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Anesthetic Depth Defined Using Multiple Noxious Stimuli during Isoflurane/Oxygen Anesthesia

I. Motor Reactions

A. M. Zbinden, M.D., M. Maggiorini, M.D.,† S. Petersen-Felix, M.D.,‡ R. Lauber, Ph.D.,§*
D. A. Thomson, M.D., Ph.D., F.R.C.Anaes.,‖ C. E. Minder, Ph.D.#

Background: **Potency of inhaled anesthetics usually is defined by determining the minimal alveolar concentration (MAC) that prevents movement in 50% of patients in response to skin incision. Skin incision, however, is usually only a single event and, thus, determination of potency cannot be repeated in one patient. Traditional $MAC_{skin\ incision}$ cannot be used to predict response to other noxious stimuli. The aim of this study was to investigate the effects of other noxious stimulation patterns and then compare these to $MAC_{skin\ incision}$ measuring the end-tidal isoflurane concentrations with the corresponding arterial concentrations.**

Methods: **In 26 patients, the end-tidal and corresponding arterial isoflurane concentrations needed to suppress eye opening to verbal command and motor response after trapezius squeeze, 50 Hz electric tetanic stimulation, laryngoscopy, skin incision, and tracheal intubation in 50% of all patients were determined.**

Results: **The end-tidal (equivalent arterial) isoflurane concentrations (mean ± SE, adjusted to sea level) expressed in vol% (to allow comparison) increased in the following order (mean ± SE): vocal command 0.37 ± 0.09 (0.36 ± 0.09); trapezius squeeze 0.84 ± 0.07 (0.65 ± 0.07); laryngoscopy 1.00 ± 0.12 (0.78 ± 0.09); tetanic stimulation 1.03 ± 0.09 (0.80 ± 0.06); skin incision 1.16 ± 0.10 (0.97 ± 0.17); and intubation 1.76 ± 0.13 (1.32 ± 0.11).**

Conclusions: **Different stimuli require different isoflurane concentrations to suppress motor responses. Tetanic stimulation and, to some extent, trapezius squeeze are reproducible and noninvasive stimulation patterns that can be used as an alternative to skin incision when evaluating potency of an anesthetic agent. In contrast to skin incision, they can be repeated. (Key words: Anesthetic techniques: tetanic stimulation; tracheal intubation; trapezius stimulation. Anesthetics, volatile: isoflurane. Potency: motor reaction.)**

MINIMUM alveolar concentration (MAC) is defined as the minimum steady-state alveolar concentration of an inhalational anesthetic required to suppress a gross purposeful motor reaction in 50% of patients (Cp_{50}) to a skin incision.[1–3] This concept is considered the standard for determination of anesthetic potency. The MAC value has been determined for various agents,[4] in different age groups,[5] in humans as well as in animals. MAC determinations usually cannot be repeated, because the skin incision is usually a single event during an operation in an individual. Thus, the determination of an individual MAC value in one patient is not possible, and any change of this value cannot be followed during anesthesia. The Cp_{95} value (no response in 95% of all patients)—although clinically more relevant—is seldom used. An ideal stimulation pattern to determine anesthetic potency should be well defined, be easy to perform, be repeatable, show consistent results, and cause no harm to the patient. $MAC_{intubation}$ (intubation) has been determined for halothane[6] and enflurane,[7] but not yet for isoflurane. The response to stimulation patterns such as trapezius squeeze, tetanic electrical stimulation, and laryngoscopy without intubation has been investigated systematically for thiopental[8] but not for inhaled anesthetics. The objective of this study was to determine the relationship of

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* Head of Section of Research.
† Resident.
‡ Staff Member.
§ Biochemist.
‖ Chairman and Professor of the Institute.
Statistician.

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Address reprint requests to Dr. Zbinden: Institute for Anesthesiology and Intensive Care, Section of Research, University Hospital, 3010 Bern, Switzerland.

the end-tidal (F_e) or arterial fraction (F_a) of isoflurane at several clinically relevant noxious stimuli and then compare the values obtained with the concentrations associated with the response to skin incision. The stimulation patterns used were vocal command, trapezius squeeze (manual squeeze of the trapezius muscle), electrical tetanic stimulation of the muscles of the forearm, skin incision, laryngoscopy, and tracheal intubation.

Materials and Methods

The study was approved by the ethical committee of the Medical Faculty of the University of Bern. Written informed consent was obtained from 26 patients (ASA physical status 1, age 39.7 ± 11.4 yr, 9 men and 17 women, weight 67 ± 11 kg, height 169 ± 7 cm; mean ± SD) scheduled for elective abdominal surgery. They received 0.005 mg/kg intramuscular glycopyrrolate 1 h before the start of anesthesia. Exclusion criteria were age older than 55 or younger than 20 yr, a history of coronary heart disease, hypo- or hypertension, drug or alcohol abuse, opioid medication, and an expected or measured blood loss of more than 500 ml. The patients received an infusion of Ringer's solution (2 $ml \cdot kg^{-1} \cdot h^{-1}$ before the peritoneum was opened and 10 $ml \cdot kg^{-1} \cdot h^{-1}$ during the rest of the operation). After breathing oxygen for 3 min, each patient took one deep breath of a mixture of 4% isoflurane in oxygen and held their breath as long as possible.[9] Thereafter, the patients breathed, through a tightly fitting mask, a gas mixture of isoflurane in oxygen from a semiclosed circle system (Sulla with an ISO 8 circle system, Drägerwerke, Lübeck, Germany). A fresh gas flow of 3 l/min oxygen was used. All patients were operated upon while supine. The following variables were monitored: electrocardiogram, intraarterial blood pressure, body temperature (rectal), end-tidal carbon dioxide, and isoflurane concentrations at the Y-piece using an infrared sideline analyzer (Capnomac Datex, Helsinki, Finland). When the patient was breathing *via* mask, the aspirating tube was placed into the gas space under the mask to obtain a "representative" alveolar gas sample. The signals of isoflurane and carbon dioxide concentration were digitized at 5 Hz and stored on the hard disk of an IBM-compatible personal computer. Arterial blood was withdrawn from a radial artery catheter before each stimulation, and the arterial isoflurane concentration was measured with a gas chromatograph with a FID detector using a previously described head space technique.[10]

Arterial blood gases, hemoglobin, hematocrit, and the blood/gas solubility coefficient of isoflurane[10] were measured at the beginning, at intubation, 1 h after intubation, and at the end of the operative procedure. These data were collected after the end-tidal isoflurane concentration had been maintained constant during 15 min after induction or during 10 min after each change of concentration during the maintenance periods.

The arterial concentration of isoflurane was determined at 10, 13, and 15 min during the initial equilibration time and 5, 8, and 10 min before all the other stimulations. Preoperatively, the patients were breathing spontaneously and, if needed, ventilation was manually assisted. The end-tidal carbon dioxide concentration was maintained at 5.5 vol% throughout the study—during spontaneous ventilation by manual assistance, if needed. After the 10-min equilibration period, at a randomly chosen end-tidal concentration of isoflurane, a defined series of stimulations was performed: supramaximal tetanic stimulation of the muscles of the forearm with 10-s bursts of 50 Hz 50 mAmp electric current from a nerve stimulator (Digistim III, Neuro Technology, Houston, TX) the output of which had been measured previously, using electrodes mounted on the skin in the middle of the ulnar side of the forearm; a manually applied squeeze of the trapezius muscle always executed by the same anesthesiologist; laryngoscopy performed to the point when the vocal cords could be inspected; laryngoscopy plus intubation; skin incision; and repeated vocal commands to open the eyes at the end of the operation. For the latter stimulation, equilibration was achieved by adjusting the fresh gas flow to the breathing circuit so that the inspired isoflurane concentration decreased at a defined rate of 0.02 vol%/min. The stimulations were performed in the following order: trapezius squeeze, tetanic stimulation, laryngoscopy, intubation, and skin incision. To avoid excessive reactions (for example laryngospasm), laryngoscopy and intubation were not tested at low concentrations. Intubation and skin incision were tested only once before the surgical procedure, whereas trapezius squeeze, tetanic stimulation, and laryngoscopy could be tested several times at different isoflurane concentrations both before and after the operation. Vocal command was tested only at the end of anesthesia. Intubation and skin incision could not be tested in all patients in all concentrations, because in some patients a vigorous motor reaction occurred during preceding

Table 1. Blood Gas, Hematocrit, Temperature, and Blood/Gas Partition Coefficients (λ) for Isoflurane Values at Various Stages of Anesthesia (Mean ± SD)

Period	*p*H	P_{CO_2} (mmHg)	P_{O_2} (mmHg)	BE (mol/l)	Hematocrit (%)	Temperature (° C)	$\lambda_{blood/gas}$
Start	7.39 ± 0.03	43 ± 4	27 ± 12	1.3 ± 2.0	37 ± 5	36.6 ± 0.5	1.39 ± 0.06
Intubation	7.37 ± 0.03	4 ± 4	36 ± 38	1.0 ± 1.7	37 ± 5	36.5 ± 0.5	1.38 ± 0.08
1 h after intubation	7.40 ± 0.04	40 ± 5	354 ± 103	0.8 ± 2.1	37 ± 5	36.0 ± 0.8	1.35 ± 0.06
End of anesthesia	7.38 ± 0.05	41 ± 6	320 ± 117	−0.24 ± 2.5	38 ± 5	35.8 ± 0.8	1.30 ± 0.08

stimulations at concentrations higher than that to be evaluated or started to move spontaneously even before the stimulation occurred. Trapezius squeeze, tetanic stimulation, laryngoscopy, and intubation were performed during spontaneous breathing preoperatively, all other stimulations after tracheal intubations. Each series of stimulations was performed after the equilibration period following each change in gas concentration or after the motor and the hemodynamic reactions caused by the previous stimulation had returned to the prestimulation conditions. All stimulations except skin incision were performed during conditions of no surgical stimulation. At each of these stimulations, an eventual motor response was noted and classified as positive if the patient showed a gross purposeful movement. Swallowing and—when tetanic stimulation was applied—a slight movement of the shoulder and/or the arm of the stimulated side during stimulation were not classified as positive responses. The reaction to skin incision and verbal command were tested only in the patient when the trachea was intubated. The total number of stimulations with each pattern varied slightly between patients, because at some (low) concentrations, certain stimulation patterns could not be tested, to avoid excessive reactions.

Responses always were observed by the same team. After performing a set of stimulations, the isoflurane concentration was increased by 0.1–0.2 vol% if the reactions had appeared very strong; otherwise, the isoflurane concentration was decreased, and the stimulations were repeated. Thus, most stimulation patterns were tested several times at different concentrations in each patient, except for vocal command, skin incision, and intubation. End-tidal concentration was not allowed to increase above a level that depressed mean arterial blood pressure to less than 50 mmHg. Apart from vecuronium given after skin incision and 2.5 mg neostigmine and 0.5 mg intravenous glycopyrrolate after skin closure no other drugs were given. Reversal of muscle relaxation was confirmed using standard train-of-four stimulation.

All gas concentrations are expressed in vol%, whereas those in blood are expressed as the concentrations measured in a gas space being equilibrated with the blood sample. Because the investigations were performed at an altitude of approximately 500 m, the obtained concentration values have to be divided by 1.065 to allow comparison to studies performed at sea level. Concentration-response data were processed applying a logistic function[11] using the software package (Glim 3.77, NAG, Oxford, United Kingdom). Standard errors of the Cp_{50} values were computed with the same package and those of the Cp_{95} values by using a bootstrapping method.[12] The Cp_{50} and Cp_{95} values obtained before operation were compared using F-tests.

The coefficient of variation was computed as a measure of precision of the measurements, and an analysis of variance was used to check for the effect of stimulation patterns. A significance level of $P < 0.05$ was applied for all tests.

Consistency of motor reactions to the same type of stimulation at various concentrations in one patient was evaluated by assigning a reaction the value of 1 if a motor reaction occurred at lower concentrations, whereas no reaction could be observed at high concentrations; if the reverse happened, the value of 0 was assigned. The mean (%) of these assigned values then was used as a measure of consistency for the individual reaction.

Results

Induction of anesthesia preceded skin incision and eye opening upon command by 121 ± 35 and 318 ± 62 min (mean ± SD), respectively. Blood gases and hemoglobin concentrations did not change significantly; body temperature measured rectally decreased from 36.6 ± 0.4° C at the beginning to 35.8 ± 0.8° C

at the end of the procedure. The blood/gas solubility coefficient was 1.39 at the beginning of anesthesia and 1.30 at the end of anesthesia ($P > 0.05$; table 1). None of the patients exhibited signs of awareness during the operation or complained of awareness after surgery. After induction, a stable arterial end-tidal isoflurane gradient was established within a 15-min equilibration period. The F_a/F_e-values (mean values ± SD) were 0.75 ± 0.11 (10 min), 0.75 ± 0.13 (13 min), and 0.78 ± 0.12 (15 min). During the rest of the procedure, a 10-min equilibration period after each step change of the concentration was considered sufficient because a constant arterial-to-end-tidal partial pressure ratio of 0.90 ± 0.16 (5 min), 0.89 ± 0.15 (8 min), and 0.89 ± 0.14 (10 min) could be observed. The mean F_a/F_e ratio was significantly greater in patients whose tracheas were intubated (0.93 ± 0.15, mean ± SD) compared to when breathing spontaneously or assisted *via* a mask (0.77 ± 0.1; $P < 0.05$). A plot of the end-tidal *versus* the arterial isoflurane concentration showed a slope of 1.1 with an intercept 0.18 when the patients were breathing through the mask and 1.1 and 0.02, respectively, in patients in whom the trachea was intubated (fig. 1).

The responses to different stimulations at various concentrations of isoflurane are shown in table 2 and in figure 2. The Cp_{50} values increased in the order of vocal command < trapezius squeeze < laryngoscopy = tetanic stimulation < skin incision < intubation. As $MAC_{trapezius\ squeeze}$ had a relatively low concentration value, this stimulation pattern could not always be tested, because patients sometimes started to move spontaneously or had other untoward reactions (*e.g.*, laryngospasm). $MAC_{intubation}$ on the other hand required very high isoflurane concentrations and, even then, patients reacted excessively (coughing, blood pressure increase by more than 50%). MAC values generally were higher preoperatively compared to after the operation, but a significant difference could be found only for the Cp_{50} end-tidal concentrations of the trapezius and tetanic stimulation, for the Cp_{50} arterial concentrations of the tetanic stimulation, and for the Cp_{95} end-tidal concentration for tetanic stimulation.

Consistency of motor reactions to various types of stimulations was 99%, *i.e.*, no patients showed motor reactions at high concentrations and failed to move at lower concentrations when stimulated with a specific stimulation pattern.

Discussion

The $MAC_{skin\ incision}$ values found in this study (1.24 ± 0.10, 1.16 when corrected to sea level) confirm the results of previous studies in adult patients (1.15 ±

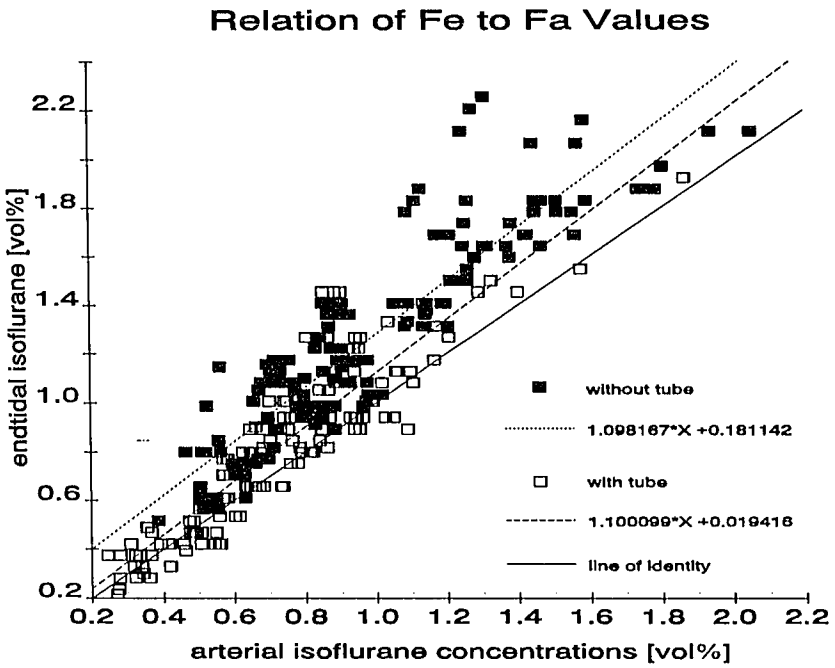

Fig. 1. End-tidal isoflurane concentration (vol%) related to arterial concentration (expressed as vol% of a gas space in equilibration with blood compartment) while breathing with mask (■) or through endotracheal tube (□). The end-tidal/arterial gradient is higher when breathing by mask.

Table 2. Cp_{50} (vol %; mean and SE) and Cp_{95} for Isoflurane to Prevent Motor Response to Various Stimuli before and after Operation

Stimulation	Before/After Operation	Frequency Distribution of Stimulus Measurements: No. of Patients (n)	Frequency Distribution of Stimulus Measurements: Measurements (n)	End-tidal Concentration (vol%): Cp_{50} / Cp_{95}	End-tidal Concentration (vol%): SE_{50} / SE_{95}	End-tidal Concentration (vol%): Coefficient of Variation (%)	End-tidal Concentration (vol%): Slope	Arterial Concentration (vol%): Cp_{50} / Cp_{95}	Arterial Concentration (vol%): SE_{50} / SE_{95}	Arterial Concentration (vol%): Slope
Vocal command	After	20	1	0.39	0.09	21.1	—	0.39	0.09	—
Trapezius	Before	9	1	0.90	0.07	8.1	6.7	0.70	0.07	7.3
		9	2							
		5	3	1.34	0.14	10.7		1.10	0.13	
		0	4							
	After	2	1	0.62	0.09	14.9	5.1	0.56	0.10	5.0
		8	2							
		7	3	1.19	0.19	15.5		1.15	0.21	
		2	4							
Laryngoscopy	Before	11	1	1.07	0.12	11.6	3.2	0.83	0.09	4.6
		10	2							
		5	3	1.99	0.31	15.7		1.47	0.22	
		0	4							
	After	4	1	1.00	0.10	10.0	3.8	0.90	0.08	4.7
		6	2							
		7	3	1.77	0.37	21.1		1.53	0.31	
		2	4							
Tetanus	Before	8	1	1.10	0.09	8.2	3.8	0.85	0.06	6.1
		12	2							
		6	3	1.87	0.26	13.8		1.33	0.16	
		0	4							
	After	4	1	0.78	0.07	8.9	5.1	0.70	0.06	4.6
		7	2							
		9	3	1.35	0.19	14.1		1.37	0.24	
		2	4							
Skin incision	Before	17	1	1.24	0.10	7.9	6.3	1.04	0.13	4.4
				1.70	0.23	13.3		1.71	0.40	
Intubation	Before	20	1	1.87	0.13	6.8	4.7	1.40	0.11	5.6
				2.50	0.34	13.5		1.92	0.29	

Values are not adjusted for sea level. The coefficient of variation was calculated as SE_{50} or SE_{95}/Cp_{50} or $Cp_{95} \times 100\%$.

0.06).[13] $MAC_{intubation}$ has been evaluated for halothane[6] and enflurane.[7] The difference between $MAC_{laryngoscopy}$ and $MAC_{intubation}$ was higher than earlier reported by Yakaitis *et al.*[6] for halothane. Differences in sampling techniques (end-tidal concentration measurements at the tip of the tube after intubation[6]) and different criteria for rating a movement as a positive or negative response may explain this difference. The present study showed that laryngoscopy followed by intubation was the strongest stimulus, confirming the results of a previous study in which thiopental was used.[8] The value for $MAC_{vocal\ command}$ (frequently termed MAC_{awake}; 0.39 ± 0.08 vol%) compares well with that found in another study by a comparable method (0.31 ± 0.04 vol%).[14] Stoelting *et al.*,[15] using two different methods, found a $MAC_{vocal\ command}$ for halothane of 0.41 ± 0.05 vol% and 0.33 vol%, respectively. Although end-tidal concentrations during this study were frequently very low

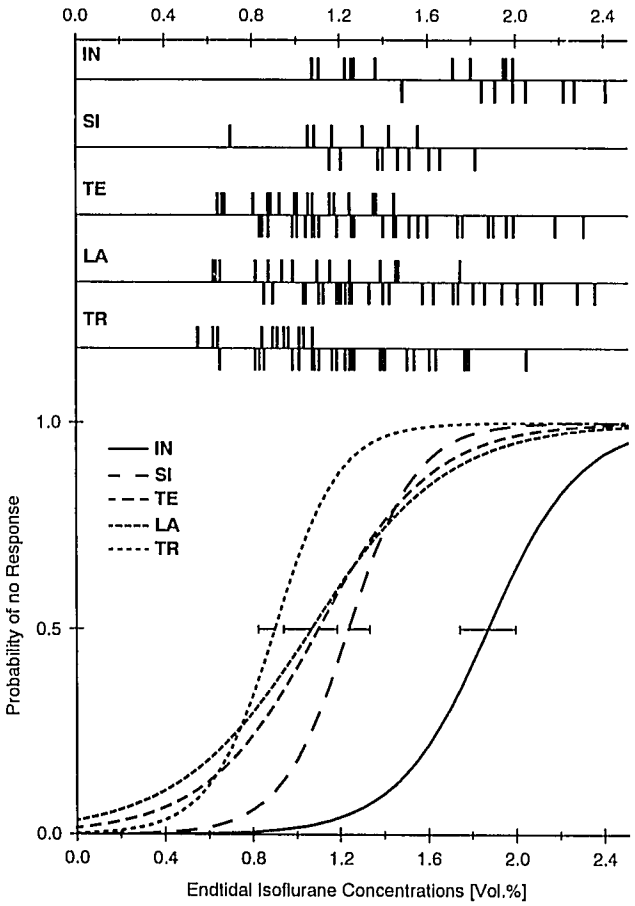

Fig. 2. Logistic regression curves using end-tidal concentrations and stimulations performed preoperatively. For the Cp_{50}, mean values and the standard error bars are shown. In the upper section, each line above the horizontal line represents movement; a line below represents no movement to stimulation. IN = intubation; LA = laryngoscopy; SI = skin incision; TE = tetanus; TR = trapezius squeeze.

(never below 0.4 vol% except at the end of the study), there were no complaints of awareness. Another investigation in unstimulated volunteers found that recall and recognition was lost at 0.2 MAC isoflurane.[16] This indicates that isoflurane at 0.4 vol% end-tidal concentration or higher will prevent recall, even if no other drugs are used. Vocal command is the least intense stimulus, followed by trapezius squeeze, tetanic stimulation, laryngoscopy, skin incision, and intubation. Intubation and vocal command are the only stimulation patterns in which the concentration values are significantly different from those of the other stimuli. $MAC_{skin\ incision}$ is also different from the other patterns but only when arterial concentrations are used.

An ideal stimulation pattern should comply with the following criteria: easy to perform, harmless to the patient, repeatable, allow a precise measurement of potency, and allow measurement of depth of anesthesia.

The stimulation patterns used in the present study are different, both in terms of producing a standardized stimulation and of measuring its effect. Obviously, all stimulations have to be performed in the nonparalyzed patient if motor response is to be evaluated. Vocal command should be applied at the end of anesthesia. The end-tidal concentration should be decreased at a defined rate, which can be achieved by adjusting the fresh gas flow when a semiclosed circuit is used. In the study by Stoelting *et al.*,[15] the concentration was decreased in a stepwise fashion, and the concentration between the values just preventing and just permitting the response was used. Another method used by Stoelting *et al.* was to allow the patients to breathe room air spontaneously, allowing the concentration to decrease at an uneven rate; gas was sampled every 3–5 min, and the average calculated between the concentration at the response and that of the last sample obtained before the response. The $MAC_{vocal\ command}$ determined in this way is not a "true" MAC determination because a logistic regression of a yes/no response is not performed. Therefore, no dose-response curve can be obtained, rather only an average value is obtainable at the concentration, when the patients open their eyes. For the other MAC values, random concentrations of isoflurane were chosen, and a positive or negative reaction to stimulation was observed. Trapezius squeeze is technically easy to perform. To obtain some consistency of stimulus intensity, it should be executed by the same person, as was done in this study. The response to trapezius squeeze has been determined for thiopental in anesthetized patients of various age groups, but the responses were not consistent and thus the MAC-value could not be computed.[17] In the present study, consistent responses to trapezius squeeze could be observed except at the low concentration ranges, when the patients started to move spontaneously (this problem also occurs when measuring $MAC_{vocal\ command}$). Tetanic stimulation needs a well defined electrical current and a standardized method of electrode placement. It has been used in place of skin incision in a nonstandardized fashion**,[18–21] but was never evaluated sys-

** Schultz A, Katz R, Pavlin E: A comparison of ulnar nerve tetanic stimulation and clamping of anterior axillary fold to surgical incision for the determination of MAC (abstract). ANESTHESIOLOGY 67:A669, 1987.

tematically. In the study of Saidman and Eger,[18] 1.2 ms pulses of 30–45 V at 50 Hz for a maximum of 1 min applied through two 20-G needles inserted through the skin of the forearm were used. The $MAC_{tetanic\ stimulation}$ obtained for halothane by this method was apparently lower than $MAC_{skin\ incision}$. On the other hand, Hornbein *et al.*[19] used 100-Hz square wave pulses of 0.17 ms duration at 80–110 V during 10 s using needle electrodes placed close to the ulnar nerves at both wrists to determine MAC for nitrous oxide. A current of 50 mA has proved sufficient to cause supramaximal stimulation.[20] A 100 Hz, supramaximal stimulus has been shown to correspond to $MAC_{skin\ incision}$** of halothane, which stands in contrast with the above cited study by Saidman and Eger[18] and the present study, in which $MAC_{skin\ incision}$ was higher than $MAC_{tetanic\ stimulation}$. Evaluating the response to tetanic stimulation may be difficult: In this study a mass reflex evolving from the forearm muscles under tetanic stimulation was not considered a positive reaction. Laryngoscopy and intubation have been determined for both inhaled[6,7] and intravenous[22] anesthetics. Both stimuli may be difficult to use in the nonparalyzed patient as they may provoke laryngospasm. Vocal command, trapezius squeeze, tetanic stimulation, and laryngoscopy can be performed in the patient whose trachea is intubated; this has the advantage of a safe airway.

The stimuli used caused no harm to the patient. Skin incision cannot be used in volunteers, and intubation also would be quite an invasive stimulation for volunteers. Laryngoscopy and intubation may cause excessive reactions such as laryngospasm in patients if isoflurane concentrations are very low. An excessive reaction at skin incision may disturb the surgical procedure.

Repetition of stimulation is possible with vocal command, trapezius squeeze, tetanic stimulation, and laryngoscopy. A significant effect of time could be found at least for the end-tidal Cp_{50} concentrations of tetanic and trapezius stimulation that were significantly lower than the preoperative ones. This finding contrasts with that of a previous publication[1] in which the authors conclude that MAC remains constant for 8 h; in contrast to our study, the measurements were started 1–2 h after induction of anesthesia, using halothane in dogs. A change of MAC over time could be explained by a change of the sensitivity of neurons to inhaled anesthetics over time. Another possibility is that the brain concentration was better equilibrated to the end-tidal concentration after compared to before the operation or that residual effects of muscle relaxation decreased MAC. In this study, brain concentration can be expected to equilibrate with end-tidal concentrations, because we allowed sufficient time for equilibration before each stimulation. Muscle relaxants may play a role for the diminished postoperative effect of tetanic stimulation, but it is unlikely that they affect the reaction to laryngoscopy or the hemodynamic effects.[23] Furthermore, reversal of muscle relaxation was confirmed by train-of-four stimulation. Solubility also slightly decreased over time despite unchanged hematocrit values. These changes in solubility with hematocrit remaining constant are contrary to the findings of Lerman *et al.*,[24] who observed a decrease of solubility over time with a concomitant decrease of hematocrit and three serum components (albumin, globulin, and cholesterol). A decrease in solubility of enflurane during cardiopulmonary bypass without correlating it to other blood components has been registered.[25] A change in solubility over time does not explain the decrease of MAC over time.

Precision of a measurement can be expressed by using the coefficient of variation. The coefficient varied between 8% and 23% for the end-tidal Cp_{50} values, being highest in response to vocal command (table 2). Precision depends not only on correct estimation of physiologic parameters of the patient but also on the stimulation technique and the measurement of the effect. Vocal command probably would have produced more consistent results if the verbal stimulation had always been exactly the same, *e.g.*, from a tape. Trapezius squeeze showed consistent results. The results might have improved if the force of the squeeze could have been measured and controlled. Skin incision is nearly impossible to standardize because it depends entirely on the size and place of the incision. Determination of whether a reaction is positive may be subjective, because not all reactions may be classified into "gross purposeful movement" as established in the original MAC concept. Even then, the coefficient of variation of skin incision was slightly lower (7.9%) than that of tetanic stimulation (8.2%). Laryngoscopy showed a high variability because stimulation during inspection of the vocal cords depends on the anatomy of the larynx; intubation shows the lowest variability (6.8%), probably because placing a tube into the trachea is a very defined and strong stimulation, irrespective of the preceding variable (and weak) stimulation caused by laryngoscopy. Most earlier investigators only measured the end-tidal concentration and thus did not account for the varying and unpredictable end-tidal/arterial

gradient.[26,27] A lower gradient was found when patients were breathing through a tube, possibly because dead space ventilation was decreased. Also, when arterial concentration was used to compute the Cp_{50} values, results did not show a lower variance, supporting the conventional MAC concept in which end-tidal concentrations are used.

The ultimate goal of these measurements was to try to provide measures of depth of anesthesia; however, that is not a defined entity. We conclude that, besides skin incision, other stimulation patterns such as tetanic stimulation can be used, because they better fulfill the criteria of an easily performed, repeatable, and harmless stimulation pattern.

This investigation shows how different noxious stimuli can be used to define anesthetic depth for isoflurane. They mirror other typical situations of clinical anesthesia and appear as clearly defined patterns that elicit a response at defined Cp_{50} values of isoflurane that are less, more, or equal to the known concentration needed to obtund the response to skin incision. Thus, skin incision is not a supramaximal stimulus. The advantage of trapezius squeeze and tetanic stimulation lies in ease of performance, repeatability, and reproducibility.

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