Suppressive effects of remifentanil on hemodynamics in baro-denervated rabbits

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Purpose: To elucidate mechanisms by which remifentanil, an ultra-short-acting μ-opioid receptor agonist, causes hypotension and bradycardia.

Methods: Mean arterial pressure (MAP), heart rate (HR) and renal sympathetic nerve activity (RSNA) were measured and recorded after bolus injections of 1, 2 or 5 $\mu g \cdot kg^{-1}$ of remifentanil in neuraxis intact (n=6 for each dose) and baro-denervated rabbits (n=6 for each dose). Arterial baroreflex sensitivity was assessed by depressor tests. An additional six baro-denervated animals received remifentanil, 5 $\mu g \cdot kg^{-1}$ after pretreatment with naloxone, 40 $\mu g \cdot kg^{-1}$.

Results: All values were expressed in % change from baseline. In the neuraxis intact animals, MAP and HR were decreased briefly immediately after remifentanil injection. RSNA was increased dose-dependently: 137 ± 8% (mean ± SE), 170 ± 14% ($P < 0.05$) and 225 ± 29% ($P < 0.05$) after 1, 2 and 5 $\mu g \cdot kg^{-1}$ remifentanil, respectively. RSNA was increased even after MAP and HR had returned to baseline values. The depressor tests revealed that remifentanil did not attenuate arterial baroreflex sensitivity. In the baro-denervated animals, MAP and HR decreased gradually to 77 ± 3% ($P < 0.05$) and 94 ± 1% ($P < 0.05$), respectively 300 sec after 5 $\mu g \cdot kg^{-1}$ remifentanil. At that time, increased RSNA (159 ± 9%, $P < 0.05$) had returned to baseline. Pretreatment with naloxone in the baro-denervated animals abolished these changes.

Conclusion: Remifentanil decreases HR and MAP by its central vagotonic effect and by stimulating peripheral μ-opioid receptors. These effects appear to be counteracted and masked by its central sympathotonic effect and by maintaining arterial baroreflex integrity.

Objectif : Expliquer les mécanismes par lesquels le rémifentanil, un agoniste à action ultra brève du récepteur de μ-opioïde, provoque de l'hypotension et de la bradycardie.

Méthode : La tension artérielle moyenne (TAM), la fréquence cardiaque (FC) et l'activité nerveuse sympathique rénale (ANSR) ont été mesurées et notées après l'injections de bolus de 1, 2 ou 5 $\mu g \cdot kg^{-1}$ de rémifentanil dans le névraxe de lapins intacts (n=6 pour chaque dose) et de lapins baroénervés (n=6 pour chaque dose). La sensibilité artérielle baroréflexe a été évaluée par des tests dépresseurs. Six animaux supplémentaires, baroénervés, ont reçu 5$\mu g \cdot kg^{-1}$ de rémifentanil après un prétraitement avec 40$\mu g \cdot kg^{-1}$ de naloxone.

Résultats : Toutes les valeurs sont exprimées en % de changement par rapport aux mesures de base. Chez les animaux intacts, la TAM et la FC ont brièvement baissé immédiatement après l'injection de rémifentanil. L'ANSR s'est accrue d'une manière dépendante de la dose : 137 ± 8 % (moyenne ± écart type), 170 ± 14 % ($P < 0,05$) et 225 ± 29 % ($P < 0,05$) après 1, 2 et 5 $\mu g \cdot kg^{-1}$ de rémifentanil, respectivement. L'ANSR a augmenté même après que la TAM et la FC ont retrouvé les valeurs de base. Les tests dépresseurs ont révélé que le rémifentanil n'a pas atténué la sensibilité artérielle baroréflexe. Chez les lapins baroénervés, la TAM et la FC ont diminué graduellement jusqu'à 77 ± 3 % ($P < 0,05$) et 94 ± 1 % ($P < 0,05$), respectivement, 300 sec après l'administration de 5 $\mu g \cdot kg^{-1}$ de rémifentanil. À ce moment, l'augmentation de l'ANSR (159 ± 9 %, $P < 0,05$) était revenue aux valeurs de base. Le prétraitement avec la naloxone chez les lapins baroénervés a aboli ces changements.

Conclusion : Le rémifentanil diminue la FC et la TAM par son effet vagotonique central et par la stimulation exercée sur les récepteurs périphériques de μ-opioïde. Ces effets semblent neutralisés et masqués par l'effet sympathotonique central et par le maintien de l'intégrité artérielle baroréflexe.

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REMIFENTANIL is an ultra-short-acting μ-opioid receptor agonist. It possesses ester linkage and undergoes widespread extrahepatic metabolism by plasma and tissue non-specific esterases, resulting in extremely rapid clearance. Remifentanil has gained popularity because of its rapid onset and rapid offset characteristics, which are desirable especially for day surgery anesthesia. Its onset is similar to that of alfentanil, but its offset is more rapid and independent of the duration of infusion.[1] Several studies have demonstrated that remifentanil causes arterial hypotension and bradycardia with *iv* anesthetic agents[2] or general anesthetics.[3,4] On the other hand, Glass *et al.*[5] observed increased arterial blood pressure and heart rate after *iv* injection of remifentanil alone without any other agents on board in unpremedicated healthy volunteers.

The purpose of this study was, therefore, to evaluate the effects of remifentanil alone on hemodynamics, sympathetic outflow and arterial baroreflex sensitivity in order to elucidate the mechanisms by which remifentanil caused arterial hypotension and bradycardia. This is the first study to assess sympathetic outflow from the central nervous system and arterial baroreflex sensitivity after remifentanil injection. Both neuraxis intact and baroreceptor denervated rabbits were used as experimental models.

Methods

The University of Kansas Institutional Animal Care and Use Committee approved this study, and appropriate guidelines for the use of animals were observed during all aspects of the study.

New Zealand white rabbits (3.0-3.8 kg) were anesthetized with 1 $g \cdot kg^{-1}$ urethane *iv*, and anesthesia was maintained with supplemental administration of 100 $mg \cdot kg^{-1} \cdot hr^{-1}$ urethane throughout the experiment. The animals were tracheotomized and the lungs ventilated with an infant ventilator (model LS 104 150; Bourns Life Systems, Riverside, CA) using oxygen in nitrogen (FiO_2 0.4). Polyethylene catheters were placed in a femoral vein for administration of drugs, and in the left femoral artery for measurement of arterial pressure and sampling of arterial blood. The animals were paralyzed with 0.1 $mg \cdot kg^{-1}$ vecuronium to avoid artifacts in the measurement of sympathetic nerve activity secondary to muscular movement. Acid-base balance was maintained within normal limits ($PaCO_2$, 35-45 mmHg; pH 7.35-7.45) by adjusting the tidal volume and frequency. The PaO_2 was maintained between 100 and 200 mmHg. Heart rate (HR) was calculated from lead II of the electrocardiogram using a cardiotachometer (Model 1321; San-ei, Tokyo, Japan). Body temperature was maintained 37.5°C by external warming. Arterial blood pressure was monitored with a pressure transducer (DTX Spectramed, Oxnard, CA) and recorded continuously. Mean arterial pressure (MAP) was derived by electronic integration of the pulsatile pressure signal. Measurement and recording of renal sympathetic nerve activity (RSNA) have been described elsewhere.[6] Briefly, the left kidney was exposed and renal sympathetic nerves were isolated and placed on a bipolar silver electrode. Nerve impulses were amplified, rectified and integrated, and continuously recorded (Nihon Kohden AVB 10, bandwidth: 50-3000 Hz, Tokyo, Japan). The amplified nerve discharge was visualized on a dual-beam oscilloscope (Nihon Kohden VC11, Tokyo, Japan) and monitored by an audio speaker. A resistance and capacitance integrator circuit (2.0 sec for RSNA) integrated the neurogram.

To quantify nerve activities, the resting spontaneous nerve discharge before drug administration was defined as 100% control value. All variables were measured continuously and recorded on DAT tape PCM recorder (RD-100T TEAC, Montebello, CA) and played back on a multichannel chart recorder (Omnicorder 8M14, San-ei, Japan).

Study 1: Neuraxis Intact Group

The effects of remifentanil on hemodynamics, RSNA and arterial baroreflex control of RSNA were evaluated. Eighteen neuraxis intact rabbits were divided into three groups (n=6 each group): 1, 2 or 5 $\mu g \cdot kg^{-1}$ remifentanil were administered *iv* as a bolus over five seconds. Sodium nitroprusside (SNP: 15 $\mu g \cdot kg^{-1}$ *iv*) was used as a control arterial baroreflex sensitivity test, which was performed before and five minutes after remifentanil administration in all groups. Arterial baroreflex sensitivity in response to SNP- and remifentanil-induced hypotension was assessed by calculating the ratio of maximum increase in RSNA (ΔRSNA) to maximum reduction of MAP (ΔMAP) (ΔRNSA/ΔMAP).

Study 2: Baro-denervated Group

The effect of remifentanil on hemodynamics and RSNA in baroreflex-denervated rabbits was determined. Twenty-four rabbits underwent combined bilateral denervation of the carotid sinus and aortic nerves, and vagal nerves to eliminate arterial and cardiopulmonary baroreflex, respectively. Complete denervation was verified by the lack of reflex changes in RSNA in response to 15 $\mu g \cdot kg^{-1}$ SNP-induced hypotension. After a steady state was established, 1, 2 or 5 $\mu g \cdot kg^{-1}$ remifentanil alone or 5 $\mu g \cdot kg^{-1}$ remifentanil after pretreatment with 40 μg naloxone were administered as a bolus over five seconds (n=6 each

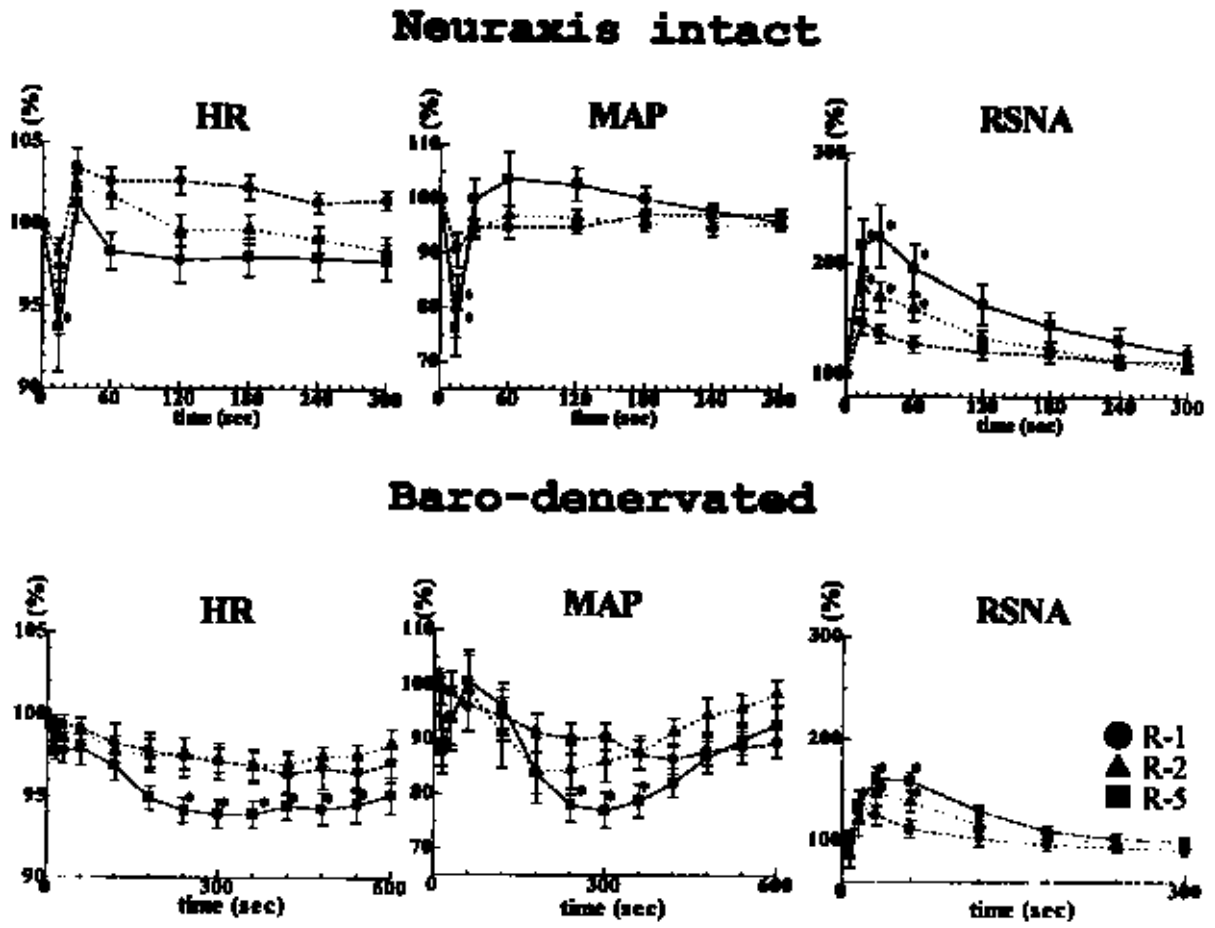

FIGURE 1 Dose-response % changes of heart rate (HR), mean arterial pressure (MAP), renal sympathetic nerve activity (RSNA) in the neuraxis intact group (upper panel) and totally baro-denervated group (lower panel). R-1 (closed circle), R-2 (closed triangle) and R-5 (closed square) denote each subgroup of 1, 2, 5 $\mu g \cdot kg^{-1}$ remifentanil *iv*. Values are mean ± SE. $^*P < 0.05$ compared to values before remifentanil injection.

group). The HR, MAP, RSNA were continuously monitored and recorded.

All data were expressed as mean ± SE. Repeated measure ANOVA followed by Newman-Keul's procedure was used for statistical analysis. Differences with a $P < 0.05$ were considered significant.

Results

In the neuraxis intact group, HR and MAP decreased dose-dependently but only briefly after injection and returned to baseline values. The RSNA increased dose-dependently and gradually returned to baseline (Figure 1, upper panel).

In the totally denervated group, HR and MAP decreased gradually for several minutes after 5 $\mu g \cdot kg^{-1}$ remifentanil. The RSNA was increased dose-dependently but to a lesser degree than in the neuraxis intact group (Figure 1, lower panel).

There were no differences in (RSNA/(MAP before, during or after three different doses of remifentanil (Figure 2).

The effects of remifentanil on HR, MAP and RSNA were completely attenuated by pretreatment with naloxone (Figure 3).

Discussion

Remifentanil is usually administered as a continuous *iv* infusion after a bolus loading dose since it is a very short lasting drug. Since the purpose of this study was to elucidate the mechanism of the hemodynamic

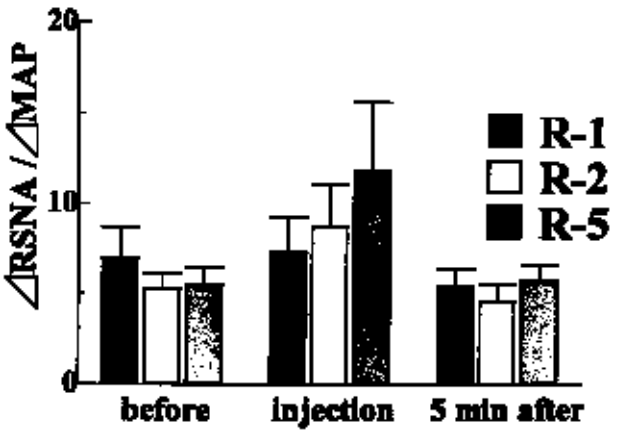

FIGURE 2 Arterial baroreflex sensitivity assessed by the ratio of maximum reflex increases in renal sympathetic nerve activity (ΔRSNA) to maximum reduction of mean arterial pressure (ΔMAP) induced by remifentanil injections (*injection*) and induced by 15 μg·kg^{-1} sodium nitroprusside (*before*) and five minutes after remifentanil injection (*5 min after*). R-1 (closed bar) R-2 (open bar) and R-5 (oblique lined bar) denote each subgroup of 1, 2, 5 μg·kg^{-1} remifentanil, respectively. Values are mean ± SE. There were no differences in RSNA/MAP at three different measurement times in all three subgroups.

effects of remifentanil, we used only bolus injections of remifentanil, and injections were performed over five seconds to potentiate the effects of remifentanil on measured variables. Urethane was used for basal anesthesia since it does not affect arterial baroreflex sensitivity and produces long-lasting anesthesia with minimal cardiovascular depression.[7]

Brief but abrupt reductions of HR and MAP soon after remifentanil injection were observed in the neuraxis intact animals (vagus intact) but not in the baro-denervated bilaterally vagotomized animals (Figure 1). This means that remifentanil exerts central vagotonic action, leading to bradycardia and hypotension. The central vagotonic effect of fentanyl, another μ-opioid receptor agonist, is well documented[8] and, clinically, patients' heart rates slow down after a bolus injection of fentanyl during anesthesia. The central vagotonic effect of remifentanil is short-lived or soon after its onset, it is opposed by increased sympatehtic activity.

Dose-dependent increased RSNA in the neuraxis intact animals is likely mediated by arterial baroreflex in response to reduced arterial pressure. However, RSNA was still increased, even after MAP had returned to baseline (Figure 1, upper panel). This suggests that the sympathetic outflow from the central nervous system may by augmented by remifentanil. Overshoot of the arterial baroreflex might have been another reason for the persistence of increased RSNA. It has been shown that direct stimulation of μ-opioid

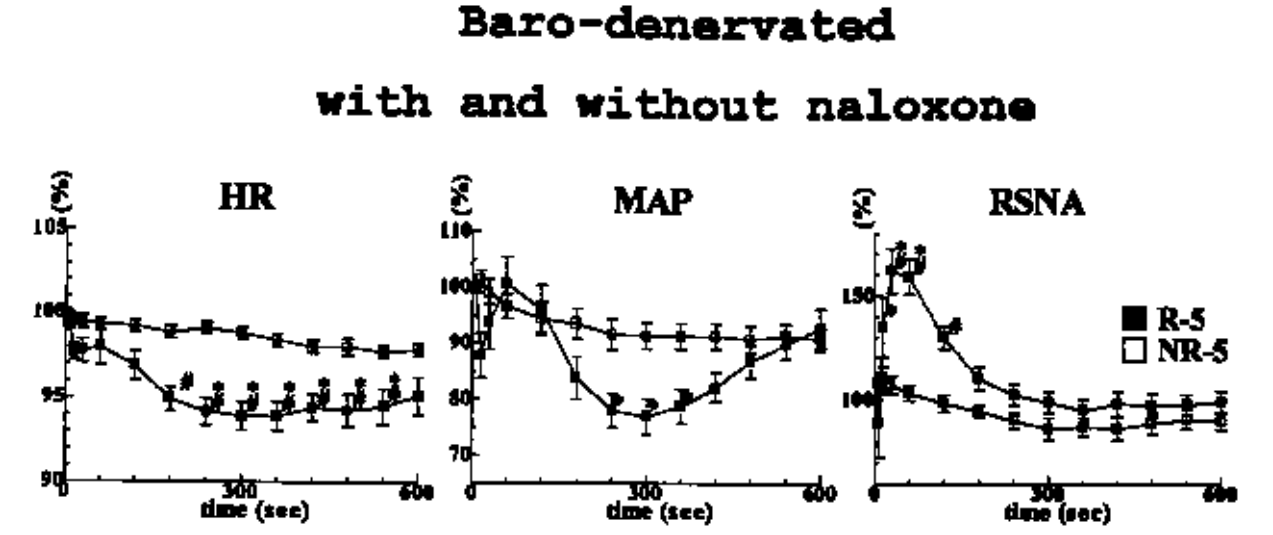

FIGURE 3 Time course % changes of HR (heart rate), MAP (mean arterial pressure) and RSNA (renal sympathetic nerve activity) after bolus injections of 5 μg·kg^{-1} remifentanil without (·R-5) and with pretreatment with 40 mcg naloxone *iv* (NR-5). Values are mean ± SE. *$P < 0.05$ compared with baseline values. #$P < 0.05$ compared with naloxone pretreated group. Note: Naloxone pretreatment completely abolished the effects of remifentanil on these variables.

receptors in the central nervous system, including nucleus tractus solitarius can elicit an increase in sympathetic outflow.[9,10] Other μ-receptor opioid agonists, fentanyl and morphine, when injected *iv*, have been shown to increase sympathetic nerve activity in rabbits[11] and rats,[12] respectively. The increased RNSA with 5 $\mu g \cdot kg^{-1}$ remifentanil was abolished by pretreatment with naloxone; a μ-receptor antagonist in the baro-denervated animals (Figure 3). This means that remifentanil stimulates μ-receptors in the central nervous system, leading to an increase in RSNA.

It has not been clearly demonstrated as to whether μ-receptor agonists increase sympathetic outflow in humans. However, increased arterial blood pressure and heart rate after *iv* injection of remifentanil alone in healthy non-premedicated volunteers[5] could have been due, at least in part. to the central sympathetic stimulating effect of remifentanil.

Unlike the neuraxis intact animals, HR and MAP decreased gradually for several minutes with 5 $\mu g \cdot kg^{-1}$ remifentanil in the baro-denervated animals. The decreased HR and MAP were unlikely to have been due to the central effects of remifentanil since the animals were vagotomized, which precludes bradycardia induced by increased central vagal tone, and sympathetic outflow was not reduced to cause arterial hypotension. It is interesting that HR and MAP started to decrease at about the time when increased RSNA returned toward baseline values (Figure 1, lower panel). Thus, the bradycardic and hypotensive effects of remifentanil were offset by increased sympathetic outflow for several minutes after bolus injections of remifentanil.

Thus, decreased HR and MAP in baro-denervated animals without decreased sympathetic outflow suggest that remifentanil exerts a peripheral action to depress the cardiovascular system. It has been suggested that approximately 10% of the bradycardic effect of fentanyl in dogs is attributable to its peripheral action rather than to its central vagotonic action.[8] Electrophysiological study demonstrated that fentanyl exerts a direct negative chronotropic action by stimulating μ-receptors in the rabbit sino-atrial node.[13] Thus, remifentanil might have exerted a negative chronotropic action similar to that of fentanyl. This is probably true because pretreatment with naloxone abolished the bradycardic effects of remifentanil in the baro-denervated and vagotomized animals (Figure 3).

Since remifentanil has been shown not to release histamine,[14] decreased MAP without reduced sympathetic outflow in the baro-denervated animals suggests that remifentanil may exert a direct negative inotropic action or other mechanism to decrease arterial blood pressure. Pretreatment with naloxone abolished the hypotensive action of remifentanil, suggesting that μ-receptors in the peripheral nervous system and the cardiovascular system may be involved in this remifentanil-induced arterial hypotension. Further study is necessary to clarify the direct effect of remifentanil on these systems.

Maintaining arterial baroreflex integrity is important in maintaining stable hemodynamics during anesthesia and surgery. Nitroprusside was used as a control baro-sensitivity study since it does not impair arterial baroreflex integrity.[15] It was found that remifentanil did not attenuate arterial baroreflex (Figure 2). Similarly, it has been demonstrated that arterial baroreflex integrity is well preserved with fentanyl in dogs.[16]

In summary, fast bolus injections of remifentanil in our experimental model were used to explore the mechanisms of the hemodynamic changes associated with remifentanil. Remifentanil produces arterial hypotension and bradycardia by its central vagotonic effect and by stimulating μ-receptors presumably in the peripheral nervous system and the cardiovascular system. These hypotensive and bradycardic effects can be counteracted by its sympathetic stimulating effect mediated through μ-opioid receptors in the central nervous system. In addition, preserved arterial baroreflex integrity contributes rather stable hemodynamics during remifentanil anesthesia.

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