Remifentanil and controlled hypotension; comparison with nitroprusside or esmolol during tympanoplasty

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Purpose: To determine whether remifentanil, combined with propofol, could induce controlled hypotension, reduce middle ear blood flow (MEBF) measured by laser-Doppler flowmetry, provide a "dry" operative field, and could be compared with nitroprusside or esmolol combined with alfentanil and propofol.

Methods: Thirty patients undergoing tympanoplasty and anesthetized with 2.5 $mg \cdot kg^{-1}$ propofol *iv* followed by a constant infusion of 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$, were randomly assigned in three groups to receive either 1 $\mu g \cdot kg^{-1}$ remifentanil *iv* followed by a continuous infusion of 0.25 to 0.50 $\mu g \cdot kg^{-1} \cdot min^{-1}$, or nitroprusside *iv*, or esmolol *iv* combined for the latter two groups with alfentanil *iv*.

Results: Controlled hypotension was achieved at the target pressure of 80 mmHg within 107 ± 16, 69 ± 4.4, 53.3 ± 4.4 sec for remifentanil, nitroprusside and esmolol respectively. MEBF decreased by 24 ± 0.3, 22 ± 3.3, 37 ± 3% and preceded the decrease in SABP, within 30 ± 6.1, 11.2 ± 3.1, 15 ± 2.8 sec for remifentanil, nitroprusside and esmolol respectively. Remifentanil, and nitroprusside decreased MEBF autoregulation less than esmolol (0.36 ± 0.1, 0.19 ± 0.2, -0.5 ± 0.2). Controlled hypotension was sustained in all three groups throughout surgery, and the surgical field rating decreased in a range of 80% in all three groups. Nitroprusside decreased pH and increased $PaCO_2$. There were no postoperative complications in any of the groups.

Conclusions: Remifentanil combined with propofol enabled controlled hypotension, reduced middle ear blood flow and provided good surgical conditions for tympanoplasty with no need for additional use of a potent hypotensive agent.

Objectif : Déterminer si le rémifentanil, associé au propofol, peut induire une hypotension contrôlée, réduire le débit sanguin de l'oreille moyenne (DSOM) mesuré par laser-Doppler, assurer un champ opératoire exsangue et être comparé au nitroprussiate et à l'esmolol associés à l'alfentanil et au propofol.

Méthode : Trente patients subissant une tympanoplastie, et anesthésiés par 2,5 $mg \cdot kg^{-1}$ de propofol *iv* suivis d'une perfusion de 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$, ont été répartis après randomisation en 3 groupes recevant soit 1 $\mu g \cdot kg^{-1}$ de rémifentanil *iv* suivis d'une perfusion de 0,25 à 0,50 $\mu g \cdot kg^{-1} \cdot min^{-1}$, soit du nitroprussiate, soit de l'esmolol *iv*, associé pour les 2 derniers à de l'alfentanil.

Résultats : Tout d'abord, l'hypotension contrôlée a été obtenue au niveau souhaité de 80 mmHg en 107 ± 16; 69 ± 4,4; 53,3 ± 4,4 sec pour le rémifentanil, le nitroprussiate et l'esmolol. Le DSOM a diminué de 24 ± 0,3; 22 ± 3,3; 37 ± 3 % et a précédé la chute de pression de 30 ± 6,1; 11,2 ± 3,1; 15 ± 2,8 sec pour le rémifentanil, le nitroprussiate et l'esmolol. Le rémifentanil et le nitroprussiate ont moins réduit l'autorégulation que l'esmolol (0,36 ± 0,1; 0,19 ± 0,2; -0,5 ± 0,2). Ensuite, l'hypotension contrôlée a été maintenue dans les 3 groupes tout au long de l'opération, et le saignement opératoire a été diminué de 80 % dans les 3 groupes. Le nitroprussiate a diminué le pH et augmenté la $PaCO_2$. Il n'y a eu aucune complication postopératoire dans chacun des groupes.

Conclusion : Le rémifentanil associé au propofol a permis de réaliser une hypotension contrôlée, de réduire le débit sanguin de l'oreille moyenne et d'assurer de bonnes conditions opératoires pour la tympanoplastie sans recours à un agent hypotenseur puissant.

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CONTROLLED hypotension is commonly used to achieve a bloodless operative field which is needed for successful middle ear microsurgery.[1] In the 1970s, systolic arterial blood pressures as low as 50 mmHg appeared to be well tolerated in healthy patients.[2] In spite of the arterial pressure being reduced to very low values in many instances, there was no morbidity or mortality which could be ascribed to the technique. Since then, various drugs have been used to facilitate the induction of controlled hypotension for middle ear surgery including vasodilators such as sodium nitroprusside,[3–6] nicardipine,[4] nitroglycerin,[4] beta-adrenergic antagonists such as propranolol,[5] esmolol,[7] alpha and beta-adrenergic antagonist such as labetalol,[8] and high doses of potent inhaled anesthetics such as halothane.[3,5] Some disadvantages have been reported for these techniques including long postanesthetic recovery for halothane,[3] resistance to vasodilators,[4] tachyphylaxis[9] and cyanide toxicity[10] for nitroprusside, or possibility of myocardial depression for esmolol.[11] Remifentanil hydrochloride, a new ultra-short-acting μ-opioid receptor agonist, is now currently used in propofol total intravenous anesthesia (propofol-TIVA). Compared with other comparable drugs such as fentanyl[12] or alfentanil,[13–15] remifentanil appears to offer a superior intraoperative hemodynamic stability during stressful surgical events and maintains intact cerebral blood flow reactivity.[12,16] Meanwhile, it appears to provoke moderate to mild hypotension.[15,17] Since we replaced alfentanil by remifentanil in our clinical practice, we noted that this side effect led us to stop the use of nitroprusside, or esmolol for controlled hypotension. This hypotensive effect of remifentanil has not yet been studied for intraoperative controlled hypotension. One advantage of remifentanil in this indication could be its short duration of action.

Accordingly, we designed this prospective study a) to determine whether remifentanil in propofol-TIVA could induce controlled hypotension at a target systolic arterial blood pressure of 80 mmHg, b) to determine whether remifentanil-induced hypotension was accompanied by a reduction in middle ear blood flow measured by laser-Doppler, c) to evaluate its effect on the quality and on the dryness of the operative field, and d) to compare its effects with the expected one of sodium nitroprusside or esmolol combined with alfentanil in propofol-TIVA.

Methods

Patients

Thirty normotensive ASA physical status I-II patients undergoing tympanoplasty for perforation were studied. Each signed consent forms that were approved by the Institution's human research review committee. They were randomly assigned to receive either remifentanil (remi), or sodium nitroprusside (snp) or esmolol (esmo) as the primary drug for inducing hypotension in a propofol-TIVA. Patients assigned to snp group or to esmo group received alfentanil instead of remifentanil.

All patients were admitted on the day before surgery and fasted for at least 12 hr before surgery. All patients received an oral medication for sedation (100 mg hydroxyzine, 1 mg alprazolam) two hours before surgery. Patients were studied while supine. The study was performed in two parts: in the first, hypotension and middle ear blood flow were investigated when no surgical stress was applied. In the second, hypotension and surgical field were investigated during surgery until end.

Hemodynamic measurements

A 22-gauge catheter was inserted into a radial artery for direct determination of arterial blood pressure (systolic, SABP, mean, MABP) and heart rate (HR), which were continuously recorded. It also allowed serial blood gas determinations. An 18-gauge catheter was inserted into a forearm vein and was used for fluid and drug administration: Ringer's solution was administered continuously at a rate of 5 $ml \cdot kg^{-1} \cdot hr^{-1}$.

Metabolic measurements

Arterial blood samples enabled us to determine changes in partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$), pH and lactate concentration. Arterial blood lactate concentration was determined by an enzymatic method using the oxidation of lactate to pyruvate (DuPont Instruments Aca) which gave a coefficient of variation of 5.6% at 1.79 $\mu mol \cdot l^{-1}$ and 1.3% at 13.1 $\mu mol \cdot l^{-1}$. Samples were taken at control (see further) and every 15 min until 20 min after end of surgery in the recovery room.

Middle ear blood flow changes

Middle ear blood flow (MEBF) changes were continuously recorded by a commercially available laser-Doppler instrument (Periflux PF3, Perimed KB, Sweden).[4] The optic fibre is inserted through the tympanic perforation and is put in place by the surgeon on the mucosa of the promontory of the tympanic cavity. The MEBF was calibrated before the study so that a true zero indicated that the flux was null: MEBF and arterial blood pressure were continuously and simultaneously recorded.[4] The relative changes in MEBF (δMEBF) and in SABP from their respective baselines

were considered for statistical analysis and comparison between groups. The MEBF autoregulatory responses to controlled hypotension were quantified by the closed-loop gain factor of autoregulation (Ga) calculated from the equation Ga= 1- (%MEBF/ %MABP). A Ga value of 1 implies perfect flow autoregulation, Ga > 1 indicates excessive, and Ga close to 0 indicates impaired autoregulation. When Ga = 0, autoregulation is abolished and MEBF follows MABP passively.[18]

Quality of the surgical field

The quality of the surgical field in terms of blood loss and dryness, was rated every 10 min by the same attending surgeon who was unaware of the pharmacological treatments, using a six-point scale (0= no bleeding, virtually bloodless field; 5= uncontrolled bleeding).[19]

Anesthesia

Anesthesia was conducted and maintained with propofol. In all cases: 2.5 $mg \cdot kg^{-1}$ propofol was followed by a constant infusion of 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$ *iv*. A laryngeal mask allowed controlled ventilation which was adjusted to an end tidal CO_2 concentration of 35 mmHg and to insure SpO_2>97% with 65% air in oxygen. Only patients assigned to receive sodium nitroprusside or esmolol received alfentanil *iv* two minutes before propofol: 100 $\mu g \cdot kg^{-1}$ alfentanil was followed by a constant infusion of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Procedures

After induction of anesthesia and insertion of laryngeal mask had been performed, the laser-Doppler optic fibre was inserted by direct microscopy by the surgeon through the tympanic perforation onto the promontorium of the tympanic cavity. A five-minute quiet rest period was observed and was followed by a two-minute period of hemodynamic measurements and blood sampling for blood gas analysis in order to obtain baseline values (control). Then, at T_0, patients underwent the treatment protocol; drugs were delivered in order to induce controlled hypotension that was considered effective when SABP reached the target pressure of 80 mmHg. Infusion rate was adapted in order to maintain hypotension and infusion rate was increased or decreased when SABP was more or less than 80 mmHg.

- patients assigned to the remifentanil group (remi) received 1 $\mu g \cdot kg^{-1}$ remifentanil *iv* in 30-60 sec., followed by a continuous infusion of 0.25 to 0.50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until systolic arterial blood pressure (SABP) was brought within 80 mmHg; then infusion rate was adapted to maintain hypotension at this level,

- patients assigned to the sodium nitroprusside group (snp) received a continuous *iv* infusion of sodium nitroprusside at a rate of 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until SABP was brought within 80 mmHg and then was adapted to maintain hypotension at this level,

- patients assigned to the esmolol group (esmo) received 500 $\mu g \cdot kg^{-1}$ esmolol *iv* in 30 sec, followed by a continuous infusion of 100-300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until SABP was brought within 80 mmHg; infusion rate was adapted to maintain hypotension at this level.

Delay in onset of hypotension and delay in start of variations in MEBF were measured from T_0. Time delay between onset of hypotension and start of variations in MEBF was calculated.

During the first study part, no surgical stress was applied during 15 min following start of hypotension. The laser-Doppler fibre was withdrawn at $T_{+15\ min}$ of experimentation to allow surgical procedure; during the second study part, direct visual analysis of the surgical field was performed from T_0 until end of surgery. To obtain a fast recovery, in the three groups all drugs were discontinued at least 10 min before end of surgery.

Statistical analysis

For each patient, variations in MEBF, SABP, MABP and HR were calculated from baseline values and were considered for comparison between the groups. All results are expressed as mean ± SE. Results were averaged before statistical analysis. Intragroup comparisons were evaluated using one-way analysis of variance for repeated measures; where indicated, Bonferroni's corrections were used to identify significant differences. Intergroup comparisons were made using the non-parametric Mann-Whitney U-test for unpaired data. Relationships between MEBF and SABP, MEBF and HR were studied by least squares linear regressions. The threshold for statistical significance was taken as $P < 0.05$.

Results

Demographic data, duration of hypotension, duration of anesthesia and baseline hemodynamic data did not differ among groups (Table I).

In the first part of the study, when surgical stress was avoided, controlled hypotension was achieved at the target systolic arterial blood pressure of 80 mmHg in the three groups (Figure 1a) within 107 ± 16 sec in remi group, 69 ± 4.4 sec in snp group ($P < 0.05$ vrs remi group), 53.3 ± 4.4 sec in esmo group ($P < 0.05$ vrs remi group).

Middle ear blood flow decreased from baseline by 24 ± 0.3% ($P < 0.001$) in the remi group, by 22 ± 3.3% ($P < 0.001$) in the snp group, and by 37 ± 3.1% ($P < 0.001$) in the esmo group. MEBF decreased more in

TABLE I Demographic data of patients undergoing tympanoplasty, duration of hypotension, duration of anesthesia, and baseline hemodynamic data.

	Remifentanil group n=10	*Nitroprusside group n=10*	*Esmolol group n=10*	*P*
- Patients				
Sex ratio				
F/M (n)	4/6	5/5	6/4	
Age (yr)	31 ± 5.2	29 ± 4.7	27 ± 7.1	NS
Weight (kg)	69 ± 9	64 ± 8	68 ± 10	NS
- Duration of hypotension (min)	47 ± 5	45 ± 5	45 ± 7	NS
- Duration of anesthesia (min)	68 ± 11	64 ± 7	70 ± 11	NS
- Baseline systolic arterial blood pressure (mmHg)	102 ± 5	98 ± 6	100 ± 4	NS
- Baseline mean arterial blood pressure (mmHg)	80 ± 3	74 ± 4	73 ± 5	NS
- Baseline heart rate (beats/min)	72 ± 6	70 ± 6	72 ± 7	NS

NS, not significant; intergroup comparison, Mann-Whitney U-test.
Results are mean values ± SE

TABLE II Doses and time delay for hemodynamic effects of drugs used for controlled hypotension in the three groups.

	Remifentanil group n=10	*Nitroprusside group n=10*	*Esmolol group n=10*	*P*
Infusion rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.31 ± 0.04	0.92 ± 0.41	210 ± 33	
- Total dose (mg)	1.1 ± 0.2	4.7 ± 1.1	612 ± 51	
- Delay in onset of hypotension (sec)	52.5 ± 4.7	35 ± 2†	40 ± 0.1*	*$P < 0.05$† < 0.01
- Time delay δMEBF-δABP (sec)	30 ± 6.1	11.2 ± 3.1*	15 ± 2.8	*$P < 0.05$
- MABP (mmHg) at SABP 80 mmHg	49 ± 2‡	53 ± 3‡	47 ± 4‡	‡$P < 0.05$

MABP, mean arterial blood pressure; SABP 80mmHg, systolic arterial blood pressure of 80 mmHg. Time delay δMEBF-δSABP (sec), time delay between start of variations in middle ear blood flow and onset of hypotension. *$P < 0.05$ †$P < 0.01$, remifentanil *vs* nitroprusside or esmolol, intergroup Mann-Whitney U-test ;‡ significant, and ‡‡, very significant from baseline values, intragroup analysis of variance for repeated measures with Bonferroni's correction.
Results are mean values ± SE.

the esmo group than in the remi and snp groups ($P < 0.01$) (Figure 1b).

Heart rate decreased from baseline (Figure 1c) by 21 ± 5% ($P < 0.001$) in the remi group, by 10 ± 5% in the esmo group (not significant intergroup), and it increased by 29 ± 9% ($P < 0.001$) in the snp group ($P < 0.01$, snp vrs remi group; $P < 0.001$, snp vrs esmo group).

Delay in onset of hypotension was longer in the remi group, 52.5 ± 4.7 sec, than in the snp group, 35 ± 2 sec ($P < 0.01$), or than in the esmo group, 40 ± 0.1 sec ($P < 0.05$)(Table II). Delay in onset of variation of MEBF was not different among groups, 22.6 ± 4 sec, 23.6 ± 3.1 sec, 25 ± 2.8 sec in the remi, snp and esmo groups, respectively, and was shorter than delay in onset of hypotension in the three groups ($P < 0.01$ in each group). Time delay between onset of variations of MEBF and onset of hypotension was 30 ± 6.1 sec in remi group, 11.2 ± 3.1 sec in snp group, 15 ± 2.8 sec in esmo group (Table II). No relationships were found between hemodynamic data within the groups (Table III). The Ga value decreased in the remi group (0.36 ± 0.1) and in the snp group (0.19 ± 0.2) less than in the esmo group (-0.5 ± 0.2; $P < 0.01$ and NS respectively).

In the second part of the study, during surgery, hypotension was sustained at the target systolic arterial blood pressure of 80 mmHg in the three groups without any difference among groups (Figure 2). The surgical field rating decreased from baseline in the three groups without any significant difference among groups (Figure 2).

There were no differences within and between groups in PaO_2 and in lactate, while $PaCO_2$ was higher and pH was lower and were slightly impaired but not critically, in snp group than in remi or in esmo group during hypotension and in the recovery room (Table IV).

There were no postoperative complications in any group, and all patients were discharged the first postoperative day.

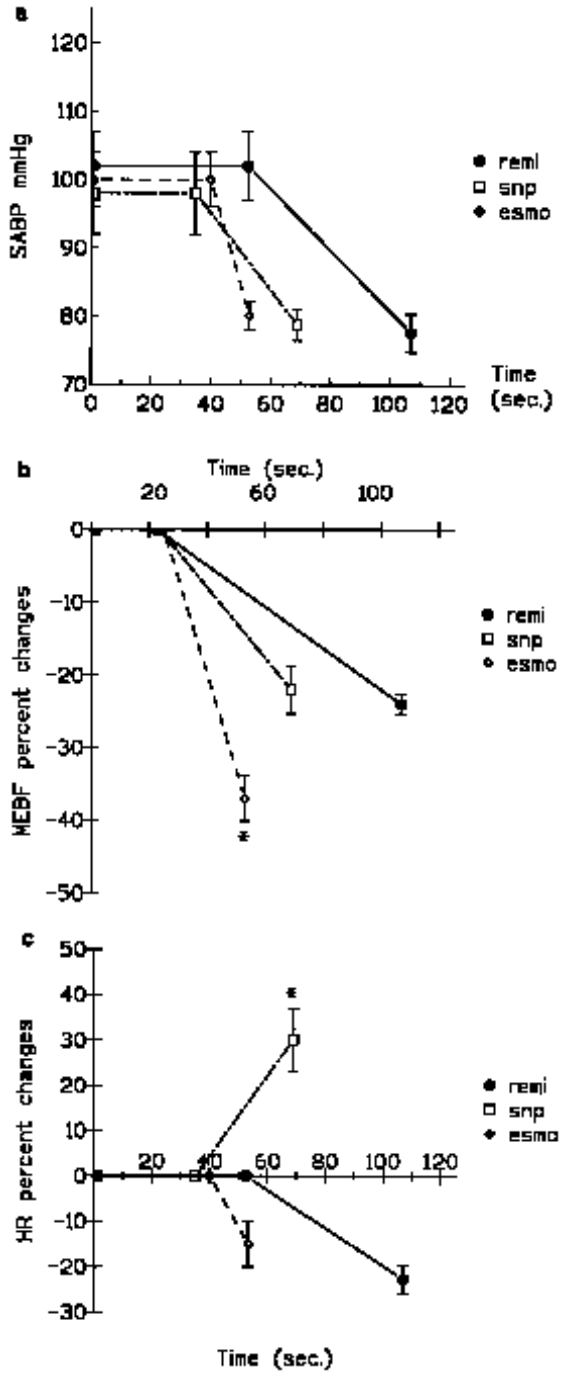

FIGURE 1 (a) Systolic arterial blood pressure (SABP), (b) Middle ear blood flow (MEBF), and (c) Heart rate (HR), were plotted against *Time in seconds* for patients receiving either remifentanil (remi), or sodium nitroprusside (snp), or esmolol (esmo) for *reaching hypotension* at the target systolic arterial blood pressure of 80 mmHg. N=10 in each group. Results are mean ± SE. **P* < 0.01, MEBF in esmolol group was very significantly different from the other two groups, and HR in nitroprusside group was very significantly different from the other two groups; intergroup Mann-Whitney U-test.

TABLE III Relationships between middle ear blood flow and systolic arterial blood pressure or heart rate. Least squares regression analysis, $P < 0.05$ significant.

		Remifentanil group n=10	*Nitroprusside group n=10*	*Esmolol group n=10*
- MEBF as a function of SABP:				
at SABP 80	r	0.49	0.15	0.09
	P	0.22	0.74	0.87
- MEBF as a function of HR:				
at SABP 80	r	0.55	0.11	-0.46
	P	0.15	0.81	0.43

The slopes are not significantly different from zero.
MEBF, middle ear blood flow; HR, heart rate; SABP 80, same legend as for Table II.

TABLE IV Metabolic data

	T0	*T+30 min*	*T+45 min*	*Trecovery*
PaO_2 mmHg				
remi	178 ± 11	180 ± 10	178 ± 9	140 ± 9
snp	183 ± 12	168 ± 12	172 ± 9	122 ± 8
esmo	182 ± 12	177 ± 10	180 ± 8	138 ± 9
$PaCO_2$ mmHg				
remi	36 ± 0.7	33 ± 0.6	32 ± 0.8	40.2 ± 0.6
snp	37 ± 0.5	42 ± 0.9*	41 ± 0.8*	43.5 ± 1.7*
esmo	36 ± 0.7	32 ± 0.9	32 ± 0.7	40.3 ± 0.7
pH				
remi	7.37 ± 0.04	7.39 ± 0.03	7.38 ± 0.04	7.4 ± 0.01
snp	7.37 ± 0.05	7.31 ± 0.02*	7.30 ± 0.03*	7.28 ± 0.05*
esmo	7.38 ± 0.04	7.39 ± 0.02	7.38 ± 0.04	7.4 ± 0.02
Lactate $\mu mol \cdot l^{-1}$				
remi	1.1 ± 0.3	1 ± 0.2	1 ± 0.3	1 ± 0.2
snp	1 ± 0.3	1.2 ± 0.3	1.1 ± 0.3	1 ± 0.2
esmo	1.1 ± 0.3	1 ± 0.2	1 ± 0.2	1 ± 0.1

**P* < 0.05, sodium nitroprusside *vs* remifentanil or esmolol, intergroup comparison, Mann-Whitney U-test; remi, remifentanil group; snp, sodium nitroprusside group; esmo, esmolol group; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide. Trecovery, 20 min after end of surgery in the recovery room. N=10 in each group. Results are mean ± SE.

Discussion

The main findings of the present study were that remifentanil hydrochloride, an ultra-short acting μ-opioid receptor agonist, which is currently known to have a hypotensive side-effect during a propofol total-intravenous anesthesia: a) was effective in inducing consistent and sustained controlled hypotension: b) was effective in reducing middle ear blood flow: and c) was effective in providing a "dry" surgical field during tympanoplasty with no need for additional use of a potent hypotensive agent. Remifentanil was as effective as esmolol or as sodium nitroprusside in reaching the target systolic arterial blood pressure of 80

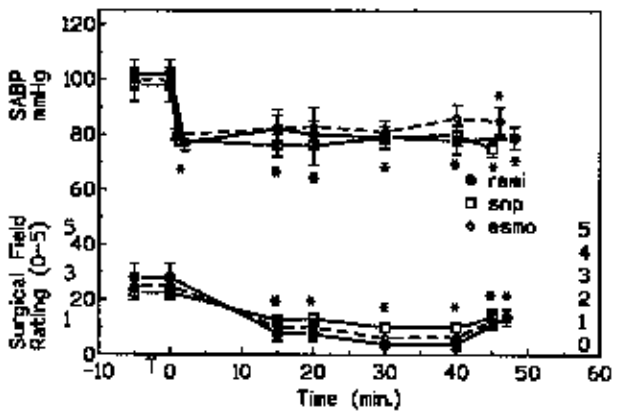

FIGURE 2 Systolic arterial blood pressure (SABP), and surgical field rating were plotted against *Time in minutes* for patients receiving either remifentanil (remi), or sodium nitroprusside (snp), or esmolol (esmo) for *maintaining controlled hypotension* at systolic arterial blood pressure of 80 mmHg. N=10 in each group. Results are mean ± SE.
* $P < 0.01$ very significantly different from baseline in each group; intragroup analysis of variance for repeated measures with Bonferroni's correction where indicated.

mmHg. Controlled hypotension with either remifentanil, or esmolol, or nitroprusside ensured "good operative conditions".

The hemodynamic data for nitroprusside and esmolol are in agreement with those previously reported in middle ear surgery[3,5,7] and in other surgery.[11,20–22] Advantages and disadvantages of sodium nitroprusside for deliberate hypotension which include potency and short duration of action, and reflex tachycardia, tachyphylaxis, rebound hypertension, potential for cyanide toxicity, have been discussed several previous studies.[3,9,10,23,24] Esmolol-induced hypotension was considered safer and more effective than nitroprusside despite myocardial failure risk at high doses.[11,20–22] Nevertheless, they are probably the most commonly used in clinical practice without any inconvenience. In many experimental studies, they serve as the gold standard to test new drugs and improve techniques of deliberate hypotension. Advantages of remifentanil for controlled hypotension, shown by the present study, include a short delay of action, an ability to ensure a satisfactory operative field, hemodynamic stability and safe anesthesia by limiting surgical stress and pain. Another advantage of remifentanil in propofol-TIVA revealed by the present study was the absence of humoral disturbance; on the contrary of remifentanil or esmolol, sodium nitroprusside involved light but significant hypercapnia and acidosis as has been previously described[10] and as was expected. The evident benefit of remifentanil for middle ear surgery shown by the present study, was the reduction of middle ear blood flow in a range of 25% and the dryness of the operative field obtained by a reduction in heart rate, blood pressure, and microcirculatory autoregulation. The mechanisms responsible for the control of middle ear blood flow act to modulate vessel tone via extrinsic (blood pressure, autonomic nervous system), or local factors (autoregulation). Autoregulation refers to the ability of an organ to maintain flow delivery relatively constant despite variations in blood pressure. An autoregulatory mechanism presumably exists for the control of middle ear blood flow, and was not fully suppressed in the present study by remifentanil, nitroprusside or esmolol, as demonstrated by, first, the Ga values and, second, by the non-linearity of the blood pressure-middle ear blood flow relationship. Techniques that reduce blood flow and induce a dry operative field must take into account mechanisms of control of the microcirculation; autoregulation may act as a local protective mechanism to ensure minimal tissue metabolism and so, may act against excessive and deleterious reduction of blood flow. In the esmolol group, autoregulation was not easy to interpret (Ga<0); large variations in middle ear blood flow were accompanied by small variations in blood pressure. In the three groups, middle ear blood flow varied before blood pressure as indicated by the time delay (Table II). The link between the two phenomena was very weak. In earlier studies that we performed on skin blood flow, we observed the same phenomenon, i.e., skin blood flow varied before blood pressure and heart rate.[25–27] In the present study, a target pressure of 80 mmHg was chosen to define hypotension in order to preserve "protective" autoregulatory mechanisms of cochlear blood flow that exist above this value;[28,29] below this level, the blood flow correlates with the arterial blood pressure.[28] The hypotensive effect of nitroprusside, esmolol and remifentanil on middle ear blood flow was a balanced result between their direct cardiac effect and/or vasomotor effect and the vasomotor drives originating from the counter-regulatory responses. The hypotensive mechanism with nitroprusside is peripheral vasodilation,[21] because it acts directly on the vascular smooth muscle.[10] In contrast, the hypotensive effect of esmolol is due to a profound decrease in cardiac output[21] that exceeds the reductions in both blood pressure and heart rate. In the present study, the hypotensive mechanism with remifentanil resembles esmolol by means of reduction in heart rate. Current studies[6,11] have shown that induced hypotension either with nitroprusside or with a beta-blocking agent enhanced norepinephrine, endocrine and metabolic

responses of small magnitude during middle ear microsurgery; this attested that there was an increase of the sympathetic tone[4,22] leading to vasoconstriction of arterioles and precapillary sphincters that resulted from unopposed alpha-adrenergic effects during esmolol or remifentanil hypotension. Because the effect of nitroprusside is directly on vascular smooth muscle, norepinephrine has little effect on arterioles in the presence of nitroprusside. Lack of relationships between hypotension, heart rate and middle ear blood flow observed in the present study and in a previous one[4] could be explained by autoregulation,[28] altered baroreceptor activation,[30] enhanced sympathetic nerve activity[6] and/or renin angiotensin secretion.[5] Reduction of heart rate and hypotension with remifentanil and esmolol could account for the impairment of baroreflex regulatory mechanisms caused by propofol.[30] Total intravenous anesthesia with remifentanil and propofol is known to induce hypotension and bradycardia compared with propofol and alfentanil.[15,17] In the present study, the role of alfentanil can be ruled out; middle ear blood flow autoregulation decreased and was not supressed in the group receiving alfentanil and sodium nitroprusside. The relative disturbance of middle ear blood flow autoregulation caused by remifentanil and alfentanil in the present study, is similar to that previously described at the level of the cerebral autoregulation in anesthetized dogs.[31] Our data did not reveal which of several mechanisms of middle ear blood flow regulation may be operative and provided no insight into the mechanisms by which anesthetics influence autoregulation. It was not the aim of this work, and further studies are needed to explore these phenomena. The infusion rates of propofol and remifentanil used in this study were those normally used for maintenance of anesthesia and showed efficacy and safety as previously described.[12,14,15,16]

In conclusion, the present study showed that remifentanil combined with propofol in a propofol-TIVA, was interesting in reducing middle ear blood flow and providing good surgical conditions in terms of quality of operative field and provided convenient induced hypotension for tympanoplasty with no need for additional use of a potent hypotensive agent.

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