PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 149, 168–171 (1975)

Cardiac Sensitivity to Hyperkalemia in Adrenalectomized Dogs[1] (38765)

NATHAN HIATT, TERUO KATAYANAGI,[2] AND ALEXANDER MILLER

Department of Surgery and Medical Research Institute, Cedars-Sinai Medical Center, Los Angeles, California 90029

In dogs that are K-loaded by infusion of 2 mEq/KCl/kg/hr until prelethal electrocardiographic (ECG) changes of hyperkalemic cardiotoxicity appear, the proportion of infused K excreted is almost constant. By the time serum K attains to approximately 10.2 mEq/l and prelethal ECG changes appear, approximately 20% of infused K is in the urine (1). This investigation was originally meant to assay the role of the adrenals in urinary K loss by K-loading bilaterally adrenalectomized dogs, but unexpectedly, it was found that the most striking result was a sharp increase in cardiac sensitivity to hyperkalemia, i.e., prelethal ECG changes made their appearance at much lower levels of serum K than in controls.

Methods. Twenty-one dogs of either sex, weighing between 15.1 and 21.8 kg, starved for 18 hr and waterless for 12, were anesthetized with 30 mg/kg sodium pentobarbital iv and infused with approximately 100 ml of 0.15 *M* NaCl/hr. The animals were divided into three groups, one experimental and two control. The 12 experimental dogs (Group A) were bilaterally adrenalectomized through a mid-line incision in 45–75 min. Five control dogs (Group B) were sham adrenalectomized for about an hour; in three, by dividing the phrenico–abdominal vein and completely mobilizing the portion of adrenal (~0.5) caudal to the divided vein, leaving the cranial half of the gland and venous pedicle to the inferior vena cava untouched, and in two, by stripping away the tissues on the lateral and posterior aspects of the inferior vena cava, abdominal aorta and common iliacs without manipulating the adrenals. Four dogs (Group C) were not operated upon, in order to ascertain the effects of saline infusion and anesthesia. Four hours after completion of an operation (or 5 hr after the start of saline infusion in unoperated dogs), each animal was connected to a Hewlett–Packard ECG machine and to a Harvard respirator. The NaCl drip was then replaced by a KCl solution that was infused by a Harvard peristaltic pump at a rate of 30 ml/hr; the concentration of the KCl solution was such (~1000–~1400 mEq/l) that each dog received 2 mEq/kg/hr Lead II of the ECG was monitored at frequent intervals and infusion continued until prelethal ECG manifestations of hyperkalemic cardiotoxicity appeared. Venous blood samples for the determination of Na and K were obtained soon after anesthesia, just before KCl administration was begun, every 30 min thereafter, and when it was discontinued, i.e., when prelethal ECG changes appeared. Na and K were measured by an Instrumentation Laboratories Flame Photometer using lithium as an internal standard.

In previous studies we found that dogs infused with 2 mEq KCl/kg/hr ultimately develop lethal ventricular fibrillation or asystole, but at serum K levels that vary quite widely (9.8–11.8 mEq/l). On the other hand, marked bradycardia, ventricular flutter or bizarre QRS, prelethal ECG changes that inevitably progress to fatal ventricular fibrillation or asystole, first appear at fairly uniform serum K levels in most dogs (~10.2 mEq/l). The abrupt appearance of prelethal ECG change has been used to mark the "end point" of an infusion (1, 2); bradycardia (20–30 beats/min) is of the ventricular type and a bizarre QRS complex is at least 10 times the usual width and looks like a sine wave. These ECG changes and ventricular flutter appeared with about equal frequency.

Results. Four hours after bilateral adrenalectomy or a sham operation, when 350 ml to

[1] Supported by: USPHS Grant No. 5 S01 RR 05468, Surgical Research Project, Blum-Kovler Foundation, the Lou Millers, and the Funds for Manny Silver and Dr. Stanley Imerman.

[2] Present address: Department of Surgery, Tokyo University, Tokyo, Japan.

TABLE I. RESULTS OF INFUSION OF 2 mEq KCl/KG/HR INTO DOGS WITH AND WITHOUT ADRENALS.

	Prelethal serum K mEq/liter	Δ serum K[a] mEq/liter	Total K infused mEq/kg	Duration infusion minutes
Group A (12)[b]				
Bilateral adrenalectomy	7.59 ± 0.09*	2.9 ± 0.04	1.89 ± 0.14	57.1 ± 4.18
Group B (5)				
Sham adrenalectomy with and without adrenal manipulation	9.68 ± 0.18	5.17 ± 0.16	7.73 ± 1.24	220 ± 31.8
Group C (4)				
Unoperated	10.17 ± 0.02	5.9 ± 0.21	6.77 ± 0.38	188 ± 16.6
p Groups A and B	<0.01	<0.01	<0.01	<0.01
p Groups A and C	<0.01	<0.01	<0.01	<0.01

* Mean and SEM.

[a] Prelethal serum K minus preinfusion serum K.

[b] Number of dogs.

500 ml of 0.15 *M* NaCl had been infused, the dogs seemed in satisfactory condition, their ECGs were within normal limits, and they were excreting volumes of urine similar to those of the unoperated animals (7.5–15 ml/hr); the last were grossly unaffected by the saline infusion and anesthesia. Each adrenalectomized dog (Group A) had a small, but consistent rise in the level of serum K, from a mean pre-operative level of 4.5 mEq/l to a preinfusion level of 4.7 mEq/l. There was no such consistent change in the dogs of the two control groups.

During subsequent KCl infusion, a typical sequence of ECG indications of hyperkalemia developed in each dog, i.e., T wave and P wave changes, widening of QRS, nodal and ventricular rhythms, and finally, prelethal abnormalities. In the dogs of Group A (bilateral adrenalectomy), prelethal manifestations of hyperkalemic cardiotoxicity appeared at a mean serum K level of 7.59 mEq/l, i.e., when the increase over the pre-infusion level (Δ serum K) was 2.9 mEq/l (Table I). In Group B (sham adrenalectomy, i.e., retroperitoneal dissection with and without adrenal manipulation), prelethal ECG changes appeared at a mean serum K level of 9.68 mEq/l (Δ K = 5.17 mEq/l, Table I). In Group C (unoperated), mean serum K level was 10.17 mEq/l (Δ K = 5.9 mEq/l) when potentially fatal cardiac abnormalities appeared on the ECG (Table I). Following adrenalectomy and during the course of KCl infusion, changes in the level of serum Na were negligible (<4 mEq/l).

The differences in total K infused and duration of infusion (Table I) reflected mainly the differing prelethal serum K levels, but also to some extent, varying quantities of K lost in the urine.

Discussion. Normal serum (extracellular fluid—ECF) K in dogs is about 4.6 mEq/l and infusion of 2 mEq KCl/kg/hr into intact and operated dogs (pancreatectomized, nephrectomized and ureter-ligated) soon after anesthesia, ultimately raises serum K to cardiotoxic levels. ECG evidences of hyperkalemic cardiotoxicity first appear when the serum K rises above 8 mEq/l, gradually progress as the K level increases and at a mean level of about 10.2 mEq/l (Δ K ~5.6 mEq/l) become prelethal, i.e., marked bradycardia, bizarre QRS or ventricular flutter signal the inevitable onset of lethal ventricular fibrillation or asystole (1, 2). These values are similar to those obtained in control sham-operated dogs (Group B), and unoperated dogs (Group C), in which the conditions affecting adrenalectomized animals are simulated more exactly by preceding KCl administration with five hours of 0.15 *M* NaCl infusion, and by dissecting about the adrenals; prelethal ECG manifestations appear between 9.5 and 10.2 mEq/l with Δ serum K = 5.0 to 6.1 mEq/l (Table I). Sham operations, saline infusion and a lengthy period of anesthesia have no

important influence on cardiac sensitivity to hyperkalemia.

Four hours after adrenalectomy, when the concentration of circulating steroids is negligible (3), the sequence of ECG changes that accompany the hyperkalemia of K-loading is still typical and the level of serum K at which the ECG evidence of prelethal cardiotoxicity appears still quite uniform, but the entire process is accelerated. ECG changes of hyperkalemic cardiotoxocity appear between 5 and 6 mEq/l and prelethal ECG changes occur at a mean serum K level of 7.6 mEq/l, when Δ serum K (2.9 mEq/l) is little more than 50% of the mean value in animals with adrenal glands (Table I).

Although hyperkalemic cardiotoxicity has been investigated very extensively both clinically and experimentally (4), it seems to have been studied very little in adrenalectomized animals, even though it is well known that ECG changes dependent on hyperkalemia may be seen in untreated Addisonian patients (5). Winkler *et al.* (6) infused K ion into adrenalectomized dogs maintained with salt, and found that its toxicity was greater than in normal animals, but observed no evidence of increased sensitivity of the heart to hyperkalemia. Zwemer and Truszkowski (7) obtained similar results in salt-maintained cats given KCl intraperitoneally. Both sets of investigators seem to have employed animals with chronic adrenal insufficiency and used the death of the animal as the "end point" for the determination of the fatal level of serum K.

In the present investigation, the unequivocal increase of cardiac sensitivity to hyperkalemia was demonstrated in animals with acute adrenal insufficiency, ones in which the "end point" of K loading was not death, but rather the appearance of prelethal ECG changes. As has been pointed out, although these changes inevitably progress to lethal ventricular fibrillation or asystole, considerable KCl may be infused and serum K may rise by 1–2 mEq/l before the fatal ECG change actually appears. This interval between prelethal and lethal ECG changes may be accentuated in animals with chronic adrenal insufficiency, thus accounting for the "high" serum K level at the time of death.

Removal of the adrenal also removes a large mass of chromaffin tissue that produces epinephrine and norepinephrine. Preliminary experiments in which epinephrine was replaced do not suggest that the increased sensitivity to hyperkalemia is due to absence of this hormone; experiments replacing various adrenal steroids are soon to be under way.

At present it is not clear how acute adrenal insufficiency accentuates the cardiotoxic ability of hyperkalemia to lower the resting membrane potential (rmp), and increase the velocity of repolarization (4). Experiments in rats with chronic insufficiency suggest that adrenal hormones are involved in permeability of the cardiac cell membranes. For while there is no rmp change in individual myocardial fibers (8), there is a 12–25% reduction when the measurement is made in whole animals (9). In the latter, beside the rise of ECF (serum) K there is a fall in the K concentration of the intracellular fluid of the cardiac cells (9) that suggests a change in membrane permeability to K, and such a change could affect the cardiotoxic effects of hyperkalemia.

Summary. In dogs with bilateral adrenalectomy loaded with K by infusion of 2 mEq KCl/kg/hr there is a marked increase of cardiac sensitivity to hyperkalemia. Typical ECG changes begin at lower serum K levels (5–6 mEq/l) and the prelethal arrhythmias that signal the imminent onset of fatal ventricular fibrillation or asystole appear when mean serum K is 7.6 mEq/l, 2.9 mEq/l above the average pre-infusion level. In control dogs, ECG changes start above 8 mEq K/liter, and prelethal arrhythmias appear between 9.5 and 10.2 mEq/l, a mean increase of 5.6 mEq/l above the average preinfusion level.

We wish to acknowledge our thanks to Mr. George Bonorris for the statistical analyses and Ms Eleanor Chapman for the chemical determinations.

1. Hiatt, N., Yamakawa, T., and Davidson, M. B., Metabolism **23**, 43 (1974).
2. Hiatt, N., Morgenstern, L., Davidson, M. B., Bonorris, G., and Miller, A., Horm. Metabol. Res. **5**, 84 (1973).
3. Lefer, A. N., and Link, E. J., Proc. Soc. Exp. Biol. Med. **118**, 1009 (1968).

4. Surawicz, B., Amer. Heart J. **73,** 814 (1967).
5. Sofer, L. J., "Diseases of the Adrenal Gland," p. 295. Lea and Febiger, Philadelphia, (1948).
6. Winkler, A. W., Hoff, H. E., and Smith, P. K., Amer. J. Physiol. **133,** 494 (1941).
7. Zwemer, R. L., and Truszkowski, R. Science **83,** 558 (1936).
8. Rovetto, M. J., and Lefer, A. N., Amer. J. Physiol. **218,** 1015 (1970).
9. Monnereau-Soustre, H., Tricoche, R., Regondaud, P., and Besson, J., Compt. Rend. Soc. Biol. **157,** 623 (1963).

Received June 14, 1974. P.S.E.B.M. 1975, Vol. 149.