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CAFFEINE ATTENUATES THE AFTERDROP IN RECTAL TEMPERATURE AFTER MILD COOLING

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TECHNICAL REVIEW AND APPROVAL
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The experiments reported herein were conducted according to the principles set forth in the current edition of the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This technical report has been reviewed by the NMRI scientific and public affairs staff and is approved for publication. It is releasable to the National Technical Information Service where it will be available to the general public, including foreign nations.

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Previous research has shown that subjects who experience immersion hypothermia often show a continued decrease in rectal temperature (afterdrop) during the initial phase of rewarming. Because caffeine, the principal constituent of coffee, influences thermoregulatory and cardiovascular responses and is occasionally administered to individuals upon removal from cold exposure, we examined whether caffeine might influence rewarming after mild cooling. Seven male subjects were given either warm decaffeinated coffee containing 3.5 mg/kg caffeine or warm water after their rectal temperature was reduced by 0.5°C via immersion in cold (13°C) water. Between 20 and 40 minutes (min) after removal from cold water a 0.8°C afterdrop in rectal temperature occurred in the noncaffeine control condition, while the condition

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9. administered caffeine showed a mean afterdrop of 0.5°C. After 120 min, he caffeine condition had rewarmed back to the pre-afterdrop criterion, while he control condition was still 0.5 below the criterion level. . These data ndicate that caffeine significantly attenuated the magnitude of the post-mmersion afterdrop in rectal temperature.

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INTRODUCTION

After removal from extended exposure in cold water, which induces core hypothermia, body temperature often continues to decline (afterdrop) during the initial phase of rewarming. If the temperature becomes low enough, the condition can be life threatening (1). Although the mechanisms underlying this phenomenon remain to be precisely elucidated, current hypotheses suggest that post-immersion afterdrop stems from a continuation of both conductive heat loss through tissue (2) and convective heat loss, resulting from the perfusion of cooled blood from the periphery into the deep core (3).

In the field, coffee is often given to individuals exposed to cold as a means of introducing warm fluids. However, the principal constituent of coffee, caffeine, produces a number of cardiovascular and metabolic effects that could influence the physiological response to cold. Oral caffeine, when given alone or in coffee, increases peripheral vasoconstriction, vascular resistance, systemic blood pressure, and heart rate (4, 5, 6, 7); caffeine has also been shown to decrease peripheral skin temperature (7). These physiological effects, which collectively result from increased heart rate and vascular resistance, are thought to be mediated by antagonism of adenosine (8), which increases the systemic release of the adrenergic catecholamines, epinephrine and norepinephrine (6, 9, 10).

Given its pervasive physiological effects as well as its use in the field, we examined whether caffeine might influence the

rate of rewarming after moderate hypothermia was induced by immersion in cold water.

METHODS

Subjects:

Seven adult male volunteers in good general health served as subjects. Once they were briefed on the risks and benefits of the study, all participants provided signed informed consent. Medical coverage was provided for all subjects. Individual subject characteristics are provided in Table 1.

All subjects were instructed to abstain from any caffeinated substance for 24 hours prior to the experimental sessions. On two occasions, separated by at least one week, each subject arrived at the laboratory after a 12 hour overnight fast and was

Table 1. Subject Characteristics

SUBJECT	% FAT	SURFACE AREA (m^2)	AGE	Ht (cm)	Wt (Kg)	IM1	IM2
1	10	1.95	23	180.3	75.9	30	35
2	11	1.77	25	172.2	64.5	28	13
3	10	1.83	29	172.7	70.5	22	30
4	11	1.87	26	177.8	70.5	20	30
5	20	2.19	30	186.7	94.0	40	35
6	17	2.06	30	177.8	88.0	50	55
7	14	1.89	27	177.8	71.8	45	36
MEAN	13	1.94	27	177.9	76.6	34	33
SD	3.6	0.13	2.5	4.52	9.8	10.7	10.7

Percent body fat (% fat) was determined by hydrostatic weighing. Surface area was calculated according to the method of DuBois and DuBois (11). Immersion times are expressed in minutes.

weighed. Subjects were instrumented with a YSI rectal probe, inserted 15 cm past the anal sphincter. Additional YSI 700 series thermistors (Yellow Springs, OH) were taped bilaterally to the index fingers, triceps, quadriceps, and great toes. Heart rate was monitored with a standard 3-lead EKG monitor. An 18 gauge indwelling catheter was placed into the antecubital vein of the non-immersed arm and was kept patent with heparinized saline. Temperature and heart rate data were recorded manually at 10-minute intervals throughout the experimental procedure.

Wearing swimming trunks only, subjects remained seated for 30 minutes in order that stable baseline measurements could be obtained. Thereafter, each subject was immersed up to the shoulder level in 13°C circulating water until his rectal temperature decreased by 0.5°C. Upon reaching the temperature criterion, subjects were immediately removed from the immersion bath, towel dried, and allowed to rewarm for 160 minutes while seated upright; ambient air temperature in the room was kept constant between 24-26°C. Within one minute after removal from the immersion bath, each subject was orally administered either caffeine (3.5 mg/kg) mixed in 500 ml of warm (49-50°C) decaffeinated coffee or warm water (control); presentation of these conditions was counterbalanced between sessions for all subjects. The amount of caffeine was approximately the amount contained in two to three cups of brewed coffee.

Blood samples were taken just before cold water immersion, at time zero when subjects reached the criterion temperature, and

at 10 and 20 minutes after removal from the immersion bath. Thereafter, samples were drawn at 20-minute intervals in the rewarming period. Samples were drawn into cooled tubes containing 14.3 USP urits/ml of heparin and were immediately cooled. The blood was subsequently separated into plasma by centrifugation at 3000 rpm for 11 minutes at 4°C. Following centrifugation, 1 ml aliquots of plasma were pipetted into tubes containing 7.5 nM EGTA and 5.0 nM glutathione in deionized water at PH 6.8; this preparation was frozen and maintained at -80°C for subsequent analysis. Thawed extracts eluted from alumina were analyzed for epinephrine and norepinephrine by use of high pressure liquid chromatography with electrochemical detection; 3,4-dihydroxybenzylamine was used as the internal standard. Interassay variation with this method of catecholamine analysis was determined to be less than 10%.

RESULTS

Cooling:

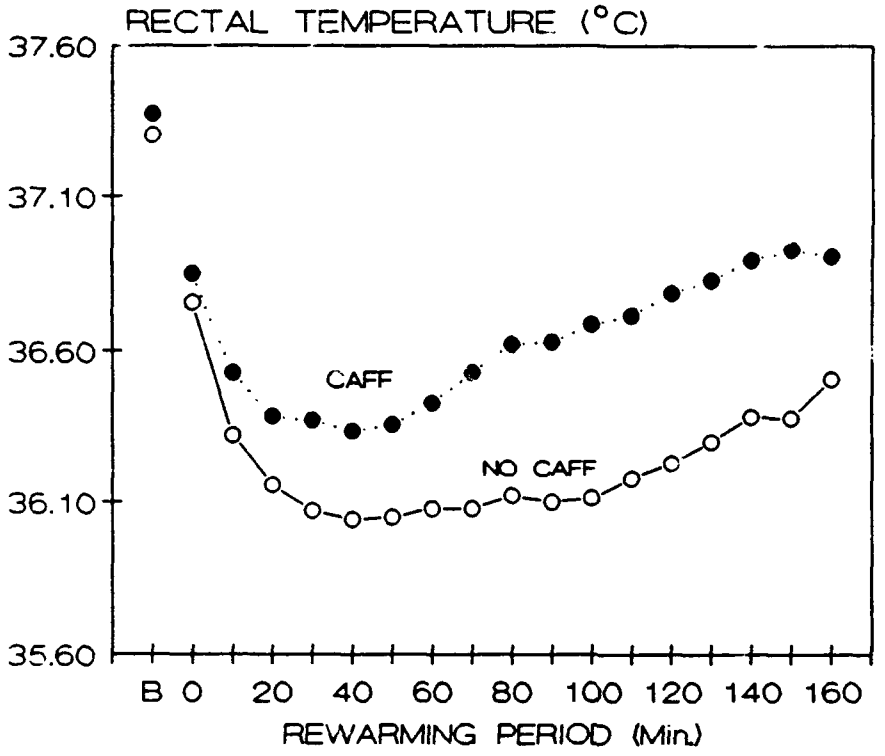
The time taken to reach a 0.5°C reduction in rectal temperature on each exposure is shown in the right-hand portion of Table 1. There were no significant differences in the length of time to reach this temperature criterion between the two experimental conditions, nor was the rate of cooling different between the first and second exposure (*p*'s > .05).

Rewarming:

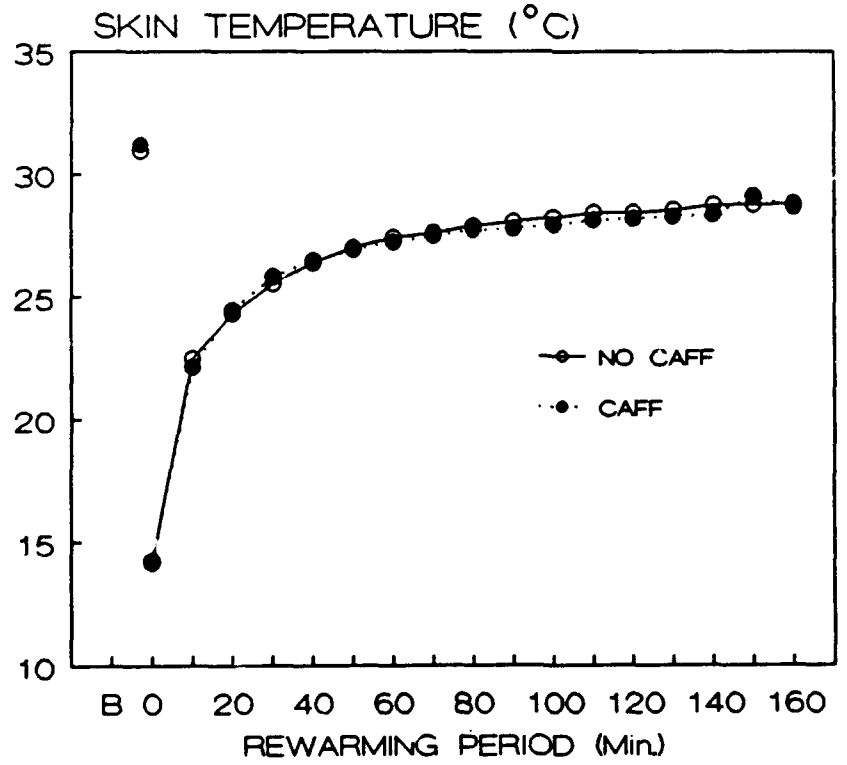
Administration of 3.5 mg/kg caffeine within one minute after subjects were removed from the cold water significantly modified

rectal temperature (Fig. 1) during the 160-min rewarming phase ($F = 2.34$, $p < .008$) such that the rectal temperature of the caffeine condition was significantly higher throughout the rewarming period. Analysis of the rate of temperature decline for each subject in the first 40 minutes of the rewarming phase indicated no significant differences between the caffeine (slope = 1.21) and control condition [(slope = 1.20), $p > .05$]. At 40 minutes into the rewarming period, rectal temperature was no longer observed to decline any further; however, the rectal temperature of the caffeine condition was approximately 0.3°C above the mean temperature of the control condition. Statistical analysis of the 50 to 160-min time period when temperatures were increasing also revealed nonsignificant differences between the caffeine (slope = 0.315) and control [(slope = 0.311), $p > .05$] conditions. This finding indicates that there were no systematic differences in the rate of rewarming after subjects had reached an asymptotic temperature level.

Analysis of the weighted skin temperatures indicated that caffeine did not significantly modify rewarming of peripheral skin temperature (Fig. 2). The temperature of the skin fell to approximately 14°C during immersion in the cold water but increased rapidly to near basal levels within the first 40 min of the rewarming period. None of the individual thermistor sites were significantly different between the treatment conditions, thus indicating that caffeine had no discernable effect on peripheral temperature during rewarming after mild hypothermia.

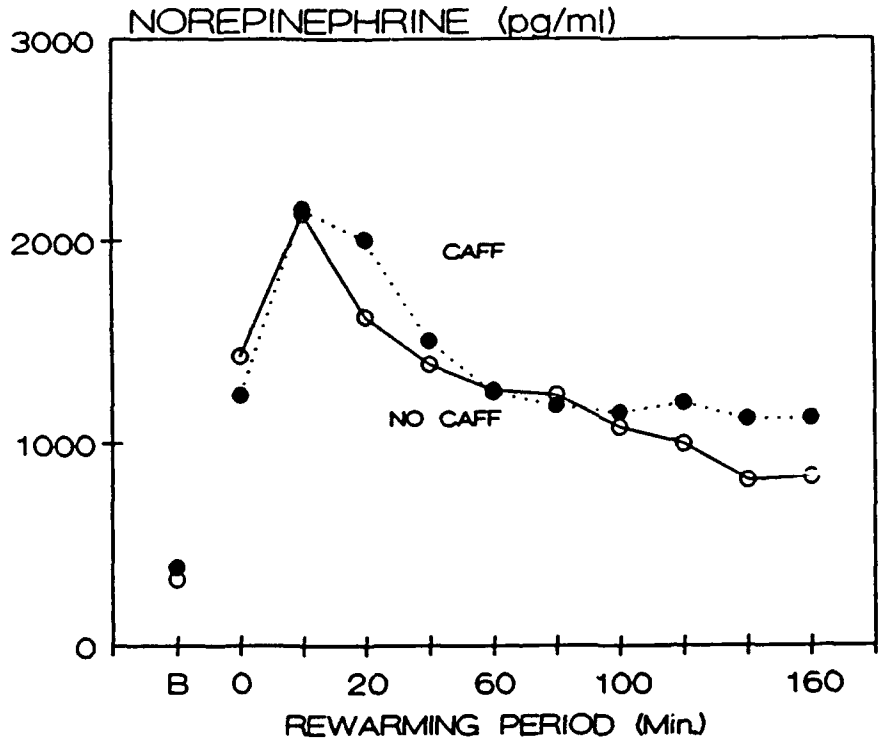


Figs. 1 and 2. Mean rectal and skin temperature, respectively, at baseline (B) and during the 160-min rewarming period.

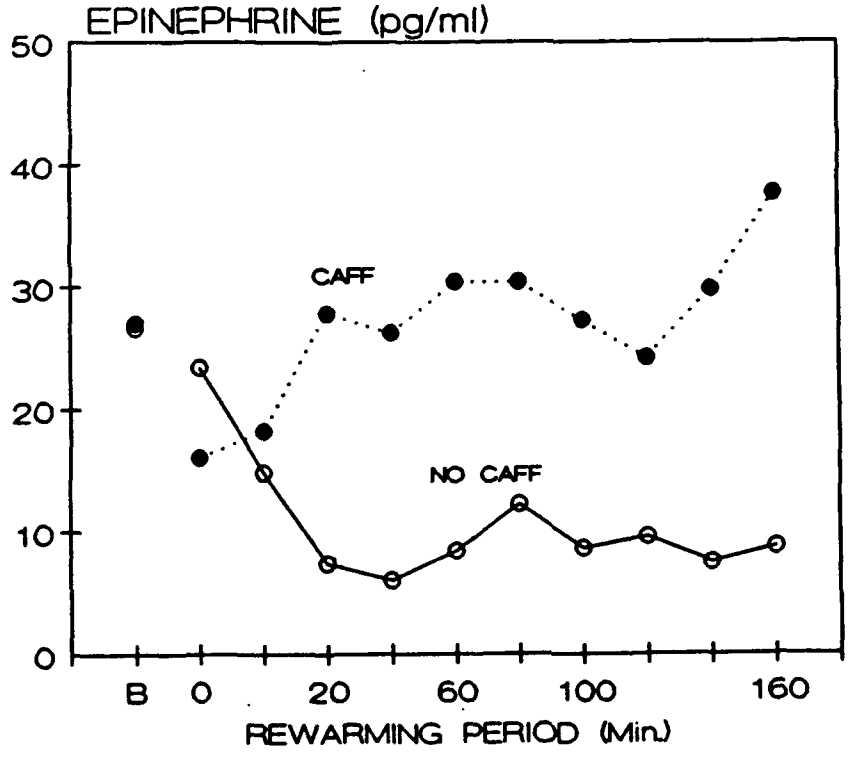


Similarly, caffeine had no effect on plasma norepinephrine (Fig. 3) during the rewarming phase in five of the seven subjects from whom complete blood samples were obtained. Subjects' norepinephrine levels were, however, substantially elevated both during and immediately after exposure to the cold. Removal from the cold water resulted in a further increase of plasma norepinephrine in the initial 10 min of the rewarming period. Thereafter, norepinephrine levels steadily declined throughout the remainder of the 160-min session.

Plasma epinephrine was substantially elevated during the post-immersion rewarming phase for the caffeine condition; however, this occurrence did not reach statistical significance above the control values ($F = 2.04$, $p = .07$) (Fig. 4), perhaps because only samples from five of the seven subjects were obtained. What is clear, however, is that after cold water immersion, subjects' epinephrine levels decreased substantially during the initial 20 minutes of the rewarming period and remained at a sustained low level during the rest of the session. Caffeine appeared to block the post-immersion reduction in epinephrine levels. A similar pattern occurred with the heart rate measure; however, in this case a significant ($F = 2.57$, $p < .025$) difference in heart rate (Fig. 5) was observed. The pattern of the heart rate appeared to parallel the observed changes in plasma epinephrine in that, without caffeine, heart rate decreased significantly during most of the rewarming period.



Figs. 3 and 4. Mean norepinephrine and epinephrine, respectively, at baseline (B) and during the 160-min rewarming period.



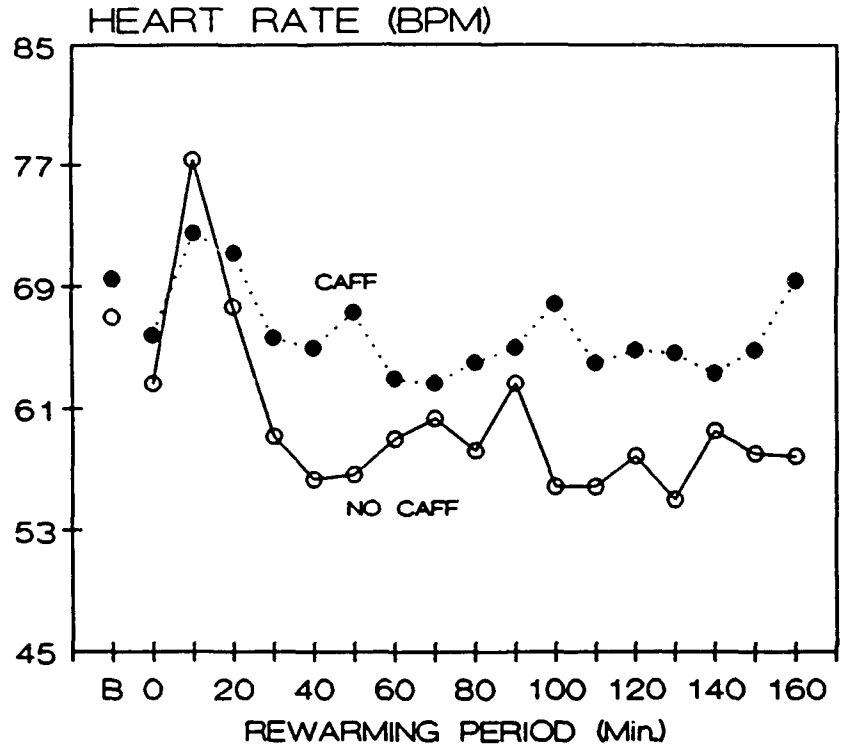


Fig. 5. Mean heart rate in beats per minute at baseline (B) and during the 160-min rewarming period.

This decrease in heart rate normally observed with immersion hypothermia was reduced by the administration of 3.5 mg/kg of caffeine immediately after subjects were removed from the cold water immersion bath.

DISCUSSION

These data demonstrate that subjects made mildly hypothermic after immersion in cold water exhibit a smaller afterdrop when given oral caffeine immediately upon removal from cold water. The lack of any differences in the skin temperature and plasma norepinephrine levels suggests that the effect of caffeine on

rewarming was not because of altered blood flow in the superficial skin. However, it is possible that skin thermistors utilized in the present study may not have been sensitive to subtle changes in vasomotor tone or sensitive to blood flow changes at deeper skin levels where caffeine could possibly have modified vascular flow (12).

As the rewarming slopes between the caffeine and control conditions were similar during the initial and latter part of the rewarming period, we believe that caffeine truncated the magnitude of the afterdrop without necessarily altering the rate of recovery. Since a direct influence on blood vessel vaso-reactivity appears unlikely to account for the observed differences, it is probable that the effect of caffeine on the afterdrop resulted from a stimulatory effect on metabolic rate or from caffeine maintaining a stable metabolic rate under conditions in which it would normally decrease (13). In this regard, studies have shown that the methylxanthines increase basal metabolism and can indeed improve cold tolerance (14). Although metabolic rate was not explicitly measured in this experiment, the sustained high levels of plasma epinephrine levels, together with a similar pattern observed in the heart rate after caffeine administration, suggest that caffeine may have induced a slight enhancement of metabolic rate during the rewarming period (13) above the level normally seen during rewarming from mild hypothermia. Such a metabolic increase, especially in the initial period following removal from cold

immersion, could have reduced the amount of afterdrop. That caffeine administration increased systemic epinephrine levels and heart rate is consistent with its mechanism of action that has been reported previously (4, 5, 6, 9, 10). The lack of a significant effect with plasma norepinephrine indicates that while caffeine is a potent stimulus to noradrenergic release (4, 6, 10), its effects are likely to be overshadowed by the profound effects of cold on peripheral circulation (15).

In summary, caffeine attenuated the magnitude of the post-immersion afterdrop normally seen upon a subject's removal from cold water. Although the mechanism for this effect is not completely understood, it is likely that events which stimulate oxygen consumption directly and influence internal heat balance are most prominent. That caffeine and possibly other methylxanthine compounds, given orally, can facilitate rewarming after hypothermia suggests that their administration, together with other rewarming methods (16, 17, 18, 19), might prove to be a potentially useful adjunctive treatment to increase patient survival from cold water immersion hypothermia.

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