



Cardioprotective Effects of Remifentanil in a Sympathetic Hyperactivity Model in Rabbits

Tavşanlarda Oluşturulan Sempatik Hiperaktivite Modelinde Remifentanilin Kardiyoprotektif Etkisi

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Objective: In this study, the antiarrhythmic and anti-ischemic effects of a 6 µg kg⁻¹ min⁻¹ infusion dose of remifentanil are investigated in a central sympathetic hyperactivity model in rabbits.

Methods: In this study, 18 New Zealand rabbits were used. The subjects were randomly divided into three groups (n=6) and received 10 µmol L⁻¹ glutamate intracerebroventricularly to provide the central sympathetic hyperactivity. In group 1, 10 µmol L⁻¹ glutamate was used; in group 2, 1 h before L-glutamate injection, 40 mg kg⁻¹ N (omega)-nitro-L-arginine methyl ester was intravenously (iv) administered; and in group 3, also 1 h before L-glutamate injection, 40 mg kg⁻¹ N (omega)-nitro-L-arginine methyl ester was iv administered. A 6 µg kg⁻¹ min⁻¹ dose of remifentanil infusion was administered 5 min before L-glutamate injection. Heart rate, systolic arterial pressure and mean arterial pressure were measured and recorded. Within 15 min of the intracerebroventricular L-glutamate injection, premature ventricular complexes, bigeminy ventricular arrhythmia, ventricular tachycardia, ST-segment shift and T-wave inversions were recorded.

Results: When incidences of heart rate, rate pressure product, premature ventricular complexes and bigeminy ventricular arrhythmia were compared between groups, significant differences were not determined. Mean arterial pressure was more significantly increased in group 2 than in the other groups (p<0.05). Ventricular tachycardia, ST-segment shift and T-wave inversions were significantly lower in group 3 than in groups 1 and 2 (p<0.05).

Conclusion: Remifentanil (6 µg kg⁻¹ min⁻¹ for 5 min of infusion) prevented life-threatening ventricular tachycardia and electrocardiographic signs of myocardial ischemia in a model of arrhythmia resulting from the association of central sympathetic overactivity.

Keywords: Central sympathetic hyperactivity, myocardial ischemia, opioids, ventricular arrhythmia

Amaç: Bu çalışmada, tavşanlarda merkezi sempatik hiperaktivite modeli yaratılarak, 6 mg kg⁻¹ dk⁻¹ remifentanil infüzyon dozunun antiaritmik ve anti-iskemik etkisi incelenmiştir.

Yöntemler: On sekiz Yeni Zelanda tavşanı rastgele üç gruba (n=6) ayrıldı ve santral sempatik hiperaktivite oluşturmak için intracerebroventriküler 10 µmol L⁻¹ glutamat kullanıldı. Grup 1'de, 10 µmol L⁻¹ glutamat, grup 2'de L glutamat enjeksiyonundan 1 saat önce, 40 mg kg⁻¹ N (omega) -nitro -L-Arginin metil ester iv ve Grup 3'te yine N -Glutamat enjekte edilmeden 1 saat önce, 40 mg kg⁻¹ N (omega) -nitro -L-Arginin metil ester iv olarak verildi. L-Glutamat enjeksiyonundan 5 dakika önce 6 mg kg⁻¹ dk⁻¹ dozda remifentanil infüzyonu başlamıştır. Kalp atım hızı, sistolik arter basıncı ve ortalama arter basıncı ölçüldü ve kaydedildi. İntraserebroventriküler L-glutamat enjeksiyonu takiben 15 dakika içinde, prematüre ventriküler kompleksler, bigemine ventriküler aritmi, ventriküler taşikardi, ST segment kayması kaydedildi.

Bulgular: Kalp hızı, hız-basınç ürünü, erken ventriküler kompleksler ve bigeminer ventriküler aritmi insidansı gruplar arasında karşılaştırıldığında, anlamlı bir fark tespit edilmedi. Ortalama arter basıncı Grup 2'de diğer gruplardan anlamlı olarak yüksekti (p<0,05). Ventriküler taşikardi, ST segment değişimi ve T dalgası inversiyonu Grup 3'te grup 1 ve 2'den daha düşük olarak bulundu (p<0,05).

Sonuç: Remifentanil (6 µg kg⁻¹ dk⁻¹ infüzyon 5 dakika) santral sempatik aşırı aktiviteden kaynaklanan aritmi modelinde yaşamı tehdit eden ventriküler taşikardi ve miyokard iskemisinin elektrokardiyografik belirtileri engellemektedir.

Anahtar Kelimeler: Santral sempatik aktivite, miyokardiyal iske-mi, opioid, ventriküler aritmi

Introduction

It has been claimed that increased sympathetic activity is potentially harmful for myocardial ischemia developed on the basis of hypertension, heart failure and arrhythmogenesis; its reversal has also been shown to be beneficial against acute myocardial ischemia in animal studies (1, 2).

The myocardium has delta and kappa types of opioid receptors (3). Both delta (particularly delta-1 subtype) (4, 5) and kappa (6, 7) opioid receptor types have been found to be responsible for the cardioprotective effects of opioids. Like morphine, fentanyl, a synthetic opioid, has cardioprotective effects in ventricular ischemia models by activating delta opioid receptors (8, 9). The protective effects of opioid agonists through the kappa and delta opioid receptors have already been attributed in experimental studies (10-12).

Remifentanil is a novel, ultra-short acting and potent phenylpiperidine opioid analgesic agent and is metabolized rapidly by blood and tissue esterases (12). It has an analgesic potency that is similar to fentanyl and is 100 times greater than morphine (13). Remifentanil has a high selectivity for mu ($EC_{50}=2.6$ nm) and low affinity for delta ($EC_{50}=66$ nm) and kappa ($EC_{50}=6.1$ nm) opioid receptors (14). In left ventricular ischemia-induced rats, pretreatment with remifentanil has led to a dose-dependent reduction of infarct size; the administration of mu, delta or kappa receptor antagonists decreased or even prevented these effects (12).

The aim of the present study was to investigate the antiarrhythmic and anti-ischemic effects of remifentanil in an experimental rabbit model of sympathetic over activity.

Methods

In this study, 18 New Zealand albino rabbits weighing 2–2.5 kg were used. Animals were housed under controlled standard conditions in the Animal Research Laboratory at the Dokuz Eylül University. The study protocol was approved by the Animal Research Committee of the Dokuz Eylül University.

The marginal vein of the right ear was cannulated, and an infusion of 0.9% NaCl solution was started at a rate of 4 mL $kg^{-1} h^{-1}$. The induction of anaesthesia was performed with sodium thiopental (40 mg kg^{-1}), and a continuous intravenous infusion of 15 mg $kg^{-1} h^{-1}$ of sodium thiopental was used for the maintenance of anaesthesia. After induction of anaesthesia, a tracheotomy was performed using an intubation tube (Portex, Portex Ltd, Hythe Kent, England), with an inner diameter of 3 mm. Then, they were artificially ventilated with 100% oxygen by an animal ventilator (Kent Scientific, Norfolk, CT, USA) at a rate of 25 strokes per minute, and tidal volume of 10 mL kg^{-1} neuromuscular blockade was induced with 0.1 μg kg^{-1} vecuronium bromide. The end-tidal carbon dioxide level was monitored (Anaesthesia Gas

Monitoring 1304, Bruel Kjaer, Copenhagen, Denmark) and maintained between 36 and 42 mmHg. Paediatric electrocardiograph electrodes were attached to both lower and right upper extremities and the lead II electrocardiogram (ECG) was continuously recorded (Biopac MP 30 and Biopac BSL prov.3.6.5, Biopac Systems, Santa Barbara, CA, USA) and stored on a hard disc for 15 min following L-glutamate injection. After rectal probe monitorization, central temperature was maintained at $37^{\circ}C \pm 0.5^{\circ}C$ with a servo-controlled lamp. The right femoral vein was catheterized with a 22 G cannula for intravenous (IV) injections. Arterial pressure was continuously monitored through a 20 G cannula via the right femoral artery with a connecting transducer (Pressure Monitoring Set, Bıçakçılar, İstanbul, Turkey) to a monitor (Petas KMA 250, Petas Ltd, Ankara, Turkey). Arterial blood gas analysis (Stat Profil M, Nova Biomedical Ltd., USA) was also performed at the start, 30 min after either N (Omega)-nitro-L arginine methyl ester (L-NAME) or saline administration, and after completion of either remifentanil or saline.

Induction of central sympathetic stimulation was accomplished with the injection of 10 μmol L-glutamamte in to the cerebral ventricles. The animal was placed in a stereotaxic frame (Harvard Apparatus, Boston, USA), and a craniotomy was performed to permit stereotaxic drug injections according to the following stereotaxic co-ordinates: AP: 4.5 mm from bregma; L: -7.5 mm and -6.0 mm down from the cranial surface. L-glutamate (10 μmol) was injected in a constant volume of 100 μL of saline solution over a time period of 1 min using a Hamilton microliter syringe (Hamilton Bonaduz AG, Switzerland).

After completion of the surgical procedures, a baseline period of 30 min, the animals were randomized.

Group 1 (n=6): Sympathetic stimulation was induced with intracerebroventricular (ICV) injection of 10 μmol L-glutamate (L-glutamate, Sigma, Strainheim, France). In this group, 2 mL of saline was infused 1 h and 5 min prior to L-glutamate injection.

Group 2 (n=6): One hour prior to ICV injection of 10 μmol L-glutamate, 40 mg kg^{-1} of L-NAME (L-NAME, Sigma Corp., St Louis, USA) was administered to induce coronary constriction and increase the intensity of myocardial ischemia by blocking the L-arginine-NO pathway. Five min before the injection of L-glutamate, 2 mL of saline infusion was started.

Group 3 (n=6): One hour prior to ICV injection of 10 μmol of L-glutamate, L-NAME (40 mg kg^{-1} iv) was administered, and remifentanil (6 μg $kg^{-1} min^{-1}$) (Ultiva, Glaxo Smith Kline Ilaclari Sanayi AS, İstanbul, Turkey) infusion was also started 5 min before L-glutamate injection.

The diagrammatic representation of the experimental protocols is shown in Figure 1.

Premature ventricular complexes (PVCs) occurred during the 15 min immediately after ICV L-glutamate injection was re-

Table 1. Haemodynamic and arterial blood gas variables

	Group 1 (n=6)	Group 2 (n=6)	Group 3 (n=6)
HR (beat min⁻¹)			
Basal	259±29	266±54	283±44 ^{§c}
L-NAME or saline	262±24	240±61 [#]	251±33
Remifentanil or saline	248±37	249±63	244±33
L-glutamate injection	291±47 [†]	298±59 [†]	248±38
MAP mmHg			
Basal	88±14	91±3	77±19
L-NAME or saline	88±12	118±10 [§]	93±32
Remifentanil or saline	94±14	119±12 [§]	82±30 [¶]
L-glutamate injection	114±18	160±19 ^{§,†}	136±29 [†]
RPP			
Basal	29±8	31±8	28±9
L-NAME or saline	29±7	36±12	28±10
Remifentanil or saline	29±6	37±10	24±7
L-glutamate injection	41±11	57±19 [†]	38±7 [†]
Temperature °C			
Basal	37±0.09	37±0.08	37±0.08
L-NAME or saline	37±0.07	37±0.09	37±0.05
Remifentanil or saline	37±0.05	37±0.08	37±0.04
pH			
Basal	7.41±0.08	7.35±0.07	7.34±0.08
L-NAME or saline	7.42±0.06	7.37±0.08	7.42±0.07
Remifentanil or saline	7.39±0.07	7.36±0.09	7.43±0.09
PaO₂ mmHg			
Basal	217±53	188±45	253±58
L-NAME or saline	198±45	195±33	255±49
Remifentanil or saline	226±67	197±40	275±57
PaCO₂ mmHg			
Basal	40±6	36±9	41±6
L-NAME or saline	38±5	38±7	36±4
Remifentanil or saline	36±7	36±7	35±5
Values are mean±SD. HR: heart rate; MAP: mean arterial pressure; RPP: rate pressure product; PaO ₂ : partial arterial oxygen pressure; PaCO ₂ : partial arterial carbon dioxide pressure [§] p<.05: Significantly different during between comparisons. [†] p<.05: Significantly different during within comparisons of post L-glutamate measurements. [#] p<.05: Significantly different from basal measurements during within comparisons with those of post L-NAME or saline. ^{§c} p<.05: Significantly different during within comparisons [¶] p<.05: Significantly different during within comparisons of saline or remifentanil with L-NAME or saline.			

corded. A PVC following each normal beat was considered a bigeminy ventricular arrhythmia. Ventricular tachycardia (VT) was determined to consist of a run of at least five ectopic PVC complexes. As a semi-quantitative indicator of myocardial ischemia, ST-segment shifts of more than 0.1 mV as well as symmetrical T-wave inversions were used.

Measurements were made of heart rate (HR), systolic arterial pressure (SAP) and mean arterial pressure (MAP). The “rate pressure product” (RPP) was calculated by multiplying the HR by the systolic blood pressure and dividing by 1000 to reduce it into convenient units. For each group, all of these measurements were performed by noting the highest value recorded at the beginning, 5 min after L-NAME or saline infusion, 5 min after the completion of remifentanil infusion and 15 min after L-glutamate injection.

At the end of each experiment, 100 µL of methylene blue dye was injected ICV using the same co-ordinates. The brain was removed after the animal was sacrificed by IV administered 120 mg kg⁻¹ sodium thiopental to check whether the dye had diffused properly throughout the ventricular space.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) for Windows version 11.0. Results are presented as mean±standard deviation. All variables were analyzed by using the Kruskal–Wallis test, and when indicated, followed by the Mann–Whitney U test. Within comparisons were performed using the Friedman test, and when indicated, followed by the Wilcoxon test. A p value less than 0.05 was considered significant.

Results

Animals in groups 1, 2 and 3 weighed 2183±194 g, 2267±206 g and 2100±200 g, respectively.

No significant difference was observed either within or between comparisons of body weight, rectal temperature, pH, PaO₂ and PaCO₂ values (Table 1).

There was no significant difference during between comparisons in HR (Table 1). In group 1, the maximum HR recorded following L-glutamate injection was found to be higher than other measurements (p<0.05). In group 2, HR recorded 5 min after L-NAME administration was significantly lower than the basal value (p=0.04). In addition, HR measured immediately after L-glutamate injection was significantly higher than the other measurements in group 2 (p<0.05). On the other hand, the group 3 basal HR was higher than that measured after L-NAME, remifentanil and L-glutamate administrations (p<0.05) (Table 1).

During between comparisons, MAP measurements were recorded 5 min after either L-NAME or saline or remifentanil infusions (Table 1). Within group comparisons revealed that

MAP recorded after L-glutamate injection was significantly higher than the other measurements in groups 2 and 3. In group 3, MAP recorded after remifentanyl infusion was lower than those recorded following L-NAME infusion ($p < 0.05$) (Table 1).

There was no significant difference between the groups for RPP (Table 1). In groups 2 and 3, RPP measured after L-glutamate injection was higher than the other measurements ($p < 0.05$) (Table 1).

The PVC incidence was 16.7% (1/6) in group 1, 66.7% (4/6) in group 2 and 16.7% (1/6) in group 3; it did not change significantly according to the treatment ($p > 0.05$).

The ventricular bigeminy incidence was 16.7% (1/6) in group 1, 66.7% (4/6) in group 2 and 16.7% (1/6) in group 3; it did not change significantly with the treatment ($p > 0.05$).

The VT incidence was 0% (0/6) in group 1, 66.7% (4/6) in group 2 and 0% (0/6) in group 3 respectively; it was markedly reduced by the treatment ($p < 0.05$) (Figure 2).

The T-wave inversion incidence was 0% (0/6) in group 1, 66.7% (4/6) in group 2 and 0% (0/6) in group 3; it was markedly reduced by the treatment ($p < 0.05$) (Figure 3).

The ST-segment shift incidence was 16.7% (1/6) in group 1, 66.7% (4/6) in group 2 and 0% (0/6) in group 3; it was significantly reduced by the treatment ($p < 0.05$) (Figure 4).

At the end of each experiment, 100 μ L of methylene blue dye was injected ICV using the same co-ordinates. In all rabbits, we observed the methylene blue dye in ICV.

Discussion

In the present study, 6 μ g $\text{kg}^{-1} \text{min}^{-1}$ of remifentanyl was found to reduce the frequency of VT, T-wave inversion and ST-segment changes in the rabbit central sympathetic overactivity model when administered intravenously for 5 min.

Doses of remifentanyl were higher than those used in patients because esterase activity is very high in rabbits, and similar effects can only be produced with such doses (15). In addition, Zhang et al. (12) reported that 6 μ g $\text{kg}^{-1} \text{min}^{-1}$ of remifentanyl was an effective dose in reducing the infarct size in rats.

The central control of human cardiac functions is situated in the paraventricular nuclei of the hypothalamus (16). Administration of the excitatory L-glutamate via ICV injection has been shown to increase cardiac contractility and myocardial oxygen consumption by stimulating the hypothalamus (16). Tibirica et al. (16) found that ICV injection of 3 μ g kg^{-1} of L-glutamate was able to raise MAP and increase myocardial oxygen consumption without inducing myocardial ischemia in rabbits. L-NAME is a type of L-arginine, which is known to competitively inhibits NO synthesis. Catelli et al. (17)

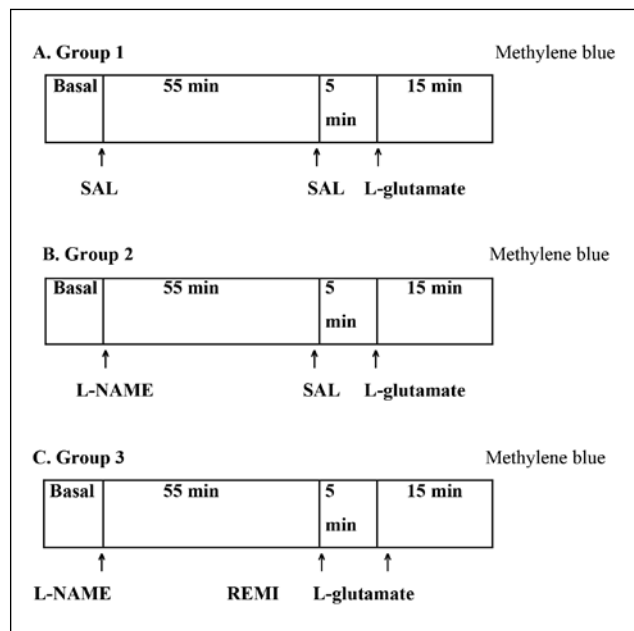


Figure 1. Diagrammatic representation of the experimental protocols
SAL: saline; REMI: remifentanyl $\mu\text{g kg}^{-1} \text{IV}$

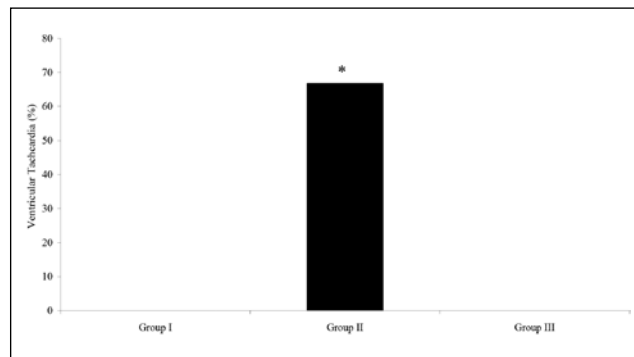


Figure 2. Effects of IV treatment with remifentanyl (Remifentanyl, $\mu\text{g kg}^{-1} \text{min}^{-1}$) on the incidence of ventricular tachycardia observed during centrally induced sympathetic overactivity periods in anaesthetized rabbits. Values are means \pm SD; n=6 in all experimental groups. * $p < 0.05$ versus Group 3.

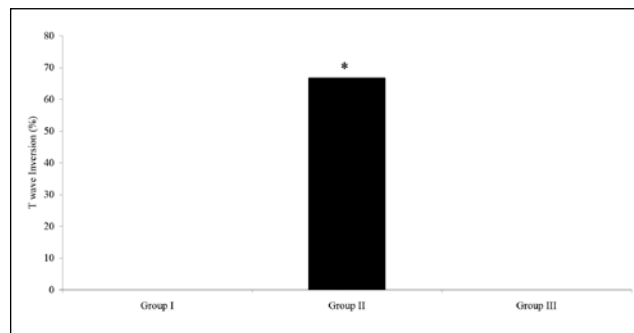


Figure 3. Effects of IV treatment with remifentanyl (Remifentanyl, $\mu\text{g kg}^{-1} \text{min}^{-1}$) on the incidence of T-wave inversion observed during centrally induced sympathetic overactivity periods in anaesthetized rabbits. Values are means \pm SD; n=6 in all experimental groups. * $p < 0.05$ versus Group 3.

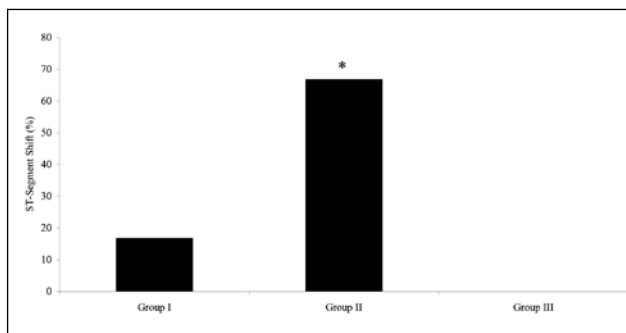


Figure 4. Effects of IV treatment with remifentanyl (Remifentanyl, $\mu\text{g kg}^{-1} \text{min}^{-1}$) on the incidence of ST-segment shift observed during centrally induced sympathetic overactivity periods in anaesthetized rabbits. Values are means \pm SD; n=6 in all experimental groups. * $p < 0.05$ versus Group 3.

reported that L-NAME could cause systemic and coronary vasoconstriction that resulted in hypertension, ventricular arrhythmia (premature ventricular complex), myocardial ischemia (ST-segment changes) and increased mortality. Similarly, Lessa et al. (1) observed increases in ventricular arrhythmia and signs of myocardial ischemia, such as ST-segment changes and T-wave inversion, when ICV L-glutamate and intravenous L-NAME administrations were combined. Moreover, Moreno et al. (18) showed that the acute intravenous administration of L-NAME resulted in extensive myocardial necrosis in rats. Therefore, we decided to combine these drugs to stimulate the central sympathetic system and induce myocardial ischemia in the present study.

One of the major results of our study was the finding that the administration of $40 \mu\text{g kg}^{-1}$ of L-NAME in anaesthetized rabbits led to a considerable increase in MAP. Signs of myocardial ischemia, such as ST-segment changes and T-wave inversion, also occurred. This haemodynamic profile suggested that the inhibition of NO synthesis provokes the reduction in coronary blood flow, which causes myocardial dysfunction. Despite of the increase in MAP and myocardial oxygen demand, L-glutamate alone did not evoke signs of myocardial ischemia.

In the present study, HR at the 5th min of L-NAME administration was found to be reduced during within comparisons with the basal measurements. This finding was parallel to those reported by others (1, 17) who used L-NAME at a dose of $40 \mu\text{g kg}^{-1}$ and may reflect a baroreceptor response following induced hypertension.

In the present study, remifentanyl prevented either the haemodynamic response resulting from central sympathetic stimulation or ventricular tachycardia and signs of myocardial ischemia. Remifentanyl had previously been shown to exhibit a dose-dependent suppression of catecholamine discharges during laparoscopic fundoplication operations (19). In addition, when combined with propofol, remifentanyl was found to be able to decrease the stress response in patients

undergoing cardiac surgery (20). However, there are reports emphasizing the increased risk of hypotension and bradycardia following bolus injections of remifentanyl during coronary artery surgery (21).

The results of our experimental model showed that not only the incidence of myocardial ischemia and ventricular arrhythmia but also the hypertensive attacks due to the activation of the sympathetic nervous system were reduced or even completely abolished in animals that were systematically treated with remifentanyl. These findings correlated with the results of some previous clinical studies (22-24). Thus, the cardioprotective effect of remifentanyl appears to be relative to direct effects on the nervous system and/or heart. Shinohara et al. (25) demonstrated that the systemic administration of remifentanyl induces a central sympathetic inhibitory effect mediated by central opioid receptors.

We determined that, in this experimental model rather than its anti-arrhythmic effect, remifentanyl at least exhibited anti-ischemic properties at this dosage. Although it did not decrease the incidence of PVC and bigeminy ventricular arrhythmia, a significant effect was seen with respect to preventing ST-segment changes and T-wave inversion, which are ECG indicators of myocardial ischemia.

The anti-ischemic action of remifentanyl was probably related to the direct effects on the heart via activation of the delta and kappa types of opioid receptors (12). In our experimental model, L-NAME-induced myocardial ischemia was aggravated by sympathetic overactivity, and remifentanyl was shown to reduce the ensuing increase in myocardial oxygen demand by inhibiting the hypertensive response. As a result, reduced cardiac activity could have led to the occurrence of an anti-ischemic effect. This effect was attributed to the activation of cardiac opioid receptors by remifentanyl, which, besides the classical action on mu receptors, is also able to stimulate the delta and kappa receptors (12). However, further investigation is still necessary to explore the anti-ischemic effect of remifentanyl that was observed in our experimental model.

Another important finding of the present study was the reduction of MAP by remifentanyl. In a number of reports, remifentanyl has been shown to reduce HR, arterial blood pressure, cardiac output and systemic vessel resistance (21, 26-28). In addition, it induced systemic arterial vasodilatation without producing any effect on the capacitance vessels in critically ill patients who underwent surgery for artificial heart valve replacement (31). Nevertheless, how remifentanyl induced vasodilatation occurs is not yet understood. Ünlügenç et al. (29) reported that remifentanyl induced vasodilatation using both endothelium-dependent and -independent mechanisms *in vitro*. Against the NOS inhibition provided with L-NAME, a decrease in arterial blood pressure due to remifentanyl-induced vasodilatation did not indicate the ex-

istence of an endothelium-dependent mechanism. Remifentanil has also been shown not to have any effect on preventing the sympathetic activity or the direct mechanisms of vasodilatation due to histamine discharge (28, 31).

Kim et al. (30) published a review article which shows that both morphine and remifentanil demonstrate cardioprotective properties. Both opioid receptors and signalling pathways were shown to be involved in this effect.

Lemoine et al. (31) also studied *in vitro* human myocardium isometric contraction after hypoxia and administered different remifentanil and sufentanil concentrations; the study demonstrated that both drugs confer cardioprotection.

Conclusion

Remifentanil ($6 \mu\text{g kg}^{-1} \text{min}^{-1}$ for 5 min) prevented life-threatening ventricular tachycardia and electrocardiographic signs of myocardial ischemia in a model of arrhythmia resulting from the association of central sympathetic overactivity with myocardial ischemia in rabbits.

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