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James P. Knochel, Edward M. Schlein

J Clin Invest. 1972;51(7):1750-1758. <https://doi.org/10.1172/JCI106976>.

Research Article

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Potassium is released from contracting skeletal muscle fibers and its rising concentration in interstitial fluid is thought to dilate arterioles thereby mediating the normal rise of muscle blood flow during exercise. If potassium release from deficient muscle were subnormal, exercise would not be accompanied by sufficient muscle blood flow and rhabdomyolysis could occur by ischemia.

This hypothesis was examined by comparing the effect of electrically stimulated exercise on muscle blood flow, potassium release, and histology of the intact gracilis muscle preparation in normal and potassium-depleted dogs. In normal dogs, muscle blood flow and potassium release rose sharply during exercise. In contrast, muscle blood flow and potassium release were markedly subnormal in depleted dogs despite brisk muscle contractions. Although minor histologic changes were sometimes observed in nonexercised potassium-depleted muscle, frank rhabdomyolysis occurred in each potassium-depleted animal after exercise.

These findings support the hypothesis that ischemia may be the mechanism of rhabdomyolysis with exercise in potassium depletion.

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On the Mechanism of Rhabdomyolysis in Potassium Depletion

JAMES P. KNOCHEL and EDWARD M. SCHLEIN

From the Department of Internal Medicine, The University of Texas Southwestern Medical School at Dallas, 75235, and The Veterans Administration Hospital, 4500 South Lancaster Road, Dallas, Texas 75216

ABSTRACT Rhabdomyolysis and myoglobinuria occur commonly in men who sustain environmental heat injury during intensive physical training in hot climates. These also occur in patients with potassium depletion. Since physical training in hot climates may be accompanied by serious losses of body potassium, the possibility was considered that performance of strenuous exercise when potassium deficient might enhance susceptibility to rhabdomyolysis.

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This hypothesis was examined by comparing the effect of electrically stimulated exercise on muscle blood flow, potassium release, and histology of the intact gracilis muscle preparation in normal and potassium-depleted dogs. In normal dogs, muscle blood flow and potassium release rose sharply during exercise. In contrast, muscle blood flow and potassium release were markedly subnormal in depleted dogs despite brisk muscle contractions. Although minor histologic changes were sometimes observed in nonexercised potassium-depleted muscle, frank rhabdomyolysis occurred in each potassium-depleted animal after exercise.

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INTRODUCTION

Rhabdomyolysis may occur in apparently normal subjects after prolonged, strenuous exercise (1) and without apparent relationship to exercise in patients who

Received for publication 5 December 1971 and in revised form 18 February 1972.

have become potassium deficient as a consequence of drug administration (2), licorice ingestion (3), or disease (4). Young men in football training or basic military training are particularly susceptible to environmental heat injury in hot weather and this is commonly accompanied by rhabdomyolysis (5). Recent studies by Knochel, Dotin, and Hamburger (6) have confirmed an earlier contention (7) that training under such conditions might lead to serious depletion of total body potassium. The latter observation and the association of rhabdomyolysis in young men with environmental heat injury suggest that intense muscular work by potassium-deficient individuals might increase their susceptibility to rhabdomyolysis.

Although the mechanism by which potassium deficiency leads to rhabdomyolysis has not been elucidated, impressive evidence (8-11) has accumulated that potassium release from contracting skeletal muscle cells into interstitial fluid of the muscle directly dilates adjoining arterioles, and thereby, the potassium ion may be a major factor mediating the rise of muscle blood flow which normally occurs with exercise. Accordingly, it might be postulated that if potassium release from potassium-deficient skeletal muscle is impaired during intense exercise, muscle injury or frank necrosis could occur as a consequence of relative ischemia.

The following study was designed to examine muscle blood flow and its possible relationship to release of potassium in response to electrical stimulation of the isolated gracilis muscle of normal and potassium-deficient dogs. The results indicate that in contrast to normal, both muscle blood flow and potassium release in the gracilis muscle of the depleted dog are markedly subnormal. Further, frank necrosis of skeletal muscle occurred after exercise in the potassium-depleted animals.

METHODS

The first series of studies were conducted on seven normal and six potassium-depleted mongrel dogs weighing 20-25 kg. Potassium depletion was induced by gavage feeding

30 g/kg body weight of a diet which was potassium deficient but otherwise nutritionally adequate.¹ Deoxycorticosterone acetate, 20 mg/day, was given intramuscularly at a site remote from the gracilis muscle. Sodium chloride intake in the depleted dog was 10 mEq/kg per day. Approximate potassium balance was estimated from recovery of potassium in daily urine collections and assumed losses of 1 mEq daily in feces (12). Studies on the depleted dogs were conducted when estimated total body potassium was reduced by approximately 25%.

All dogs were anaesthetized with sodium pentobarbital 30 mg/kg and intubated with an endotracheal tube. Large bore polyethylene catheters were placed in the right jugular vein and the left common carotid artery for purposes of sampling, monitoring of systemic blood pressure, administration of drugs, and return of venous effluent blood from the gracilis muscle. Sodium heparin was used for anticoagulation.

For studies examining muscle blood flow and potassium release, the left gracilis muscle was prepared in a manner similar to that described by Skinner and Powell (13) except that the main artery to the gracilis muscle was not disturbed. The nerve to the gracilis muscle was then isolated and cut. After denervation and stabilization of blood flow for a minimum of 20 min, faradic stimulation of the distal stump of the nerve was begun at a rate of 5/sec using supramaximal voltage of 0.175 sec duration.

A second series of experiments was conducted to determine if muscle blood flow in potassium-depleted animals could be increased at rest and during contractions by simultaneous infusion of KCl. For this purpose, P. E. 90 tubing was inserted into the distal femoral artery and the tip advanced retrograde to the orifice of the gracilis artery in five normal and four potassium-depleted dogs. The gracilis muscle was then prepared in the previously described fashion.

Using a Harvard² syringe pump (model 944) solutions of 0.15 M KCl and 0.15 M NaCl were alternately infused into the femoral artery both before and during stimulated gracilis muscle contractions. The infusion rates of KCl for each experiment were empirically selected as (a) the minimum rate necessary to cause an increase in resting muscle blood flow and (b) the rate necessary to produce vasoconstriction and diminished blood flow. The infusion rates varied from one experiment to another due to differences in muscle size and resting muscle blood flow.

Blood flow rates were determined with a Gilford³ photoelectric drop counter until stable for successive periods and repeated at 1, 3, 5, 10, 20, 30, 40, 50, and 60 min of stimulation. Blood samples were obtained simultaneously from the carotid artery and the gracilis vein.

Arterial blood pressure was monitored throughout each experiment using a Statham⁴ strain gauge.

Biopsies of the gracilis muscle for histologic examination were obtained from normal and potassium-deficient dogs under three conditions: (a) before electrical stimulation, (b) immediately after stimulation for 60 min, and (c) 48 hr after stimulation for 60 min. In the latter experiment, preparation for stimulation was limited to only that dissection necessary to identify and stimulate the unsectioned

TABLE I
Potassium

	Serum	Muscle
	mEq/liter	mEq/100 g F. F. D. S.
Normal	4.1 (3.3-4.9)	42.7 (37.6-48.2)
K-depleted	2.3 (1.8-3.3)	22.2 (20.2-23.8)

Serum potassium concentration (milliequivalents per liter) and muscle potassium content (milliequivalents per 100 g fat-free dry solids) in normal dogs and after establishment of potassium deficiency. (Mean and range of values).

gracilis nerve under sterile conditions thus avoiding possible effects produced by denervation or infection.

For measurement of potassium and sodium, quantities of gracilis muscle weighing 0.15-0.30 g were obtained from the site opposite to that used for blood flow studies. After removal of all apparent fat and connective tissue, the specimens were minced, placed in a screwtop tube, accurately weighed, and dried in an oven at 150°C for 2 hr. After ether extraction to remove fat, specimens were again dried and weighed. 2 ml of 10% acetic acid was added to the residue. The mouth of the tube was covered with aluminum foil and while tightly capped, the tube and its contents were autoclaved at 120°C for 30 min. Sodium and potassium concentration in the supernate were measured by flame photometry.

Concentrations of electrolytes in plasma and urine were measured by standard laboratory procedures. Activity of creatine phosphokinase in serum was determined by an enzymatic procedure.⁵ "Potassium release" was estimated by the Fick principle ($[K]_v - [K]_a \times \text{flow}$). The authors are cognizant that estimation of potassium release by this method may be inaccurate in the absence of the steady state. However, such was not possible under the conditions of these experiments.

RESULTS

Mean values for serum potassium concentration and muscle content of potassium are shown in Table I. After depletion, mean muscle potassium content diminished 48%. This value suggests that since skeletal muscle comprises approximately 50% of body weight, nearly all of the deficit of approximately 25% was lost from skeletal muscle.

Blood flow and potassium release. Muscle blood flow and potassium release during a representative experiment on a normal dog are shown in Fig. 1. In the resting state, potassium release was observed to be virtually zero. With stimulation, potassium release rose sharply to 28 $\mu\text{Eq}/100$ g per min, slowly diminished, and by 20 min had stabilized between 10 and 13 $\mu\text{Eq}/100$ g per min. Resting blood flow, shown in the lower panel, was 6.2 ml/100 g per min and, similar to the

⁵ Sigma Chemical Co., St. Louis, Mo. (Technical Bulletin No. 40-UV).

¹ General Biochemicals, Div. North American Mogul Products Co., Chagrin Falls, Ohio.

² Harvard Apparatus Co., Inc., Millis, Mass.

³ Gilford Instrument Laboratories, Inc., Oberlin, Ohio.

⁴ Statham Instruments, Inc., Los Angeles, Calif.

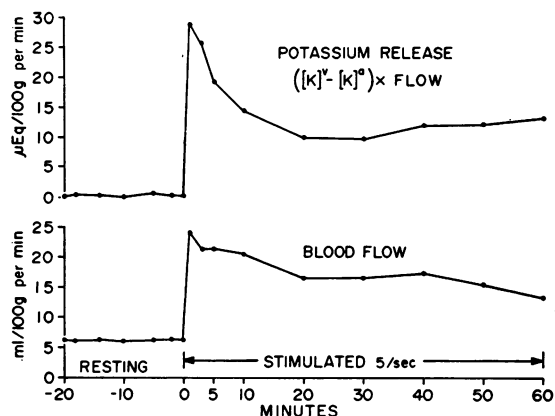


FIGURE 1 Serial values for potassium release and blood flow before and during stimulation of normal gracilis muscle.

pattern of potassium release, rose sharply to 24 ml/min after 1 min of stimulation and subsequently stabilized at a slightly lower rate.

A similar experiment on a potassium-deficient dog is shown in Fig. 2. Potassium release, similar to observations on normal dogs, was virtually zero at rest; however, with stimulation, release of potassium rose to only 2.1 $\mu\text{Eq}/100\text{ g}$ per min. Muscle blood flow was also comparable to that of normal dogs at rest. However, despite brisk and forceful contractions, muscle blood flow increased from 6 to only 7.8 ml/100 g per min.

Average values for potassium release and muscle blood flow from both groups of experimental animals are shown in Fig. 3. Potassium release, shown in the upper panel, was virtually absent in both normal and potassium-deficient dogs before stimulation. By the 1st min, potassium release in normal dogs rose from 0.4 to 32 $\mu\text{Eq}/\text{min}$, diminished slowly for the following

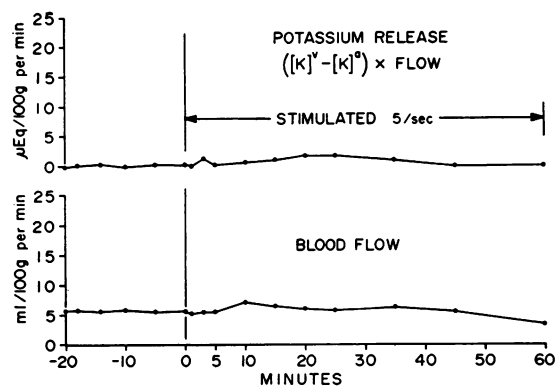


FIGURE 2 Serial values for potassium release and blood flow before and during stimulation of potassium-depleted gracilis muscle.

30 min, and stabilized for the remainder of the experiment at approximately 12 $\mu\text{Eq}/100\text{ g}$ per min.

In potassium-deficient dogs, potassium release at rest was not different from normal. In contrast, mean potassium release in deficient dogs rose only to 2.8 $\mu\text{Eq}/100\text{ g}$ per min during stimulation.

Mean muscle blood flow in normal dogs was 6.1 ml/100 g per min at rest and after stimulation rose to 23.2 ml/min. Thereafter flow diminished slightly but remained at values considerably above base line throughout the experiment. Muscle blood flow in potassium-depleted dogs at rest was normal. However, despite brisk contractions, the rise in muscle blood flow was negligible.

Statistical comparison of the maximum increase of both potassium release and blood flow between normal and depleted groups of dogs showed that the differences were highly significant ($P < 0.001$).

Muscle blood flow and potassium infusion. Table II shows the results of the intra-arterial potassium infusion studies. The data shown represent the maximum blood flow and simultaneous venous plasma potassium concentration in each instance. Intra-arterial potassium infusion consistently resulted in increased blood flow through the resting gracilis muscle in both the normal and potassium-depleted dogs as shown in Fig. 4. Compared to control values the mean maximal increase was $92.1 \pm 4.6\%$ (SEM) in normal dogs ($P < 0.05$) and $62.4 \pm 2.4\%$ (SEM) in potassium-depleted dogs ($P < 0.05$). Although the mean rise of blood flow during potassium infusion was greater in the normal than in the potassium-depleted dogs, the difference was not significant.

After stabilization of blood flow during stimulated contractions potassium infusion in normal dogs in-

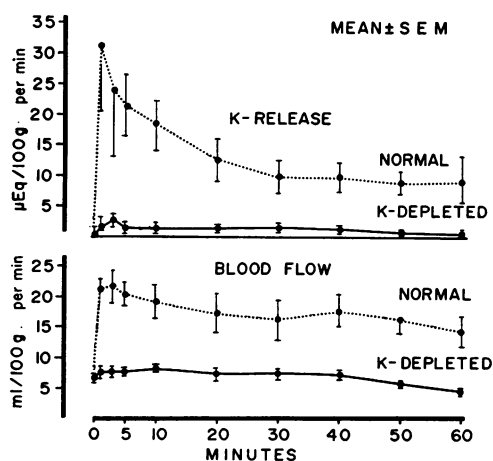


FIGURE 3 Effect of exercise on potassium release and blood flow from gracilis muscle of normal (● --- ●) and potassium-depleted (● — ●) dogs. (Mean \pm SEM).

TABLE II
*Maximal Blood Flows and Simultaneous Venous Plasma Potassium Concentrations
in Potassium Infusion Studies*

	Base line		Potassium infusion		Stimulated contractions		Stimulated contractions and potassium infusion	
	Flow*	[K]‡	Flow	[K]	Flow	[K]	Flow	[K]
	ml/100 g per min	mEq/ liter	ml/100 g per min	mEq/ liter	ml/100 g per min	mEq/ liter	ml/100 g per min	mEq/ liter
Normals								
Exp. 1	5.8	3.0	9.6	10.6	8.2	3.9	12.0	7.4
2	4.4	4.3	10.0	7.4	—	—	—	—
	6.0	4.2	11.6	15.0	17.0	6.5	18.0	12.8
	6.5	4.5	13.0	14.0	—	—	—	—
	4.7	3.0	8.2	7.4	13.8	5.4	17.5	9.2
Mean±SEM	5.5±0.9	3.8±0.8	10.5±1.3	10.9±1.8	13.0±1.9	5.3±1.0	15.8±1.7	9.8±1.5
Potassium depleted								
	6	2.1	9.6	11.0	5.5	2.3	7.9	16.0
	4.2	1.7	6.5	9.8	6.0	3.0	7.9	10.9
	5.5	2.0	9.6	14.3	7.7	2.7	9.1	17.2
	5.0	2.3	8.2	3.1	5.7	2.5	8.4	7.0
Mean±SEM	5.2±0.8	2.0±0.5	8.5±1.1	9.6±2.0	6.2±0.9	2.6±0.5	8.3±0.7	12.8±2.0

* All flows are expressed as milliliters/100 g per min.

‡ [K] is the venous potassium concentration in milliequivalents per liter.

creased the rate of muscle blood flow from 13.0 ± 1.9 to 15.8 ± 1.7 ml/100 g per min ($P < 0.05$). In the potassium-depleted dogs potassium infusion during contractions increased muscle blood flow from 6.2 ± 0.9 to 8.3 ± 0.7 ml/100 g per min ($P < 0.01$). Thus, potassium infusion increased muscle blood flow at rest and during stimulated contractions in both the normal and potassium-depleted dogs (Fig. 5). However, blood flow during contractions was never restored to normal levels by potassium infusion in the depleted dogs.

The effect of potassium deficiency on creatine phosphokinase activity in serum independent of exercise is shown in Fig. 6. These samples were collected before

depletion and again before initiation of gracilis muscle stimulation. All values were initially normal, but after potassium depletion ranged from 28 to 582 U/ml.

Hematoxylin- and eosin-stained sections of gracilis muscle obtained from normal dogs before and 48 hr after stimulation for 60 min were invariably normal (Fig. 7). Those obtained from normal dogs immediately after 60 min stimulation showed edema and mod-

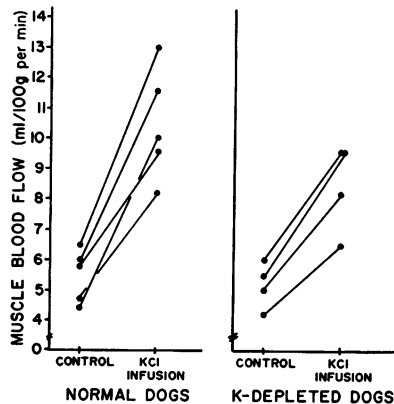


FIGURE 4 Effect of potassium infusion on resting muscle flow rate.

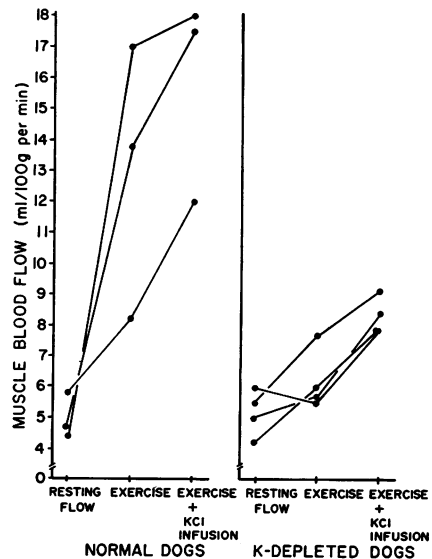


FIGURE 5 Effect of potassium infusion during exercise on muscle blood flow rate.

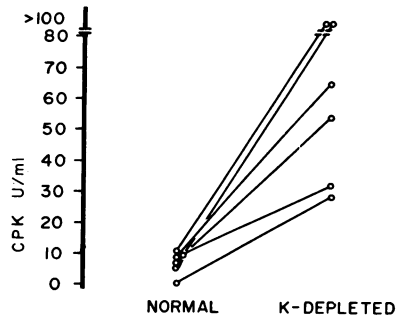


FIGURE 6 Creatine phosphokinase (CPK) activity before and after potassium depletion.

erate vascular congestion (Fig. 8). Sections of gracilis muscle taken before stimulation from four of six depleted animals appeared normal. In the remaining two there were rare focal areas of round cell infiltration but otherwise no remarkable changes. Muscle specimens obtained immediately after stimulation showed no distinctive changes, but in marked contrast, all those from depleted animals collected 48 hr after stimulation showed widespread focal necrosis, infiltration with

polymorphonuclear leucocytes, lymphocytes, and macrophages, loss of cross-striations, vacuolation, and sarcolemmal nuclear aggregation, (Figs. 9 and 10). None of the specimens showed evidence of arterial or venous obstruction.

DISCUSSION

In 1941, Dawes showed that intra-arterial infusion of KCl increased muscle blood flow and suggested that potassium ions might be released during exercise from the intracellular to the extracellular space and act there by dilating the muscle vessels (8). Thus, a physiologic role was tentatively assigned to the well-established observation that concentration of potassium in venous plasma rises during muscular work (14).

Strong support for the role of potassium as an important mediator of exercise hyperemia was provided by the extensive studies of Kjellmer (15, 16). Using the cat hind limb preparation, he showed that during maximum exercise, potassium concentration in interstitial fluid of the gastrocnemius muscle rose 2-4 times more than the rise observed simultaneously in venous

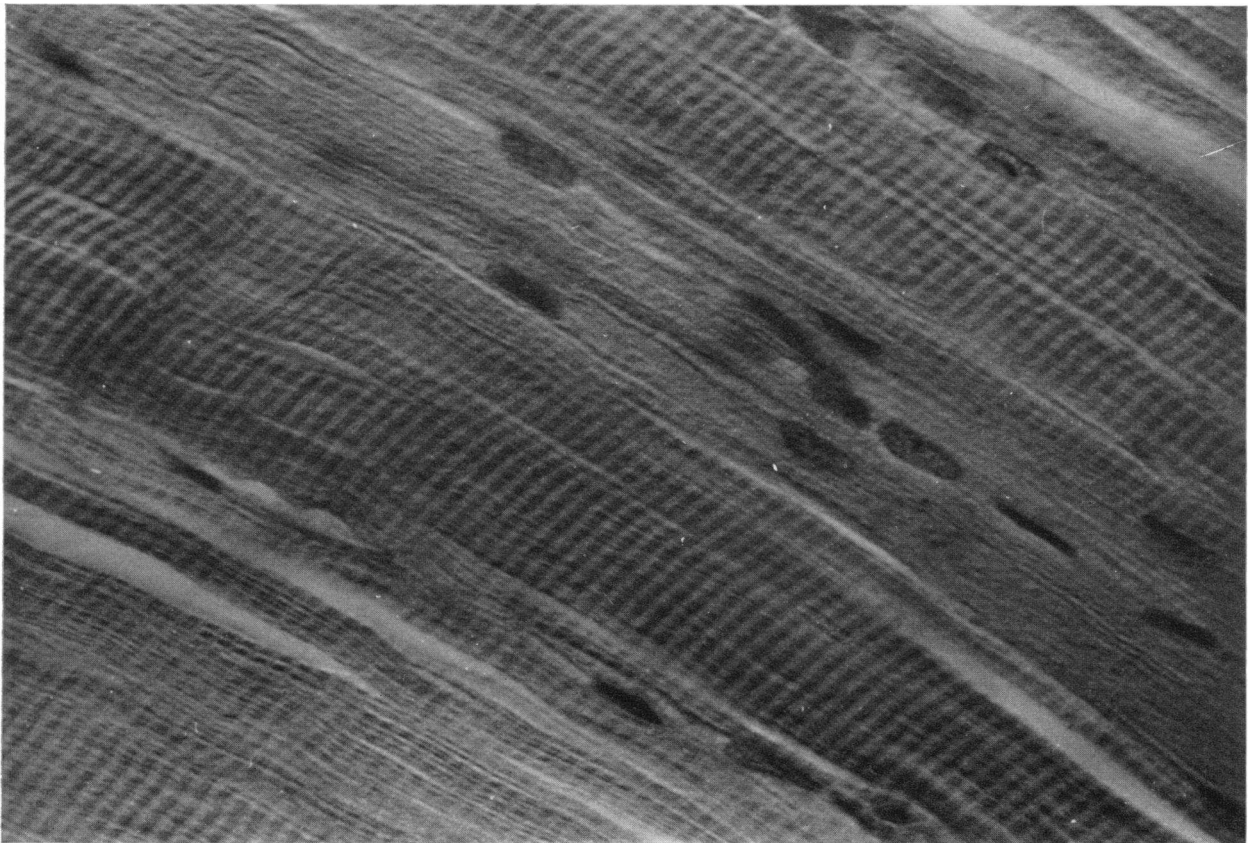


FIGURE 7 Normal muscle before contractions showing cross striations and small inter-fibrillar spaces. $\times 440$.

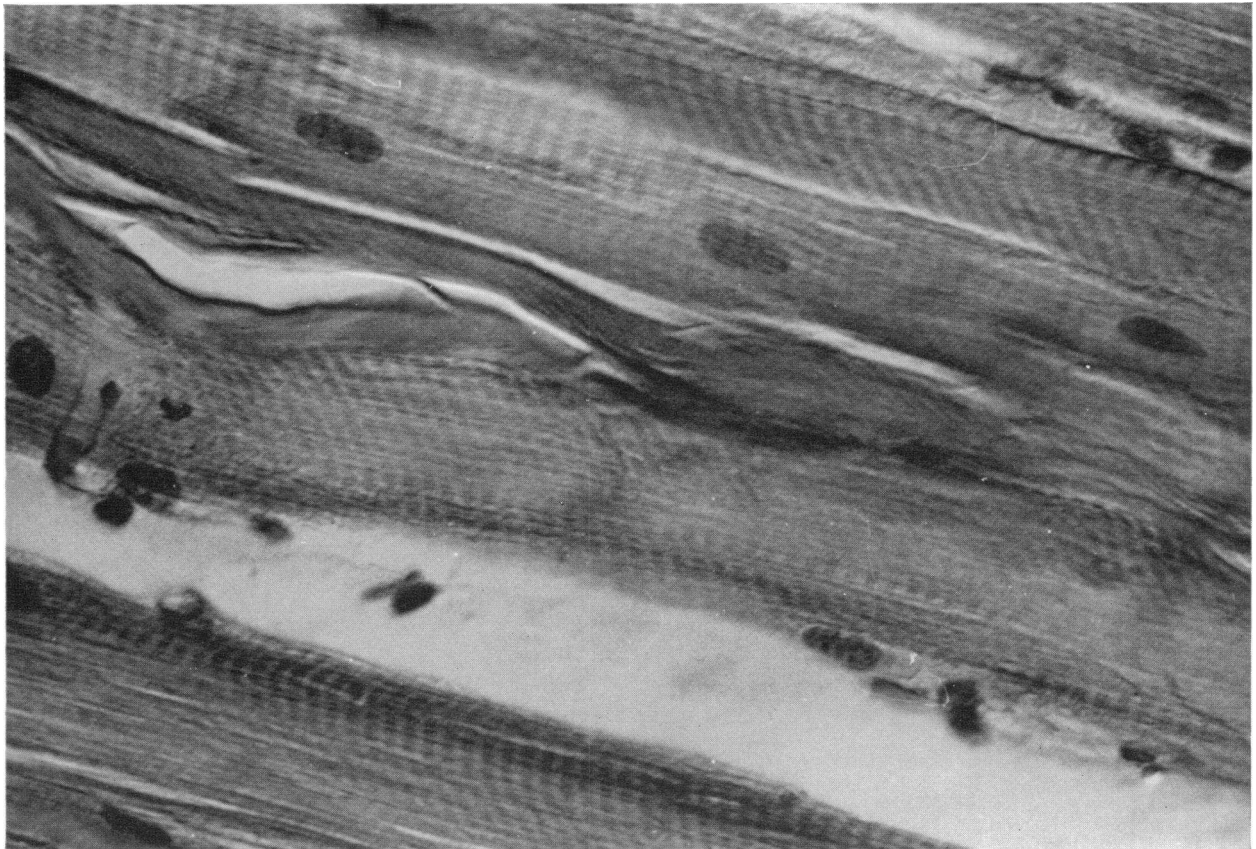


FIGURE 8 Normal muscle immediately after 60 min contractions showing edema and normal cross-striations. $\times 440$.

plasma. This concentration of potassium in interstitial fluid corresponded very closely to that observed in venous plasma, viz. 20 mEq/liter when maximum muscle blood flow was induced by intra-arterial infusion of KCl solutions. In each experiment, Kjellmer showed a close relationship between the degree of exercise, the increase in potassium concentration in venous plasma or interstitial fluid, and the increase of muscle blood flow. The relationship between muscle blood flow and potassium release observed in these studies is shown in Fig. 11. The maximum percentage by which muscle blood flow rose above base line values in each experiment was plotted against simultaneous values for potassium release. Although the intensity and frequency of stimulation were identical in both groups, values for depleted dogs (\blacktriangle), were much less than those for normal dogs (\circ). Since the points for the depleted and normal experiments were widely separated, the possibility was entertained that there was no true relationship of potassium release to blood flow and therefore that the regression shown was spurious. Accordingly, additional normal animals were studied utilizing

stimuli of lesser intensity to elicit flow rates comparable to those observed in potassium-depleted animals. The values obtained (\bullet), fell sufficiently close to the regression line to suggest that the relationship between potassium release and muscle blood flow was indeed factual over a broader range of values.

The results of the potassium infusion studies show that vascular smooth muscle in potassium-depleted animals is responsive to elevation of plasma potassium concentration at rest and during stimulated contractions and thus support our contention that failure to release potassium per se, in a major way is responsible for diminished hyperemia during skeletal muscle contractions in potassium-depleted dogs. Potassium infusion increased muscle blood flow comparably in both normal and depleted dogs. However, failure of potassium infusion to restore blood flow to normal levels during exercise in the depleted dogs suggests that other factors controlling exercise hyperemia might have been disturbed by potassium deficiency.

The studies reported herein indicate that prolonged electrically stimulated exercise of the gracilis muscle in

the potassium-depleted dog is followed by frank necrosis. In contrast, potassium depletion per se without exercise was only irregularly associated with histologic abnormalities of the gracilis muscle which when observed were always minor. Exercise of the gracilis muscle in normal dogs for the time selected in these studies was never followed by significant histologic abnormalities.

All potassium-depleted animals demonstrated elevated activity of creatine phosphokinase in serum suggesting a loss of skeletal muscle integrity.

Because of inherent difficulties associated with alternating variations of fiber length, muscle contractile force was not quantitated. In depleted dogs, contraction of the muscle in response to stimulation and resulting adduction of the thigh appeared equally responsive and forceful as that observed in normal dogs. However, diminished response to stimulation appeared as early as 20 min in depleted dogs but seldom before 50 min in normal dogs. Although admittedly only limited interpretation is warranted, no evidence was observed that the subnormal blood flow response in potassium-depleted dogs was associated with diminished intensity of muscle contraction.

The latter contention is supported by the findings of Miller and Darrow (17), who showed that the force of muscle contraction in response to a tetanic stimulus in potassium-depleted rats could not be differentiated from that observed in normal animals.

Besides release of potassium from contracting muscle, anoxia (18), phosphate (19), adenine nucleotides (20), and osmolality (21) have been given consideration as mediators or at least participants in the mediation of exercise hyperemia. While our studies were not designed to examine the role of these substances or effects, there has been mounting evidence (22) that potassium release is of critical importance for the necessary rise of muscle blood flow with exercise.

The results of the studies reported herein offer support for our postulation that release of potassium ions from skeletal muscle and the associated rise of muscle blood flow during exercise is impaired by potassium deficiency and as a consequence, rhabdomyolysis under these circumstances could in large part be ischemic in origin.

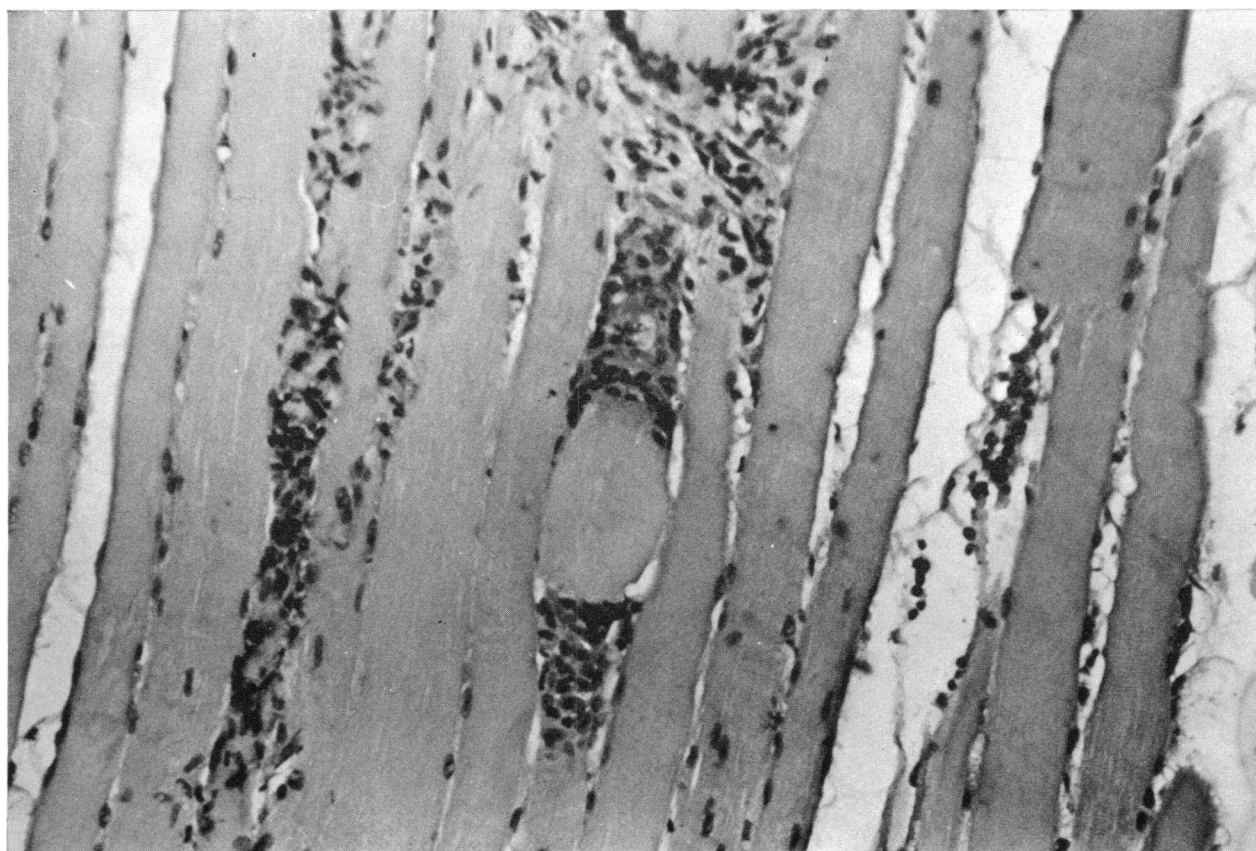


FIGURE 9 Potassium deficient muscle 48 hr after stimulation showing necrotic muscle adjacent to fibers that have normal appearing cross striations. $\times 100$.

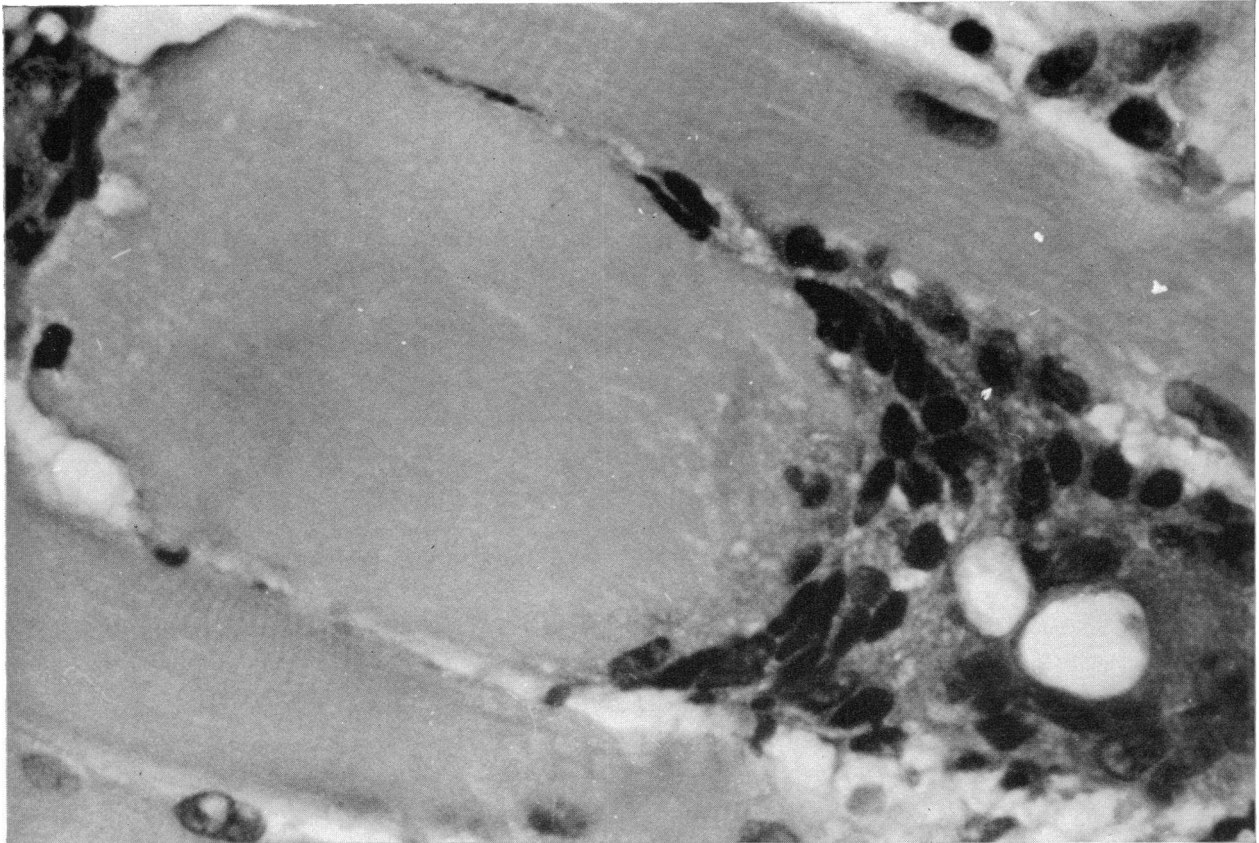


FIGURE 10 Potassium deficient muscle 48 hr after stimulation showing necrotic fiber with vacuolar changes and round cell infiltrates. Neighboring fibers show indistinct cross-striations and have homogeneous appearance. $\times 440$.

Our clinical experience and that of others (23) indicates that most cases of environmental heat injury in basic military recruits occur during the 2nd wk of basic training. In serial studies of normal subjects, it

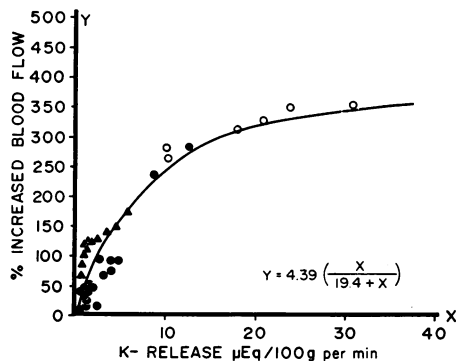


FIGURE 11 Plot of maximum rise of muscle blood and simultaneous potassium release from gracilis muscle during exercise in normal (○) and potassium-deficient (▲) dogs. Additional normal points (●) were obtained to clarify interpretation of regression (see text).

was observed that maximum potassium depletion also occurred at this time (6) and was comparable in degree to that produced in the experimental studies herein reported. The observation that heat injury and rhabdomyolysis in military recruits and football players follows intense physical exertion may bear particular relevance to our experimental findings that frank necrosis in potassium-depleted dogs was observed only after intense and prolonged stimulation of the gracilis muscle.

ACKNOWLEDGMENTS

The technical assistance of James Long, Deloia Morris, James Hedgeman, Allen Kasten, Stafford Cassel, John Huff, James Hoback, and Russell Horn is gratefully acknowledged. The secretarial assistance of Mrs. Barbara Gaylor is also acknowledged.

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