Stress hormone responses to major intra-abdominal surgery during and immediately after sevoflurane-nitrous oxide anaesthesia in elderly patients

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We studied the responses of plasma epinephrine, norepinephrine, adrenocorticotrophic hormone (ACTH), cortisol, and antidiuretic hormone (ADH) during and immediately after sevoflurane-nitrous oxide anaesthesia supplemented with vecuronium in seven elderly patients (mean 76.6 ± 1.7 SEM) who underwent major intra-abdominal surgery. The plasma concentrations of norepinephrine, ACTH, cortisol, and ADH increased in response to surgical procedures ($P < 0.05$). The plasma concentration of ADH increased to a peak concentration of 189.1 ± 20.7 pg $\cdot$ ml $^{-1}$ 30 min after skin incision ($P < 0.05$). The plasma concentrations of epinephrine, norepinephrine, ACTH, and cortisol increased to peak concentrations of 408.6 ± 135.5 pg $\cdot$ ml $^{-1}$, 635.7 ± 167.8 pg $\cdot$ ml $^{-1}$, 222.6 ± 48.0 pg $\cdot$ ml $^{-1}$, and 113.6 ± 67.5 μ g $\cdot$ dl $^{-1}$, respectively immediately after tracheal extubation ($P < 0.05$). We conclude that, in the elderly patients, the responses of stress hormones to major intra-abdominal surgery were preserved during sevoflurane-nitrous

oxide anaesthesia sufficient to prevent increases in arterial pressure and heart rate. The strongest responses of epinephrine, norepinephrine, ACTH, and cortisol were elicited immediately after tracheal extubation.

Cette étude porte sur les réponses de l'épinéphrine, de la norépinéphrine, de ACTH, du cortisol, et de l'ADH pendant et immédiatement après l'anesthésie au sévoflurane-protoxyde d'azote supplémentée par du vécuronium chez sept patients avancés en âge (moyenne $76,6 \pm 1,7$ SEM) opérés pour une chirurgie viscérale majeure. Les concentrations plasmatiques de norépinéphrine, d'ACTH, de cortisol, et d'ADH augmentent en réponse à la chirurgie ($P < 0,05$). La concentration plasmatique d'ADH atteint un maximum de $189,1 \pm 20,7$ pg $\cdot$ ml $^{-1}$ après l'incision ($P < 0,05$). La concentration plasmatique de l'épinéphrine, de la norépinéphrine, de l'ACTH et du cortisol atteignent respectivement un maximum de $408,6 \pm 135,5$ pg $\cdot$ dl $^{-1}$, $635,7 \pm 167,8$ pg $\cdot$ ml $^{-1}$, $222,6 \pm 48,0$ pg $\cdot$ ml $^{-1}$, et de $113,6 \pm 67,5$ μ g $\cdot$ dl $^{-1}$ immédiatement après l'intubation ($P < 0,05$). En conclusion, la réponse des hormones de stress à une chirurgie viscérale majeur chez le sujet âgé est conservées pendant une anesthésie au sévoflurane-protoxyde d'azote suffisamment profonde pour prévenir une montée de la pression artérielle et de la fréquence cardiaque. Les réponses les plus intenses de l'épinéphrine, de la norépinéphrine, de l'ACTH et du cortisol sont survenues immédiatement après l'intubation de la trachée.

Key words

ANAESTHESIA: geriatric;
ANAESTHETICS, VOLATILE: sevoflurane;
HORMONES: adrenocorticotrophic, antidiuretic,
catecholamines, corticosteroids.

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Although there is a functional decline in most vital organs and consequent loss of organic reserve with increasing age, no change in adrenocortical function could be demonstrated with advancing age in response to ACTH stimulation in the elderly ranging between 60 and 96 yr,¹

and the adrenocortical response to major surgery and anaesthesia is found to be well preserved in elderly patients.² However, the responses of stress hormones such as epinephrine, norepinephrine, adrenocorticotrophic hormone (ACTH), and antidiuretic hormone (ADH) to major intra-abdominal surgery during sevoflurane-nitrous oxide anaesthesia remain unknown in elderly patients.

Sevoflurane, a new inhaled anaesthetic agent, provides rapid anaesthetic induction and recovery consistent with its low blood solubility (a blood/gas partition coefficient of 0.60)³ and rapidly and easily controllable anaesthetic depth. In addition, it has many advantages associated with the characteristics of an ideal inhaled anaesthetic.⁴

We investigated, in terms of circulating stress hormones, how elderly patients respond to major intra-abdominal surgery during and immediately after sevoflurane-nitrous oxide anaesthesia.

Methods

Seven patients (five men and two women, mean 76.6 ± 1.7 SEM yr) scheduled to undergo major intra-abdominal surgery were studied. All patients were in ASA class II. The profiles of the patients are shown in Table I. They did not have severe physiological or psychological disorders such as malnutrition, depression, or senile dementia. None of them had apparent endocrine, metabolic, renal, and hepatic diseases. Informed consent to perform the study was obtained at the time of the preoperative visit and the study was approved by our institutional human investigation committee. All the patients received premedication with atropine sulfate 0.3 mg and hydroxyzine 12.5 mg *im* one hour before induction of anaesthesia. On arrival in the operating room, the radial artery was cannulated under local anaesthesia for monitoring arterial pressure and drawing blood samples. An epidural catheter was inserted through the middle thoracic interspace (T₇-T₈) for postoperative pain relief. No local anaesthetics were administered epidurally throughout the anaesthetic course.

Anaesthesia was induced by stepwise increases in sevoflurane concentration from 1% to 4% in 70% nitrous oxide until eyelash reflex disappeared. The trachea was intubated after the administration of vecuronium $0.15 \cdot \text{mg} \cdot \text{kg}^{-1}$ *iv*. Ventilation was controlled with a volume-cycled ventilator to maintain adequate PETCO₂ (35 to 40 mmHg). Vecuronium was administered intermittently during the surgical procedures to provide optimal surgical conditions. The concentration of sevoflurane was varied from 1.5% to 3% in 70% nitrous oxide to maintain optimal anaesthetic depth judged by changes in arterial pressure and heart rate throughout the surgical and anaesthetic course. After the end of surgery, residual neuromuscular blockade was reversed with atropine sul-

TABLE I Patients' profiles

Patient	Sex	Age (yr)	Weight (kg)	Operation
1	Woman	83	47	Hemicolectomy
2	Man	71	45	Sigmoidectomy and total cystectomy
3	Woman	72	53	Total gastrectomy
4	Man	74	52	Total gastrectomy and cholecystectomy
5	Man	77	43	Subtotal gastrectomy
6	Man	77	53	Total gastrectomy
7	Man	82	66	Subtotal gastrectomy
Mean		76.6	51.3	
SEM		1.7	2.9	

fate 1.0 mg and neostigmine 2.5 mg *iv*, followed by discontinuation of sevoflurane and nitrous oxide, and 100% oxygen was administered. The trachea was extubated after the patient responded to a simple verbal command. After the last blood sample was drawn, the patient was transferred to the recovery room and a local anaesthetic was administered through the epidural catheter for postoperative pain relief.

Plasma was separated at 4°C and then frozen at -20°C until assayed. Plasma epinephrine and norepinephrine concentrations were measured by high-performance liquid chromatography.⁵ The plasma ACTH concentration was determined by radioimmunoassay⁶ using the Allegro ACTH Kit (Nihon Med+Physics, Inc., Hyogo, Japan). The plasma cortisol concentration was determined by radioimmunoassay⁷ using the Gamma Cortisol Kit (Baxter, Inc., Tokyo, Japan). The plasma ADH concentration was determined by radioimmunoassay⁸ using AVP-RIA Kit (Mitsubishiyuka, Inc., Tokyo, Japan). Reference values for epinephrine, norepinephrine, ACTH, cortisol, and ADH in unrestrained patients during supine rest in the morning are 0 to 120 pg · ml⁻¹, 60 to 450 pg · ml⁻¹, 30 to 60 pg · ml⁻¹, 4.0 to 18.3 µg · dl⁻¹, and 0.3 to 3.5 pg · ml⁻¹, respectively.

The sampling times for the hormone measurements were: anaesthetic induction (#1), within one minute before tracheal intubation (#2), within one minute after tracheal intubation (#3), immediately before skin incision (#4), 30 min after skin incision (#5), when active intra-abdominal surgical procedures were being performed, 60 min after skin incision (#6), within one minute after tracheal extubation (#7), when all anaesthetic agents were discontinued.

The data were presented as mean $\pm$ SEM. The non-parametric Wilcoxon signed-rank test was used to compare values within group. All statistical analyses were car-

TABLE II Haemodynamic and hormonal data

Sampling time	MAP (mmHg)	HR (beat · min ⁻¹)	Epinephrine (pg · ml ⁻¹)	Norepinephrine (pg · ml ⁻¹)	ACTH (pg · ml ⁻¹)	Cortisol (µg · dl ⁻¹)	ADH (pg · ml ⁻¹)
1	102.3 ± 6.3	77.7 ± 4.6	67.1 ± 24.9	165.7 ± 42.3	51.7 ± 4.1	12.7 ± 1.0	1.1 ± 0.2
2	71.4 ± 7.7*	72.9 ± 6.3	18.6 ± 6.3*	235.7 ± 62.9*	53.1 ± 5.6	11.6 ± 1.1	6.2 ± 4.7
3	89.9 ± 8.2	95.1 ± 7.2*	15.7 ± 6.5*	350.0 ± 70.9*	51.9 ± 5.8	11.8 ± 1.2	5.0 ± 3.6*
4	64.4 ± 6.7*	71.7 ± 5.5*	8.6 ± 3.4*	207.1 ± 50.5	45.5 ± 4.6	11.2 ± 1.3	1.4 ± 0.4
5	77.3 ± 3.2*	76.0 ± 4.1	111.4 ± 24.0	411.4 ± 57.0*	131.7 ± 18.6*	17.9 ± 0.8*	189.1 ± 20.7*
6	81.7 ± 2.6*	78.9 ± 5.1	104.3 ± 27.4	448.6 ± 76.0*	150.1 ± 20.7*	19.7 ± 0.7*	167.4 ± 34.6*
7	107.6 ± 4.9	83.6 ± 8.5	408.6 ± 135.5*	635.7 ± 167.8*	222.6 ± 48.0*	113.6 ± 67.5*	127.3 ± 19.2*

MAP, mean arterial pressure; HR, heart rate; ACTH, adrenocorticotrophic hormone; ADH, antidiuretic hormone; sampling time 1, before placement of an epidural catheter and anaesthetic induction; 2, before tracheal intubation; 3, immediately after tracheal intubation; 4, before skin incision; 5, 30 min after skin incision; 6, 60 min after skin incision; 7, within one minute after tracheal extubation.

* $P < 0.05$ compared with sampling time 1.

FIGURE 1 Changes in mean arterial pressure and heart rate (mean $\pm$ SEM). *Denotes $P < 0.05$, compared with sampling time 1.

Sampling time 1 represents control values before placement of an epidural catheter and anaesthetic induction. Sampling time 2 and 3 represents values before and immediately after tracheal intubation, respectively. Sampling time 4 represents values before skin incision. Sampling time 5 and 6 represent values at 30 and 60 min after skin incision, respectively. Sampling time 7 represents values immediately after tracheal extubation.

ried out using STATVIEW SE+GRAPHICS® software (Abacus Concept, Inc., version 1.04, 1991). A P value < 0.05 was considered statistically significant.

Results

Haemodynamic and hormonal data in the seven patients are shown in Table II. Mean arterial pressure (MAP) decreased before tracheal intubation, before skin incision, and during surgical procedures ($P < 0.05$ vs sampling time 1). Heart rate increased only immediately after tracheal intubation ($P < 0.05$). After tracheal extubation mean arterial pressure and heart rate did not differ from control (Figure 1). Changes in plasma concentrations of epinephrine and norepinephrine were within the normal range during anaesthetic induction and surgical procedures (Figure 2). The plasma concentrations of ACTH and cortisol did not change during anaesthetic induction, but increased 30 min and 60 min after skin incision (P

FIGURE 2 Changes in plasma concentrations of epinephrine and norepinephrine. See legend in Figure 1 for identification of symbols. The shaded areas represent the normal range of each hormone.

< 0.05) (Figure 3). The plasma cortisol concentrations immediately after tracheal extubation varied from patient to patient over a wide range from $21.6 \mu\text{g} \cdot \text{dl}^{-1}$ to $502 \mu\text{g} \cdot \text{dl}^{-1}$ over the normal range. The plasma concentration of ADH increased from $1.1 \pm 0.2 \text{ pg} \cdot \text{ml}^{-1}$ before anaesthetic induction (sampling time 1) to $189.1 \pm 20.7 \text{ pg} \cdot \text{ml}^{-1}$ 30 min after skin incision ($P < 0.05$) and thereafter remained at higher concentrations than preanaesthetic value (Figure 4). Immediately after tracheal extubation, the plasma concentrations of epinephrine, norepinephrine, ACTH, and cortisol increased to peak concentrations of $408.6 \pm 135.5 \text{ pg} \cdot \text{ml}^{-1}$, $635.7 \pm 167.8 \text{ pg} \cdot \text{ml}^{-1}$, $222.6 \pm 48.0 \text{ pg} \cdot \text{ml}^{-1}$, and $113.6 \pm 67.5 \mu\text{g} \cdot \text{dl}^{-1}$, respectively ($P < 0.05$) (Figures 2, 3, and 4).

Discussion

Our study demonstrated that elderly patients responded to major intra-abdominal surgical stress during an ade-

FIGURE 3 Changes in plasma concentrations of ACTH and cortisol. See legend in Figure 1 for identification of symbols.

quate depth of sevoflurane-nitrous oxide anaesthesia and showed the strongest response immediately after tracheal extubation.

Murakawa *et al.*⁹ evaluated the effects of sevoflurane-nitrous oxide anaesthesia and surgery on plasma concentrations of epinephrine and norepinephrine in 12 patients aged from 15 to 65 yr who underwent gastrointestinal or gynaecological surgery and found that plasma epinephrine and norepinephrine concentrations increased during and after surgery. The plasma concentrations of epinephrine and norepinephrine were 1.3 to 2.7 times higher in our patients than in their patients before induction of anaesthesia, at 30 min and 60 min after skin incision, and after surgery. This suggests that the adreno-medullary glands and the sympathetic nervous system were more strongly activated by surgical procedures and during emergence from anaesthesia in elderly patients than in the younger adult patients. A difference in plasma catecholamine concentrations between young and old healthy males has been reported by Fleg *et al.* They demonstrated that for any relative level of aerobic stress incurred by healthy men during treadmill exercise, plasma catecholamine concentrations were higher in the elderly.¹⁰

In our study the plasma concentrations of ACTH and cortisol were increased by surgical procedures, though their peak values were seen immediately after tracheal extubation. Murakawa *et al.*¹¹ reported that plasma ACTH and cortisol concentrations increased with surgical stimulation and reached peak values during sevoflurane-nitrous oxide anaesthesia. Bowen *et al.*² reported that plasma cortisol concentrations increased in 12 elderly patients aged 74 to 83 yr (mean 79 yr) who underwent major surgery under halothane anaesthesia. These findings suggest that the pituitary-adrenocortical response to surgical procedures may be well preserved in elderly patients during anaesthesia.

Our findings that the plasma concentrations of epinephrine, norepinephrine, ACTH, and cortisol increased in response to tracheal extubation are in agreement with those of Udelsman *et al.*¹² They found that the immediate

FIGURE 4 Changes in plasma concentrations of ADH. See legend in Figure 1 for identification of symbols.

postoperative period was associated with profound elevations of plasma ACTH, cortisol, and epinephrine concentrations in 11 patients (mean 45 ± 15 SD yr) after parathyroid or thyroid surgery under isoflurane anaesthesia and concluded that the major determinant of ACTH, cortisol, and epinephrine secretion was anaesthesia reversal and recovery, and not surgical trauma. Our results showed that emergence from anaesthesia in the absence of adequate pain control should elicit the strongest stress response throughout the anaesthetic course in elderly patients as well as in young adult patients examined by Udelsman *et al.*

The plasma ADH concentration increased by 190 times 30 min after skin incision, compared with the preanaesthetic value, but the act of tracheal extubation was not followed by an increase in the plasma concentration of ADH. This suggests that surgical procedures may release more strongly ADH than tracheal extubation.

Mean arterial pressure and heart rate did not increase during surgical procedures or immediately after tracheal extubation in spite of considerable increases in plasma catecholamines. The fact that cardiovascular adrenergic receptor sensitivity to agonists decreases with aging may explain the reduced responsiveness of the cardiovascular system to increased stress hormones acting on the autonomic nervous system.¹³ This indicates that haemodynamic changes are not sensitive indicators of change in stress hormones.

Since plasma concentrations of stress hormones represent the integration of production, release, degradation, and clearance of stress hormones, certain limitations of using plasma concentrations of stress hormones as an index of stress responses should be recognized. Plasma stress hormones may remain high in elderly patients

whose diminished hepatic function may slow down clearance of plasma stress hormones. Increased plasma stress hormones may exert metabolic effects that include hyperglycaemia, increased protein catabolism, and sodium and water retention, but no data are available on the effects of stress hormones on the metabolic responses to anaesthesia and surgical procedures in elderly patients.

Further studies are needed to examine the pharmacokinetic, pharmacodynamic, and metabolic effects of stress hormones during and immediately after sevoflurane-nitrous oxide anaesthesia in elderly patients.

In conclusion, we confirmed that the responses of stress hormones in elderly patients of 70 yr and above were preserved during surgical procedures under sevoflurane-nitrous oxide anaesthesia and that tracheal extubation elicited the strongest responses of stress hormones throughout the course of anaesthesia.

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