Propofol sequestration within the extracorporeal circuit

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Various drugs administered during cardiac anaesthesia are sequestered in the extracorporeal circuit in vitro, but it is uncertain whether this sequestration phenomenon affects plasma drug concentration in vivo. The present study was undertaken to evaluate (1) in vitro sequestration of propofol in the extracorporeal circuit and (2) whether the change in plasma propofol concentration induced by initiation of cardiopulmonary bypass in vivo can be explained by haemodilution. For the in vitro evaluation, three separate experiments with a closed circuit (membrane oxygenator, reservoir, and tubings) were performed. The pH and PCO_2 of the circulating solution (a mixture of Ringer's acetate and whole blood) were maintained within the normal physiological range, and the temperature of the solution was 28° C. The solution was circulated at a flow of 4 $L \cdot min^{-1}$ and propofol was added to the solution to achieve a concentration of 2 $\mu g \cdot ml^{-1}$. Serial samples were taken from the circulating solution for measurement of propofol concentration by high performance liquid chromatography. In the in vivo part of the study, 14 patients received a continuous infusion of propofol, and samples for the determination of plasma propofol concentration and blood haematocrit were taken before and five and ten minutes after initiation of cardiopulmonary bypass. In vitro, at 5 and 120 min after addition of propofol into the circulating solution, approximately 65% and 25%, respectively, of the predicted propofol level was measurable in the solution. In vivo, five minutes after initiation of the cardiopulmonary bypass plasma propofol concentration decreased ($P < 0.001$) more (from 2.8 ± 0.7 (mean ± SD) to 1.5 ± 0.5 $\mu g \cdot ml^{-1}$, a 45 ± 12% decrease) than would have been predicted on the basis of acute haemodilution (a decrease in haematocrit from 0.39 ± 0.04 to 0.28 ± 0.03 is a 29 ± 4% decrease). Ten minutes after initiation of cardiopulmonary bypass, plasma propofol concentration was 1.6 ± 0.5 $\mu g \cdot ml^{-1}$ (a 37 ± 27% decrease from the pre-bypass level) and haematocrit was 0.27 ± 0.04 (a 30 ± 6% decrease): the decrease in plasma propofol concentration was not different from the decrease observed in the haematocrit. In conclusion, propofol is markedly sequestered within the extracorporeal circuit in vitro. This sequestration may, to some extent, affect plasma propofol concentration in vivo.

Cette étude vise à déterminer 1) l'importance de la séquestration in vitro du propofol dans le circuit de circulation extracorporelle (CEC) et 2) si l'hémodilution seule peut expliquer in vivo les changements de concentration plasmatique qui surviennent après l'initiation de la CEC. Pour l'étude in vitro, trois expériences en circuit fermé séparées (oxygénateur à membrane, réservoir et tubulures) sont effectuées. Le pH et la PCO_2 de la solution circulée sont maintenus dans les limites de la normale physiologique avec une température de 28° C. La solution circule avec un débit de 4 $L \cdot min^{-1}$ et du propofol est ajouté à la solution pour obtenir une concentration de 2 $\mu g \cdot ml^{-1}$. Des échantillons en série sont prélevés pour la mesure de la concentration du propofol par chromatographie en phase liquide à haute performance. Pour l'étude in vivo, 14 patients reçoivent du propofol en perfusion continue et des échantillons sont prélevés pour déterminer la concentration plasmatique de propofol et l'hématocrite à cinq et dix minutes après le début de la CEC. In vitro, à 5 et 120 min après l'ajout du propofol dans la solution circulée, environ 65% et 25% respectivement du niveau de propofol prédit sont mesurables dans la solution. In vivo, cinq minutes après l'initiation de la CEC, la concentration plasmatique de propofol diminue ($P < 0,001$) à un degré plus considérable (de 2,8 ± 0,7 moyenne ± SD à 1,5 ± 0.5 $\mu g \cdot ml^{-1}$, une baisse de 45 ± 12%) qu'on pouvait le prédire sur la base de l'hémodilution aiguë (une baisse de l'hématocrite de 0,39 ± 0,04 à 0,28 ± 0,03, soit une baisse de 29 ± 4%). Dix minutes après l'initiation de la CEC, la concentration plasmatique de propofol est de 1,6 ± 0,5 $\mu g \cdot ml^{-1}$ (une baisse de 37 ± 27% du niveau pré-CEC) et l'hématocrite se situe à 0,27 ± 0,04 (une baisse de 30 ± 6%); la baisse de la concentration plasmatique de propofol n'est pas

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différente de la baisse de l'hématocrite. En conclusion, la séquestration in vitro du propofol dans le circuit de CEC est considérable. Cette séquestration peut affecter jusqu'à un certain point la concentration de propofol in vivo.

The use of propofol in cardiac anaesthesia has been previously described.[1-5] In combination with opioids a mean blood propofol concentration of 2.4 $\mu g \cdot ml^{-1}$ was associated with the prevention of untoward haemodynamic responses to noxious stimuli during the pre-bypass period of cardiac surgery.[1] Likewise, with opioids, mean blood propofol concentrations of "greater than 1 $\mu g \cdot ml^{-1}$"[2] or 2.4 $\mu g \cdot ml^{-1}$,[1] were associated with sufficient depth of anaesthesia to prevent recall and awareness during the cardiac surgical procedure. Although a stable plasma anaesthetic drug level can be maintained before cardiopulmonary bypass (CPB), the initiation of the CPB phase of cardiac surgery induces a decrease in plasma concentration of many drugs.[6,7] This phenomenon has also been reported with propofol.[1] The decrease in blood propofol concentration during CPB was attributed to haemodilution,[1] but an additional factor might be the sequestration of propofol to the components of the CPB circuit. The present investigation was performed to evaluate whether or not propofol is sequestered to the CPB circuit under *in vitro* conditions. Also, in 14 patients undergoing coronary artery bypass surgery, we evaluated the changes in plasma propofol concentration following initiation of extracorporeal circulation.

Methods

In vitro experiments

Three separate extracorporeal circuits comprising a hollow fibre membrane oxygenator and a reservoir (D 703 Compactflo® System, Dideco, Mirandola, Italy) and silicone and polyvinylchloride tubings were used. The circuit was primed with a mixture of two units of just outdated whole blood and Ringer's acetate solution. The total volume of the priming solution was 2000 ml. Heparin 5000 IU was added to the solution. The solution was circulated at a flow rate of 4 $L \cdot min^{-1}$, and oxygen 2 $L \cdot min^{-1}$ was added into the circuit. Carbon dioxide was added to maintain PCO_2 between 35–45 mmHg (4.7–6.0 kPa) and the pH was adjusted to 7.35–7.45 with trometamol (Addex®–THAM, Kabi Vitrum AB, Stockholm, Sweden), as assessed according to the α-stat principle, i.e., the values were measured at 37°C and they were not corrected to the actual temperature. The temperature of the circulating solution was maintained at 28°C with a heat exchanger.

Propofol was infused as a bolus dose through a stopcock as rapidly as possible into the venous site of the circuit to achieve a calculated concentration of 2 $\mu g \cdot ml^{-1}$ in the solution. The concentration of the propofol bolus was 10 $mg \cdot ml^{-1}$ and 0.4 ml was infused. Samples for the determination of propofol concentration were drawn from the arterial site of the circuit through the arterial-venous sampling stopcock before, and at 5, 10, 20, 40, 60 and 120 min after the addition of the drug. The samples were taken into prechilled heparinized tubes and centrifuged at +4°C with 3000 rpm for ten minutes, and the plasma samples were stored at −70°C until assayed. Propofol concentration was determined by an HPLC method.[8] The lower limit of detection was 5 $ng \cdot ml^{-1}$, and the intra-assay coefficient of variation was about 5%.

In vivo study

Fourteen patients undergoing elective coronary artery bypass graft surgery were studied. The protocol was accepted by the Ethical Committee, and each patient gave his/her informed consent. The patients received their regular cardiovascular medications on the morning of surgery, and they were premedicated with scopolamine 5 $\mu g \cdot kg^{-1}$ and morphine 160 $\mu g \cdot kg^{-1}$ *im* one hour before their arrival in the operating room. Anaesthesia was induced with fentanyl 30 $\mu g \cdot kg^{-1}$ and pancuronium 0.1 $mg \cdot kg^{-1}$. Simultaneously, a maintenance infusion of fentanyl 0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was started. At the start of CPB, the rate of the fentanyl infusion was reduced to 0.075 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to be continued until the end of the study. Anaesthesia was supplemented with isoflurane ($n = 7$) or enflurane ($n = 7$), if systolic arterial pressure increased to >120 mmHg (16 kPa). Before the start of surgery, a continuous infusion of propofol was started into the right ventricular port of the pulmonary artery catheter at a rate of 10 $mg \cdot kg^{-1} \cdot hr^{-1}$ according to Russell *et al.*[1] After 20 min, the rate of the infusion was reduced to 3 $mg \cdot kg^{-1} \cdot hr^{-1}$ to be maintained unchanged until the end of the study. After induction of anaesthesia, the trachea was intubated and the lungs were mechanically ventilated with a mixture of oxygen and air (FIO_2 0.50). Normocarbia was maintained as assessed by continuously monitoring the end-tidal CO_2 concentration and by intermittently measuring the arterial PCO_2. During CPB, the lungs were vented to ambient air. During CPB, the pulmonary artery catheter was withdrawn to a position, where a pulmonary capillary wedge pressure curve could not be obtained in order to avoid inadvertent wedging during CPB.

Cardiopulmonary bypass was conducted with non-pulsatile flow (Stöckert, Munich, Germany) and a similar circuit as described above in the "*in vitro*" section. The circuit was primed with 2000 ml Ringer's acetate solution

TABLE I Study conditions in an *in vitro* extracorporeal circulation of 120-min duration (mean ± SD)

	Time (min) from start of the experiment				
Variable	*0*	*10*	*30*	*60*	*120*
pH	7.38 ± 0.04	7.37 ± 0.02	7.38 ± 0.02	7.39 ± 0.02	7.37 ± 0.02
PCO_2 (kPa)	5.0 ± 0.2	5.6 ± 0.6	5.3 ± 0.4	5.1 ± 0.4	5.5 ± 0.5
PO_2 (kPa)	94 ± 2	100 ± 2	93 ± 4	91 ± 2	87 ± 17
Haematocrit	0.15 ± 0.02	NA	NA	NA	0.11 ± 0.01

NA = not assessed.

and heparin 5000 IU. The pump flow was maintained at 2.4 $L \cdot min^{-1} \cdot m^{-2}$ until the end of the study (until the last blood sample). Systemic anticoagulation was achieved with an initial dose of 300 $IU \cdot kg^{-1}$ heparin and with subsequent additional doses of heparin to maintain the ACT-value >480 sec. The patients were cooled to a nasopharyngeal temperature of 28° C.

Blood samples for the determination of plasma propofol concentration and haematocrit were taken into prechilled heparinized tubes from a radial artery cannula before CPB and from the oxygenator (arterialized blood) during CPB. The samples were taken (1) five minutes after the administration of heparin (at least 40 min after the start of the loading infusion of propofol and at least 20 min after the start of the maintenance infusion), (2) immediately before the start of CPB (during the cannulation of the caval veins/right atrium, 16 ± 3 min (range 10–22) after sample 1), (3) five minutes after the start of CPB and (4) ten minutes after the start of CPB. The samples were further handled as the "*in vitro*" samples described above.

Statistical analysis

In the *in vivo* study, analysis of variance for repeated measures was used to detect any change over the course of the study in the variables. For subsequent multiple comparisons, t test for paired data was used adjusted by the Bonferroni correction. A *P*-value <0.05 was considered significant. The results are given as the mean ± SD.

Results

In vitro experiments

The study conditions were stable during the 120-min circulation period (Table I). Propofol concentrations were lower than predicted, i.e., 2 $\mu g \cdot ml^{-1}$, even in the five-minute sample (Figure 1). Propofol concentrations continued to decrease during the experiment, and at the end (at 120 min) only approximately 25% of the initial predicted concentration could be measured in the circulating extracorporeal solution.

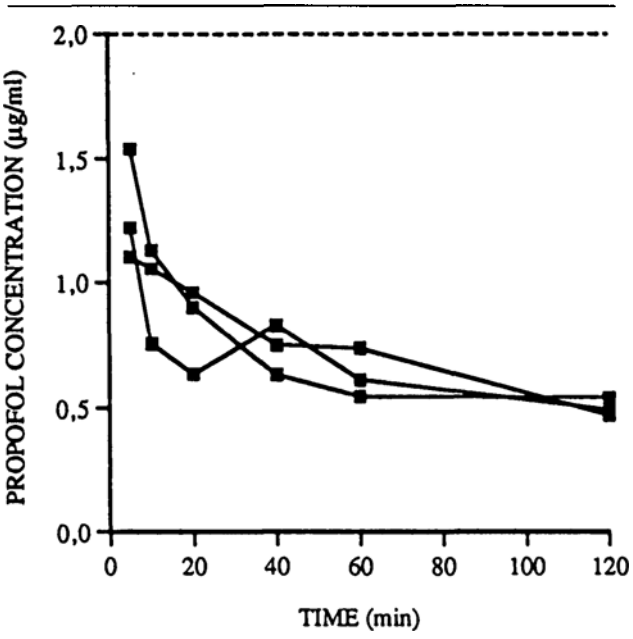

FIGURE Propofol concentration of three experiments in isolated cardiopulmonary bypass systems during a 120-min circulation. The predicted propofol concentration (as indicated by a dashed line) was 2 $\mu g \cdot ml^{-1}$.

TABLE II Preoperative patient characteristics (number of patients or mean ± SD)

Sex (M/F)	12/2
Age (yr)	57 ± 8
Weight (kg)	89 ± 11
Height (cm)	172 ± 6
Ejection fraction of left ventricle	0.52 ± 0.15
Regular drug therapy	
- Beta-adrenergic blocker	14
- Calcium-channel blocker	9
- Long-acting nitrate	14

M/F = male/female.

In vivo study

The preoperative patient data are given in Table II. During the pre-bypass period, haematocrit and propofol concentrations remained stable. During CPB, i.e., five and

TABLE III Haematocrit and plasma propofol concentration ($\mu g \cdot ml^{-1}$) in 14 patients receiving a continuous infusion of propofol and undergoing cardiopulmonary bypass (individual values and mean ± SD)

	After heparin		*Before CPB*		*During CPB (5 min)*				*During CPB (10 min)*			
Patient #	*Hct*	*Propofol*	*Hct*	*Propofol*	*Hct*	*Percent decrease‡*	*Propofol*	*Percent decrease*	*Hct*	*Percent decrease*	*Propofol*	*Percent decrease*
1	0.41	3.7	0.40	3.0	0.31	23	1.0	67	0.29	28	0.8	73
2	0.45	4.3	0.44	4.0	0.30	32	2.7	33	0.31	30	2.7	33
3	0.35	4.0	0.35	3.9	0.25	29	2.1	46	0.26	26	1.8	54
4	0.40	2.8	0.39	2.3	0.30	23	1.3	43	0.29	26	1.3	43
5	0.36	2.6	0.35	3.0	0.23	34	1.4	53	0.22	37	1.6	47
6	0.44	2.6	0.43	2.5	0.33	23	1.1	56	0.34	21	1.5	40
7	0.30	1.8	0.32	1.5	0.23	28	1.1	27	0.22	31	1.9	−27
8	0.43	2.3	0.43	2.7	0.29	33	1.4	48	0.28	35	1.3	52
9	0.37	3.0	0.38	2.2	0.27	29	1.0	55	0.27	29	2.4	−9
10	0.42	4.0	0.41	3.1	0.27	34	1.3	58	0.26	37	1.3	58
11	0.39	1.8	0.38	2.5	0.29	24	1.8	28	0.28	26	2.1	16
12	0.39	2.8	0.38	3.0	0.28	26	1.9	37	0.29	24	1.8	40
13	0.45	2.4	0.45	2.4	0.32	29	1.3	46	0.31	31	1.0	58
14	0.37	2.4	0.35	2.6	0.23	34	1.6	38	0.21	40	1.4	46
Mean	0.40	2.9	0.39	2.8	0.28*	29	1.5*	45†	0.27*	30	1.6*	37
SD	0.04	0.8	0.04	0.7	0.03	4	0.5	12	0.04	6	0.5	27

CPB = cardiopulmonary bypass. Hct = haematocrit.
*$P < 0.001$ vs the "Before CPB"-sample.
†$P < 0.001$ vs the corresponding change in haematocrit.
‡Percent decrease indicates the decrease from the "before CPB"-value.

ten minutes after the start of CPB, haematocrit and propofol concentrations were lower than the values before CPB (Table III).

Rectal temperature decreased ($P < 0.001$) from the pre-bypass value of 36.1 ± 0.8°C to 35.3 ± 1.1°C within five minutes from the start of CPB and to 34.6 ± 1.4°C within ten minutes. There was no correlation (R = 0.169, P = NS) between the change in plasma propofol concentration from the pre-bypass value until the ten-minute value and the corresponding change in rectal temperature.

In all patients, propofol concentrations were lower after five minutes from the start of CPB than before CPB. Still, after ten minutes from the start of CPB, propofol concentrations were lower than the pre-bypass concentrations in all except two patients (#7 and #9) (Table III). Five minutes after the start of CPB, the decrease in propofol concentration from the pre-bypass level was greater ($P < 0.001$) than the corresponding change in haematocrit. Ten minutes after the start of CPB, the decreases from the pre-bypass level were not different in propofol concentration and haematocrit.

Discussion

The present experiment demonstrates that propofol is markedly sequestered to the extracorporeal circuit *in vitro*. Thus, propofol is another among an increasing number of drugs now known to become sequestered to the CPB circuit. Others, relevant for anaesthesia, are e.g., nitroglycerin,[9] fentanyl[10] and thiopentone.[11] The clinical importance of this phenomenon is uncertain, but the sequestration might, at least in part, contribute to the decrease in plasma anaesthetic drug concentration of the patient observed during CPB.[1,10] Such a sequestration might also increase the consumption of an anaesthetic drug during CPB. Rosen *et al.*[12] have suggested that the capacity of a CPB oxygenator to absorb an anaesthetic drug (fentanyl in their case) might be considerable.

Our observation of the sequestration of propofol to the CPB circuit seems to be in accordance with the preliminary observation of Tarr and Kent.[13] They found that the propofol concentrations in the extracorporeal circuit decreased to 50% or less of the predicted value within 10 to 15 min. There are some differences in the experimental conditions between the study of Tarr and Kent and that of ours: (1) a temperature of 37°C in the former vs 28°C in the latter, (2) no comment of the pH and PCO_2 adjustment by Tarr and Kent vs the normal physiological range of pH 7.35–7.45 and of PCO_2 35–45 mmHg in the present study and (3) no exact value in the predicted propofol concentration in the study of Tarr and Kent, i.e., the concentration was expected to be somewhere between 2–4 $\mu g \cdot ml^{-1}$, vs. that of exactly 2 $\mu g \cdot ml^{-1}$ in our experiment. In addition, a Cobe CML® membrane oxygenator was used by Tarr and Kent vs a Compactflo® membrane oxygenator by us, and an arterial line filter in the cited study vs no filter in the present

experiment. In spite of these differences, both studies describe the phenomenon of propofol sequestration to the CPB circuit.

We also measured plasma propofol concentrations in a clinical setting in patients undergoing CPB. The mean decrease in plasma propofol concentration with initiation of CPB was greater than would have been expected on the basis of haemodilution only. This may indicate that the sequestration of propofol to the CPB circuit can affect the plasma concentration of propofol to a clinically relevant degree. However, the anaesthetic drug concentrations during CPB are affected by many other factors,[14,15] such as the change in plasma protein binding of the drug and the temperature, among others. Russell *et al.*[1] reported that, as assessed in three patients, the unbound fraction of propofol increased by a factor of 1.5 to 3 during CPB compared with the pre-bypass values. This is well in accordance with the observations of others that plasma protein binding of drugs, e.g., thiopentone[7] and alfentanil,[16] is decreased during CPB. Unfortunately, Russell *et al.*[1] did not report the unbound concentrations of plasma propofol in their three subjects. Nevertheless, the possible change in the unbound fraction of propofol might be another contributory factor in the change observed in plasma total propofol concentration in our patients at the onset of CPB. The issue of unbound concentration of plasma propofol during CPB requires further evaluation.

Although the mean plasma propofol concentration was decreased during CPB from the pre-bypass level, there existed considerable inter-individual variability. In two patients, ten minutes after the start of CPB, plasma propofol concentrations were even higher than before CPB. This might be an expression of a redistribution phenomenon of propofol occasionally seen as relatively high secondary peaks in propofol blood concentration.[8] In addition, especially in patients undergoing CPB and receiving drugs through a central route, there may exist secondary concentration peaks with delayed appearance of a drug into the arterial outflow cannula.[17] In our patients, who received propofol into the right ventricular port of the pulmonary artery catheter, surgical manipulation of the heart might also have been responsible for the unexpected variation in propofol concentrations in samples drawn from the outflow (arterial) cannula. The metabolism of propofol, being a cytochrome P450-dependent process, is likely to be influenced by temperature. Therefore, we evaluated the possibility that the change in the temperature from the pre-bypass period until that during CPB might explain the variability in plasma propofol concentration. However, no relationship was observed between the change in the core temperature and that in plasma propofol concentration. This seems to indicate that temperature did not contribute to the changes observed in propofol concentration in our patients.

The fact that we measured the propofol concentration in the cell-free solution, while many previous investigators[1,2,13] have measured propofol concentration in whole blood, should not influence the results. As studied *in vitro* with human blood, propofol is uniformly distributed between whole blood and plasma.[18] Although we did not measure the distribution in our system, it is quite probable that the propofol concentration in the cell-free fraction of the centrifugate was equal to the concentration in the circulating solution.

In conclusion, we have shown that propofol is sequestered to the CPB circuit under *in vitro* conditions which simulate clinical circumstances. However, the contribution of this phenomenon to the anaesthetic care of the cardiac surgical patient remains to be determined. The nonuniform changes in plasma propofol concentration in our patients suggest a drug-specific and possibly a procedure-specific influence on circulating propofol concentrations.

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