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Original article

Influence of +Gz exposure on serum biochemical and hematological parameters

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Background: Exposure to high +Gz provoke a unique physiological stress and various potential harmful effects in humans. Despite the importance of monitoring physical alterations related to +Gz exposure, there have been only a few studies concerning the physical status of human centrifuge trainees.

Objective: We investigated alterations in serum biochemical and complete blood count parameters occurring in subjects exposed to high +Gz.

Methods: One hundred fifty eight flight-naive subjects (group A), who had never experienced flight or centrifuge training, and 80 experienced jet fighter pilots (group B) were exposed to +6Gz and +7.3Gz, respectively. Blood samples were obtained before and immediately after the centrifuge runs.

Results: In group A, creatine phosphokinase (CPK) was increased from a mean of 136.56±17.87 IU/L pre-run to 236.33±23.71 IU/L post-run, a significant 73.1% increase. In 26 of 158 (16.5%) group A subjects, CPK was elevated over 400 IU/L, with a maximum of 1904 IU/L. Δ CPK of group A (99.77±16.94 IU/L) was significantly greater than that of group B (0.53±5.67 IU/L). In addition, Δvalues of total protein, white blood cell count, red blood cell count, hemoglobin, and hematocrit of group A were significantly greater than those of group B.

Conclusion: We demonstrated that the extent of post-centrifuge CPK elevation and hemoconcentration was significantly greater in flight-naive subjects than in experienced jet fight pilots. Our data raise the possibility that the level of experience in flight and centrifuge training can affect the extent of +Gz-induced alterations in blood constituents.

Keywords: Complete blood count, flight experience, human centrifuge training, serum chemistry, +Gz acceleration

The new generation of fighter aircraft is becoming more complex at the same time as flight operations are increasingly performed over longer distances, for longer durations, and across multiple time zones. Furthermore, the workload imposed on pilots has increased considerably. During flight, pilots must be able to assimilate and manage heavy loads of information in a timely and efficient manner. Aviation actually subjects pilots to a number of stressors, including dynamic workload, heat, vibration, noise, low pressure, physical exertion, and the various effects of gravitational (G) force. Particularly, modern jet fighter aircraft is capable of achieving G force profiles that subject pilots to extremely high inertial forces in the head-to-foot direction (+Gz). Severe physical stress is imposed by the environment of rapid-onset, high-sustained +Gz in which the aircraft operate. Numerous investigations of human responses to +Gz have demonstrated many physiologic changes, including changes in cerebral blood flow, coronary blood flow, renal blood flow, endocrine reactions, and cardiovascular reflexes [1-5].

Current efforts in aviation medicine to enhance tolerance to +Gz have included human centrifuge training [6]. The performance of anti-G straining maneuver (AGSM) on the human centrifuge has proven effective in enhancing +Gz tolerance. The human centrifuge simulates +Gz akin to that encountered in aircraft, which helps pilots to learn the correct skills of practicing the AGSM under a more realistic high +Gz environment and maintaining their situational awareness and performance skills. However, inevitably, the physical stress caused by centrifugation is nearly the same as that during actual

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flight. Exposure to high +Gz provokes a wide range of unique pathophysiological stress, including interruption in arterial blood flow to the brain, elevation of heart rate and blood pressure through activation of sympathetic nervous system, ventilation-perfusion mismatch with reduction in lung compliance and increase in the serum levels of epinephrine, norepinephrine and cortisol. Furthermore, the various potential harmful effects, including loss of consciousness, cardiac dysrhythmia, atelectasis, mechanical visceral injury, and musculoskeletal symptoms have been documented in the centrifuge studies. In this regard, it is very important to examine and monitor the physical status of trainees exposed to +Gz, both before and after the centrifugation.

Every national military aviation organization has a system of monitoring the health status of pilots. These systems rely on periodical medical examinations in order to maintain good health in aircrew members. They endeavor to detect clinical disease and subclinical conditions as early as possible. They are used as tools in risk assessment and management. Routine blood testing is affordable, convenient, and informative. Most physicians are familiar with the notion that a routine serum biochemical and hematological testing may identify unsuspected subtherapeutic or toxic drug levels, subclinical biochemical conditions, or hematological deterioration. Pilots of the Republic of Korea Air Force are examined medically by flight surgeons on a yearly basis, and they undergo periodical routine blood testing.

Despite the importance of monitoring pathophysiological alterations related to +Gz exposure, there have been only a few studies concerning the pre- and post-run physical status of centrifuge trainees and, particularly, investigating the influence of +Gz exposure on the serum biochemical and hematological parameters. The aim of the present study was to investigate alterations in the serum biochemical and complete blood count (CBC) parameters occurring in subjects exposed to +Gz on the human centrifuge, and to further determine whether the experiences in flight and training affected the extent of observed alterations in blood constituents.

Materials and methods

Subjects

The subjects consisted of 158 flight-naive subjects (rank, second lieutenant; median age, 24 years; group A) who had never experienced flight or centrifuge training and 80 experienced jet fighter pilots (rank, first lieutenant or captain; median age, 29 years; group B) who had taken high-G centrifuge training periodically. Before the centrifuge runs, all subjects were examined by flight surgeons. The subjects were healthy without cardiovascular problems, and none of them took medication. The Institutional Review Board at the Aerospace Medical Center, Republic of Korea Air Force approved the study protocol in advance. Each subject provided written informed consent before participating in the present study.

Human centrifuge tests

The centrifuge tests were carried out on the computer-controlled human centrifuge located in the Aerospace Medical Training Center, Aerospace Medical Center, Republic of Korea Air Force. The gondola of the centrifuge was equipped with two-way audio and a one-way video communication system. The back of the gondola seat was reclined 13 degrees from the vertical. Baseline +Gz (+1.4Gz) was attained in 5 seconds and was the immediate start point for all subsequent +Gz excursions within a profile. All subjects were exposed to a single +Gz acceleration, without anti-G suit. Acceleration exposure was rapid onset of 1 G/s to +6Gz (for group A) or +7.3Gz (for group B), with peak G force sustained for 30 seconds.

Hematological and serum biochemical tests

Pre-run samples of blood were drawn into collection tubes containing lithium heparin or ethylenediaminetetraacetic acid 15 minutes before the centrifugation by venipuncture of the antecubital vein of the arm. Immediately after the centrifugation, additional post-run samples were taken from the opposite arm. The serum biochemical and hematological analyses were carried out in the Department of Pathology, Aerospace Medical Research Center, Aerospace Medical Center, Republic of Korea Air Force, using standard commercial reagent kits. Blood for biochemical analyses was allowed to clot at room temperature for 45 minutes, and then centrifuged at 2000 rpm for 10 minutes to separate the serum from the cells. A clinical chemistry autoanalyzer (Olympus AU 400; Olympus Corporation, Tokyo, Japan) was used to perform standard biochemical profiles on the serum samples, including amylase, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), aspartate

aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (γ-GGT), uric acid, total protein, blood urea nitrogen (BUN), creatinine, total bilirubin, direct bilirubin, calcium and inorganic phosphate. An automated hematology analyzer (Sysmex SE 9000; Sysmex Corporation, Kobe, Japan) was used to measure CBC parameters, including white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin (Hgb), hematocrit (Hct) and platelets. The subjects who developed symptoms after the centrifugation or showed abnormal laboratory findings were re-examined by flight surgeons and, if necessary, additional medical evaluations were performed.

Statistical analyses

The laboratory results are presented as the mean and standard error of mean (SEM). A paired t-test was performed to determine if there was a significant difference in the mean value of each parameter between pre- and post-run. An independent t-test was also performed to determine if there was a significant difference between the extent of post-run alteration (Δ value) of groups A and B. Statistical analyses were performed using SPSS ver. 15.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as a p value of less than 0.05.

Results

Table 1 shows the pre- and post-run values of serum biochemical and CBC parameters. In all subjects, the pre-run values of all 14 biochemical and five CBC parameters were within normal range. In group A, 15 of 19 parameters, except AST, BUN, total bilirubin, and direct bilirubin, showed significant differences between the pre- and post-run values. The serum amylase increased from a mean of 45.79±1.21 IU/L to 56.54±1.42 IU/L, a significant increase of 23.5% (p <0.001). The serum LDH and CPK also increased from a mean of 153.81±1.94 IU/L and 136.56±17.87 IU/L to 175.91±2.08 IU/L and 236.33±23.71 IU/L, respectively, with significant elevations of 14.4% (p <0.001) and 73.1% (p <0.001). In addition, total protein (9.2%, p <0.001) and all CBC parameters, including WBC count (59.3%, p <0.001), RBC count (7.2%, p <0.001), Hgb (5.9%, p <0.001), Hct (9.3%, p <0.001) and platelet count (10.4%, p <0.001), increased significantly after the centrifugation. However, despite significant elevations, the post-run values of all parameters, except CPK, did not exceed the upper limit of the normal range. The post-run CPK increased over 400 IU/L in 26 of 158 (16.5%) group A subjects, with a maximum of 1904 IU/L; these subjects reported mild myalgia of the lower extremities immediately after the centrifugation but no cardiac symptoms including discomfort, heaviness or pain in the chest and breathing difficulties. Auscultation of the heart and lungs revealed no significant differences between pre- and post-run condition. No abnormality was visible on chest roentgenography, and no evidence of dysrhythmia was detected on electrocardiography.

In group B, the difference between the pre- and post-run values was significant in 12 of 19 parameters, except CPK, ALT, γ-GTP, uric acid, BUN, total bilirubin, and direct bilirubin. The serum amylase (17.6%, p = 0.001) and LDH (11.4%, p <0.001), WBC count (38.2%, p <0.001), RBC count (4.0%, p <0.001), Hgb (2.0%, p <0.001), Hct (5.1%, p <0.001) and platelet count (8.7%, p <0.001) increased significantly after the centrifugation. The post-run values of all parameters were below the upper limit of the normal range. In contrast to that of group A, the serum CPK of group B scarcely increased after the centrifugation (0.4%, p = 0.926), and the maximum post-run CPK (268 IU/L) did not exceed the upper limit of the normal range.

Table 2 shows +Gz-induced Δ values of serum biochemical and CBC parameters. Δ CPK, Δ total protein (**Figure 1**), Δ WBC count, Δ RBC count, Δ Hgb and Δ Hct (**Figure 2**) of Group A were significantly greater than those of Group B. Particularly, Δ CPK was 99.77±16.94 IU/L and 0.53±5.67 IU/L in Groups A and B, respectively (p <0.001). Δ amylase, Δ LDH and Δ platelet count of Group A were greater than those of Group B, but the differences were not statistically significant.

Discussion

Some previous studies have reported an increased serum level of CPK during +Gz exposure, and suggested intense muscular exertion to be the cause for CPK elevation [7, 8]. Gillingham et al. [8] demonstrated that the CPK rose 24 hours after the centrifugation, but no myocardial (MB) CPK isoenzyme was found in the serum taken from the subjects exposed to +Gz. Burns [7] showed that straining to tolerate +Gz increased the serum level of skeletal muscle (MM) CPK isoenzyme. CPK-MM increased considerably because of the muscle straining during AGSM, but no CPK-MB was observed in the

Table 1. Influence of +Gz exposure on serum biochemistry and complete blood count

	Group A				Group B			
	Pre-centrifuge	Post-centrifuge		*p*-value	Pre-centrifuge	Post-centrifuge		*p*-value
		Mean±SEM	Max.			Mean±SEM	Max.	
Amylase (IU/L)	45.79±1.21	56.54±1.42	131	<0.001*	49.23±1.57	57.91±1.61	98	0.001*
LDH (IU/L)	153.81±1.94	175.91±2.08	255	<0.001*	150.14±2.59	167.29±2.78	248	<0.001*
CPK (IU/L)	136.56±17.87	236.33±23.71	1904	<0.001*	143.68±9.60	144.20±7.43	268	0.926
AST (IU/L)	23.44±0.68	24.97±0.97	101	0.122	22.15±0.65	24.48±0.91	73	0.004*
ALT (IU/L)	22.52±0.94	25.76±1.75	152	0.048*	24.60±1.52	27.14±2.07	144	0.132
γ-GTP (IU/L)	22.01±0.76	25.56±0.85	105	<0.001*	26.99±1.90	28.45±2.10	134	0.183
Uric acid (mg/dL)	5.90±0.08	5.53±0.10	8.5	0.001*	5.91±0.14	5.80±0.13	8.5	0.302
Total protein (g/dL)	7.41±0.02	8.09±0.03	8.9	<0.001*	7.63±0.04	7.98±0.04	8.9	<0.001*
BUN (mg/dL)	12.02±0.20	11.64±0.16	16.0	0.117	13.71±0.29	13.88±0.30	20.4	0.626
Creatinine (mg/dL)	1.11±0.01	1.13±0.01	1.4	0.023*	1.09±0.01	1.14±0.02	1.5	0.001*
Total bilirubin (mg/dL)	0.86±0.03	0.83±0.02	1.4	0.230	0.90±0.04	0.88±0.04	1.3	0.428
Direct bilirubin (mg/dL)	0.143±0.01	0.13±0.01	0.4	0.382	0.19±0.01	0.18±0.01	0.4	0.376
Calcium (mg/dL)	9.57±0.02	9.79±0.03	11.0	<0.001*	9.60±0.04	9.75±0.03	10.6	0.006*
Phosphate (mg/dL)	3.73±0.03	3.46±0.05	5.8	<0.001*	3.40±0.05	3.09±0.05	4.0	<0.001*
WBC count ($\times 10^3/\mu L$)	6.31±0.09	10.05±0.14	13.9	<0.001*	6.47±0.17	8.94±0.17	12.7	<0.001*
RBC count ($\times 10^6/\mu L$)	5.01±0.03	5.37±0.02	6.0	<0.001*	5.06±0.03	5.26±0.03	6.0	<0.001*
Hgb (g/dL)	15.53±0.09	16.45±0.07	18.5	<0.001*	16.11±0.10	16.44±0.10	18.6	<0.001*
Hct (%)	44.76±0.22	48.94±0.20	54.7	<0.001*	45.69±0.26	48.01±0.27	53.4	<0.001*
Platelet count ($\times 10^3/\mu L$)	241.91±3.37	267.09±3.92	432	<0.001*	241.20±4.41	262.18±4.86	424	<0.001*

*Statistically significant

Table 2. Intergroup differences in Δ value of serum biochemistry and complete blood count

	Group A	Group B	*p* value
Δ Amylase (IU/L)	10.75±1.86	8.69±1.61	0.441
Δ LDH (IU/L)	22.10±2.50	17.15±2.69	0.348
Δ CPK (IU/L)	99.77±16.94	0.53±5.67	<0.001*
Δ AST (IU/L)	1.53±0.98	2.33±0.78	0.524
Δ ALT (IU/L)	3.24±1.62	2.54±1.67	0.763
Δ γ-GTP (IU/L)	3.56±0.64	1.46±1.09	0.080
Δ Uric acid (mg/dL)	-0.37±0.11	-0.11±0.10	0.090
Δ Total protein (g/dL)	0.68±0.03	0.35±0.04	<0.001*
Δ BUN (mg/dL)	-0.38±0.24	0.17±0.34	0.191
Δ Creatinine (mg/dL)	0.03±0.01	0.05±0.15	0.206
Δ Total bilirubin (mg/dL)	-0.03±0.03	-0.02±0.04	0.462
Δ Direct bilirubin (mg/dL)	-0.01±0.01	-0.01±0.01	0.811
Δ Calcium (mg/dL)	0.22±0.03	0.15±0.04	0.224
Δ Phosphate (mg/dL)	-0.27±0.05	-0.31±0.06	0.614
Δ WBC count ($\times 10^3/\mu L$)	3.74±0.16	2.47±0.13	<0.001*
Δ RBC count ($\times 10^6/\mu L$)	0.36±0.03	0.20±0.02	<0.001*
Δ Hgb (g/dL)	0.92±0.09	0.33±0.06	<0.001*
Δ Hct (%)	4.18±0.26	2.33±0.18	<0.001*
Δ Platelet count ($\times 10^3/\mu L$)	25.18±4.79	20.98±2.56	0.440

*Statistically significant

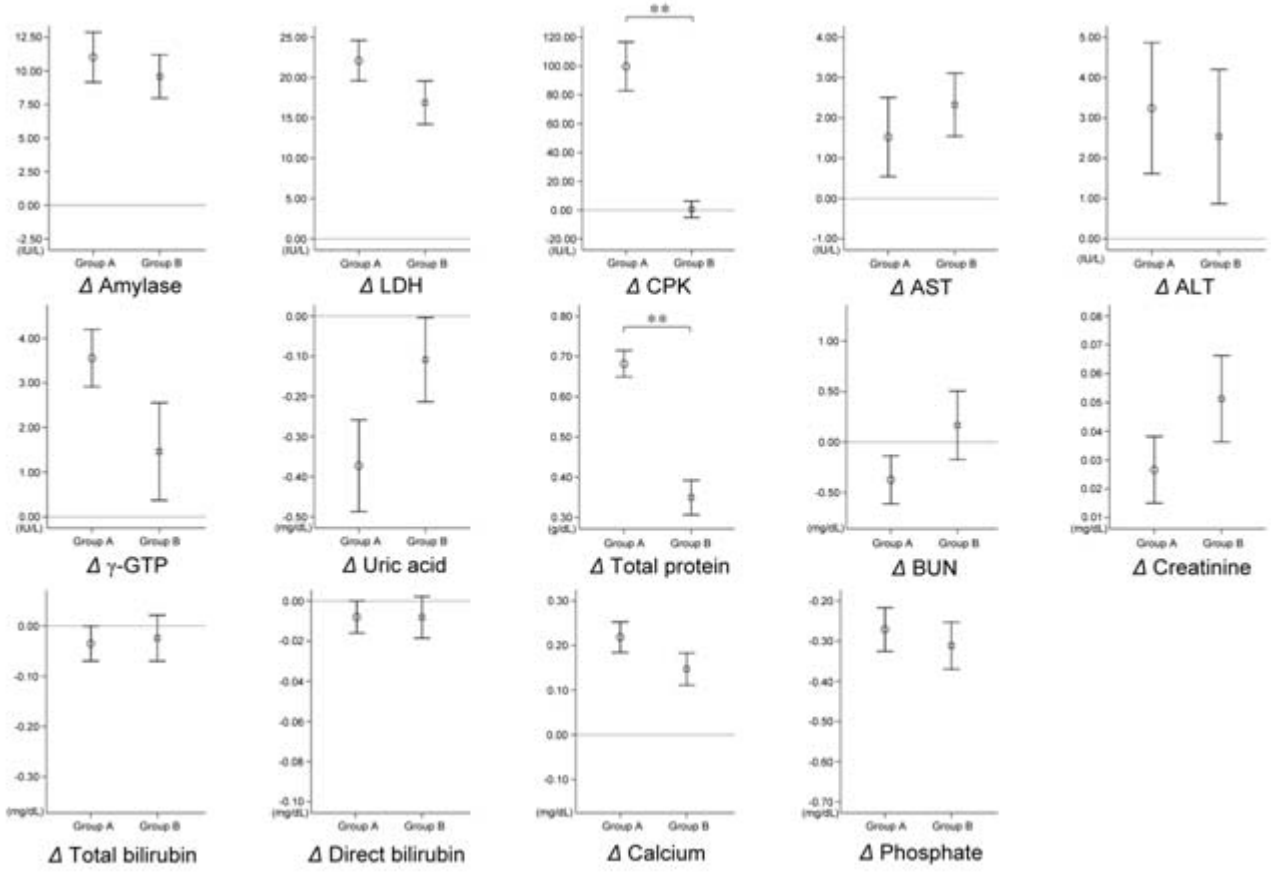

Figure 1. Δ value of serum biochemistry after high +Gz exposure. ***p* <0.001

Figure 2. Δ value of complete blood count after high +Gz exposure. ***p* <0.001

serum following the centrifugation. The level of required muscular exercise coupled with the absence of large increases in CPK-MB implies that elevation of CPK during +Gz exposure was due to enhanced permeability of skeletal muscle cell membranes and not to myocardial injury. Consistent with these data, we demonstrated that the serum CPK level was significantly elevated after +Gz exposure up to nearly 2000 IU/L. Heavy muscular exertion was required in the present study for successful performance of the tracking task and maintenance of consciousness by the subjects at high +Gz. They were encouraged to perform the AGSM, which requires isometric contraction of the muscles in the abdomen and lower extremities. Even though we did not specifically determine the serum level of CPK-MB, the absence of cardiac symptoms and pathological changes in the auscultatory findings, chest roentgenography, and electrocardiography strongly suggest that elevation of the CPK level was due to intense muscular activity related to the AGSM rather than myocardial damage.

We further demonstrated that Δ CPK amounted to nearly 100 IU/L in flight-naive subjects, in contrast to less than 1 IU/L in experienced jet fighter pilots. Generally, the activity of serum enzymes increases more with exercise in the untrained than the trained [9]. Stansible et al. [10] reported that the lesser rise in CPK level in a physically well-trained person was attributable to the capability to maintain cell membrane stability and ionic gradients effectively and to retain a high level of the intracellular adenosine triphosphates. Based on this, it is reasonable to assume that the greater Δ CPK in jet fighter pilots in the present study was partly attributable to their accumulated experiences in flight and centrifuge training. In other words, jet fighter pilots are exposed to rapid-onset, high-sustained +Gz during routine flight operations. Furthermore, they are required to attend a regular high-G centrifuge training program to reinforce the proper performance of the AGSM and to make the correct performance an automatic skill. In this case, skeletal muscles may have more capability to adapt in response to +Gz stress. In contrast, flight-naive, untrained subjects might have difficulty in performing the AGSM effectively during their first exposure to high +Gz. Our findings raise the possibility of an association between +Gz-induced Δ CPK and the level of experiences in flight and training.

CPK level is widely used to measure muscle injury at different settings. However, it was well documented that it CPK usually peaks 24 to 48 hour after stressful events. For example, it has been shown that CPK level rose near 900 IU/L 24 hour after Rugby games, which are associated with the gravitational force and heavy collisions, as well as extensive running [11, 12]. In another study, basic military training led up to about 6 times elevation of CPK level, from 223 IU/L to 1,226 IU/L [13]. Kim et al. [14] reported that plasma CPK was increased at 10 km of the marathon race and up to 3-fold at the end of the race, and this was further increased during the first 24 hour, only returning to pre-race level after 6 days. Although in the present study change in CPK level, even significant, was still within the physiological range, the possibility cannot be excluded that CPK level may further increase during certain period of time after centrifugation. We are currently investigating serial alteration in biochemical parameters associated with +Gz exposure.

Serum amylase, often along with lipase, helps diagnose and monitor acute pancreatitis and other disorders that may involve the pancreas. In their study using murine pancreatic ischemia-reperfusion model, Dembinski et al. [15] demonstrated that temporary partial ischemia followed by reperfusion induced acute hemorrhagic and necrotizing pancreatitis with a

significant increase in the serum level of amylase. Hoffmann et al. [16] indicated that ischemia-reperfusion of the pancreas induced pancreatic microvascular failure and inflammatory reaction. Gullo et al. [17] also showed a significant association between an increase in the serum amylase level and the duration of aortic clamping-induced ischemia, suggesting that acinar cell injury is a constant consequence of pancreatic ischemia. In the present study, the serum amylase level increased significantly after +Gz exposure. Based on the finding that exposure to +Gz caused decrease in blood flow to the visceral organs including the pancreas [18], we speculated that +Gz exposure on the centrifuge might induce transient pancreatic ischemia. Exposure to high +Gz with duration of 30 s might decrease blood flow to the pancreas, and cessation of the centrifugation might lead to rapid recovery of blood flow. A series of steps including transient ischemia and reperfusion would cause a certain amount of damage on the pancreatic acini. However, our finding that the post-run amylase level was within normal range indicates that pancreatic tissue damage due to +Gz-induced ischemia-reperfusion was not as great as that of acute pancreatitis, which elevates the amylase to 4 to 6 times higher than the upper limit of the normal range. In addition to the change in blood flow, the sympathetic nervous system has also been shown to play a role in modulating pancreatic enzyme secretion. Joehl et al. [19] observed that the physiological sympathetic nerve discharge of norepinephrine enhanced amylase release from dispersed pancreatic acini. Physiological responses to centrifuge training or any unusual G exposure elicit an immediate fight-or-flight response with increased serum levels of epinephrine, norepinephrine and cortisol [20]. These data support the notion that activation of the sympathetic nervous system during the centrifugation increased the release of pancreatic amylase into the bloodstream. Further studies are necessary to clarify the precise mechanism by which the serum amylase level increases during +Gz exposure.

We demonstrated a significant increase in total protein level, WBC count, RBC count, Hgb and Hct after +Gz exposure. This finding is consistent with previous data showing +Gz-induced hemoconcentration [2, 7, 21, 22]. Greenleaf et al. [22] observed a significant increase in Hct, along with a decrease in plasma volume, after the centrifugation. Similarly, Van Beaumont et al. [21] revealed that +Gz-induced elevation in total protein level, albumin level and Hct accompanied plasma volume loss. Taken together, we considered that heavy muscular exertion during the AGSM could be one of the causes of hemoconcentration. Hemoconcentration caused by physical exercise can be attributed to three things. First, with the onset of exercise, there is an almost immediate loss of plasma from the blood to the interstitial fluid space. Increased blood pressure causes an increase in vascular permeability and hydrostatic pressure in the capillaries thus forcing plasma from vasculature to interstitial compartment. Second, as metabolic waste products rise in the active muscles, intramuscular osmotic pressure increases and this draws fluid out of the capillaries to the muscles. Third, sympathetic-mediated splenic contraction induces hemoconcentration [23, 24]. Splenic contraction is observed in conditions of increased sympathetic activity, such as exercise and physical restraint [25, 26]. In addition, the blood cell content of the spleen alters depending on pressure in the splenic veins or the intra-abdominal pressure. Intense muscular straining and increase in intra-abdominal pressure, both of which are essential to the performance of AGSM, might involve, partly at least, elevation of CBC parameters. In addition, similar to the pattern of Δ CPK, Δ total protein and Δ CBC of flight-naive subjects were significantly higher than those of experienced jet fighter pilots. This finding is in line with the observation of Burns et al. [7] that an increase in total protein level and Hct was significant in the first +Gz exposure, but became very small during subsequent exposures. These data raise the possibility that alterations in the blood constituents, including serum protein, CBC and plasma volume, could reflect the extent of physiological adaptation in response to +Gz stress.

The results of the present study need to be tempered against their limitations. First, the subjects were screened to be otherwise young and healthy. Therefore, they may not be representative of all aircrews. The generalizability of our data to medically compromised subjects remains unknown. Second, no untreated control group of pilots was available for comparison purposes to better understand the current alterations of values. Third, the human centrifuge training programs of our institution include an elementary course (+6Gz) for flight-naive, beginning pilots and a supplementary course (+7.3Gz and +9Gz) for highly-trained, deeply-experienced jet fighter pilots;

this was the reason why the intensity of +Gz was not constant. It is noteworthy, however, that in flight-naive pilots, a much greater extent of biochemical and hematological changes were observed despite the exposure to the smaller +Gz. Further investigations of large numbers of subjects with exposure to a constant +Gz are necessary to confirm our results.

Conclusion

We demonstrated that the serum biochemical and hematological parameters are significantly altered during high +Gz exposure. We also demonstrated that the extent of alteration in the serum CPK level and hemoconcentration was significantly greater in flight-naive subjects than in experienced jet fight pilots. Our data raise the possibility that the level of experiences in flight and G-training can affect the extent of alterations in blood constituents during high +Gz exposure.

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