Time-Dependent Changes in Heart Rate and Pupil Size During Desflurane or Sevoflurane Anesthesia

Farzin Tayefeh, MD©, Merlin D. Larson, MD©, Daniel I. Sessler, MD©, Edmond I Eger II, MD©, and Terri Bowland, BS©,

*Department of Anesthesia and Perioperative Care, University of California, San Francisco, California; and †Department of Anesthesia and General Intensive Care, University of Vienna, Vienna, Austria

To better characterize alterations in autonomic function associated with prolonged anesthesia, we tested the hypothesis that the time-dependent effects of sevoflurane and desflurane differ. We studied seven male volunteers, each anesthetized for 8 h with 1.25 minimum alveolar anesthetic concentration desflurane on one study day and with 8 h sevoflurane on another. These volunteers did not undergo surgery and were minimally stimulated during the study. Measurements included blood pressure, heart rate, pupillary size and light reactivity, concentrations of serum catecholamines, and carbon dioxide production. Over time, heart rate and pupil size increased significantly. During 6 of the 14 anesthetics (45%), heart rate at some point exceeded 95 bpm; similarly, pupil size at some time exceeded 5 mm during 8 anesthetics (57%). In contrast, plasma catecholamine concentrations and carbon dioxide production remained unchanged, and blood pressure remained nearly constant. There are thus substantial time-dependent changes in autonomic functions during prolonged anesthesia, even in unstimulated, nonsurgical volunteers, but we could not detect a difference in these changes during desflurane compared with sevoflurane anesthesia. Implications: Pupillary size and heart rate changes are used to guide the delivery of anesthesia. In volunteers, pupil size and heart rate increased with increasing duration of constant desflurane or sevoflurane anesthesia. Thus, anesthetic duration alters heart rate and pupil size independent of surgery and changes in anesthetic delivery. (Anesth Analg 1997;85:1362-6)

Measures of autonomic function, such as blood pressure and heart rate, are frequently used to guide anesthetic administration. However, these measures change over time during prolonged anesthesia, even without surgical stimulation. For example, during prolonged anesthesia with some volatile agents, cardiac output during the fifth hour of anesthesia exceeds that observed during the first hour (1-6).

Desflurane and sevoflurane differ in their effects on the autonomic nervous system. Rapid increases in the inspired desflurane concentration (above 5-6%) augment heart rate, blood pressure, and sympathetic nerve activity (7), whereas similar increases in sevoflurane concentration do not (8). These observations suggest that changes in autonomic function associated with prolonged anesthesia might differ during desflurane versus sevoflurane administration.

Accordingly, to better characterize alterations in autonomic function associated with prolonged anesthesia, we measured blood pressure, heart rate, pupillary size and light reactivity, concentrations of serum catecholamines, and carbon dioxide production during desflurane and sevoflurane administration in unstimulated volunteers. Specifically, we tested the hypothesis that the time-dependent autonomic effects of sevoflurane and desflurane differ.

Methods

With approval of the University of California-San Francisco Committee on Human Research and informed written consent, we studied seven male volunteers who simultaneously participated in an evaluation of anesthetic toxicity (9). Each was given one anesthetic with de: Three were initial 2 wk separated the into the study in physical examination: that did not reveal volunteers fasted a

Protocol

On each study day, a padded table w pillow. A canula Anesthesia was inc tovecuronium bromide: then intubated and to maintain end-tidal gas inflow rate equ itently maintain each anesthetic equ: sevoflurane (50%)

Lactated Ringer's basal rate of 1-3 solutions less than 50% fluid administration the table. Total fluid anesthesia was typ w were repeatedly fThe position of the heac administration was pired from the at position. On awa whether they expected

Measurements

End-tidal volatile partial pressures were measured as a dedicated analyzer (Datex) also measured mid from samples gathered through a 1.5-L breathing circuit was measured. From mixed expired ventilation, we called hourly intervals saturation (SPO2) with three-lead electrocardiogram pulse oximeter (Hellige) to diastolic blood pressure (Dinamap TM) from the right arm. Core temperature was maintained with a thigh-warmer. We san
anesthetic with desflurane and one with sevoflurane. Three were initially given sevoflurane, and at least 2 wk separated the two anesthetics. Criteria for entry into the study included a normal medical history, physical examination, and a urine toxicology study that did not reveal the presence of illicit drugs. The volunteers fasted at least 8 h before each study.

Protocol

On each study day, the volunteers were positioned on a padded table with their heads on a plastic foam pillow. A cannula was inserted into an arm vein. Anesthesia was induced with propofol (2 mg/kg) and vecuronium bromide (0.1 mg/kg); the trachea was then intubated and the lungs mechanically ventilated to maintain end-tidal Pco2 near 35 mm Hg. The fresh gas inflow rate equaled 2 L/min. Anesthesia was subsequently maintained with end-tidal concentrations of each anesthetic equal to 1.25 minimum alveolar anesthetic concentration (MAC) (9% desflurane and 3.0% sevoflurane) in 50% oxygen and 50% nitrogen.

Lactated Ringer’s solution was administered at a basal rate of 1–3 mL·kg⁻¹·h⁻¹. Mean blood pressures less than 50 mm Hg were treated by additional fluid administration and/or by lowering the head of the table. Total fluid administration during 8 h of anesthesia was typically 1 L. The subjects’ extremities were repeatedly flexed and extended each hour, and position of the head was changed. After 8 h, anesthetic administration was discontinued, secresions were aspirated from the throat, and the endotracheal tube was removed. On awakening, the volunteers were asked whether they experienced any painful sensations.

Measurements

End-tidal volatile anesthetic concentrations and CO₂ partial pressures were measured with an Ultima infrared analyzer (Datex Corp., Helsinki, Finland). We also measured expired CO₂ concentrations from samples gathered after passage of exhaled gases through a 1.5-L mixing chamber. Expired minute ventilation was measured with a calibrated spirometer. From mixed expired CO₂ concentration and ventilation, we calculated carbon dioxide production at hourly intervals. Heart rate and oxyhemoglobin saturation (SpO₂) were monitored continuously using a three-lead electrocardiography and a Nellcor N200 pulse oximeter (Hayward, CA). Systolic, mean, and diastolic blood pressures were measured oscillometrically (Dinamap TM 1846 SX; Critikon Inc., Tampa, FL) from the right arm.

Core temperatures were monitored with distal esophageal thermocouples (Mon-a-Therm, Inc., St. Louis, MO), and maintained near 37°C with a forced-air warmer. We sampled venous blood after 1, 4, and 8 h of anesthesia; these specimens were subsequently analyzed by the University of California-San Francisco clinical laboratory for serum catecholamines (total, epinephrine, dopamine, and norepinephrine).

As previously described (10), we used a portable infrared pupillometer (Fairville Medical Optics, Inc., Amersham, UK) to measure pupillary responses from the right eye of each volunteer. The pupillometer was programmed to provide a 0.5-s, 130-candela/m² pulse of light, then scan the pupil for 2 s. Three scans were averaged before the induction of anesthesia, and again at hourly intervals throughout anesthesia. Pupil size and the light-reflex amplitude (expressed as a percentage of pupil size) were calculated from the scans. During these measurements, the left eye was covered with an opaque bandage, and ambient light was excluded from the right eye with a rubber cup.

Data Analysis

Induction of anesthesia was considered elapsed time zero. We compared pupil size, heart rate, mean arterial pressure, pupillary light reflex (%), carbon dioxide production, core temperature, norepinephrine, and total catecholamines 1 and 8 h after each anesthetic and 1 and 8 h between anesthetic types using two-tailed, paired t-tests. Data are expressed as means ± SD; P < 0.05 was considered statistically significant.

Time-dependent changes in heart rate, pupil size, light reflex, blood pressure, and CO₂ production were evaluated using linear regression over the period from 1 to 8 elapsed hours. Comparisons between desflurane and sevoflurane were made using analysis of variance of regression coefficients between groups (11).

Results

Induction of general anesthesia significantly decreased systolic, mean, and diastolic blood pressures; heart rate; pupil size; and reactivity. Over time, however, heart rate and pupil size gradually increased (Figs. 1 and 2). As a result, heart rate and pupil size each increased significantly from 1 to 8 h of anesthesia. During 6 of the 14 anesthetics (45%), heart rate at some point exceeded 95 bpm; similarly, pupil size at some time exceeded 5 mm during 8 anesthetics (57%). Light reactivity decreased significantly during sevoflurane but not during desflurane anesthesia. Other measures of autonomic function, including pupil size, heart rate, blood pressure, and CO₂ production, did not differ significantly between desflurane and sevoflurane (Table 1). The slopes of linear regression curves for heart rate and pupil size versus time were not different for desflurane compared with sevoflurane anesthesia.
Discussion

An abrupt increase in the concentration of desflurane above 1 MAC can produce substantial but transient sympathetic activation and increases in heart rate and blood pressure (7). Under the steady-state circumstances of our study, however, we did not observe clinically important differences between sevoflurane and desflurane. In this respect, our results are similar to those showing that desflurane and sevoflurane comparably influence baroreceptor function (8). Thus, our data do not support our hypothesis that the time-dependent effects of sevoflurane and desflurane differ.

Measures of autonomic function one hour after induction of anesthesia were consistent with a parasympathetic predominance compared with the unanesthetized state. Pupils were hyporeactive and constricted, and blood pressures and heart rates were below control values. Similar changes are observed during the transition from wakefulness to the initial stage of slow-wave sleep (12). Over time, however, parasympathetic activity seemed to wane. The observed changes in autonomic function were clinically important, and included pupil diameters >5 mm and heart rates >95 bpm during approximately half the anesthetics. During surgery, these responses might suggest an autonomic “stress response” and provoke administration of additional anesthetic or analgesic agents.

Price et al. (2) demonstrated that the initial halothane-induced reduction of cardiac output recovered to unanesthetized levels by the third hour of anesthesia. Return of the heart rate to and above pre-anesthetic values was associated with a gradual decrease in peripheral vascular resistance. Similar changes have been demonstrated during the administration of other volatile anesthetics (3–6). For example, heart rates and blood pressures increase during prolonged methoxyflurane anesthesia, although cardiac output and peripheral resistance remain unchanged (4). Heart rates also consistently increase over time during halothane, isoflurane, flurxene, ether, cyclopropane, and desflurane anesthesia (5).

Price et al. (2) observed that blocking β-adrenergic receptors with intravenous sotalol prevented these changes. They thus suggested that β-adrenergic activity during halothane anesthesia increases over time. However, recent evidence indicates that sotalol, in addition to its β-adrenergic blocking activity, has a bradycardic action mediated via changes in potassium conductance (13). It thus remains possible that the absence of autonomic changes in their sotalol-treated volunteers resulted from actions of the drug not mediated by β-adrenergic receptors.

The theory that halothane activates β-adrenergic receptors (2) has not been substantiated. Subsequent studies demonstrate that β1-receptors (cardiac β-adrenergic receptors (15). Depressor effect diminish over time. Why heart rate increases in anesthetics remains unclear. Plasma catecholamine increase over time. The release of catecholamines would be expected in a system that increases catecholaminergic activity. The secretion of adrenaline is likely to be influenced by the heart rate and p-value.

Table 1. Autonomic

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Desflurane</th>
<th>Sevoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pupil size (mm)</td>
<td>6.5 ± 0.5</td>
<td>7.0 ± 0.7</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>75 ± 5</td>
<td>80 ± 6</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>100 ± 5</td>
<td>105 ± 8</td>
</tr>
<tr>
<td>CO2 production (%)</td>
<td>5 ± 1</td>
<td>6 ± 1</td>
</tr>
<tr>
<td>Core temperature</td>
<td>36.5 ± 0.5</td>
<td>36.8 ± 0.5</td>
</tr>
<tr>
<td>Norepinephrine (pg)</td>
<td>20 ± 5</td>
<td>25 ± 6</td>
</tr>
<tr>
<td>Total catecholamine</td>
<td>150 ± 10</td>
<td>130 ± 12</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard error of the mean. *P < 0.05 was considered significant. Differences between groups were analyzed using the Tukey-Kramer post-hoc test.

The pupils dilate. Others have similar pupillary dilation and accommodation after both isoflurane and halothane (5). Although β-adrenergic receptors are not present on the pupillary dilator muscle in humans, they do not occur in humans. Does it not dilate the pupil or induce pupillary constrictions? Consecutive dilations would suggest that the receptor is responsible for the dilator response.

As an alternative, propose that prolonged general anesthesia may have been associated with a decrease in the number of available sympathetic nerve fibers.

Although norepinephrine, epinephrine, dopamine, and total catecholamine concentrations always remained within the normal range, norepinephrine concentrations were significantly greater during desflurane than sevoflurane anesthesia. Norepinephrine concentrations decreased slightly during desflurane and sevoflurane anesthesia (Table 1). All volunteers complained of nausea, mental cloudiness, and headache during the initial postsurgical period. One subject complained of pain and numbness in the left leg, which resolved over the 3-h recovery period. During recovery, two volunteers complained of discomfort resulting from a full bladder; their autonomic changes during those anesthetics were similar to those observed in other volunteers.

Figure 1. Pupil size gradually increased during prolonged desflurane and sevoflurane anesthesia. Desflurane: heavy regression line, $r^2 = 0.68$. Sevoflurane: light regression line, $r^2 = 0.76$. Time zero (before induction of anesthesia) was excluded from the regression calculations. See Table 1 for additional statistical analysis.

Figure 2. Heart rate gradually increased during prolonged desflurane and sevoflurane anesthesia. Desflurane: heavy regression line, $r^2 = 0.76$. Sevoflurane: light regression line, $r^2 = 0.91$. Time zero (before induction of anesthesia) was excluded from the regression calculations. See Table 1 for additional statistical analysis.
Table 1. Autonomic Responses During Prolonged Sevoflurane or Desflurane Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Desflurane</th>
<th>Sevoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before 1 h</td>
<td>8 h</td>
</tr>
<tr>
<td>Pupil size (mm)</td>
<td>7.3 ± 1.4</td>
<td>2.2 ± 0.5</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>77 ± 20</td>
<td>73 ± 11</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>74 ± 12</td>
<td>56 ± 5</td>
</tr>
<tr>
<td>Light reflex (%)</td>
<td>34 ± 13.7</td>
<td>8 ± 5.6*</td>
</tr>
<tr>
<td>CO₂ production (mL/min)</td>
<td>245 ± 30</td>
<td>243 ± 20*</td>
</tr>
<tr>
<td>Core temperature (°C)</td>
<td>36.1 ± 0.1</td>
<td>36.8 ± 0.3*</td>
</tr>
<tr>
<td>Norepinephrine (ng/L)</td>
<td>—</td>
<td>346 ± 39*</td>
</tr>
<tr>
<td>Total catecholamine (ng/L)</td>
<td>—</td>
<td>396 ± 56*</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD.

P < 0.05 was considered statistically significant.

MAP = mean arterial pressure.

* Differences between 1 h and 8 h.

Significant differences between the anesthetic types at each measurement time.

studies demonstrated that halothane depresses cardiac β1-receptors (14); similarly, sevoflurane inhibits cardiac β-adrenergic receptors through an action on G proteins (15). Depression of β-adrenergic receptors might diminish over time. However, that would not explain why heart rates increased to values exceeding preanesthetic rates in many of our volunteers. Prolonged desflurane anesthesia also fails to alter muscle blood flow, which further suggests that the β-receptor function remains unchanged (6).

Plasma catecholamine concentrations did not increase over time during general anesthesia. Carbon dioxide production also remained constant, although it would be expected to increase with sympathetic nervous system activation (16). The absence of increased catecholamine concentrations suggests that generalized activation of the sympathetic nervous system is unlikely to have caused the observed increases in heart rate and pupil size.

The pupils dilated progressively during anesthesia. Others have similarly documented time-dependent pupillary dilation during stable ether, fluroxene, isoflurane, halothane, and cyclopropane anesthesia (5). Although β-adrenergic receptors control pupillary size in some mammalian species (17), they apparently do not in humans. Topical isoproterenol, for example, does not dilate pupils in humans (18). Furthermore, β-adrenergic receptors do not mediate stimulation-induced pupillary dilation during desflurane anesthesia (19). Consequently, activation of β-adrenergic receptors alone are unlikely to explain concurrent pupillary dilation and tachycardia. Instead, these observations would require changes in at least two different receptor types: β-adrenergic receptors at the sinoatrial node and either muscarinic or α1-adrenergic receptors at the iris (20).

As an alternative to β-adrenergic activation, we propose that autonomic changes associated with prolonged general anesthesia result from progressive inhibition of two parasympathetic loci: the pupilloconstrictor nucleus (21) and the vagal nucleus (22). We recently demonstrated that pupillary dilation in response to noxious stimulation during desflurane anesthesia is not sympathetically mediated (23). Experimental evidence in animals suggests that pupillary dilation during anesthesia results largely from inhibition of the pupilloconstrictor nucleus (21). Progressive inhibition of these nuclei would thus produce the observed increase in heart rate and pupillary dilation and would similarly explain the gradual reduction in the light reflex (24). Apparent sympathetic dominance would, in this case, result when tolerance to volatile anesthetic effects allowed reemergence of normal, tonic inhibition of parasympathetic nuclei. This hypothesis would also explain why these autonomic changes are rarely observed with opioid-supplemented anesthetics. Opioids are thought to interfere with inhibition of the pupilloconstrictor nucleus (19,25) and are known to increase vagal tone via a central effect (26).

Other potential causes for the time-dependent changes in autonomic functions during prolonged anesthesia have been examined and rejected. Prolonged anesthesia decreases neither plasma volume nor pH (2), both factors that might alter heart rate. Similarly, systemic oxygen consumption remains constant over time (2), and we strictly controlled body temperature and end-tidal PCO₂. That the observed changes in autonomic function might result from active metabolites of the primary anesthetics seems unlikely, because sevoflurane is metabolized nearly 200 times more than desflurane (27), yet heart rates and pupil sizes were comparable with each. We used propofol and vecuronium during the induction of general anesthesia. The elimination of these drugs should be nearly complete after one hour of anesthesia; it is therefore unlikely that these were a factor in the changes that occurred over the following seven hours.

One hour after intubation with a paralyzing anesthetic and constricting muscle, we were able to observe eye movement during the initial stage of anesthesia, whereas, parasympathetic tone was low. The observed moderate impairment of pupillary movement was noted to provoke anotologic and analgesic agents. It then became obvious that the initial systolic blood pressure was elevated. For example, during prolonged anesthesia, although myocardial function unchanged, the cardiac output decreased over time in patients, ether, cyclopropane (5). Preventing β-adrenergic activation prevented these adrenergic activities over time. That sotalol, in g. activity, has a role in potassium channels that predilates the heart, and that sotalol-treated patients did not maintain β-adrenergic blockade. Subsequent

A potential etiology for progressive autonomic activation might be a gradually increasing noxious stimulus. Hypertension and tachycardia may result from a full bladder (28). However, fluid administration during anesthesia in our fasting volunteers equaled approximately I L and only two of the seven volunteers complained of any bladder discomfort on emerging from anesthesia. However, we did not insert Foley catheters in our volunteers; it therefore remains possible that bladder discomfort contributed to the autonomic activation we observed. We also cannot exclude time-dependent alterations in smooth muscle function or sinus node excitability. Prolonged anesthesia might gradually alter the expression of G protein-coupled receptors within the brain or peripheral autonomic nervous system.

We manipulated the participants' arms and legs hourly. Nonetheless, one volunteer suffered postanesthetic musculoskeletal discomfort. Changes in his autonomic functions did not differ noticeably from the other volunteers, none of whom experienced similar pain. It thus seems unlikely that musculoskeletal pain or positional discomfort was the etiology of the observed autonomic changes. On emergence, volunteers did complain of headache, but whether this sensation would stimulate the anesthesitized subject is unknown. Norepinephrine, epinephrine, and dopamine concentrations did not increase over time, as might be expected if noxious stimulation were the cause. Price et al. (2) were also unable to detect a source of noxious stimulation that might alter the autonomic nervous system function.

In summary, we observed substantial time-dependent changes in autonomic functions during prolonged anesthesia in unstimulated, nonsurgical volunteers. Increased heart rates and enlarged pupils may arise from progressive inhibition of brainstem parasympathetic nuclei. These autonomic nervous system changes were similar during desflurane and sevoflurane anesthesia.

References
17. Mochizuki M. The beta adrenergic effects in the spindriller pu-

Argon Pneumopel
Claude Mann, M Jean M. Fabre, M
*Department of Anes

We investigated gas, as a replace erance of argo with that of CO2 were anesthetiz or CO2 (n = 9 15 min Hg ove rations of each ga made. Cardion Transesophageal ing were assess argon pneumonia change from bary excretion c (MAP), mean pitemic and pult

L aparoscopic st bon dioxide (accurate visu tions. This pneumo hemodynamic char ise of hypercap ated with laparoscoc ported (3). The o pa tients with cardi clinically important sive surgery require moperitoneum and of vascular injury. cur and may invol cations (6). Thus, c s and treatment i

Interestingly, sit be found in a porc searches for an alte flation. The ideal i

L

Address corresponds DAR B, Hôpital Saint-E