Target-controlled infusion of propofol and remifentanil in cardiac anaesthesia: influence of age on predicted effect-site concentrations


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Background. Propofol-anaesthesia administrated via target-controlled infusion (TCI) has been proposed for cardiac surgery. Age-related changes in pharmacology explain why propofol dose requirement is reduced in elderly patients. However, the Marsh pharmacokinetic model incorporated in the Diprifusor propofol device does not take age into account as a covariable. In the absence of depth of anaesthesia monitoring, this limitation could cause adverse cardiovascular effects resulting from propofol overdose in older patients. We assessed the influence of age on effect-site propofol concentrations predicted by the Diprifusor and titrated to the bispectral index score (BIS) during cardiac anaesthesia.

Methods. Forty-five patients received propofol by Diprifusor and remifentanil by software including Minto model. Propofol and remifentanil effect-site concentrations were adapted to BIS (40–60) and haemodynamic profile, respectively. The influence of age on effect-site concentrations was assessed by dividing patients into two groups: young (<65 yr) and elderly (≥65 yr).

Results. For a similar depth of anaesthesia, effect-site propofol concentrations were significantly lower in elderly patients at the different stages of cardiac surgery. The mean dose of propofol required to perform tracheal intubation was significantly lower in elderly patients. However, the overall doses of propofol were comparable in both groups. Neither effect-site remifentanil concentrations nor overall doses of remifentanil were significantly different between the two groups.

Conclusions. In cardiac anaesthesia, target concentrations of propofol must be reduced in elderly patients. Although this probably contributes to improving intraoperative haemodynamic stability, the absence of decrease in overall dose requirement of propofol suggests that this adjustment is relatively moderate.


Keywords: anaesthetic techniques, i.v.; anaesthetics i.v., propofol; analgesics opioid, remifentanil; drug delivery, infusion; monitoring, bispectral index; pharmacology, propofol; surgery, cardiovascular

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Total i.v. anaesthesia based on propofol and remifentanil has been proposed as a safe anaesthetic procedure in cardiac surgery. Target-controlled infusion (TCI) induces and maintains a drug concentration by using an internal pharmacokinetic model. In cardiac anaesthesia, clinical studies reported beneficial effects of TCI compared with manual infusion. Therefore, anaesthesia via TCI has become increasingly popular in cardiac surgery. To date, the Diprifusor propofol infusion device remains the only
commercially available TCI device in Europe. The principle limitation of this device is that the age of the patient is not taken into account by the internal pharmacokinetic model. The dose requirement of propofol in elderly patients is reduced by age-related changes in pharmacokinetics and pharmacodynamics. Consequently, in the absence of depth of anaesthesia monitoring, this limitation could cause adverse cardiovascular effects resulting from propofol overdose in older patients. Therefore, in cardiac surgical patients, we evaluated the influence of age on effect-site propofol concentrations, calculated by the Diprifusor device and titrated to the bispectral index score (BIS) between 40 and 60, to determine whether an adjustment should be applied when the anaesthetist is unable to monitor the depth of anaesthesia.

Patients and methods

After obtaining institutional ethics committee approval (Pitié-Salpêtrière University Hospital, Paris, France), 45 patients scheduled for elective cardiac surgery with cardiopulmonary bypass (CPB) were prospectively enrolled in this study. Exclusion criteria were surgical procedure requiring hypothermic circulatory arrest, preoperative inotropic drugs and/or intra-aortic balloon pump support, severe impaired hepatic or renal function, and a history of drug or alcohol abuse.

Premedication consisted of hydroxyzine 1.5 mg kg⁻¹ given orally with morphine 0.15 mg kg⁻¹ administered s.c. Preoperative medications were continued until the morning of surgery with the exception of angiotensin-converting enzyme inhibitors. Three sets of systolic arterial pressure (SAP) and heart rate (HR) measurements were obtained during the 24 h before surgery and averaged to define the baseline value. To monitor the depth of anaesthesia, Zipprep™ electrodes (Aspect Medical System, MA, USA) were placed in frontal-temporal regions as recommended by the manufacturer. The BIS was calculated and displayed continuously using an Aspect A-2000 EEG analyser (Aspect Medical System). Routine monitoring included electrocardiogram (ECG), pulse oximetry and invasive arterial pressure. Anaesthesia was based on propofol (Diprivan, AstraZeneca, Rueil-Malmaison, France) and remifentanil (Ultiva, Glaxo Welcome, Marly-le-Roi, France) both simultaneously administered via TCI and as close as possible to the i.v. catheter to maximally reduce the dead space. Anaesthesia was induced with a low target plasma concentration of propofol (1.5 μg ml⁻¹ over 3 min), as recently reported in cardiac surgical patients, by using the Diprifusor propofol infusion device (Master TCI infusion system, Fresenius-Vial, Brezins, France). If loss of consciousness was not obtained with this initial target plasma concentration, anaesthetists were authorized to increase it by steps of 0.5 μg ml⁻¹. Consciousness was assessed every 10 s by asking the patients to open their eyes. After anaesthesia was induced, target plasma concentrations of propofol were titrated to maintain BIS values between 40 and 60 throughout the intraoperative period. We chose this range because it appears not to be associated with any explicit recall during cardiac anaesthesia. TCI of remifentanil was simultaneously administered with a syringe Orchestra Module DPS (Fresenius-Vial) operated with an Acer TravelMate 202 TE computer. The software used to control the infusion rate of remifentanil incorporated Minto’s pharmacokinetic model. The initial target effect-site concentration of remifentanil was 3 ng ml⁻¹ for the induction of anaesthesia. Then, effect-site concentrations of remifentanil were adapted to intraoperative haemodynamics throughout the surgical procedure. TCI of remifentanil was stopped at the last surgical suture. During this study, we did not measure actual anaesthetic drug concentrations. The plasma-site and effect-site concentrations were predicted only via pharmacokinetic parameters and plasma effect-site equilibration rate constant (kₑₒ), respectively.

Tracheal intubation was facilitated by cisatracurium 0.15 mg kg⁻¹, this was repeated for muscle paralysis, as necessary. The lungs were ventilated with oxygen/air (FIO₂, 0.5) to maintain an E¢O₂ between 30 and 35 mm Hg. Thirty minutes before the end of surgery, morphine 0.15 mg kg⁻¹ and propacetamol 2 g were infused. CPB was undertaken with a membrane oxygenator using non-pulsative flow. The choice of normothermic (36–37°C) or moderate hypothermic (32–36°C) CPB was left to the surgeon’s discretion.

The effect-site concentrations of anaesthetic drugs predicted and displayed on the device, and haemodynamic parameters (SAP and HR) were recorded before induction of anaesthesia; on loss of consciousness; after induction of anaesthesia; after tracheal intubation; at the beginning and the end of the patient’s preparation (including central venous catheter placement and surgical installation); after incision; after pericardectomy; at aortic canulation; at the beginning of the CPB; 5, 10 and 20 min after CPB onset; at weaning from CPB; 10 and 20 min after weaning from CPB; and after sternal closure.

Hypotension, defined as a SAP <90 mm Hg or a decrease >30% from baseline value lasting more than 1 min, was first treated by i.v. volume expansion and a decrease in remifentanil delivery. If hypotension was not successfully corrected, bolus doses of phenylephrine (50 μg i.v.) or ephedrine (6 mg i.v., if hypotension was associated with bradycardia) were administrated. Hypertension was defined as a SAP of >160 mm Hg or an increase of >30% from baseline value lasting more than 1 min. Tachycardia was defined as a HR of >90 beats min⁻¹ or an increase of >30% from baseline value lasting more than 1 min. Hypertension and/or tachycardia were first treated by incremental increases in remifentanil while propofol was only increased if BIS was >60. If haemodynamic stability was not obtained with a effect-site remifentanil concentration up to 20 ng ml⁻¹, cardiovascular therapies were used (nicardipine 1 mg or propanolol 1 mg if tachycardia was noted). Bradycardia,
defined as an HR <40 beats min⁻¹ or a decrease of >30% from baseline value lasting more than 1 min, was treated with atropine 0.5 mg i.v. During CPB, mean arterial pressure (MAP) was maintained between 50 and 80 mm Hg. The number of patients experiencing at least one haemodynamic event, as defined above, was calculated for both groups during induction of anaesthesia, and pre-CPB (i.e. during the preparation of patient), CPB and post-CPB periods.

In the intensive care unit (ICU), all patients were ventilated under propofol sedation to enable early tracheal extubation. Pain was assessed as early as possible by using a visual analogue scale (VAS). Initial analgesia consisted of morphine titration if VAS was >40 mm. Subsequently, analgesia comprised propacetamol and morphine. Pain scores were recorded by nurses every 3 h in the ICU until 24 h after surgery.

Data are expressed as mean (SD). Comparison of two means was performed using the unpaired Student’s t-test or Fisher’s exact method, when appropriate. Comparison of several means was performed using repeated-measure analysis of variance and the Newman–Keuls test. A P-value <0.05 was considered significant. Statistical analysis was performed using NCSS 6.0 (Statistical Solutions Ltd, Cork, Ireland).

### Results

The mean age was 72 (5) [range 65–83] yr in elderly patients and 47 (15) [18–61] yr in young patients. All variables were comparable in both groups except diabetes mellitus, which was significantly more frequent in elderly patients (Table 1).

Table 1 The characteristics of studied patients: young (<65 yr) and elderly (≥65 yr). Values are mean (SD) or number. *P<0.05 vs young patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Young patients (n=21)</th>
<th>Elderly patients (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>75 (18)</td>
<td>77 (12)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>18/3</td>
<td>18/6</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic hypertension</td>
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<td>16</td>
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<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>11*</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
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<td>4</td>
</tr>
<tr>
<td>Preoperative medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>ACEI</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Nitrates</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Surgery procedures</td>
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<td></td>
</tr>
<tr>
<td>CABG</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Valvular surgery</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Combined surgery</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>238 (45)</td>
<td>221 (47)</td>
</tr>
<tr>
<td>Duration of CPB (min)</td>
<td>80 (40)</td>
<td>67 (20)</td>
</tr>
<tr>
<td>CPB temperature</td>
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<td></td>
</tr>
<tr>
<td>Normotherma</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Mild hypotherma</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

ACEI=angiotensin converting enzyme inhibitors, CABG=coronary artery bypass graft, CPB=cardiopulmonary bypass.

The effect-site propofol concentrations required in elderly patients were significantly lower while BIS values were comparable in both groups (Fig. 1). The effect-site remifentanil concentrations and SAP values were comparable in both groups (Fig. 2).

During induction of anaesthesia, loss of consciousness occurred significantly later in young patients [6.3 (3.2) min young, 3.7 (1.0) min elderly]. The amount of propofol administered from induction until tracheal intubation was significantly lower in elderly patients [1.58 (0.57) mg kg⁻¹ young, 1.13 (0.17) mg kg⁻¹ elderly]. Time to tracheal intubation was significantly shorter in elderly patients [11.7 (3.4) min young, 9.6 (1.4) min elderly]. Table 2 summarizes haemodynamic events during induction of anaesthesia.

Fig 1 Intraoperative effect-site concentrations of (A) propofol, and (B) bispectral index in young (n=21) and elderly patients (n=24). Data are mean (SD). Control = before induction of anaesthesia; induction = after induction anaesthetic just before laryngoscopy; preparation 1, 2 = respectively, at the start and the end of the preparation of the patient, including central venous catheter and surgical installation; post CPB 1, 2 = respectively, 10 and 20 min after termination of CPB; end of surgery = after sternal closure. CPB = cardiopulmonary bypass. P<0.05 for propofol between-group differences.
Although hypotension was noted more frequently in elderly patients, this difference was not significant (Table 2). The need for phenylephrine was significantly reduced in young patients \( [75 (35) \text{ mg young}, 142 (66) \text{ mg elderly}] \).

During the pre-CPB period, no significant difference between groups was found regarding the incidence of hypotension (24% young, 38% elderly) and hypertension (38% young, 25% elderly), and neosynephrine requirement \( [244 (153) \mu \text{g young}, 320 (222) \mu \text{g elderly}] \). The need for nicardipine was significantly greater in young patients \( [2.8 (1.3) \text{ mg young}, 1.3 (0.8) \text{ mg elderly}] \).

After CPB, no significant difference between groups was found concerning incidence of hypotension (29% young, 25% elderly). After weaning from CPB, a similar percentage of patients required i.v. inotropes or vasoressors (10% young, 25% elderly).

Neither the total dose of propofol \( [4.5 (0.9) \text{ mg kg}^{-1} \text{ h}^{-1} \text{ young}, 4.3 (0.8) \text{ mg kg}^{-1} \text{ h}^{-1} \text{ elderly}] \) nor the total dose of remifentanil \( [0.18 (0.07) \text{ mg kg}^{-1} \text{ min}^{-1} \text{ young}, 0.15 (0.05) \text{ mg kg}^{-1} \text{ min}^{-1} \text{ elderly}] \) was significantly different between groups.

On awakening in the ICU, no significant difference was found in pain VAS \( [56 (25) \text{ mm young}, 50 (25) \text{ mm elderly}] \). The percentage of patients requiring morphine titration was similar in both groups (81% young, 79% elderly). Morphine requirement was 7.6 (2.7) mg in young patients and 9.0 (5.2) mg in the elderly \( (P>0.05) \). Exubation time (time lapse from arrival in the ICU to extubation) was similar in both groups \( [5.2 (1.6) \text{ h young}, 5.8 (1.7) \text{ h elderly}] \). All patients were questioned during the first postoperative day about intraoperative events and no patient had recall of surgery.

Discussion

This study provides a prospective analysis of predicted effect-site concentrations of propofol and remifentanil during cardiac anaesthesia and demonstrates that, for a similar depth of anaesthesia, predicted propofol effect-site concentrations were significantly lower in elderly patients.

To date, early tracheal extubation has been widely performed. To facilitate this procedure, authors have suggested the use of new anaesthetic procedures.\(^{10-13}\) Total i.v. anaesthesia based on propofol and remifentanil has been recently proposed as a safe anaesthetic procedure in cardiac surgical patients.\(^3\) Technological progress allows us to induce and maintain a constant effect-site concentration of a drug by using a TCI device. Cardiac surgical patients should benefit from this modern technique. Indeed, Alvis and colleagues\(^3\) reported that the TCI device provided greater haemodynamic stability compared with the manual technique. Propofol-anaesthesia via TCI has been reported in cardiac surgical patients.\(^5,6\)

The Diprifusor propofol infusion device (Master TCI infusion system, Fresenius) was used in this study because it remains the only commercially available TCI device for this anaesthetic agent in Europe. As previously reported in cardiac surgical patients,\(^8\) we chose a low target plasma concentration of propofol \( (1.5 \mu \text{g ml}^{-1}) \) to induce anaesthesia. Although age-related changes in the pharmacology of propofol are now well demonstrated,\(^7\) age is not taken into account by the Marsh pharmacokinetic model incorporated in the Diprifusor device. As the number of elderly patients
requiring cardiac surgery increases, we assessed the influence of age on effect-site propofol concentrations calculated by the Diprifusor device and titrated to obtain a BIS of 40–60. Our findings suggest that an adjustment of propofol targeted concentrations in elderly patients should be applied. This should be particularly necessary when the anaesthetist does not have access to BIS monitoring. These results emphasize that an internal pharmacokinetic model taking age into account should be incorporated into the TCI propofol device. However, this adjustment appears to be relatively moderate because the overall dose of propofol was similar in both groups. This result is surprising as we expected elderly patients to require less hypnotic. Indeed, less propofol was needed for induction in elderly patients. The similar total amount of propofol given for the whole procedure may be explained by two factors. First, CPB may have significantly altered the pharmacokinetic properties of propofol and that the influence of age on this remains unknown. Second, the delivery of propofol was adapted to the depth of anaesthesia which was monitored by bispectral EEG analysis. However, hypothermic CPB interferes with BIS values14 and consequently renders the assessment of depth of anaesthesia with this device relatively hazardous during this period.

Remifentanil was administrated via TCI. We chose the Minto pharmacokinetic model, which does take into account some covariables such as height, weight and age.15 This probably explains why no significant difference was found between groups as to the predicted effect-site remifentanil concentrations required. Since the overall amount of remifentanil was comparable in both groups, we cannot eliminate a possible contribution of remifentanil to the anaesthetic state of the older group.

In our study, a small percentage of patients experienced haemodynamic instability. Our results are consistent with those previously reported by other authors6,16 and confirm that propofol based anaesthesia is a safe anaesthetic procedure for cardiac surgical patients. However, vasopressors were more frequently used to maintain blood pressure in elderly patients.

As previously reported,6 we observed a large proportion of patients requiring morphine titration after remifentanil-based anaesthesia. Because remifentanil has a short half-life whatever the duration of infusion, specific postoperative analgesia must be provided.

Table 2 Incidence of haemodynamic events during induction of anaesthesia in young (<65 yr) and elderly patients (≥65 yr). Values are number (%)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Young patients (n=21)</th>
<th>Elderly patients (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with hypotension</td>
<td>2 (10)</td>
<td>6 (25)</td>
</tr>
<tr>
<td>Patients with hypertension</td>
<td>2 (10)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Patients with bradycardia</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Patients with tachycardia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

SAP=systolic arterial pressure, HR=heart rate.

The following points must be considered when assessing the clinical relevance of our study. First, the optimal concentrations of propofol and remifentanil were titrated at the different stages of cardiac surgery by anaesthetists who were not blinded. Thus, we could not eliminate the fact that physicians may have been influenced by results obtained in previous patients. Nevertheless, as recently pointed out by Coriat and colleagues,17 observational investigations must be performed to establish the clinical relevance of further controlled and blind-studies. Second, the target of the anaesthetic drugs differed between propofol and remifentanil. It would be better to target the effect-site for both drugs. Unfortunately, the Diprifusor propofol infusion device only allows the targeting of the plasma-site concentration. Third, temperature during CPB was left to the discretion of surgeons. Consequently, moderate hypothermic and normothermic CPB were used in our study. As recently reported,18 pharmacokinetic parameters of remifentanil are modified during hypothermic CPB. Nevertheless, hypothermia was only moderate (32–36°C) and the proportion of patients experiencing hypothermic CPB was comparable in both groups.

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References


