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Moderate Hypothermia Depresses Arterial Baroreflex Control of Heart Rate during, and Delays Its Recovery after, General Anesthesia in Humans

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Background: **Effects of hypothermia on arterial baroreflex function during, and on its recovery after, general anesthesia were examined in humans.**

Methods: **Twenty healthy volunteers were randomly assigned to a normothermic group (n = 10 each, active forced-air warming) or to a hypothermic group (no active warming) during anesthesia. Measurements of R-R intervals and systolic blood pressure were made at conscious baseline and at 20, 60, and 120 min after the induction and 20, 60, 120, and 180 min after emergence from general anesthesia with sevoflurane for 2 h. Ventilation was mechanically controlled, and end-tidal sevoflurane concentration was maintained at 2% during anesthesia. Baroreflex responses were triggered by bolus intravenous injections of phenylephrine and nitroprusside. The linear portions of the baroreflex curves relating R-R intervals and systolic blood pressure were determined to obtain baroslopes.**

Results: **During anesthesia, the mean lowest tympanic temperature of the hypothermia group (33.9 ± 0.5°C [mean ± SD]) was significantly lower than that of the normothermia group (36.1 ± 0.7°C, $P < 0.001$). The baroslopes of the pressor and depressor tests were decreased by 19–39% during and by 27–53% after general anesthesia in the hypothermia group, compared with the normothermia group ($P < 0.05$). The baroslopes of the normothermia group returned to the baseline values at 60 min after anesthesia, whereas the pressor test sensitivity of the hypothermia group was significantly less than that of the normothermia group for the entire course of recovery.**

Conclusions: **The results indicate that moderate hypothermia enhances anesthesia-induced depression of baroreflex function in anesthetized humans and delays its recovery after general anesthesia.**

PERIOPERATIVE hypothermia produces undesirable manifestations of adrenergic responses, including increased norepinephrine release, peripheral vasoconstriction, hypertension, and myocardial ischemia.[1,2] Hypothermia also predisposes patients to shivering with associated increases in metabolic demand and cardiac output.[3] These hemodynamic consequences may be explained by a direct effect of hypothermia *per se* on the cardiovascular and central nervous system[4] or failure of baroreflex function, which is an important short-term neural control system for maintaining cardiovascular stability during hemodynamic perturbations.

In animals, baroreflex sensitivity may be enhanced,[5] attenuated,[6,7] or unchanged[8] by moderate hypothermia to 25–30°C, depending on the species and experimental models. In awake, unmedicated humans, skin surface cooling by air (18°C) elicited parasympathetic activation but did not alter baroreflex sensitivity assessed by the spontaneous sequence method.[9] In another human study, skin surface cooling resulted in augmentation of the sympathetic vasoconstrictor efferent activity.[10] However, in both studies, core temperature was not determined. Hypothermia has also been reported to depress aortic (depressor) nerve activity in rabbits,[6] increase cardiac muscarinic receptor affinity to agonists in rats,[11] and modify sinus node electrophysiologic activity in the isolated dog atrium.[12] Furthermore, hypoxia-induced ventilatory response is markedly depressed during mild hypothermia (35°C) *via* the central nervous system involving nucleus tractus solitarius in piglets.[13] These results suggest that hypothermia may modulate arterial baroreflex function at multiple sites of the reflex arc, including the central nervous system. However, the extent to which core hypothermia influences arterial baroreflex function during and after general anesthesia has not been studied in humans.

Accordingly, the purpose of the current study is of twofold. First, we have determined whether moderate hypothermia to a degree that may be encountered during general anesthesia modifies arterial baroreflex control of heart rate (HR) in healthy volunteers anesthetized with sevoflurane. Second, whether hypothermia alters the recovery profile of baroreflex control of HR has also been investigated.

Methods

Twenty volunteers who were classified as American Society of Anesthesiologists physical status I and aged 22–27 yr were studied. Subjects who consumed alcoholic beverages daily or smoked cigarettes and those with a history of cardiovascular, pulmonary, or neurologic disorders or who had taken medication in the 2 weeks before the study were excluded. Also, these volunteers did not drink caffeine-containing beverages for at least 24 h before the study. The study protocol was approved by the Human Research Committee of the University of Akita, School of Medicine (Akita-city, Japan), and informed written consent was obtained from each subject. All subjects arrived at the operating room after an 8- to 10-h fast, without premedication.

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An electrocardiograph monitor (lead II), a peripheral intravenous catheter, an arterial (radial) blood pressure catheter, and a beat-to-beat basic HR monitor (tachometer) were placed in each subject while the subject breathed room air supplemented with 2 l/min oxygen *via* a face mask and was in the supine position. Electrocardiographic data, HR, and systolic blood pressure (SBP) were continuously recorded on a polygraph. Tympanic temperature was measured throughout the study period. Pressor and depressor tests were performed using intravenous bolus injections of phenylephrine (100–200 μg) and nitroprusside (100–250 μg) to increase and decrease SBP by 15–30 mmHg, respectively, before the induction of general anesthesia (Awake). Pressor test was always performed first. These doses were chosen based on a previous study as well as our pilot study of a similar age group.[14] A period of stabilization, usually 5 min, between the pressor and depressor tests allowed HR and SBP to return to the pretest values ± 5%.[14]

The volunteers were then randomly assigned to the normothermia or hypothermia group (n = 10 each). The normothermia group received whole-body forced-air warming set to 38°C during anesthesia to maintain conscious baseline temperature, whereas the hypothermia group received no active warming. All subjects were allowed to wear only a short-sleeved cotton shirt and trousers. The ambient temperature was set to 20°C during and to 25–30°C after general anesthesia to avoid postanesthesia shivering. A circulating water mattress and blanket were not used at any time during the study. General anesthesia was induced in all subjects using 5% sevoflurane (inspiratory) in air (5 l/min) and oxygen (1 l/min), and a laryngeal mask airway was inserted without any other adjuvant. Their lungs were mechanically ventilated (tidal volume 10–12 ml/kg at a respiratory rate of 8–10 breaths/min). Anesthesia was maintained with 2% end-tidal sevoflurane in air and oxygen (fraction of inspired oxygen [$F_{I}O_2$] = 34%) while end-tidal carbon dioxide tension was maintained at 35 mmHg throughout the anesthesia period. To ensure anesthetic equilibration, end-tidal sevoflurane concentration was maintained at 2% for 20 min by frequently adjusting inspiratory sevoflurane concentrations before the second set of pressor and depressor tests was performed (Anesthesia-20). These tests were repeated in a similar manner after maintaining the desired sevoflurane concentration for 60 and 120 min (Anesthesia-60 and -120, respectively). Sevoflurane was then discontinued, and after confirming the return of adequate spontaneous respiration and responses to verbal commands, the laryngeal mask airway was removed. The volunteers were left undisturbed with supplemental oxygen 2 l/min *via* a face mask. The pressor and depressor tests were repeated at 20, 60, 120, and 180 min after removal of the laryngeal mask airway (Recovery-20, -60, -120, and -180, respectively). Each set of tests was preceded by determination of end-tidal sevoflurane concentration through a cannula advanced 2–3 cm into a naris and by having subjects take 5 or 6 deep and regular breaths separated by 2–3 s. Arterial blood samples were collected for measurements of arterial blood gas tensions, plasma concentrations of potassium, sodium, ionized calcium, and glucose before each set of tests. Balanced salt solution containing 5% dextrose was administered to all subjects at a rate of 2 ml · kg^{-1} · h^{-1} throughout the study. Fluid temperature was 20°C for both groups. No other anesthetics, sedatives, or narcotics were used during the study.

Power analysis based on a previous similar study and our pilot study showed that eight patients would provide a power greater than 0.8 ($P = 0.05$) for 50% difference in temporal baroslope changes and baroslopes of regression lines between groups.[14] Data from the pressor and depressor tests were analyzed using least-square regression analysis on the linear portion of the sigmoid relation between SBP and R-R interval, when each R-R interval was plotted as a function of the preceding SBP. We used 7–12 pairs of corresponding SBP and R-R intervals to analyze each test result. The square values of all correlation coefficients were greater than 0.8. Data are presented as mean ± SD throughout the article. Changes in baroreflex sensitivities during various stages were first analyzed by two-way analysis of variance for repeated measurements, and, if significant difference was detected with respect to time or group, it was followed by the Scheffé' F test as a *post hoc* test to compare pretest hemodynamic data and baroslopes between and within groups. The chi-square test and unpaired *t* test were used to compare demographic data of volunteers between groups. A *P* value less than 0.05 was considered statistically significant.

Results

There were no significant differences in volunteers' demographic data, Awake pretest SBP and HR, and Awake tympanic temperature between the groups (table 1). All three female volunteers were in the luteal phase. The temperature of the normothermia group decreased significantly compared with the Awake value from Anesthesia-20 to Anesthesia-60, whereas that of the hypothermia group decreased significantly from Anesthesia-20 to Recovery-60. There were significant differences in the tympanic temperature from Anesthesia-60 to Recovery-60 between groups (table 1). The mean lowest temperature of the hypothermia group (33.9 ± 0.5°C) was significantly lower than that of the normothermia group (36.1 ± 0.7°C, $P < 0.001$). However, no significant difference was observed in end-tidal sevoflurane concentration, *p*Ha, arterial carbon dioxide tension [Pa_{CO_2}], arterial oxygen tension [Pa_{O_2}], or sodium, po-

Table 1. Demographic Data, Pretest Systolic Blood Pressure and Heart Rate, Tympanic Temperature, and End-tidal Sevoflurane Concentration

	Normothermia	Hypothermia
Sex (male/female)	9/1	8/2
Age (yr)	23 ± 1	24 ± 1
Weight (kg)	65 ± 9	62 ± 8
Height (cm)	171 ± 7	170 ± 7
Awake		
Pretest SBP (mmHg)	123 ± 10	126 ± 10
Pretest HR (beats/min)	59 ± 8	60 ± 4
Temperature (°C)	36.4 ± 0.6	36.3 ± 0.3
ET_{sevo}	0.00 ± 0.00	0.00 ± 0.00
Anesthesia—20 min		
Pretest SBP (mmHg)	91 ± 6†	88 ± 4†
Pretest HR (beats/min)	66 ± 7†	65 ± 10
Temperature (°C)	36.0 ± 0.8†	35.1 ± 0.5†
ET_{sevo}	2.02 ± 0.04	1.99 ± 0.03
Anesthesia—60 min		
Pretest SBP (mmHg)	91 ± 10†	86 ± 5†
Pretest HR (beats/min)	67 ± 7†	63 ± 9
Temperature (°C)	36.0 ± 0.8†	34.3 ± 0.5*†
ET_{sevo}	2.04 ± 0.07	2.02 ± 0.04
Anesthesia—120 min		
Pretest SBP (mmHg)	94 ± 14†	86 ± 8†
Pretest HR (beats/min)	70 ± 8†	63 ± 10
Temperature (°C)	36.1 ± 0.7	33.9 ± 0.5*†
ET_{sevo}	2.02 ± 0.07	2.00 ± 0.07
Recovery—20 min		
Pretest SBP (mmHg)	129 ± 10	138 ± 13†
Pretest HR (beats/min)	72 ± 12†	69 ± 12
Temperature (°C)	36.3 ± 0.7	34.6 ± 0.6*†
ET_{sevo}	0.15 ± 0.04	0.17 ± 0.05
Recovery—60 min		
Pretest SBP (mmHg)	125 ± 10	137 ± 10†
Pretest HR (beats/min)	66 ± 14	58 ± 7
Temperature (°C)	36.3 ± 0.6	35.4 ± 0.6*†
ET_{sevo}	0.08 ± 0.02	0.10 ± 0.03
Recovery—120 min		
Pretest SBP (mmHg)	122 ± 12	130 ± 10
Pretest HR (beats/min)	62 ± 9	63 ± 7
Temperature (°C)	36.4 ± 0.7	36.0 ± 0.5
ET_{sevo}	0.05 ± 0.01	0.06 ± 0.02
Recovery—180 min		
Pretest SBP (mmHg)	123 ± 15	129 ± 13
Pretest HR (beats/min)	64 ± 8	63 ± 11
Temperature (°C)	36.4 ± 0.6	36.4 ± 0.3
ET_{sevo}	0.03 ± 0.01	0.04 ± 0.01

Values are mean ± SD or numbers.

* $P < 0.05$ *versus* the normothermia group. † $P < 0.05$ *versus* awake values.

SBP = systolic blood pressure; HR = heart rate; ET_{sevo} = end-tidal sevoflurane concentration.

tassium, ionized calcium, or blood glucose concentrations between groups at any time during the study (data not shown).

Pretest SBP values were significantly lower during anesthesia than the Awake values in both groups (table 1). Compared with the Awake period, HR significantly increased during anesthesia in the normothermia group, whereas HR was unchanged in the hypothermia group. Throughout the recovery period, SBP remained unchanged compared with the Awake value in the normothermia group but was significantly increased at Recovery-20 and -60 periods in the hypothermia group. There were no significant differences in the pressor and depressor test sensitivities (baroslope) during the Awake period between groups (fig. 1). Compared with Awake values, both sensitivities decreased significantly during general anesthesia in both groups ($P < 0.001$ by two-way analysis of variance for repeated measurements with respect to time). The pressor and depressor test sensitivities of the hypothermia group were significantly less than those of the normothermia group during general anesthesia ($P = 0.02$ and 0.04, respectively, by two-way analysis of variance for repeated measurements with respect to temperature). Conversely, both sensitivities of the normothermia group returned to the conscious baseline levels at Recovery-60, whereas the pressor test sensitivities of the hypothermia group remained depressed from Recovery-20 to Recovery-180 compared with the baseline value and those of the normothermia group ($P = 0.003$–0.04 by Scheffé F test). The depressor test sensitivity of the hypothermia group returned to the baseline value at Recovery-120. Significant difference in

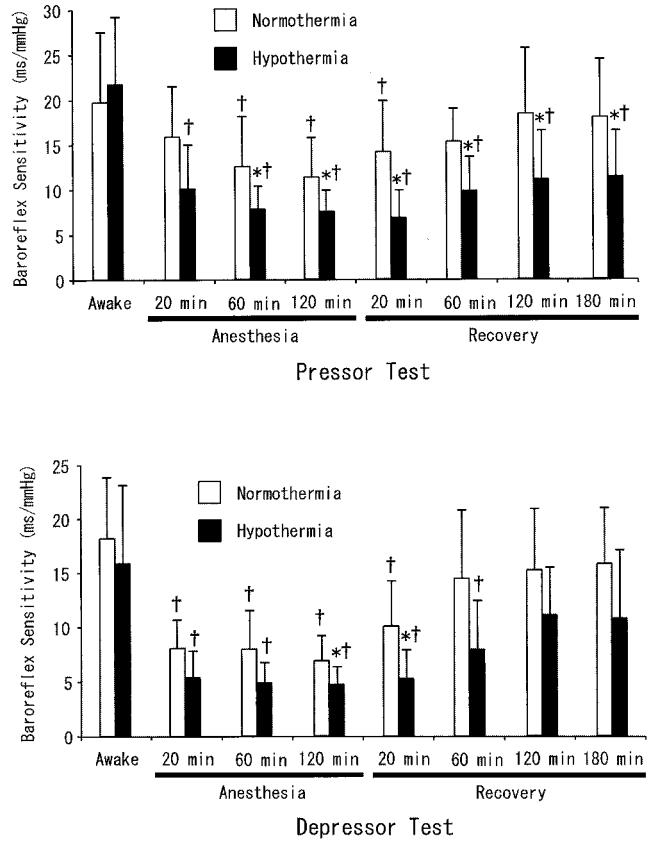

Fig. 1. Pressor (phenylephrine) and depressor (nitroprusside) test sensitivities of healthy volunteers before (Awake), during (Anesthesia), and after (Recovery) sevoflurane anesthesia. The normothermia group subjects (n = 10) received whole-body forced-air heat, whereas the hypothermia group (n = 10) received no active warming during the entire course of the study. Values are mean ± SD. *$P < 0.05$ *versus* the normothermia group by Scheffé F test. †$P < 0.05$ *versus* the Awake values by Scheffé F test.

the depressor test sensitivity between groups was seen only at Recovery-20 ($P = 0.01$ by Scheffé F test). The baroslopes of both tests were decreased by 19–39% during and by 27–53% after emergence from anesthesia in the hypothermia group compared with the normothermia group.

The mean time from discontinuance of sevoflurane administration until laryngeal mask airway removal in all subjects was 20 ± 7 min (no significant difference between groups). The mean change in SBP during the pressor test was 23 ± 5 mmHg in the normothermia group and 21 ± 6 mmHg in the hypothermia group ($P = 0.63$), whereas that during the depressor test was 22 ± 9 mmHg in the normothermia group and 21 ± 5 mmHg in the hypothermia group ($P = 0.81$). In the hypothermia group, there were no significant correlations between the lowest temperature achieved and the percent depression of the baroslopes for the pressor and depressor tests during general anesthesia ($R^2 = 0.044$ and 0.076, respectively). No ventricular or supraventricular arrhythmia was observed at any time during the study.

Discussion

One of the major findings of our study is that moderate core hypothermia depresses arterial baroreflex control of HR during and after sevoflurane anesthesia, indicating that temperature is an important determinant of baroreflex function in humans. It is well-known that volatile anesthetics, including halothane,[15,16] enflurane,[17,18] isoflurane,[19] sevoflurane,[20] and desflurane,[21] all attenuate baroreflex function in a concentration-dependent manner in humans. However, neither thermal management nor core temperatures of study subjects were reported in those investigations. In our study, tympanic temperature spontaneously decreased time-dependently without active warming during general anesthesia, and cardiac baroslopes of the hypothermia group were less than those of the normothermia group by as much as 40%. These considerations raise a question of whether the reported depressive effects of volatile anesthetics on baroreflex function were the results of volatile agents *per se* rather than the combination of volatile agents and hypothermia. Our results also showed that the depression of the pressor test sensitivity of the hypothermia group persisted considerably longer than that of the normothermia group. In addition, the pressor test sensitivity of the hypothermia group remained significantly less than that of the normothermia group even after the difference in tympanic temperatures between groups had disappeared. Therefore, maintaining normothermia seems to be essential to minimize the persistent, detrimental effect of hypothermia on the recovery characteristics of arterial baroreflex function after general anesthesia.

Baroreflex sensitivities of the pressor and depressor tests were significantly depressed in the immediate recovery period, even in the normothermia group, and at less than one tenth of the minimum alveolar anesthetic concentration of end-tidal sevoflurane. Whether subanesthetic concentrations of sevoflurane depress arterial baroreflex function remains to be determined. More importantly, if normothermia was maintained, 1 h was required until full recovery of baroreflex sensitivities occurred after sevoflurane anesthesia. This is in contrast with a previous report in which pressor test sensitivity but not depressor test sensitivity returned to the conscious baseline level within 20 min after minor surgery performed under sevoflurane and nitrous oxide anesthesia.[14] Postganglionic sympathetic efferent nerve stimulation has been shown to directly sensitize carotid sinus baroreceptors in cats,[22] and clinically relevant plasma norepinephrine concentration increases impulse frequency of carotid baroreceptor afferent (depressor branch) fibers in rabbits.[23] Therefore, neurologic or endocrinologic alterations elicited by surgery and noxious stimulation may have accelerated recovery of the pressor test sensitivity after surgery. Other studies suggest rapid return of baroreflex sensitivity to preanesthesia and premedicated conditions after surgeries under halothane[16] and isoflurane anesthesia.[18] However, the results of these studies could be confounded by the use of morphine[16] and atropine[18] as premedication before baseline determinations of the baroreflex function, as well as for patients with advanced age.[18]

The mechanism by which hypothermia depresses arterial baroreflex control of HR is not clear from our study. Initial bradycardia associated with hypertensive perturbation is considered to be primarily mediated by parasympathetic augmentation rather than sympathetic withdrawal. Cardiac cholinergic receptor affinity to agonists has been reported to increase during hypothermia in rats,[11] whereas aortic depressor nerve activity determined by impulse frequency is attenuated at a given blood pressure by decreasing perfusate temperature.[6] Conversely, the subjects in the current study were relatively stress-free during the postanesthesia period as opposed to surgical patients; therefore, hypothermia may have increased cardiac vagal nerve activity, which could have counteracted HR response to hypotensive perturbation.[9,24] Also, one cannot exclude a possible involvement of the central nervous system, *i.e.*, interaction of hypothalamus and the medulla, because thermal receptors activate afferent fibers, which terminate in the hypothalamus, and hypothalamic stimulation modifies the HR response to baroreflex activation in cats.[25] The mechanism by which hypothermia produces persistent depression of baroreflex function after sevoflurane anesthesia remains to be determined.

The results of our study should be interpreted with caution. First, our study subjects did not undergo surger-

ies; therefore, recovery profile of baroreflex sensitivities may not reflect those of surgical patients. Baseline baroreflex function and the autonomic nervous system may be influenced by various physiologic and pathophysiologic factors, including sex,[26] age,[27] and history of cardiopulmonary disorders.[27,28] Furthermore, recovery of baroreflex function may be modulated by concomitant uses of narcotics,[29] sedatives,[30] intravenous anesthetics,[31] and sympathetic blockade by epidural anesthesia[32,33] during and after anesthesia. However, we constructed our protocol to isolate effects of a volatile anesthetic agent, hypothermia, and their interaction by eliminating other confounding factors. Therefore, whether perioperative hypothermia influences the recovery profile of baroreflex function remains to be determined in actual surgical patients. Second, we have measured end-tidal sevoflurane concentrations after general anesthesia through a cannula advanced into a naris and tried to minimize the effect of dilution with room air. However, we cannot completely exclude the possibility of underestimating the true value of the end-tidal sevoflurane concentration during the recovery period. Third, conclusions regarding the precise association of temperature changes with baroreflex responses are limited because there was no controlled steady-state temperature during which baroreflex sensitivities were determined in the absence of time-related changes in anesthetic concentration.

Conclusion

In conclusion, moderate hypothermia amplified sevoflurane-induced depression of arterial baroreflex control of HR determined by the pressor (phenylephrine) and depressor (nitroprusside) tests in healthy volunteers not undergoing surgery. Recovery of both the pressor and the depressor test sensitivities to the conscious baseline levels occurred within 60 min after sevoflurane anesthesia in subjects with normothermia but was considerably prolonged in those with hypothermia. Further study is warranted to determine the mechanism of prolonged depressive effect of hypothermia on the recovery characteristics of arterial baroreflex control of HR in humans.

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