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Anesthetic Doses Blocking Adrenergic (Stress) and Cardiovascular Responses to Incision–MAC BAR

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The reaction to stress, while vital to the conscious animal, may be detrimental to the surgical patient. To assess the stress-ablating action of different anesthetics (halothane, enflurane, morphine, and spinal) and anesthetic doses, we studied the responses in plasma norepinephrine, muscle movement, pupil diameter, heart rate, and blood pressure to induction of anesthesia and incision in 170 unpremedicated healthy adults. The age-adjusted dose (mean ± SD) of anesthesia that blocked the adrenergic response in 50 per cent of individuals who had a skin incision (MAC BAR) was 1.45 ± 0.08 MAC for halothane, 1.60 ± 0.13 MAC for enflurane, or 1.13 ± 0.09 mg/kg for morphine sulfate (each anesthetic was given with 60 per cent nitrous oxide). No patient with a level of spinal anesthesia that blocked the pain of incision had an adrenergic response to incision.

Increasing doses of halothane and morphine were associated with less of a cardiovascular response to incision (as measured by rate-pressure product); this was not true for enflurane. No patient with an adequate level of spinal anesthesia had a cardiovascular response to skin incision.

The changes in heart rate, blood pressure, rate-pressure product, and plasma norepinephrine content that occurred with induction of anesthesia tended to equalize these values between patients, regardless of anesthetic dose, and for all individual and combined anesthetics. That is, if a patient's heart rate while awake was below 63 beats/min, heart rate tended to rise 58 per cent of the difference between heart rate while awake and 63 beats/min, and vice versa. Similarly, the change in blood pressure with induction averaged 75 per cent of the difference between systolic blood pressure while awake and 88 torr. The average for the change in rate-pressure product with induction was 79 per cent of the difference between rate-pressure product while awake and 5917 torr·beats/min.

It was concluded that all the anesthetics tested can prevent the neuroendocrine response to skin incision at clinically attainable doses. Thus, comparisons of neuroendocrine stress during surgery require quantitation of anesthetic dose. If adverse effects of surgery are related to the neuroendocrine stress that surgical manipulations induce, the hypothesis "the less anesthetic the better" may be wrong. (Key words: Anesthetics, intravenous: morphine. Anesthetic techniques: spinal. Anesthetics, volatile: enflurane; halothane. Potency, anesthetic: ED_{50}; MAC. Sympathetic nervous system: catecholamines, norepinephrine.)

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THE CARDIOVASCULAR RESPONSE to surgery may be an important determinant of patient morbidity. For example, the tachycardia and hypertension that follow sympathetic activation may compromise myocardial oxygenation in the presence of coronary artery occlusive disease.[1] By blocking the neuroendocrine response to stress, anesthesia may protect against such potentially deleterious effects of surgery.[2] To assess this possible protective action, we studied the changes in plasma norepinephrine levels and cardiovascular responses to skin incision during different levels of spinal anesthesia and during anesthesia with combinations of nitrous oxide and halothane, enflurane, or morphine. We correlated the norepinephrine and cardiovascular response with induction and incision to each other and to the dose of anesthetic administered.

Materials and Methods

We obtained approval from the UCSF Committee on Human Research and informed consent from 170 unpremedicated ASA I or II adult patients. We selected patients who were to have skin incisions on the abdomen, neck, or extremities. After the anesthesiologist chose the anesthetic, the anesthetic dose was randomly assigned. Anesthesia consisted of the following: 1) 60 per cent nitrous oxide and oxygen with an age-adjusted[3] halothane MAC value (halothane plus nitrous oxide) of 1.0, 1.3, 1.6, or 1.9; 2) 60 per cent nitrous oxide and oxygen with an age-adjusted enflurane MAC value of 1.3, 1.6, or 1.9; 3) 60 per cent nitrous oxide with 0.4, 0.9, or 1.4 mg/kg morphine sulfate; or 4) spinal anesthesia to either a T4 to T10 dermatome level. All patients received approximately 10 $ml \cdot kg^{-1} \cdot hr^{-1}$ of 5 per cent dextrose in half normal saline for the duration of this study; no patient received any drugs other than those stated. Age adjustments were made based on available published data for halothane and isoflurane.[3,4] A similar age-related slope was assumed for enflurane and morphine and the dose adjusted accordingly (table 1). For the patients given halothane or enflurane, anesthesia was induced by inhalation or by the intravenous administration of thiopental, 1.0 mg/kg (18 and 14 patients, respectively, for halothane and enflurane), at least 25 min prior to the first sample period. For the patients given morphine, anesthesia

was induced with three-fourths of the morphine dose intravenously, followed by thiopental, 4 mg/kg, and *d*-tubocurarine, 3 mg. Succinylcholine, 1.5 mg/kg, was then given intravenously to those patients in the morphine group. Spinal anesthesia was induced by injection of tetracaine through lumbar puncture; the level of anesthesia was tested by pin prick 12 min after removal of the lumbar puncture needle.

The trachea of all patients given general anesthesia was sprayed with 2 mg/kg lidocaine and intubated. Ventilation was controlled, and end-tidal anesthetic concentrations were held constant thereafter until the study was completed. For patients given morphine, the remaining one-fourth dose was administered intravenously 5 min before incision. Nitrous oxide end-tidal concentrations were monitored indirectly with an oxygen analyzer (IL402®, Instrumentation Laboratories) or directly with a Med Spec mass spectrometer. End-tidal enflurane and halothane concentrations were monitored by infrared (Beckman® LB-1) or ultraviolet analysis (Cavitron), respectively; or by mass spectrometry (Med Spec). All instruments used for analysis were calibrated daily. Plasma morphine levels were not measured. In approximately 50 per cent of patients, oscillatory blood pressure and heart rate were recorded, and 10 ml of blood were drawn in the awake state 20 min after the intravenous line was placed.

In all patients, at 4 and 1 min before skin incision (*i.e.*, 15 and 18 min after endotracheal intubation) and at 3 and 10 min after skin incision, 10 ml of blood were drawn from an indwelling peripheral venous catheter. Oscillatory blood pressure, heart rate, and pupil diameter, estimated by approximation with a ruler, were recorded at each of these times. Analysis of venous blood gases was performed and plasma catecholamine concentrations were also determined, the latter by radioenzymatic analysis.[5,6]

A patient was excluded from the study if *p*H was not between 7.33 and 7.45, if P_{CO_2} was not between 30 and 44 torr, or if P_{O_2} was below 40 torr. A difference of 10 per cent or more in any pair of preincision cardiovascular or norepinephrine measurements also excluded a patient from the study. Inability to draw blood at one of the four time periods during anesthesia (28 patients) or existence of one of four abnormal conditions (P_{CO_2}, 19 patients; *p*H, three patients; duplicates, three patients) excluded 53 patients from the study. An increase of 10 per cent or more from mean preincision value to mean postincision value in heart rate, blood pressure, pupil

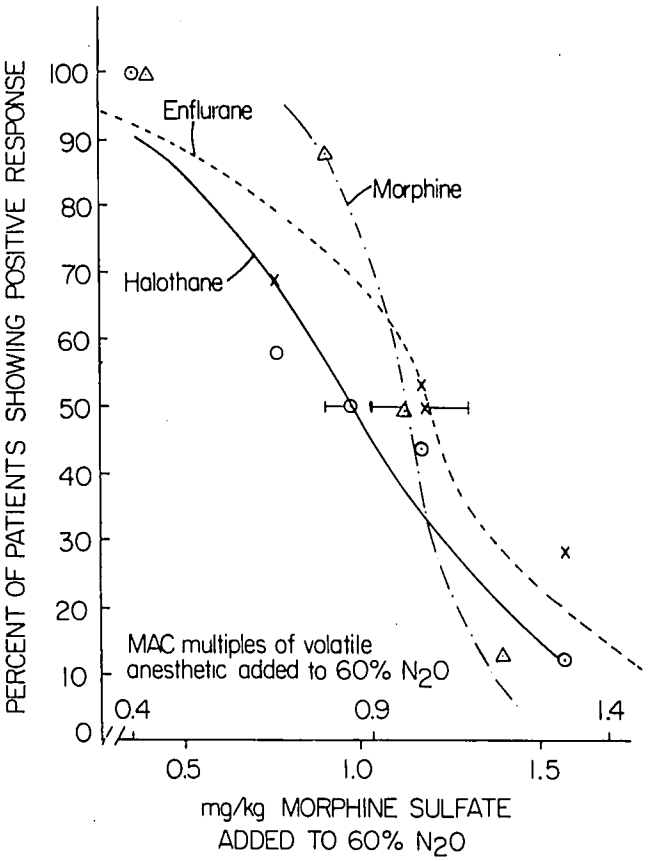

FIG. 1. The anesthetic dose necessary to block adrenergic response to incision. (Patients were responders if they had a 10 per cent or greater increase in norepinephrine upon skin incision. See "Methods" and "Results" for method of calculation.) The 50 per cent values are interpolated with bars representing ± 1 SD. *Note*: The x-axis MAC values in this figure do not include the 0.57 MAC contribution of nitrous oxide that is included in the text and tables.

TABLE 1. Anesthetic Doses Adjusted for Age*

	Dosage Group†	Patient Age (Years)		
		18–30	31–54	55–65
Enflurane plus 60 per cent N_2O	1.3 MAC	1.26	1.13	1.00
	1.6 MAC	1.76	1.58	1.39
	1.9 MAC	2.27	2.04	1.79
Halothane plus 60 per cent N_2O	1.0 MAC	0.38	0.34	0.27
	1.3 MAC	0.63	0.57	0.48
	1.6 MAC	0.88	0.80	0.68
	1.9 MAC	1.13	1.02	0.89
Morphine plus 60 per cent N_2O	0.4 mg/kg	0.4 mg/kg	0.36 mg/kg	0.32 mg/kg
	0.9 mg/kg	0.9 mg/kg	0.81 mg/kg	0.71 mg/kg
	1.4 mg/kg	1.4 mg/kg	1.26 mg/kg	1.11 mg/kg

* Values for patients given enflurane plus 60 per cent N_2O or halothane plus 60 per cent N_2O are percentages of the MAC values for each dosage group. The dosages for patients receiving morphine plus 60 per cent N_2O are expressed in units of mg/kg.

† MAC multiple includes calculated MAC for nitrous oxide.

TABLE 2. Anesthetic Dose, Patient Norepinephrine Responses, and Calculated Doses Blocking Adrenergic Response

	MAC Multiple/Morphine Dose (mg/kg)*					
	1.0	1.3/0.4	1.6/0.9	1.9/1.4	MAC BAR_{50}†	MAC BAR_{95}
Enflurane	——	34 (9)‡	43 (14)	73 (11)	1.60 ± 0.13 MAC	2.57 MAC
Halothane	0 (6)	42 (12)	56 (9)	87 (15)	1.45 ± 0.08 MAC	2.10 MAC
Morphine	——	0 (8)	13 (8)	87 (8)	1.13 ± 0.09 mg/kg plus 60 per cent N_2O	1.45 mg/kg plus 60 per cent N_2O

* Sixty per cent nitrous oxide was administered as a background to all general anesthetics. MAC doses for enflurane and halothane include calculated MAC contribution of nitrous oxide.

† Dose for blocking adrenergic response ± 1 SD.

‡ Results are given as percentages of patient population whose plasma level of norepinephrine did not increase by 10 per cent or more following skin incision; the number of patients studied is given in parentheses.

diameter, or norepinephrine level was treated as an all-or-none positive response. Changes in the multiple of heart rate multiplied by systolic blood pressure (rate-pressure product) were used to determine the dose of anesthetic that blocked the cardiovascular response to incision. Statistical analysis was performed using the Waud technique.[7] In addition, the changes with incision (in percentages and absolute values) in heart rate, mean blood pressure, and rate-pressure product were compared with changes in norepinephrine levels and anesthetic dose by mean least-squares regression. Also, the changes in each cardiovascular variable and in plasma norepinephrine concentration both from awake to postinduction/preincision and from postinduction/preincision to postincision were compared with the values for those variables during the awake state. Analysis of covariance was used to determine the acceptability of pooling different agent groups.[8]

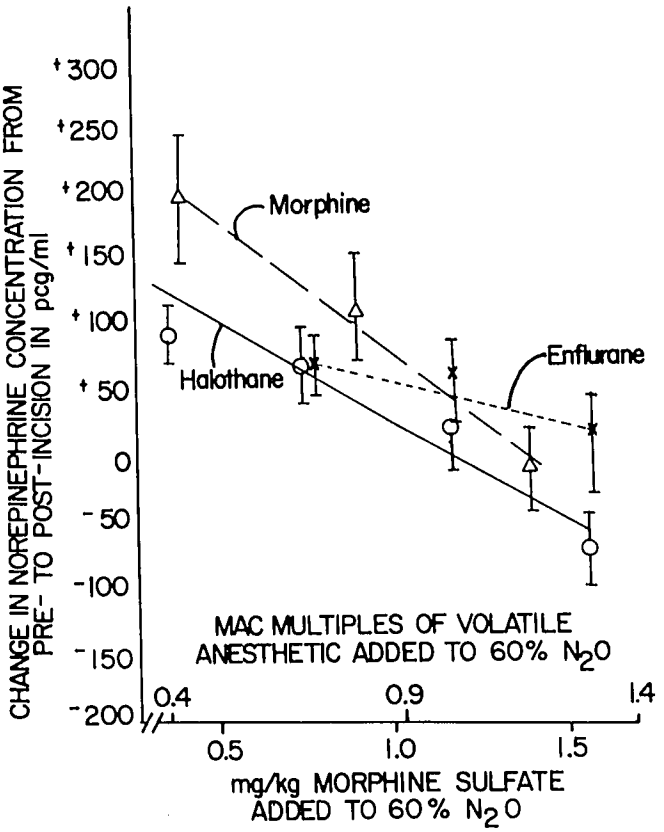

FIG. 2. Absolute change in plasma norepinephrine levels (pg/ml) after incision *vs.* the end-tidal dose of anesthesia the patient was receiving. The lines are described as follows: for morphine, the change in norepinephrine = (−207) (mg/kg dose of morphine) + 292 (r = 0.60); for halothane, the change in norepinephrine = (−199) (MAC dose of halothane including 60 per cent N_2O) + 326 (r = 0.60); for enflurane, the change in norepinephrine = (−80) (MAC dose of enflurane including 60 per cent N_2O) + 179 (r = 0.56). *Note*: These equations represent an alternate method of depicting data presented in the text. The x-axis MAC values in the figure do not include the 0.57 MAC contribution of nitrous oxide that is included in the text and tables.

Results

The groups did not differ significantly in average age, site of incision, preoperative cardiovascular variables, or norepinephrine levels. Thiopental was used (<1 mg/kg) in 42 per cent of the volatile anesthetic inductions; no difference in any of the variables studied existed between those patients who had received thiopental and those who had not.

TABLE 3. Correlation Coefficients of Changes in Plasma Norepinephrine Concentration and Cardiovascular and Pupillary Changes before and after Incision for Various Anesthetics

Changes in:	Enflurane	Halothane	Morphine Sulfate Plus 60 Per Cent N_2O	Spinal Anesthesia
Heart rate	r = 0 (n = 34)	r = 0.36 (n = 42)	r = 0.51 (n = 24)	r = 0.09 (n = 17)
Mean arterial blood pressure	r = 0.03 (n = 34)	r = 0.22 (n = 42)	r = 0.58 (n = 24)	r = 0.34 (n = 17)
Rate-pressure product	r = 0.04 (n = 34)	r = 0.28 (n = 42)	r = 0.63 (n = 24)	r = 0.22 (n = 17)
Pupil diameter	r = 0.47 (n = 12)	r = 0.04 (n = 17)	r = 0.12 (n = 13)	——

The ED_{50} for blocking an adrenergic response to incision (MAC BAR) is 1.60 ± 0.13 MAC for enflurane-60 per cent nitrous oxide, 1.45 ± 0.08 MAC for halothane-60 per cent nitrous oxide, and 1.13 ± 0.09 mg/kg for morphine sulfate plus 60 per cent nitrous oxide (fig. 1, table 2. *Note*: The x-axis MAC values in the figures do *not* include the 0.57 MAC contribution of nitrous oxide that is included in the text and tables). Norepinephrine did not increase with skin incision in patients with adequate spinal anesthesia (*i.e*, those who were pain-free on incision). Two of ten patients with an anesthetic level to the T10 dermatome had pain at time of incision; both had increases in plasma norepinephrine concentration. For blocking adrenergic response to incision, the "logit" transformation[7] of the data yielded ED_{95} values of 2.57 MAC for enflurane, 2.10 MAC for halothane, and 60 per cent nitrous oxide plus 1.45 mg/kg for morphine. Anesthetic dose-response curves plotted against changes in norepinephrine (in absolute values or percentages) give similar values as the logit transformation for the dose of each anesthetic that blocks an adrenergic response (fig. 2).

When changes in heart rate, blood pressure, and rate-pressure product with incision were correlated with changes in plasma norepinephrine concentration with incision, the correlation was significant during morphine anesthesia, weak but significant during halothane anesthesia, and insignificant during enflurane or spinal anesthesia (table 3). Three of six patients in the 1.0 MAC halothane group and 19 of 24 patients given morphine moved in response to incision. Six of eight patients given 1.4 mg/kg morphine exhibited this movement response to incision. Mean preincision values for norepinephrine were not statistically different among agents, nor among dosage groups of any one agent (table 4).

As doses of halothane and morphine were increased, the cardiovascular response to incision (as determined by measurement of heart rate, blood pressure, and rate-pressure product) decreased. Increasing doses of enflurane did not decrease the cardiovascular response to incision. However, at all levels of enflurane anesthesia, the mean cardiovascular response to incision was less than the mean cardiovascular response occurring with the lowest dose of morphine (figs. 3–5). No patient with an adequate level of spinal anesthesia had a cardiovascular response to incision.

The values for cardiovascular variables and plasma norepinephrine levels for the awake state were not different among agents, nor among dosage groups of any one agent. Deeper anesthesia was associated with a greater decrease in blood pressure from the awake state to the period before incision during halothane and enflurane anesthesia, but not during morphine anesthesia.

TABLE 4. Preincision Plasma Norepinephrine Concentrations

	Age-adjusted MAC Level	Preincision Plasma Norepinephrine Concentration (pg/ml)*
Enflurane plus 60 per cent N_2O	1.3 MAC	292 ± 117
	1.6 MAC	282 ± 171
	1.9 MAC	360 ± 172
Halothane plus 60 per cent N_2O	1.0 MAC	415 ± 186
	1.3 MAC	393 ± 276
	1.6 MAC	441 ± 247
	1.9 MAC	515 ± 310
Morphine plus 60 per cent N_2O	0.4 mg/kg	308 ± 200
	0.9 mg/kg	330 ± 139
	1.4 mg/kg	324 ± 100
Spinal anesthesia	T10 level	255 ± 150
	T4 level	235 ± 135

* Values are means ± SD.

The changes in heart rate, blood pressure, rate-pressure product, and plasma norepinephrine levels that occurred with induction of anesthesia correlated inversely with the values for those variables during the awake state, regardless of the dose of anesthetic

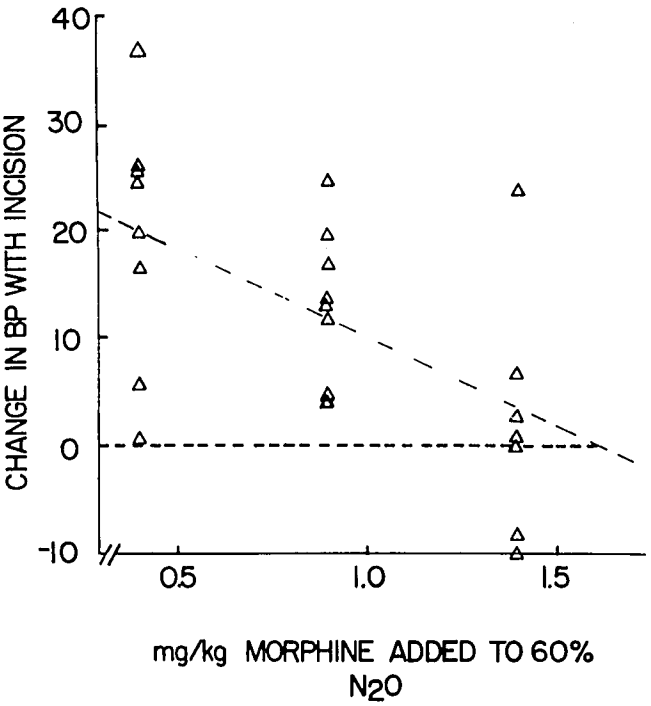

FIG. 3. Dose of morphine–N_2O anesthesia *vs.* change in blood pressure (BP) with incision. The line can be described as follows: Change in BP with incision = (−16.4) (mg/kg dose of morphine) + 27 (r = 0.60). *Note*: Some triangles represent two patients.

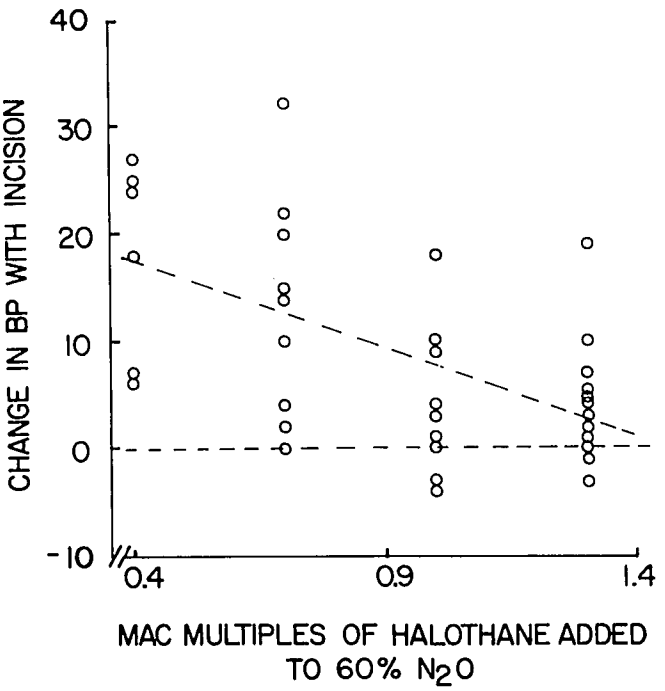

FIG. 4. Dose of halothane–N_2O anesthesia *vs.* change in blood pressure (BP) with incision. The line can be described as follows: Change in BP with incision = (−16.6) (MAC dose of halothane including 60 per cent N_2O) + 34 (r = 0.60). *Note*: Some circles represent two patients. The x-axis MAC values in this figure do not include the 0.57 MAC contribution of nitrous oxide that is included in the text and tables.

and for all anesthetics individually and in combination (figs. 6–8). (*Note*: Since this study was initially designed to concentrate on the period just prior to and just after incision, only 80 per cent of all patients studied during the incision period had both blood pressure and heart rate recorded 20 min after placement of an intravenous line during the awake state, and only 50 per cent had plasma norepinephrine concentration measured 20 min after placement of an intravenous line during the awake state).

Discussion

Enflurane, halothane, morphine, and spinal anesthesia can all prevent the neuroendocrine response to skin incision at clinically attainable doses. Thus, comparisons of neuroendocrine stress during surgery and anesthesia require quantitation of anesthetic dose.

We chose plasma norepinephrine concentration as our index of stress because of its rapid rise and fall (half-life < 3 min).[9] This rapid rise and fall permitted us to focus on a relatively constant stimulus, that of skin incision and the subsequent dissection, in isolation from the rest of the day. This focus is both a strength and a weakness of the study: a weakness because it excludes other perioperative periods that might be more stressful to the patient; and a strength, because it probably produced less variance in the dose-response curve. We chose the sampling times of 3 and 10 min after incision because prior studies indicated that norepinephrine response was relatively stable at these times.§[10–12]

We do not know why the changes in cardiovascular parameters and norepinephrine concentration were not more closely related. Perhaps plasma norepinephrine levels should be noted for cardiovascular variables that are measured 2 to 3 min earlier, as it takes approximately 2–3 min for adrenal or peripheral nerve release of norepinephrine to increase peripheral blood norepinephrine content.[9,13] Other neuroendocrine stress reactants may have more effect or may have different times of effect on the cardiovascular system than does norepinephrine. Other manifestations of stress—increased production of antidiuretic hormone,[14] growth hormone,[15] cortisol,[15] cyclic AMP,[16] prostaglandins,[17] and renin[18]

§ Roizen MF, Forbes AR, Gerson JI, et al: Plasma norepinephrine increases with induction of halothane anesthesia. Abstracts of Scientific Papers. Annual meeting, American Society of Anesthesiologists, 1978, pp 15–16.

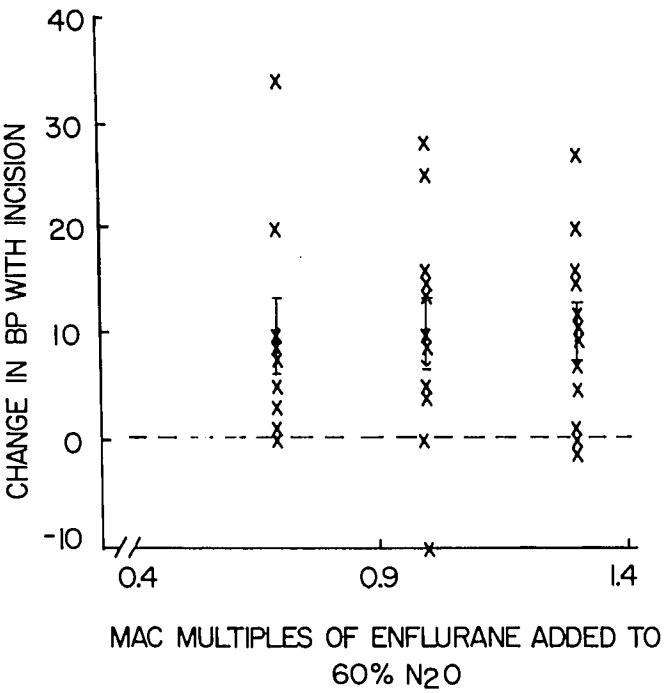

FIG. 5. Lack of relationship between dose of enflurane and change in blood pressure (BP) with incision. *Note*: some X marks represent two patients. The x-axis MAC values in this figure do not include the 0.57 MAC contribution of nitrous oxide that is included in the text and tables.

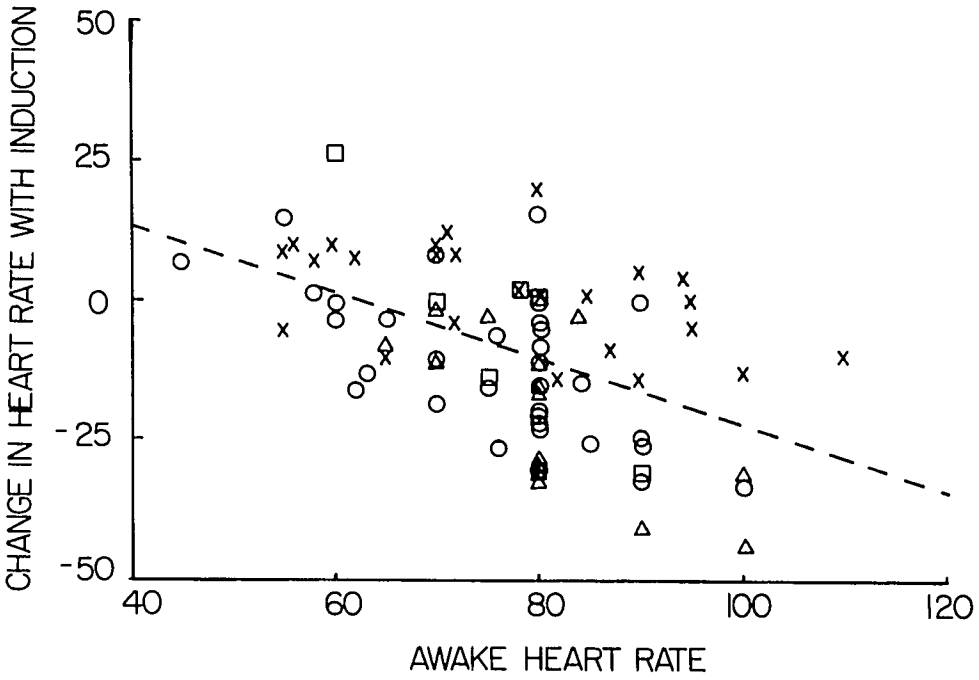

FIG. 6. Heart rate (beats/min) while awake *vs.* change in heart rate with induction of anesthesia. Analysis of covariance demonstrated no significant difference between agents; thus, the data for all four anesthetic agents (x = enflurane, O = halothane, Δ = morphine, □ = spinal) were pooled. The line can be described as follows: Change in heart rate with induction = (−0.58) (heart rate while awake) + 37 (r = 0.51).

—also appear to decrease after initiation of anesthesia, although this decrease occurs at different times than it does with norepinephrine. These manifestations of stress in response to surgical stimuli appear to be blocked by increasing the anesthetic dose, although no dose-response curves have been defined for these other reactants. Thus, the different times of blockade or lack of parallelism between the dose-response curves of the other reactants and those for norepinephrine may account for this lack of close correlation between changes in cardiovascular variables and norepinephrine content.

The slopes for the anesthetic dose *vs.* absolute change in plasma norepinephrine concentration are less steep than those for the movement response (*i.e.*, the curve defining MAC).[19,20] This difference in

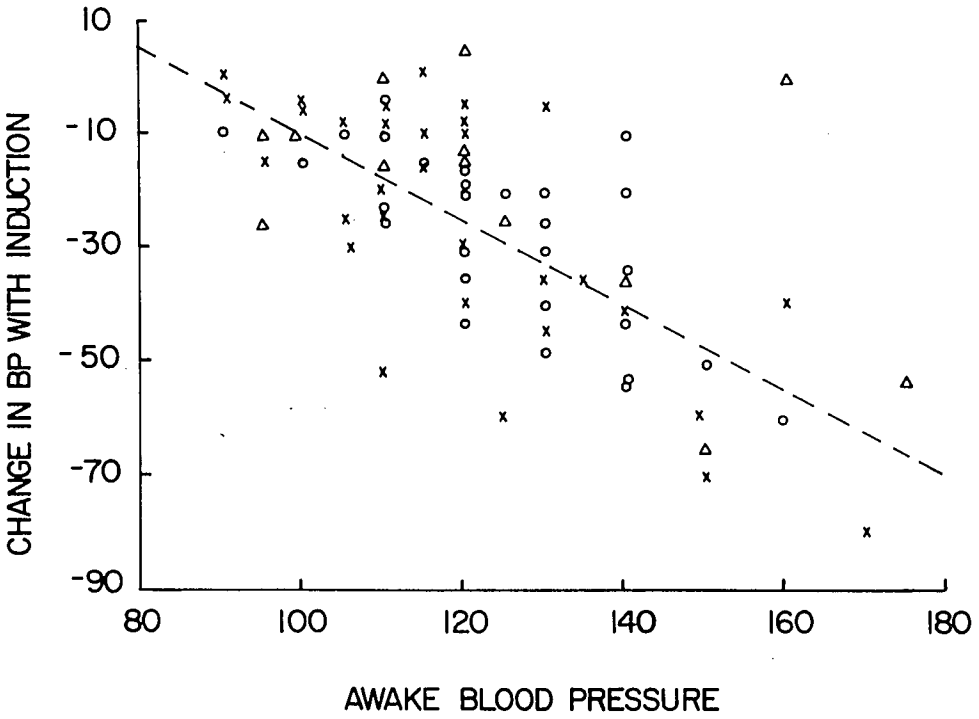

FIG. 7. Blood pressure (BP; torr) while awake *vs.* change in BP with induction of anesthesia. Analysis of covariance demonstrated no significant difference between agents; thus, the data for of all four anesthetic agents (x = enflurane, O = halothane, Δ = morphine) were pooled. The line is described as follows: Change in BP with induction = (−0.75) (BP while awake) + 66 (r = 0.71). *Note*: The change in rate-pressure product with induction can be described by the line obtained with the following formula: Change in rate-pressure product with induction = (−0.79) (rate-pressure product while awake) + 4699 (r = 0.77).

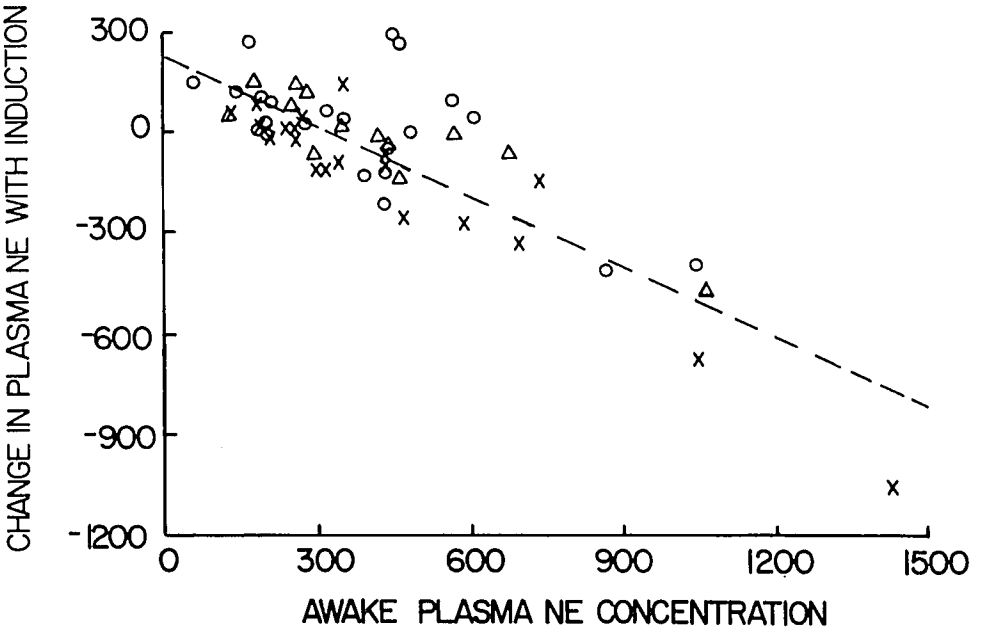

FIG. 8. Plasma norepinephrine (NE) concentration (pg/ml) while awake *vs.* changes in plasma NE concentration with induction of anesthesia. Analysis of covariance demonstrated no significant difference among agents; thus, the data for all three agents (x = enflurane, O = halothane, Δ = morphine) were pooled. The line can be described as follows: Change in plasma NE level with induction = (−0.70) (plasma NE level while awake) + 228 (r = 0.83).

slopes defining MAC and MAC BAR reflects the variable adrenergic response: At the highest concentration of each anesthetic, some patients had as great a response as the average patient did at the lowest concentration group for that anesthetic (fig. 9). Thus, deeper levels of anesthesia do not guarantee that individual sympathetic responses will be abolished, but do decrease or ablate the response for the population as a whole. The much greater steepness of the dose-response curve defining MAC compared with that for the adrenergic response also implies either that the site of anesthetic blocking action for each is different, or that the sensitivity of the sites is different.

While halothane, morphine-nitrous oxide, and spinal anesthesia all block the cardiovascular response to incision in a dose-dependent fashion, enflurane does not. Thus, early in an operative procedure, the cardiovascular response to incision may indicate the depth of halothane or morphine anesthesia; however, as anesthesia time increases, the cardiovascular response during halothane anesthesia may not be a reliable indicator.[21] Over the dosage range we studied (1.3–1.9 MAC), the cardiovascular response to incision did not help reveal the depth of enflurane anesthesia.

The changes in blood pressure, heart rate, or rate-pressure product from the awake state to the period after induction, regardless of anesthetic dose, show that anesthesia is the "great equalizer." Patients with higher heart rates and systolic blood pressures in the awake state had greater decreases in those variables with induction than did patients having lower values (figs. 6 and 7). In fact, if a patient's heart rate while awake was below 63 beats/min, heart rate tended to rise with induction, and vice versa. The change in heart rate with induction averaged 58 per cent of the difference between heart rate while awake and 63 beats/min. The change in blood pressure with induction averaged 75 per cent of the difference between systolic blood pressure while awake and 88 torr. The average for the change in rate-pressure product with induction was 79 per cent of the difference between rate-pressure product while awake and 5917 torr·beats/min. This great "equalizing" effect of anesthesia may be caused by the change in "anxiety" with induction of anesthesia. Thus, patients with high "anxiety" levels while awake experience more relief with induction; those who are not anxious have either a small change or no change in cardiovascular variables. This hypothesis is supported by the change in our stress reactant, plasma norepinephrine concentration with induction: the higher the plasma norepinephrine concentration, the greater the decrease (fig. 8). The change in plasma norepinephrine concentration averaged 70 per cent of the difference between plasma norepinephrine concentration while awake and 328 pg/ml. The dependence of the change in plasma norepinephrine concentration with induction of anesthesia on the initial level of plasma norepinephrine may explain the differing results of several animal studies.[5,22,23] Dupocas and Behrens[22] report increases in plasma norepinephrine from very low levels with induction of halothane anesthesia. During maintenance of halothane anesthesia in rats, Roizen *et al.*[5] found decreases from higher plasma norepinephrine levels while awake, and Perry and co-workers[23] reported

modest decreases in dogs during halothane anesthesia compared with levels after premedication.

Are MAC BAR_{50} or MAC BAR_{95} appropriate clinical doses? We do not know. In 1910, Crile[24] postulated that the stress response impeded patient recovery from surgery. However, according to Woodbridge,[25] stress-free or reflex-free surgery required a "deep" level of anesthesia; how much deeper was not quantified. The concept of MAC BAR is presented to quantitate how much deeper, to resolve further the question of what an appropriate depth of anesthesia would be and to guide assessment of the response to incision. MAC BAR_{50} or MAC BAR_{95} are larger doses than necessary in most patients to prevent movement in response to incision[3,19,20] or reflex coughing in response to endotracheal intubation[26,27] (table 5), but yet are able to be tolerated (only three healthy patients of more than 40 entering the study to whom the highest dose level was given could not tolerate that level). In addition, this data results from study of unpremediated healthy patients in acid-base balance; premedicated or sick patients, or those not in acid-base balance, may respond differently. The logit analysis transformation we used to obtain doses for MAC BAR_{50} and MAC BAR_{95} gives conservative approximations when extrapolations are necessary (*i.e.*, their variances are larger than need be).[7,28] When the use of such a high anesthetic dose is being considered, the risks and benefits should be compared with those associated with an alternative dose. One of the benefits of a high anesthetic dose would be reduction of the response to stress during surgery.

The conscious animal, including man, reacts to stress to survive. This reaction includes mobilization of energy stores, an increase in demands upon the heart and circulation, and a diversion of blood flow from tissues serving a less primary function (*e.g.*, gut, liver, kidney). Although these responses may be vital to the conscious animal on a short-term basis, they may be of no value or may be detrimental to the anesthetized patient undergoing surgery. No functional gain may result, and the cost in myocardial work, the expenditure of energy, and the potential inadequacy of oxygen delivery relative to need may be significant. Studies in healthy animals and humans have not demonstrated that increasing or decreasing stress by altering anesthetic concentrations is either harmful or beneficial.[14–18,29–31] In pregnant ewes,[29] the administration of less anesthesia, while associated with a decrease in uterine blood flow and an increase in plasma norepinephrine concentra-

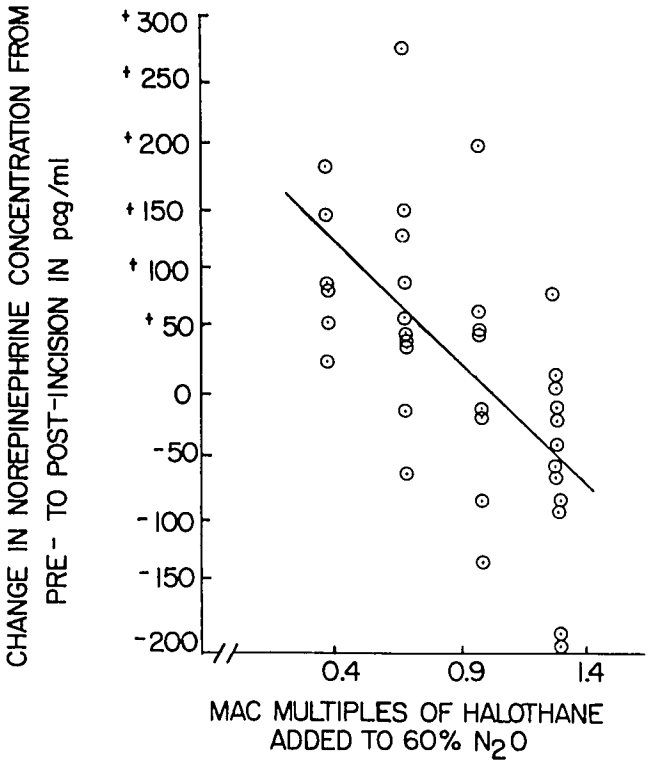

FIG. 9. Dose of halothane *vs.* change in plasma norepinephrine for individual patients (⊙) (r = 0.60). *Note*: Some circles represent two patients. The x-axis MAC values in this figure do not include the 0.57 MAC contribution of nitrous oxide that is included in the text and tables.

TABLE 5. Comparison of MAC with MAC EI and MAC BAR*

	MAC_{50}†	MAC_{95}	MAC EI_{50}‡	MAC EI_{95}	MAC BAR_{50}§	MAC BAR_{95}
Halothane	1.0 MAC 0.74 ± 0.03 per cent	1.2 MAC	1.3 MAC	1.7 MAC	1.5 ± 0.1 MAC	2.1 MAC
Enflurane	1.0 MAC 1.68 ± 0.04 per cent	1.1 MAC	1.4 MAC	1.9 MAC	1.6 ± 0.1 MAC	2.6 MAC
Morphine sulfate	—	—	—	—	1.13 ± 0.1 mg/kg plus 60 per cent N_2O	1.5 mg/kg plus 60 per cent N_2O

* Decimals for MAC equivalents have been rounded off to first order.

† Minimum alveolar concentration that inhibits movement in response to a noxious stimulus in 50 per cent of individuals.

‡ Minimum alveolar concentration that inhibits movement and coughing to endotracheal intubation in 50 per cent of individuals.

§ Minimum alveolar concentration that inhibits adrenergic response to skin incision in 50 per cent of individuals.

tion did not result in fetal compromise. In a study of patients with coronary artery disease,[31] although anesthesia lessened some of the increase in neuroendocrine response after incision, not enough anesthesia was given to fully block the stress response to sternal incision. Thus, the hypothesis that increasing anesthesia to decrease stress also decreases morbidity has not been tested.

This reasoning supposes that an "adequate" level of anesthesia should do more than render a patient immobile. If adverse effects (*e.g.*, metabolic, hepatic, renal, myocardial) result from a neuroendocrine response to stimulation, the hypothesis, "the less anesthetic the better," may be wrong. The use of MAC BAR_{50}, MAC BAR_{95}, or high levels of spinal anesthesia would markedly diminish or essentially abolish the intraoperative neuroendocrine stress response. However, greater depression of myocardial and respiratory function and an increased possibility of chemical (anesthetic) toxicity might result. The overall effect of using high anesthetic doses *vs.* "the-less-anesthetic-the-better" approach on perioperative morbidity and mortality remains to be determined.

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References

1. Braunwald E: Thirteenth Bowditch Lecture. The determinants of myocardial oxygen consumption. Physiologist 12:65–93, 1969
2. Hamilton WK: Do let the blood pressure drop and do use myocardial depressants! ANESTHESIOLOGY 45:273–274, 1976
3. Gregory GA, Eger EI II, Munson ES: The relationship between age and halothane requirement in man. ANESTHESIOLOGY 30:488–491, 1969
4. Stevens WC, Dolan WM, Gibbons RT, et al: The minimum alveolar concentrations (MAC) of isoflurane with and without nitrous oxide in patients of various ages. ANESTHESIOLOGY 42:197–200, 1975
5. Roizen MF, Moss J, Henry DP, et al: Effects of halothane on plasma catecholamines. ANESTHESIOLOGY 41:432–439, 1974
6. Henry DP, Starman BJ, Johnson DG, et al: A sensitive radioenzymatic assay for norepinephrine in tissues and plasma. Life Sci 16:375–384, 1975
7. Waud DR: On biological assays involving quantal responses. J Pharmacol Exp Ther 183:577–607, 1972
8. Snedecor GW, Cochran WG: Statistical Methods. Sixth edition. Ames, Iowa, Iowa State College Press, 1967, pp 419–460
9. Kopin IJ, Lake CR, Ziegler M: Plasma levels of norepinephrine. Ann Int Med 88:671–680, 1978
10. Roizen MF, Forbes AR, Miller RD, et al: Similarity between effects of pancuronium and atropine on plasma norepinephrine levels in man. J Pharmacol Exp Ther 211:419–422, 1979
11. Lake CR, Ziegler MG, Kopin IJ: Use of plasma norepinephrine for evaluation of sympathetic neuronal function in man. Life Sci 18:1315–1325, 1976
12. Weise VK, Kopin IJ: Assay of catecholamines in human plasma: Studies of a single isotope radioenzymatic procedure. Life Sci 19:1673–1685, 1976
13. Bevan JA: Some functional consequences of variation in adrenergic synaptic cleft width and in nerve density and distribution. Fed Proc 36:2439–2443, 1977
14. Philbin DM, Coggins CH: Plasma antidiuretic hormone levels in cardiac surgical patients during morphine and halothane anesthesia. ANESTHESIOLOGY 49:95–98, 1978
15. Reier CE, George JM, Kilman JW: Cortisol and growth hormone response to surgical stress during morphine anesthesia. Anesth Analg (Cleve) 52:1003–1010, 1973
16. Madsen SN, Brandt MR, Engquist A, et al: Inhibition of plasma cyclic AMP, glucose and cortisol response to surgery by epidural analgesia. Br J Surg 64:669–671, 1977
17. Watkins WD, Moss J, Lappas DG, et al: Vasoactive mediators and human cardiopulmonary bypass. ANESTHESIOLOGY 51 (3S):S97, 1979
18. Philbin DM, Emerson CW, Coggins CH, et al: Renin, catecholamine, and vasopressin response to the "stress" of anesthesia and surgery. ANESTHESIOLOGY 51(3S):S121, 1979
19. Eger EI II, Saidman LJ, Brandstater B: Minimum alveolar anesthetic concentration: A standard of potency. ANESTHESIOLOGY 26:756–763, 1965
20. Gion H, Saidman LJ: The minimum alveolar concentration of enflurane in man. ANESTHESIOLOGY 35:361–364, 1971
21. Eger EI II, Smith NT, Stoelting RK, et al: Cardiovascular effects of halothane in man. ANESTHESIOLOGY 32:396–409, 1970
22. Depocas F, Behrens WA: Effects of handling, decapitation, anesthesia, and surgery on plasma noradrenaline levels in the white rat. Can J Physiol Pharmacol 55:212–219, 1977
23. Perry LB, Van Dyke RA, Theye RA: Sympathoadrenal and hemodynamic effects of isoflurane, halothane, and cyclopropane in dogs. ANESTHESIOLOGY 40:465–470, 1974
24. Crile GW: Phylogenetic association in relation to certain medical problems. Boston Med Surg J 163:893–894, 1910
25. Woodbridge PD: Changing concepts concerning depth of anesthesia. ANESTHESIOLOGY 18:536–550, 1957
26. Yakaitis RW, Blitt CD, Angiulo JP: End-tidal halothane concentration for endotracheal intubation. ANESTHESIOLOGY 47:386–388, 1977
27. Yakaitis RW, Blitt CD, Angiulo JP: End-tidal enflurane concentration for endotracheal intubation. ANESTHESIOLOGY 50: 59–61, 1979
28. de Jong RH, Eger EI II: MAC expanded: AD_{50} and AD_{95} values of common inhalation anesthetics in man. ANESTHESIOLOGY 42:384–389, 1975
29. Shnider SM, Wright RG, Levinson G, et al: Uterine blood flow and plasma norepinephrine changes during maternal stress in the pregnant ewe. ANESTHESIOLOGY 50:524–527, 1979
30. Roizen MF, Moss J, Henry DP, et al: Effect of general anesthetics on handling- and decapitation-induced increases in sympathoadrenal discharge. J Pharmacol Exp Ther 204:11–18, 1978
31. Roizen MF, Wilkinson PL, Chatterjee K, et al: Does anesthesia alter myocardial stress during coronary artery surgery . . . A–V myocardial norepinephrine differences, a new index of myocardial stress, Catecholamines and Stress. Volume II. Edited by Usdin E, Kvetnansky R, Kopin IJ, New York, Elsevier 1980, pp 811–816