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

II. Hemodynamic Responses

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Background: **The hemodynamic effects of isoflurane have been studied extensively. However, most data are obtained from volunteers or patients in the absence of surgical stimulation. The hemodynamic responses to various stimulation patterns of different intensity have not been evaluated.**

Methods: **In 26 patients, the ability of isoflurane to suppress motor and hemodynamic reactions in response to noxious stimulations of variable degree (trapezius squeeze, tetanic stimulation, laryngoscopy, skin incision, and laryngoscopy plus intubation) was evaluated by measuring arterial blood pressure and heart rate before and after stimulation.**

Results: **At concentrations that inhibited motor response to these stimuli in 50% of all patients, systolic blood pressure increased by 9 (trapezius squeeze), 15 (tetanic stimulation), 23 (laryngoscopy), 35 (skin incision) and 49 (intubation) mmHg, and heart rate by 5 (trapezius squeeze), 15 (tetanic stimulation), 17 (laryngoscopy), 36 (skin incision), and 36 (intubation) min^{-1} compared to the prestimulation values. An analysis using multiple regression showed that blood pressure response was influenced most by the type of stimulation followed by the concomitantly occurring motor reaction, the anesthesia time, and least by the isoflurane concentration *per se*. A high isoflurane concentration had no influence on the magnitude of blood pressure or heart rate increase to stimulation, but it decreased the prestimulation blood pressure and slightly increased the prestimulation heart rate. Heart rate responses were less consistent than those of blood pressure.**

Conclusions: **Isoflurane used as a sole agent is unable to suppress hemodynamic reactions (blood pressure and heart rate) to painful stimuli. A "normal" blood pressure following stimulation can be achieved only if prestimulation blood pressure is depressed to levels that may be clinically unacceptable. The lack of motor response is not an accurate predictor of the ability of an agent to depress hemodynamic reaction. (Key words: Anesthetic techniques: tetanic stimulations; tracheal intubation. Anesthetics, volatile: isoflurane. Hemodynamics: blood pressure; heart rate.)**

BLOOD pressure and heart rate may increase considerably even at end-tidal isoflurane concentrations greater than those needed to obtund motor reaction in patients exposed to noxious stimuli. In patients who suffer, for example, from coronary heart disease, such hemodynamic responses may be dangerous. An ideal inhaled anesthetic should be able to suppress motor and hemodynamic reactions to surgery without overtly depressing the cardiovascular system. Isoflurane has been investigated in terms of its ability to depress motor response[1] and also, separately, in terms of depressing the cardiovascular system.[2] Motor effects have been investigated using a standardized surgical stimulation such as a skin incision[1] or following tracheal intubation (only for halothane[3] and enflurane[4]). Hemodynamic effects of isoflurane mainly have been investigated in unstimulated volunteers.[2,5] In another study, the concentrations of halothane and enflurane needed to blunt hemodynamic stress response to skin incision[6] were determined. The hemodynamic effects of other standardized stimulation patterns of various intensities have not yet been studied. This study determines the ability of isoflurane as the sole anesthetic agent to abolish or attenuate hemodynamic responses when various well defined painful stimulation patterns are applied before and after abdominal surgery using techniques similar to those used with intravenous agents.[7–9]

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Materials and Methods

The methods used in this study are described in the accompanying paper. 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. Exclusion criteria were age older than 55 or younger than 20 y, a history of coronary heart disease, hypo- or hypertension, drug or alcohol abuse, opioid medication, or an expected or measured blood loss of more than 500 ml. Anesthesia was induced and maintained with isoflurane in oxygen. End-tidal and arterial blood concentrations of isoflurane were determined before each of the below mentioned stimulations. Blood pressure was measured *via* a radial arterial catheter (20G Venflon) attached to a transducer (Utah DPT200). The damping and resonance properties of the system in use had been determined previously with the method described by Gardner.[10] The damping coefficient of the complete system was 0.25 and the natural frequency 21 Hz, thereby lying in the ideal sector as defined by Gardner.[10]

After an equilibration period of at least 10 min at a randomly chosen end-tidal concentration of isoflurane, the patients were exposed to a series of defined stimulations in the following order: manual squeeze of the trapezius muscle, tetanic electric stimulation of the forearm muscles with a 50 Hz 50 mAmp current, laryngoscopy with inspection of the vocal cords, laryngoscopy plus intubation, and skin incision. To avoid excessive reactions such as laryngospasm, laryngoscopy and intubation were not tested at lower isoflurane concentrations. Intubation and skin incision could be tested once before the operation and not in all patients (intubation: some of the patients had to be paralyzed because of difficult intubation conditions; skin incision: the surgical procedure was not exactly the same in all patients; postexperimental data evaluation revealed that reaction depended on the place and size of the incision). Trapezius squeeze, tetanic stimulation, and laryngoscopy were tested several times at different isoflurane concentrations before and after the surgical procedure. At the preoperative measurements for trapezius squeeze, tetanic stimulation, laryngoscopy, and intubation, the patients were breathing *via* mask. For all the other stimulations, the trachea of the patients was intubated. After a change in gas concentration, stimulations were performed after a 10-min equilibration period. Subsequent stimulations at the same gas concentration were performed only when the motor reaction of the previous stimulation had ceased and the blood pressure and heart rate values had reached prestimulation values. Except for skin incision, no other surgical stimulation was performed during the measurements. Immediately before each stimulation, end-tidal carbon dioxide, isoflurane and arterial concentrations, systolic arterial blood pressure, and heart rate were measured. After each stimulation peak, the maximal systolic arterial blood pressure and the heart rate were measured. Blood pressure data were sampled at a rate of 50 Hz, and data of carbon dioxide and isoflurane concentrations at 5 Hz. All data were stored in an IBM-compatible computer system. The digitized data were processed using a dedicated program that created a plot for each stimulation, as shown in figure 1. For systolic pressure, the peak value was used. The systolic blood pressure and the heart rate values before stimulation were averaged and recorded at 1-s intervals. To account for changes in blood pressure caused by respiration, half of the average amplitude of one pressure change before stimulation was subtracted from the peak value after stimulation (fig. 1). The mean of these values during the 2 min before stimulation was used as the prestimulation value. For the post-stimulation value, the maximum value after stimulation was taken, and half of the full amplitude of cyclic changes was manually subtracted.

A two-way analysis of variance was used to test for the effects of stimulation and time ("before/after op-

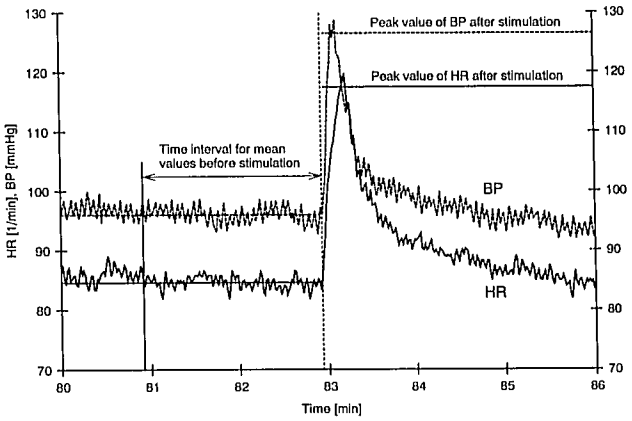

Fig. 1. An example of the computation of the systolic blood pressure (BP) and heart rate (HR) response observed in one patient after tetanic stimulation.

eration") on the increase of systolic blood pressure or heart rate after stimulation. Then each single comparison between either the type of stimulation or the effect of time (pre- or postoperative) was tested for significance taking into account the effect of multiple comparisons (Bonferroni's correction). A statistical package RS/1 Explore (Bolt Beranek) was used. A P value of 0.05 was used as significance limit.

Systolic blood pressure and heart rate values of all patients was correlated to the respective end-tidal isoflurane partial pressure using linear regression (figs. 2 and 3). Multiple regression was used to evaluate the influence on the absolute increase of blood pressure (in mmHg) or heart rate (beats/min) by the following parameters: the stimulation pattern, the time since start of anesthesia, the concomitant observation of a positive motor reaction and the end-tidal isoflurane concentration. The numeric values at each stimulation pattern were obtained by taking the average blood pressure (or heart rate) increase at the Cp_{50} value (end-tidal isoflurane concentration where 50% of the patients showed motor reaction) of each stimulation calculated by using linear regression (see arrows in figs. 2 and 3). The occurrence of a motor reaction was expressed with 1 for positive reaction and 0 for absence of reaction.

To test whether an individual patient reacted consistently to the same stimulation pattern repeated at different isoflurane concentrations a rating procedure was applied: a reaction was assigned the value of 1 if after a stimulation the blood pressure (heart rate) increased more at a lower compared to a higher concentration; a value of 0 was assigned, if the reverse was the case. The mean of all reactions was then computed and the result expressed as percentage of consistent reactions among all reactions.

All isoflurane concentrations are expressed in vol%, neglecting the influence of barometric pressure (Bern is 500 m above sea level). The concentration in the blood is expressed as the concentration in a gas-space in equilibrium with the blood, thus accounting for inter- and intraindividual variability of blood/gas partition coefficients.

Results

Patient characteristics in detail and blood gas values are shown in table 1 of the accompanying paper.[11] The systolic blood pressure values are given in figure 2. The increase of the average systolic blood pressure (heart rate) calculated with linear regression for the corresponding MAC_{50} value of each stimulation amounted to 9 mmHg (5 beats/min) for trapezius squeeze, 15 (15) for tetanic stimulation, 23 (17) for laryngoscopy, 35 (36) for skin incision, and 49 (36) for intubation (table 1). A statistically significant difference both for blood pressure and for heart rate increase existed only between trapezius squeeze and tetanic stimulation as well as trapezius squeeze and laryngoscopy. The mean increase of blood pressure following trapezius squeeze and laryngoscopy appeared to be greater before the operation than afterward though analysis of variance did not show this difference to be significant. The regression line drawn through all the prestimulation values is virtually parallel to the line drawn through the post-stimulation values of each stimulation. This means that isoflurane depresses the prestimulation blood pressure rather than decreasing the pressure increase caused by the stimulation. Hence, at high isoflurane concentrations the increase of blood pressure to a stimulation starts from lower values, and thus after stimulation blood pressure is lower than at low isoflurane concentrations. The comparable plots for the heart rate are shown in figure 3. The results are comparable with those of blood pressure with the exception that prestimulation heart rates are not decreased by high isoflurane concentrations. Heart rate increases also appeared to be higher when the stimulation occurred before operation, but again analysis of variance did not prove this to be significant.

As shown by multiple regression the increase in blood pressure is most closely related to the type of the stimulation pattern, followed by the observation of positive/negative motor reaction and, to a lesser extent, the time elapsed since the beginning of anesthesia and least, to the end-tidal isoflurane concentration (table 2). Substituting arterial for end-tidal concentrations in this regression analysis did not improve the correlation.

Consistency of the hemodynamic reaction of an individual patient was less for hemodynamic compared to motor reactions: 80% (219 of 274 measurements) of blood pressure and 83% (226 of 273 measurements) of heart rate reactions were consistent, *i.e.*, the blood pressure or heart rate reactions measured in one patient were lower at higher isoflurane concentrations than at lower concentrations. This compares to 99% (269 of 271 measurements) for movement.

Discussion

This study has shown that isoflurane does not cause a dose-related attenuation of blood pressure or heart

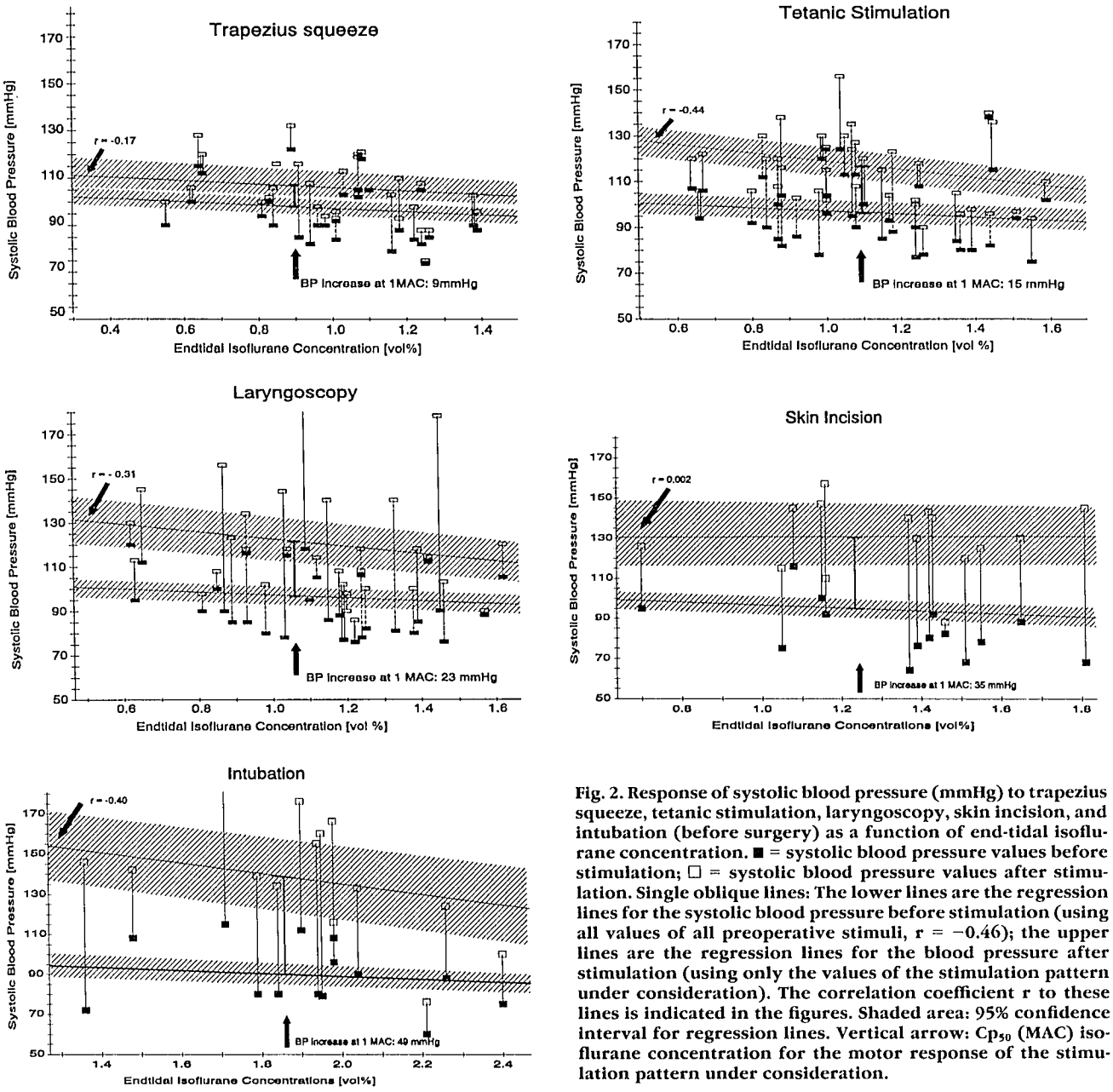

Fig. 2. Response of systolic blood pressure (mmHg) to trapezius squeeze, tetanic stimulation, laryngoscopy, skin incision, and intubation (before surgery) as a function of end-tidal isoflurane concentration. ■ = systolic blood pressure values before stimulation; □ = systolic blood pressure values after stimulation. Single oblique lines: The lower lines are the regression lines for the systolic blood pressure before stimulation (using all values of all preoperative stimuli, r = −0.46); the upper lines are the regression lines for the blood pressure after stimulation (using only the values of the stimulation pattern under consideration). The correlation coefficient r to these lines is indicated in the figures. Shaded area: 95% confidence interval for regression lines. Vertical arrow: Cp_{50} (MAC) isoflurane concentration for the motor response of the stimulation pattern under consideration.

rate responses to various types of noxious stimuli. A recent study using desflurane in six young volunteers[12] has shown comparable results; in this study, hemodynamic responses after electric tetanic stimulation of the ulnar nerve were not abolished by 0.83 and 1.24 MAC desflurane. The hemodynamic response was similar for both concentrations. Only at 1.66 MAC desflurane, hemodynamic reactions were diminished, but then the mean arterial blood pressure control value also was depressed to 55 ± 3 (mean ± SE) mmHg. Thus, desflurane was able to attenuate the hemodynamic response (for example blood pressure increase), but only at the price of decreasing the prestimulation blood pressure values to unacceptably low levels. At the lower desflurane concentration the heart rate was substantially increased by stimulation. At 1.66 MAC

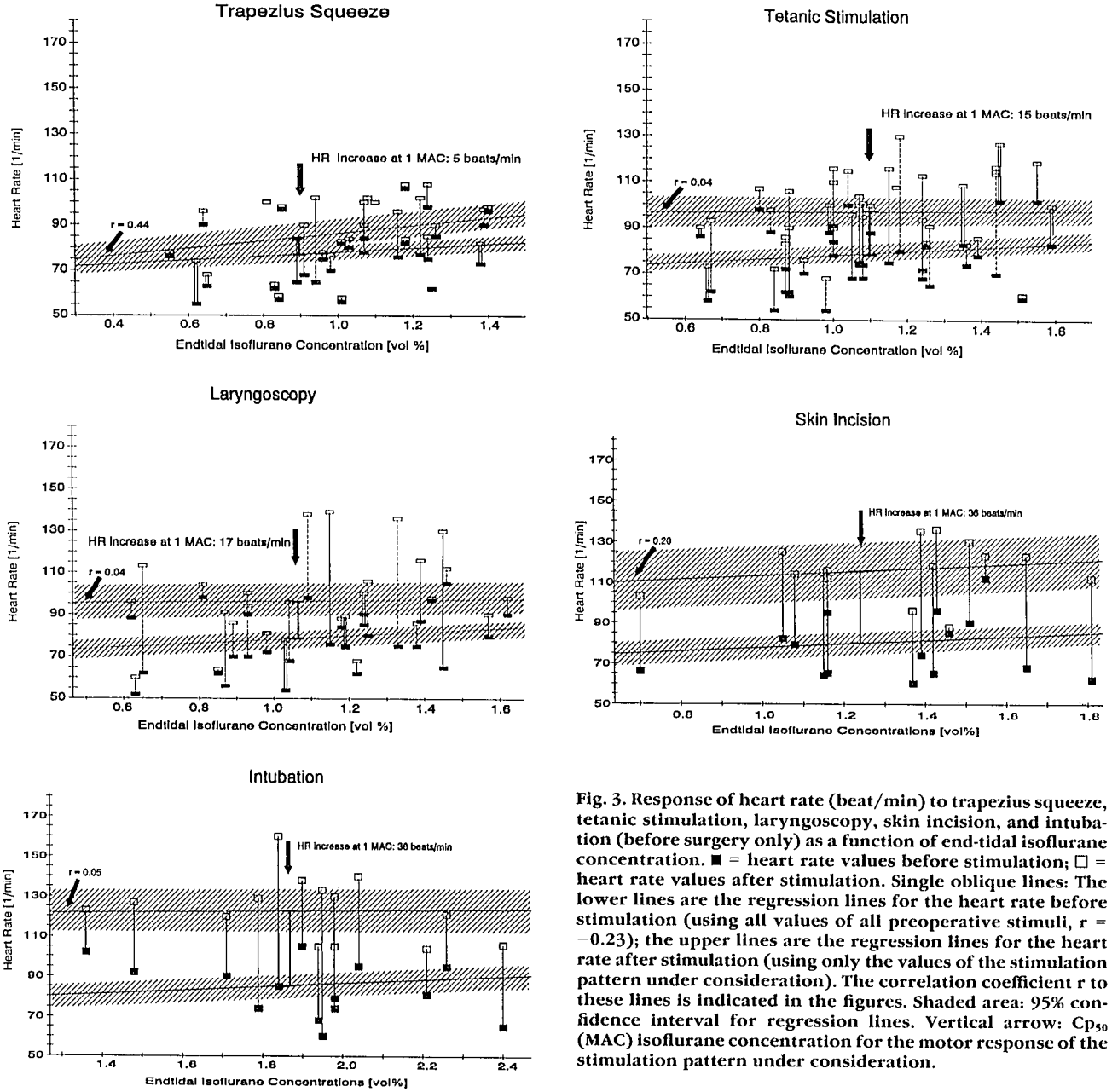

Fig. 3. Response of heart rate (beat/min) to trapezius squeeze, tetanic stimulation, laryngoscopy, skin incision, and intubation (before surgery only) as a function of end-tidal isoflurane concentration. ■ = heart rate values before stimulation; □ = heart rate values after stimulation. Single oblique lines: The lower lines are the regression lines for the heart rate before stimulation (using all values of all preoperative stimuli, r = −0.23); the upper lines are the regression lines for the heart rate after stimulation (using only the values of the stimulation pattern under consideration). The correlation coefficient r to these lines is indicated in the figures. Shaded area: 95% confidence interval for regression lines. Vertical arrow: Cp_{50} (MAC) isoflurane concentration for the motor response of the stimulation pattern under consideration.

desflurane, prestimulation heart rate was increased and did not further increase after stimulation. As in the present study, there was a large variability in individual responses.

Roizen *et al.*[6] studied the ability of an anesthetic agent to attenuate hemodynamic reactions to skin incision, defining MAC_{BAR} as the concentration of halothane or enflurane required to block the adrenergic reaction to skin incision in 50% of all patients. He defined an increase of 10% or more of the mean pre-incision values for heart rate, blood pressure, pupil diameter or norepinephrine level as an all-or-none positive response. MAC_{BAR} of halothane (enflurane) was 1.5 ± 0.1 (1.6 ± 0.1) $MAC_{skin\ incision}$ including a 0.57 MAC contribution of nitrous oxide as 60% N_2O was used in this study. The dose-related effect of both, halothane and enflurane

Table 1. Blood Pressure (mmHg) and Heart Rate (beats/min; Initial Value and Absolute Increase to Stimulation) at the Cp_{50} of the Motor Reaction of Each Stimulation Obtained Using Linear Regression to All Prestimulation Values and the Poststimulation Values Only of the Values to Each Stimulation

Stimulation	Before/After Surgery	Systolic Blood Pressure at 1 MAC of a Stimulus		Heart Rate at 1 MAC of a Stimulus		End-tidal Concentration	
		Initial (mmHg)	Increase (mmHg)	Initial (l/min)	Increase (l/min)	Cp_{50} (vol%)	Cp_{59} (vol%)
Trapezius	Before	98	9	78	7	0.99 ± 0.07	1.34 ± 0.14
	After	118	12	78	8	0.62 ± 0.09	1.19 ± 0.19
	All	111	9	77	5	0.71 ± 0.07	1.36 ± 0.15
Tetanus	Before	97	20	79	18	1.10 ± 0.09	1.87 ± 0.26
	After	112	15	79	9	0.78 ± 0.07	1.35 ± 0.19
	All	106	15	78	15	0.90 ± 0.08	1.85 ± 0.25
Laryngoscopy	Before	97	26	78	18	1.07 ± 0.12	1.99 ± 0.31
	After	106	19	80	13	1.00 ± 0.10	1.77 ± 0.37
	All	103	23	79	17	1.06 ± 0.90	2.13 ± 0.31
Skin incision	All	95	35	81	36	1.24 ± 0.10	1.70 ± 0.23
Intubation	All	90	49	86	36	1.87 ± 0.13	2.50 ± 0.34

Concentration values are not adjusted to sea level.

on the magnitude of the hemodynamic response demonstrated by Roizen *et al.* stands in contrast to the present study. In the Roizen *et al.* study, however, the criteria for circulatory response, patient age (patients were younger) and the application of nitrous oxide together with other intravenous agents (4 mg/kg thiopental for induction, 2 mg/kg lidocaine for tracheal spray) differed from our study.

There was a poor correlation between motor and hemodynamic responses (table 2). This means that from an observation of motor response one cannot draw conclusions about the magnitude of the hemodynamic response. Motor reactions are more consistent than hemodynamic reactions and the intraindividual variability of such reactions is also very high. Increase in blood pressure or heart rate is virtually concentration-inde-

Table 2. Results of Multiple Regression Used to Evaluate the Influence of the Stimulation Pattern, the Observed Motor Reaction Time, and Isoflurane Concentration on the Degree of the Absolute Rise of Systolic Blood Pressure (mmHg) and Heart Rate (beats/min; n = 292)

Effect to Be Tested by Multiple Regression	Independent Variables Used			Correlation Coefficient	
		Assigned Values*		Blood Pressure	Heart Rate
		Blood Pressure (mmHg)	Heart Rate (beats/min)		
Stimulation pattern	Trapezius	9	5		
	Tetanus	15	15	0.64	0.56
	Laryngoscopy	23	17		
	Incision	35	36		
	Intubation	49	36		
Motor reaction	Positive = 1 Negative = 0			0.30	0.26
Time	Time from start of induction [min]			−0.21	−0.23
Isoflurane concentration	Concentration [vol%]			0.16	0.16

* Mean blood pressure and heart rate increase at Cp_{50} of each stimulation (see also figs. 2 and 3).

pendent which renders prediction of the hemodynamic reaction to an abrupt and/or strong stimulation, such as intubation, difficult. The clinical implication of this finding is that isoflurane—at least when used as sole agent—is unable to suppress hemodynamic and motor reactions to painful stimulations; high isoflurane concentrations will decrease the prestimulation blood pressure and thus after an intense stimulation such as intubation blood pressure will more likely lie within a normal range. This means that with a strong and abrupt painful event a low prestimulation blood pressure value will have to be accepted to avoid post-stimulation hypertension. Heart rate is known to be increased by isoflurane, as the baroreceptor reflex control of heart rate is less depressed by isoflurane than by other inhalational anesthetics.[13] After stimulation, the increase in heart rate may be even greater if high isoflurane concentrations are used. A combination of post-stimulation hypertension and tachycardia may be potentially harmful in patients with preexisting coronary artery disease. Isoflurane is rarely used as a sole agent; if doing so, the concentration must rapidly and constantly be adjusted to the varying surgical stimulations. It is probably better to blunt hemodynamic reactions to strong stimulations by using combinations of volatile anesthetics with nitrous oxide and/or opioids. The response to intubation has for example been investigated by Randell *et al.*[14] comparing anesthesia with a mixture of nitrous oxide and isoflurane to that with nitrous oxide alone. It was found that the increase of plasma norepinephrine concentrations, heart rate, systolic and diastolic pressures occurring after intubation were less in the group with isoflurane/nitrous oxide than in that with nitrous oxide only. In this study, however, end-tidal concentrations were not allowed to equilibrate, and thus a dose-effect relationship could not be established.

In conclusion, this study quantified motor and hemodynamic reactions to various painful stimuli. Hemodynamic reaction showed a large inter-individual and intra-individual variability. Isoflurane used as a sole agent depresses prestimulation blood pressure, but the blood pressure response *per se* to stimulation is virtually concentration-independent. This means that the prestimulation blood pressure has to be decreased to unacceptably low levels before stimulation. Isoflurane slightly increases heart rate and does not decrease the heart rate increase to stimulation. Motor, blood pressure, and heart rate responses seem to be less after operation than before operation. Finally, the correlation between motor response and hemodynamic response is poor.

References

1. Stevens WC, Dolan WM, Gibbons RT, White A, Eger EI II, Miller RD, DeJong RH, Elashoff RM: Minimum alveolar concentrations (MAC) of isoflurane with and without nitrous oxide in patients of various ages. ANESTHESIOLOGY 42:197–200, 1975

2. Stevens WC, Cromwell TH, Halsey MJ, Eger EI, Shakespeare TF, Bahlman SH: The cardiovascular effects of a new inhalation anesthetic, Forane, in human volunteers at constant arterial carbon dioxide tension. ANESTHESIOLOGY 35:8–16, 1971

3. Yakaitis RW, Blitt CD, Angiulo JP: End-tidal halothane concentration for tracheal intubation. ANESTHESIOLOGY 47:386–388, 1977

4. Yakaitis RW, Blitt CD, Angiulo JP: End-tidal enflurane concentration for tracheal intubation. ANESTHESIOLOGY 50:59–61, 1979

5. Cromwell TH, Stevens WC, Eger EI, Shakespeare TF, Halsey MJ, et al: The cardiovascular effects of compound 469 (Forane) during spontaneous ventilation and carbon dioxide challenge in humans. ANESTHESIOLOGY 35:17–25, 1971

6. Roizen MF, Horrigan RW, Frazer BM: Anesthetic doses blocking adrenergic (stress) and cardiovascular responses to incision-MAC BAR. ANESTHESIOLOGY 54:390–398, 1981

7. Ausems MEM, Hug CC, Stanski DR, Burm AGL: Plasma concentrations of alfentanil required to supplement nitrous oxide anesthesia for general surgery. ANESTHESIOLOGY 65:362–373, 1986

8. Brett CM, Fisher DM: Thiopental dose-response relations in unpremedicated infants, children and adults. Anesth Analg 66:1024–1027, 1987

9. Hung RO, Varvel JR, Shafer SL, Stanski DR: Thiopental pharmacodynamics: II. Quantitation of clinical and electroencephalographic depth of anesthesia. ANESTHESIOLOGY 77:237–244, 1992

10. Gardner RM: Direct blood pressure measurement—Dynamic response requirements. ANESTHESIOLOGY 54:227–236, 1981

11. Zbinden AM, Maggiorini M, Petersen-Felix S, Lauber R, Thomson DA, Minder CE: Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia: I. Motor reactions. ANESTHESIOLOGY 80:253–260, 1994

12. Yasuda N, Weiskopf R, Cahalan M, Ionescu P, Caldwell J, Eger EI II, Rampil IJ, Lockhart SH: Does desflurane modify circulatory responses to stimulation in humans? Anesth Analg 73:175–179, 1991

13. Kotrly KJ, Ebert TJ, Vucins E, Igler FO, Barney JA, Kampine JP: Baroreceptor reflex control of heart rate during isoflurane anesthesia in humans. ANESTHESIOLOGY 60:173–179, 1984

14. Randell T, Seppälä T, Lindgren L: Isoflurane in nitrous oxide and oxygen increases plasma concentrations of noradrenaline but attenuates the pressure response to intubation. Acta Anaesthesiol Scand 35:600–605, 1991