



## Ephedrine-caffeine mixture in wet-cold stress

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### Abstract:

Our investigations were aimed at studying the possibility of enhancement of homeostatic processes protecting against excessive body cooling by using thermogenic drugs. We studied the influence of ephedrine (1 mg/kg) and caffeine (2.5 mg/kg) mixture in males immersed in cold water (12°C) on core temperature and plasma catecholamines, cortisol, energy substrates and chosen cognitive functions in subjects without or after previous submission to short cold acclimation procedure by five repeated brief cold-water immersions. The tested drugs did not significantly influence core temperature during immersion both in acclimated and non-acclimated subjects, however, they enhanced metabolic response. There were observed faster mobilization and higher increase in energy substrates, more pronounced in acclimated subjects (free fatty acids, glucose). Tested drugs slightly improved some psychosomatic reactions. Although the results of our study suggest that a single application of ephedrine-caffeine mixture might probably support physiological mechanisms protecting against excessive body cooling when used in people in wet-cold conditions, further research is needed to confirm the clinical significance.

### Key words:

ephedrine, caffeine, cold acclimation, metabolic response, wet-cold stress

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**Abbreviations:** ADR – adrenaline, BMI – body mass index, CAT – cold acclimation trial, CI – control immersion, COR – cortisol, FFA – free fatty acids, GLU – glucose, GLY – glycerol, NDR – noradrenaline, TI – test immersion,  $T_{re}$  – rectal temperature

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## Introduction

Human's resistance to cold is very poor, therefore, much effort has been devoted to searching for methods increasing cold tolerance. Current technologies enable manufacturing excellent clothing improving body insulation and serving good protection against heat loss, but the risk of accidental hypothermia is al-

ways high, especially in persons during long-term exposure to cold environment or unprotected individuals in wet-cold conditions.

Exposure to severe cold induces rapid changes in thermoregulatory processes that lead to the increase in heat conservation and production. Hypothermia develops when heat loss surpasses these two processes. Heat conduction is the greatest in wet conditions, therefore, maintenance of normal body temperature is a critical problem for subjects immersed in cold water. In such environment, hypothermia may occur very quickly and is especially dangerous. Disturbances of motor co-ordination and attenuation of muscle power accompanying thermoregulatory system failure makes execution of survival activities difficult if not impossible [20, 28].

Whereas several rewarming techniques are available [7, 13], methods of delaying the onset of hypothermia are still uncertain. Numerous animal and human studies have aimed at finding methods enhancing cold tolerance by modifying the thermoregulatory response to cold. Various diets, hormones, pharmacological treatments, physical exercise regimens and repeated exposures to cold air or cold water have been applied [43, 59].

Studies investigating mechanisms of cold adaptation confirmed the possibility of cold acclimatization in humans [25, 40, 45, 66]. Three different patterns of human cold adaptation: metabolic, hypothermic and insulative have been reported. In the first mode of reaction to cold, metabolic heat production is greater in adapted individuals. In the hypothermic type during exposure to cold stress, metabolic heat production is reduced and core temperature is lower in adapted subjects comparing to non-adapted ones. The insulative pattern of cold adaptation is characterized by little or no increase in metabolic heat production and lowered skin temperature, thereby the thermal gradient between the skin and environment is reduced, favoring less heat loss to the environment. It was demonstrated that repeated immersions in cold water produced mainly this type of cold adaptation in humans [66].

Knowledge from these studies is of great benefit for the improvement of human physical and psychosomatic efficiency in cold environment but there is still great need to develop the complex methods of effective protection against rapid hypothermia that could be used for example by rescue parties.

Promising results have been obtained in animal and human studies by pharmacological enhancement of thermogenesis with ephedrine, a non-selective  $\beta$ -adrenergic receptor agonist and methylxantines (e.g. caffeine), adenosine antagonists and phosphodiesterase inhibitors, [11, 12, 34, 38, 56, 60, 62, 63]. These drugs, known to be thermogenic when tested in thermoneutral conditions [3, 5, 55], significantly increased energy expenditure and produced warmer body temperatures in subjects exposed to cold air, especially after concomitant administration. [56, 60]. Considering the possibility of increased risk of adverse reactions or abuse potential involved in prolonged taking ephedrine alone or in combination with caffeine [16, 50], the adverse events accompanying acute dosing are mild and transient [17, 27] and it seems that a single administration of these drugs in combination, es-

pecially in life-threatening conditions, is reasonable and rather safe.

On the basis of studies mentioned above, the aim of our investigations was testing the possibility of enhancement of homeostatic processes that protect against excessive body cooling by using a mixture of ephedrine and caffeine in humans immersed in cold water. We wanted also to study the influence of these drugs on thermoregulatory and metabolic response of subjects previously submitted to cold acclimation procedure by repeated brief cold-water immersions. Taking into account not only thermogenic but also psycho-stimulating properties of these drugs we estimated their influence on cognitive functions of subjects under stressful conditions.

## Materials and Methods

### Subjects

Fifteen healthy, male volunteers, aged 18–25, were chosen for the experiments. Their physical characteristics: age, height, weight, percent body fat and body mass index (BMI) are shown in Table 1. Percent body fat was calculated from values of skin-fold thickness measured with caliper (Holtain Tanner, UK) over four areas: triceps, biceps, sub-scapular and supra-iliac. The nature, purpose and possible risk of the study were carefully explained to each subject before he gave his consent to participate. Prior to the experiment, the volunteers were subjected to the general medical examinations as well as to the selected laboratory tests. Throughout the course of experiments the subjects were under permanent medical surveillance. The Human Ethics Committee of the Military Institute of Aviation Medicine approved the experimental protocol.

Tab. 1. Subject characteristics

	Mean $\pm$ SE
Height (cm)	181.36 $\pm$ 1.72
Weight (kg)	84.85 $\pm$ 2.98
BMI	25.76 $\pm$ 0.78
Body fat (%)	15.72 $\pm$ 0.87

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## Experimental protocol

Subjects reported to the laboratory 1 h before immersion. They refrained from drugs, alcohol, caffeine and smoking for 24 h and from food 8 h before the tests. An indwelling catheter (18 gauge, Becton Dickinson) was inserted into their right antecubital vein for blood sampling. They were instrumented with rectal probe and two chest electrodes for temperature and ECG monitoring, respectively. The experiments were performed in research pool measuring 1.6 m × 1.6 m × 1.1 m (depth). Water was kept at a stable temperature (12.0 ± 0.1°C). After instrumentation was completed blood sample and baseline measurements were taken. Then subjects dressed in bathing trunks were immersed in water in sitting position to the shoulder level except their right upper extremity for collecting blood samples. Rectal temperature was monitored continuously and recorded every 5 min.

Subjects divided in three groups (n = 5) underwent two 45-min immersions – control (CI) and test (TI) immersion, separated at least by one week interval. In the groups II and III, before the TI, subjects were submitted to the cold acclimation trial (CAT, five 10-min immersions, one per day) one week after the CI. Thirty minutes before CI or TI, the subjects from the groups I and III ingested placebo or ephedrine (FarmImpex, Poland) 1mg/kg and caffeine (Merck, Germany) 2.5 mg/kg dissolved in 50 ml of water, respectively. Subjects from the group II received placebo before both immersions. After cold exposures subjects were rewarmed using warming blankets.

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## Measurements

### Temperature

T<sub>re</sub> was monitored by thermistor probe inserted 10 cm past the anal sphincter. It was continuously recorded (Ellab, Denmark) during immersion and data were collected at five-minute intervals. The immersion was terminated when the subjects' rectal temperature had fallen to 34.5°C.

### Biochemical parameters

Blood samples of 15 ml were drawn before, during (at 20 minutes) and just at the end of immersion. In CAT

blood samples were taken on the first and the last day before and after immersion. Blood samples were centrifuged to separate the plasma. Plasma samples were frozen at -70°C and then assayed for adrenaline (ADR), noradrenaline (NDR), cortisol (COR), free fatty acids (FFA), glycerol (GLY), and glucose (GLU) in CI and TI. In CAT plasma samples were assayed for ADR, NDR and COR. Catecholamine concentrations were determined with high-performance liquid chromatography with electrochemical detection (Antec Leyden, DECADE). FFA and GLY were estimated spectrophotometrically ( $\lambda = 546$  nm and  $\lambda = 340$  nm, respectively) by enzymatic method using Roche Diagnostics GmbH and R-Biopharm GmbH tests. Plasma COR level was determined using fluorescence polarization immunoassay (FPIA, TDX SLX Abbott).

### Cognitive performance tests

Cognitive functions of the subjects were tested by means of instruments evaluating simple visual perception, reaction times, short-term and working memory. These tests were carried out before and after control and test immersions. In CAT choice reaction time and Vanderplas-type figures comparison test was performed on the first and the fifth day.

#### Choice reaction time and Vanderplas-type figures comparison test

The test described by Szatkowska et al. [52] consisted of presentations of the Vanderplas-type figures [61]. The stimuli were displayed in pairs on a computer monitor for 100 msec, one after another. The first stimulus appeared either 2 degrees to the left or 2 degrees to the right from the central fixation point. The second stimulus appeared 500 ms later exactly at the central fixation point. The subject's task was to decide whether the second stimulus was smaller, bigger, or of the same size as the first one, choice was made by pressing one of the three buttons. The figures used in the study had two different shapes and four different sizes; figures presented as a pair always had the same shape and either the same or different sizes. The order of trials in a series was pseudorandom: the same relation between the size of stimuli that created the pair (the same, smaller or bigger) could not be repeated more than three times in a row. Also, the first stimulus of a pair could not appear in the same visual field more than three times in a row. Two different param-

ters were recorded: (1) the accuracy score, reflected by the number of incorrect responses in all the experimental trials and (2) the speed of reaction, reflected by the average choice reaction time.

The short-term and working memory tests (the digits span test – a part of the Wechsler's battery)

In these tests [64] subjects were exposed to the increasing amount of information and, by repeating what they heard, they indicated how much of the information was immediately remembered. In the short-term memory test, immediate repetition of digits (forward span) is required. In the working memory test, the order of digits in a sequence must be reversed, i.e. the last digit in a sequence is repeated as the first one (reversed span). In the present study, two trials were performed for each span length; the length

of the digit sequences in the forward span ranged from three to eight, in the reversed span – from two to seven. The examiner pronounced the digits once per second.

### Statistics

Significant differences between the studied groups were determined by analysis of variance for repeated measures (Statistica for Windows package) and *post-hoc* Newman-Keuls test. Data are reported as the mean values  $\pm$  SE. Significance was accepted at  $p < 0.05$ .

## Results

Beside slight heart rate acceleration, there were no adverse effects after a single application of drugs at the studied doses.

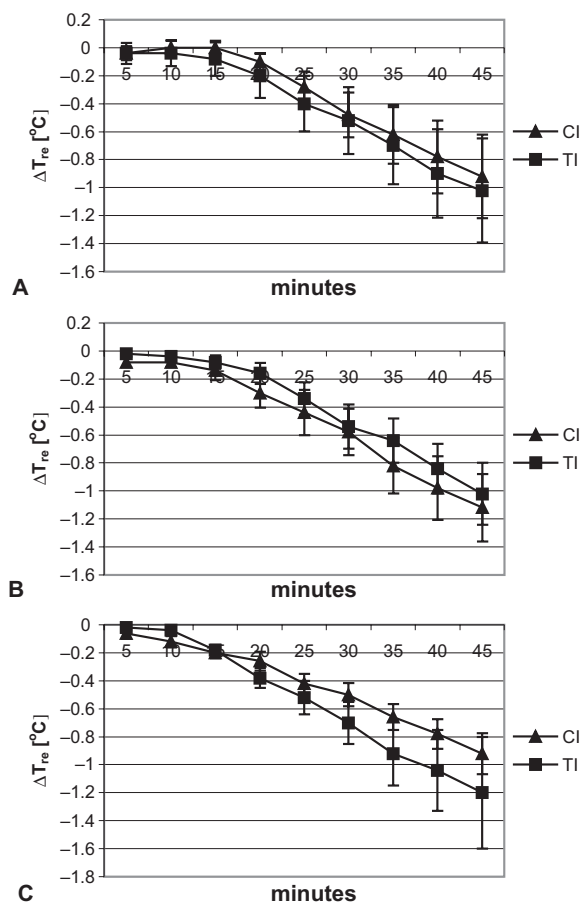
### Rectal temperature

The mean decrease in  $T_{re}$  during TI did not significantly differ in comparison to CI in all three studied groups of subjects. The mean  $T_{re}$  drop at 45 minutes of immersion during CI was:  $0.92^{\circ}\text{C} \pm 0.29$ ;  $1.12^{\circ}\text{C} \pm 0.24$ ;  $0.93^{\circ}\text{C} \pm 0.24$ , and during TI:  $1.02^{\circ}\text{C} \pm 0.37$ ;  $1.02^{\circ}\text{C} \pm 0.22$ ;  $1.2^{\circ}\text{C} \pm 0.33$  in the group I, II and III, respectively (Fig. 1). There were no significant differences in subjects'  $T_{re}$  between the first and the fifth day of CAT.

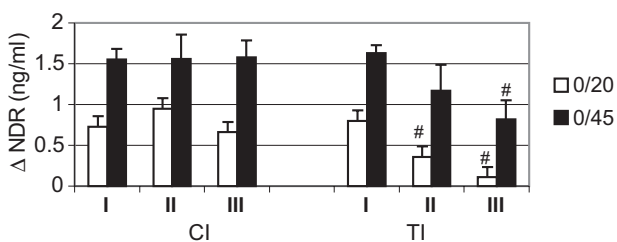
### Biochemical parameters

#### Catecholamines

Significant changes in catecholamine concentrations between TI and CI concerned only NDR. In both groups after cold acclimation, the increment of plasma NDR was lower than during CI. In the group II, it was lower by 68.8% ( $p < 0.05$ ) at 20 minutes and by 24.6% lower (n.s.) at 45 of TI, whereas in the treated group (III) it was lower by 85.8% ( $p < 0.01$ ) and 117%; ( $p < 0.05$ ) at 20 and 45 minutes, respectively (Fig. 2).



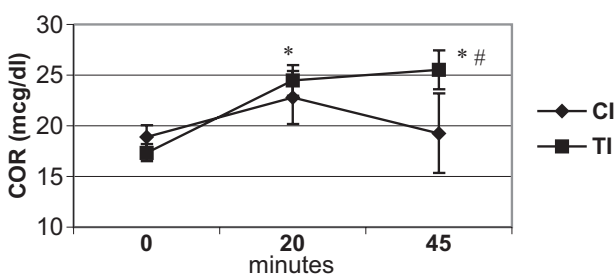
**Fig. 1.** Rectal temperature drop ( $\Delta T_{re}$ ) during control (CI) and test (TI) immersion in the group I (A, non-adapted with drugs), II (B, cold-adapted without drugs) and III (C, cold-adapted with drugs). Values are presented as the mean  $\pm$  SE



**Fig. 2.** Changes in plasma noradrenaline (NDR) during control (CI) and test (TI) immersion in the group I (non-adapted with drugs), II (cold-adapted without drugs) and III (cold-adapted with drugs). Values are presented as the mean  $\pm$  SE. # – statistically significant difference between CI and TI in  $\Delta$  values (difference between pre-immersion value and values of measurements at 20 or 45 min of immersion)

### Cortisol

Immersion in cold water induced insignificant increase in plasma COR level. Application of the drugs induced higher increase in COR level both in non-adapted and in adapted subjects, however, significant changes in comparison to CI were observed only in the group I at 45 minutes of TI ( $p < 0.05$ ). During TI plasma COR concentrations increased by 40% ( $p < 0.01$ ) and by 50% ( $p < 0.01$ ) the baseline values at 20 and 45 min, respectively (Fig. 3). CAT resulted in insignificant



**Fig. 3.** Plasma cortisol (COR) concentrations during control (CI) and test (TI) immersion in the group I (non-adapted with drugs). Values are presented as the mean  $\pm$  SE. \* – statistically significant to pre-immersion value; # – statistically significant difference between CI and TI

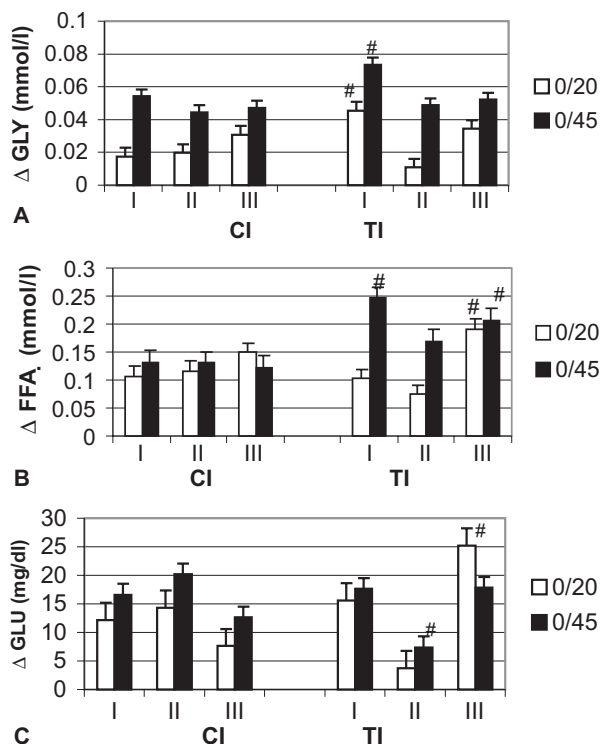
decrease in COR level both before and after immersion on the last day in comparison with the first day (group II and III). The level of COR during TI was insignificantly lower than in CI in the group II, whereas the application of drugs in the group III slightly increased COR level (by 23% the baseline), therefore, it was similar in both immersions.

### Glycerol and free fatty acids

Significant changes in GLY concentration was observed only in the group I, and the increment of GLY during TI was higher by 45% ( $p < 0.05$ ) and 46% ( $p < 0.05$ ) at 20 and 45 min than during CI, respectively (Fig. 4A). Comparison between CI and TI revealed significantly higher increase in FFA after the drugs application in the group I (by 51.2%;  $p < 0.05$ ) and III (by 81.3%;  $p < 0.05$ ) after 45 min of TI. Furthermore, in the group III significantly higher increase in FFA was observed already after 20 min of immersion (by 57.6%;  $p < 0.05$ ), (Fig. 4B).

### Glucose

The drug mixture caused significantly higher increase in GLU level only in adapted subjects (by 22.7% at 20 minutes;  $p < 0.05$ ) during TI (group III), whereas in non-acclimated ones changes in GLU did not significantly differ (group I). In the group II, the increase in



**Fig. 4.** Changes in plasma: (A) – glycerol (GLY), (B) – free fatty acids (FFA), and (C) – glucose (GLU), during control (CI) and test (TI) immersion in the group I (non-adapted with drugs), II (cold-adapted without drugs) and III (cold-adapted with drugs). Values are presented as the mean  $\pm$  SE; # – statistically significant difference between CI and TI in  $\Delta$  values (difference between pre-immersion value and values of measurements at 20 or 45 min of immersion)

GLU level was significantly lower (by 15% after 45 min,  $p < 0.05$ ) than during CI (Fig. 4C).

#### Cognitive performance tests

The results of cognitive performance tests revealed that immersion in cold water with or without the drug mixture did not influence significantly subjects' scores in memory tests in respective groups. There were no significant changes in choice reaction times after CI. Application of drugs in non-adapted subjects shortened the choice reaction times after TI in comparison to CI ( $0.69 \pm 0.03$  vs.  $0.82 \pm 0.06$ ;  $p < 0.05$ ). The number of incorrect responses in the Vanderplas-type figures comparison test was significantly lower in the group I after TI in comparison to CI ( $12.6 \pm 1.8$  vs.  $21.2 \pm 5$ ;  $p < 0.05$ ), while in remaining groups the differences were insignificant.

## Discussion

During cold water immersion large conductive heat transfer from the body surface causes that compensatory mechanisms offsetting heat loss, which despite being more pronounced than in equivalent air temperatures [54], are often insufficient to maintain core temperature. The advantage from thermogenic properties of ephedrine and methylxantines, especially their metabolic synergism was taken to investigate the possibilities of enhancing cold tolerance in humans. In studies of Vallerand et al. [56] ephedrine and caffeine used at the same doses as in the present study, improved cold tolerance and produced warmer rectal and mean body temperatures in volunteers exposed to cold air. The mechanism of improved cold tolerance by these drugs was related rather to greater heat production but not greater heat conservation, as the heat loss after drugs was similar to the placebo condition. The results of the present study have shown that ingestion of ephedrine and caffeine by subjects immersed in cold water enhanced metabolic response manifested by higher elevation of energy substrates in comparison to the values during control immersion without drugs. Unfortunately, this reaction was not accompanied by warmer  $T_{re}$ . However, subjective estimate of perceiving less severe cold after drugs, may

be due to the less intense shivering as was reported by volunteers (not estimated).

Acute exposure to cold triggers stimulation of metabolic rate through shivering thermogenesis to prevent hypothermia. It is well documented that carbohydrates and lipids are the main fuel for shivering skeletal muscles. It has been established that plasma free fatty acid oxidation and turnover, peripheral glucose uptake and muscle glycogen utilization are greatly enhanced during cold exposure [17–19, 41, 42, 57, 58]. Experimental conditions in our study induced significant elevation of FFA, GLY and plasma GLU concentrations. The increase in plasma lipids was markedly higher than plasma GLU, what is in line with previous data reporting that exposure to wet-cold is preferentially connected with elevation of plasma FFA [42, 53]. Data from studies in humans exposed for 2 h to 10°C with liquid conditioned suit reported that 50% of total heat production was fuelled by lipids [19].

Application of drugs to non-adapted subjects induced higher increment of plasma FFA and GLY, instead it did not influence significantly GLU concentration comparing to control immersion. Elevation of plasma lipids as energy substrates after ephedrine and methylxantines, either after separate or concomitant administration, was observed by many authors in various studies [14, 39, 56, 58]. This lipolytic activity of ephedrine and caffeine appears to be related to the enhanced release of catecholamines and stimulation of sympathetic nervous system [10, 49]. Caffeine through inhibition in cAMP phosphodiesterase and increase in cellular cAMP can lead to prolongation of the effect of sympathetic stimulation [33], and this way may enhance thermogenic effect of ephedrine. Animal studies have shown that caffeine up-regulates expression of uncoupling proteins, key molecules related to thermoregulation [29]. In addition, other studies provided evidence that FFA are not only energy substrates but also activators of uncoupling processes [23].

Data from animal studies reported the increased responsiveness of adipose tissue to catecholamines and other lipolytic hormones (glucagon, ACTH) after cold adaptation [29, 31, 48]. In our study, the level of FFA and GLY in the subjects after cold adaptation was higher than in control immersion, but not significantly. Ingestion of drugs increased metabolic response both in subjects non-adapted to wet-cold stress and those submitted to CAT, but in the latter group energy substrate mobilization was considerably greater and faster. In this group the elevation of plasma FFA

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was markedly higher in both measurements, whereas in the non-adapted subjects the increase in FFA was significantly higher only at the end of immersion. Contrary to non-adapted subjects, the increment of plasma GLU was also significantly higher during immersion after drugs. These results confirm observations from animal studies reporting enhanced metabolic response due to more marked accelerated oxidation of plasma FFA during NDR infusion in cold-acclimated than in control rats [44]. NDR also significantly stronger increased glucagon and glucocorticosteroids level in cold-acclimated rats [31]. Probably, these thermogenic factors, at least partly stimulated by NDR, enhance metabolic rate through accelerated utilization of energy substrates such as FFA and glucose. However, infusion of NDR in three volunteers after ten-day cold-acclimation did not induce non-shivering thermogenesis [9].

Activation of sympatho-adrenal response, especially fast increment of plasma catecholamines due to cold exposure is a well-known reaction both from animal and human studies [2, 24, 32]. Cold adaptation usually leads to its attenuation [35, 47]. Similar results were obtained in our research after five repeated brief bouts in cold water. It has been previously shown that habituated response can be apparent even after few immersions in cold water [4, 25, 40]. The employed adaptation protocol induced a degree of habituation of physiological response to cold in our subjects. It was expressed through markedly lower levels of plasma NDR and GLU during test immersion. NDR level was increasing more slowly and at 20 min of immersion the increment was lower by 68% than during control immersion. The increase in plasma ADR and COR concentrations were also lower, but not significantly.

Application of drugs to acclimated subjects evoked even lesser elevation of plasma catecholamines, especially NDR, which was lower by 85.5 and 117% at 20 and 45 min of test immersion, respectively. It has been suggested that repeated activation of sympathetic nerves during cold adaptation lead to decline in NDR release [6]. It could be possible that additional sympathetic stimulation by drugs was responsible for lower increase in catecholamine level in adapted subjects, though ephedrine and caffeine are known to evoke just opposite effects [4, 14, 38]. The drop of rectal temperature was slightly higher in the group III in comparison with the two other groups, what might be related to the lowest NDR level. Positive correlation between plasma NDR concentrations and core

temperature, shown in previous studies could explain our results [26, 40].

It is known that many stressful situations are accompanied by an increase in plasma COR concentration. Data from studies investigating the influence of cold stress on human adrenal response are inconsistent. There exist results showing either the increment [21, 22] or the drop [60] of COR level, and no changes in some research [40, 51]. It seems that it depends on various experimental conditions. Under conditions of our study, cold stress induced slight, insignificant increment of COR level. Application of drugs produced significantly higher increase in COR level in non-adapted subjects. It has been shown that caffeine in connection with stressful conditions evoked elevation of COR level [1]. In acclimated subjects after drugs, the average increment of COR level was similar as during CI, whereas the increase in COR level was lower in non-treated group after CAT.

Cognitive performance in humans exposed to cold stress has been shown to be disturbed [46]. Psychostimulants like caffeine or ephedrine are known to improve psychomotor functions in various stress conditions [30, 36, 37], therefore we attempted to estimate the effect of these drugs in cold-exposed subject applying cognitive and memory tests. The results of these tests revealed only slight beneficial effect of ephedrine and caffeine on psychomotor tasks (choice reaction times and number of incorrect responses). Application of drugs did not influence scores in memory test in both groups.

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## Conclusions

Summing up, a single application of ephedrine-caffeine mixture in humans under conditions of wet-cold stress did not influence rectal temperature significantly, but induced the enhancement of metabolic response, more pronounced in subjects after cold adaptation. Such treatment could probably serve as supporting factor in methods of protection against rapid hypothermia used by rescue parties or military troops, but further studies on this topic are needed to precisely estimate these effects.

### Acknowledgments:

This work was supported by the State Committee for Scientific Research (KBN) under Grant No 148247/C-T00/99. The authors thank volunteers for enduring all trials, and dr Andrzej Truszczyński and dr Jarosław Bogdański for medical supervision of experiments.

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**Received:**  
January 7, 2005; in revised form: April 20, 2006.