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Secretion of 17-Hydroxycorticosteroids in Conscious and Anesthetized Dogs Exposed to Simulated Altitude.* (28691)

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Armstrong and Heim were the first to observe adrenal hypertrophy in rabbits exposed daily to a pressure equivalent to 18,000 feet (1). Metabolic and histologic extensions of these studies(2,3) revealed that maximal activation of the adrenal cortex occurred in rats, rabbits and dogs within 2-3 days. Others have demonstrated that, although urinary 17-ketosteroids (17-KS) and 17-hydroxycorticosteroids (17-OHCS) of men living at altitudes of 15,000-21,000 feet for over 2 weeks were not significantly different from those observed in subjects living at sea level(4,5), urinary and peripheral plasma 17-OHCS markedly increase during the first 3 days at high altitude before returning to sea level values(6). Hale *et al*(7), however, reported that plasma 17-OHCS were not significantly elevated in humans breathing ambient air for 45 minutes at 14,000 feet simulated altitude.

Increased urinary excretion of 17-KS in humans(8-10) and accelerated adrenocortical secretion of 17-OHCS in anesthetized dogs (11) have been observed during hypoxia induced at ground level by breathing gas mixtures low in oxygen. Under similar conditions Biddulph *et al* reported that peripheral plasma 17-OHCS and corticosterone-like steroids of dogs remained essentially unaltered (12). Since concentrations of peripheral plasma and urinary adrenocortical steroids are dependent on their secretion by the adrenal gland, metabolism and excretion, the present study was undertaken to determine the effect of hypoxia induced by simulated altitude on the secretion of 17-OHCS of conscious and anesthetized dogs.

Materials and methods. Eight male dogs, weighing 11 to 16 kg, were prepared 1 to 2 months prior to collection of adrenal venous blood in anesthetized and conscious dogs by a modification(13) of the method of Satake *et al*(14). Essentially the procedure consisted of bilaterally sectioning the dorsal spinal roots (T_{11}-L_3) through which the sensory nerve fibers from the lumbar region run. Approximately 24 hours prior to collection of blood samples, the accessory branches of the lumbo-adrenal vein were doubly ligated and a glass cannula fitted with a small length of rubber tubing was inserted into the vessel lateral to the adrenal gland. The cannula and tubing were filled with a heparin-saline solution and then clamped. A silk ligature was placed loosely around the central vein which drains adrenal secretions into the inferior vena cava. The skin was sutured and the animal allowed to recover.

Eighteen experiments (both right and left lumbo-adrenal veins were used in 5 dogs) were conducted in a continuously ventilated decompression chamber at 23°C for 2 hours. The dogs respired ambient air which resulted in oxygen tensions of 150 mm Hg in 10 ground level experiments (4 conscious; 6 anesthetized; sodium pentobarbital, 30 mg/kg), and 78 mm Hg in 8 experiments (4 conscious; 4 anesthetized) at 17,000 feet simulated altitude (395 mm Hg). Ascents and

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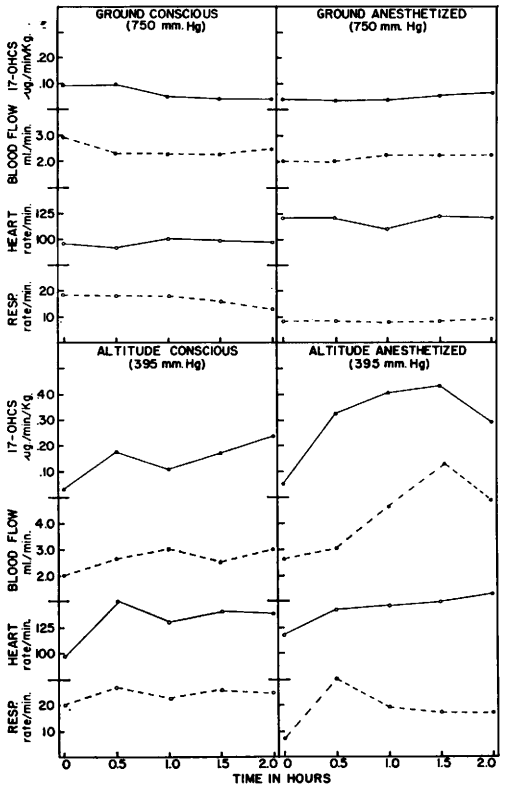

FIG. 1. Secretion of 17-OHCS μg/min/kg body weight, lumbo-adrenal vein blood flow, heart rate and respiratory rate of conscious and anesthetized dogs at ground level (750 mm Hg) and at 17,000 feet simulated altitude (395 mm Hg).

descents in the altitude groups were made at approximately 5,000 feet/minute. After the animals became accustomed to the chamber (about 1 hour), pulse rates, respiratory rates and adrenal venous samples were obtained at 0, 0.5, 1.0, 1.5 and 2.0 hours. The latter was accomplished by removing the clamp on the rubber tubing connected to the cannula and timing the flow of blood into graduated conical test tubes, while gently pulling on the ligature around the central vein. At the end of the collection period (1-4 minutes) the ligature was released, the cannula filled with a heparin solution and the tubing clamped. Blood samples were immediately centrifuged for hematocrits and the plasma stored at −25°C until analyzed for 17-OHCS(15).

Results. The initial average secretions of 17-OHCS of conscious and anesthetized ground level dogs were .09 ± .02 and .04 ± .01 μg/min/kg body weight, respectively, and did not change significantly from these levels during the succeeding 2 hours (Fig. 1). The secretory rates of anesthetized animals decompressed to 17,000 feet rapidly increased from an initial rate of .06 ± .01 to .32 ± .10 μg/min/kg within 0.5 hour and reached maximum rates (7-fold increase) at 1.5 hours. Subsequently, 17-OHCS secretion tended to decrease, yet remained significantly ($p > .01$) above pre-decompression levels. Although 17-OHCS levels of conscious dogs during hypoxia were not as markedly elevated as those observed in anesthetized animals under similar conditions, significant 4- to 8-fold increases from control values (.03 ± .01 μg/min/kg) occurred.

The initial lower heart rates (20%) and higher respiratory rates (100%) in conscious than in anesthetized dogs illustrate vagal inhibition by sodium pentobarbital anesthesia. In general, these rates remained essentially unaltered in all animals at ground level for 2 hours. Decompression to 17,000 feet caused marked increases in adrenal vein blood flow and respiratory rates of anesthetized animals, whereas only moderate increases were observed in conscious dogs. Heart rates significantly increased in both groups during hypoxia.

Discussion. The sustained elevations in 17-OHCS secretions of both conscious and anesthetized dogs decompressed to 17,000 feet simulated altitude confirm our previous finding on anesthetized dogs breathing 10% oxygen at ground level(11). Sodium pentobarbital had no discernible effect on the adrenocortical response to hypoxia since 4- to 8-fold increases were observed in both groups. These data are consistent with those of others who have shown that pentobarbital anesthesia does not inhibit the adrenal ascorbic acid response of rats to adrenaline and histamine(16).

The development of respiratory alkalosis at high altitudes may stimulate release of adrenocorticotropin (ACTH) and cause subsequent increase in secretion of 17-OHCS, since altered acid-base balance increases the adrenocortical secretion of these steroids in intact but not hypophysectomized dogs(17,

18). Furthermore, the work of Anichkov *et al*(19) illustrates that plasma 17-OHCS (blood taken from the inferior vena cava at the level of adrenal glands) increases when hypoxia is produced by perfusing the isolated intact and not the denervated carotid body with hypoxemic drugs. These data suggest that during hypoxia altered acid-base balance resulting from hyperventilation and not hypoxemia *per se* is the stimulus for ACTH release. The liberation of catecholamines during hypoxia(19) may also stimulate the release of ACTH(20) and cause the observed increase in 17-OHCS secretion.

Since others have shown that maximum adrenocortical activity occurs during the first 3 days of hypoxia and then gradually returns to pre-hypoxic levels(2,6,21), it is not surprising that no significant differences were observed in urinary and peripheral plasma 17-OHCS of subjects maintained at high altitudes for over 2 weeks(4,5). However, the findings that exposure of humans to simulated altitude for 45 minutes(7) and the induction of hypoxemia in dogs by breathing 5% oxygen for 30 minutes(12) did not cause significant increases in peripheral 17-OHCS are difficult to reconcile with the data presented herein. The relatively high oxygen tension (100 mm Hg) to which humans were exposed at 14,000 feet(7), in comparison to the 17,000 feet (pO_2 78 mm Hg) used in our experiments, may not have been sufficient to cause marked alterations in acid-base balance. In addition, since peripheral plasma 17-OHCS are dependent on the 1) secretion by the adrenal cortex, 2) dilution by body fluids, 3) metabolism and 4) excretion, it is not surprising that these investigators observed a tendency for the levels of these steroids to increase, but not significantly.

Summary. Eighteen experiments were performed on 8 conscious and anesthetized dogs in which the dorsal roots (T_{11}-L_3) had been severed and a glass cannula inserted in the lumbo-adrenal vein. Decompression to 17,000 feet simulated altitude for 2 hours while breathing ambient air (pO_2 78 mm Hg) caused marked elevations in 17-OHCS secretions in both conscious and anesthetized dogs.

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