Endocrine response to surgical stress in three patients over 100 yr

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Purpose: To report the change of plasma epinephrine, norepinephrine, cortisol, plasma renin activity, plasma aldosterone and plasma atrial natriuretic peptide during general anesthesia in three centenarian patients.

Clinical features: Three patients aged 101, 101 and 102-yr, underwent a screw fixation of femoral fracture under general anesthesia. Plasma concentrations of epinephrine, norepinephrine, cortisol, renin activity, aldosterone and atrial natriuretic peptide were measured before the induction of anesthesia, 15 min after incision and 60 min after the end of surgery. Plasma epinephrine concentrations in the three patients increased from 419, 344 and 377 $pg \cdot ml^{-1}$ before anesthesia to 688, 534 and 478 $pg \cdot ml^{-1}$ 15 min after skin incision. Plasma norepinephrine concentrations increased markedly from 408, 513 and 606 $pg \cdot ml^{-1}$ before anesthesia to 2950, 1864 and 1574 $pg \cdot ml^{-1}$ 15 min after skin incision. The cortisol response to surgery was similar to that of young adults. Plasma aldosterone and renin activity was low throughout anesthesia. Plasma atrial natriuretic peptide increased from 353, 367 and 109 $pg \cdot ml^{-1}$ before induction to 479, 487 and 168 $pg \cdot ml^{-1}$ 15 min after skin incision.

Conclusion: Plasma norepinephrine concentration in patients over 100 yr increased markedly during anesthesia, while plasma renin activity and aldosterone were lower.

Objectif : Rendre compte des changements plasmatiques d'adrénaline, noradrénaline, cortisol, activité rénine, aldostérone et peptide natriurétique auriculaire pendant l'anesthésie générale de trois patients centenaires.

Éléments cliniques : Trois patients de 101, 101 et 102 ans ont reçu une anesthésie générale pendant la fixation de vis pour une fracture fémorale. Les concentrations plasmatiques d'adrénaline, noradrénaline, cortisol, activité rénine, aldostérone et peptide natriurétique auriculaire ont été mesurées avant l'induction de l'anesthésie, 15 min après l'incision et 60 min après la fin de l'intervention. Les concentrations plasmatiques d'adrénaline ont augmenté chez les trois patients, passant de 419, 344 et 377 $pg \cdot ml^{-1}$ avant l'anesthésie à 688, 534 et 478 $pg \cdot ml^{-1}$ 15 min après l'incision cutanée. Les concentrations plasmatique de noradrénaline se sont élevées de façon marquée, allant de 408, 513 et 606 $pg \cdot ml^{-1}$ avant l'anesthésie à 2950, 1864 et 1574 $pg \cdot ml^{-1}$ 15 min après l'incision cutanée. La réponse du cortisol a été similaire à celle qu'on observe chez de jeunes adultes. L'aldostérone plasmatique et l'activité rénine sont demeurées faibles pendant toute l'anesthésie. Les peptides natriurétiques auriculaires sont passés de 353, 367 et 109 $pg \cdot ml^{-1}$ avant l'induction à 479, 487 et 168 $pg \cdot ml^{-1}$ 15 min après l'incision cutanée.

Conclusion : La concentration plasmatique de noradrénaline a beaucoup augmenté pendant l'anesthésie de patients de plus de 100 ans, tandis que l'activité rénine et l'aldostérone sont demeurées faibles.

THE autonomic nervous system, and water and electrolyte balance are frequently altered by aging. The change is considered to be a compensatory mechanism to maintain the homeostasis of cardiovascular, water balance and central nervous system. The catecholamine system plays an important role in cardiovascular and central nervous system in the elderly. Increase in NE with age may be caused by both decreased baroreflex function and decreased ß-adrenoceptor responsiveness.[1] Atrial natriuretic peptide (ANP), aldosterone and renin activity regulate water and electrolyte balance and ANP increases with age[2] whilst aldosterone and renin activity decrease with age.[3] Anesthesia for patients > 100 yr is rare and their endocrine response to surgical stress has not been clarified. We describe the hormonal profile of three patients > 100 yr who underwent orthopedic surgery under general anesthesia.

Case report

The study was approved by our medical ethics committee. Informed consent was obtained from patients and their family.

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Case 1

A 101-yr-old, 38 kg woman was brought to our hospital due to a right femoral neck fracture. She had a medical history of a mild hypertension and an ischemic heart disease which had been treated by nitroglycerin and calcium channel blocker. ST depression of 0.1 mV at $V_{5,6}$ lead was observed on ECG tracing. She had been suffering from dementia as judged by 14.5 points of Mini-Mental state examination and was diagnosed as Alzheimer's disease using DSM-III-R criteria . She was scheduled for fixation with a screw. The systolic / diastolic blood pressure and heart rate before the anesthesia were 185 / 94 mmHg and 82 bpm. Anesthesia was induced with 125 mg thiopental and 100 µg fentanyl *iv* at a slow rate and the tracheal intubation was facilitated by 20 mg succinylcholine. Anesthesia was maintained with isoflurane 0.8-1.0% in combination with nitrous oxide 70% and oxygen 30% . The systolic / diastolic blood pressure 15 min after the induction and skin incision were 165 / 80 and 160 / 80 mmHg and the heart rates were 83 and 75 bpm, respectively. The blood pressure and heart rate were maintained around 140-165 / 70-80 mmHg and 80-90 bpm without any vasoactive drugs. The durations of surgery and anesthesia were 70 min and 121 min and she recovered from anesthesia uneventfully. She died from pneumonia on the 43th day after surgery.

Case 2

A 101-yr-old, 47 kg woman was admitted with a right femoral neck fracture. She had a history of mild hypertension, diabetes mellitus and ischemic heart disease. ST depression at V_{2-6} lead was observed on ECG tracing. She has been suffering from dementia, 12.5 points on Mini-Mental state examination. She was scheduled for femur fixation. The systolic / diastolic blood pressure and heart rate before induction were 157 / 88 mmHg and 68 bpm. Anesthesia was induced with 175 mg thiopental and 100 µg fentanyl *iv* at a slow rate and tracheal intubation was facilitated by 30 mg succinhylcholine. Anesthesia was maintained with isoflurane 0.6-1.0% with nitrous oxide 70% and oxygen 30%. The systolic / diastolic blood pressures 15 min after induction and skin incision were 92 / 70 and 152 / 84 mmHg and the heart rates were 72 and 80 bpm, respectively. The blood pressure and heart rate were maintained at 140-160 / 75-85 mmHg and 70-85 bpm without vasoactive drugs. She recovered from anesthesia uneventfully. She was discharged on the 27th day after surgery.

Case 3

A 102-yr-old, 42 kg woman was admitted with a left femoral neck fracture. She had ischemic heart disease treated with nitroglycerin. She suffered from dementia, 16.0 points Mini-Mental state examination. She was scheduled for screw fixation. The systolic / diastolic blood pressure and heart rate before induction were 162 / 85 mmHg and 70 bpm. Anesthesia was induced with 175 mg thiopental and 100 µg fentanyl *iv* at a slow rate and tracheal intubation was facilitated with 30 mg succinhylcholine. Anesthesia was maintained with isoflurane 0.8-1.2 % with nitrous oxide 70% and oxygen 30%. The systolic / diastolic blood pressure 15 min after induction and skin incision were 88 / 67 and 146 / 80 mmHg and the heart rates were 68 and 75 bpm, respectively. The blood pressure and heart rate were maintained at 130-150 / 70-80 mmHg and 70-85 bpm without vasoactive drugs. She recovered from anesthesia uneventfully and was discharged on the 24th day after surgery.

Plasma concentrations of epinephrine (EPI) and norepinephnne (NE) were measured by gas chromatography. Plasma concentrations of cortisol, plasma renin activity (PRA), plasma aldosterone (PA) and plasma atrial natriuretic peptide (ANP) were measured by radioimmunoassay.

Plasma EPI concentrations in Cases 1-3 increased from 419, 344 and 377 (mean 380.0 ± 21.7) $pg \cdot ml^{-1}$ before the anesthesia to 688, 534 and 478 (mean 566.7 ± 62.8) $pg \cdot ml^{-1}$ at 15 min after the skin incision. Plasma NE concentrations increased markedly from 408, 513 and 606 (mean 509.0 ± 57.2) $pg \cdot ml^{-1}$ before the anesthesia to 2950, 1864 and 1574 (mean 2129.3 ± 418.8) $pg \cdot ml^{-1}$ at 15 min after skin incision. Plasma cortisol concentrations elevated from 14.5, 11.5 and 15.0 (mean 13.7 ± 1.1) $\mu g \cdot dl^{-1}$ before induction to 24.5, 17.0 and 24.0 (mean 21.8 ± 2.4) $\mu g \cdot dl^{-1}$ at 15 min after skin incision. PA concentrations were 1.1, 1.5 and 2.0 (mean 1.5 ± 0.3) $pg \cdot ml^{-1}$ before induction and 3.2, 1.8 and 2.6 (mean 2.5 ± 0.4) $pg \cdot ml^{-1}$ at 15 min after skin incision. Renin activity was 0.6, 0.8 and 0.8 (mean 0.7 ± 0.07) $ng \cdot ml^{-1} \cdot hr^{-1}$ before anesthesia induction and 0.8, 1.0 and 0.8 (mean 0.9 ± 0.07) $ng \cdot ml^{-1} \cdot hr^{-1}$ at 15 min after skin incision. ANP increased from 353, 367 and 109 (mean 276.3 ± 83.8) $pg \cdot ml^{-1}$ before induction to 479, 487 and 168 (mean 378.0 ± 105.0) $pg \cdot ml^{-1}$ at 15 min after skin incision. We compared the endocrine response of this patient to surgical stress with endocrine data of elderly patients aged 80 to 99 yr and young adults aged 40 to 59 yr as shown the Figure.[4,5] The young adults, aged 40-59 yr (mean age 52.6 ± 1.7, n=18, nine female and nine male) and elderly patients aged 80-99 yr (mean age 88.2 ± 1.3, n=18, 10 female and eight male for EPI, NE and cortisol, mean age 86.5 ± 1.3, n=18, 10 female and eight male for PRA, PA and ANP) patients were undergoing screw fixation of the femoral neck under isoflurane anesthesia.

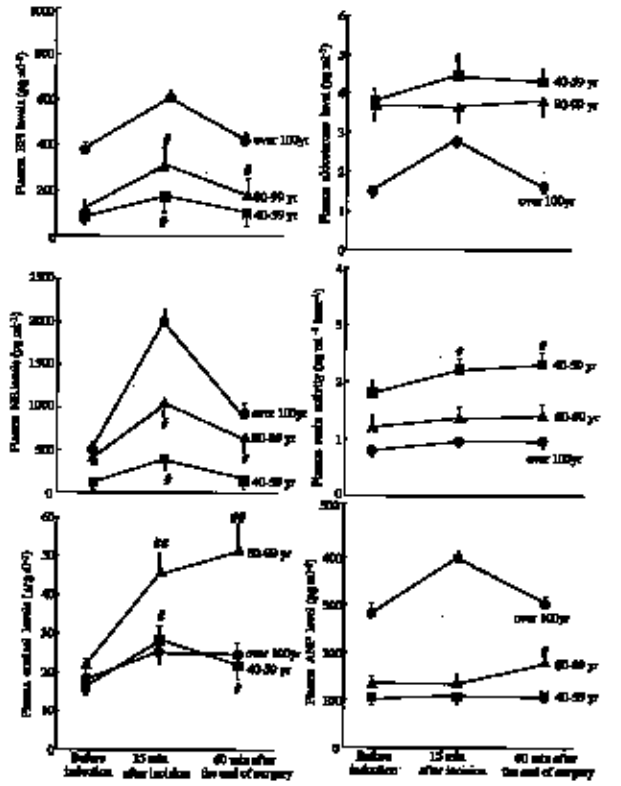

FIGURE Change in mean plasma concentrations of epinephrine, norepinephrine, cortisol, aldosterone, renin activity and atrial natriuretic peptide concentrations in three patients over 100 yr before induction of anesthesia, 15 min after incision and 60 min after the end of surgery. 40-59 yr (mean age 52.6 ± 1.7, n=18, 9 female and 9 male) and 80-99 yr (mean age 86.5 ± 1.3, n=18, 10 female and 8 male) patients were done under isoflurane anaesthesia for screw fixation of femoral neck fracture.

Discussion

In this study, plasma NE concentrations of three patients over 100 yr increased markedly during surgery. The plasma NE concentrations were higher than those of patients aged 80-99 yr, which were higher than those of 40-59 yr patients. Lehmann and Keul[1] reported that plasma NE concentrations were higher in the elderly. The increase in plasma NE concentrations is caused by both an increase in NE appearance into plasma and a decrease in plasma NE clearance.[6] The rise in plasma NE concentrations during a variety of stress including mental stress, isometric and aerobic exercise and hypoglycemia is greater in the elderly patients than in young adults.[7,8] The NE change may depend on an activated sympathetic system in aging.[9] Thus, it is possible that the increased plasma NE response to surgical stress in three patients over 100 yr may result from elevated sympathetic activity with aging, which would be a compensatory mechanism to inhibit hypotension in the elderly patients.

Plasma EPI concentrations of patients over 100 yr were also higher than those of 80-99 yr patients. The EPI response to stress in the elderly patients is reported to be similar[1] or high[10] to as compared with that of young adults. Plasma EPI and NE concentrations are also affected by depth of anesthesia. In this study, the depth of anesthesia was decided according to clinical symptoms such as increase of heart rate, arterial blood pressure and the anesthetic method is widely recognized. The three patients had a stable hemodynamics during anesthesia. In addition, cortisol response to surgery in these patients was similar to that observed in the young adults. As cortisol response is considered to be a indicator of degree of surgical stress, the depth of anesthesia in the three patients appears to be adequate. In this study, high plasma EPI and NE in patients over 100 yr did not alter hemodynamic responses. This appears to be associated with reduction in ß-adrenergic receptor responsiveness in aging.[1] On the other hand, changes in the sympathetic nervous system during anesthesia may be a cause of postoperative cardiovascular complications. An intraoperative increase in plasma NE concentrations correlates with postoperative myocardial ischemia.[11] In addition, increased catecholamine release may lead to postoperative paralytic ileus.[12] The three patients had no postoperative complications. It is unclear whether increased plasma catecholamine concentrations during anesthesia are associated with postoperative complications in the centenarian patients. To investigate catecholamine response to surgical stress in the centenarian patients will be needed to clarify this issue.

The PRA and PA decrease with aging and the decrease is caused by alterations of the kidney glomerulosclerosis, decreased number of functional nephrons, diminished synthesis of angiotensinogen by the liver.[13,14] In patients over 100 yr, PRA and PA concentrations during anesthesia were lower than those of 80-99 yr patients, which were lower than those of 40-59 yr patients. This indicates that PRA and PA concentrations during anesthesia decrease with age. The suppressed increase in PRA in the elderly during anesthesia would be associated with responsiveness to a volume expansion or sodium suppressed by age[15] and inhibiting increase in renal sympathetic drive due to the down-regulation of ß-adrenergic receptors.[16]

Release of ANP in patients over 100 yr elevated during anesthesia. ANP is known to increase in the elderly.[2] The increase is caused by an increase in secretion, decreased plasma clearance, suppressed renin and aldosterone concentrations or the receptor-mediated mecha-

nism.[3] The release of ANP is stimulated by atrial distension, stimulation of sympathetic activity or elevation in blood pressure as well as volume expansion.[2] Elderly patients have an exaggerated ANP response to volume expansion, probably reflecting reduced atrial or ventricular compliance.[13] Accordingly, the elevation of ANP in patients over 100 yr during anesthesia might be affected by mixture of activation of sympathetic activity, suppressed renin and aldosterone concentrations and an exaggerated ANP response to volume expansion. The suppressed plasma renin activity and aldosterone concentrations and increased ANP concentrations in the patients over 100 yr may be required for an maintenance of water, potassium and sodium balance during anesthesia.

In Alzheimer's disease, NE activity of the central nervous system has potentially an important implication for pathogenesis of this disorder and the elevated plasma NE concentrations may indicate severity of Alzheimer's disease.[17] In addition, the hyperactivity of the adrenal cortex has been described in Alzheimer's disease.[18] The cortisol concentrations after corticotropin-releasing factor administration are higher in patients with Alzheimer's disease than normal elderly.[19] Accordingly, the plasma NE and cortisol response to surgery is affected partly by dementia.

In conclusion, plasma epinephrine, norepinephrine and atrial natriuretic peptide were increased during anesthesia, while plasma renin activity and aldosterone were lower in patients over 100 yr.

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