Adrenal Function During Long-Term Anesthesia in Man[1] (35158)

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The present studies were designed to elucidate the effect of long-term general anesthesia with endotracheal nitrous oxide and halothane upon adrenocortical and medullary function in man. Cortisol blood levels are known to increase in man during short-term general anesthesia without surgery (1). However, cortisol secretion during long-term general anesthesia without additional surgery has not been studied. Cortisol release from the adrenal cortex is stimulated by pituitary ACTH, which in turn is activated by the hypothalamus via corticotropin releasing factor (CRF) (2). An intricate negative feedback regulation between cortisol blood levels and the pituitary and hypothalamic centers keeps this system in balance (3). The CRF-producing nerve cells are connected by neuronal synapses with higher brain centers (4). One might, therefore, assume that reduction of neocortical activity during general anesthesia would alter cerebro–hypothalamo–pituitary–adrenal function. However, it is surprising that the reduction in cortical activity of the brain should cause an increase rather than a decrease in cortisol blood levels.

The present work suggests that, in fact, a decrease in adrenocortical activity does occur and that the increase previously found may be related to extraneous factors such as excitement during the second stage of anesthesia.

Materials and Methods. Twelve healthy unmedicated male volunteers (age 21 to 30 years) were selected for study. In 5 subjects anesthesia was induced with 40 to 80% nitrous oxide (N_2O) at approximately 9:30 a.m. After 10 to 15 min, halothane was added. The subjects' tracheae were intubated without the aid of muscle relaxants and the alveolar halothane concentration was adjusted to 0.5% with 70% nitrous oxide. The alveolar halothane was subsequently increased every 15 min to 1 and 1.5%. The subjects were then maintained on 1% alveolar halothane and 70% N_2O for 3.5 hr, after which the halothane concentration was varied again in 15-min intervals (0.5, 1, 1.5, and 2%). No other stresses were imposed during the anesthesia. In the remaining 7 subjects, N_2O was omitted and general anesthesia was induced and maintained with halothane alone. After endotracheal intubation, the alveolar halothane concentration was maintained at 1.0 or 1.6%. Five percent glucose was slowly infused after onset of anesthesia to assure a constant blood glucose level during the procedure. In addition, the subjects who received only halothane were challenged with increasing endotracheal CO_2 concentrations before and during the anesthesia to obtain cardiorespiratory CO_2 responses. The results of these studies will be reported elsewhere. Of this group, one subject was infused with 1 mg of hydrocortisone succinate/hr anesthesia and the second subject with 4 mg. In all subjects, blood for plasma corticosteroids was obtained every 15 to 30 min before and during general anesthesia. Three to 5 hr after terminating the anesthesia, all subjects emptied their bladders and the urine was saved for catecholamine and creatinine determinations. A control 24 hr urine for catecholamine and creatinine measurements was obtained before the experiment. Plasma

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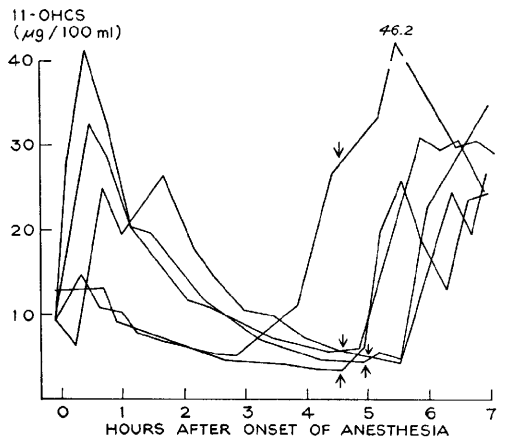

FIG. 1. Plasma 11-hydroxycorticosteroids (11-OH CS) in 5 healthy volunteers during 7 hr of general anesthesia with endotracheal nitrous oxide (N_2O) and halothane. N_2O alone was used for the induction of anesthesia. Changes in concentration of anesthetic are marked by the arrow.

corticosteroids were measured as fluorogenic 11-hydroxycorticosteroids (11-OHCS) according to the method of Mattingly (5). Urinary epinephrine and norepinephrine were determined by fluorometry according to Von Euler and Floding (6), using the modification of Price and Price (7).

Results. All subjects had normal plasma 11-OHCS at 8 a.m. at basal conditions (mean 14.2 ± 1.0 μg/100 ml, SE). In the 5 subjects induced with N_2O we observed a rise in plasma 11-OHCS, which appeared to be directly proportional to the length and severity of the excitation phase (stage II anesthesia) (Fig. 1). The mean rise in plasma 11-OHCS after induction of anesthesia in the 5 subjects showing various degrees of excitement was 25.7 ± 2.7 μg/100 ml (SE). Following the peak of 11-OHCS, after induction of anesthesia, the level of plasma 11-OHCS fell in all 5 subjects to a mean nadir of 4.5 ± 0.4 μg/100 ml. Four to 5.5 hr after start of anesthesia the plasma 11-OHCS rose again, reaching a maximum of 32.9 ± 2.0 μg/100 ml. This rise in 11-OHCS was not correlated to changes in halothane concentration. In the group induced with halothane alone no significant excitation occurred. There was also no rise in plasma 11-OHCS (Fig. 2). Instead, the 11-OHCS levels fell right after induction of anesthesia to a mean nadir of 3.1 ± 0.2 μg/100 ml (Fig. 2). After 2 to 4.5 hr of anesthesia a rise in 11-OHCS again was observed, reaching a maximum of 30.8 ± 1.8 μg/100 ml. The rise did not correlate with change in halothane concentration. Challenge with CO_2 did not increase plasma 11-OHCS in the conscious state (Fig. 3), nor could we correlate changes in the 11-OHCS secretion pattern during anesthesia with changes in CO_2 levels (Fig. 2). The subject who was infused with 1 mg of hydrocortisone succinate showed no rise in plasma 11-OHCS immediately after onset of anesthesia (rapid induction), and the plasma 11-OHCS fell to 6.8 μg/100 ml before rising late during anesthesia to 36.3 μg/100 ml (Fig. 4). The subject who received 4 mg of hydrocortisone succinate showed no fall in plasma 11-OHCS, though he also exhibited the late rise to 35.3 μg/100 ml (Fig. 4). In two of the subjects in whom blood glucose was measured, the level remained constant at 80–110 mg/100 ml during the entire procedure.

The mean urinary epinephrine during control was 6.2 ± 1.4 μg/g creatinine (SE) and 8.4 ± 1.2 after general anesthesia. Urinary norepinephrine was 32.4 ± 6.2 μg/g creatinine during control and 29.1 ± 4.5 after anesthesia (Table I.).

Discussion. Our results agree with the pre-

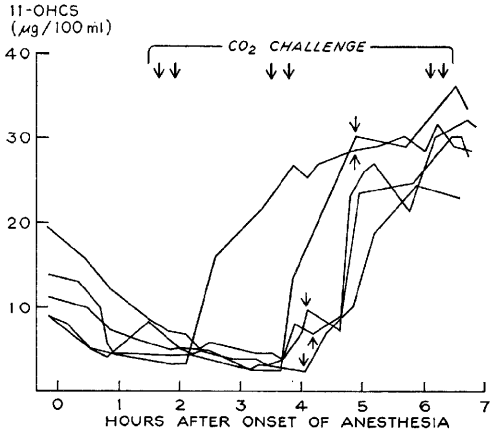

FIG. 2. Plasma 11-hydroxycorticosteroids (11-OH CS) in 5 healthy volunteers during 7 hr of general anesthesia with endotracheal halothane (rapid induction of anesthesia) and three periods of hypercarbia. Changes in halothane concentration are marked by the arrow.

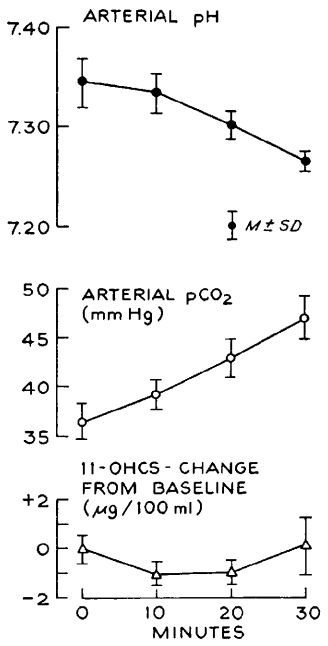

FIG. 3. Arterial pH, arterial pCO_2 and plasma 11-hydroxycorticosteroids (11-OHCS) in 6 subjects during a challenge with CO_2-enriched air in the conscious state.

vious finding that short-term general anesthesia with halothane may increase the cortisol blood levels significantly before the start of surgery in unmedicated patients (1). The magnitude of the 11-OHCS rise in our study was directly proportional to the duration of the excitation phase during induction of the anesthesia. The subjects who were anesthetized with halothane alone and in whom the anesthesia was rapidly introduced with minimal excitation demonstrated no rise in plasma 11-OHCS (Fig. 2). Thus, induction of anesthesia itself does not activate the hypothalamo–pituitary–adrenal axis (HPAA). The earlier findings, demonstrating an activation of the HPAA with a rise in plasma cortisol levels shortly after the onset of anesthesia (1), may be explained by the short excitation phase most patients go through in routine general anesthesia for surgery.

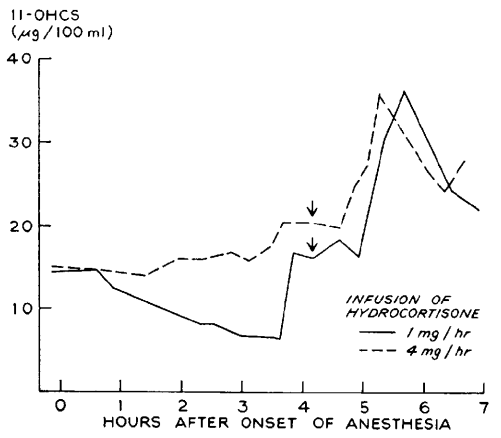

FIG. 4. Plasma 11-hydroxycorticosteroids (11-OHCS) during 7 hr of halothane anesthesia in 2 subjects, who received a continuous hydrocortisone infusion during the period of anesthesia.

TABLE I. Urinary Catecholamine Excretion During General Anesthesia and a 24-hr Control Period.

	Epinephrine (μg/g creatinine)		Norepinephrine (μg/g creatinine)	
Subject[a]	Control	Anesthesia	Control	Anesthesia
1	2.3	6.9	15.6	25.9
2	2.5	5.9	8.7	10.2
3	6.5	10.1	30.0	23.0
4	5.5	9.7	89.0	28.9
5	4.7	0.8	36.5	51.0
6	8.7	11.4	35.0	12.8
7	13.0	11.4	26.0	16.3
8	3.0	5.8	34.0	27.5
9	9.6	11.8	37.9	45.9
10	0.6	6.0	16.4	19.7
11	2.1	16.4[b]	21.3	29.5[b]
12	16.0	4.8[b]	38.0	59.0[b]
Mean	6.2	8.4	32.4	29.1
±SE	1.4	1.2	6.2	4.5

[a] Subjects 1–5 received N_2O and halothane, subjects 6–12 received halothane only.

[b] Infusion of hydrocortisone succinate during anesthesia.

Plasma cortisol levels during long-term general anesthesia for a period of 7 hr without concomitant surgical stress have not been previously reported. In all our subjects we found a fall in the plasma 11-OHCS to hypoadrenal levels in the first 4 hr after onset of anesthesia. The plasma 11-OHCS fell in those who were anesthetized with halothane only (rapid induction) without an initial rise right after onset of anesthesia (Fig. 2). A similar observation was made by Moore who found that deep sleep with full surgical relax-

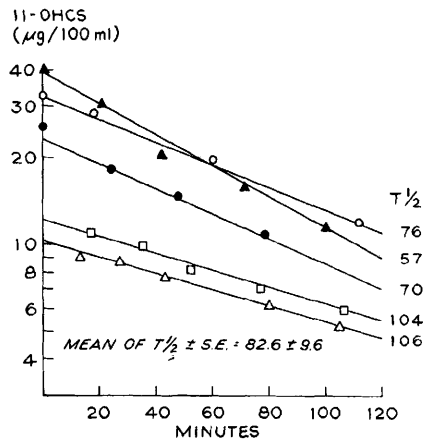

FIG. 5. Fall in plasma 11-hydroxycorticosteroids (11-OHCS) and half-life after the initial rise in plasma 11-OHCS during N_2O-halothane anesthesia in 5 subjects.

ation for up to 3 hr, induced with a combination of pentothal, nitrous oxide, and curare, did not stimulate the adrenal cortex (8). The group in whom the induction of anesthesia was performed with N_2O showed an initial rise related to the excitation phase followed by a similar fall in plasma 11-OHCS. The half-life of plasma 11-OHCS in the group anesthetized with N_2O and halothane was calculated as 82.6 ± 9.6 min (SE), suggesting complete inhibition of adrenal cortisol secretion (Fig. 5). Two to 5 hr after the onset of anesthesia, plasma 11-OHCS started rising again and remained elevated until the end of anesthesia (Figs. 1 and 2). This was unrelated to changes in anesthetic concentration or to the raising of arterial pCO_2 or the lowering of the arterial pH. This was to be expected since the challenge with CO_2 was not stressful even in the conscious state. Because this late rise in plasma 11-OHCS also occurred in the two subjects who were infused with hydrocortisone, this phenomenon cannot be explained as a rebound rise due to an anesthesia-induced change in feedback threshold, since these subjects never reached hypoadrenal levels of plasma 11-OHCS (Fig. 4). Therefore, at this time, we have no explanation for the late rise in plasma 11-OHCS during long-term anesthesia, other than being caused by a central activation of ACTH release following a 2 to 5 hr quiescence.

Our findings demonstrate that the reduced neocortical activity of the CNS due to general anesthesia induces at first a suppression of the hypothalamic–pituitary–adrenal axis with inhibition of pituitary ACTH secretion, which is reflected by the rapid fall in plasma 11-OHCS. This inhibition can be overcome by the stress of surgery, which induces elevated cortisol blood levels despite general anesthesia (9). That halothane anesthesia interferes with steroid biosynthesis directly or enhances catabolism of steroids in the liver is unlikely, since patients with Cushing's syndrome and a fixed steroid output from their adrenal glands show a constant level of plasma 11-OHCS during general anesthesia (10). The late activation of the HPAA, which we found in all our subjects, must be due to mechanisms in the CNS that can overcome the anesthesia-induced inhibition. This is not related to a feedback mechanism. Whether this late rise in plasma 11-OHCS is specific for halothane anesthesia remains to be explored, since different anesthetics might have different effects on the hypothalamo–pituitary–adrenal axis (11).

That general anesthesia alone can influence anterior pituitary hormone release, which is under control of the hypothalamus, has also been demonstrated for growth hormone (12).

The data obtained from the urinary catecholamine measurements suggest that halothane anesthesia does not change medullary secretion of catecholamines. There was no significant increase of the epinephrine and norepinephrine secretion during anesthesia compared to a control period. We could not detect any reduction in medullary catecholamine secretion since basal catecholamine secretion is already low in normal subjects (13).

Summary. Plasma 11-OHCS were measured in 12 subjects during 7 hr of general anesthesia with endotracheal nitrous oxide (N_2O) and halothane, and halothane alone. The 5 subjects who received the N_2O-halothane anesthesia showed an early rise in plasma 11-OHCS, which corresponded to the duration of the excitation phase. After the short rise, the plasma 11-OHCS fell to hypoadrenal levels. The subjects who received halothane only (rapid induction of anesthe-

sia) showed no rise in plasma 11-OHCS, but the 11-OHCS fell to hypoadrenal levels after induction. After 2 to 4.5 hr of general anesthesia, the plasma 11-OHCS rose spontaneously and remained elevated until the end of anesthesia. The sudden rise was not due to changes in feedback threshold and did not correlate with changes in concentration of the anesthetic. The urinary catecholamine secretion was not significantly altered during the anesthesia compared to a control period.

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