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Response to surgical stress in elderly patients and Alzheimer's disease

Purpose: To determine the effect of surgical stress on plasma epinephrine, norepinephrine, ACTH and cortisol concentrations in patients aged 80-99 yr and in patients complicated with Alzheimer's disease.

Methods: A prospective controlled study was undertaken in 55 undergoing surgical reduction of femur neck fracture in Hirosaki University hospital and Hakodate Watanabe hospital; 18 patients in 80-99 yr (Group 1) and 18 patients in 40-59 yr (Group 2) and 7 patients (Group A) with and 12 patients (Group B) without Alzheimer's dementia (AD) aged 60-79 yr.

Results: The increase in plasma norepinephrine level (274%) of group 1 patients, 15 min after skin incision was higher than that in group 2 (191%) ($P < 0.01$). Mean plasma cortisol levels (40.4 ± 4.7 and $44.1 \pm 5.2 \mu\text{g}\cdot\text{dl}^{-1}$) of group 1, 15 min after skin incision and 60 min after the end of surgery were significantly higher than the 29.8 ± 3.5 and $22.3 \pm 3.0 \mu\text{g}\cdot\text{dl}^{-1}$ of group 2 ($P < 0.05$). Plasma norepinephrine ($1092.9 \pm 112.0 \text{ pg}\cdot\text{ml}^{-1}$) and cortisol concentrations ($53.4 \pm 5.8 \mu\text{g}\cdot\text{dl}^{-1}$) in group A were higher than in group B ($772.6 \pm 82.4 \text{ pg}\cdot\text{ml}^{-1}$ and $41.7 \pm 4.3 \mu\text{g}\cdot\text{dl}^{-1}$) 15 min after skin incision ($P < 0.05$).

Conclusions: Plasma norepinephrine and cortisol responses to surgical stress are activated in elderly patients and in patients with Alzheimer's disease.

Objectif : Déterminer l'effet du stress chirurgical sur la concentration plasmatique d'épinéphrine, de norépinéphrine, d'ACTH et de cortisol chez des patients de 80-99 ans et chez des patients atteints de la maladie d'Alzheimer.

Méthode : On a entrepris l'étude prospective et contrôlée de 55 patients, devant subir une réduction de fracture du col du fémur aux hôpitaux Hirosaki University et Hakodate Watanabe, répartis comme suit : 18 dans le Groupe 1 (80-99 ans) et 18 dans le Groupe 2 (40-59 ans) ; 7 dans le Groupe A (démence d'Alzheimer DA) et 12 dans le Groupe B (sans DA) âgés de 60-79 ans.

Résultats : L'augmentation de la norépinéphrine plasmatique (274 %) était plus grande chez les patients du Groupe 1 que chez ceux du Groupe 2 (191 %), 15 min après l'incision cutanée ($P < 0,01$). Les niveaux moyens de cortisol ($40,4 \pm 4,7$ et $44,1 \pm 5,2 \mu\text{g}\cdot\text{dl}^{-1}$) du Groupe 1, 15 min après l'incision cutanée et 60 min après la fin de la chirurgie, ont été plus élevés que les niveaux enregistrés dans le Groupe 2 ($29,8 \pm 3,5$ et $22,3 \pm 3,0 \mu\text{g}\cdot\text{dl}^{-1}$) de façon significative ($P < 0,05$). Les concentrations plasmatiques de norépinéphrine ($1092,9 \pm 112,0 \text{ pg}\cdot\text{ml}^{-1}$) et de cortisol ($53,4 \pm 5,8 \mu\text{g}\cdot\text{dl}^{-1}$) étaient plus élevées dans le Groupe A que dans le Groupe B ($772,6 \pm 82,4 \text{ pg}\cdot\text{ml}^{-1}$ et $41,7 \pm 4,3 \mu\text{g}\cdot\text{dl}^{-1}$) 15 min après l'incision cutanée ($P < 0,05$).

Conclusion : Les changements plasmatiques de norépinéphrine et de cortisol reliés au stress chirurgical sont plus marqués chez les patients âgés ou souffrant de la maladie d'Alzheimer.

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REDUCED homeostatic capacity is a typical characteristic of the aging process and is most pronounced in changes in the neuroendocrine control to maintain cardiovascular homeostasis. As elderly patients have not only decreased β -adrenoceptor responsiveness, but also decreased baroreflex function and parasympathetic control of heart rate, they are often sensitive to vasodilators and anesthetics, leading to severe hypotension. Plasma concentrations of norepinephrine (NE) are higher in the elderly.¹ The increase in NE with age may be caused by a compensatory mechanism for neuroendocrine change.² The NE response to a variety of stress is also enhanced in elderly patients.^{3,4} On the other hand, the central noradrenergic system (CNS) is markedly vulnerable to the aging process. A decline in hypothalamic and hippocampal catecholamine activity has a critical role in the development of aging.⁵ Noradrenergic activity in Alzheimer's dementia (AD) is potentially important in the pathogenesis of this disorder and plasma NE concentrations may be an indication of the severity of AD.⁶ Thus, NE plays an important role in cardiovascular and CNS homeostasis in the elderly.

Alteration in hypothalamic-pituitary-adrenal (HPA) axis function frequently accompanies aging and results in increased plasma cortisol concentrations and increased adrenocortical responses to ACTH and stress.^{7,8} The change in the HPA axis would be associated with age-related hippocampal dysfunction, since the hippocampus plays an important role in HPA system.⁹ On the contrary, Brett *et al.* reported that elderly patients have a diminished adrenocortical response to acute and chronic stress.¹⁰ Patients with AD also develop disturbed regulation of HPA due to hippocampal degeneration.^{11,12} Thus, the endocrine response to surgical stress in the elderly patient or in patients with AD may differ from that in younger adults. This study was designed to investigate the effects of surgical stress on plasma epinephrine (EPI), NE, ACTH and cortisol concentrations during general anesthesia in patients aged 80-99 and to determine whether AD influences stress hormone concentrations during surgery.

Patients and methods

The study was performed in Hirosaki University Hospital and Hakodate Watanabe hospital. The protocol was approved by institutional ethical committee of each hospital and informed consent was obtained from each patient.

Effect of aging on endocrine response to surgical stress

Eighteen patients aged 80-99 yr (Group 1) and 18 aged 40-59 yr (Group 2) were randomly chosen

before the study. All patients were undergoing surgical reduction of femoral neck fracture.

Effect of Alzheimer disease on response to surgical stress

Seven patients (Group A) with and 12 (Group B) without Alzheimer's dementia (AD) aged 60-79 yr were randomly chosen before the study. The patients were undergoing surgical reduction of femoral neck fracture. The diagnosis of AD was made by psychiatrists according to DSM-IV.

All patients with a history of anemia ($Hb < 10 \text{ g}\cdot\text{dl}^{-1}$), marked cardiovascular or respiratory disease and endocrine disorders were excluded and patients with vasopressor as ephedrine were excluded in this study. Patients with dehydration preoperatively were corrected by lactated Ringer's solution. Anesthesia was induced with $5 \text{ mg}\cdot\text{kg}^{-1}$ thiopental *iv* and tracheal intubation was facilitated by $0.5\text{-}1.0 \text{ mg}\cdot\text{kg}^{-1}$ succinylcholine *iv*. Anesthesia was maintained with isoflurane, $0.8\text{-}2.0\%$ inspired, in nitrous oxide (N_2O) 50% in oxygen (O_2) 50% and vecuronium. Isoflurane concentrations were adjusted according to response to vital signs such as systolic blood pressure and heart rate, which were controlled within 20% of preoperative values. No opioids or other analgesics were used during anesthesia. A 20 gauge arterial catheter was placed in the left radial artery to measure blood pressure and to obtain arterial blood samples. The end-expiratory (ET) concentration of oxygen, carbon dioxide (CO_2) and anesthetics were monitored throughout anesthesia using a 5250 RGM Analyzer (Ohmeda, Madison, USA). The lungs were mechanically ventilated to maintain $P_{ET}CO_2$ at $35\text{-}45 \text{ mmHg}$ and $7 \text{ ml}\cdot\text{kg}^{-1}$ lactated Ringer's solution was infused. Patients received no other fluid replacement or packed red blood cells. Naso-pharyngeal temperature was monitored continuously with an electric thermistor and maintained at $36.0\text{-}37.0^\circ\text{C}$ using a warming blanket and the temperature in the operating room was controlled to avoid hormonal effects. Postoperatively, all patients were treated with a non-steroidal analgesic (50 mg diclofenac *pr*) every eight hours for incisional pain.

Blood samples, 5 ml , were obtained from the arterial cannula before and 15 min after induction of anesthesia, 15 min after skin incision, and 60 min after the end of surgery, into tubes containing EDTA. The first sample was taken at $8:30 \text{ a.m.}$ The samples were immediately centrifuged and stored at -80°C until analysis. Plasma EPI and NE concentrations were measured by gas chromatography and electron impact mode mass spectrometry with selected ion method (JMS-D300 GC-MS, Japan electronic CO, Tokyo, Japan). 1 ml of plasma were acidified (1 ml 0.2 M Tris HCL) and extracted using alumina cartridges (Wako

TABLE Background and hemodynamic status during anaesthesia.

	Group 1	Group 2	Group A	Group B
Number of patients (F/M)	18 (10/8)	18 (9/9)	7 (4/3)	12 (6/6)
Age (yr)	88.2 ± 1.3†	52.6 ± 1.7	71.5 ± 1.8	69.7 ± 1.2
Weight (kg)	43.9 ± 1.8*	53.5 ± 1.8	48.5 ± 1.7	51.0 ± 1.6
Body mass index (BMI)	19.5 ± 0.6*	21.2 ± 0.9	20.1 ± 0.5	20.4 ± 0.6
Duration of surgery (min)	66.3 ± 3.9	71.3 ± 3.6	67.1 ± 3.4	62.7 ± 3.8
Duration of anaesthesia (min)	123.4 ± 4.6	134.5 ± 5.0	126.3 ± 5.4	120.5 ± 4.5
Blood loss (ml)	102.0 ± 9.2	94.8 ± 9.4	94.5 ± 7.4	99.5 ± 11.7
Systolic blood pressure (mmHg)				
before induction	151.7 ± 2.3*	130.6 ± 2.5	148.3 ± 3.5	143.8 ± 2.6
15min after induction	137.4 ± 3.2*	117.1 ± 3.2	140.2 ± 2.9	139.3 ± 2.8
15min after skin incision	164.7 ± 3.5*	138.9 ± 3.4	157.0 ± 2.7	154.6 ± 3.4
60 min after end of surgery	147.1 ± 3.5*	135.9 ± 3.3	150.6 ± 3.4	145.0 ± 2.7
Diastolic blood pressure (mmHg)				
before induction	77.5 ± 3.3	74.5 ± 3.5	76.3 ± 2.1	75.1 ± 2.3
15 min after induction	73.1 ± 2.8	71.6 ± 2.8	73.9 ± 2.5	73.0 ± 2.7
15 min after skin incision	79.6 ± 2.5	76.1 ± 3.0	79.3 ± 2.2	76.9 ± 2.5
60 min after end of surgery	77.2 ± 2.7	74.3 ± 3.5	76.6 ± 3.0	74.7 ± 3.1
Heart rate (bpm)				
before induction	79.5 ± 3.0	74.7 ± 2.5	79.8 ± 2.3	78.8 ± 2.0
15 min after induction	76.9 ± 2.7	72.0 ± 2.3	79.2 ± 2.5	75.0 ± 3.5
15min after skin incision	80.3 ± 2.4	76.6 ± 2.8	81.4 ± 2.9	78.4 ± 3.4
60 min after end of surgery	78.1 ± 2.8	78.2 ± 3.0	77.5 ± 3.2	76.2 ± 2.7

Mean ± SEM. *: $P < 0.05$, †: $P < 0.01$ group 1 *vs* group 2.

purechemical industries CO, Tokyo, Japan). The lower limit of assay detection were 2 pg·ml⁻¹ for E and 1 pg·ml⁻¹ for NE. The coefficient of variation (CV) was < 8.4% for E and < 9.3% for NE. Plasma ACTH and cortisol were measured by radioimmunoassay using ACTH kit (CIS, Tokyo, Japan). Plasma ACTH levels were determined with the intra-assay and interassay coefficient of variation of 5.6% and 8.7%, respectively. Plasma cortisol levels were determined with spectrometry using cortisol kit (Daiich Pharmaceutical Co, Tokyo, Japan) with CV of 1.5%.

Patient data were analyzed with Student's unpaired *t* test. Changes in endocrine data over time within each group were analyzed by using repeated measures ANOVA followed by Bonferroni's correction. Data were expressed as mean ± standard error of the mean. Difference in mean values were considered significant at $P < 0.05$.

Results

Mean age was 88.2 ± 1.3 yr for the group 1, 52.6 ± 1.7 yr for the group 2, 71.5 ± 1.8 yr for the group A and 69.7 ± 2.2 yr for the group B. Systolic BP of patients in group 1 at all measurement points was higher than those of group 2. There were no differences in any other hemodynamic data throughout the perioperative course between group 1 and 2. There

were no differences in hemodynamic data between group A and B during anesthesia (Table I).

Endocrine response of elderly patients to surgical stress

The increasing plasma EPI concentrations during surgery were not different between groups 1 and 2. Plasma NE level of group 1 before the induction of anesthesia was higher than that of group 2. The increase in the plasma NE level in group 1 (274%), 15 min after skin incision, was higher than that in group 2 (191%). There was no relationship between plasma norepinephrine concentration and the increase of systolic blood pressure in groups 1 and 2. Plasma ACTH concentrations of group 1 were not observed no differences as compared with those of group 2 through perioperative course. Mean plasma cortisol concentrations (40.4 ± 4.7 and 44.1 ± 5.2 µg·dl⁻¹) of group 1, 15 min after skin incision and 60 min after the end of surgery, were higher than in group 2 (29.8 ± 3.5 and 22.3 ± 3.0 µg·dl⁻¹) (Figure 1).

Endocrine response of patients with Alzheimer disease to surgical stress

Plasma NE (1092.9 ± 112.0 pg·ml⁻¹) and cortisol levels (53.4 ± 5.8 µg·dl⁻¹) of group A were higher than in group B (772.6 ± 82.4 pg·ml⁻¹ and 41.7 ± 4.3 µg·dl⁻¹) 15 min after the skin incision. The increase of

plasma NE (261%), 15 min after skin incision, in group A was higher than in group B (206 %) (Figure 2). There were no differences in plasma EPI and ACTH levels between groups A and B.

Discussion

Endocrine response of elderly patients to surgical stress

The present study showed that the increase of plasma NE during surgical stress was greater in 80-99 yr old patients than in those aged 40-59 yr, but the response of plasma EPI to surgical stress did not change with age. Lehmann and Keul² reported that baseline NE concentrations were higher in the elderly and plasma EPI concentrations were similar to those of young adults. The alteration in NE with age may be caused by a compensatory mechanism which depends both on decreased baroreflex function and on decreased β -adrenoceptor responsiveness.² As a result, the increases in sympathetic nerve firing rate and a decrease in

plasma NE clearance and impairment of the neuronal reuptake of the neurotransmitter by sympathetic nerve would contribute to the increase in plasma NE concentration in the elderly.^{13,14} The increase in plasma NE concentration in response to a variety of different stress including mental stress, isometric and aerobic exercise and hypoglycemia is also greater in older than in younger people.^{3,4} Thus, in this study, the increased plasma NE response to surgical stress appears to be affected by sympathetic activation with aging. On the other hand, the exercise-induced EPI response was less prominent in the elderly compared to the NE response.² Our results showed that no change in the response of plasma EPI to surgical stress was associated with aging. The differences between EPI and NE would be related to their clearance from the circulation, as EPI clearance is not different in the old and young.⁹ Although the increase in plasma NE concentrations in group 1 were greater than that in group 2, there was no relationship between plasma norepinephrine concentration and the increase of systolic blood pressure in group 1 compared with group 2 patients. This may be due to decreased β -adrenoceptor responsiveness with elderly patients.

The effects of aging on baseline HPA function remain controversial. Issa *et al.*⁷ proposed that stressors elicit greater activation of the HPA axis in aging. De Leon *et al.*¹⁶ suggested that the degree of hippocampal

FIGURE 1 Plasma epinephrine, norepinephrine, ACTH and cortisol levels before and 15 min after induction, 15 min after skin incision, and 60 min after end of surgery. Mean $\pm$ SEM.

*: $P < 0.05$, †: $P < 0.01$ vs before induction of anesthesia. ‡: $P < 0.05$, §: $P < 0.01$ vs group 2.

FIGURE 2 Plasma norepinephrine and cortisol levels in elderly with (group A) and without (group B) Alzheimer's disease before and 15 min after induction, 15 min after skin incision, and 60 min after end of surgery. Mean $\pm$ SEM.

*: $P < 0.05$, †: $P < 0.01$ vs before induction of anesthesia. ‡: $P < 0.05$ vs group B.

damage paralleled the magnitude of hypercortisolism, since the hippocampus is thought to exert an inhibitory control on the HPA axis. The activity of the HPA system is controlled by mineralocorticoid and glucocorticoid receptor systems in hippocampus.¹⁷ Thus, hyperactivation of the HPA with aging may be caused by decreased hippocampal inhibition due to a negative feedback regulation in response to a decreased sensitivity of the mineralocorticoid and corticosteroid receptor. On the other hand, Ait-Chaoui *et al.*¹⁸ showed that there was marked age-related attenuation in the ACTH-induced increase in plasma cortisol of old rats. This discrepancy may have resulted from methodological differences. Our result supports that of Issa *et al.*⁷ However, no difference in the plasma ACTH response to surgical stress was observed in young and elderly patients. Sonntag *et al.*⁸ demonstrated that adrenal sensitivity to ACTH was greater in old rats than in young or middle-aged rats. Thus, the greater increase in adrenal sensitivity of old patients appears to be related to increase in cortisol release from adrenal medulla. In addition, as the cortisol secretion is increased not only by the stimulation of ACTH, but also by the activated NE,¹⁹ the activated NE system with aging may partly result in the elevated plasma cortisol during surgery. Therefore, the age-related increase in plasma cortisol response to surgical stress would include several factors.

Endocrine response of patients with Alzheimer disease to surgical stress

The decline in hypothalamic and hippocampal catecholamine activity has a critical role in the development of the aging process.⁵ In AD, hippocampal noradrenergic activity has a potentially important implication for pathogenesis of this disorder and the elevated plasma NE concentrations may indicate the severity of AD.⁶ The present study showed that plasma NE concentration during surgery in patients with AD was higher than that in patients of the same ages without AD. This confirms the report that sympathetic response to stress is functionally impaired in AD.¹⁵ Thus, the age-related elevation of plasma NE may become more pronounced when patients complicated with AD.

The elevated cortisol response to surgical stress was elevated also in patients with AD. Hyperactivity of the adrenal cortex has been described in AD.¹⁰ The cortisol levels after corticotropin-releasing factor administration are higher in patients with AD than in normal elderly patient.²⁰ The hippocampus is a brain site that plays an important role in the regulation of the stress-adaptive and -responsive HPA system and is nearly always damaged in AD.¹¹ In AD, it was shown that the degree of hippocampal damage paralleled the magnitude of

hypercortisolism.¹⁶ Thus, hippocampal degeneration is likely to play a remarked role in the cortisol activation with aging and AD.

We reported previously that isoflurane has no influence on plasma catecholamine, ACTH, and cortisol concentration and, after skin incision, these hormones are increased and continue to increase during isoflurane anesthesia.²¹ Thus, as isoflurane does not affect these hormones, we can estimate the effect of surgical stress on pituitary adrenal function without intervention. On the other hand, the use of opioids suppresses the endocrine response to surgical stress. In addition, the fentanyl concentration required to provide adequate analgesia varies over a wide range of 1–5 ng·ml⁻¹.²² The individual broad variability in the serum levels reflects diverse individual sensitivities to fentanyl. The difference of the individual sensitivities to opioids may affect the endocrine response. Thus, no opioids were used in this study. We may have underestimated the true adrenergic response in this study. Compared with venous blood, arterial blood contains lower concentrations of NE.²³ This may be associated with the release of NE at sympathetic nerve terminal, which is taken up as the blood passes from the arterial to the venous circulation. Thus, the true plasma NE concentration in this study may have been higher than reported.

In summary, we found an increase of plasma NE and cortisol response to surgical stress in orthopedic patients aged 80–99 yr. Plasma NE and cortisol responses to surgical stress were also stimulated in elderly patients with Alzheimer's disease. These findings suggest that NE and cortisol play an essential role in maintaining homeostasis in old patients during surgery.

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