Randomized Clinical Trial. Int J Biomed Res 2018; 09: 320-324.

29) Prandota J. Drug disposition in cystic fibrosis: Progress in understanding pathophysiology and pharmacokinetics. Pediatr Infect Dis J 1987; 6: 1111-1126.

30) Suarez AL, Edelson J, Zhang J, Rockey DC. Sedation during endoscopy in hospitalized patients with cirrhosis: safety profile and predictors of adverse events. Gastroenterology 2017; 152: 1142.

31) Oda Y, Hamaoka N, Hiroi T, Imaoka S, Hase I, Tanaka K, Funae Y, Ishizaki T, Asada A. Involvement of human liver cytochrome P4502B6 in the metabolism of propofol. Br J Clin Pharmacol 2001; 51: 281-285.

32) Lian QQ, Pan PP, Li JW, Lin H, Hu HX, Zuo MZ, Cai JP. Impact of CYP2C9 polymorphism found in the Chinese population on the metabolism of propofol in vitro. Biol Pharm Bull 2015; 38: 531-535.

33) Kuipers JA, Boer F, Olieman w, Burm AGL, Bovill J., First-pass lung uptake and pulmonary clearance of propofol. Anesthesiology 1999; 91: 1780.

34) Linnane B, Clarke D, Murray P, O'Sullivan N, Dunne C, McNally P. The benefit of taking a control sample when performing bronchoalveolar lavage. Thorax 2015; 70: 990.

35) Dawidowicz AL, Fornal E, Mardarowicz M, Fijalkowska A. The role of human lungs in the biotransformation of propofol. Anesthesiology 2000; 93: 992-997.

36) He YL, Ueyama H, Tashiro C, Mashimo T, Yoshiya I. Pulmonary disposition of propofol in surgical patients, Anesthesiology 2000; 93: 986-991.

37) Raoof AA, van Obbergh LJ, Ville de Goyet J. VRK. Extrahepatic glucuronidation of propofol in man: possible contribution of gut wall and kidney. Eur J Clin Pharmacol 1996; 50: 91-96.

38) McGurk KA, Brierley CH, Burchell B. Drug Glucuronidation by human renal UDP-glucuronosyltransferases. Biochem Pharmacol 1998; 55: 1005-1012.

39) Soars MG, Riley RJ, Findlay KAB, Coffey MJ, Burchell B. Evidence for Significant differences in microsomal drug glucuronidation by canine and human liver and kidney. Drug Metab Dispos 2001; 29: 121-126.

40) Prandota J. Clinical Pharmacology of antibiotics and other drugs in cystic fibrosis. Drugs 1988; 35: 542-578.

41) Bunney PE, Zink AN, Holm AA, Billington CJ, Kotz CM. Orexin activation counteracts decreases in nonexercise activity thermogenesis (NEAT) caused by high-fat diet. Physiol Behav 2017; 176: 139-148.

42) Calella P, Valerio G, Brodlie M, Donini LM, Siervo M. Cystic fibrosis, body composition, and health outcomes: a systematic review. Nutrition 2018; 55-56: 131-139.

43) Procedures H. Diprivan. Hosp Formul 1994; 29: 83.