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Comparison of the effects of fentanyl and remifentanil on splanchnic tissue perfusion during cardiac surgery

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Abstract
The purpose of this study was to compare the effects of fentanyl and remifentanil on splanchnic perfusion during coronary artery bypass graft (CABG) surgery. Fifty patients were randomized to receive either fentanyl ($10\,\mu g \cdot kg^{-1}$ at induction and $5\,\mu g \cdot kg^{-1} \cdot h^{-1}$ infusion for maintenance) or remifentanil ($3\,\mu g \cdot kg^{-1}$ at induction and $1\,\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion for maintenance). Patients in both groups were comparable with regard to demographics. Intraoperative volume management and inotropic therapy were similiar in both groups. Regarding heart rate, there were no significant differences between the groups at any measurement time ($P > 0.05$). Compared to the fentanyl group, the remifentanil group showed a significant decrease in mean arterial pressure during induction. Also, the gastric intramucosal CO_2 pressure (Pg_{CO_2}) and the P_{CO_2}-gap, defined as the difference between Pg_{CO_2} and Pa_{CO_2}, were significantly increased and the gastric mucosal pH (pHi) was significantly decreased in the remifentanil group in the postinduction period ($P < 0.05$). However, there were no statistically significant differences in respiratory data at any time between the two groups ($P > 0.05$). Both fentanyl and remifentanil seemed to be effective and well tolerated in this CABG population. Episodes of hypotension and transient reduction in splanchnic perfusion were more common in patients treated with remifentanil when compared to those receiving the fentanyl opioid regimen.

Key words Cardiopulmonary bypass · Remifentanil · Fentanyl · Splanchnic perfusion

Cardiovascular stability is an essential prerequisite for cardiac anesthesia, where optimum tissue oxygenation is vital in patients who already have compromised cardiovascular functions. Traditionally, intraoperative manangement has been provided by using opioid-based anesthesia to suppress hormonal and metabolic stress responses to surgical stimuli. Such regimens have resulted in reduced morbidity and mortality after cardiac surgery, but the effects of opioids on splanchnic perfusion are still unknown [1–3]. Splanchnic perfusion contributes to the regulation of the circulating blood volume and blood pressure in humans. Splanchnic ischemia and reperfusion in cardiac surgery may lead to an injury of the intestinal mucosa and induce a systemic inflammatory response, which is the leading cause of morbidity and mortality in the intensive care unit [4,5]. Systemic cardiovascular and oxygen variables are not reliable predictors of regional hypoperfusion and associated hypoxia. Invasive monitoring of global variables such as cardiac output and arterial and mixed venous oxygen saturation can provide estimates of global oxygen delivery, oxygen consumption, and oxygen extraction ratios, but unfortunately, such monitoring lacks the sensitivity to detect splanchnic perfusion [6]. The monitoring of gastric intramucosal pH (pHi) by gastric tonometry has been proposed as a sensitive method to assess the adequacy of splanchnic perfusion [5,6]. Nevertheless, the pHi value cannot be interpreted without considering the systemic acid-base status in the arterial blood [7]. For this reason, the PCO_2 gap, defined as the difference between gastric intramucosal CO_2 pressure (Pg_{CO_2}), measured by gastric tonometry, and arterial CO_2 pressure (Pa_{CO_2}), appears to be a meaningful marker of splanchnic perfusion [5,7]. The purpose of this study was therefore to compare the effects of two opioid agents—fentanyl and remifentanil—on splanchnic perfusion, using gastric tonometry.

Fifty New York Heart Association (NYHA) class 1–3 patients undergoing first-time elective coronary artery bypass graft (CABG) surgery, using hypothermic cardiopulmonary bypass (CPB), constituted the study population, during the period from May 2002 to August 2002. Study approval was obtained from the local ethics

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committee. Written informed consent was obtained from all study patients. Exclusion criteria included the following: left ventricular ejection fraction (EF) less than 40%; multiple organ dysfunction syndrome (MODS), esophageal or gastric abnormalities, coagulopathy, and age older than 80 years. All patients received 150 mg of ranitidine orally the evening before surgery, 150 mg 2 h before induction of anesthesia, and then 50 mg at 8-h intervals intravenously until the end of the study, to inhibit gastric acid secretion and to improve the reliability of pHi measurement. All patients received standard premedication of oral diazepam 10 mg, IM morphine 5 mg, and oxygen delivered via a face mask at 5 L·min^{-1}.

Patients were randomly allocated to two groups. Patients in both groups were induced with midazolam bolus 0.15 mg·kg^{-1} intravenously, followed by fentanyl 10 µg·kg^{-1} infusion in group I (n = 25) and remifentanil 3 µg·kg^{-1} infusion in group II (n = 25). Total induction doses of opioids were infused within a 3-min period by an infusion pump in each group. After loss of consciousness, pancuronium 0.1 mg·kg^{-1} was administered to facilitate tracheal intubation. After intubation, continuous infusion of fentanyl was reduced to 5 µg·kg^{-1}·h^{-1}, and remifentanil was reduced to 1 µg·kg^{-1}·min^{-1}. Additional pancuronium, 0.03 mg·kg^{-1}, was given when necessary. In both groups, doses of opioids used were adapted to maintain optimal anesthetic and surgical conditions, while maintaining hemodynamic stability. Further drug dosage adjustments were standardized by protocol, according to adverse hemodynamic responses and bispectral index (BIS) measurments.

Routine clinical monitoring was done with a five-lead electrocardiogram, radial artery cannulation, and a pulmonary artery catheter (Opticath; Abbott, Mountain View, CA, USA), placed by way of the right internal jugular vein. Heart rate (HR), mean arterial pressure (MAP), pulmonary capillary wedge pressure (PCWP), cardia output (CO), and mixed venous oxygen saturation (SVO_2) were measured. CO was measured using the mean of three values obtained by a thermodilution technique (Explorer; Baxter, Irvine, CA, USA). SVO_2 was measured by fiberoptic reflectance spectrophotometry (Explorer, Baxter). The cardiac index (CI) was calculated with a standard equation. BIS was measured at the frontal lobe (Fp-Fz), using a Patient Care Monitoring System (SpaceLabs Medical, Redmond, WA, USA).

Before induction of anesthesia, a gastric tonometer catheter (Trip NGS Catheter; Tonometrics, Worcester, MA, USA) was inserted nasally under sedation with 2 mg intravenous midazolam. Air in the silicone balloon of the tonometric catheter was equilibrated for 10 min and the CO_2 pressure in the air was measured by capnometry, using automated air tonometry (Tonocap; Tonometrics) [8]. Measurements of Pg_{CO_2} were obtained at the same time as the corresponding arterial blood gas analysis. All arterial CO_2 pressure (Pa_{CO_2}) values were measured with a blood gas analyzer (865 Blood Gas and Critical Analyze System; Chiron Diagnostics, Medfield, MA, USA). All Pa_{CO_2} measurements were corrected for esophageal temperature by using an established equation, as described by Andritsch et al. [9]. Gastric intramucosal pH (pHi) was automatically calculated by tonometry from the Henderson-Hasselbach equation, using Pg_{CO_2} and Pa_{CO_2}. P_{CO_2}-gap was calculated by subtracting Pa_{CO_2} from Pg_{CO_2} (Pg_{CO_2}-Pa_{CO_2}) determined with Tonocap. These parameters were obtained before induction (T1); after the induction (T2); after sternotomy (T3); at the end of bypass (T4); and at the end of surgery (T5).

Randomization of patients was achieved using a computer-generated table. Variables were reported as means ± SD, except where indicated. Baseline values of variables were compared by using unpaired t-tests. Analysis of variance (ANOVA) for repeated measurements was used to assess differences between outcome values and baseline values within groups and to compare these differences between groups. For adjusting P values for multiple comparisons, the Bonferroni test was applied. Nonparametric data were analyzed with Mann-Whitney rank sum tests. Statistical evaluations were carried out by using SPSS 10.0 software (SPSS, Chicago, IL, USA). Values of $P < 0.05$ were accepted as significant.

Patients in both groups were similar with respect to preoperative demographics (Table 1). Durations of anesthesia, CPB, and aortic cross-clamping, and number of bypasses did not differ between the two groups. The two study groups experienced smiliar intensive care unit (ICU) and hospital stays.

Hemodynamics are shown in Table 2. Regarding HR, a slight decrease was seen in both groups with induction, but there were no significant differences between groups ($P > 0.05$). During induction, remifentanil-treated patients showed a significant decrease in MAP compared to the fentanyl-treated patients ($P < 0.05$). There were no statistically significant differences in PCWP and CI values at any time between the two groups ($P > 0.05$). In both groups, no BIS values greater than 50 (indicating inadequate anesthesia) or lower than 40 (indicating too deep anesthesia) were found.

Respiratory data are shown in Table 3. There were no significant differences at any time between the two groups ($P > 0.05$). The lowest Pa_{CO_2} values were obtained at T2 in both groups. The highest SVO_2 values were at T4 in the fentanyl group and at T1 in the remifentanil group.

At baseline, tonometric-derived variables were not statistically different between the two groups (Fig. 1).

Table 1. Demographic characteristics and CPB-related parameters in fentanyl and remifentanil groups

	Fentanyl group ($n = 25$)	Remifentanil group ($n = 25$)	P value
Age (years)	59 ± 12	63 ± 10	NS
Sex (male/female)	14/11	15/10	NS
BMI (kg/m^2)	28.5 ± 6.7	26.8 ± 4.7	NS
EF (%)	67± 10.7	66 ± 11.0	NS
NYHA			NS
I	7	5	
II	14	17	
III	4	3	
Operative duration (min)	288 ± 44	264 ± 43	NS
CPB duration (min)	121 ± 17	126 ± 19	NS
Aortic cross-clamp duration (min)	84 ± 15	90 ± 19	NS
Time to ICU discharge	2.1 ± 1.1	1.7 ± 1.2	NS
Time to hospital discharge	7.4 ± 2.6	8.8 ± 2.9	NS

Values for results are expressed as means ± SD or numbers of patients
BMI, body mass index; NYHA, New York Heart Association; EF, ejection fraction; CPB, cardiopulmonary bypass; ICU, intensive care unit; NS, not significant

Table 2. Hemodynamics and BIS values for patients who underwent cardiac surgery

Variable	T1	T2	T3	T4	T5
Hct (%)					
Fentanyl	38.7 ± 3.6	39.2 ± 2.9	37.2 ± 2.6	24.1 ± 2.0*	32.4 ± 2.3
Remifentanil	41.1 ± 5.2	40.4 ± 3.8	39.4 ± 2.7	27.6 ± 1.8*	35.1 ± 3.6
BIS					
Fentanyl	96 ± 13	47 ± 8	46 ± 10	43 ± 7	96 ± 13
Remifentanil	97 ± 16	46 ± 11	48 ± 9	44 ± 12	98 ± 11
HR (bpm)					
Fentanyl	76 ± 16	69 ± 16	72 ± 126	88 ± 20	82 ± 20
Remifentanil	78 ± 10	61 ± 12	65 ± 15	84 ± 22	90 ± 22
MAP (mmHg)					
Fentanyl	90 ± 11	71 ± 15*.**	83 ± 20	63 ± 13*	75 ± 12*
Remifentanil	92 ± 15	61 ± 9*	74 ± 16*	69 ± 15*	68 ± 11*
PCWP (mmHg)					
Fentanyl	11.4 ± 3.9	13.2 ± 3.3	13.5 ± 5.3	10.8 ± 3.8	12.2 ± 3.3
Remifentanil	10.5 ± 3.5	14.2 ± 6.4	12.3 ± 5.0	13.9 ± 5.2	12.0 ± 4.2
CI (l/min per m^2)					
Fentanyl	3.3 ± 0.6	2.8 ± 0.5	2.8 ± 0.3	3.8 ± 0.4	3.0 ± 0.2
Remifentanil	3.1 ± 0.7	2.6 ± 0.8	2.6 ± 0.5	3.4 ± 0.7	2.9 ± 0.8

* $P < 0.05$ versus T1; ** $P < 0.05$ fentanyl group versus remifentanil group
Values for results are expressed as means ± SD
Hct, hematocrit; BIS, bispectral index; HR, heart rate; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure

Pg_{CO_2} in the remifentanil group showed a significant incerease ($P < 0.05$) after induction compared to the fentanyl group. In both groups, Pg_{CO_2} reached the maximum value at the end of bypass. In both groups, pHi showed a permanent and significant decrease following induction. In the remifentanil group, pHi was significantly lower than that in the fentayl group at T2 ($P < 0.05$). The lowest pHi values were obtained at T2 for the remifentanil group, and at T4 for the fentanyl group. In both groups, P_{CO_2}-gap showed an increase following induction, but this increase was significantly higher ($P < 0.05$) in the remifentanil group. The highest value of Pg_{CO_2}-gap was at T2 in the remifentanil group and at T4 in the fentanyl group.

During cardiac surgery, cardiac output (CO) decrease causes a reduction in the blood flow to the splanchnic area and CO_2 accumulation [1,10]. Although the pathophysiology of splanchnic hypercapnia is not known clearly, abnormal perioperative values are very important for patient prognosis [11]. For this reason, in patients undergoing major surgery, maintenance of spanchnic tissue perfusion is very important for the prevention of MODS. But intraoperative systemic cardiovascular hemodynamics and respiratory data are not

Table 3. Respiratory data for patients who underwent cardiac surgery

Variable	T1	T2	T3	T4	T5
Sp_{O_2} (%)					
Fentanyl	97 ± 4	96 ± 3	99 ± 3	98 ± 2	96 ± 2
Remifentanil	98 ± 2	99 ± 2	97 ± 4	100 ± 3	97 ± 2
End-tidal P_{CO_2} (mmHg)					
Fentanyl		35 ± 3	33 ± 2	36 ± 4	35 ± 3
Remifentanil		32 ± 4	34 ± 3	34 ± 5	37 ± 4
Pa_{CO_2} (mmHg)					
Fentanyl	25 ± 4	24 ± 64	27 ± 4	29 ± 7	30 ± 4
Remifentanil	27 ± 5	22 ± 3	31 ± 7	28 ± 5	27 ± 5
SVO_2 (%)					
Fentanyl	82 ± 3	75 ± 5	75 ± 4	85 ± 5	84 ± 3
Remifentanil	84 ± 4	77 ± 6	75 ± 6	81 ± 3	80 ± 4

Values for results are expressed as means ± SD
Sp_{O_2}, systemic oxygen saturation; end-tidal P_{CO_2}, end-tidal partial pressure of CO_2; Pa_{CO_2}, arterial CO_2 pressure; Sv_{O_2}, mixed venous oxygen saturation

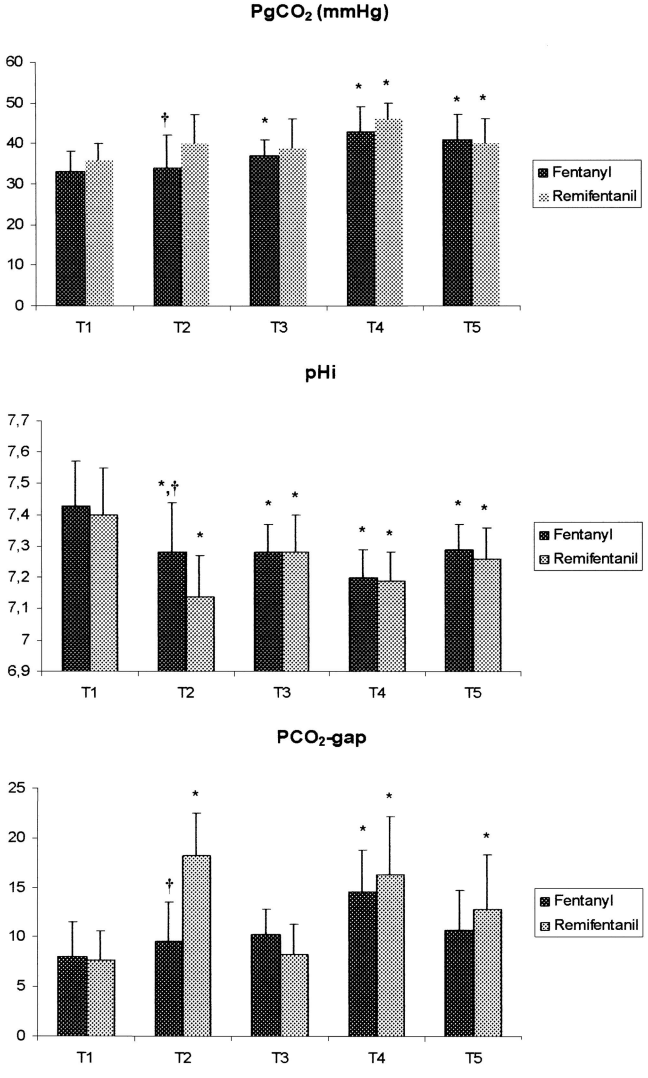

Fig. 1. Effects of fentanyl and remifentanil on changes in gastric CO_2 pressure (P_{gCO_2}), gastric intramucosal pH (*pHi*), and the gap of the CO_2 pressure (P_{CO_2}-*gap*) during cardiac surgery. * $P < 0.05$ versus T1; † $P < 0.05$ fentanyl group versus remifentanil group. T1, before induction

reliable for detecting regional hypoxia. Bennett-Guerrero et al. [5], in one of their studies, showed that systemic hemodynamic measurements and blood gas analysis were not sufficient to show the complications seen in the postoperative period. Without any change in arterial pH, reduction in mucosal pH is an indicator of local acidosis and frequently is a result of local acid production. Many studies have shown that intramucosal pH measurements can provide a reliable prognostic indicator in critically ill patients [12]. In our study, especially after induction (T2) and at the end of bypass (T4), a decrease in pHi and an increase in PCO_2-gap were correlated with hypotension and synchronous respiratory data measurements were found to be normal. Although Pg_{CO_2} was higher throughout the whole procedure when compared with baseline, clinically significant arterial hypercarbia did not occur in any of our patients.

Gastric tonometry establishes regional CO_2 accumulation by measuring Pg_{CO_2}. The gastric-arterial CO_2 differences correlated with Pg_{CO_2}, Pa_{CO_2}, and pHi values, calculated by tonometry, are significant markers of regional perfusion. Ohri and colleagues [13] showed that, post CPB, gastrointestinal hypoperfusion was maximal at 3 and 5 h. In our study, gastric hypoperfusion was maximam at T2 in the remifentanil group and at T4 in the fentanyl group. Furthermore, MAP was lowest at these times in both groups. Although Pg_{CO_2} was not the highest at T2 measurement in the remifentanil group, we evaluated gastric tonometmc values at that time as showing maximum hypoperfusion. Fiddian-Green [14] showed that, for evaluating gastric hypoperfusion, a decrease in pHi (≤7.32) and an increase in PCO_2-gap (≥8 mmHg) were more significant than a Pg_{CO_2} increase only. Yet in our study, the increase in Pg_{CO_2} at T2 in the remifentanyl group was significant compared to the T1 measurement. Gastic tonometric data such as Pg_{CO_2}, are directly affected by Pa_{CO_2}, so changes in Pg_{CO_2} are seen as

being related to changes in ventilation. Also, in our study, Pa_{CO_2} was lowest at T2 in the remifentanil group, and this may explain why the PCO_2-gap was the highest while Pg_{CO_2} was not the highest. An elevated gastric-arterial CO_2 difference (PCO_2-gap) is regarded as indicative of an imbalance between gastric perfusion, metabolism, and alveolar ventilation [8]. So, the PCO_2-gap is believed to be the most accurate reflection of splanchnic ischemia, because it does not take into account the degree of metabolic acidosis. The normal value for the difference between gastric and arterial PCO_2 was found to be 7 mmHg in healthy volunteers [15]. Even if PCO_2-gap values over 11 mmHg show significant hypoperfusion, such values may not show absolute gut hypoxia. In our study PCO_2-gap values did not reach this level in either group at any measurement times. The highest PCO_2-gap value that we observed was 18.

The primary goal of an anesthetic approach is to maintain hemodynamic stability and tissue perfusion. Although total opioid anesthesia is one of the most popular techniques, the effects of opioids on splanchnic perfusion are unknown and the ideal opioid choice is still controversial. In this study we studied the splanchnic perfusion effectiveness of fentanyl compared with remifentanil regimens in patients having CABG surgery. The hypothesis that we intended to test was that splanchnic ischemia would precede or accompany CPB, and that the opioids used in anesthesia would have an effect on it. We expected to find a relationship between the severity of intramucosal acidosis and the opioid drugs we used. When pHi and PCO_2-gap values were compared, we concluded that in the remifentanil group, splanchnic hypoperfusion was significant after the induction period. Similar to Howie et al. [2], we found that significantly more patients with the remifentanil regimen experienced hypotension during induction compared with the patients on the fentanyl regimen. We think that splanchnic hypoperfusion is the result of hypotension caused by remifentanil induction.

In conclusion, both fentanyl and remifentanil seemed to be effective and well tolerated in this CABG population. Episodes of hypotension and transient reduction in splanchnic perfusion were more common in patients treated with remifentanil when compared to those receiving a fentanyl opioid regimen. There were no apparent clinically significant effects, although this study was not adequately powered to detect a difference in serious adverse outcomes.

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