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# Population pharmacokinetic-pharmacodynamic model of dexmedetomidine in elderly patients undergoing sedation after abdominal aortic surgery

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## ABSTRACT

**Background.** Dexmedetomidine (DEX) is a widely used sedative agent for treating post-surgery patients. It also acts on hemodynamic parameters like heart rate or cardiac output. This study aimed to develop a pharmacokinetic-pharmacodynamic (PK/PD) model of DEX using bispectral index (BIS) and cardiac output (CO) as a response.

**Methodology and results.** 21 mechanically ventilated elderly cardiac patients undergoing abdominal aortic surgery were enrolled in the study. DEX was given to maintain moderate or deep sedation. Genotypes

of *ADR2A*55* were identified using real-time PCR-HRM. Data were analyzed using nonlinear mixed-effect modelling. A two-compartment model described DEX pharmacokinetics. The sigmoid $E_{max}$ and linear models were used to describe BIS and CO measurements. The typical value of $EC_{50}$ for DEX effects on BIS was 3.62 ng/ml, and the slope between CO and DEX concentrations was 0.819 (L/min)/(ng/ml). We were unable to show the effects of considered covariates on DEX pharmacodynamics.

**Conclusions.** We proposed the PK/PD model of DEX to understand better the BIS and CO changes observed after surgery. The measured CI values were in the reference range showing that the used doses of DEX ensured stable cardiac function in the studied patients.

## Introduction

Dexmedetomidine (DEX) is a highly selective $\alpha_2$-agonist with anxiolytic, analgesic, and sedative effects [1]. It binds to $\alpha_{2A}$-adrenergic receptors in locus coeruleus that causes sedation similar to natural sleep [2]. DEX is used in all age groups in perioperative, procedural and ICU sedation, premedication, withdrawal syndrome treatment, delirium, or as an adjuvant to anaesthesia [3]. It is also recommended to achieve minimal and moderate sedation whenever a patient state does not require deep sedation [4]. Its use is also associated with an analgesic-sparing effect [5]. DEX causes a dose-dependent decrease in heart rate (HR), cardiac output (CO), systolic (SBP), and diastolic blood pressure (DBP) [6]. However, a high dose and a quick application of DEX can increase blood pressure [7]. DEX does not cause respiratory depression in an approved dosage range (0.2–1.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$) contrary to other sedative drugs [8]. Another advantage of this drug is the possibility of contact with a patient during drug administration, which is compatible with current guidelines [9].

DEX, for the first time, was approved for sedation for continuous infusion not exceeding 24 hours, in the range of 0.2–0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (Precedex®). The producer specified a therapeutic concentration of this drug as the range of 0.4 to 1.2 ng/ml for the registered dosage [10]. Over time, new science reports were published, and EMA registered DEX (Dexdor®) in Europe for sedation for up to 14 days with the range of 0.2–1.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$. The therapeutic concentration has been assessed up to 2.4 ng/ml [8]. A concentration higher than 1.9 ng/ml causes loss of consciousness [11]. Consequently, DEX concentration should be kept below 1.9 ng/ml to achieve minimal to moderate sedation.

DEX is widely used in elderly patients. It decreases the number of postoperative cognitive dysfunction and delirium incidences, particularly vulnerable in geriatric patients [12, 13]. Perioperative use of DEX decreases in-hospital and operative mortality and reduces incidences of postoperative stroke in elderly patients following cardiac surgery [14]. It improves sleep quality and decreases the administration and risk of side effects of opioids [15].

The patient's age, body mass index, cardiac output, serum albumin levels, and liver and kidney function were identified as covariates influencing DEX pharmacokinetics [16]. Also, genetic polymorphism of $\alpha_2$-adrenergic receptor (2A subtype) was identified to affect pharmacological response after DEX administration, e.g. rs1800544 or rs553668 [17, 18]. However, the influence of this polymorphism on the sedative effect of DEX is yet to be fully established.

The present study aims to characterize the pharmacokinetics and pharmacodynamics of DEX in cardiac patients after abdominal aortic surgeries. The secondary aim of this work was to identify potential factors explaining inter-individual variability in PK/PD parameters, including age, body weight, and polymorphism of the $\alpha_{2A}$-adrenergic gene.

## Materials and methods

### Patients and genotype identification

All procedures performed on human participants were under the ethical standards of the institutional research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The institutional Bioethical Committee approved the study protocol with permission numbers 213/13 and 572/16.

It was an observational study on elderly surgical patients from Anaesthetics and Critical Care Department (University Hospital of Lord's Transfiguration, Poznan University of Medical Sciences) sedated with DEX after abdominal aortic surgery. General anaesthesia was started with induction by a single dose of propofol and continued with sevoflurane. DEX administration was initiated immediately after arrival in the ICU (< 1h). Patients were mechanically ventilated during analgosedation. Patients were excluded if they had bradycardia, significant hemodynamic instability, and confirmed allergies to DEX.

Dexmedetomidine hydrochloride (Dexdor, Orion Pharma Poland sp. z.o.o.) infusion was initiated at a rate of 0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$ without a loading dose and followed by continuous infusion at a rate ranging from 0.08 to 1.39 $\mu g \cdot kg^{-1} \cdot h^{-1}$. The drug was given to obtain moderate or deep sedation [9, 19, 20] in monotherapy (four patients additionally received a single dose of propofol/midazolam, and one patient obtained a continuous infusion of propofol with ketamine). The administration of DEX was combined with analgesics (oxycodone, acetaminophen, tramadol, or metamizole). It was discontinued when there was significant hemodynamic instability, after patient extubation, or at the physician's discretion. DEX doses and co-administration of other drugs depended on the patient's health status, sedation scale, vital parameters, cardiovascular function, and implemented procedures. Clinical adverse hemodynamic instability was bradycardia (heart rate <50 beats per minute) and/or hypotension (systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg).

The depth of sedation was assessed using the bispectral index (BIS), which was monitored by IntelliVue MX800 (Philips, Netherlands). BIS values were kept between 50 and 80 to maintain moderate to deep sedation [9, 19, 20]. Cardiac index, a hemodynamic parameter related to cardiac output, was measured by FloTrac System (Edwards Lifesciences, USA). In addition, the following vital parameters were also monitored: heart rate, stroke variation volume (SVV), and systolic, diastolic, and mean arterial pressure (SBP, DBP, MAP). All parameters were measured and recorded in the study protocol immediately before (baseline values), during the infusion, and after its cessation.

The Supplementary Material describes genotype identification.

## Pharmacokinetic-pharmacodynamic model

A pharmacokinetic model was built in the first step and described in our previous publication together with the analytical method [21].

The population nonlinear mixed-effect modelling was done using NONMEM (Version 7.2.0, Icon Development Solutions, Ellicott City, MD, USA) and the Fortran compiler 9.0. NONMEM runs were executed using Wings for NONMEM (WFN720, http://wfn.sourceforge.net). The FOCE estimation method with the interaction option in NONMEM was applied. The minimum value of the NONMEM objective function (OFV), typical goodness of fit diagnostic plots, and evaluation of the precision of the PK/PD parameters and variability estimates were used to discriminate between various models during the model-building process. The NONMEM data processing, simulations, and plots were carried out using Matlab® Software version 7.0 (The MathWorks, Inc., Natick, MA, USA).

A two-compartment model with parameters fixed to the previously estimated values was used to describe DEX PK [21]. The BIS values were linked to DEX concentrations ($C_{DEX}$) and hypothetical concentration ($C_X$) of drugs administered prior to DEX administration (propofol and sevoflurane) through the following $E_{max}$ model:

$$BIS = BIS_0 \left( 1 - \frac{E_{\max} \left( \frac{C_{DEX}}{EC_{50,DEX}} + \frac{C_X}{EC_{50,X}} \right)}{1 + \frac{C_{DEX}}{EC_{50,DEX}} + \frac{C_X}{EC_{50,X}}} \right) \quad (1)$$

This equation was further rearranged, assuming $C_X$ decreases mono-exponentially with a rate $k$. It leads to the following equation assuming an additive interaction between all the drugs:

$$BIS(P_i, t_j) = BIS_{0,i} \cdot \left( 1 - \frac{C(t_j) + X_{0,i} \cdot \exp(-k_i \cdot t_j)}{C(t_j) + X_{0,i} \cdot \exp(-k_i \cdot t_j) + EC_{50,DEX}} \right) \quad (2)$$

In Eq. 2, denotes the baseline $C_{X,0}$ multiplied by the ratio of $EC_{50}$ of DEX and $EC_{50}$ of propofol and sevoflurane, $BIS_0$ denotes the baseline BIS score

(fully awake), $E_{max}$ is the maximal effect fixed to 1 (BIS value of zero at sufficiently high concentrations of DEX), $EC_{50}$ is the drug concentration leading to half-maximal effects.

The cardiac output was finally described using the following linear model:

$$CO(P_i, t_j) = CO_{0,i} \cdot (1 - SL_i \cdot C(t_j)) \quad (3)$$

where $CO_0$ denotes the baseline CO, and $SL$ denotes the change in CO per unit change in DEX concentrations.

Inter-individual variability (IIV) for all PD parameters was modelled assuming log-normal distribution:

$$P_i = \theta_P \exp(\eta_{P,i}) \quad (4)$$

where $P_i$ is the set of PK/PD parameters for $i^{th}$ individual, $\theta_P$ is the population estimate of PK parameters, $\eta_{P,i}$ is a random effect for a particular parameter with mean 0 and variance $\omega_P^2$.

Any $j^{th}$ observation of BIS and CO measured at time $t_j$, as defined by the following equation:

$$BIS_{\text{Obs, ij}} = \text{BIS}(P_i, t_j) + \varepsilon_{BIS,ij} \quad (5)$$

$$CO_{\text{Obs, ij}} = \text{CO}(P_i, t_j) + \varepsilon_{CO,ij} \quad (6)$$

CO and BIS denote the basic structural population model (Eq. 2 and 3). $P_i$ is a pharmacokinetic parameter for the $i^{th}$ individual, and $\varepsilon_{COij}$ and $\varepsilon_{BISij}$ represent the proportional residual intra-individual random error. We assumed that $\varepsilon$ was symmetrically distributed around a mean of 0, with variance denoted by $\sigma^2$.

### Covariance Analysis

The covariate search was performed by plotting individual (post-hoc) estimates of the PK parameters against covariates (weight, age) to identify their potential effects. The categorical covariates (i.e. noradrenaline use, polymorphism) were included in the model based on indicator variables. The difference in the minimum NONMEM OFV obtained for the two hierarchical models (likelihood ratio) is approximately $\chi 2$ distributed. During the covariate search, the effect of each covariate was examined by adding an appropriate equation to the base model. When the difference in OFV between the models amounted to 3.84 for one degree of freedom, it was considered statistically significant (at $p < 0.05$) for the covariate to be included in the base model. This process was repeated until all significant covariates were added. Then backward elimination was performed by removing one covariate at a time. The least important covariate was dropped from the model according to the OFV unless that difference in OFV was more significant than 6.63 (corresponding to $p < 0.01$). The final model was established when no more covariates could be excluded.

### Model evaluation

The model performance was assessed using Visual Predictive Check (VPC). The VPC calculation was based on 1000 datasets simulated with the final parameter estimates. This study used the 10th, 50th, and 90th percentile to summarize the data and VPC prediction. The VPC compares the confidence intervals obtained from prediction with the observed data over time. If the corresponding percentile from the observed data falls outside the 95% confidence interval derived from predictions, it indicates the model misspecification. Since PD data deviated from nominal times to some extent, binning across time was done.

Evaluation of model robustness was based on the non-parametric bootstrapping with 1000 replicates. From the bootstrap empirical posterior distribution, 90% confidence intervals ($5^{th}$–$95^{th}$ percentile) were obtained for the parameters described by Parke et al. [22].

## Results

### Patients and genotype identification

Twenty one elderly patients were enrolled in the study (eighteen male and three female) from the Anaesthetics and Critical Care Department (University Hospital of Lord's Transfiguration, Poznan University of Medical Sciences). The patient's age and weight were 68 (IQR = 9) and 75 (IQR = 13) kg. DEX was given to maintain moderate (n = 13) or deep (n = 7) sedation after abdominal aortic surgery in mechanically ventilated patients. DEX administration was initiated 38.9 (±20.0) min-

utes after the end of anaesthesia with an infusion rate of 0.7 μg·kg$^{-1}$·h$^{-1}$. The infusion was continued with a rate ranging from 0.08 to 1.39 μg·kg$^{-1}$·h$^{-1}$ and lasted 295 (IQR = 156) minutes (four patients received DEX for >24 hours). The cumulative dose equalled 331.47 (IQR = 186.53) μg.

Genotypes of *ADR2A*55* were identified for all patients except patient number 1003. Eighteen had a wild type (G|G), and two people were heterozygous (A|G, ID: 1008 and 10016). According to the Ensembl database [23], genotype distribution in the European population is 0.702, 0.276, and 0.022 for G|G, A|G, and A|A, respectively. The corresponding values in this study are 0.90 (G|G) and 0.10 (A|G), and 0.0 (A|A).

## Pharmacodynamic and hemodynamic data

PD parameters included depth of sedation (bispectral index, BIS) and cardiac output (cardiac index converted to cardiac output). For two patients (ID = 1002 and 1005), the CO and for one patient (1002), the BIS measurements were missing. The observed time profiles of BIS and CO are presented in **Figure 1**. Baseline and mean (over the infusion duration) values of hemodynamic parameters are presented in **Table S1**, along with PD data.

Observed median (range) values of PD parameters during DEX infusion were 65.7 (40.4–80.4) for BIS, 2.69 (1.96–3.86) L·min$^{-1}$·m$^{-2}$ for CI, 6.60 (3.00–15.25) % for SVV, 66.5 (59.5–94.7) beats/min for HR, 120.00 (83.67–167.50) mmHg for SBP, 58.57 (44.67–

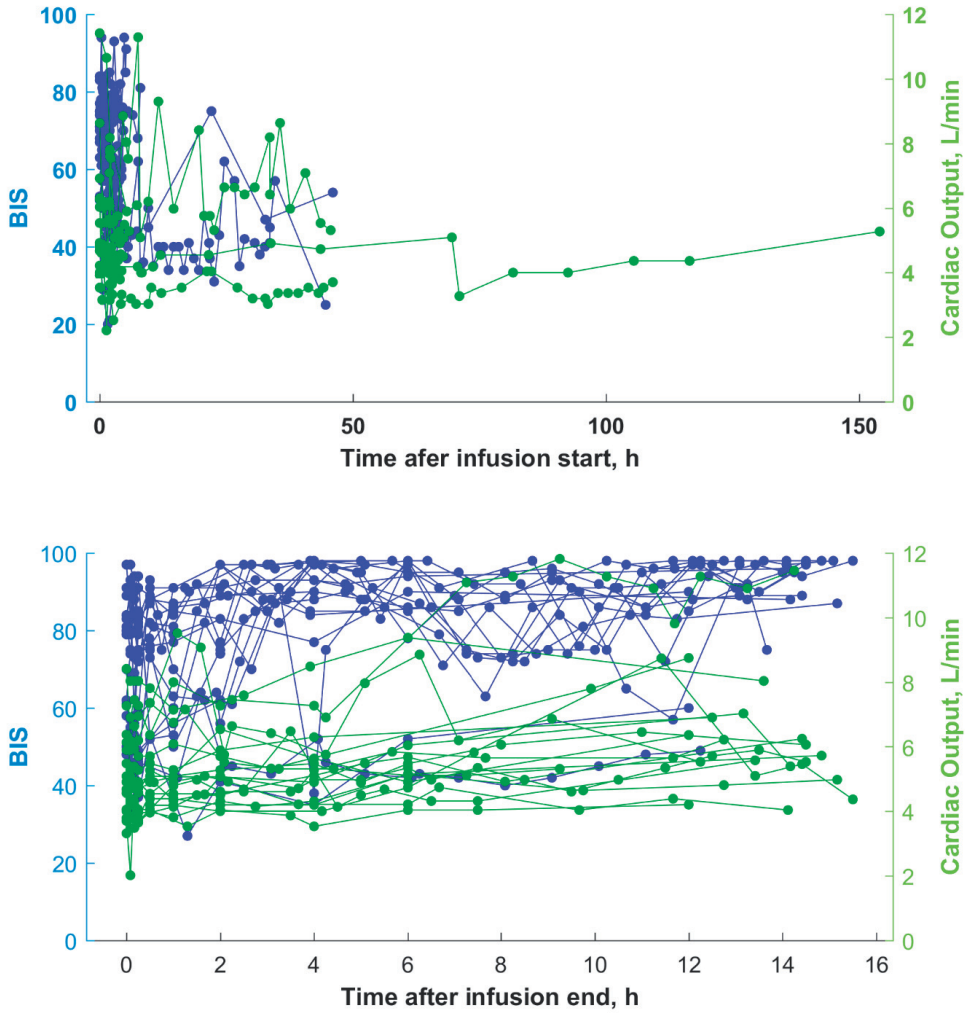


**Figure 1.** The observed time profiles of bispectral index and cardiac output. Straight lines connect dots representing measurements.

78.50) mmHg for DBP, and 79.94 (66.71–110.00) mmHg for MAP. All values were lower during the infusion period when compared to the baseline.

One hundred fifty-one heart rate measurements (from 805) were below 60. Incidences of bradycardia recurred in 6 patients (1002, 1008, 10015, 10018, 10020, and 10021). We noticed 48 (from 933) SBP values below 90 and 80 (from 830) MAP values below 65. Incidences of hypotension recurred in 6 patients (1007, 10012, 10013, 10014, 10018, and 10021).

## PK/PD model parameters and simulations

The previously described pharmacokinetic model was built for 70 patients, including the studied group [21]. The individual PK parameters were used as a driving force of PD responses. The typical values of PK parameters were estimated at 22.5 L for the volume of the central compartment, 86.1 L for the volume of the peripheral compartment, 34.7 L/h (for a typical patient) for systemic clearance, and 40.8 L/h for the distribution clearance. These values are consistent with the literature findings [24, 25]. The sigmoid $E_{max}$ model was used to describe the BIS effect and the linear model for the CO effect.

**Table 1** provides the final parameter estimates and bootstrap results. All parameters and inter-subject and residual error variances were estimated with low (<50%) coefficients of variation (%CV). The shrinkage was small for baseline cardiac output and bispectral index and moderated for other parameters. The inter-individual variability (IIV) was estimated for all parameters, except *k*. It was moderate (<60%) for the $CO_0$ and $BIS_0$ and high (60–99%) for other parameters.

**Table 1.** The parameter estimates of the final PK/PD model of DEX. The bootstrap estimates are given for comparison. 1 out of 1000 bootstrap runs terminated early. RSE denotes relative standard errors whereas CV coefficient of variation.

| Parameter [unit] | Description | θ, Estimate (%RSE) [Shrinkage] | Estimate, Bootstrap Median [5th–95th CI] |
|---|---|---|---|
| $\theta_{CO,0}$ [L/min] | Baseline cardiac output | 5.79 (6) | 5.81 [5.28–6.43] |
| $\theta_{SL}$ [(L/min)/(ng/ml)] | Slope between CO and DEX concentrations | 0.819 (31.9) | 0.845 [0.461–1.31] |
| $\theta_{BIS,0}$ | Baseline BIS | 87.9 (4.5) | 88.6 [81.1–93.9] |
| $\theta_{X,0}$[ng/ml] | Hypothetical concentrations of other than DEX at the infusion start | 0.923 (34.6) | 0.951 [0.518–2.01] |
| $\theta_{EC50}$ [ng/ml] | $EC_{50}$ of DEX | 3.62 (25.1) | 3.66 [2.42–6.21] |
| $\theta_k$ [1/h] | Elimination rate constant of drugs given prior to DEX administration | 0.299 (15.4) | 0.291 [0.217–0.371] |
| **Between Subject Variability** | | | |
| $\omega^2_{CO,0}$ [%CV] | Inter-individual variability of $CO_{,0}$ | 24.1 (18.2) [8.4] | 23.3 [14.7–30.4] |
| $\omega^2_{SL}$ [%CV] | Inter-individual variability of *SL* | 88.5 (27.0) [27.6] | 83.7 [37.6–129] |
| $\omega^2_{BIS,0}$ [%CV] | Inter-individual variability of *BIS,0* | 17.0 (4.5) [7.8] | 16.1 [1.4–25.6] |
| $\omega^2_{X0}$ [%CV] | Inter-individual variability of $X_0$ | 92.5 (22.7) [24.2] | 87.3 [.9–120] |
| $\omega^2_{EC50}$ [%CV] | Inter-individual variability of *EC50* | 77.7 (18.0) [17.4] | 73.8 [36.6–96.7] |
| **Residual Error Model** | | | |
| $\sigma^2$ | Additive residual error variability for BIS | 9.66 (6.4) [5] | 9.72 [8.7–10.8] |
| $\sigma^2$[L/min] | Additive residual error variability for CO | 0.874 (12.8) [4.2] | 0.873 [0.681–1.05] |

The typical values of $EC_{50}$ for DEX effects on BIS were estimated at 3.62 ng/ml, and the slope between CO and DEX concentrations in the linear model for CO was estimated at 0.819 (L/min)/(ng/ml). Baseline values of CO and BIS were 5.79 L/min and 87.9, respectively. The following covariates that potentially impact DEX pharmacodynamics were analyzed during the model-building process: age, body weight, noradrenaline use, and single nucleotide polymorphism of *ADRA2A*. **Figures 2** and **3** present the results. None of the analyzed covariates has an impact on DEX PD. However, since only two patients had a mutation of ADRA2A*55 and four patients received noradrenaline, these results should be treated as exploratory.

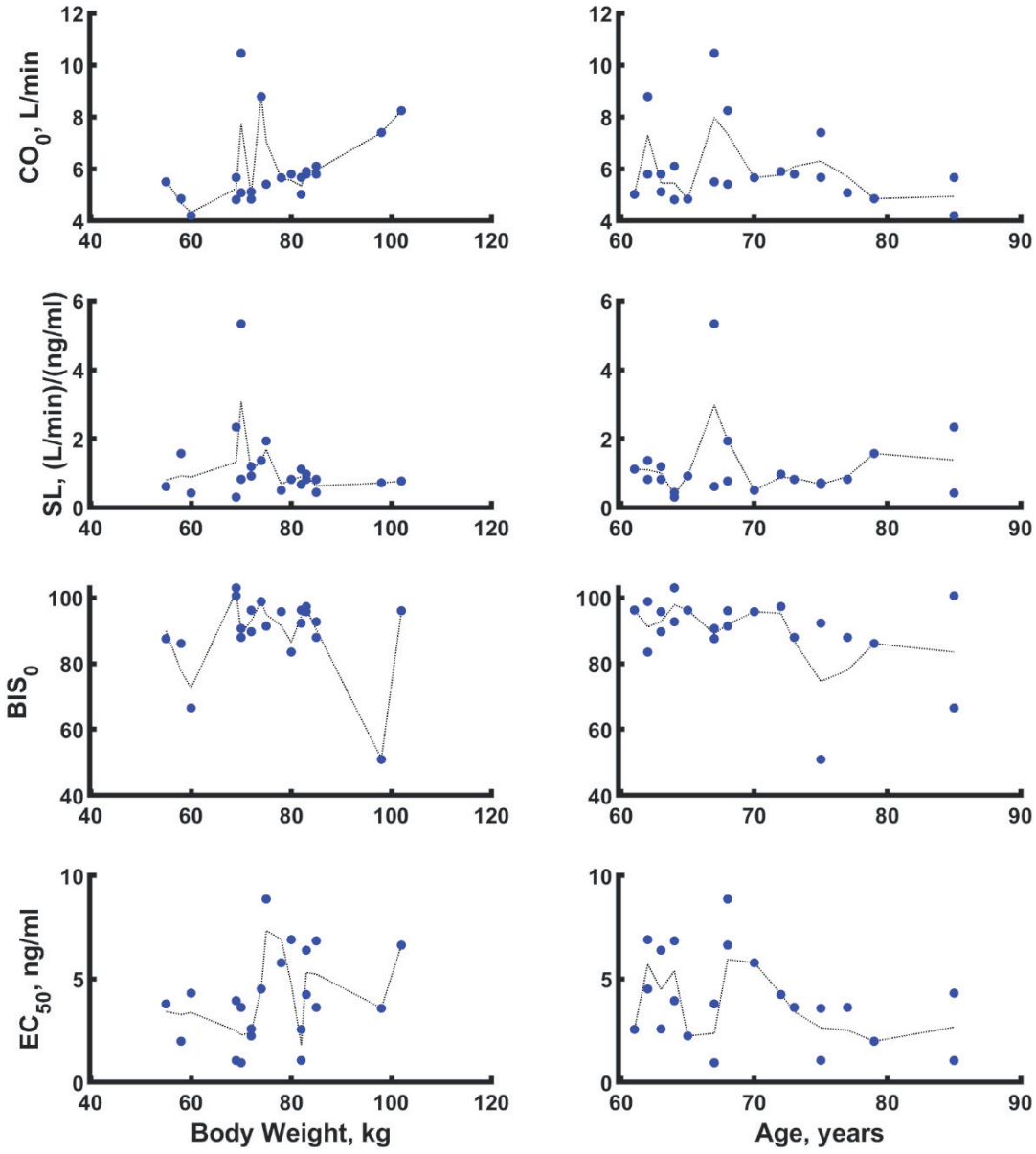


**Figure 2.** The relationship between individual values of PD parameters and subject body weight or age.

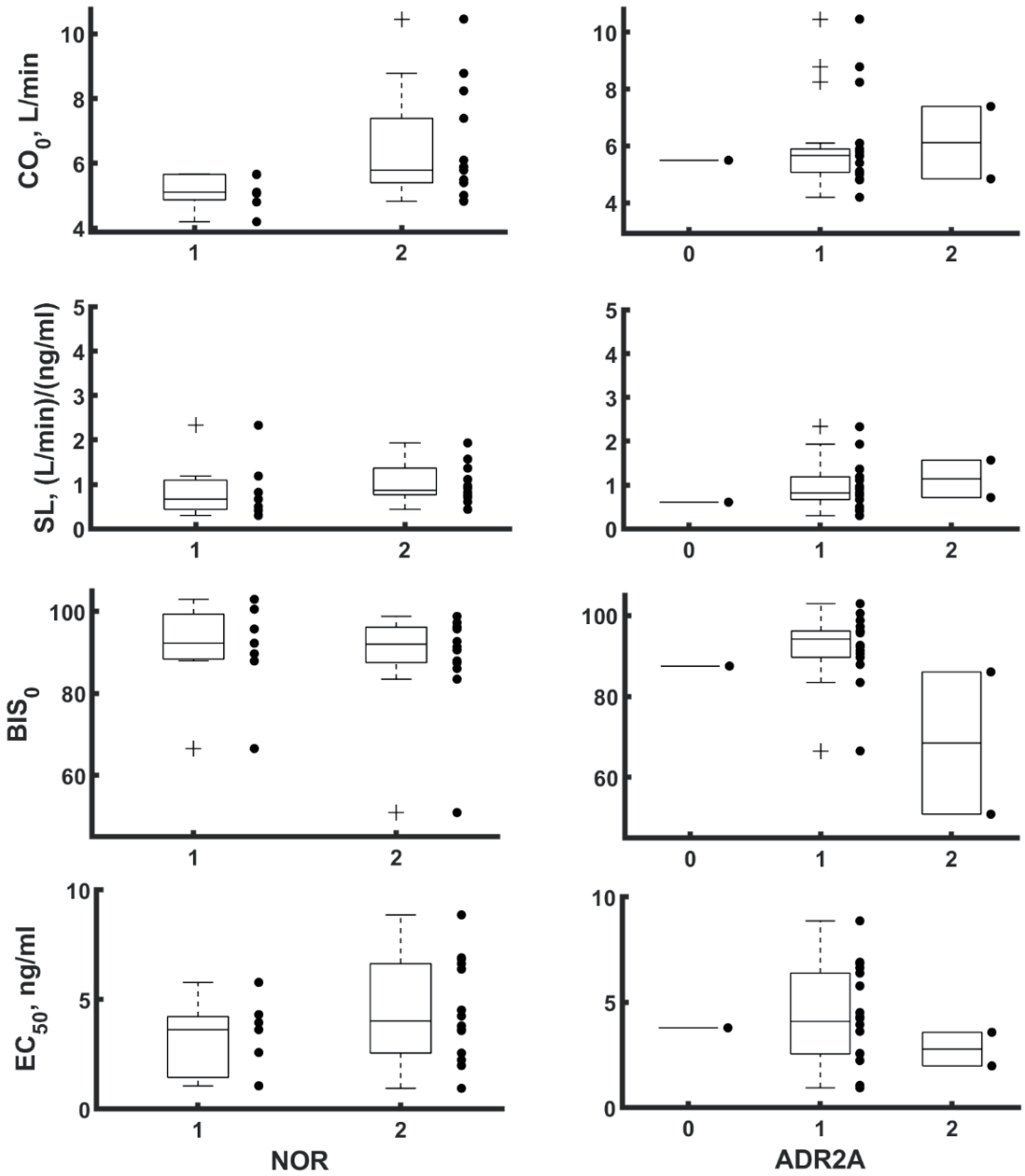


**Figure 3.** Relationship between PD parameters versus noradrenaline use (NOR, 1 – yes, 2 – no) and polymorphism of *ADR2A* (0 – patients with missing information on genetic polymorphism, 1 – G|G, 2 – A|G).

**Figure 4** shows goodness-of-fit plots for the final model. The individual predictions are close to the experimental data with no significant systematic bias, indicating the model's good performance. Other goodness-of-fit plots also confirmed this performance. Finally, a visual predictive check (VPC) for DEX PD was used to assess the simulation properties of the model. **Figures 5** (for CO) and **6** (for BIS) depict the results. VPC plots did not show any major misspecifications as both the central tendency of the data and the variability at a particular sampling time are adequately recaptured well.

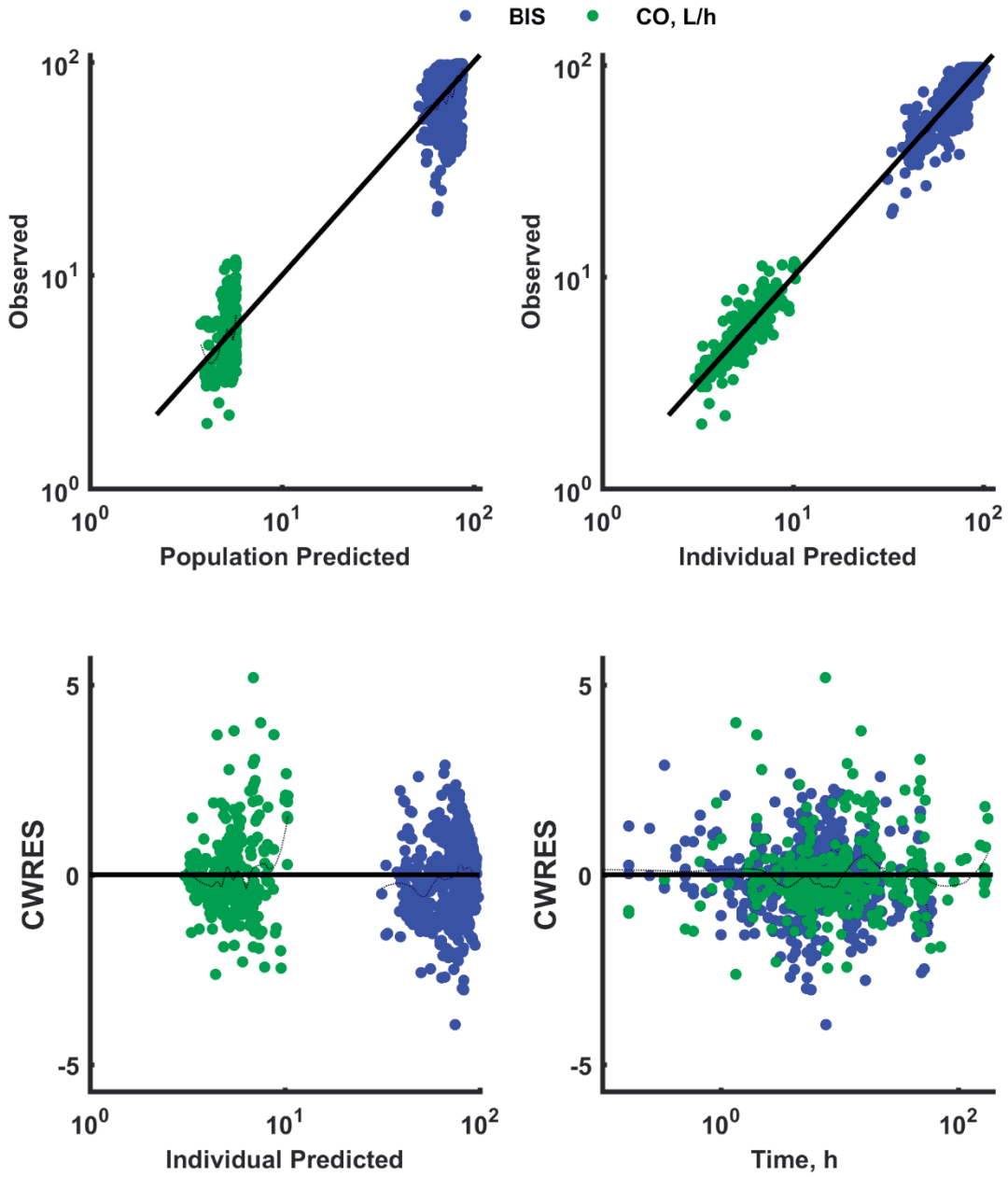


**Figure 4.** Goodness-of-fit plots for the final PK/PD model: the observed versus the population predicted responses, the observed versus the individual predicted responses, the conditional weighted residuals (CWRES) versus the individual predicted responses and the CWRES versus time.

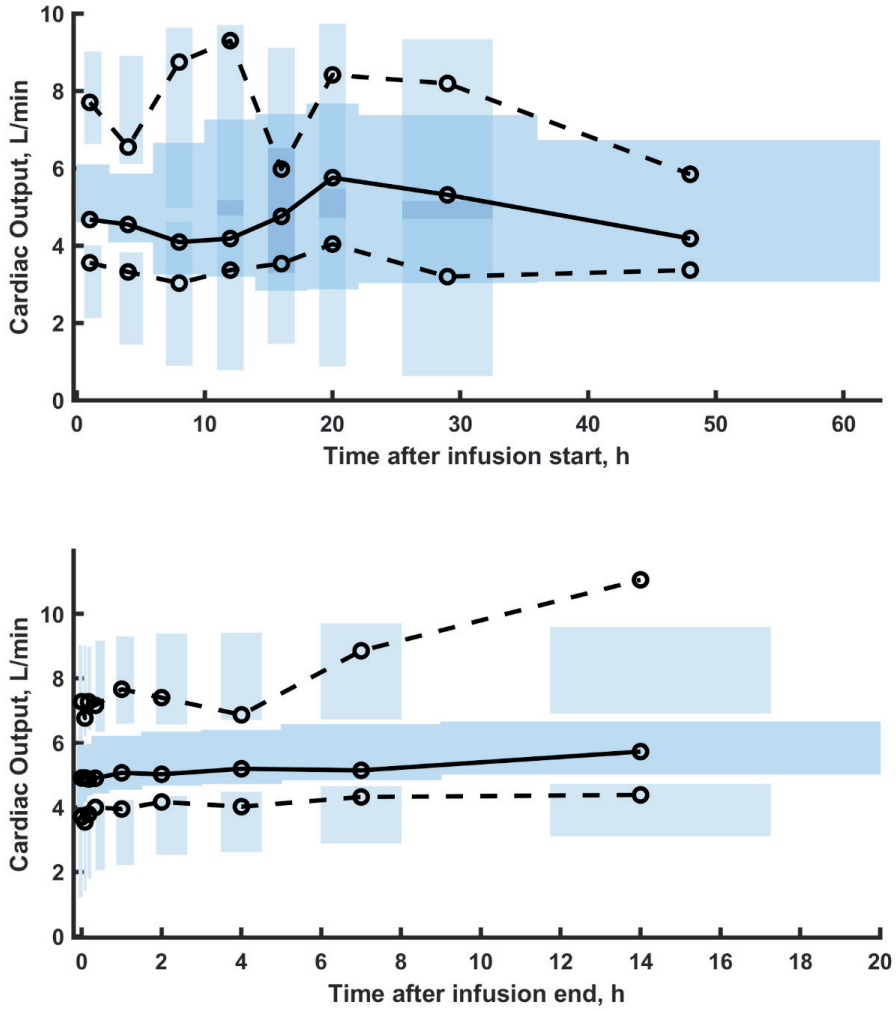


**Figure 5.** The VPC plots for dexmedetomidine PD (cardiac output). The VPC plots show the simulation-based 90% confidence intervals around the 10th, 50th, and 90th percentiles of the PD data in the form of blue (50th) and grey (10th and 90th) areas. The corresponding percentiles from the observed data are plotted in black colour.

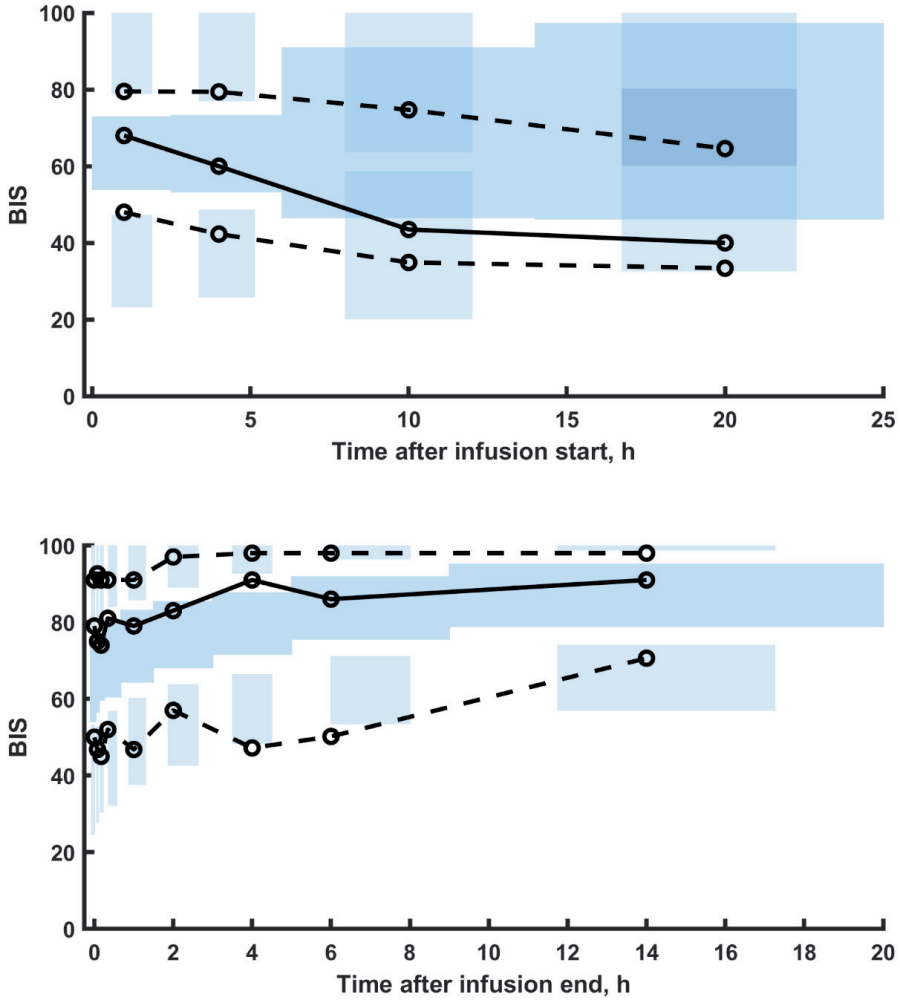


**Figure 6.** The VPC plots for dexmedetomidine PD (BIS). The VPC plots show the simulation-based 90% confidence intervals around the 10th, 50th, and 90th percentiles of the PD data in the form of blue (50th) and grey (10th and 90th) areas. The corresponding percentiles from the observed data are plotted in black colour.

## Discussion

The present study aimed to perform a population PK/PD analysis of DEX in elderly patients after abdominal aortic surgery.

The DEX concentrations were measured in all subjects. According to the earlier findings, the therapeutic range (0.4–2.4 ng/ml) was achieved in 18 patients, and all concentrations were in the range of 0.4–1.9 ng/ml. The plasma concentrations <0.4 ng/ml were noted in patients 1005 and 10016. Patient no 1001 had two measured concentrations >2.4 ng/ml, and the mean BIS value during analgosedation was 54.17 (deep sedation). Nevertheless, the mean BIS values in patients 1005 and 10016 were 51.86 (deep sedation) and 77.00 (moderate sedation), respectively. Five patients had a mean BIS value <60 (deep sedation), whereas drug concentrations were <1.2 ng/ml during infusion. Our findings show high inter-individual variability in drug response in this homogeneous group of patients.

The bispectral index was chosen to estimate the sedative effect of DEX based on the sigmoidal $E_{max}$ model. The $E_{max}$ model was also used to describe bispectral index as a pharmacodynamic effect of other drugs, e.g. propofol [26, 27], sevoflurane [28], or propofol with fentanyl [29]. DEX

infusion was initiated on average 38.9 min after the end of anaesthesia. Thus, patients were still under the influence of drugs used in anaesthesia (mainly propofol and sevoflurane) and the estimated baseline BIS values were 87.9 (the value for minimal sedation and anxiolysis). Drug concentrations at the start of DEX infusion (X0) were incorporated into the model to consider this. The estimated $EC_{50}$ was 3.62 ng/ml. Colin et al. [30] developed a PK/PD model of DEX in healthy volunteers (9 females and 9 males aged: 18–72 years). They observed a relationship between $C_{50}$ (an effect-site concentration necessary to reach half of the maximal effect) and BIS values. The estimated $C_{50}$ was 2.63 ng/ml in healthy volunteers with a baseline BIS value of 96.8 and 4.78 ng/ml in healthy volunteers with a baseline BIS value of 89.7. The second group had similar BIS and slightly higher $EC_{50}$ than our patients. Furthermore, older adults enrolled on the study are likely to present sensitivity to many drugs [31]. Additionally, Colin et al. examined healthy volunteers, whereas we researched surgical patients. Wang et al. [32] showed that the DEX dose should be decreased with the increasing age of the patient. Acceptable sedation using DEX was achieved in patients aged 65–74 and 75–85 years when the drug dose was 0.57 and 0.38 μg/kg, respectively. Because of few scientific reports about DEX PD models (using BIS as a response), comparing our results with other research is challenging. The differences in side effects of DEX related to patient's age were observed by Shehabi et al. [33], who conducted SPICE III randomized controlled trial and noticed that the early use of DEX in ventilated critically ill patients is likely beneficial in patients older than 65 years regardless of diagnostic categories and illness severity. They observed a high probability of reduced 90-day mortality in this group of patients. On the other hand, the study showed that early DEX-based sedation in younger patients appears likely to increase 90-day mortality, particularly in non-operative critically ill patients with high severity of illness [33]. They reported that bradycardia and hypotension were more frequently occurring side effects in patients with DEX-based sedation than in another group [34]. We did not observe bradycardia episodes among elderly ICU patients included in our previous study, which was not the case for hypotension episodes. We concluded that DEX could be safely used in geriatric population, but hemodynamic parameters need careful monitoring during DEX administration [35]. The European Medicine Agency based on SPICE III warned about increased mortality risk in intensive care unit patients ≤65 years [36].

Yoo et al. [37] focused on noradrenaline decrease due to the DEX effect and described this relationship using an indirect response model. They related noradrenaline concentrations to BIS, BP or HR. DEX effect on the bispectral index was described using a sigmoidal $E_{max}$ model controlled by noradrenaline in an effect compartment. They estimated $EC_{50}$ at 3.9 nnmol/L (noradrenaline). Unfortunately, they did not estimate $EC_{50}$ for DEX concentrations. Li et al. [38] developed the PD model of DEX, but they used the Ramsay score to evaluate the sedation effect of the drug. Moreover, DEX was administered as a single intranasal dose to healthy volunteers.

### PD model for cardiac function

Cardiac output was monitored in the studied subjects as a pharmacodynamic response to DEX [39, 40]. The hemodynamic effect was described by a linear model. $E_{max}$ model was also tested, but $EC_{50}$ tended to large values implying a linear relationship between CO and DEX. A linear relationship between the drug effects on cardiac output was also described for other drugs, e.g. dobutamine [41], dopamine [42], and ketamine [43]. Occasionally an $E_{max}$ model was used, e.g. for propofol [44]. Cardiac output (converted to cardiac index) was monitored in 19 patients (17 of them were measured baseline value). Baseline CI was 2.9 (2.1–6.0) $L{\cdot}min^{-1}{\cdot}m^{-2}$ whereas the average value during DEX infusion was 2.69 (1.96–3.86) $L{\cdot}min^{-1}{\cdot}m^{-2}$. It is worth remembering that parameters baseline values were measured after anaesthesia when patients were still under anaesthetic drugs. Drug concentrations were inversely proportional to cardiac output. All measured CI values were in the reference range for the elderly (>60 years) – 1.88–4.71 $L{\cdot}min^{-1}{\cdot}m^{-2}$ [45]. That confirms DEX's influence on cardiac output and shows safe use doses. There were only a few incidents when the values were below the recommended threshold (patient 1001). Furthermore, there were noted high plasma concentrations in patient 1001, whereas the infusion rate was 0.13–0.80 $\mu g{\cdot}kg^{-1}{\cdot}h^{-1}$. Cardiac output influenced DEX clearance which could be a reason for high plasma drug concentrations [46].

### Covariate testing

This work assessed the effect of single nucleotide polymorphisms of the *ADR2A* gene (*ADR2A*55*, rs553668) on clearance. There is a higher gene expression level in mutated forms than in wild types. A mutant allele variant increases the risk of hypertension, childhood attention-deficit hyperactivity disorder, increased platelet-induced platelet aggregation, increased heart rate in response to lower-body negative pressure, and lower levels of haemoglobin $A_{1c}$ and total cholesterol [47]. Kurnik et al. [18] proved that mutation in one position (rs553668) affects DEX pharmacodynamics, causes a more robust drug response, and also more considerable differences in blood pressure than in patients with wild-type genotype. Among the researched group, two patients had a mutated form of the examined polymorphism – A|G. Nobody was mutated homozygous (A|A). *ADR2A*55* genotype was tested as a covariate during the model-building process, and we could not to find any relationship. We see the need to expand the researched group to re-examine this effect with more mutated forms.

Four patients received noradrenaline during DEX infusion (10015, 10018, 100116, 10021). Noradrenaline influences cardiovascular functions, e.g. increases mean arterial pressure. However, its effect on cardiac output is ambiguous. It causes both an increase and a decrease in cardiac output. Maas et al. [48] examined cardiac output changes in cardiosurgical patients that received noradrenaline. They found that stroke volume variation could predict this catecholamine effect on cardiac output. They observed that a high SVV baseline value (14.4 ± 4.2) provoked a rise in cardiac output after noradrenaline, whereas low values (9.1 ± 2.4) – a decrease in CO. In three researched patients that received noradrenaline baseline SVV value was ≤5, in one case – 12 (**Table S2**). Two cases followed Maas' results. It is 50% of the analyzed group. We could not draw a definitive conclusion about the relationship between SVV and CO in patients who obtained noradrenaline.

We are aware that our research has some limitations. The study is small, with 21 patients, of which only two people had the mutation in the *ADRA2A* gene (*ADR2A*55*) and only four patients received noradrenaline. Therefore, we could not prove the influence of mutation and noradrenaline use on DEX pharmacodynamics. Patients were under the impact of anaesthetic drugs at the beginning of DEX infusion, which affected the PD responses. We did not have sufficient data to evaluate the effect of anaesthetics on PD DEX. Other drugs presenting an effect on CO were not assessed. We measured only DEX concentrations. We did not undertake to asses a DEX influence on hemodynamic parameters, e.g. SBP, DBP, HR, because the administration of the drugs affects blood pressure and heart rate. We should have also taken into account fluid management. However, the study provided a model describing DEX PD in patients with low BIS values at baseline. The results indicate that the DEX dose depends on the BIS value at baseline. The finding is a clinically significant example of drug interactions at the pharmacodynamic level. It also indicates that measuring the concentration of all drugs affecting BIS is necessary to understand DEX pharmacodynamics in real clinical scenarios fully.

## Conclusions

The PK/PD model of DEX was built based on data from 21 patients treated in ICU. Cardiac output was described using a linear model, whereas BIS was with the *Emax* model. The measured CI values were in the reference range showing that the used doses of the drug ensured stable cardiac function in the examined elderly patients group.


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**Conflict of interest statement**
The authors declare no conflict of interest.

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## Supplementary material

### Genetic method

As a first step, DNA was isolated from frozen anticoagulated whole blood using an E.Z.N.A.® Blood DNA Kit (Omega Bio-Tek). The DNA purification procedure was carried out according to the manufacturer's instruction [1]. The isolated DNA was stored at 20°C.

Genotype identification was carried out by real-time polymerase chain reaction with high-resolution melting analysis (real-time PCR-HRM) using a LightCycler® 480 II system (Roche® Diagnostic GmbH, Mannheim, Germany). One single nucleotide polymorphism (SNP) of an α2-adrenergic receptor gene was selected for the study – *ADR2A*55* (rs553668).47 A primer pair was designed for a PCR amplification reaction using Oligo 7.6 software (Primer Analysis Software, Colorado, USA) and is presented below.

F: 5′ GCTGCCCTTAGCATTTTTCTT 3′
R: 5′ GCTAATTCCCCTTCCATTCC 3′

The optimal annealing temperature (50°C) was evaluated by real-time PCR amplification with a gradient of annealing temperature using LightCycler® 96 (Roche® Diagnostic GmbH, Mannheim, German. Software: LightCycler® 96 1.1.0.1320, 2011, Roche Diagnostic International Ltd.). LightCycler® 480 High Resolution Melting Master kit was used to perform real-time PCR. The reaction was performed according to the manufacturer's instruction [2]. The amplification products were analyzed by high resolution melting curve analysis. The obtained data were evaluated using LightCycler® 480 Gene Scanning Software.

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**Table S1.** The hemodynamic and pharmacodynamic parameters monitored before and during dexmedetomidine infusion.

| Patient's symbol | Baseline values | | | | | | | Mean values | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BIS | CI [L/min/m$^2$] | SVV [%] | HR [beats/min] | SBP [mmHg] | DBP [mmHg] | MAP [mmHg] | BIS | CI [L/min/m$^2$] | SVV [%] | HR [beats/min] | SBP [mmHg] | DBP [mmHg] | MAP [mmHg] |
| 1001 | 71 | 2.1 | 17.0 | 91 | 161 | 85 | 107 | 54.17 | 2.01 | 13.08 | 75.80 | 128.44 | 65.02 | 79.17 |
| 1002 | – | – | – | 94 | 187 | 87 | 120 | – | – | – | 59.79 | 146.33 | 67.85 | 108.63 |
| 1003 | 53 | 2.4 | 9.0 | – | 80 | 38 | 53 | 77.00 | 3.45 | 9.75 | 60.00 | 105.37 | 45.62 | 73.67 |
| 1004 | 70 | – | – | 125 | 153 | 74 | 101 | 66.40 | 3.45 | 7.25 | 72.80 | 167.50 | 78.50 | 110.00 |
| 1005 | 67 | – | – | – | 190 | 82 | 116 | 74.25 | – | – | 62.50 | 154.00 | 75.75 | 98.12 |
| 1006 | 77 | 2.9 | 7.0 | 81 | 128 | 81 | 102 | 72.83 | 2.70 | 6.00 | 72.71 | 102.87 | 55.00 | 73.12 |
| 1007 | 63 | 2.4 | 10.0 | 73 | 120 | 73 | 76 | 66.50 | 2.69 | 8.00 | 74.00 | 83.67 | 52.89 | 66.71 |
| 1008 | 39 | 3.9 | 9.0 | 72 | 172 | 61 | 86 | 40.40 | 3.11 | 5.81 | 62.74 | 151.90 | 57.82 | 85.24 |
| 1009 | 52 | 6 | 11.0 | – | 158 | 64 | 91 | 53.37 | 3.86 | 6.60 | 94.67 | 106.20 | 57.40 | 74.90 |
| 10010 | 83 | 3.2 | 3.0 | 86 | 137 | 63 | 94 | 80.40 | 3.10 | 3.90 | 72.50 | 122.60 | 51.80 | 73.00 |
| 10011 | 71 | 2.9 | 8.0 | – | 139 | 75 | 100 | 65.00 | 2.25 | 9.50 | 66.50 | 103.43 | 58.57 | 75.57 |
| 10012 | 75 | 2.6 | 7.0 | 83 | 190 | 106 | 140 | 80.20 | 2.07 | 15.25 | 71.86 | 119.50 | 64.37 | 91.00 |
| 10013 | 77 | 3.0 | 5.6 | 73 | 185 | 63 | 109 | 55.00 | 3.67 | 6.25 | 60.17 | 137.50 | 44.67 | 70.33 |
| 10014 | 74 | 2.7 | 14.0 | 106 | 115 | 70 | 85 | 70.00 | 2.48 | 7.33 | 80.75 | 89.44 | 55.87 | 69.13 |
| 10015 | 70 | 2.6 | 4.0 | 65 | 142 | 79 | 103 | 62.50 | 2.17 | 3.00 | 59.47 | 135.23 | 74.47 | 95.06 |
| 10016 | 53 | 3.0 | 3.8 | 75 | 166 | 80 | 119 | 50.86 | 1.96 | 10.60 | 70.17 | 114.12 | 66.50 | 84.75 |
| 10017 | 70 | 2.3 | 2.0 | 60 | 107 | 53 | 72 | 76.29 | 2.56 | 3.75 | 63.33 | 119.00 | 54.25 | 72.50 |
| 10018 | 84 | 3.8 | 4.0 | – | 194 | 68 | 106 | 55.14 | 2.37 | 5.75 | 59.92 | 139.93 | 62.36 | 86.21 |
| 10020 | 75 | – | – | 88 | 155 | 78 | 110 | 78.29 | 3.50 | 6.00 | 64.73 | 113.82 | 58.82 | 79.94 |
| 100116 | 77 | 3.2 | 7.0 | 65 | 142 | 60 | 90 | 51.86 | 2.93 | 9.17 | 64.79 | 132.29 | 58.57 | 83.64 |
| 10021 | 56 | 2.2 | 5.0 | 68 | 122 | 58 | 83 | 63.32 | 2.42 | 5.62 | 71.41 | 120.33 | 56.14 | 79.97 |
| median | 70.5 | 2.9 | 7.0 | 78 | 153 | 73 | 101 | 65.70 | 2.69 | 6.60 | 66.50 | 120.00 | 58.57 | 79.94 |
| range | 39–84 | 2.1–6.0 | 2.0–17.0 | 60–125 | 80–194 | 38–108 | 53–140 | 40.4–80.4 | 1.96–3.86 | 3.00–15.25 | 59.50–94.70 | 83.67–167.50 | 44.67–78.50 | 66.71–110.00 |

**Table S2.** Changes in cardiac output and stroke volume variation baseline value in patients received noradrenaline.

| Patient's symbol | Cardiac index [Lmin$^{-1}$m$^{-2}$] | | Stroke volume variation [%] |
|---|---|---|---|
| | Baseline value | Mean value during dexmedetomidine infusion | |
| 10015 | 2.6 | 2.1 | 4 |
| 10018 | 3.8 | 2.0 | 4 |
| 100116 | 3.2 | 2.6 | 12 |
| 10021 | 2.2 | 2.4 | 5 |