PRACA ORYGINALNA

Remifentanil and fentanyl during induction of anesthesia for coronary artery surgery – a comparative hemodynamic study

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ABSTRACT

BACKGROUND

Remifentanil is metabolized by non-specific esterases and is very short-acting. It is eliminated from all body compartments at the same time.

AIM

The aim of this study was to compare anesthetic induction with standard dose of etomidate and isoflurane combined either with fixed rate remifentanil infusion or a single bolus dose of fentanyl.

MATERIAL AND METHODS

54 patients (57.0±7.6 years) with stable CAD and EF > 40% scheduled for elective coronary revascularisation were recruited for this prospective, randomized trial. During induction, patients in group I received remifentanil infusion 0,5 mcg/kg/min., while group II received bolus dose 5 mcg/kg fentanyl. After initiation of remifentanil infusion or the injection of fentanyl, 0,2 mg/kg etomidate was given, followed by the injection of 0,1 mg/kg pancuronium and the administration of 1% isoflurane. Haemodynamic parameters were measured before induction and after tracheal intubation.

RESULTS

Cardiac index decreased in both groups, heart rate and systemic blood pressure decreased only in remifentanil group, while systemic vascular resistance index increased only in fentanyl group. Heart rate, systemic blood pressure and systemic vascular resistance index after induction were significantly higher in fentanyl group.

CONCLUSIONS

Remifentanil is more potent than fentanyl in blunting a cardiovascular response to tracheal intubation in patients with coronary artery disease. Low dose of fentanyl, used for the anaesthetic induction, may result in a clinically important increase of systemic vascular resistance.

KEY WORDS

anaesthetic induction, remifentanil, coronary artery surgery

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INTRODUCTION

Remifentanil is becoming increasingly popular in cardiac anesthesia [1, 2, 3, 4]. This opioid is metabolized by non-specific esterases in blood and various tissue and is therefore very short-acting. It is eliminated from all body compartments at the same time [2, 5, 6].
Remifentanil exerts its maximal effect very rapidly and the concentration between blood and the central nervous system equilibrates in 1 to 1.5 minutes. It therefore fulfils all criteria of an ultra short-acting agent with a half-life being as short as 3 to 10 minutes. It has also been confirmed that this half-life is totally independent from the duration of the infusion [2, 7, 8, 9]. Many previous studies have demonstrated that the use of remifentanil in cardiac surgery is safe and effective [3, 10, 11, 12, 13].
Induction period is crucial for a cardiac patient, because it might cause haemodynamic instability. Kazmaier et al. have shown that the cardiac index may decrease even by 25% in comparison to baseline values during anesthetic induction with remifentanil [14]. Other authors have noted serious haemodynamic impairment during induction with remifentanil in patients with coexisting diseases of the circulatory system [15, 16].
Various dosing regimens for both remifentanil and fentanyl are used for fast-track coronary artery sugery. Induction with 1 mcg/kg remifentanil was safely combined with both propofol [10] and isoflurane [11, 12], however anesthesia is often initiated with a remifentanil infusion of 0,5 mcg/kg/min. Fentanyl dose on induction may also vary from 6 mcg/kg [11] to 15 mcg/kg [17]. Haemodynamic parameters on induction of anesthesia are not usually analyzed in detail by the authors.
Inhalational anesthetic agents remain very popular in cardiac anesthesia. There is now growing evidence that inhalation agents have cardioprotective properties and may therefore reduce myocardial ischaemia [18, 19, 20, 21]. The comparison of anesthetic induction with either remifentanil or fentanyl combined with an inhalation agent has the potential to answer some important questions.
In our previous paper published in 2006 in Medical Science Monitor, we compared the course of anaesthesia with remifentanil and fentanyl for coronary artery surgery and found that remifentanil appears to be more effective than fentanyl in blunting haemodynamic response before the initiation of the cardiopulmonary bypass [22]. This was a very important finding, therefore we decided to examine it more closely, increasing a sample size and concentrating entirely on anesthetic induction.
Popular and previously confirmed as safe dosing regimens of both opioids have been used. We compared anaesthetic induction with standard doses of etomidate and isoflurane, combined either with fixed rate remifentanil infusion or a single bolus dose of fentanyl. The haemodynamic status of the patients has been analyzed and the data before and after anesthetic induction have been compared.

MATERIAL AND METHODS

All the patients in the study group had coronary artery disease (CAD). The study was performed during anesthetic induction for elective coronary revascularisation. 54 patients aged 40 – 74 (mean 57.0 ± 7.6 years) have been prospectively evaluated. Patients with stable CAD and good left ventricular ejection fraction (EF) (>40%) were randomly allocated into 2 groups. In 30 patients (group I), remifentanil infusion was used during anaesthetic induction. In the other 24 patients (group II) a bolus injection of fentanyl was used.
The local Ethical Committee approved the study protocol and all patients gave informed consent. Patients with renal or hepatic disorders, chronic obstructive airway disease, or those who were haemodynamically unstable were excluded from the study. The presence of diabetes, peripheral vascular disease, previous myocardial infarction and arterial hypertension was noted. Other important data included ejection fraction, the degree of coronary syndromes assessed by Canadian Coronary Score (CCS) [23] and the operative risk estimated by EuroSCORE [24].
All patients were premedicated with oral midazolam approximately one hour before surgery – patients with body weight less than 55 kg received 7.5 mg, those between 55 and 80 kg received 11 mg, and those above 80 kg received 15 mg. The sedation score according to Ramsay was registered on arrival at the operating theatre. Venous and arterial cannulae as well as a pulmonary artery catheter were inserted

under local anesthesia. At this stage the patients were randomized into a study group by the independent observer. The times from premedication to arrival in the operating theatre (T1), and from arrival in the operating theatre to anesthetic induction (T2), was registered.

During induction, patients in group I received remifentanil (Ultiva, Glaxo Wellcome) by intravenous infusion at a constant rate of 0.5 mcg/kg/min., while patients in group II received bolus dose of 5 mcg/kg fentanyl (Fentanyl, Polfa). One minute after initiation of remifentanil infusion or injection of fentanyl, 0.2 mg/kg etomidate (Hypnomidate, Janssen) was given. This was followed by the injection of 0.1 mg/kg pancuronium (Pavulon, Organon) and the administration of 1% isoflurane (Isoflurane, Abbott Laboratories). Positive pressure ventilation with 100% oxygen was carried out for 3 minutes via face mask before tracheal intubation was performed. After intubation, ventilation was continued through the endotracheal tube.

Baseline haemodynamic parameters were registered twice:

- before anesthetic induction (e.g. directly before the start of remifentanil infusion or injection of the bolus dose of fentanyl),
- after anesthetic induction (one minute after tracheal intubation – that is 5 minutes from the onset of opioid administration).

Isoflurane concentrations as well as the administration rate and the dose of the opioid were not planned to be modified during anesthetic induction with the exception only for significant haemodynamic disturbances. This was recognized when the heart rate or systemic arterial pressure changed by more than 50% from baseline values.

Numerical data are presented as mean and standard deviation. For continuous variables, Mann-Whitney test was used for comparison between groups and Wilcoxon test was used for repeated measurements. Pearson test was used to test correlation and Fischer exact tests was used to test discrete variables. P value below 0.05 was considered significant.

RESULTS

The demographic data of both groups were very similar (Table I). Mean patient's Ramsay scores on admission to the operating theatre were also similar: 2,7 ± 1,0 in group I and 2,6 ± 0,9 in group II. The time from premedication to arrival in the operating theatre was 51.3 ±13.2 min. in group I and 55.0 ± 12.8 min. in group II. The time from arrival in the operating theatre to anesthetic induction was also comparable (29.0 ±10.4 min. in group I and 26.7 ± 11.6 min. in group II). There was also no difference between groups in all baseline haemodynamic parameters registered before induction of anesthesia (upper part of Table II).

Tab. 1. Demographic data.

Parameter		Remifentanil (n=30)	Fentanyl (n=24)
Age (years)		58.2 ± 7.2	55.4 ± 8.0
Height (cm)		169.3 ± 8.3	169.8 ± 8.1
Body weight (kg)		82.9 ± 13.2	80.5 ± 10.6
Body mass index (kg/m^2)		28.8 ± 3.2	28.0 ± 3.9
Body surface (m^2)		2.0 ± 0.2	1.9 ± 0.2
Ejection fraction (%)		55.3 ± 8.9	55.2 ± 8.6
EUROscore		2.0 ± 1.7	1.8 ± 1.8
Canadian Coronary Score		2.4 ± 0.7	2.3 ± 0.8
Gender	male	28 (93%)	19 (79%)
	female	2 (7%)	5 (21%)
Previous myocardial infarction	yes	17 (57%)	8 (33%)
	no	13 (43%)	16 (67%)
History of arterial hypertension	yes	19 (63%)	16 (67%)
	no	11 (37%)	8 (33%)
Peripheral vascular disease	yes	5 (17%)	3 (13%)
	no	25 (83%)	21 (87%)
Diabetes	yes	10 (33%)	4 (17%)
	no	20 (67%)	20 (83%)
Preoperative treatment with beta-blocking agents	yes	22 (73%)	18 (75%)
	no	8 (27%)	6 (25%)

Tab. 2. Haemodynamic status before and after anaesthetic induction.

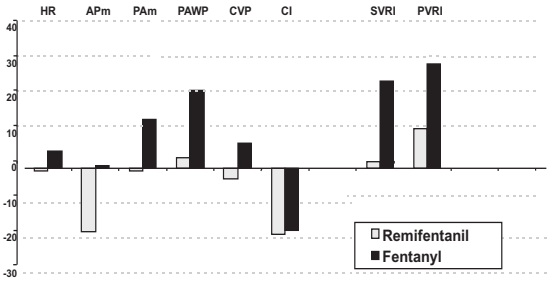
Parameter		Remifentanil (n=30)	Fentanyl (n=24)	p
Before induction	Heart rate (beats/ min.)	72.6 ± 12.6	76.4 ± 12.5	NS
	Systolic arterial pressure (mmHg)	145.3 ± 24.6	135.6 ± 21.2	NS
	Diastolic arterial pressure (mmHg)	76.2 ± 10.1	77.5 ± 13.0	NS
	Mean arterial pressure (mmHg)	99.2 ± 13.7	96.8 ± 14.8	NS
	Mean pulmonary pressure (mmHg)	20.0 ± 4.5	18.5 ± 3.1	NS
	Pulmonary wedge pressure (mmHg)	11.8 ± 2.8	11.4 ± 2.9	NS
	Cardiac index (l/min./m^2)	2.72 ± 0.54	2.50 ± 0.45	NS
	SVR index (dyn s cm^{-5} m^2)	2733 ± 636	2872 ± 614	NS
	PVR index (dyn s cm^{-5} m^2)	263 ± 105	234 ± 78	NS
	Rate-pressure product (1)	10541 ± 2468	10408 ± 2594	NS
After induction	Heart rate (beats/ min.)	71.3 ± 11.3	79.0 ± 11.7	**0.018**
	Systolic arterial pressure (mmHg)	*112.2 ± 16.3	130.8 ± 31.3	**0.007**
	Diastolic arterial pressure (mmHg)	*64.1 ± 9.3	78.9 ± 15.7	**<0.001**
	Mean arterial pressure (mmHg)	*80.2 ± 10.8	96.2 ± 20.3	**<0.001**
	Mean pulmonary pressure (mmHg)	19.1 ± 3.5	*20.8 ± 3.4	NS
	Pulmonary wedge pressure (mmHg)	11.9 ± 3.1	*13.5 ± 3.0	NS
	Cardiac index (l/min./m^2)	*2.17 ± 0.42	*2.04 ± 0.47	NS
	SVR index (dyn s cm^{-5} m^2)	2735 ± 759	*3535 ± 1046	**<0.001**
	PVR index (dyn s cm^{-5} m^2)	285 ± 182	*290 ± 108	NS
	Rate-pressure product (1)	*8029± 1890	10459 ± 3278	**0.001**

* values significantly different from those registered before anesthetic induction – comparison within the group
p value – comparison between the groups

There were no patients excluded from the analysis and no rescue measures were used because none of the patients met the set criteria for that. Arterial pressures were significantly lower after induction only in the remifentanil group The cardiac index after induction was not different between groups, but was significantly lower in both groups in comparison to the baseline values. The systemic vascular resistance index post induction was found to be higher in patients who received fentanyl. This was also a significant increase from the baseline value in this group. The pulmonary vascular resistance index was similar in both groups after induction, however, this was a significant increase from baseline only in the fentanyl group (lower part of Table II).

Changes resulting from anesthetic induction have been analyzed to answer the question as to what degree a change from baseline values could be expected for various parameters as a result of anesthetic induction with remifentanil or fentanyl. Deviation from baseline has therefore been converted to the percentage of baseline value and compared between groups. Changes in arterial pressures were found mainly in group I (a decrease), while changes in pulmonary artery pressures and wedge pressure were registered mainly in group II (an increase). The cardiac index decreased by nearly 20% in both groups, regardless of the type of opioid that had been used for the induction of anesthesia (Figure 1).

Baseline values have been correlated with changes in systolic blood pressure (Figure 2). Patients in group I showed a significant positive correlation between baseline systolic blood pressure and a decrease in systolic blood pressure during induction of anesthesia, while in patients in group II there was no correlation between these values. The decrease in systolic blood pressure after induction of anesthesia was therefore more proportional to the baseline systolic blood pressure in group I (Figures 2 and 3).



HR-heart rate; **APm**-mean arterial pressure; **PAm**-mean pulmonary pressure; **PAWP**-pulmonary wedge pressure; **CVP**-central venous pressure; **CI**-Cardiac index; **SVRI**-SVR index; **PVRI**-PVR inde

Fig. 1. Changes in haemodynamic parameters as a result of anesthetic induction.

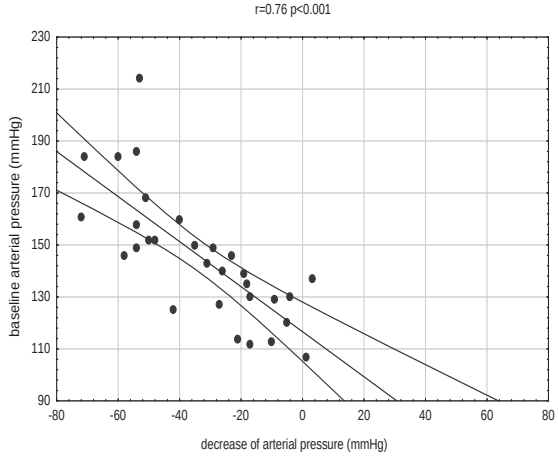


Fig. 2. Correlation of baseline systolic arterial pressure with changes in arterial pressure as a result of induction with the use of remifentanil.

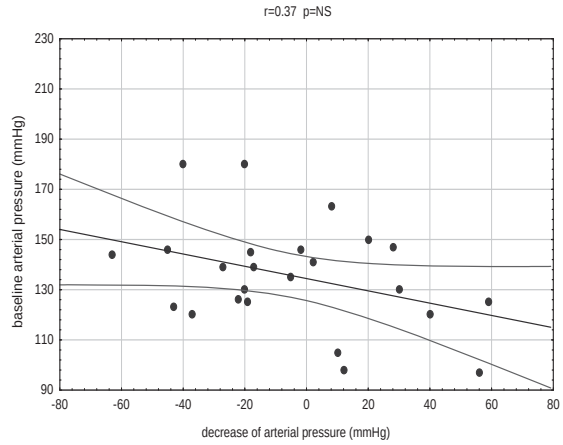


Fig. 3. Correlation of baseline systolic arterial pressure with changes in arterial pressure as a result of induction with the use of fentanyl (lower figure).

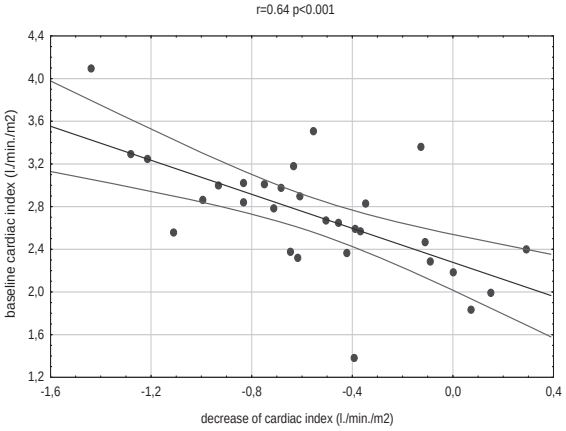


Fig. 4. Correlation of baseline cardiac index with changes in cardiac index as a result of induction with the use of remifentanil.

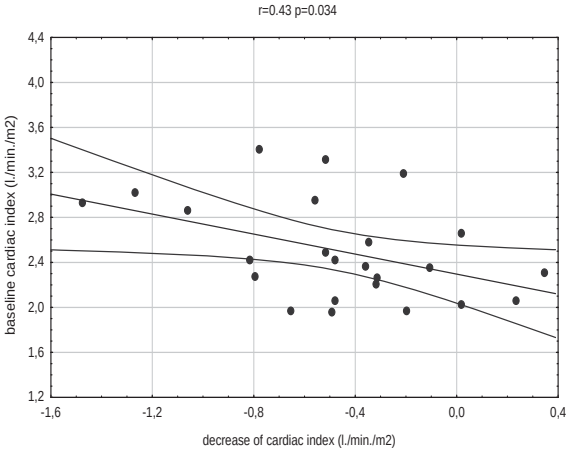


Fig. 5. Correlation of baseline cardiac index with changes in cardiac index as a result of induction with the use of fentanyl.

Baseline values of cardiac index have also been correlated with changes in cardiac index after anesthetic induction (Figure 3). Patients in group I showed a significant correlation between baseline cardiac index and the decrease in cardiac index, while in group II there was only a poor correlation of these values. A decrease in cardiac index during induction of anesthesia was therefore more proportional to the baseline cardiac index in group I (Figure 4) than in group II (Figure 5).

DISCUSSION

The results of our study confirm that the use of remifentanil is associated with haemodynamic

stability during induction of anesthesia. Heart rate and arterial pressure after induction were significantly lower in the remifentanil group, but this effect was not clinically significant. Such effects have been previously demonstrated in the literature; however, most of the studies were using an intravenous propofol technique and only few investigators described the use of remifentanil in cardiac anesthesia in a combination with the inhalational agents [11, 12, 21, 25]. Also, analysis was usually not focused on the anesthetic induction.

The results of our study suggest that remifentanil is more potent than fentanyl. The comparison of the analgesic potential of different agents is not easy and there are some methods to perform it – one of the most popular ones is to assess what concentration of the chosen opioid is able to reduce a minimal anesthetic concentration (MAC) of a given inhalational agent. Using this method, 50% reduction of MAC for isoflurane may be obtained with a remifentanil serum concentration of 1.37 ng/ml – similar concentrations for other opioids are 1.67 ng/ml for fentanyl, 0.14 ng/ml for sufentanil and 28.8 ng/ml for alfentanil [26]. The power of remifentanil is therefore comparable to fentanyl and the differences are probably due to a rapid transfer of this opioid to the effect site [7, 27]. In this situation, it is not surprising, that the perioperative endocrine stress response was found to be attenuated in patients supplemented with continuous remifentanil infusion as compared to intermittent fentanyl, as it has been shown by Winterhalter et al. [28].

It has to be mentioned, however, that the dosing of both opioids in our study did not provide equipotent concentrations and a dose of fentanyl was probably less potent than remifentanil dose – but this was a case also in the other studies. During induction of anaesthesia for coronary artery surgery, Herregods et al. compared 15 mcg/kg of fentanyl and 1 mcg/kg/min of remifentanil [17], while Howie et al. [12] and Cheng et al. [19] compared 10 mcg/kg of fentanyl with 1 mcg/kg/min of remifentanil. The dosing regimen for fentanyl proposed in our study (5 mcg/kg) is frequently used in a clinical practice during induction in cardiac anesthesia for fast-track coronary artery surgery [29] and is widely used in our center.

In our study, cardiac index decreased by approximately 17%, regardless of the technique used. These findings are not surprising, because a study by Katzmaier et al. confirmed that after remifentanil injection cardiac index may decrease by 25% in comparison to baseline values [14]. Significant decrease of heart rate and cardiac output after induction with propofol and remifentanil was observed in patients with good left ventricular function [30] and with impaired contractility [17].

Anesthesia with remifentanil is usually initiated with a bolus dose followed by a continuous infusion. In our study a bolus dose of remifentanil was not used and a continuous remifentanil infusion with the rate of 0,5 mcg/kg/min. was used instead during induction. This solution was chosen for safety reasons. Elliott et al. [15] performed their investigations only on 8 patients and prematurely terminated the study due to serious haemodynamic instability after bolus doses of remifentanil. Wang et al. [16] used a remifentanil bolus in the presence of inhalational agents and terminated the study even earlier – after analyzing only 4 patients. In this study inhalational induction with sevoflurane was used, together with a small remifentanil bolus (just 0,5 mcg/kg). Despite that, 3 patients developed severe bradycardia and one patient even had a temporary asystole during induction [16].

Other authors did not confirm these findings and Elliott's study has been heavily criticized in a letter to the editor of *Anesthesia and Analgesia* by Lehmann and Boldt [31]. They claimed that problems seen by Elliott et al. [15] were not created by the use of remifentanil itself, but rather by premedication with opioid and scopolamine together with the intravenous propofol induction. This combination, according to the authors, resulted in profound hypotension due to a sudden decrease of systemic vascular resistance. In our study we have confirmed that the use of remifentanil for anesthetic induction was not associated with a significant decrease of systemic vascular resistance. This parameter remained almost unchanged during induction with remifentanil, while the systemic vascular resistance in the fentanyl group significantly increased after intubation. The latter was probably due to the vascular response resulting from insufficient analgesia.

Many authors describe the use of initial bolus doses of remifentanil for cardiac procedures, without reporting any problems. An initial bolus dose of 1 mcg/kg remifentanil was used in many trials [10, 11, 12, 13] and it was also

found to be safe when assessed by transoesophageal echocardiography [32]. Ahonen et al. [33] even used 2 mcg/kg for MIDCAB procedures. The highest bolus dose has been described in the literature by Paris et al. [34]. Authors of this paper used 5 mcg/kg remifentanil bolus followed by 10 minutes of continuous infusion of 3 mcg/kg/min. to assess the influence of this opioid on cerebral blood flow, but the arterial blood pressure was kept on a constant level with norepinephrine infusion [34].
Glass et al. recommend, that anaesthesia should be best initiated with a remifentanil infusion of 0,5 mcg/kg/min., 30 seconds before the anesthetic induction agent is administered [26]. This method has been used in our study, however remifentanil infusion has been initiated slightly earlier (one minute before etomidate injection). Haemodynamic results of the bolus dose are dependent on the speed of intravenous injection and very slow administration may be not different from continuous infusion. For example, a careful reading of a study by Cheng et al. reveals that the remifentanil bolus of 1 mcg/kg used was in fact given over 1 minute [19]. Remifentanil is a very potent opioid. Many authors do not describe how quickly the injection of a bolus dose was given to the patient and this factor may explain some striking differences in the results from different studies.
In our study, we decided to correlate baseline values of systolic blood pressure with changes observed after anaesthetic induction and found a significant positive correlation for both parameters only in a remifentanil group. One may ask, what is a clinical interpretation of this finding. To our understanding, it means that a decrease of blood pressure or cardiac index resulting from anaesthetic induction was proportional to the baseline values. Therefore, the most significant decrease was observed if baseline values were exceptionally high, while relatively small decrease was observed if baseline values were normal or decreased. This proves that remifentanil is a safe agent during anaesthetic induction.
These findings do not change the fact that, in general, remifentanil caused some degree of depression of the circulatory system. This has been also confirmed by other authors who state that remifentanil causes a visible, but not clinically significant depression of cardiac index, stroke volume, heart rate and myocardial oxygen demand [14]. Thomson et al. [35] proved that a bolus dose may often result in bradycardia (in their study – 50%) and that glycopyrolate may be useful to prevent this side effect.
It seems that although remifentamil is already used in cardiac anaesthesia for a relatively long time, any data which may provide more information about its safety are desirable. According to a most recent paper, remifentanil reduces the release of biochemical markers of myocardial damage [36]. If there will be more such reports, popularity of remifentanil in cardiac anaesthesia can dramatically increase.

CONCLUSION

Remifentanil is more potent than fentanyl in blunting a cardiovascular response to tracheal intubation in patients with coronary artery disease. Low dose of fentanyl, used for the anaesthetic induction, may result in a clinically important increase of systemic vascular resistance. Induction with the use of inhalational agents and remifentanil infusion in patients with good left ventricular function is safe and effective, resulting in comparable depression of haemodynamics to a fentanyl bolus.

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