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Influence of Epinephrine upon Plasma Potassium Concentration: Changes with Time during Constant Infusion* (32975)

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Many investigators have observed that injection of epinephrine in the dog under hydrocarbon anesthesia will produce cardiac arrhythmia (1,2). D'Silva (3) showed that injection of epinephrine also increased the serum potassium concentration, $[K^+]$, and that most of the extra potassium came from the liver. O'Brien and co-workers (4) found that when the liver was isolated from the circulation, thereby preventing hyperkalemia, a significant number of animals anesthetized by hydrocarbon was protected from arrhythmia during injection of epinephrine. Subsequently, Davis *et al.* (5) reported that animals thus protected developed arrhythmia when potassium chloride was given along with the epinephrine injection. They concluded that hyperkalemia contributed to the development of cyclopropane–epinephrine ventricular tachycardia in many of the animals. These studies indicating a possible relationship between the hyperkalemic effect of epinephrine and the arrhythmia all involved only single injections of epinephrine.

Other studies have utilized continuous infusion of epinephrine to study changes in serum or plasma $[K^+]$. Many investigators (6–9) have shown that under these circumstances the hyperkalemia is only temporary, occurring significantly in the first 1–3 min of the infusion, with $[K^+]$ falling to less than control values after 3–20 min, despite continued infusion of epinephrine.

In 1966, Vick (10) noted that animals anesthetized by chloroform and infused continuously with epinephrine for 30 min or longer often sustained arrhythmia for the entire period of the infusion. This finding was difficult to explain in terms of the hypothesis of Davis *et al.*, since it is apparent that arrhythmia continuing beyond the point where plasma $[K^+]$ returns to control levels cannot be dependent upon an elevated plasma $[K^+]$. However, this conclusion was based upon the studies of others showing that plasma $[K^+]$ was only temporarily elevated, and might not parallel the time course of the cardiac arrhythmia.

It became apparent that the available studies on serum or plasma $[K^+]$ changes with continuous epinephrine infusion were not adequate because of insufficient information about levels of epinephrine infused with respect to body weight (6); use of only one rate of infusion, which was two to three times that dose applicable to the chloroform-anesthetized animal (7–9); or results not complete enough to support a precise statement of the temporal course of the change in $[K^+]$ during continuous infusion of epinephrine (6–9).

The work reported here was undertaken to delineate the changes in plasma $[K^+]$ during

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continuous infusion of epinephrine in dogs anesthetized by chloroform, to determine if these changes are dose-related, and to study the relation of the changes to the occurrence of cardiac arrhythmia. The first two of these aims will be dealt with here. The relation of arrhythmia production to plasma [K^+] will be reported later.

Methods. A total of 18 dogs of either sex weighing from 18 to 30 kg was used. They were all treated in the following manner. Initially, they were anesthetized with thiopental sodium (20 mg/kg i.v.), and a tracheal cannula, connected to a Harvard air pump, was inserted to provide artificial respiration. A variable portion of the air intake of the pump was bubbled through chloroform, permitting gradual substitution of chloroform anesthesia for that of the short-acting thiopental.

Both vagus nerves were isolated and cut in the neck. A catheter was passed through the left femoral vein into the inferior vena cava for epinephrine infusion. Epinephrine (synthetic l-epinephrine, Suprarenin, Winthrop) was diluted to 100 μg/ml with double distilled water containing no measurable [K^+] and infused at a constant rate of 1.5 μg/kg per min in nine animals, and at 2.0 μg/kg per min in the nine others. The maximum volume infused during 29 min was 17.7 ml. Infusion of this medium alone produced no effect.

After the administration of heparin to prevent clotting, arterial blood samples were removed from a catheter passed through the right carotid artery into the aorta. A total of 12 samples (2.4 ml each) was taken at intervals during 17 min, and in 8 animals of one group (those given 2.0 μg/kg per min of epinephrine) an additional 4 samples were taken to extend the period of study to 29 min. The total amount of blood removed this way did not exceed 3% of blood volume, or 0.2% of body weight. The samples were immediately centrifuged, and the plasma was analyzed for potassium on a Baird atomic internal standard flame photometer.

Arterial blood pressure was measured with a Statham transducer connected by plastic tubing to a 12-gauge needle placed in the left femoral artery. The output of the transducer

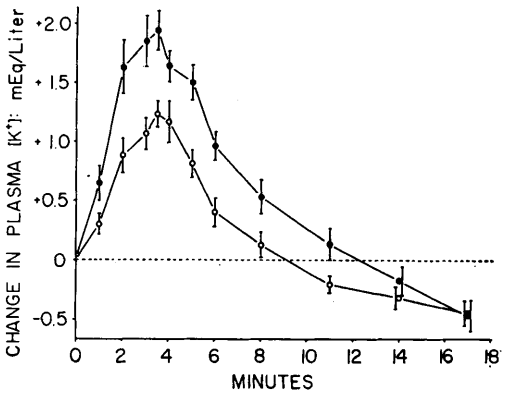

FIG. 1. Effects of constant infusion of epinephrine at two different rates upon arterial plasma potassium concentration. (○) 1.5 μg/kg per min; (●), 2.0 μg/kg per min. Infusion began at 0 time and continued through the remainder of the experiment. Each curve presents the data from a separate group of nine dogs (mean ± SE).

was amplified by a carrier preamplifier and recorded, along with conventional lead II ECG, by a rectilinear pen writing system.

Results. The mean control value of the plasma potassium concentration was 4.8 ± 0.12 (SE) meq/liter in the 9 dogs infused at 1.5 μg/kg per min epinephrine, and 4.2 ± 0.24 (SE) meq/liter in the 9 dogs infused at 2.0 μg/kg per min. In order to facilitate comparison, the results are expressed as the means of the change from control [K^+] in each experiment. The effects upon plasma [K^+] of epinephrine infused at two different rates are shown in Fig. 1. The pattern was the same in each case—an initial increase in [K^+] followed by a decline and reversal to a sustained decrease in [K^+], despite continued infusion of epinephrine. The rate of the rise of plasma [K^+] increased with the rate of infusion, although the time of the maximum value was not changed. The magnitude of the increase was greater at the higher rate of infusion, and exceeded that achieved at the lower rate during all of the time that the values were above control. The duration of the period of increased [K^+] was prolonged by increasing the rate of infusion of epinephrine. It cannot be determined from these experiments whether the magnitude of the delayed decrease in [K^+] is related to the rate

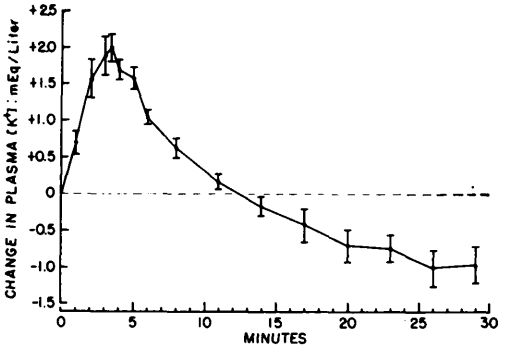

FIG. 2. Effects of constant infusion of epinephrine upon plasma potassium concentration. Infusion at a rate of 2.0 μg/kg per min begun at 0 time and continued through the remainder of the experiment. Means of 8 experiments ± SE.

of infusion of epinephrine, since the maximum effect was not seen.

The infusion of epinephrine at a rate of 2.0 μg/kg per min was continued to 29 min in 8 of the 9 animals represented in Fig. 1 and the results of these experiments are shown in Fig. 2. During the extended period of infusion plasma [K^+] continued to decline below the value of 0.5 meq/liter less than control reached at 17 min, and became constant at a level of 1 meq/liter less than control after 26–29 min of infusion.

Discussion. In earlier work the pattern of change of serum or plasma [K^+] during constant infusion of epinephrine has not been clearly established. Flock *et al.* (11) were the first to show that infusion of epinephrine (2–3 hours) decreased serum [K^+], but only the final result, and nothing of the changes in time, was reported. Brewer *et al.* (6) reported an initial small decrease in serum [K^+] followed by a rise, and then a larger decrease during 10 min of epinephrine infusion, but the results are difficult to evaluate. The rate of infusion of epinephrine was not related to animal size; it is not clear whether arterial or venous samples were taken; and the data, while pooled, were not analyzed statistically. Other investigators have specified the rate of infusion of epinephrine, and their work indicates an early rise in serum or plasma [K^+] followed by a fall to less than control levels, but none of them took frequent enough samples to definitely portray the pattern of change with time (7–9). The work of Craig and Honig (7) may be representative of this group. Using an infusion rate of 5 μg/kg per min of epinephrine, they report that plasma [K^+] reaches a maximum at approximately 1 min, begins to decline after 4 min, and falls below control by the fifteenth minute. However, no samples were taken between 1 and 4 min, and no data which show any net decrease in [K^+] during infusion of epinephrine are presented. In one other way the earlier work is incomplete, since, where the rate of infusion can be discerned, only relatively high rates were studied. Indeed, the lowest rate used is 4 μg/kg per min (double the highest used in the work reported in this paper).

The report of Robertson and Peyser (9) suggests that the increases in serum [K^+] they saw after single intravenous injections of epinephrine (5, 50, and 500 μg/kg) were dose-related. Although obtained under different conditions, their results are compatible with our finding that increasing the rate of infusion of epinephrine from 1.5 μg/kg per min to 2.0 μg/kg per min significantly increased the magnitude and duration of the initial rise in plasma [K^+]. Comparison of our data with those taken at comparable times in other available studies (7,8) (Table I) suggests that further increases in the rate of infusion of epinephrine should lead to even higher plasma [K^+].

Further studies are needed to determine if the magnitude of the maximum decrease in plasma [K^+] and the time at which it is reached are affected by changes in the rate of infusion of epinephrine. The rate-related changes in other parameters suggest that such a relationship will be found. The time of the maximum decrease with one rate of infusion (2.0 μg/kg per min) appears to be 26–29 min, but longer durations of infusion may be needed to better establish this point.

Summary. The changes in plasma [K^+] which occur during constant infusion of epinephrine into dogs have been studied. Frequent sampling of arterial blood during periods of 17 and 29 min duration has confirmed the indications of earlier studies that an early rise in plasma [K^+] is followed by a decline and a sustained decrease in

TABLE I. Effect of Infusion of Epinephrine at Different Rates on Potassium Concentration at Times Available for Comparison.

Rate of epinephrine infusion (μg/kg per min)	No. of animals	Potassium concentration (meq/liter) changes at varying intervals (min) during epinephrine infusion					Ref.
		1	2	4	6	20	
1.5	9	0.3	0.9	1.2	0.4		Fig. 1
2.0	8	0.7	1.6	1.7	1.0	—0.7	Fig. 2
5.0	8		4.6			—1.02	(8)
5.0	4	3.6		3.2	2.0		(7)

$[K^+]$. The magnitude of the early increase in $[K^+]$ and the time from the beginning of infusion to the return of $[K^+]$ to control levels appear to be related to the rate of infusion of epinephrine. Further study is needed to determine how the later decrease in $[K^+]$ is related to the rate of infusion.

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Complement Fixing Antibody Response of Man to Yolk Sac-Grown Rocky Mountain Spotted Fever Vaccine* (32976)

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The first Rocky Mountain spotted fever (RMSF) vaccine was made from infected tick tissues in 1924 (1). It protected animals against virulent challenge, elicited antibodies in man, and lowered mortality in vaccinated persons who subsequently developed disease (1–3). In 1939 a vaccine was made from infected yolk sacs of embryonated hen's eggs (4) and in 1948 manufacture of the tick vaccine was discontinued. The assumption of efficacy in man of the yolk sac vaccine rests on (a) the field and laboratory data obtained with the earlier tick vaccine, (b) the capacity of the yolk sac vaccine to protect guinea pigs against lethal challenge with *Rickettsia rickettsi*, and (c) the fact that "Rocky Mountain spotted fever vaccines prepared from infected yolk sacs and tick tissue were about equally active in producing immunity in guinea pigs" (5). There is a paucity of published data on the serological response of man to the yolk sac type of spotted fever vaccine; no information is available on its efficacy in preventing

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