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# Effect of High-Altitude Ecological and Experimental Stresses on the Platelet-Vascular Wall System

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Ecological stress is typically observed not only among people working in Antarctica, but also among those working in high mountains in Kyrgyzstan [5,9]. In the mountains stress is induced by hypoxia, whose effect is heightened by cold. The neurohormonal indicator of high-altitude ecological stress (HES) is a twofold increase in the output of corticosteroids, the level of which returns to normal only after 30-45 days [4]. The stress is characterized by a hyperaggregation of platelets, which leads to an accumulation of thrombocytic (spontaneous) aggregates in the circulating blood and, eventually, to the occlusion of blood vessels [8]. Platelets resemble nerve cells, and are therefore convenient for testing the effect of ecological factors on the body and the pathophysiology of adaptation [10,11]. Prostacycline, an anticoagulant

of the blood vessel wall (endothelium), behaves as a "counter-system" [2] with respect to platelets. The platelet and the vascular wall form a single functional system (PVWS), and homeostasis between them prevents thrombogenesis of the blood [3]. Under normal ecological conditions thrombogenesis is often caused by epinephrine and epinephrine-induced cardionecrogenic stress (ECNS) [1].

The purpose of the present work is to study the effect of high-altitude ecological and experimental stresses on the platelet-vessel wall system in animals and man.

## MATERIALS AND METHODS

In experiments carried out on 64 white rats of both sexes weighing 200-250 g we determined the anticoagulant activity of the wall of the aorta (AAWA) [2,3,12], the index of spontaneous aggregation of platelets (SAP) [13], and the aggregation and disaggregation of platelets (AP and DP) [2]. The index of thrombophilia (TPh) was determined according to the formula  $(SAP/AAWA) \times 100$  arbi-

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trary units. The prostacycline reaction ( $\text{PGI}_2\text{-rx}$ ) of the blood vessels was determined in 48 shepherds of both sexes aged from 22 to 58 with the aid of a blood pressure cuff or by dosed occlusion of the peripheral vessels (DOPV) [6,8]; platelet aggregation and disaggregation were determined at the same time [2,3]. The magnitude of  $\text{PGI}_2\text{-rx}$  (in %) was calculated according to the formula  $[(I - II)/I] \times 100$ , where I is the control (sample prior to DOPV), and II the sample after DOPV [7]. The reciprocal hyperaggregation of platelets (RHP) was determined by calculating the percentage of cases of negative  $\text{PGI}_2\text{-rx}$  following DOPV from the total number of  $\text{PGI}_2$  reactions.

A study was made of the emotional-nervous stresses of social genesis experienced by the shepherds both in the plains (i.e., not in high mountains) while tending sheep during the breeding season under conditions of insufficient sleep and food, anxieties over epizootic diseases among the young animals, and so on; and in the mountains during the shearing season, a period often marked by conflicts between shepherds and shearers, lack of sleep, interpersonal conflicts during the mingling of herds in a limited area, and so on. The arterial blood pressure of the shepherds was measured by Korotkov's method, including the systolic ( $\text{AP}_s$ ), and diastolic ( $\text{AP}_d$ ), and the mean ( $\text{AP}_m$ ) pressure (mm Hg).  $\text{AP}_m$  was calculated according to Wetzler and Boger's formula:

$$\text{AP}_m = (\text{AP}_s - \text{AP}_d) \times 0.43 + \text{AP}_d.$$

By modifying this formula we determined the overall peripheral resistance of the vessels (OPRV):

$\text{OPRV} = (1/3)(\text{AP}_s \times \text{AP}_d) \times 0.43$ . The autonomic-vascular tonus (AVT) was calculated with account taken of OPRV:

$$\text{AVT} + (\text{OPRV})/(\text{PGI}_2\text{-rx} \times \text{DP}),$$

in arbitrary units (DP being disaggregation of platelets following DOPV). The vasodilative-anti-aggregation status (VAS) of the body was determined according to the formula:

$$\text{VAS} = (\text{PGI}_2\text{-rx})/\text{AP}_m, \text{ arb. units.}$$

The prostacycline-dependent coronary reserve of the heart ( $\text{PCR}_h$ ) was determined according to the formula:

$$\text{PCR}_h = [\text{DP} \times (\text{PGI}_2\text{-rx})]/100, \text{ arb. units.}$$

The "double product" (dp) - the clinical-physiological marker of the coronary reserve and of the heart rate (HR) - was determined according to the formula:

$$\text{dp} = (\text{AP}_s \times \text{HR})/100, \text{ arb. units.}$$

And lastly, the overall adaptation reserve of the cardiovascular system ( $\text{AR}_{\text{cvs}}$ ) was determined according to the formula:

$$\text{AR}_{\text{cvs}} = 100 - (\text{AVT} - \text{PCR}_h) + \text{VAS}, \text{ arb. units.}$$

Experimental adrenergic cardioneurogenic stress (ECNS) was modeled with the use of epinephrine in a dose of 2 mg/kg, and immobilization stress (IMS) was provoked by making the rats lie supine in a fixed position for 4, 8, and 16 hours.

"Pure" high-altitude ecological stresses in combination with experimental stresses were stud-

TABLE 1. Effect of Ecological and Experimental Stresses on the Platelet-Vascular Wall System

| Series, period of observation       | AAWA. %     | SAP index  | TPh index   |
|-------------------------------------|-------------|------------|-------------|
| HES at 2200 m + ECNS                |             |            |             |
| Urban ecology (760 m)               | 29.0±0.1    | 1.0±0.3    | 3.8±0.3     |
| 2nd day HES at 2200 m               | 6.1±1.0*    | 1.1±0.2*** | 1.6±0.1*    |
| 10th day at 2200 m                  | 4.4±0.6*    | 1.0±0.3*** | 2.2±0.1**   |
| 15th day HES at 2200 m              | 24.3±0.6*** | 1.4±0.3*** | 5.7±1.0**   |
| UE - 760 m + ECNS                   | 10.0±0.5    | 1.8±0.3    | 18.0±0.4    |
| 2nd day HES at 2200 m + ECNS        | 3.8±0.4*    | 1.7±0.3*** | 44.8±2.0*   |
| 10th day HES at 2200 m + ECNS       | 3.0±0.2*    | 1.7±0.4*** | 56.6±4.2*   |
| 15th day HES at 2200 m + CNS        | 5.9±1.1***  | 1.8±0.3*** | 30.5±2.3*   |
| HES at 2200 m + IMS                 |             |            |             |
| 10th day HES at 2200 m + IMS (4 h)  | 9.1±1.5     | 3.3±0.3    | 36.6±4.0    |
| 18th day HES at 2200 m + IMS (8 h)  | 8.2±1.8***  | 2.3±0.4*** | 26.5±3.0*   |
| 30th day HES at 2200 m + IMS (16 h) | 7.9±0.6***  | 2.2±0.4*** | 27.9±2.4*** |
| 30th day HES at 2200 m + IMS + ECNS | 6.2±0.3**   | 2.1±0.6*** | 33.8±1.6*** |
| HES at 3200 m + ECNS                |             |            |             |
| 15th day HES at 3200 m              | 19.4±1.0    | 1.3±0.4    | 6.8±1.0     |
| 15th day HES at 3200 m + ECNS       | 5.1±0.9*    | 1.6±0.3*** | 31.5±4.2*   |

Note: here and in Table 2: one asterisk indicates  $p < 0.01$ , two asterisks indicate  $p < 0.1$ , three asterisks indicate  $p < 0.5$ .

**TABLE 2.** Changes in the Platelet-Vascular Wall System (PVWS) among Shepherds Working in High Mountains During their Migration (3000–3500 m) as compared with Field-Crop Workers

| Series of observations  | AP, %       | DP, %       | $\frac{DP}{AP}$ | PGI <sub>2</sub> -rx, % | RHP, %     | $\frac{(PGI_2-rx)}{RHP}$ | PCR <sub>h</sub> | VAS         | AR <sub>ovs</sub> |
|---|-------------|-------------|-----------------|-------------------------|------------|--------------------------|------------------|-------------|-------------------|
| I. Field-crop workers (800 m)   | 46.03±3.0   | 52.8±2.0    | 1.1             | 31.0±2.0                | 13.3±2.0   | 2.2                      | 26.3±3.1         | 34.0±2.3    | 36.3±2.5          |
| II. Shepherds working in high mountains (3000–3500 m) after their descent to the plain (800 m)            | 49.2±2.0*** | 42.5±1.0**  | 1.2             | 36.6±4.0***             | 8.6±0.5*** | 4.2                      | 25.6±2.0***      | 40.0±3.5*   | 49.8±3.2*         |
| III. Shepherds working in high mountains after their ascent and monthly readaptation to 3000–3500 m       | 42.5±4.0*** | 44.0±6.0*** | 1.0             | 40.4±4.0**              | 21.4±2.0** | 1.8                      | 30.0±2.5***      | 43.0±5.0**  | 36.0±4***         |
| IV. Shepherds working in high mountains after monthly readaptation (after being exposed to social stress) | 24.3±5*     | 30.4±7.0*   | 1.2             | 24.3±2.0**              | 13.3±1.0*  | 1.8                      | 19.1±2.3*        | 11.2±2.3*   | 77.4±5.0*         |
| V. Shepherds working in high mountains during rest (1600 m)   | 25.0±5*     | 43.0±3.1*** | 1.6             | 31.0±4.0***             | 33.0±4*    | 0.9                      | 27.9±5.0***      | 31.0±2.0*** | 30.5±4.2***       |

ied on rats under conditions corresponding to altitudes of 2200 m and 3200 m above sea level (Chunkurchak and Muster). Social stresses during the sheep breeding season were studied at an altitude of 800 m above sea level and during the shearing season at an altitude of 3000 m above sea level.

## RESULTS

In rats under conditions corresponding to the plains (800 m above sea level) AAWA was 29%, SAP was 1.0, and the AAWA/SAP ratio was 3.4 (Table 1). ECNS, which is lethal in itself, caused the death of animals in 30% of the cases, while among the rats that survived there was a sharp decrease in AAWA and an increase in the SAP index, i.e., an increase in the thrombogenic potential of the blood. The other type of stress, IMS, also lowered AAWA considerably with an increase in the SAP and TPh indices, but without causing death.

Table 1 shows the changes in PVWS that were due solely to ecological factors. At 2200 m, in the emergency phase of adaptation (from the 2nd to the 10th day), AAWA decreased somewhat, but without an increase of the SAP and TPh indices. By the 15th day, when the ecological adaptation began, AAWA returned to normal. However, this did not prevent mortality when HES (at 2200 m) was combined with ECNS, that is, with "lethal" stress; at a level of mortality corresponding to 14.5% of the experimental rats AAWA decreased sharply and the SAP and TPh indices increased (Table 1).

HES at 2200 m for 4.8 hours in combination with IMS for 16 hours had no lethal effect; this is also true at a higher level of AAWA (1.4 times higher) than in the case of ECNS. Ecological adaptation notably reduced the stress level. This is seen in the fact that on the 15th day of IMS (for 16 hours) HES proved to be more benign than in the earlier periods of adaptation (on the 10th and 18th day) with a shorter exposure (4 and 8 hours, respectively). HES at 3200 m, caused by more pronounced hypoxia than HES at 2200 m, within a brief period of adaptation (15 days) was marked by a relatively low level of prostacycline synthetase activity (19.4 as against 24.3%) of the vascular wall. At the same time, ECNS caused a sharp decrease in the initial AAWA (by 73.6%, or as much as at 2200 m. The SAP and TPh indices showed a similar pattern. Thus, within the range of 2200 m to 3200 m there was definitely an adaptive recovery of the disrupted homeostasis of PVWS during HES, and PVWS was again disrupted following ECNS.

In contrast to the animals, each year it took the shepherds a long time (up to 6–7 months) to become adapted to HES at an altitude of 3000 m and higher. This left a deep "structural imprint" on PVWS. As is shown in Table 2, among the shepherds of group II, after they had descended from the mountains (3000–3500 m) to the plain, where they were exposed to stress of a social origin during the sheep breeding season, the magnitude of PGI<sub>2</sub>-rx remained great and the frequency of RHP was low. However, the vasodilative-anti-aggregation status (VAS) remained high, and the magnitude of PGI<sub>2</sub>-rx, on which the coronary

reserve of the heart depends, increased nearly two-fold. When, in summer, the shepherds of group III again became adapted to HES at 3000-3500 m, the coronary reserve of the heart increased still more through adaptation.

Within a month  $PCR_h$  and VAS reached the level corresponding to the high-altitude ecological level. However, among another group of shepherds (group IV), who had readapted to HES at 3000-3500 m, but who were exposed to social stress at shearing time, the effect of adaptation was nullified:  $PGI_2$ -rx decreased, RHP increased, and  $PCR_h$  and VAS decreased. In other words, the attained anticoagulant potential of the blood declined as there took place a maximal mobilization not only of the prostacycline-dependent coronary reserve, but also of all the adaptational reserves of the cardiovascular system ( $AR_{cvs}$ ). Among the shepherds (groups V and II), who rested at sanatorium situated at 1600 m above sea level, with social stress absent, VAS and  $AR_{cvs}$  increased (Table 2).

Thus, acute experimental stresses, reproduced under conditions of HES at 2000 m and 3200 m above sea level, led to a sharp disruption of platelet function (hyperaggregation and hypodisaggregation) and of the vascular wall function (a decrease in the anticoagulant potential). On the other hand, among the shepherds experiencing prolonged and repeated adaptation to HES (at 3000 and 3500 m) PVWS became stable in relation to both natural (high-altitude ecological) and social stress.

The basis of the resistance of the PVWS to natural-ecological and social-ecological stress consists of the following: social protection of shep-

herds working in high mountains, who are provided access to sanatorium in mountains situated at an average altitude of 1600 m; the stability of PVWS with respect to any type of stress due to living and working in the mountains; and the adaptational reserve of the cardiovascular system. A combination of all these factors is a typical feature in the life of people of Kyrgyzstan, and especially of its mountain shepherds.

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