Neuroanesthesia and Intensive Care

A low-dose remifentanil infusion is well tolerated for sedation in mechanically ventilated, critically-ill patients

[La perfusion d'une faible dose de rémifentanil est bien tolérée comme sédation chez des malades gravement atteints, ventilés mécaniquement]

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Purpose: To study the analgesic and sedative effects of remifentanil in critically-ill patients.

Methods: Remifentanil infusion was started at 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in ten mechanically ventilated critically-ill patients, and the infusion rate was increased to 0.05, 0.10, 0.15, 0.20, and 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ every 30 min. Basally and 25 min after each increase we measured: the Ramsey sedation score (RSS) and the respiratory response subscore of comfort scale (CSRR); the bispectral index (BIS) before and after lightly touching tracheal mucosa; heart rate and systemic arterial pressure; respiratory variables; plasma epinephrine and norepinephrine levels.

Results: Infusion rates up to 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ were effective against agitation and achieved a good degree of adaption to the respirator in all patients (RSS 2 or more and CSRR 3 or less); BIS decreased significantly; respiratory and circulatory variables were unaffected; mean plasma epinephrine levels decreased. At infusion rates higher than 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ RSS but not BIS decreased further and patient arousability caused by noxious stimuli was not prevented; respiratory drive suppression occurred at the infusion rates higher than 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in four patients; bradycardia and arterial hypotension was observed in three patients; plasma epinephrine levels decreased significantly, while norepinephrine was unaffected; severe itching was experienced by one patient.

Conclusions: Low doses of remifentanil (up to 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$) can be useful in critically-ill patients in order to achieve calm and sedation. Higher doses can inhibit respiratory drive and require controlled mechanical ventilation.

Objectif : *Étudier les effets analgésiques et sédatifs du rémifentanil chez de grands malades.*

Méthode : *Une perfusion de rémifentanil a été amorcée à 0,02 $\mu g \cdot kg^{-1} \cdot min^{-1}$ chez dix grands malades ventilés mécaniquement. La vitesse de perfusion a été augmentée à 0,05, 0,10, 0,15, 0,20 et 0,25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ toutes les 30 min. Au début, et 25 min après chaque augmentation, nous avons mesuré : les scores de sédation de Ramsey (SSR) et le score auxiliaire de réponse respiratoire de l'échelle de confort (RREC); l'index bispectral (BIS) avant et après avoir légèrement stimulé la muqueuse trachéale; la fréquence cardiaque et la tension artérielle générale; les variables respiratoires; les niveaux plasmatiques d'adrénaline et de noradrénaline.*

Résultats : *Les vitesses de perfusion allant jusqu'à 0,05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ont été efficaces contre l'agitation et ont permis une bonne adaptation au respirateur chez tous les patients (2 ou moins à SSR et 3 ou moins à RREC); le BIS a diminué de manière significative; les variables respiratoires et circulatoires n'ont pas été affectées; il y a eu une baisse des niveaux plasmatiques d'adrénaline et de noradrénaline. Sous des vitesses de perfusion plus élevées que 0,05 $\mu g \cdot kg^{-1} \cdot min^{-1}$, le SSR, mais non le BIS, a baissé davantage et la réaction des patients aux stimuli nuisibles n'a pu être empêchée; la suppression de la commande respiratoire s'est produite avec des perfusion au-dessus de 0,05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ chez quatre patients; on a observé de la bradycardie et de l'hypotension chez trois patients; les niveaux plasmatiques d'adrénaline ont baissé significativement, mais ceux de la noradrénaline n'ont pas changé; un prurit sévère a été noté chez un patient.*

Conclusion : *Des doses faibles de rémifentanil (jusqu'à 0,05 $\mu g \cdot kg^{-1} \cdot min^{-1}$) peuvent apporter calme et sédation chez de grands malades. Des doses plus élevées peuvent inhiber la commande respiratoire et exiger une ventilation mécanique contrôlée.*

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ANALGESIA and sedation with opioids are used widely to obtain quietness and cooperation from critically ill patients as most diagnostic and therapeutic procedures performed in intensive care units (ICUs) are painful or cause psychologic distress. In this context remifentanil, a μ-agonist opioid characterized by a short blood-brain equilibration time and a rapid metabolism by non specific esterases, could be particularly useful because adjustments of the infusion rate quickly achieve correspondent and stable new plasma levels and because the short and constant context-sensitive plasma half-time allows the patient fast arousability[1–3]

Only few authors have investigated the safety and feasibility of remifentanil infusion for sedation in ICUs.[4–6] A high incidence of undesirable effects, like respiratory depression, nausea and emesis, has been pointed out by a multicenter study focused on postoperative analgesia with remifentanil.[4] However both desirable effects of remifentanil infusion, like sedation, analgesia, and decreased adrenergic tone, and undesirable effects, like respiratory drive depression, nausea, and emesis, are dose-dependent and could be obtained or prevented by choosing the appropriate dosage. The aim of this study was to investigate the safe dosage of remifentanil in patients ventilated in pressure support mode and the effects of analgesia and sedation with remifentanil on some neurological, hormonal, and cardiovascular variables.

Methods

Patients

This prospective study was performed in the 21-bed ICU of the Catholic University in Rome. After obtaining approval of the study from the local Ethics Committee and informed consent from relatives, ten patients, aged 49–80 (median 71.5 yr), five males and five females, Simplified Acute Physiology Score (SAPS) II 24–49 (median 40.5 yr), were included. Inclusion criteria were: a) age > 18 yr; b) need for mechanical ventilation; c) Glasgow coma score (GCS) > 10; d) need for sedation (Ramsey sedation score 1); e) presence of an endotracheal tube and of an arterial line. Criteria for exclusion were: a) reported allergy to opioids; b) pregnancy; c) chronic obstructive pulmonary disease; d) presence of major painful stimuli, such as recent surgical wound or trauma injuries; e) clinically relevant hepatic or renal failure.

All patients were connected to a Siemens 300 ventilator (Siemens-Elema, Sweden) in pressure support mode (18 ± 2 cm H_2O). Pressure support level was adjusted to obtain a tidal volume (TV) between 8 and 10 $mL \cdot kg^{-1}$ of ideal body weight and a respiratory rate lower than 30 $breaths \cdot min^{-1}$; positive end-expiratory pressure and FIO_2 were adjusted in order to obtain PaO_2 values higher than 90 mmHg. No patient was under the effect of opioids, benzodiazepines, propofol, or other medications that could reasonably affect the study.

Procedure

An *iv* infusion of remifentanil (50 $\mu g \cdot mL^{-1}$, diluted in saline) was started at the rate of 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$; the initial infusion rate was increased to 0.05, 0.10, 0.15, 0.20, up to 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ every 30 min, until suppression of spontaneous respiration was achieved. Spontaneous respiratory drive was considered as suppressed if no breathing activity was registered during 15 sec or a reduction of the minute ventilation to values lower than 60% of basal values was detected. Before starting the infusion and 25 min after each increase of infusion rate neurological, hormonal, respiratory, and cardiovascular variables were measured. The degree of agitation and synchrony with the ventilator was assessed by the Ramsey Sedation Score (RSS: 1: patient anxious or agitated or both; 2: patient cooperative, orientated, and tranquil; 3: the patient responds to commands only; 4: a brisk response to a light glabellar tap; 5: a sluggish response to a light glabellar tap; 6: no response)[7] and by the respiratory response subscore of comfort scale (CSRR: 1: no coughing and no spontaneous respiration; 2: spontaneous respiration with little or no response to ventilation; 3: occasional cough or resistance to ventilator; 4: the patient actively breathes against ventilator or coughs regularly; 5: fights ventilator, coughing or choking).[8] Patient cortical activity was determined by the bispectral index (BIS) with an A-2000 electrocardiograph monitor (Aspect Medical Systems, USA); the index was registered prior to (BIS) and immediately following (BIS_1) a standard stimulus obtained by lightly touching the tracheal mucosa with a suction catheter; this maneuver was performed only after starting remifentanil infusion. Heart rate (HR) and systolic, diastolic and mean systemic arterial pressure (SAP, DAP, and MAP) were recorded. Arterial blood gas analysis was performed with a stat profile Ultra L Haemogasanalyzer (Nova Biomedical, USA). Respiratory mechanics variables were measured with a Bicore system. For this purpose, the endotracheal tube was directly connected to a differential pressure transducer for airflow and airway opening pressure recording. The transducer was connected to a Bicore CP 100 respiratory mechanics monitor (Bicore, USA). Airflow, airway opening pressure, and tidal volume obtained by airflow signal integration were digitized, stored on a personal computer via specific interface software, and analyzed with a specifically designed program (Anadat™

TABLE I Patient characteristics. Reasons for stopping the infusion and final rates are given. Minor side-effects did not require stopping the infusion, being slight (itching) or controlled by fluid infusion (arterial hypotension).

Patient	*Age*	*Sex*	*SAPS II*	*Diagnosis*	*Pressure support cm H_2O*	*PEEP cm H_2O*	*PaO_2 / FIO_2 mmHg*	*Outcome*	*End of infusion*		*Minor side-effects*
									Final rate $\mu g \cdot kg^{-} \cdot min^{-1}$	*Cause*	
1.	73	F	37	Pneumonia	18	5	220	Deceased	0.20	Hypoventilation	Itching
2.	75	M	45	ARDS	20	8	167	Deceased	0.25	Protocol	Arterial hypotension
3.	78	M	40	ALI	20	5	222	Alive	0.15	Hypoventilation	—
4.	71	F	49	ALI	15	10	163	Alive	0.20	Bradycardia	Arterial hypotension
5.	80	M	35	Pneumonia	15	5	247	Deceased	0.25	Protocol	—
6.	72	F	44	Stroke	20	5	287	Alive	0.25	Protocol	—
7.	71	F	41	Stroke	20	5	252	Alive	0.25	Protocol	Arterial hypotension
8.	53	F	24	Trauma	15	5	247	Alive	0.20	Hypoventilation	Itching
9.	49	M	48	Pneumonia	20	8	175	Alive	0.20	Itching	—
10.	53	M	32	Stroke	15	5	410	Deceased	0.10	Hypoventilation	—

ALI = acute lung injury; ARDS = acute respiratory distress syndrome; SAPS II = simplified acute physiology score II; PEEP = positive end-expiratory pressure.

5.1, Bicore CP 100 edition, Canada). The system has been already described and validated.[9–11] Ten consecutive respiratory cycles were averaged to determine respiratory rate (RR), tidal volume (TV), inspiratory time (Ti), inspiratory duty cycle, i.e., the duration of a whole breathing cycle (Ttot), and mean inspiratory flow (TV/Ti). Airway occlusion pressure after 100 msec (P_{01}) was obtained by activating the expiratory pause knob of the ventilator. With this maneuver the inspiratory valve remains closed at the end of expiration, while the expiratory valve closes, resulting in a respiratory effort against a completely closed system. After the inspiratory effort is completed, the knob is released and spontaneous respiratory rhythm continues.[12] P_{01} was evaluated in triplicate at 20 sec intervals. This variable is an indirect index of the central respiratory drive depending on the intensity by which respiratory centres, mechano- and chemo-ceptors stimulate the inspiratory peripheral motoneurons, both in spontaneously breathing subjects[13,14] and in ICU patients during assisted ventilation.[15,16] Finally, the inspiratory impedance of the respiratory system was calculated as $P_{01}/[VT/Ti]$; this variable represents a measure of the inspiratory mechanical transformation of the respiratory drive signal, defining the linkage between central drive (P_{01}) and the effectiveness of airflow generation for a given level of respiratory system resistance and compliance.[17] Plasma epinephrine and norepinephrine levels were also determined. Arterial heparinized blood was collected and immediately put into ice-cold water; plasma was obtained with a refrigerated centrifuge and stored at -80°C. Catecholamines were analyzed within ten days by high performance liquid chromatography with electrochemical detection (HPLC-EC) by employing the ESA plasma catecholamine analysis kit (ESA, Inc., USA).

Statistical analysis

The values of discrete variables, BIS, and BIS_1 are reported as median and range. Continuous variables were graphically examined to detect major deviations from normal distribution values; values were consequently shown as mean (standard deviation) or median and range. Statistical analysis was performed with Kruskal-Wallis test and comparisons to basal values with Dunn test. P values < 0.05 were considered as statistically significant.

Results

Main patient characteristics are presented in Table I. The initial infusion rates of 0.02 and 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ did not produce significant modifications of the respiratory variables evaluated for the purposes of this study. In more detail we did not observe variations in respiratory drive, respiratory pattern, respiratory impedance, and gas exchange (Table II). The study was interrupted at the infusion rate of 0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in patient #10 (hypoventilation), at the rate of 0.15 in patient #3 (hypoventilation), at the rate of 0.20 in patients #1 (hypoventilation), #4 (bradycardia, HR 44 beats·min^{-}, spontaneously resolved after ending remifentanil infusion), #8 (hypoventilation), and #9 (itching); the maximal infusion rate of 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was reached in only four patients, #2, 5, 6 and 7. Three patients (#2, 4, 7) required the infusion of colloids, 500–800 mL to correct arterial hypotension (systolic pressure < 90

TABLE II Respiratory variables during remifentanil infusion

	P	*Baseline*	*Infusion μg·kg⁻¹·min⁻¹*					
			0.02	*0.05*	*0.10*	*0.15*	*0.20*	*0.25*
					Respiratory variables			
n patients		10	10	10	10	9	8	4
RR (beats·min^{-1})	0.0050	20 (9)	17 (7)	13 (6)	10 (3)*	9 (2)*	9 (2)**	9 (1)
Ti (sec)	0.1173	1.3 (0.5)	1.2 (0.5)	1.5 (0.4)	1.6 (0.5)	1.5 (0.5)	1.5 (0.3)	2.1 (0.3)
Ti/Ttot (%)	0.8105	44 (6)	41 (7)	44 (6)	41 (10)	35 (15)	38 (20)	40 (10)
TV (L)	0.7571	0.58 (0.11)	0.58 (0.09)	0.56 (0.09)	0.53 (0.09)	0.53 (0.08)	0.53 (0.08)	0.55 (0.08)
Vmin (L)	0.0080	11.6 (5.7)	9.9 (4.8)	7.3 (4.4)	5.3 (2.2)*	4.8 (1.5)*	4.8 (1.7)**	5.0 (1.1)
TV/Ti (L·sec^{-1})	0.1257	0.53 (0.19)	0.53 (0.21)	0.40 (0.14)	0.36 (0.11)	0.37 (0.11)	0.37 (0.08)	0.26 (0.08)
P_{01} (cm H_2O)	0.4425	1.53 (0.62)	1.17 (0.94)	1.30 (1.13)	0.87 (0.49)	1.69 (1.27)	0.81 (0.36)	1.25 (0.67)
P_{01}/(TV/Ti) (cm $H_2O \cdot L^{-1} \cdot sec^{-1}$	0.4271	3.30 (2.23)	2.17 (1.39)	3.19 (2.43)	2.43 (1.26)	5.07 (4.45)	2.20 (1.04)	4.92 (2.76)
					Blood gases			
n		10	10	10	10	9	8	4
PaO_2 (mmHg)	0.7680	124 (28)	127 (27)	127 (31)	132 (23)	128 (23)	127 (33)	145 (18)
$PACO_2$ (mmHg)	0.8118	40 (9)	40 (10)	41 (12)	43 (9)	43 (10)	43 (10)	43 (10)

RR = spontaneous respiratory rate; Ti = inspiratory time; Ttot = duty cycle; TV = tidal volume; Vmin = minute volume; TV/Ti = mean inspiratory flow; P_{01} = airway occlusion pressure after 100 msec; P_{01}/[TV/Ti] = inspiratory impedance of the respiratory system. The number of patients is variable according to the increasing number of subjects that showed the suppression of spontaneous respiratory drive. Data are given as mean (standard deviation). The *P*-value obtained with Kruskal-Wallis test is reported; comparisons with basal values by Dunn test: $*P < 0.05$; $**P < 0.01$

mmHg) at the infusion rate of 0.15 μg·kg^{-1}·min^{-1}. Three patients (#1,8,9) complained of itching, one of them (#9) was given an antihistaminic drug and finally required cessation of the remifentanil infusion; itching ended a few minutes after stopping the infusion.

Table III shows RSS, CSRR, BIS, plasma catecholamine levels, and cardiovascular variables. Remifentanil significantly decreased RSS, providing a score of 2 or more in all patients at an infusion rate of 0.05 μg·kg^{-1}·min^{-1}. The score was roughly proportional to the infusion rate, however some patients remained calm, but awake (RSS = 2) even at the rate of 0.15 μg·kg^{-1}·min^{-1}; a RSS of 5 was recorded in patient #10 at 0.05 μg·kg^{-1}·min^{-1} and a RSS of 1 was recorded in patient #9 at 0.20 μg·kg^{-1}·min^{-1}, caused by itching. In all patients remifentanil infusion improved patient adaptation to mechanical ventilation; CSRR decreased progressively and all patients scored 3 or less, i.e., exhibited cough or only occasional ventilatory asynchrony at the rate of 0.10 μg·kg^{-1}·min^{-1} or more. The BIS was also significantly lowered by remifentanil, but differed from RSS since the lowest values were observed at 0.10 μg·kg^{-1}·min^{-1} and BIS did not decrease further at higher doses. Finally, remifentanil did not abolish the response to noxious stimuli; even at 0.25 μg·kg^{-1}·min^{-1}, tracheal stimulation elicited an increase of BIS up to values that characterize awake subjects. Remifentanil decreased epinephrine plasma levels at infusion rates higher than 0.10 μg·kg^{-1}·min^{-1} and this effect was associated with a significant decrease of arterial pressure.

Discussion

This study confirms that remifentanil infusion can provide analgesia and sedation in critically ill patients, as already reported.[5,6] By increasing remifentanil doses, a state of increasing depression of the central nervous system is obtained, as reflected by clinical scores, BIS, plasma catecholamine levels, respiratory and cardiovascular variables. According to clinical needs, sedation can be titrated to different targets, such as to obtain calmness or loss of consciousness (LOC), to decrease sympathetic tone, or even to inhibit respiratory drive. In this context, remifentanil pharmacokinetics offer some advantages over other analgesics and sedatives. A constant-rate infusion of remifentanil achieves steady plasma levels in about ten minutes[18] and the half-time for equilibration between plasma and its effect compartment is about 1–1.5 min.[2] Therefore a stable level of sedation and analgesia is achieved in a few minutes following any infusion rate adjustment; on this basis, in this study we chose to perform the measures 25 min following each infusion rate adjustment. A further advantage of remifentanil is represented by its constant and short context-sensitive plasma half-time, which allows a prompt recovery after stopping the infusion to evaluate the neurological state of the patient.[6]

TABLE III Neurological and circulatory variables during remifentanil infusion

	P	*Baseline*	*Infusion μg·kg⁻¹·min⁻¹*					
			0.02	*0.05*	*0.10*	*0.15*	*0.20*	*0.25*
			Neurologic scores as median (range)					
n patients		10	10	10	10	9	8	4
RSS	0.0001	1	2	2*	4**	3**	4*	5**
	(1-1)	(1-3)	(2-5)	(2-5)	(2-5)	(1-5)	(4-6)	
CSRR	0.0002	3	3	3	2*	2*	2*	2*
	(2-4)	(2-4)	(1-3)	(1-3)	(1-3)	(1-3)	(1-2)	
BIS (%)	0.0000	93	88	60*	54**	48**	49**	50**
	(80-98)	(50-98)	(40-83)	(35-60)	(36-60)	(40-68)	(28-60)	
BIS_1 (%)	0.0114	—-	93	82	77	70	68	70
	—-	(80-98)	(60-98)	(50-90)	(49-85)	(50-98)	(60-94)	
			Circulatory variables as mean (standard deviation)					
n		10	10	10	10	9	8	4
HR (beats·min⁻¹)	0.8918	94 (22)	93 (26)	89 (24)	84 (24)	82 (26)	79 (24)	87 (23)
SAP (mmHg)	0.0050	140 (22)	132 (27)	115 (18)	106 (16)**	110 (19)*	108 (21)*	100 (12)*
DAP (mmHg)	0.0592	68 (15)	72 (25)	57 (18)	59 (17)	57 (19)	55 (19)	49 (6)
			Plasma catecholamines as median (range)					
n		10	10	10	10	9	8	4
E pg·mL⁻¹	0.0010	82	55	40	16	5*	5**	8*
	(14-245)	(7-235)	(4-154)	(3-69)	(1-52)	(1-44)	(1-22)	
NE pg·mL⁻¹	0.4373	564	554	535	527	465	434	1965
	(238-7824)	(177-6528)	(172-6528)	(165-6311)	(129-6185)	(316-6009)	(265- 7212)	

RSS = Ramsey sedation score; CSRR = respiratory response subscore of comfort scale; BIS = bispectral index; BIS_1 = bispectral index following tracheal mucosa stimulation (the test was performed only during remifentanil infusion); HR = heart rate; SAP = systolic arterial pressure; DAP = diastolic arterial pressure; E = epinephrine; NE = norepinephrine. The number of patients is variable according to the increasing number of subjects that showed the suppression of spontaneous respiratory drive. The *P*-value obtained with Kruskal-Wallis test is reported; comparison with basal values by Dunn test: $*P < 0.05$; $**P < 0.01$.

In our patients the neurological depression produced by remifentanil infusion was measured both with clinical and instrumental scores. From a clinical point of view, infusion rates up to 0.05 μg·kg⁻¹·min⁻¹ induced sedative effects without LOC, while higher rates induced LOC in most patients. Remifentanil sedation showed at least two peculiarities. Some patients were calm, but still conscious (awake, eyes open) even at high infusion rates (0.15 μg·kg⁻¹·min⁻¹), and a noxious stimulus caused a patient to awake promptly during remifentanil infusion at 0.20 μg·kg⁻¹·min⁻¹ . Our findings are consistent with those of Wilhelm *et al.*,[5] who achieved a RSS of 4 in critically-ill patients with a mean infusion rate of 0.14 μg·kg⁻¹·min⁻¹, but required a propofol infusion to obtain LOC in some patients. In this study, remifentanil caused a significant decrease of BIS, however the mechanism remains unclear. Studies during anesthesia suggest that remifentanil influences BIS only in the presence of painful stimuli. Some authors observed that the increase of BIS after endotracheal intubation was significantly attenuated by infusing remifentanil and propofol rather than propofol alone, while basal values were unaffected.[19] In another study, BIS was not modified by adding a remifentanil to a propofol infusion in absence of painful stimuli.[20] It seems reasonable that also in critically-ill patients remifentanil could decrease BIS values only by removing pain. Patients with surgical or traumatic wounds were excluded from this study, hence the significant decrease of BIS observed suggests that the pain caused by monitoring and therapeutic procedures was not negligible. However remifentanil did not provide complete protection against painful manoeuvres since patients' awakening caused by endotracheal suction was not prevented even at the highest infusion rate tested in this study.

Both bradycardia and arterial hypotension are well-known effects of opioids and are probably related to a vagomimetic action and to a centrally-mediated reduction in systemic vascular resistance, respectively; remifentanil, as other fentanyl analogues, probably does not cause histamine release or myocardial depression.[21] In this study, remifentanil infusion caused a

decrease of heart rate and blood pressure that was already clinically relevant at an infusion rate of 0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Arterial hypotension was observed in three patients, but was successfully treated with fluid administration. A marked, but well tolerated bradycardia was observed in one patient; however the patient recovered spontaneously and atropine administration was not necessary since heart rate increased a few minutes after ending remifentanil infusion. In this regard, remifentanil's prompt elimination after stopping the infusion is particularly valuable to control circulatory adverse effects.

Plasma catecholamine concentration is a commonly used index of sympathetic activity in man.[22–25] In healthy subjects, sleep is associated with low levels of plasma catecholamines.[23] In critically ill patients, plasma epinephrine and norepinephrine have been utilized to assess sympathetic tone during sedation.[24,25] We observed a significant decrease of plasma epinephrine concentration associated with increasing infusion rates of remifentanil, while norepinephrine did not change significantly since its values fell in a wider range than epinephrine and decreased only in some patients. We have no clear explanation for the different trends of epinephrine and norepinephrine. In another study performed after myocardial revascularization, deep sedation with propofol compared with intermittent administration of midazolam and morphine, decreased plasma epinephrine concentration more than norepinephrine concentration.[25] These findings could possibly originate from differences between the two catecholamines. Plasma epinephrine reflects adrenomedullary release, while plasma norepinephrine mainly originates from neuronal discharge; moreover various stimuli could elicite different degrees of release of epinephrine and norepinephrine.[26] Further studies are necessary to clarify this point.

Itching is a common adverse effect of opioids, probably caused by a μ-receptor mediated central mechanism.[27] In our study, three patients complained of itching; in one case it caused enough discomfort to require interruption of the infusion. The association with midazolam could decrease the incidence of itching during remifentanil sedation;[28] in other cases droperidol could be useful.[27] Remifentanil's prompt elimination can stop itching in patients who do not respond to pharmacological therapy.

The present study was designed also to assess the effects of increasing doses of remifentanil on several respiratory variables directly related to respiratory drive (as $P_{0.1}$, TV/Ti, and RR), respiratory impedance ($P_{0.1}$/[TV/Ti]), respiratory pattern (Ti/Ttot), and respiratory output (Vmin). We did not observe significant effects on respiratory drive, respiratory pattern, minute volume, and gas exchanges at the first two levels of infusion. At doses higher than 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$, hypoventilation started to occur as demonstrated by a slight, but significant reduction of Vmin. Only when doses higher than 0.10 were administered was patient spontaneous breathing activity inhibited, as shown clearly by a reduction of $P_{.01}$ and, subsequently, by the presence of respiratory pauses and by a significant reduction of spontaneous respiratory rate. Finally, the observed stability in $P_{0.1}$/[TV/Ti], a reliable index of the mechanical transformation of the respiratory centre output signal,[17] indirectly demonstrates the absence of effects of remifentanil on respiratory mechanics variables.

In conclusion, our observations suggest that low doses of remifentanil (up to 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$) can be useful in patients requiring partial respiratory support (such as intermittent mandatory ventilation or pressure support ventilation) in order to achieve calm and sedation. Higher doses are necessary to obtain respiratory drive depression and to lower sympathetic tone, but require controlled mechanical ventilation and are associated with an increased incidence of adverse effects.

References

1 *Reves JG.* Educational considerations for the clinical introduction and use of remifentanil. Anesth Analg 1999; 89(4 Suppl): S4–6.

2 *Glass PS, Gan TJ, Howell S.* A review of the pharmacokinetics and pharmacodynamics of remifentanil. Anesth Analg 1999; 89(4 Suppl): S7–14.

3 *Cohen J, Royston D.* Remifentanil. Curr Opin Crit Care 2001; 7: 227–31.

4 *Bowdle TA, Camporesi EM, Maysick L, et al.* A multicenter evaluation of remifentanil for early postoperative analgesia. Anesth Analg 1996; 83: 1292–7.

5 *Wilhelm W, Dorscheid E, Schlaich N, Niederprum P, Deller D.* The use of remifentanil in critically ill patients. Clinical findings and early experience (German). Anaesthesist 1990; 48: 625–9.

6 *Tipps LB, Coplin WM, Murry KR, Rhoney DH.* Safety and feasibility of continuous infusion of remifentanil in the neurosurgical intensive care unit. Neurosurgery 2000; 46: 596–601.

7 *Ramsay MA, Savege TM, Simpson BR, Goodwin R.* Controlled sedation with alphaxalone-alphadolone. Br Med J 1974; 2: 656–9.

8 *Ambuel B, Hamlett KW, Marx CM, Blumer JL.* Assessing distress in pediatric intensive care environments: the COMFORT scale. J Pediatr Psychol 1992; 17: 95–109.

9 *Banner MJ, Kirby RR, Blanch PB, Layon AJ.* Decreasing imposed work of the breathing apparatus to zero using pressure-support ventilation. Crit Care Med 1993; 21: 1333–8.
10 *Kirton OC, Banner MJ, Axelrad A, Drugas G.* Detection of unsuspected imposed work of breathing: case reports. Crit Care Med 1993; 21: 790–5.
11 *Petros AJ, Lamond CT, Bennett D.* The Bicore pulmonary monitor. A device to assess the work of breathing while weaning from mechanical ventilation. Anaesthesia 1993; 48: 985–8.
12 *Perrigault PF, Pouzeratte YH, Jaber S, et al.* Changes in occlusion pressure (P0.1) and breathing pattern during pressure support ventilation. Thorax 1999; 54: 119–23.
13 *Whitelaw WA, Derenne JP, Milic-Emili J.* Occlusion pressure as a measure of respiratory center output in conscious man. Respir Physiol 1975; 23: 181–99.
14 *Rosa G, Conti G, Orsi P, et al.* Effects of low-dose propofol administration on central respiratory drive, gas exchanges and respiratory pattern. Acta Anaesthesiol Scand 1992; 36: 128–31.
15 *Conti G, De Blasi R, Pelaia P, et al.* Early prediction of successful weaning during pressure support ventilation in chronic obstructive pulmonary disease patients. Crit Care Med. 1992; 20: 366–71.
16 *Conti G, Cinnella G, Barboni E, Lemaire F, Harf A, Brochard L.* Estimation of occlusion pressure during assisted ventilation in patients with intrinsic PEEP. Am J Respir Crit Care Med 1996; 154: 907–12.
17 *Hussain SN, Pardy RL, Dempsey JA.* Mechanical impedance as determinant of inspiratory neural drive during exercise in humans. J Appl Physiol 1985; 59: 365–75.
18 *Rosow CE.* An overview of remifentanil. Anesth Analg 1999; 89(4 Suppl): S1–3.
19 *Guignard B, Menigaux C, Dupont X, Fletcher D, Chauvin M.* The effect of remifentanil on the bispectral index change and hemodynamic responses after orotracheal intubation. Anesth Analg 2000; 90: 161–7.
20 *Lysakowski C, Dumont L, Pellegrini M, Clergue F, Tassonyi E.* Effects of fentanyl, alfentanil, remifentanil and sufentanil on loss of consciousness and bispectral index during propofol induction of anaesthesia. Br J Anaesth 2001; 86: 523–7.
21 *Bowdle TA.* Adverse effects of opioid agonists and agonist-antagonists in anaesthesia. Drug Saf 1998; 19: 173–89.
22 *Grassi G, Esler M.* How to assess sympathetic activity in humans. J Hypertens 1999; 17: 719–34.
23 *Maling TJ, Dollery CT, Hamilton CA.* Clonidine and sympathetic activity during sleep. Clin Sci (Lond) 1979; 57: 509–14.
24 *Hall RI, MacLaren C, Smith MS, et al.* Light versus heavy sedation after cardiac surgery: myocardial ischemia and the stress response. Maritime Heart Centre and Dalhousie University. Anesth Analg 1997; 85: 971–8.
25 *Plunkett JJ, Reeves JD, Ngo L, et al.* Urine and plasma catecholamine and cortisol concentrations after myocardial revascularization. Modulation by continuous sedation. Multicenter Study of Perioperative Ischemia (McSPI) Research Group, and the Ischemia Research and Education Foundation (IREF). Anesthesiology 1997; 86: 785–96.
26 *Robertson D, Johnson GA, Robertson RM, Nies AS, Shand DG, Oates JA.* Comparative assessment of stimuli that release neuronal and adrenomedullary catecholamines in man. Circulation 1979; 59: 637–43.
27 *Kjellberg F, Tramer MR.* Pharmacological control of opioid-induced pruritus: a quantitative systematic review of randomized trials. Eur J Anaesthesiol 2001; 18: 346–57.
28 *Avramov MN, Smith I, White PF.* Interactions between midazolam and remifentanil during monitored anesthesia care. Anesthesiology 1996; 85: 1283–9.