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# STUDIES OF THERMAL INJURY. VI.<sup>1</sup> HYPERPOTASSEMIA CAUSED BY CUTANEOUS EXPOSURE TO EXCESSIVE HEAT

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## INTRODUCTION

That the rapid release of potassium from erythrocytes during an episode of generalized cutaneous hyperthermia may cause an increase in plasma potassium sufficient to contribute to the occurrence of circulatory failure and death was suggested by Schjerning in 1884 (1). The suggestion was based in part on the fact that postmortem examination of extensively burned persons often disclosed evidence of severe intravascular hemolysis and in part on the fact that a sufficient amount of potassium may be released from erythrocytes *in vitro* to raise the plasma concentration of that element to a level incompatible with continued cardiac function.

In a foregoing study (2) in this series, it was observed that generalized cutaneous exposure to excessive heat may lead to rapidly fatal circulatory failure. In several pigs that died in this manner and whose deaths were preceded by electrocardiographic evidence of severe disturbances in cardiac function, the plasma potassium was found to be increased to levels ordinarily considered incompatible with life. The implication of this observation was such as to warrant further study of the effects of hyperthermia on the potassium concentration of the plasma.

## EXPERIMENTAL PROCEDURE

Samples of blood for chemical analysis were obtained from the heart by means of an inlying jugular cannula. Potassium determinations were carried out on the trichloroacetic acid filtrate of plasma and lysed blood according to the method of Lowry and Hastings (3) as modified by Cohn and Tibbetts. Hematocrit was determined in Wintrobe tubes after centrifuging for 30 minutes at 2,500 r.p.m. The method of Bing, *et al* (4), as modified by Ham (5) was used for determining plasma hemoglobin.

<sup>1</sup> This work has been done under Contract NDCrc-169 between the President and Fellows of Harvard College and the Office of Scientific Research and Development who assume no responsibility for the accuracy of the statements contained herein.

Whole blood hemoglobin was determined on 0.1 ml. of  $\frac{1}{10}$  dilution of blood in 5 ml. dilute ammonia by the Klett-Summerson colorimeter.

Before undertaking further investigation of the relationship of hyperthermia to the development of hyperpotassemia, an experiment was undertaken to determine the effect of systemic anoxia on the potassium concentration of the plasma independently of hyperthermia.

A control sample of blood was taken from an 8.2 kgm. pig. The trachea was then exposed and clamped and 4 and 8 minutes later, additional samples of blood were obtained. The animal died at the end of 8 minutes and was allowed to remain on the operating table at room temperature for an hour thereafter, at which time, the fourth and last sample of blood was withdrawn. The analytical results are shown in Table I.

TABLE I  
*Changes in the blood of a pig during and after  
death by strangulation*

Blood with-drawn	Volume packed cells	Hemo-globin in cells	Hemo-globin in plasma: Hemo-lysis	Potassium in red cells	Potassium in plasma
		grams per 100 ml.	per cent	meq. per L.	meq. per L.
Control	45	33	0	132	5.2
0 min.	Trachea clamped				
4 min.	49	31	0	128	9.1
8 min.	48	34	0	130	9.3
8 min.	Animal died				
68 min.	?	?	0	?	16.8

It may be seen that the plasma potassium level was almost doubled during the 8 minutes that elapsed between the onset of asphyxia and death. Most of the increase occurred during the first 4 minutes of this period. There are two obvious sources from which the increment may have been derived, one being the erythrocytes and the other the extravascular tissue. A comparison of hematocrit and hemoglobin content of cells at the end of the 4-minute period indicates that swelling of erythrocytes had occurred. The hematocrit rose from 45 to 49, whereas the hemoglobin dropped from 33 to 31 grams per 100 ml. of cells. It appears that the observed decrease in the con-



TABLE II—Continued

Fig. no.	Time	Thermal exposure	Body temperature	Time of death	Blood samples time taken	Volume packed cells	Hemo-globin in cells	Hemo-globin in plasma: Hemolysis	Potas-sium in red cells	Potassium in plasma					
										Total	Change	Potential increment $\mu$ from hemolysis	Increment from sources other than hemolysis		
919	<i>minutes</i>		$^{\circ}$ C.		Control		<i>grams per 100 ml.</i>	<i>per cent</i>	<i>meq. per L.</i>	<i>meq. per L.</i>					
	Control					45	33	0.8	118	4.2					
	0	Started	75 $^{\circ}$	37.1	4M	56	29	7.8	81	25.5	+21.3	8.6	12.7		
	4					47	26	25.5	67	21.4	+17.2	20.2			
	5	Stopped	75 $^{\circ}$	37.1	4M	40	32	22.2	?	18.3	+14.1	?			
	8					35	37	23.1	77	17.0	+12.8	12.6			
	10					33	31	30.1	72	17.5	+13.3	15.2			
	14														
17															
18			44.3												
				+											
913	Control				Control	26	37	0.0	116	3.5					
	0	Started	75 $^{\circ}$	38.6	2M	35	32	12.3	103	14.2	+10.7	7.7	3.0		
	2					32	33	24.5	96	17.7	+14.2	14.7			
	6	Stopped	75 $^{\circ}$	40.8	8M	30	32	25.3	111	17.4	+13.9	16.0			
	7														
8															
907	Control				Control	42	34	0.6	125	3.5					
	0	Started	75 $^{\circ}$	37.3*	8M	53	31	2.7	100	17.4	+13.9	3.1	10.8		
	8														
10	Stopped		42.5*												
910	Control				Control		?	?		3.0					
	0	Started	75 $^{\circ}$	36.8	2M		?	?		19.1	+16.1				
	2					5M	?	?		18.1	+15.1				
	5					7M	?	?		24.0	+21.0				
	7	Stopped	75 $^{\circ}$	43.7	14M		?	?		17.3	+14.3				
13															
14															
908	Control				Control	32	?	?	106	3.8					
	0	Started	75 $^{\circ}$	?	4M	?	?	?	?	16.7	+12.9				
	4					9M	33	?	?	98	18.5	+14.7			
	9	Stopped	75 $^{\circ}$	?	11M	32	?	?	90	17.1	+13.3				
	11														
14															
912	Control				Control	33	37	0.0	125	4.1					
	0	Started	75 $^{\circ}$	36.0	1M	45	31	1.9	102	16.7	+12.6	1.6	11.0		
	1					4M	33	37	19.2	?	?	?		?	
	4					5M	34	34	24.2	100	16.4	+12.3		16.5	
	5	Stopped	75 $^{\circ}$	43.1	10M	40	31	19.9	85	16.4	+12.3	14.2			
	10														
	14														

\* Right heart temperature.

merge animals in hot water rather than expose them to hot air. By the former method, the temperature of the surface of the skin could be controlled with greater precision than was possible by the latter.

The experimental procedure that was followed in submerging animals in hot water is described in detail in Study VII of this series (6). The animals were anesthetized with pentobarbital sodium and between 60 and 75 per cent of the total body surface was immersed in hot water. The effects on the blood of exposing 4 pigs in

this manner at 47 $^{\circ}$  C. and 8 pigs at 75 $^{\circ}$  C. are shown in Table II.

## RESULTS

*Exposure at 47 $^{\circ}$  C.:* Although all of these animals developed an acute and rapidly fatal systemic hyperthermia, none showed a rise in plasma potassium significantly greater than that which may result from anoxia independently of hyperthermia.

In none of these was the magnitude of the increase comparable to that which was observed in some of the hot air exposures reported in Study IV of this series (2).

In the first two animals, it appeared that the potassium increase in the plasma was derived from extravascular sources. In one sample from the third animal the increase could have been due to leakage from red blood cells. In the fourth animal it could have been due in part to leakage from intact erythrocytes, and in part to diffusion from extravascular tissue. Cutaneous hyperthermia of the kind produced in these animals did not result in a significant amount of intravascular hemolysis.

*Exposure at 75° C.:* The chemical changes in this group were of a different order of magnitude than those observed in animals exposed at 47° C. All animals exposed for more than 3 minutes at 75° C. developed plasma potassium levels in excess of 16 meq. per L. In most instances, such levels were reached during the first few minutes of exposure and were either maintained or increased as the period of exposure was prolonged. If the pig survived for more than a few minutes after the termination of the exposure, there was a slow decline in plasma potassium concentration. Thus, in animal No. 919 the plasma potassium rose from 4.2 to 25.5 meq. during the first 4 minutes of exposure, and during the next 4 minutes declined to 17.4.

The rapidity with which an excessively high plasma potassium level may fall is indicated by the discrepancies that were observed between estimated increments by hemolysis and total amounts actually present in the plasma. Thus, it may be seen in the case of pig No. 913 that with an increment of 7 meq. per L. between the 2- and 6-minute samples by hemolysis, the actual plasma level rose by only 3.5 meq. Similarly, in pig No. 912 the increment by hemolysis between the 1- and 5-minute samples was 14.9 meq. per L. whereas the total plasma potassium actually changed from 16.7 to 16.4 during this period.

In most of the animals exposed at 75° C., there was some increase in the volume of packed cells. The comparison of cell volume and hemoglobin content indicated that most, if not all, of the early increase in cell volume was due to swelling of erythrocytes rather than to loss of plasma or mobilization of cells from storage depots.

It is of interest to note that plasma hemoglobin values as high as 24 per cent hemolysis were observed as early as 5 minutes after the onset of cutaneous hyperthermia. It was estimated that during this period the temperature in the vicinity of the most superficial blood vessels probably rose to approximately 70° C.

*Chemical changes in the blood of dogs caused by cutaneous hyperthermia:* It was inferred from the foregoing experiments on pigs that most of the potassium responsible for these potentially fatal plasma levels either leaked out of intact red blood cells or escaped from hemolyzed cells. If this inference is correct, fatal hyperpotassemia due to cutaneous hyperthermia would occur only in animals having a high concentration of potassium in the erythrocytes such as man or pig. Its occurrence could not be expected in an animal having a low cellular concentration of potassium as is the case in dog's blood.

To test this assumption, samples of blood were taken from each of 5 dogs before and during immersion in hot water. The results of these experiments are shown in Table III.

The animals were exposed at temperatures ranging between 55° and 75° C. until death occurred. The highest potassium concentration observed in the erythrocytes in control samples of blood from these animals was 9.4 meq. per L., in contrast to the pig whose erythrocyte concentrations ranged between 106 and 145 meq. per L. The greatest potassium increase that occurred in the plasma of the dogs that died as a result of cutaneous exposure to heat was from 3.9 to 8.2 meq. per L.

The increments to the plasma potassium that were observed in these animals could not be accounted for by loss of potassium from the erythrocytes. The potassium content of the red blood cells of the dogs characteristically rose during exposure in contrast to the loss of potassium that occurred from the erythrocytes of the pig. As in the case of the pig, there was severe intravascular hemolysis in animals exposed at 75° C. until death occurred.

It can be inferred, therefore, that the development of a potentially fatal level of hyperpotassemia following cutaneous exposure to heat results from the rapid release of potassium from thermally in-

TABLE III  
*Changes in blood of dogs caused by immersion in hot water*

Dog no.	Time	Thermal exposure	Body temp.	Time of death	Blood samples time taken	Volume packed cells	Hemoglobin in cells	Hemoglobin in plasma: Hemolysis	Potassium in red cells	Potassium in plasma
	<i>minutes</i>	<i>° C.</i>	<i>° C.</i>				<i>grams per 100 ml.</i>	<i>per cent</i>	<i>meq. per L.</i>	<i>meq. per L.</i>
931	Control	Started   55°  Stopped	35.4   41.4		Control	35	37	0	9.9	2.8
	0				5M	41	36	0	8.1	5.2
	5				13M	57	32	0	10.7	4.7
	13				21M	57	33	0	11.2	6.9
	21				23					
930	Control	Started   60°  Stopped	36.9   39.1		Control	49	34	0.1	4.3	4.0
	0				5M	66	27	17.9	6.4	3.3
	5				8M	65	28	20.2	5.5	4.7
	8				11M	62	28	23.8	6.1	5.3
	11				17					
929	Control	Started   75°  Stopped	37.2   44.1		Control	49	34	0.3	6.3	3.9
	0				3M	57	29	26.1	7.0	4.8
	3				9M	42	37	31.8	5.7	6.1
	9				13M	39	34	35.8	7.9	8.2
	13				14					
922	Control	Started   75°  Stopped	37.9   39.3		Control	42	35	0.2	8.8	3.1
	0				3M	47	30	22.9	8.9	5.8
	3				7M	47	30	29.5	12.6	6.4
	7				10M	43	29	33.5	7.9	5.8
	10				15					
934	Control	Started 75° Stopped	34.6*		Control	41	35	0.1	5.6	3.1
	0		25M		40	34	31.9	6.5	6.9	
	25		43.5*	+						

\* Right heart temperature.

jured red blood cells and that a high erythrocyte content of potassium is essential to its occurrence.

*In vitro effects of heat on pigs' blood:* It was thought that more precise information regarding the reciprocal relationships of temperature, time and the release of potassium from erythrocytes could be obtained by heating samples of pigs' blood *in vitro*.

Heart's blood was collected from normal pigs by cardiac puncture in a heparinized syringe where it was mixed and then discharged into heparinized glass stoppered vials. One vial was kept at room temperature as a control; the others were strapped to a mechanical mixer and immersed in a constant temperature bath. Exposure temperatures ranged between 44° and 63° C. during which time the blood was mechanically decanted from one end of the vial to the other at a rate of 6 times per minute. It required approximately 2 minutes

for the temperature of the blood to reach that of the water bath. As soon as a sample was removed from the water bath, it was immediately cooled in ice water and analyzed.

It is apparent that there was a progressive increase in the rate at which potassium passed out of the erythrocytes and into the plasma of the blood as its temperature was raised (Table IV). The amount of the plasma increment at the end of 1 hour's exposure at 40°, 44°, 48°, 51°, 52° and 55° C. were respectively 0.6, 1.6, 6.4, 6.4, 6.7 and 14.3 meq. per L. At the lower temperatures (51° C. and under), the increments were due almost entirely to leakage from intact cells. At the end of 30 minutes exposure at 52° and 55° C., the proportion of the plasma increment contributed by hemolysis was 24 and 38 per cent respectively.

Unequivocal evidence of swelling of erythrocytes was first observed at 55° C. although there

TABLE IV  
In vitro effects of heat on pigs' blood

Specimen	Temp.	Time	Volume packed cells	Hemoglobin in cells	Hemoglobin in plasma: Hemolysis	Potassium in red cells	Potassium in plasma			
							Total	Change	Increment from hemolysis	Increment from leakage
	° C.	minutes		grams per 100 ml.	per cent	meq. per L.	meq. per L.			
1-947	Control 40°	Control	30	34	0.1	105	3.2			
		15	30	34	0.1	113*	3.5	+0.3		0.3
		30	30	32	0.3	114*	3.5	+0.3	0.1	0.2
		60	30	34	0.1	102	3.8	+0.6		0.6
2-949	Control 44°	Control	32	33	0	99	3.2			
		15	31	33	0.1	107*	3.9	+0.7		0.7
		30	31	34	0.1	102*	4.0	+0.8		0.8
		60	31	33	0.3	97	4.8	+1.6	0.1	1.5
3-949	Control 48°	Control	31	34	0	104	4.6			
		15	32	31	0.1	101	7.5	+2.9		2.9
		30	32	32	0.1	90	9.2	+4.6		4.6
		60	32	29	0.4	90	11.0	+6.4	0.1	6.3
4-950	Control 51°	Control	33	32	0.0	109	4.3			
		15	35	31	0.8	96	10.2	+5.9	0.4	5.5
		30	34	34	0.5	98	11.8	+7.5	0.2	7.3
		60	36	31	0.7	92	10.7	+6.4	0.4	6.0
5-950	Control 52°	Control	34	35	0.1	120	4.2			
		15	35	34	0.8	103	10.0	+5.8	0.5	5.3
		30	35	32	2.7	101	10.4	+6.2	1.5	4.7
		60	36	32	2.7	100	10.9	+6.7	1.6	5.1
6-947	Control 55°	Control	31	33	0.1	109	4.2			
		15	40	28	1.3	85	7.5	+3.3	0.7	2.6
		30	37	30	5.7	87	12.1	+7.9	3.0	4.9
		60	37	30	9.6	71	18.5	+14.3	4.4	9.9
7-1052	Control 60°	Control	38	33	0.0	119	3.6			
		5	48	28	1.4	83	12.6	+9.0	1.2	7.8
8-1052	Control 61°	Control	36	35	0.1	121	4.1			
		5	45	28	3.5	76	20.8	+16.7	2.4	14.3
9-1052	Control 62°	Control	34	36	0.0	122	3.9			
		5	33	34	11.7	69	30.8	+26.9	4.5	22.4
10-1052	Control 63°	Control	36	36	0.1	121	4.1			
		5	26	34	31.6	58	40.2	+36.1	9.6	26.5

\* These values must be due to analytical errors.

may have been some swelling in all specimens exposed for more than 30 minutes at 48° and higher.

The rate of change in the blood was much more rapid during exposures at 60° C. and higher. In these experiments the blood remained in the bath for only 5 minutes and the actual time during which it was at the temperature of the water was approximately 3 minutes. The rises in plasma potassium after such brief periods at 60°, 61°, 62° and 63° were respectively 9.0, 16.7, 26.9 and 36.1 meq. per L. The blood was totally hemolyzed at 65° C.

Not until blood was heated at 60° C. or higher in a test tube were the observed increases in plasma potassium comparable to those that occurred in living pigs after cutaneous exposures at 75° C. This is not to imply that the effects of hyperthermia on blood in a test tube are necessarily similar to those effects in a living animal. Attention has already been called to the fact that asphyxia without rise in temperature may cause hyperpotassemia in a living animal. Although the mean temperature of the blood of a living pig is never raised to 60° C., most or all of its blood

may in the course of its circulation through the over-heated dermis be brought to a much higher temperature than would be recorded by a rectal thermometer or intracardiac thermocouple. It will be recalled from the calculations made in Study I (7) of this series that the superficial portion of the dermis of a living pig reaches a temperature of 60° C. within a second after the surface of the skin has been brought to 75° C. It would appear quite possible then that the temperature of a considerable portion of the blood of an animal that had received an extensive cutaneous exposure to water at 75° C. for as long as 5 minutes would have been raised briefly to the neighborhood of 60° C. during its passage through the superficial subcutaneous tissue.

Not until the temperature of the bath was raised to 62° C. did a 5-minute exposure of blood in a test tube result in hemolysis comparable to that observed in living pigs exposed to 75° C.

Attention has already been directed to the fact that unequivocal swelling of erythrocytes was first observed in a test tube after a 15-minute exposure at 55° C. So far as could be judged by the hemoglobin-hematocrit ratios, swelling of erythrocytes continued through 61° C., beyond which it was not observed.

#### SUMMARY

These experiments have established that severe and extensive cutaneous burning may result in a rapid rise in plasma potassium to levels ordinarily considered incompatible with life. Such levels are attained when a large proportion of the body surface of an animal whose erythrocytes normally have a high potassium content is maintained at temperatures as high as 75° C. for more than a few minutes. That lower surface temperatures may also be responsible for fatal hyperpotassemia is suggested by the fact that potassium may be released rapidly from blood cells *in vitro* at temperatures of 60° C. Because of the slowness with which potassium is released at lower temperatures and the rapidity with which excess potassium leaves the blood stream, it is not likely that thermal exposures of insufficient intensity to cause severe cutaneous burning could cause sufficient damage to the erythrocytes to produce dangerously high plasma levels.

*In vitro* experiments on pigs' blood indicate that there is rapid leakage of potassium from intact erythrocytes when the temperature is raised over 60° C. and that rapid hemolysis occurs when the temperature is raised above 62° C. Leakage is accompanied by swelling at temperatures ranging between 55° and 61° C. So far as could be judged by the hemoglobin content of the cells, rapid release of potassium occurs without cell swelling at temperatures above 61° C.

It was demonstrated that leakage from and lysis of red blood cells are the principal sources of the hyperthermic potassium increments of plasma. At the lower temperatures (47° C. *in vivo* and 48° C. *in vitro*) hemolysis is negligible. The increase in plasma potassium *in vivo* at these temperatures is due either to diffusion from extravascular sources or to leakage from erythrocytes. It was obvious that in the *in vitro* exposures at relatively low temperatures leakage from erythrocytes was the only source of the plasma increment. Although theoretically enough potassium could be released by leakage alone to account for potentially fatal plasma levels (in excess of 16 meq. per L.) no such increases were observed without accompanying hemolysis. When blood was heated *in vitro* leakage contributed more than hemolysis to the attainment of such levels. In thermal exposures *in vivo* of sufficient duration and intensity to produce such high levels, hemolysis was the more important causal factor.

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