Arterial baroreflex function in humans anaesthetized with sevoflurane†

M. Tanaka* and T. Nishikawa

Department of Anaesthesia, Akita University School of Medicine, Hondo 1-1-1, Akita-shi, Akita-ken 010-8543, Japan

*To whom correspondence should be addressed

Volatile anaesthetic agents attenuate arterial baroreflex function, while noxious stimuli may modify baroreflex-induced circulatory responses during anaesthesia. We have examined baroreflex control of heart rate during the entire course of sevoflurane anaesthesia in adult patients undergoing surgical procedures. Baroreflex sensitivity was assessed in nine healthy patients undergoing general anaesthesia with sevoflurane. After an 8–10-h fast and no premedication, measurements of R-R intervals were made at conscious baseline (awake), during 2% end-tidal sevoflurane and 67% nitrous oxide before incision (anaesthesia), during surgery at 2% end-tidal sevoflurane and 67% nitrous oxide (surgery) and 20 min after extubation (recovery). Baroreflex responses were triggered by bolus i.v. injections of phenylephrine 50–100 µg and nitroprusside 100–200 µg to increase and decrease systolic arterial pressure by 20–30 mm Hg, respectively. Baroreflex sensitivities to both pressor and depressor tests were significantly depressed during anaesthesia, surgery and the recovery periods compared with awake values. Pressor test sensitivity during recovery increased significantly from that during surgery (mean 6.16 (SD 2.95) vs 4.42 (3.19) ms mm Hg⁻¹; P<0.05), but was still significantly less than the awake value (22.50 (17.02) ms mm Hg⁻¹). No improvement in the depressor test sensitivity was seen during the recovery period.

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Arterial baroreflex function, an important neural control system for maintaining cardiovascular stability, is depressed by volatile anaesthetic agents in both humans and animals.1–8 Halothane,1,2 enflurane,3 isoflurane4,5 and desflurane6 attenuate baroreflex control of heart rate (HR) in humans, while nitrous oxide exerts minimal or slightly stimulatory effects.1–3 Sevoflurane is also a depressant of the baroreflex–sympathetic reflex system in rabbits.7 However, the effects of sevoflurane on arterial baroreflex function have not been examined in humans.

In contrast to the isolated effect of each anaesthetic agent, perioperative alterations of arterial baroreflex function have not been well documented in humans. Noxious stimuli elicited by surgical procedures may modify baroreceptor-mediated circulatory responses,9 while stress-induced increases in circulating catecholamines during surgery and recovery may modulate baroreflex sensitivity through sensitizing baroreceptors.10,11 Previous studies suggest rapid recovery of baroreflex sensitivity,12,13 but these data are confounded by the use of morphine12 and atropine13 premedication, in addition to elderly patients.13

In this study, we have examined the effects of sevoflurane anaesthesia on arterial baroreflex control of HR over the entire course of clinical anaesthesia. We hypothesized that baroreflex sensitivity would recover rapidly as sevoflurane has relatively low blood and tissue solubilities.14 We investigated young, healthy, unpremedicated surgical patients.

Patients and methods

We studied nine ASA I patients, aged 20–53 yr, undergoing general anaesthesia for elective superficial surgery. Surgery included removal of a median cervical cyst (two patients), plastic surgery involving the hand and forehead (five) and maxillary sinus surgery (two). Patients consuming alcoholic beverages daily, those with a history of cardiovascular, pulmonary or neurological disorders or receiving any medication in the 2 weeks before the study were excluded. Also, patients were not allowed caffeine-
containing beverages for at least 48 h before the study. The study was approved by the Institutional Research Committee, and informed consent was obtained from each patient. All patients arrived at the operating room after an 8–10-h fast. No premedication was given.

An electrocardiograph monitor (lead II), peripheral i.v. catheter, arterial (radial) pressure catheter and a HR monitor (tachometer) were placed in each patient while breathing supplementary oxygen 6 litre min\(^{-1}\) via a face mask in the supine position. The electrocardiogram, HR and systolic arterial pressure (SAP) were recorded continuously on a polygraph. To assess overall cardiac accelerator nerve function, each patient was asked to give three forceful coughs spaced evenly over 3 s when instructed, each beginning with an explosive expiratory effort followed by rapid inspiration.

Pressor and depressor tests were then performed using i.v. injections of phenylephrine 50–100 µg and nitroprusside 100–200 µg to increase and decrease SAP by 20–30 mm Hg, respectively, before induction of general anaesthesia (awake). These doses were chosen based on a previous study\(^{13}\) and on our pilot study in a similar age group. A period of stabilization (usually 5 min) between the pressor and depressor tests allowed HR and SAP to return to pre-test values (±5%).

Patients were anaesthetized in the supine position with thiamylal 5 mg kg\(^{-1}\) i.v., and tracheal intubation was facilitated by vecuronium 0.1 mg kg\(^{-1}\) i.v. After tracheal intubation, patients’ lungs were ventilated mechanically (tidal volume 10–12 ml kg\(^{-1}\) at a ventilatory frequency of 8–10 bpm) with 67% nitrous oxide and 2% end-tidal sevoflurane in oxygen, while end-tidal carbon dioxide was maintained at approximately 4.7 kPa. Inspired sevoflurane concentration was adjusted frequently to maintain end-tidal concentrations at 2%. The desired end-tidal sevoflurane concentration was maintained constant for at least 20 min before the next test was performed. The second pressor and depressor tests were performed in a similar manner before the beginning of the surgical procedure (anaesthesia). The third set of tests were performed 60 min after the start of surgery (surgery). Although inspired sevoflurane concentrations were changed according to the degree of stimulation and haemodynamic responses during surgery, end-tidal sevoflurane concentration was maintained at 2% for at least 20 min before the tests.

On completion of surgery, sustained tetanic contracture for 5 s was documented by a nerve stimulator with its electrodes located over the ulnar nerve, and hence neuromuscular block was not antagonized. After confirming return of adequate spontaneous respiration, responses to verbal commands, and when end-tidal sevoflurane concentration was less than 0.2%, the trachea was extubated. Patients were then left undisturbed breathing supplementary oxygen 6 litre min\(^{-1}\) via a face mask for 20 min with a stable HR and SAP. Then, the last set of pressor and depressor tests were performed (recovery). No other drugs, including opioids, were given during the entire study.

Arterial blood samples were obtained for measurement of arterial blood-gas tensions, plasma concentrations of potassium, sodium, ionized calcium and glucose before each set of tests. During surgery, all patients received lactated Ringer’s solution only, at a rate adjusted to maintain urinary output at more than 1 ml kg\(^{-1}\) h\(^{-1}\). No patient received blood or blood products during surgery.

Pressor and depressor test data were analysed using least squares linear regression analysis on the linear portion of the sigmoid relation between SAP and R-R interval, where each R-R interval was plotted as a function of the preceding SAP during expiration. Only the regression slopes with the square of the correlation coefficient ($r^2$) greater than 0.6 were included for analysis. All data are presented as mean (SD). Changes in baroreflex sensitivity during various stages were analysed by repeated measures analysis of variance (one-way ANOVA) followed by paired $t$ test with Bonferroni’s correction to adjust for multiple comparisons. $P<0.05$ was accepted as the minimum level of statistical significance.

**Results**

We studied three men and six women. Mean age, weight and height were 31 (range 20–53) yr, 56.8 (SD 7.5) kg and 165 (10) cm, respectively. Mean increase in HR in response to three forceful coughs was 20 (7) beat min\(^{-1}\). Duration of surgery was 154 (110) min and that of anaesthesia 213 (116) min. Estimated blood loss was 161 (185) ml and 1883 (1289) ml of lactated Ringer’s solution were administered during operation.

SAP decreased significantly during anaesthesia and surgery, but returned to awake baseline values during the recovery period (Table 1). HR did not change during anaesthesia or surgery, but increased significantly during the recovery period (Table 1). Arterial blood-gas analysis revealed that $P_{O_2}$, obtained while patients were breathing oxygen via a face mask, was significantly greater than that while patients were maintained at an $F_{O_2}$ of 0.33 during controlled ventilation. Oxygen saturation was ≥99%. In contrast, $P_{ACO_2}$ remained unchanged during anaesthesia and surgery, but increased significantly during the recovery period (Table 1). There was no significant difference in plasma electrolyte values, glucose or haemoglobin concentrations.

After i.v. injection of phenylephrine and nitroprusside, SAP increased and decreased by 20–30 mm Hg, respectively (Table 1). Pressor and depressor test sensitivities decreased significantly after induction of general anaesthesia, before surgery, compared with awake values (68 (15)% decrease for the pressor test and 29 (17)% decrease for the depressor test; $P<0.05$ (Fig. 1). During surgical stimulation, the slopes of both tests were depressed significantly by 2% end-tidal sevoflurane and 67% nitrous oxide in oxygen (77
Table 1 Pre-test systolic arterial pressure (SAP) and heart rate (HR), mean changes in SAP after the pressor and depressor tests, pre-test arterial blood-gas and electrolyte analysis, and blood glucose and haemoglobin (Hb) concentrations while awake (Awake), after induction of anaesthesia (Anaesth.), during surgery (Surg.) and recovery (Recov.) (mean (sd)). *P<0.05 vs awake values.

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<tbody>
<tr>
<td>Pre-test SAP (mm Hg)</td>
<td>137 (14)</td>
<td>97 (13)*</td>
<td>110 (14)*</td>
<td>144 (17)</td>
</tr>
<tr>
<td>Pre-test HR (beat min⁻¹)</td>
<td>66 (11)</td>
<td>70 (10)</td>
<td>67 (11)</td>
<td>83 (15)*</td>
</tr>
<tr>
<td>Mean changes in SAP (mm Hg)</td>
<td>Pressor test</td>
<td>23</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Depressor test</td>
<td>-27</td>
<td>-25</td>
<td>-23</td>
</tr>
<tr>
<td>pHa</td>
<td>7.40 (0.02)</td>
<td>7.41 (0.02)</td>
<td>7.40 (0.02)</td>
<td>7.36 (0.03)*</td>
</tr>
<tr>
<td>pCO₂ (kPa)</td>
<td>5.3 (0.3)</td>
<td>5.1 (0.4)</td>
<td>5.1 (0.4)</td>
<td>5.7 (0.4)*</td>
</tr>
<tr>
<td>pO₂ (kPa)</td>
<td>36.7 (7.4)</td>
<td>24.1 (2.9)*</td>
<td>24.0 (3.1)*</td>
<td>36.7 (8.9)</td>
</tr>
<tr>
<td>Na (mmol litre⁻¹)</td>
<td>137 (1)</td>
<td>137 (1)</td>
<td>137 (2)</td>
<td>138 (2)</td>
</tr>
<tr>
<td>K (mmol litre⁻¹)</td>
<td>3.5 (0.2)</td>
<td>3.6 (0.2)</td>
<td>3.5 (0.1)</td>
<td>3.5 (0.2)</td>
</tr>
<tr>
<td>Ca²⁺ (mmol litre⁻¹)</td>
<td>0.98 (0.12)</td>
<td>0.94 (0.09)</td>
<td>0.97 (0.06)</td>
<td>0.95 (0.11)</td>
</tr>
<tr>
<td>Blood glucose (mmol litre⁻¹)</td>
<td>5.5 (0.4)</td>
<td>5.7 (0.8)</td>
<td>6.1 (0.8)</td>
<td>6.3 (0.8)</td>
</tr>
<tr>
<td>Hb (g dl⁻¹)</td>
<td>12.6 (0.7)</td>
<td>12.3 (0.6)</td>
<td>12.3 (0.8)</td>
<td>12.0 (1.0)</td>
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(15)% decrease for the pressor test and 37 (27)% decrease for the depressor test compared with awake values; P<0.05 (Fig. 1). Twenty minutes after tracheal extubation, when end-tidal sevoflurane concentration was <0.2%, pressor test sensitivity recovered partially and increased significantly compared with that during surgery, but was still significantly less than that of awake baseline values. Recovery of baroreflex sensitivity after surgery was not documented with the depressor test (Fig. 1). All but five $r^2$ values between SAP and R-R intervals were greater than 0.7. No significant correlation was demonstrated between age and duration of surgery vs the baroreflex slope of either test, during any study interval. There were no significant differences in pressor and depressor sensitivities between the three types of surgery.

Analysis of post-cough peak HR changes and baroreflex sensitivities revealed statistically significant correlations after the awake pressor ($r^2 >0.7$) and depressor ($r^2 >0.9$) tests. However, there was no significant correlation between post-cough HR changes and baroreflex sensitivities during anaesthesia, surgery or the recovery period ($r^2$ all <0.3).

**Discussion**

The major finding of our study was that arterial baroreflex sensitivity, determined by both pressor and depressor tests, was depressed significantly during the entire course of sevoflurane anaesthesia in humans. Profound depression of baroreflex function during anaesthesia in our study was considered to be caused primarily by sevoflurane because of several factors. First, according to similar work using halothane and enflurane, concomitant administration of nitrous oxide exerts minimal or slightly stimulatory effects on baroreflex sensitivity. Second, although thiopental was used for induction of anaesthesia in our study, its depressive effect on arterial baroreflex function dissipates within 10 min of administration. In our study, more than 20 min had elapsed before the second set of tests (anaesthesia period). Third, hyperoxia, seen while awake and during anaesthesia in our study, would not have played a role in modulating baroreflex function, as hyperoxia either alone or in combination with halothane does not alter baroreflex sensitivity.
Our results also indicated that baroreflex sensitivity was similarly depressed during surgery. Although noxious stimuli caused by surgery, which produces 'cortical arousal', may modify baroreceptor-mediated circulatory responses and may evoke sensitization of baroreceptors through increases in plasma catecholamines, depression of baroreflex sensitivity was found to be of a similar extent to that determined during anaesthesia before surgery. In our study, the surgical procedure was not terminated while performing the pressor and depressor tests, and baroreflex slopes had $r^2$ values $>0.77$ (mostly $>0.9$). These results suggest that the theoretical antagonistic effects of neurological and endocrinological alterations elicited by surgery on baroreflex function were overridden by the predominantly depressive effect of sevoflurane. Indeed, previous clinical studies failed to demonstrate changes in arterial baroreflex function during surgery with methohexitol, halothane, enflurane or isoflurane anaesthesia. However, we cannot exclude the possibility that baroreflex sensitivity may be improved with more invasive surgical procedures.

Recovery of arterial baroreflex function was delayed considerably after sevoflurane anaesthesia. Even though partial recovery of pressor test sensitivity was observed 20 min after extubation, 73% and 50% reductions in pressor and depressor test sensitivities, respectively, imply that patients are still vulnerable to haemodynamic perturbations in the immediate postoperative period. Depressed baroreflex sensitivity during the recovery period does not seem to be the result of technical difficulties inherent in obtaining stable SAP and HR, as all patients were undisturbed, breathing quietly and haemodynamically stable. In addition, all $r^2$ values during the recovery period were greater than 0.85. The effect of mild hypercapnia on baroreflex function, of the degree seen in our study, is considered to be minimal. Limited data on perioperative changes in baroreflex function showed that pressor test sensitivity recovered rapidly within 5 min of discontinuing halothane and nitrous oxide (before return of consciousness). However, in this study, all patients received opioid premedication, a potent inhibitor of baroreflex control of the sympathetic and cardiovascular system, and hence, baseline baroreflex sensitivity may have been depressed already. Takeshima and Dohi also found that both pressor and depressor test sensitivities recovered incompletely towards awake baseline values, 10–15 min after isoflurane anaesthesia, which was not evident after enflurane anaesthesia. In their study, results were also clouded by the use of atropine premedication, which may have distorted autonomic balance between the sympathetic and parasympathetic system. In the light of increasing numbers of ambulatory anaesthesia using sevoflurane, it is clinically important to know how long it takes for full recovery of baroreflex function after sevoflurane.

Apart from subanaesthetic concentrations of sevoflurane which may be present in the central nervous system or the effector organ, persistent depression of baroreflex function after surgery may also be explained by interaction with the low pressure cardiopulmonary reflex system. Simultaneous changes in right atrial pressure elicited by bolus injections of phenylephrine and nitroprusside can restrain arterial baroreflex-mediated HR changes via activation of the cardio-pulmonary reflex. More importantly, changes in right atrial pressure induced by volume loading and sympathectomy by epidural anaesthesia have been shown to significantly attenuate and augment arterial baroreflex function, respectively, when arterial pressure was maintained unchanged. Furthermore, the speed of changes in arterial pressure can affect baroreflex sensitivity. Therefore, we cannot exclude the possibility that our patients had higher right atrial pressures immediately after surgery than before. Similarly, i.v. injections of phenylephrine and nitroprusside may have produced greater fluctuations in right atrial pressure caused by increased circulating blood volume after surgery, thus reflexly provoking greater opposing effects on HR through stimulation of low pressure cardiopulmonary receptors.

The discrepancy between pressor and depressor test sensitivities during recovery is not clearly explained by our results. A greater increase in carotid sinus afferent nerve activity for a given increase in arterial pressure (i.e. increased receptor sensitivity) has been reported with halothane. However, greater rather than less attenuation of baroreflex sensitivity to the pressor tests compared with the depressor tests during anaesthesia and surgery suggest that volatile anaesthetic-induced sensitization of the carotid sinus nerve played a minor role. In contrast, pain-induced catecholamine surge, if it occurred after surgery in our patients, might have preferentially accelerated return of pressor test sensitivity, as the sensitization of the carotid sinus afferent nerve occurs over a wide range of arterial pressures. Another possibility is that the stretch reflex from the lung, activated by positive pressure ventilation, may have caused preferential depression of cardiac vagal tone during anaesthesia and surgery, which may explain more profound depression of pressor test sensitivity during anaesthesia and more accelerated recovery after surgery by restoration of spontaneous respiration. Moreover, volatile anaesthetics can profoundly depress cardiac vagal tone, which approaches the conscious level within 30 min after anaesthesia.

As post-cough HR changes have been shown to reflect the integrity of cardiac accelerator nerve function, independent of basal arterial pressure, we used this non-invasive method to analyse data obtained from our patients. We found that increases in HR were within the reported normal range of healthy unmedicated subjects of similar age, suggesting that our patients were screened successfully for normal integrity of cardiac accelerator nerve function. Highly significant correlations between post-cough peak HR changes and awake pressor ($r^2 > 0.7$) and depressor ($r^2 > 0.9$) test sensitivities suggest that this simple test may be an aid for detecting baroreflex abnormalities before operation. However, absence of and failure to demonstrate
clearly significant correlations between post-cough HR changes and intra- and postoperative baroreflex sensitivities may limit its clinical value.

In summary, arterial baroreflex function determined by pressor (phenylephrine) and depressor (nitroprusside) tests was significantly depressed during anaesthesia, surgery and recovery from sevoflurane and nitrous oxide anaesthesia in healthy surgical patients. Ongoing surgery did not antagonize depressed baroreflex function. While depressor test sensitivity remained decreased, pressor test sensitivity partially recovered after anaesthesia.

References
22 Bainbridge FA. Influence of venous filling upon the rate of the heart. J Physiol 1915; 50: 65–84
27 Jewett DL. Activity of single efferent fibers in the cervical vagus nerve of the dog, with special reference to possible cardioinhibitory fibers. J Physiol 1964; 175: 321–57