

## Haemodynamics during remifentanil induction by high plasma or effect-site target controlled infusion

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**Abstract :** *Background :* During total intravenous anaesthesia, the target controlled infusion concentration of remifentanil can be achieved either in limiting maximum plasma concentration ( $C_p$ ) to the effect site target concentration which corresponds to a plasma TCI technique (pTCI) or as fast as possible to achieve the effect-site target without limiting  $C_p$  (eTCI). The aim of this study was to compare the haemodynamic effects of remifentanil pTCI and eTCI during induction of anaesthesia in ASA III patients undergoing cardiac surgery.

*Methods :* 28 ASA III patients, scheduled for cardiac surgery, were randomized in two groups : Group pTCI received remifentanil to achieve an effect-site target of  $15 \text{ ng ml}^{-1}$  by limiting  $C_p$  to  $15 \text{ ng ml}^{-1}$  and group eTCI received remifentanil to achieve an effect-site target of  $15 \text{ ng ml}^{-1}$  without limiting remifentanil  $C_p$ . Before induction, all patients received  $30 \mu\text{g kg}^{-1}$  of midazolam intravenously and  $2 \text{ ml kg}^{-1}$  of a gelatin solution. Heart rate, invasive arterial pressure and bispectral index were continuously measured. Differences from baseline values were compared between the two groups using a Mann-Whitney U test. Baseline population characteristics were compared using an analysis of variance.

*Results :* There were no significant differences in haemodynamic parameters between the two groups. In the group pTCI final effect-site concentration was reached in  $7.3 \pm 1.4$  minutes and in the group eTCI in  $2.2 \pm 0.2$  minutes ( $p < 0.05$ ).

*Conclusion :* In ASA III patients scheduled for elective cardiac surgery, remifentanil eTCI can be preferred to remifentanil pTCI for induction because of its shorter onset with the same haemodynamic stability.

**Key words :** Remifentanil ; target controlled infusion ; bispectral index.

In the past, high doses of opioids were considered the standard induction technique in cardiac surgery because of its haemodynamic stability. Remifentanil can be administered successfully in high-risk cardiac patients without the risk of delayed respiratory depression observed with long-acting opioids (1, 2).

Recently plasma (pTCI) and effect site target controlled infusion (eTCI) systems have been

developed (3, 4, 5). eTCI systems allow to reach the desired effect-site concentration much faster than pTCI systems. In order to achieve this goal, the plasma concentration has a large overshoot and this high plasma concentration could be responsible for haemodynamic instability. Whereas for propofol, eTCI shortened the time to loss of consciousness (LOC) without causing more hypotension compared to pTCI, this has not been shown for remifentanil (6). The aim of this study was to compare remifentanil pTCI and eTCI during induction of anaesthesia in ASA III patients undergoing cardiac surgery. Primary outcome was haemodynamic stability during induction before tracheal intubation, evaluated by arterial blood pressure and heart rate.

### METHODS

After approval of the ethics committee of our institution, written informed consent was obtained from 28 ASA III adult patients (40-70 years) scheduled for elective cardiac surgery. Obese patients (body mass index  $\geq 27$ ) or patients having a preoperative left ventricular ejection fraction less than 40% were excluded. Preoperative treatment was continued until the day of surgery, except converting enzyme inhibitors.

Patients were randomized in two groups : group pTCI and group eTCI. Group pTCI received remifentanil to achieve an effect-site target to  $15 \text{ ng ml}^{-1}$  by limiting  $C_p$  (plasma concentration) to  $15 \text{ ng ml}^{-1}$  which corresponds to a plasma remifentanil TCI technique (pTCI) and group eTCI received remifentanil to achieve an effect-site target

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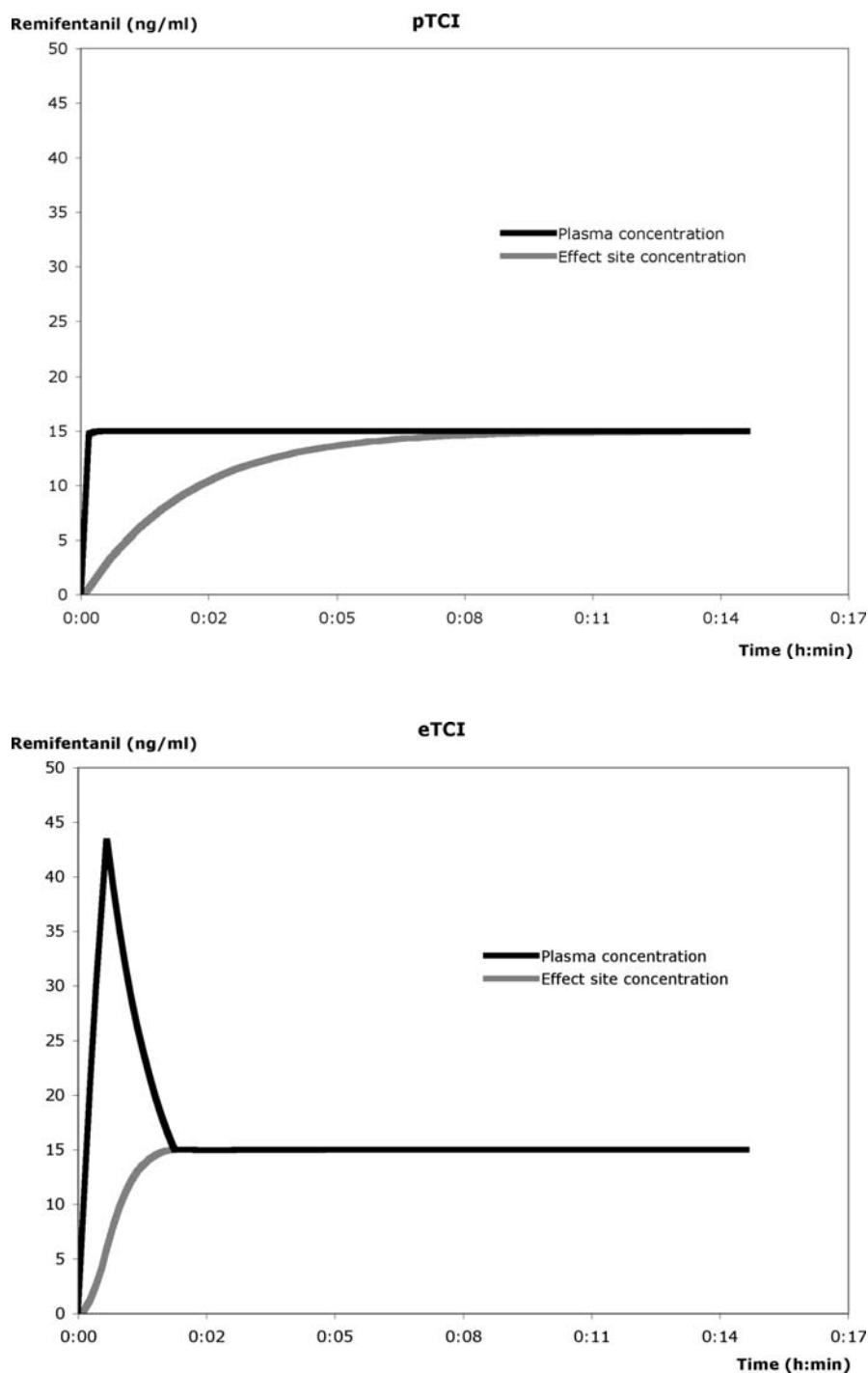


Fig. 1. — Evolution of plasma and effect site concentrations in group pTCI (top) and eTCI (bottom)

to 15 ng ml<sup>-1</sup> without limiting remifentanyl Cp (Fig. 1).

All patients were premedicated with oral alprazolam 0.5 mg one hour before induction of anaesthesia. Invasive arterial pressure, heart rate and peripheral oxygen saturation were measured at baseline and continuously throughout the study period. An Aspect A-2000 (Aspect Medical

Systems, Natick, MA) was used to monitor Bispectral index (BIS). Ten minutes before starting remifentanyl TCI, all patients received 30 µg kg<sup>-1</sup> of midazolam intravenously and 2 ml kg<sup>-1</sup> of a gelatine solution.

Heart rate, invasive arterial pressure and BIS were recorded at baseline and at maximum peak Cp and Ce (effect-site concentration). After LOC,

Table 1  
Demographic data

Group	eTCI	pTCI
Age (years)	63.9 ± 14.9	55.6 ± 15.3
Gender	3 F / 11 M	4 F / 10 M
Weight (kg)	68.8 ± 13.8	71.6 ± 14.7
Height (cm)	171.6 ± 7.2	170.1 ± 6.3

defined as lack of response to verbal command and mild shaking, patients were paralyzed with intravenous rocuronium 0.9 mg kg<sup>-1</sup> and manually ventilated with 100% oxygen. Thereafter the trachea was intubated. The total dose of remifentanil administrated and the time to peak effect-site concentration were recorded in both groups.

Baseline population characteristics were compared using an analysis of variance. Differences in BIS values and haemodynamic variables from baseline values were compared between the groups using a Mann-Whitney-U test. A p value < 0.05 was considered significant.

## RESULTS

28 patients were included in the study, 14 in each group. There were no significant differences in patients' characteristics as shown in Table 1 (age, gender, weight, height).

All patients except one lost consciousness. This patient in the group eTCI required additional intravenous midazolam and was excluded from the analysis.

Calculated remifentanil Ce was achieved after 7.3 ± 1.4 minutes in group pTCI and after 2.2 ± 0.2 minutes in group eTCI (p < 0.05). The total dose of remifentanil administrated at that time was 416 ±

32 mg in group pTCI and 225 ± 24 mg in group eTCI (p < 0.05). Mean maximum theoretical Cp in the group eTCI was 48 ± 7 ng ml<sup>-1</sup>. In both groups, there was no significant difference in haemodynamic parameters at maximum Cp and at final Ce (Table 2). No severe bradycardia, defined as less than 45 beats minute<sup>-1</sup>, nor arterial hypotension, defined as mean arterial pressure less than 60 mm Hg, were observed.

BIS value before remifentanil administration was 87.9 ± 8.3 in the group pTCI and 87 ± 7.5 in the group eTCI. At final Ce, the drop of BIS was 20 ± 21 in the group eTCI and was 40 ± 8 in the group pTCI, which was not significant.

A power analysis indicated a power of 29%. A sample of at least 2 groups of 54 patients would be necessary to achieve a power of 80%. However the differences between both groups are so small that the possibility of a type II error can be accepted; indeed such small differences (ex. 8 mm Hg of systolic blood pressure) would have no clinically relevance.

## DISCUSSION

This study shows that high doses of remifentanil by TCI delivery with or without peak plasma overshoots associated with very low doses of midazolam can be administrated for anaesthesia induction in ASA III adult cardiac patients. Calculated remifentanil Ce of 15 ng ml<sup>-1</sup> and LOC were attained earlier in the eTCI group than in pTCI group due to the different method of TCI delivery. These results were similar to the results of Struys and colleagues for propofol TCI induction in healthy women. They observed that targeting Ce shortened the time to LOC without causing more

Table 2  
Baseline values and changes from baseline to max Cp and from baseline to max Ce

	Baseline	Max Cp	Δ (baseline to max Cp)	Ce = 15 ng/ml	Δ (baseline to Ce)
<b>eTCI</b>					
Heart rate (beats/min)	65 ± 10	65 ± 15	1 ± 9	57 ± 10	-7 ± 5
Systolic blood pressure (mm Hg)	148 ± 24	145 ± 27	-3 ± 6	126 ± 21	-22 ± 12
Diastolic blood pressure (mm Hg)	65 ± 13	63 ± 14	-2 ± 6	54 ± 10	-11 ± 7
Mean blood pressure (mm Hg)	93 ± 15	92 ± 17	-1 ± 6	77 ± 12	-15
BIS	87 ± 8	86 ± 6	-1 ± 6	67 ± 20	-22 ± 21
<b>pTCI</b>					
Heart rate (beats/min)	69 ± 15	68 ± 12	-1 ± 6	61 ± 11	-8 ± 9
Systolic blood pressure (mm Hg)	129 ± 17	128 ± 21	0 ± 9	99 ± 17	-30 ± 15
Diastolic blood pressure (mm Hg)	64 ± 11	63 ± 12	-1 ± 4	50 ± 11	-13 ± 8
Mean blood pressure (mm Hg)	86 ± 13	86 ± 14	0 ± 4	67 ± 13	-19 ± 8
BIS	88 ± 8	87 ± 9	-2 ± 4	48 ± 7	-34 ± 16

hypotension in 120 healthy women without pre-medication (6).

Compared to the baseline heart rate, no significant difference in heart rate at maximal  $C_p$  or final  $C_e$  was observed using either remifentanil pTCI or eTCI technique. There was also no significant difference in blood pressure changes between both groups. Volume loading before induction may explain the lack of early hypotensive episode. The risk of late episodes of hypotension was not evaluated in the study protocol because tracheal intubation was performed when remifentanil  $C_e$  was  $15 \text{ ng ml}^{-1}$ .

The BIS evolution during this remifentanil TCI induction technique shows that cardiac patients lost consciousness in the eTCI group with a BIS superior to 60. This value was recorded when the theoretical calculated  $C_e$  was attained. However BIS monitoring requires minimum 30 to 45 seconds to compute a new value which could partially explain the slightly higher BIS value in the eTCI group. The BIS value obtained 60 seconds after reaching final  $C_e$  was identical in both groups (Data not shown).

In conclusion, in ASA III patients scheduled for elective cardiac surgery, for anaesthesia induction when combined with low doses of benzodiazepines, high peak plasma concentrations of

remifentanil do not impair haemodynamic stability. Remifentanil eTCI may be preferred to remifentanil pTCI for induction because of the shorter delay to reach the target  $C_e$  and LOC with the same haemodynamic stability and a reduced total dose of remifentanil.

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