STATE RESEARCH CENTER OF RUSSIAN FEDERATION –
INSTITUTE FOR BIOMEDICAL PROBLEMS

REPORT

«RESULTS OF STUDIES OF THE EFFECTS OF SPACE FLIGHT FACTORS ON HUMAN PHYSIOLOGICAL SYSTEMS AND PSYCHOLOGICAL STATUS, AND SUGGESTIONS OF FUTURE COLLABORATIVE ACTIVITIES BETWEEN THE NSBRI AND THE IBMP»

Section 3. Muscles

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(The work is made in accordance with the Contract Amendment No. 1 from December 23, 1999 between the National Space Biomedical Research Institute (NSBRI), Houston, Texas, USA and the State Research Center of Russian Federation – Institute for Biomedical Problems (SRC RF - IBMP)

Moscow 2000

EFFECTS OF SPACE FLIGHT FACTORS ON MUSCULAR SYSTEM

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1. Introduction

Muscular system, which controls all the motor activity of the human body, both dynamic and static, is one of the primary targets of microgravity. Microgravity conditions substantially alter both integral properties of the muscular system and individual muscle groups (muscle strength, performance at the various motor regimes), as well as elementary muscular characteristics (tone, volume of the contractile apparatus, energy potential, and autonomous supply of muscular work).

Study of the aforementioned alterations, as a rule, utilizes two main approaches:

Generally, main microgravity phenomena, related to the muscular system, their dynamics, intensity, interrelationship with each other, and with alterations in physiological systems, are studied in human subjects and animals under conditions of actual weightlessness, utilizing various methodologies. Similar investigations are frequently carried out using ground-based simulations of microgravity. It is seldom possible to perform in-flight studies, aimed at revealing physiological and cellular mechanisms of muscle plasticity under conditions of altered gravitational environment, because of the difficulties in obtaining enough material, in standardization of experimental conditions, for reasons of in-flight security and fitness of the cosmonauts, lack of research and medical aid on board of spaceships. It is also important to remember, that actual microgravity affects muscular system in a complex manner, its effects being realized in human muscular system by a number of biochemical factors (see later).

Mechanisms of microgravity effects on skeletal musculature are usually studied in ground-based simulation experiments, where, along with a number of favorable conditions, exists a possibility for individual, comparative analysis of the various biomechanical factors of weightlessness.

Utilization of those main approaches is characteristic for the Russian researchers, as well as for the researchers of the other countries. Specific features of the Russian methodology are based on participation in a number of complex in-flight and ground-based large scale projects (long-term missions to space orbital stations, biosatellite missions, complex head down tilt bed rest, immersion, and other studies). Russian researchers are comparatively less involved in laboratory rodent studies; nevertheless, those studies have also served to reveal a number of consistent patterns of gravity-dependent mechanisms in the muscular system.

2. Force-velocity properties

2.1. Postflight data

Decrease in the contractile and endurance properties of the muscular apparatus is a constant effect of microgravity. A number of pre- and postflight examinations of "Soyuz" space missions revealed that in 12 cosmonauts, tested on the second day after landing, 2 – 5 day exposure to weightlessness have induced considerable alterations in contractile properties of the skeletal muscles, their intensity varying in different muscle groups. Strength of trunk extensors, and of hand flexors was evaluated by means of torso and hand dynamometers; endurance was evaluated by amplitude changes in the reflex EMG response of m. quadriceps femoris (calf extensor) after the cosmonauts performed 5 min bicycle incremental test with a load of 600 – 1400 kgm/min. Postflight hand dynamometry has not revealed any alterations in strength of hand muscles, however, in all the cosmonauts (excluding one) strength of the trunk extensors was significantly decreased (table 1.): average decrease amounted to 13.7%, range of individual variability comprised –6.9% - -28% (3 cosmonauts) /52/.

Table 1.

Changes in torso strength, and in tonus of hip muscles in crew members from "Soyuz" space mission

Cosmonauts, NN	Spaceship	Flight duration	Transversal rigidity of m. quadriceps femoris	Torso force
1	Souz-3	91 h 51 min	-16	have not change
2	Souz-4	71h 14 min	-5	-28.5
3	Souz-5	72h 39 min	-8	-9.0
4	Souz-5	47h 39 min	-13	-12.9
5	Souz-5	47h 39 min	-10	+0.4
6	Souz-6	118h 42 min	-6	-28.4
7	Souz-6	118h 42 min	-11	-28.9
8	Souz-7	118h 41 min	-3	-6.9
9	Souz-7	118h 41 min	-7	-16.7
10	Souz-7	118h 41 min	-11	-10.0
11	Souz-8	118h 41 min	-10	-20.0
12	Souz-8	118h 41 min	-10	-9.1

In all the cosmonauts (excluding one) postflight 5 min incremental bicycle test was accompanied by considerable decrease in reflex EMG response of m. quadriceps femoris. Before the flight, post exercise decrease in response amplitude was either lacking (in 8 cosmonauts), or was small (4 cosmonauts). The authors think, that elevated electromyography (EMG) amplitude of the working muscles, which was strongly pronounced in all the cosmonauts at the 3rd min of test (average: postflight 165 μV against baseline 125 μV), and sharply decreased frequency characteristics of EMG during the last min of test, indicated increased muscle fatigue, i.e., decreased postflight muscle endurance. American investigators have also obtained similar data from one astronaut after the 9 day space flight, having revealed decreased muscle EMG efficiency, expressed as ratio between the integrated muscle EMG amplitude and muscle force output, as well as significant decrease in frequency characteristics of m. gastrocnemius by the end of 1 min sustained contraction test (50% from the maximal load) /17/. Those changes were not observed in hand muscles.

After the 18 day flight all the mentioned above phenomena were considerably more marked, and persisted for a longer period /17/. By the 3rd day postflight, decrease in torso strength in two crew member comprised 40 **kG** and 65 **kG**, reduction in hip and calf perimeters was very pronounced. Both indices returned to baseline level only by the 11th day postflight. Strength characteristics of hand muscles were not considerably altered, as after the short-term flights.

Results of the pioneer studies by L. I. Kakurin group were confirmed and developed by other authors, who utilized advanced methods, as well as involved more subjects (cosmonauts/astronauts). For instance, W.E. Thornton and G.A. Rummel studied strength in hand and knee extensors and flexors in crews of the three "Skylab" missions of 28, 59, and 84 day duration /133/. Strength was evaluated by isokinetic dynamometry at 45^0/s velocity. The results showed that during the first two flights, having applied bicycle and resistive training were used as countermeasures, force of knee extensors was considerable decreased (21%, and 28%, accordingly), loss for hip flexors was apparently less (13%, and 17%), and hand muscles revealed only insignificant changes. During the third, the longest flight, when cosmonauts performed daily 10 min locomotor exercises on a treadmill along with the aforementioned exercises, loss of strength in knee extensors and flexors did not exceed 10%, and maximal strength of hand muscles was even somewhat increased /66/.

Conventional isokinetic dynamometry studies of force-velocity properties in skeletal muscles after the short-term, and long-term "Salyut-6", "Salyut-7", and "Mir" missions, have produced convincing evidence of the acute phase in dynamics of force-velocity and endurance alterations in skeletal muscles on transition to weightlessness; of microgravity predominantly affecting leg and back muscular apparatus, and, especially, posture muscles; of reversibility of all that weightlessness-induced changes, and of corrective properties of in-flight countermeasures /28,31,65, 66,67,68,/.

Force-velocity properties of the ankle joint muscles: flexor- m. tibialis anterior (MTA), and extensor - m. triceps surae (MTS), were studied on the 2nd and 4th –5th day after landing in 11 crew members of the rendezvous missions, usually of 7 day duration. The study revealed significant ($p<0.01$) decrease in MTS strength in all the subjects over the whole range of test velocities, including isometric regime /68/. At all the velocities an average decrease comprised 20-30% from the baseline, excluding isometric regime, where decrease was less pronounced – about 15%. Along with that, MTA strength was not considerably altered at either of the test velocities, including isometric. Results of the strength study were confirmed by analysis of the ratio between the EMG amplitude and torque output, which revealed significant increase (by 1.5 – 2 times, $p<0.01$) of that ratio over the whole range of velocities, and in isometric regime in MTS, and lack of significant changes in MTA indices. Later, similar data were obtained from a larger group of subjects /67/, and in flights of longer duration /15,70/. After the long-term space flights muscular apparatus was evaluated by anthropometry method (measurement of the perimeters of extremities, and body weight), and by isokinetic dynamometry ("Cybex" dynamometer). In the course of dynamometry force-velocity properties of the calf, hip, and, in some cases, back and neck muscles were evaluated by torque and EMG of the working muscles at the high (180^0/s), medium (120^0/s), and low (60^0/s) velocities, and under isometric contraction. Muscle endurance was evaluated by the same indices, obtained during performing cyclic concentric movements up to fatigue at 120^0/s velocity.

Crew members of the 2nd and 3rd missions to "Salyut-6" orbital station of 140 and 175 day duration, accordingly /65/, had contractile properties of hip and calf muscles examined using "Miotest" method, developed by the Russian investigators. The method is based on evaluation of electromechanical efficiency coefficient, calculated as a ratio between the integrated EMG, and the value of the standard load. It is known, that relationship between muscle force output and EMG value is linear within a range of small loads (from 0 to 20% of the maximal voluntary contraction) /15/; and that decline in muscle contractile properties is characterized by increase in EMG caused by elevated number of involved motor units, increase in frequency, and in synchronization of their discharge at standard load. The test motor task was to perform a series of flexion with a given fixed amplitude. At the given amplitude the value of the selected standard load of movement comprised 8-12% from the maximal voluntary contraction (MVC).

The movements were performed in dynamic and static regimes. As the quantitative relationship between the EMG value and force output depends on the initial length of muscle, the tests were always performed in a supine position, with fixed adjacent joints of the extremity.

In crew members of the 2nd and 3rd missions to "Salyut-6" orbital station anthropometric measurements have not revealed marked alterations in muscular periphery , excluding atrophy of the long muscles of the back in the engineer (the 2nd mission, FE-2), and some atrophy of the broadest muscles of the back in both cosmonauts from the 3rd mission. Measurement of the perimeter of extremities, performed the 1st day postflight, revealed small decrease in calf circumference, however, those changes were not persistent: by the middle of the 3rd day in BI-3 calf circumferences were equal to the preflight value, and in commander (Cr-3) they were only 0.5 cm less than preflight. Together with the body weight values, which revealed slight weight loss in FE-2 and Cr-3, lack of changes in Cr-2, and even some increase in Cr-3, overall data have suggested that crew members of both missions did not have any considerable in-flight muscle loss. The same was correct for the large group of cosmonauts from four missions to “Salyut-6” orbital station /66/.

Along with that, physiological tests of muscular apparatus revealed consistent pattern in decrease of contractile properties of the individual muscular groups, characterized by extraordinary variability in comparison with that, observed in short-term flights. For instance, in both cosmonauts from the 3rd mission “Myotest” revealed twice increased postflight EMG cost of the standard muscular force output in group of ankle joint extensors in comparison with the preflight values. By the 6th – 11th day postflight that increase had reached its peak; it was mostly manifested under static regime, and persisted up to the end of observation. In both cosmonauts isokinetic dynamometry has revealed significant decrease of m. gastrocnemius strength characteristics, especially pronounced in the isometric and high velosity (180^0/s) regimes. In Cr the force deficit value was somewhat greater than in FE, and its compensation was slower: for the 8 postflight days his maximal force output has increased only by 5 –30%. In crew members of the 2nd mission changes in “Myotest” values were more variable; however, in that case, static test has also revealed significant increase in Cr-2 EMG cost of torque in m. gastrocnemius, which persisted for 42 days postflight.

Table 2.

Range of changes in force-velocity properties of calf muscles after “Soyuz-6” mission /66/

Parameters	2nd mission (140 days)		3rd mission (185 days)		4th mission (175 days)		5th mission (73 days)	
	Cr	FE	Cr	FE	Cr	FE	Cr	FE
Maximal force output (180^0/s)								
Flexors	Not measured		0	0	0	0	0	0
Extensors	Not measured		0	0	0	0	0	0

Maximal force output (60^0/s)								
Flexors	Not measured		0	0	-3	-2	-1	0
Extensors	Not measured		0	0	-2	0	-1	0
Duration of EMG discharge								
Flexors			+1	+2		+4	+2	+4
Extensors			+2	0		+2	+2	+5
Coefficient of EMG efficiency (F/IEMG)								
Extensors	-8		-1	-8	-4			

Comments: value for the 1st range: 25% of the maximal force output; for F/IEMG: 10% from the baseline value.

After the long-term space flight, force-velocity properties of calf muscle were decreased, however, intensity of changes considerably varied: from the total lack of changes (data from velocity isokinetic tests of the 5th mission crew), or even 50% increased indices (FE-3, the same regime), to sharp (50-70% from the baseline) decrease revealed by resistive test (Cr, 4th mission) (Table 2.). Decrease in the contractile properties was manifested not only by reduction in the amplitude of maximal force output, but, to a greater extent, by decreased (up to 80%) EMG efficiency coefficient, and by increased time to peak tension, evaluated by duration of the increment in agonist EMG. In FE-5 the latter index was increased by 100%, and by 125% for the calf flexor and extensor, accordingly.

Dynamometry tests of force-velocity properties of neck muscles, performed after the 18-day space flight, have revealed considerable (from 40% to 55%) decrease of the maximal force output over the whole range of velocities in both members of the 3rd mission.

Wide variability in force-velocity properties, revealed at the first stage of study in cosmonauts from the long-term missions to "Salyut-6" station, was later confirmed during subsequent examination of the large groups of cosmonauts from "Salyut-7" and "Mir" missions. The aforementioned material was presented in detail: data on 15 cosmonauts from 75 to 237 day long missions /70/, data on 25 and 29 cosmonauts from 60 to 366 day long missions /71, 69, accordingly/.

Schedule of investigations was analogous for all the studies, and comprised preflight tests, performed 45 and 5 days before launching, and postflight tests, performed on the 2nd-4th, 6th, 11th and 45th-72nd day after landing.

After long-term space flights changes in force-velocity characteristics of m. triceps surae varied from 50% decrease to 40% increase at velocity regimes, from –40% to +20% at resistive regimes, only at isometric (static) regime voluntary force was invariably decreased.

Another specific feature of the long-term space flight effects was that they extensively involved other muscular groups. In particular, tests, performed after the long-term space flights exposed, in a sense, paradoxical fact: force-velocity and endurance properties were more consistently decreased in knee flexors than in extensors.

The data processing results show that duration of weightlessness exposure could not be considered as a crucial factor, determining distribution and intensity of muscular disorders. That conclusion could be confirmed by data comparing changes in force-velocity properties in crew members from the 2nd and 3rd "Mir" missions. That data show that the least changes (and even some increase at velocity regimes) were found in participants of the longest (year long) flights, and the most marked changes were observed in the cosmonauts, who were exposed to weightlessness twice as less (160 days). Therefore, it is quite natural to assume that countermeasure training should be considered as deforming factor of the effects of weightlessness.

2.2. Inflight Investigations

Without doubt, postflight alterations in muscle functions reflect actual events on board of space vehicle. However, return to 1g environment, after achieving stable adaptation to microgravity conditions, may considerably distort picture of alterations, introducing new phenomena, related to acute readaptation processes. Thereby, it seems very important to perform direct in-flight studies of the muscular properties, along with pre- and postflight investigations. In 1988-95 such studies have been carried out within a framework of the joint Russian-Austrian investigation, utilizing isokinetic dynamometer "Motomir" (Fig.1). Ergometer, which was very compact for that type of devices, enabled highly accurate evaluation of force-velocity and endurance properties of the hand and leg muscles over the wide range of motor velocities: concentric, eccentric, and isometric, cyclic and acyclic, various amplitudes, velocities and force output (Table 3.). Automatic control, and specially developed hardware and software provided wide opportunities for standardization of investigations, as well as for registration of kinematic (angles, rates, torques), and EMG (EMG of agonist and antagonist muscles) characteristics of movements /4/.

Results of the study of 1 member from the 7 day rendezvous mission, and 9 members from the main mission (from 125 to 429 days) /5/ revealed main patterns of changes in contractile properties, induced by weightlessness, and confirmed earlier concept, based on the postflight tests, on existence of two pronounced phases in microgravity-induced changes of muscle properties: the first one, characterized by swift development, and relative independence of countermeasure, and later phase, fully manifested from the second and further months of flight, highly dependent on the level of physical countermeasures applied.

Contractile properties of leg extensors were decreased by 40% already by the 4th-7th day of flight (Fig. 2.). Contractile properties of flexors were also decreased, although intensity of changes was somewhat less (about 30% at the dynamic, and about 25% at static regimes). Decrease of strength was manifested both at eccentric, and at concentric regimes, in movements with the various amplitude at the various velocities, indicating decreased contractile properties in all the types of muscle fibers (Fig. 2.). Decrease in force-velocity properties, achieved by the end of the first day of flight, have persisted in all the cosmonauts from the long-term space flight for the further 30 days, in spite of the fact that from the 5th-10th day they have started complex of physical exercises, gradually increasing volume of loading (Fig. 2.).

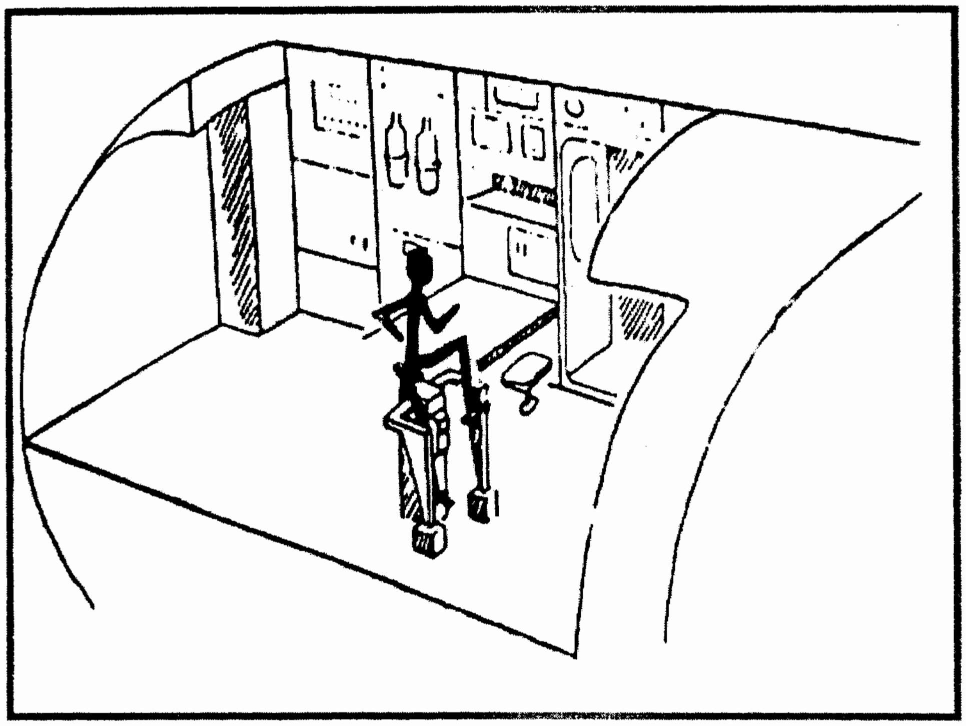


Fig.1 Leg exercise on MOTOMIR device

Table 3. Performance characteristics of Motomir program

Acyclic regime

Table 3a	Joint angle		Range of joint flexion		
Progr. 01 & 07	Isometric regime		Dynamics (eccentric regime)		
	Extension	Flexion	Extension	Flexion	Velocity
Contraction 1	90^0	90^0	90^0 - 110^0	90^0 - 20^0	0.15m/s
Contraction 2	60^0	60^0	60^0 - 110^0	60^0 - 20^0	0.15 m/s
Contraction 3	30^0	30^0	30^0 - 110^0	30^0 - 20^0	0.15 m/s
Table 3b					
Progr. 02 & 08	Isometria		Dynamics (eccentria)		
	Extension	Flexion	Extension	Flexion	Rate
Contraction 1	90^0	90^0	90^0 - 20^0	90^0 - 110^0	0.15m/s
Contraction 2	60^0	60^0	60^0 - 20^0	60^0 – 110^0	0.15 m/s
Contraction 3	30^0	30^0	30^0 - 20^0	30^0 - 110^0	0.15 m/s

Table 3c	Joint angle		Range of joint flexion		
Progr. 03 & 09	Isometric regime		Dynamics (eccentric regime)		
	Extension	Flexion	Extension	Flexion	Velocity
Contraction 1	20^0	110^0	$20^0 – 110^0$	$110^0 – 20^0$	0.15m/s
Contraction 2	20^0	110^0	$20^0 – 110^0$	$110^0 – 20^0$	0.30 m/s
Contraction 3	20^0	110^0	$20^0 - 110^0$	$110^0 - 20^0$	0.60 m/s

Table 3d	Joint angle		Range of joint flexion		
Prog. 04 & 10	Isometric regime		Dynamics (eccentric regime)		
	Extension	Flexion	Extension	Flexion	Rate
Contraction 1	110^0	20^0	$20^0 – 110^0$	$110^0 – 20^0$	0.15m/s
Contraction 2	110^0	20^0	$20^0 – 110^0$	$110^0 – 20^0$	0.30 m/s
Contraction 3	110^0	20^0	$20^0 - 110^0$	$110^0 - 20^0$	0.60 m/s

Cyclic regime

Table 3e		
Progr. 05 & 11	Range of joint flexion	
Intensity	Extensions & flexions, eccentric	Number of repetitions
30% MVC	$20^0 – 110^0$	30 ext. and 30 flx.
50% MVC	$20^0 – 110^0$	30 ext. and 30 flx.
80% MVC	$20^0 – 110^0$	30 ext. and 30 flx.

Table 3f		
Progr. 06 & 12	Range of joint flexion	
Intensity	Extensions & flexions, eccentric	Number of repetitions
30% MVC	$110^0 – 20^0$	30 ext. and 30 flx.
50% MVC	$110^0 – 20^0$	30 ext. and 30 flx.
80% MVC	$110^0 – 20^0$	30 ext. and 30 flx.

From the 2nd month of flight changes in force-velocity properties of leg muscle manifested a marked tendency to increase, and, as a rule, to stabilization at the certain, characteristic for the given individual level, with periodical fluctuations, directly reflecting fluctuations in level of applied physical exercises (Fig. 2.).

Lastly, at the final stage of flight, before landing part of examined cosmonauts demonstrated further increase in force-velocity properties, probably, reflecting increased level of physical exercises at that stage of flight (Fig. 2).

Rapid increase of strength indices, observed during the first days after landing, is a very interesting and representative fact. Independent of the duration of space mission, and of level of in-flight strength loss, for the first 3-5 days after landing strength indices increased considerably (by 15 –25%), indicating functional basis of the in-flight losses.

The described above dynamics was true for all the muscle groups of legs and hands, for flexors and extensors. However, at all the aforementioned stages of flight changes in strength characteristics were usually more marked in leg extensors, than in leg flexors, and in leg than in hand muscles in all 10 cosmonauts.

Data on the rate of peak tension development during acyclic hand exercise was most interesting, and fully agreed with the other postflight data. Rate of peak tension development, evaluated by its increment from 10% to 50% of the MVC, was markedly decreased in-flight in both muscle groups (more in extensors) (Fig. 2..). The same pattern was preserved during the early postflight period, when the force amplitude had, already, manifested tendency to normalization.

All the aforementioned data, obtained from a considerable number of the cosmonauts (and astronauts) in the course of in-flight, pre- and postflight studies, convincingly demonstrates the following:

- decrease in force-velocity and contractile properties of the skeletal muscles is a naturally determined consequence of exposure to weightlessness after the long-term and short-term space flights, as well;
- posture-tonic gradient determines intensity of changes in contractile properties, which are the most decreased in leg, neck, and, presumably, back muscles; in leg muscular apparatus the most intensive changes are found in ankle and hip joints (decline may amount to 60 – 70%), and least intensive - in hand muscles, where decrease in resistive properties is, usually, insignificant, or completely lacking;

- under weightlessness conditions, development of alterations in muscle properties has two pronounced phases: the first phase of acutely decreasing strength, which develops during the first days of flight, when loss can amount to 30 –40%; and later, slow phase, replacing or complementing the first one from the 3rd – 4th week of flight.
- during the acute phase, regular on board exercises do not have any notable corrective effect on muscle strength; during the slow phase, intensity of changes directly and closely correlates with the volume and intensity of applied exercises.

Thus, analysis of force-velocity characteristics in skeletal muscles of the cosmonauts enabled to make an assumption about the complex nature of decrease in contractile properties under microgravity conditions. That decrease may be induced by changes in the central nervous control of movement, as well as by changes in periphery unit of the neuromuscular system; contribution of each factor depending on duration of the exposure.

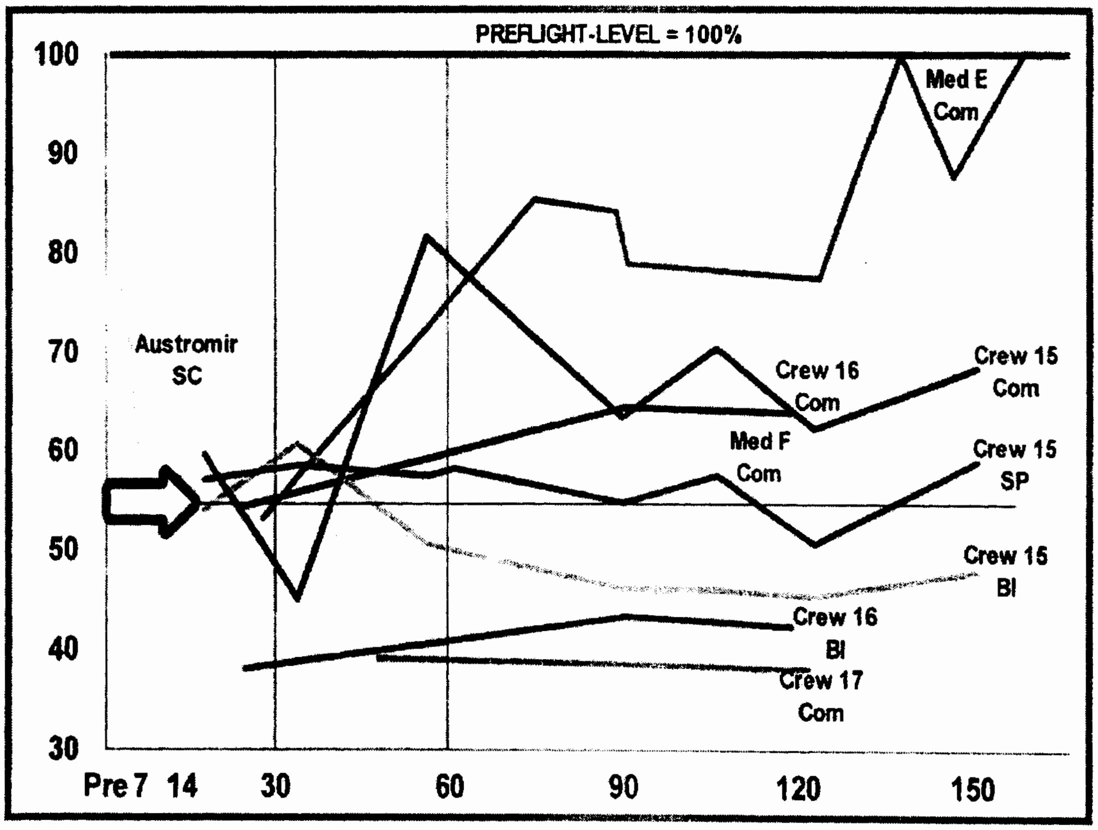


Fig. 2 Time-course of strength changes in leg extensors during flight (individual data).

2.3. Short-term effects. Immersion

Study of 12 volunteers, using isokinetic dynamometer "Cybex", showed that 7 day exposure to immersion environment was accompanied by considerable decrease in strength indices in m. triceps surae at all the regimes /32/. Decrease was highly significant over the whole range of velocities ($p< 0.01$) and, on the average, comprised 27 – 34%. Individual analysis showed high variability of losses: from –10% (in less than 10% of subjects) to 40% (in 20 – 40% of subjects at the various velocities). At all the test regimes maximal frequency of distribution (40 –50%) corresponded to 30% of losses, the most **homogenous losses** observed at isometric regime. In m. tibialis anterior, providing dorsal flexion of the foot, changes in strength characteristics did not exceed 10% at all the velocity regimes (except isometry). Only in isometric regime strength loss comprised up to 20 – 25%. Changes in strength properties of calf muscles were also manifested as altered ratio of mechanical and bioelectrical effects of tension: on the 1st day post-immersion the ratio between m. soleus EMG amplitude and muscle force output was significantly ($p < 0.01$) increased at all the test regimes. An increment comprised 50 – 80%, on the average, being relatively more pronounced at low velocity, and in isometric regimes. Indices of m. tibialis anterior were considerably changed only in isometric tests.

By the 3rd day after immersion strength characteristics of m. triceps surae were somewhat lower than the initial; they were completely restored only by the 5th day after immersion cessation. Similar data were obtained from the further studies, performed with more subjects. Considering the nature of previously revealed changes in antigravity muscle strength, the authors conclude that their genesis is not of muscular, but of neuroreflex origin. Authors think, that a number of facts are in favor of that concept, namely: rapidness and intensity of development, short period of correction after cessation of exposure (3 – 5 days), as well as specific pattern of changes, mostly marked in antigravity musculature, and at regimes, realized with considerable contribution of tonic motor units /67/.

That concept was directly confirmed by comparative analysis of voluntary contraction, and electrically evoked tension of m. triceps surae after the7 day immersion /59/. Applying tendometry method, the author studied amplitude and time parameters of the MVC of calf m. triceps surae, its maximal single (evoked by single electrical discharge), and tetanic (evoked by a series of a 2 min rhythmical electrical stimuli at 50 Hz) tensions. After 7-day immersion MVC strength was significantly ($p < 0.01$) decreased (by 18.9% on the average), along with lack of similar significant decrease in maximal force of evoked tensions, both single, and, especially, tetanic. After the 7-day immersion the value of strength deficit, calculated as the ratio between the difference in tetanic tension and voluntary contraction, and tetanic tension, increased from 26% to 45%, showing that decrease in maximal strength, observed after the short term exposure to microgravity, was related, mainly, to changes in innervation mechanisms of the contractile muscular apparatus, and not to changes in contractile muscular apparatus itself.

2.4 Long-term effects: head down tilt bed rest

Study of 14 volunteers showed that long-term (120 days) exposure to head down tilt (HDT) bed rest induce significant decrease in calf muscle strength over the whole range of velocities /31/. However, as was observed in in-flight studies, the greatest reduction in m. triceps surae strength was found at the isometric and low velocity regimes, the average loss amounting to 40%. At the higher velocities the losses did not exceed 30%, as a rule. Analysis of individual variety of changes showed that maximal losses fluctuated between 30% and 60%, individual reduction correlating with duration of rehabilitation period, which, in case of the given HDT bed rest, comprised 45 – 60 days in most subjects, and was independent of the initial level of the individual strength potential. Comparative analysis of the individual changes, obtained from HDT bed rest studies, and from space missions revealed considerably higher variability in members of the long term space missions (40 – 60% against 20 – 30%, accordingly).

In contrast to the effects of short-term exposures, strength characteristics of m. tibialis anterior (MTA) were also considerably reduced under HDT bed rest conditions. In that case, decrease of strength indices was relatively less, comprising about 35% in isometric regime, 30% at low and medium velocities, and 20% at high velocity. However, tendency to more intensive changes in resistive regimes, and less intensive at velocity regimes was preserved carried out on board of "Mir" orbital station /36/, changes **in** concentric and eccentric regimes did not differ considerably, and were somewhat **more marked in the former regime.**

Similar changes in force-velocity properties of knee extensors and flexors (-21%, and – 10%, accordingly) were observed in the course of 30 day -6^0 HDT bed rest in 11 subjects /18/. Reference data enables to study dynamics in muscle force-velocity properties, induced by HDT bed rest conditions, accurately enough. Seven day exposure was not accompanied by considerable changes in maximal concentric strength of knee flexors and extensors in 11 subjects; the only marked effect being significant increase in muscle fatigability ($p< 0.05$) /18/. After 14 day HDT bed rest, the authors have observed reduction in force-velocity properties of calf muscles, manifested in m. triceps surae predominantly **in** resistive and isometric regimes; changes not exceeding 15 – 20%, on the average. Finally, monthly dynamics of changes in force-velocity potential of calf extensors was followed in 9 subjects in the course of 120 day HDT bed rest /30/. The dynamics was characterized by gradually incrementing changes, especially marked from the 60th to the 120th day of HDT bed rest. If during the first and the second month of exposure decrease in force-velocity properties was approximately similar, comprising 20% on the average (thus, it was not considerably different from changes, observed in the course of 14 day HDT bed rest, see above). By the 90th day of exposure the decrease amounted to 26%, and by the 120th – to 37% from the initial level. During the first months of exposure variability of changes was extremely wide: from –5% to –30%, then by the 4th month variability was considerably less. Similar to other long-term HDT bed rest studies, after the 120th day of exposure changes in force-velocity properties were the most intensive in isometric and resistive regimes, comprising –42.7 ± 6.7%, and –36.3 ± 3.5%, accordingly.

Efficiency of 4 various regimes of physical training (PhT) was compared in 8 volunteers. During the first month of HDT bed rest was revealed high tolerance to PhT in changes of force-velocity properties: during that period decrease in force-velocity properties was greater in group, applying PhT, than in control group, on the average, comprising 26% against 20%, accordingly. The further efficiency of PhT was steadily increasing, and by the 120th day, reduction in force-velocity potential in PhT group was similar to that, observed after the 2nd week of HDT bed rest, and, on the average, comprising 18 – 20% in resistive and isometric regimes, and practically lacking in velocity regimes.

Analysis of changes in muscle force-velocity properties under conditions of simulated microgravity could be summarized as following:

- both exposures, namely, immersion and HDT bed rest, induce decrease in force-velocity and endurance properties of skeletal muscles;
- pattern of changes, produced by both exposures in various muscle groups, is similar, and close to that observed during space flights: alterations in force-velocity properties are

more intensive in extensor muscles, greater changes being found in isometric and resistive regimes;

- immersion and HDT bed rest induce considerably different dynamics and intensity of changes: immersion causes rapid decrease in force-velocity properties, reaching high values (up to 30%) by the 5th-7th day; in contrast, during HDT bed rest changes become evident only by the 14th day, gradually increasing and reaching values, recorded by the 7th day of immersion, only by the 90th day;
- specific dynamic pattern of force-velocity changes during HDT bed rest: small alterations for the first 60 days, and larger increment by the 90th – 120th day, as well as difference in reaction to physical training (PhT) - tolerance to PhT during the first month of exposure, and clearly increasing PhT efficiency during subsequent months,- suggest contribution of, at least, two mechanisms into genesis of decline in muscle properties, implying existence of two phases, which fully corresponds to the in-flight data, and is experimentally confirmed by dynamics in muscle atrophy development. For instance, analysis of changes in ratio between the integrated EMG, and standard muscle force output (in the range of 12 – 15% from the MVC) convincingly demonstrated existence of two phases in an increment of that ratio; by the time scale the phases correlate with the aforementioned changes. The first phase reached its peak by the 14th day of HDT bed rest, and stayed at plateau until the end of the first month; the second phase developed for 2 –3 months with the different increment, reaching peak values by the 90th day of exposure.

In that case, contribution of the reflex and periphery mechanisms was also different. Post 120 day HDT bed rest comparative analysis of changes in m. triceps surae strength and time characteristics of the MVC, and electrically evoked single and tetanic maximal contraction, revealed that 36% decrease in MVC (in comparison with the control data) was accompanied by similar decrease in electrically induced single (by 37%), and tetanic (by 34%) contraction /60/. It should be mentioned again that after 7 day dry immersion 20% decrease in voluntary contraction was not accompanied by any considerable changes of evoked contractions /59/. In total, those data indicate mainly central nature of decrease in contractile properties of skeletal muscles during the first days of microgravity exposure, and mainly peripheral (intramuscular) genesis of that phenomenon at the second stage. That concept is also confirmed by difference in changes of time characteristics of the single evoked contraction in m. triceps surae, namely: if after immersion duration of the maximum contraction phase was not changed, then, after the 120 day HDT bed rest it exceeded the initial by 15%. Along with that, force deficit, which increased nearly twofold after 7 day immersion, was also increased after HDT bed rest, though to a lesser extent, indicating persisting contribution of central mechanisms into genesis of decreased contractile properties. Data from the joint Russian-Japanese study indicate that under long term hypokinesia conditions decreased contractile properties of the muscle itself considerably contribute into decrease of force-velocity properties of voluntary contraction. Isolated human m. soleus fibers showed considerably reduced contraction force after the 60 day HDT bed rest. However, from the 60th to 120th day of exposure that index failed to demonstrate any marked changes [Yoshioka et al, 1998]. On the whole, such a pattern agrees with changes in m. soleus fiber size, observed in the course of that study (see later).

2.5. In-flight studies of the contractile properties in animal muscles

In the USSR along with human investigations were carried out complex in-flight animal studies utilizing biosatellites "Kosmos". Those studies analysed contractile properties of the isolated muscles [99], and of isolated glycerinated fiber bundles, as well as of the single muscle fibers (jointly with the French authors) /37/. Application of those methods enabled to evaluate changes in contractile properties directly in the muscular apparatus of mammals, and in its muscle fibers.

After the short term flights on board of "Kosmos-1514" and "Kosmos-1667" biosatellites (5 day flight of pregnant female rats, 7 day flight of male rats), maximal tension in m. soleus glycerinated fiber bundles was considerably decreased: in comparison with the cage controls (by 49.6% -44.5%) (Fig.3), in comparison with the synchronous control (rats were kept in a capsule of biosatellite model on Earth) the decrease amounted to 42.5 - 42.7%. After 7 day flight, similar decrease in strength was found in m. gascrocnemius medialis fibers, somewhat less - in medial head of m. triceps brachii, and in m. EDL and m. brachialis fibers the decrease was practically lacking. In that study French authors have showed that postflight decrease of the maximal contraction amplitude was less marked in the isolated skinned m. soleus fibers (comprising 28%) than in fiber bundles, or in the whole isolated muscle (37). That decrease was found to be insignificant for m. gastrocnemius lateralis, and for m. plantaris.

After the short term flights contraction velocity of fiber bundles was also decreased in all muscles, excluding m. EDL [105].

Effects of the 14 day exposure of rats to weightlessness were studied using "Kosmos-1887" and "Kosmos-2044" biosatellites. Specific feature of the first experiment was that

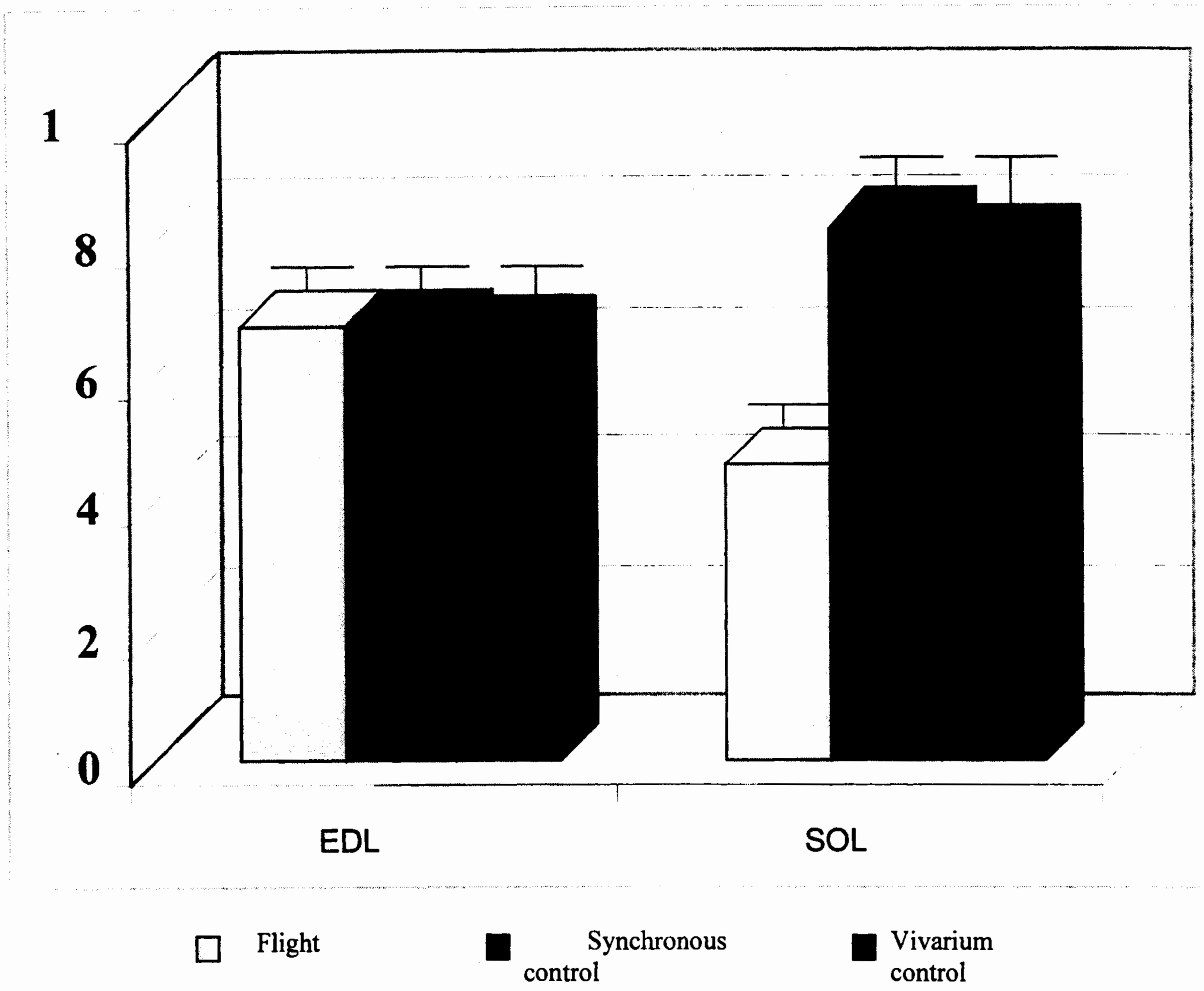


Fig.3 Muscle contractile properties in space-flown rats.

Analysis of the results suggests that, most probably, changes were induced by the joint effect of weightlessness, and environment in the capsule of biosatellite model. In particular, manifestation of m. brachialis hyperfunction the authors attribute to behavior adaptation of animals to the supportless environment [102]. It is likely, that in that environment stabilization of the body position is implemented, mainly, by the increased forelimb activity. That conception has been confirmed by significant increase in the total in-flight motor activity of the animals, which was observed in biosatellite studies [Klinovetskiy et al., 1979].

Joint Russian-French investigations of the Rhesus, flown for 12 –14 days on the "Kosmos-2229" and "Bion-11" biosatellites, have revealed that more than twofold decrease of fiber contraction force, observed in "slow" deep portion of m. triceps brachii, was more marked than corresponding reduction of fiber diameter. Interestingly, the Rhesus, kept for 14 days in flight capsules on the Earth (under forelimb unloading conditions) have also demonstrated decreased contraction amplitude of the fibers, though less profound than space flown animals.

Thus, in-flight animal studies, performed on board of the Soviet and Russian biosatellites, revealed marked changes in contractile properties of examined isolated muscles, and of their fibers. Those studies indicate that:

- even relatively short term exposure to weightlessness induces marked decrease in the maximal tension amplitude of muscle fibers in slow postural extensors; the decrease does not progress so rapidly with the further duration of exposure, and does not reveal any linear correlation with flight duration;
- postflight maximal tension of fast muscles fibers turns out to be much less decreased, and in a number of cases remains constant (and, in some cases, it is found to be somewhat increased for the forelimbs, probably, due to behavior adaptation);
- contraction rate of rat slow postural extensors changes differently at the various stages of exposure to weightlessness: it decreases after 7 –14 day flights, and increases after longer exposure to weightlessness.

Studies of the contractile properties of rodent muscles, obtained after the space flights, were complemented by suspension rodent studies. Those studies have also showed decreased contractile characteristics in the isolated muscle, in m. soleus force of the single contraction having been much more decreased than the amplitude of tetanic tension [1], and of glycerinated fiber bundles [105]. Under those conditions, decrease in the contractile properties of flexors and fast extensors was insignificant.

Comparing data on force-velocity characteristics in rodent and human muscles after various terms of exposure to weightlessness, apparently, one should consider different rates of studied changes in the various mammals species, that considerably differ in body sizes, and, consequently, in rates of metabolic processes.

In-flight studies of contractile properties of rodent muscles, along with data obtained from the cosmonauts, suggest that weightlessness induces considerable changes in properties of the peripheral mammal motor system. Those changes may be provoked by a number of causes:

- decreased volume of the contractile muscular apparatus (atrophy);
- changes in characteristics of the excitation contraction coupling;

qualitative structural and functional changes in muscle fibers (story, changes in expression of

3. Changes in volume of contractile apparatus

3.1. Volume of human muscle contractile apparatus under actual weightlessness conditions

One of the most well-studied and noticeable consequences of weightlessness exposure is decrease in muscle mass (atrophy), which was predicted by classics of cosmonautics. Loss in muscle mass was observed in the cosmonauts after flying "Soyuz" spaceships /55/, and after longer missions to "Salyut" orbital station. For instance, crew members from "Salyut" space mission had their calf volume decreased by 10 – 15%, on the average. Judging by changes in calf circumference during the first days after landing (as a result of restored fluid balance), nearly 50% of the in-flight calf volume decrease could be attributed to loss in muscle mass.

For instance, in two crew members from the main "Mir" missions volume of m. soleus comprised 85.1± 2.0% from the preflight level by the 2 –4th day after landing (Table.4). Volume of m. tibialis anterior was found to be 86.3± 1.4%, and volume of m. gastrocnemius – 84.6± 1.3% from the preflight level. Hip muscles were less affected: volume of m. quadriceps fem. comprised 89.0± 1.0%, and volume of m. biceps fem - 88.1± 1.5% from the preflight level. One cosmonaut from that mission was examined immediately after, and on the 4th day after landing. If loss in m. soleus comprised 15.4% immediately after landing, than by the 4th day it was found to be 10.6%. Thus, for the period of 4 postflight days the decrease was compensated by 5%. The volume of training practically failed to have any effect on the volume loss in main leg muscles. Level of muscle volume loss also failed to correlate with flight duration.

Table 4. Postflight volume of the cosmonauts' muscles (% from the initial level)

Cosmonaut	**Flight duration (days)**	**Tibialis anterior**	**Soleus**	**Gastrocnemius**	**Gastrocnemius +soleus**	**Biceps femoris**	**Quadriceps femoris**
1	180	83.1	79.9	82.9	80.7	82.4	85.6
2	180	88.9	86.6	81.9	84.9	88.2	90.2
3	180	84.3	78.8	82.3	80.2	89.2	91.5
4	194	82.4	86.2	84.0	85.5	89.0	86.1
5	194	89.2	90.3	90.4	90.4	93.7	82.9
6	188	89.4	88.4	84.0	87.2	86.3	91.1
M±m	186 ± 6	86,2±3.0	84,9±4.0	84,2±2,1	84,8±2,9	88,1±2,5	88.0±3,1

Thus, after the long-term space flight most of the examined cosmonauts demonstrated decrease in volume of calf and hip muscles, reduction in calf volume being more marked. Especially deep changes were found in calf of the cosmonauts (NN1–3) from a certain mission, in the course of which it was impossible to adequately perform recommended program of exercises for the technical reasons. Changes in muscle volume of those cosmonauts were comparable with those, observed earlier after the short term missions [84].

At the same time, three cosmonauts from the long term (120 days), and super long term missions were practically lacking decrease in cross sectional area (CSA) of calf and hip muscles (see table 5). Those cosmonauts faithfully followed in-flight countermeasure training program, paying special attention to locomotor exercises on a treadmill.

Table 5. CSA of calf and hip muscle of the cosmonauts (cm^2)

Cosmonaut	**Flight duration**	**m.soleus**		**m.gastrocnemius lateralis**		**m.gastrocnemius medialis**		**m. vastus lateralis**	
		pre	post	pre	post	pre	Post	pre	Post
Pol	438 days	36,6	34,1	12,1	14,4	20,8	21,15	75,4	72,7
Mus	120 days	25,1	27,8	6,0	5,3	15,8	16,11	------	-------
Mal	120 days	27,8	31,0	9,4	9,8	15,9	16,8	------	-------

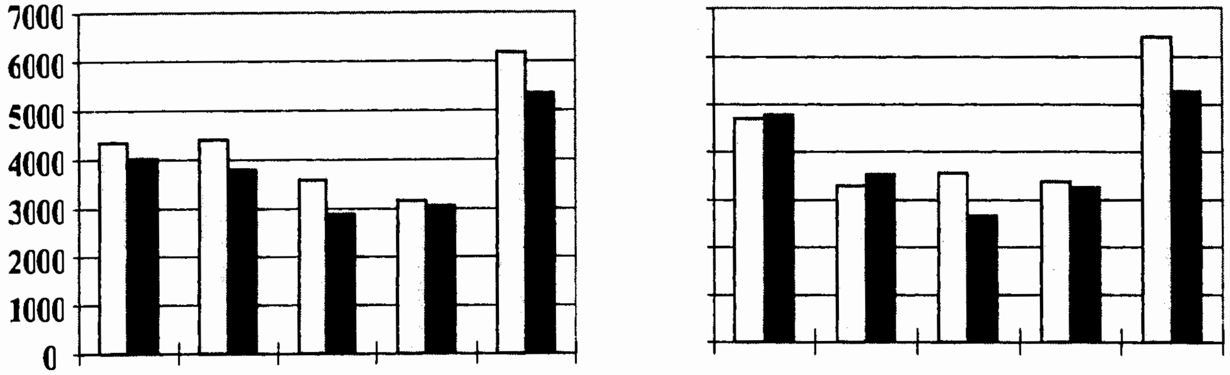
Data on the volume and CSA of calf and hip muscles do not expose any relation to flight duration. Evidently, volume of physical training mostly affects character of changes.

It is noticeable, that volume loss in flexors and extensors was similar: analogous phenomenon was observed earlier, analyzing muscles under conditions of actual and simulated weightlessness [83-85]. Those data are in certain conflict both with the physiology data, indicating markedly lesser loss in flexor strength in comparison with extensors under conditions of both actual and simulated (see above) weightlessness; and with the animal studies, which provide evidence of the more intensive atrophy in extensor fibers in comparison with flexor fibers in actual and simulated weightlessness [see later]. That phenomenon could be explained, probably, by the fact that muscles, whose volume was evaluated by MRI (see later), are composed not only of the contractile, but also of the non-contractile components. Therefore (as well as due to other causes), study of changes in muscle mass of the cosmonauts should be complemented by investigations at the tissue level.

Small postflight decrease in CSA of m. vastus lateralis fibers was found in cosmonauts A, B, and D (Table 6, Fig.4) [119,124]. In cosmonaut C (“jogger”), and in cosmonaut E decrease in CSA of I and II muscle fiber types was the most intensive, reduction in type 1 fiber CSA being somewhat more marked.

Table 6. Cross sectional area of m. vastus lateralis of the cosmonauts

Cosmonaut		**Type 1 μm^2 CSA**	**Type2 μm^2 CSA**
A	Preflight	4356	4700
	Postflight	4017	4786
	Difference %	-7.8	+1.8
B	Preflight	4406	3296
	Postflight	3800	3517
	Difference %	-13.7	+6.7
C	Preflight	3594	3550
	Postflight	2886	2682
	Difference %	-19,7	-24,5
D	Preflight	3137	3392
	Postflight	3053	3277
	Difference %	-2,7	-3,4
E	Preflight	6192	6408
	postflight	5359	5289
	difference %	-13,5	-17,5



SLOW-TWITCH FIBERS FAST-TWITCH FIBERS

Fig. 4 Fiber cross-sectional area (μm^2) in biopsies from m. vastus lateralis of MIR crewmembers (pre- and postflight data). Light bars – pre-, dark bars – postflight.

Decrease in CSA of muscle fibers (atrophy) is one of the most evident consequences of human exposure to actual or simulated weightlessness. At the same time, after the long term space missions individual decrease of m. vastus lateralis fiber size was found to be either insignificant, or similar to that obtained after the ground-based simulation studies (HDT bed rest, unilateral suspension of leg, or dry immersion) [36,12-14, 7, 123], as well as after the short term space flight on "SPACE SHUTTLE" [23]. One of the most probable explanations of that fact could be influence of countermeasure physical exercises, used for preventing development of unfavorable consequences of weightlessness. It is known that under conditions of simulated weightlessness increased physical activity results in considerable reduction of the atrophy level in humans, and in animals [see later].

Dynamics in contractile characteristics of human muscles during long term space flight revealed influence of the on-board regular training program on the intensity of decrease in contractile properties of antigravity muscles [see above].

It is evident, that in-flight application of the Russian system of physical countermeasures according to individual recommendations resulted in a minimal muscle fibers atrophy in participants of the 76 day mission, and in engineer from the 180 day flight. In commander from 180 day mission muscle CSA was reduced approximately by 20% in fibers of both types. That cosmonaut informed that during the last 2 months of flight he had performed predominantly locomotor anaerobic exercises of low intensity. Earlier it was shown that low intensity anaerobic exercises are not efficient for preventing fiber atrophy in animals, and for preventing decrease in contractile properties in humans.

Thus, data obtained in the present study, show that

- after the long-term missions, when cosmonauts use regular countermeasures, degree of the muscle atrophy, on the average, does not exceed that induced by the short-term exposure to actual or simulated weightlessness;
- in cosmonauts degree of the atrophy depends on the volume, intensity, and structure of training countermeasure exercises, performed during long-term space missions; the efficiency of those exercises should be specially evaluated in in-flight animals studies, as well as in simulation studies, utilizing and lacking countermeasures.

Thus, it looks quite probable, that during long term space flight physical exercises considerably prevent development of the muscle atrophy (predominantly of the extensors: for instance, posterior muscles of the calf).

Unfortunately, the cause of muscle size decrease is still quite obscure: whether it is loss of protein or fluid. Earlier it was shown, that during space flight cosmonauts experience considerable dehydration. At present, there are no data that enable to evaluate, with a more or less degree of probability, contribution of intra- and intercellular fluids into skeletal muscles atrophy, and to compare that data with loss in muscle protein. Only future studies will be able to clarify that problem.

At the same time, alterations in the nitrogen balance clearly indicate intensification of the protein catabolism at the organism level. Scattered data on the protein synthesis (incorporation of non-radioactive labeled aminoacids) do not give ground for making conclusions on significant decrease of protein synthesizing processes in humans under conditions of space flight.

Thus, decrease of muscle mass (atrophy) both at the tissue, and at the organic level, may regarded as one of the most characteristic consequences of human exposure to actual weightlessness. That kind of atrophy affects fibers of the both types, and, evidently, functional capacity of muscles. Probably, reduction of muscle fiber size is caused by decreased volume of intracellular fluid, and/or by decreased concentration of contractile proteins. Atrophy could be considerably prevented by regular physical training (especially, by locomotor exercises). At the same time, it is evident that, at present, skeletal muscle atrophy of humans, exposed to actual weightlessness, is studied insufficiently, and obligatory in-flight use of countermeasure physical exercises is clearly an obstacle for correct examination of weightlessness effect on muscle mass. Therefore, investigation of the muscle atrophy in humans under conditions of actual space mission can not be considered as an adequate approach for studying physiological triggering mechanisms of in-flight atrophy development.

3.2. Postflight changes in contractile apparatus of Rhesus monkeys

Studies of the space-flown Rhesus monkeys not only enabled to evaluate the nature of skeletal muscle structural changes in an object, whose motor system is very similar to that of human, but also to examine the nature of the effect of actual weightlessness without countermeasures.

Pre- and post-flight investigations of the Rhesus monkeys from "Kosmos-2229" biosatellite flights comprised the first series of studies, aimed at revealing the main structural and metabolic changes in skeletal muscles under conditions of space flight. The second series, performed within framework of "Bion-11" flight, enabled to study the main causes of the observed changes, utilizing a number of control experiments.

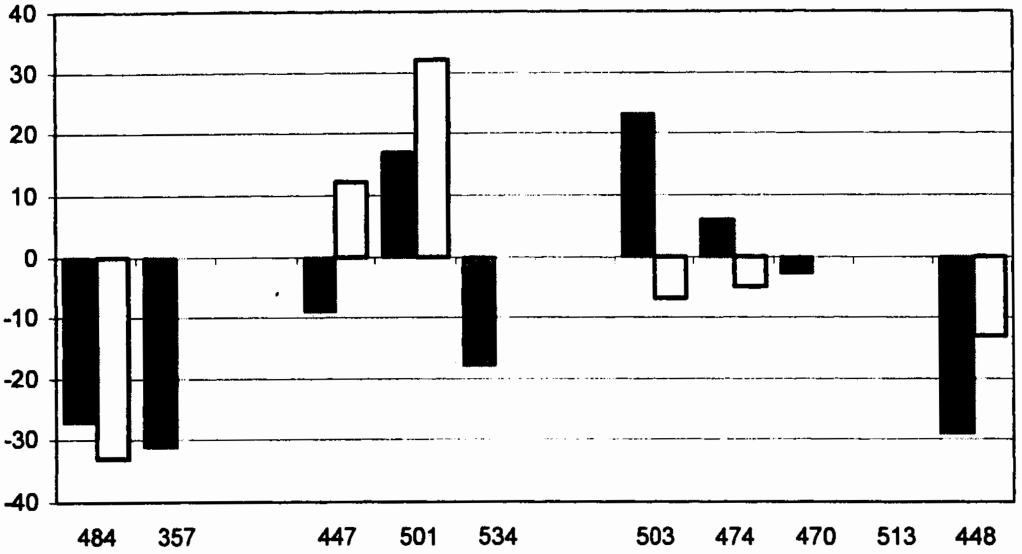


Fig.5 Relative changes in soleus fiber cross-sectional area in monkeys after spaceflight (#484 and 357), restraint (447, 501,534) and cage living (other monkeys). Dark bars – slow-twitch fibers, light bars – fast-twitch fibers.

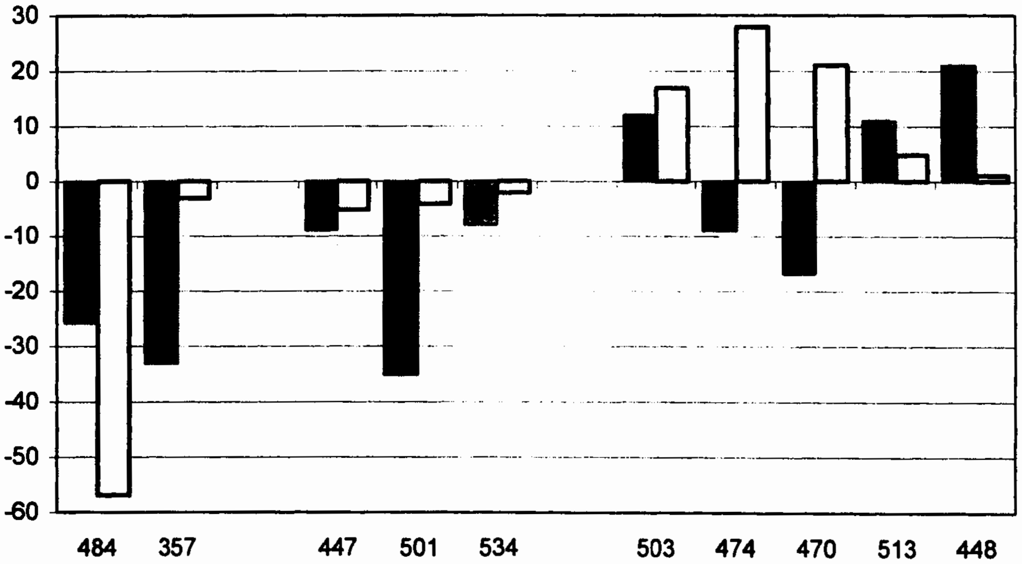


Fig.6 Relative changes of vastus lateralis fiber cross-sectional area in Rhesus monkeys after spaceflight (#484 and 357), exposure to restraint (#447, 501, 534) and cage living (other monkeys). Dark bars – slow-twitch fibers, light bars – fast-twitch fibers.

After 12.5 – 14 day space flight Rhesus monkeys had considerably decreased CSA of fibers of both types in all the examined muscles, except m. gastrocnemius medialis, and m. biceps brachii [118]. The atrophy changes were most marked in extensor muscles (m. soleus, deep portion of m. triceps brachii, and m. vastus lateralis). In most of the examined muscles (except m. tibialis anterior) postflight type I fiber atrophy was somewhat more pronounced; however, degree of the type 2 fiber atrophy was also large enough. Thus, results, obtained from Rhesus monkeys, were considerably different from those obtained earlier from rat muscles, where postflight type 2 fiber atrophy was much less [see later]. In Rhesus monkeys, m. gastrocnemius medialis, and m. biceps brachii fiber sizes were not changed after the flight. In agreement with the rat studies, atrophy in m. tibialis anterior was observed predominantly in type 2 fibers [see later]. Acute in-flight decrease of phasic activity, characteristic for that muscle, could result in the corresponding decrease in type 2 fiber size. Neither of the control groups demonstrated significant changes of the same intensity, which enables to attribute them mainly to the effects of actual weightlessness [118, 122, 11, 88]. .

It is known that one of the consequences of animal exposure to microgravity is intracellular, as well as extracellular dehydration. However, space-flown animals have not revealed increased protein concentration, which may indicate proportional in-flight loss of protein and water in Rhesus monkey muscle fibers [11,122].

Certain tendency to decreased fiber size of m. vastus lateralis (but not m. soleus) in animals, exposed in flight capsule under 1 g conditions, is rather noticeable (Figs. 5, 6). In most cases, those changes did not reach level of significance, nevertheless, indicating that restraint knee joint is one of the factors, affecting pattern of in-flight fiber changes predominantly in locomotor muscles [11].

Ultrastructural examinations have not revealed considerable reduction of volume density in myofibrils of m. soleus [89], m. vastus lateralis [89], m. triceps brachii, and m. biceps brachii [88]. At the same time, numerous qualitative destructive changes in myofibrillar apparatus were found after space flight: thinning of myofibrils, contracture areas, disruption areas with microgranular content, striation disturbances, as well as fragmentation of Z-lines, and loosening of fibers in postflight Rhesus monkeys.

Studies of the Rhesus monkeys, exposed to actual weightlessness for 12 –14 days on board of biosatellite, revealed that:

- postflight decrease in CSA of muscle fibers of both types has been mostly marked in extensors, though some decrease in fiber size (especially, of type 2) has been found in flexors as well;

- degree of the atrophy in type 1 and type 2 fibers of hindlimb extensors has been similar; at the same time, in deep potion of m. triceps brachii considerable (up to 50%) decrease of type 1 fiber size has not been accompanied by significant changes in type 2 fiber size;
- fibers of the ankle and knee joint extensors have not revealed elevated concentration of the total protein, indicating proportional in-flight decrease in both protein and water components of fiber; while decrease in m. soleus protein concentration, observed in both animals, indicates predominant reduction of that component in the course of space flight;
- lack of considerable postflight changes in volume density of myofibrils in Rhesus muscles indicates proportional decrease of the absolute volume in myofibrillar and sarcoplasmic compartments under actual microgravity conditions;
- decreased fiber sizes in m. vastus lateralis, and, somewhat lesser decrease in m. soleus, could be partially attributed to restraint of the animals, though data indicate that the main cause of reduced CSA is effect of actual weightlessness.

In spite of the fact that Rhesus monkey studies possess high informative potential (they enabled to examine microgravity-induced structural and functional changes without countermeasures, in evolutionary close to human species), still, they have limitations of their own. Only large rodent studies enabled Russian investigators for the first time to reveal main phenomena, related to development of hypogravitational atrophy in muscle fibers, as well as to considerably enlarge knowledge of the physiological and cellular mechanisms of the atrophy.

3.3. In-flight rodent studies

Significantly decreased CSA in muscle fibers of rats, exposed to weightlessness on board of “Kosmos-605” biosatellite for 22 days, was found in early studies by E.I. Ilyina-Kakueva and V. V. Portugalova. That decrease was more marked in m. soleus than in locomotor, predominantly “fast” muscles. The greatest changes were observed in slow-twitch fibers (at that time, they were exposed as “intermediate” fibers according to staining for succinate dehydrogenase) [38].

Subsequent studies have also revealed postflight atrophy of rat muscle fibers. Space flight of 5 –7 day duration on board of “Space Shuttle” and biosatellites resulted in type 1 fibers, as well as in type 2 fiber atrophy of rat m. soleus [47 and others]. Most of the authors showed that space flights of longer duration (12.5 – 14 days) induced more marked type 1 fiber atrophy in posture-tonic muscles [19,20,115]. Considerable decrease in type 1 fiber size was also found in other muscles; as a rule, type 2 fiber atrophy was less marked.

3.4 Ground-based simulation studies of dynamics and mechanisms in structural muscle fiber atrophy

The study, carried out by our department/laboratory, showed that 30 day long HDT bed rest have induced reduction in CSA of m. gasrocnemius lateralis fibers of both slow, and fast types [74]. The American and Swedish authors have observed similar changes in m. vastus lateralis: decreased fiber size of type I, and type II by 11%, and 17%, accordingly, after the 30 day hypokinesia [36]; and by 18% and 10%, accordingly, after the 6 week hypokinesia [14,34]. Up to now, studies on the atrophy dynamics in human muscle fibers under gravitational unloading conditions are quite scare. We have shown that by the 60th day of HDT bed rest size of type I fibers in m. gastrocnemius lateralis comprised 74%, and of type II – 88% from the initial level [76,78]. By the 120th day, size of type I fibers was insignificantly altered, and comprised 88% from the initial, and size of type II fibers was corresponding to the initial value. By the 180th day, the atrophy was found to reach 50 – 40%, and was similar in fibers of both types, in spite of the physical training. By the 240th day of hypokinesia, the fiber sizes were restored to the initial level, and later were a little declining predominantly in type I fibers. Similar pattern of changes in muscle fiber sizes was observed in the course of the 120 day female HDT bed rest study. In that study we have observed that if by the 60th day of hypokinesia atrophy in similar in fibers of both types (23% in type , and 16% in type),than, by the 120th day, size of type II fibers practically reaches plateau, differing from the initial level by 16%, and the atrophy of type I "slow" fibers is further increasing, reaching 33.5%. Interestingly, that morphology changes in skeletal muscles have been found to be insignificant after the short term (7-14 days) hypokinesia.

MRI studies have disclosed significant decrease of calf muscle volume after 60 day HDT bed rest; changes in volume of main calf muscles groups were similar in all the subjects. By the 120th day of hypokinesia changes have not considerably differed from the previous examination. Still, MRI data do not allow to make a conclusion which components contributed to changes in muscle volume: contractile (muscle fibers), or non-contractile elements (connective tissue, extracellular fluid).

Comparison MRI-disclosed changes in volume of both muscles with the results of histomorphometry of muscle fibers, reveals that under hypokinesia conditions changes in muscle volume reflect changes in its fiber sizes only to a certain extent (Fig. 7.).

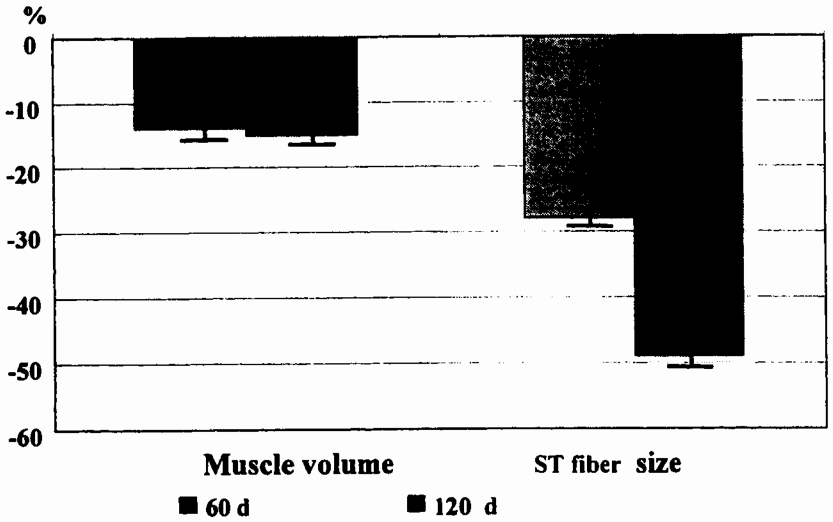


Fig.7 Changes in soleus volume (MRI) and ST fiber size after long-duration head-down tilt bed rest.

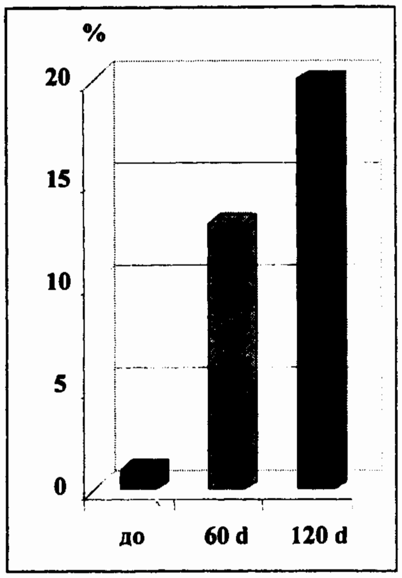


Fig.8 Area percentage, occupied by non-fiber compartment in human soleus pre- and post-bedrest.

That phenomenon may be related to increase in fraction of the non-contractile muscle elements in the course of hypokinesia. In the same 120 day HDT bed rest study, by the 60th day we have observed considerable increase in CSA of non-fiber structures of muscle sample (from approximately 1 to 13%) (Fig.8). By the 120th day, those structures have occupied 20% of CSA. That fact is confirmed by other works, exposing increase of connective tissue in rat muscle tissue under conditions of gravitational unloading (see later).

Data, obtained in our laboratory,[81,121] indicate that by the 60th day of hypokinesia intensity of decrease in CSA of type 1 and type 2 fibers was similar; that pattern having been characteristic for both male and female subjects, for calf muscles (m. soleus, and m. gastrocnemius lateralis), as well as for m. vastus lateralis, the intensity of changes being more marked in m. soleus (Fig. 9). In rats, as a rule, unloading, induces much more marked atrophy in type 1 than in type fibers 2 (see corresponding sections). Various explanations of that conflict could be provided, however, results of our study indicate that between the 120th and 60th day of HDT bed rest m. soleus atrophy of type 2 fibers does not progress further, while type 1 fiber CSA continues to reduce (Fig.9).

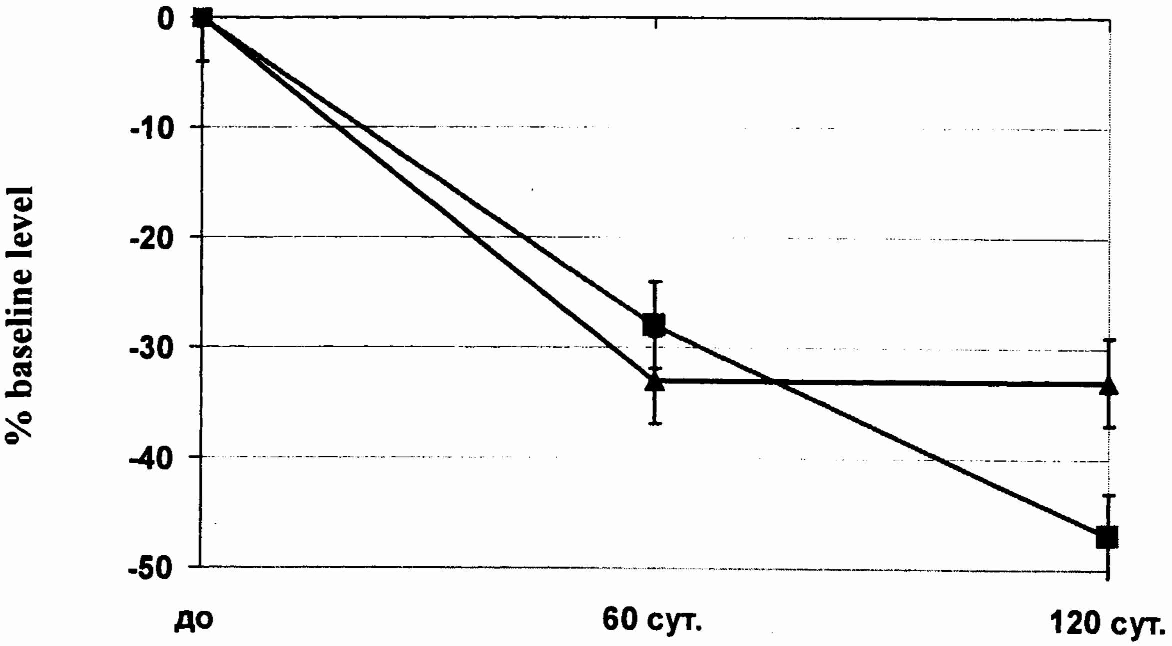


Fig.9. Time-course soleus fiber size development during the 120-day head-down tilt bed rest (light curve – ST fibers, dark curve – FT fibers)

Thus, longer hypokinesia induces pattern of fiber atrophy in human m. soleus similar to that repeatedly observed in rats.

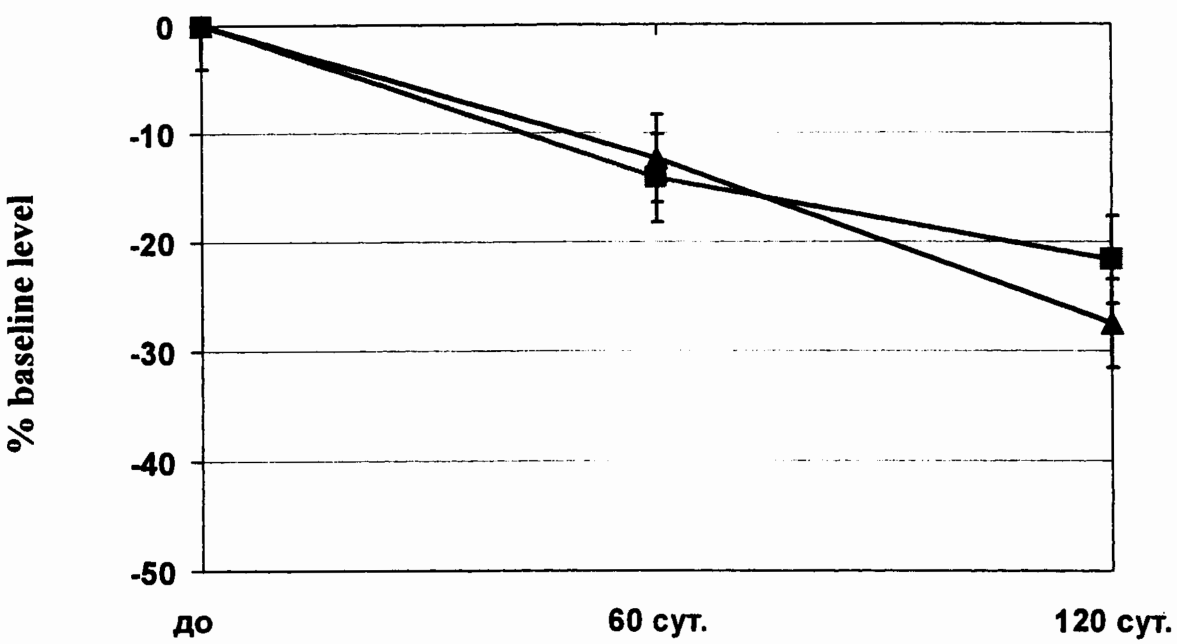


Fig.10. Time-course vastus lateralis fiber size development during the 120-day head-down tilt bed rest

(light curve – ST fibers, dark curve – FT fibers)

It is likely that causes for the aforementioned contradictions may be related to different rates in development of hypogravitational changes in muscles of the various species, however, various studies reveal different stages of the same process.

Table 7. CSA of m. vastus lateralis fibers (μm^2, M ± m) under HDT bed rest conditions

.	Before bed rest	60th day of bed rest	Δ %	120th day of bed rest	Δ%
Type1	4083± 573	3502± 451	14.2*	3199±299	21,6*
Type 2	5105± 779	4470± 845	12.4*	3701±313	33*

At the same time, dynamics of changes in m. vastus lateralis fibers was somewhat different (Fig.10,Table 7.). More marked type 2 fiber atrophy was observed at the second stage of the process. Probably, under normal conditions functional loading of type 2 fibers in that predominantly locomotor muscle is considerably greater in contrast to calf muscles; therefore, on transition from normal to hypokinesia conditions loading gradient is steeper, and stabilization of type 2 fiber sizes occurs later than in calf muscles.

By the 120th day of HDT bed rest variability in muscle fiber size decreased approximately by 1.5 – 2 times, which may indirectly indicate that by that time muscle fiber size reach certain adequate level of contractile activity, characteristic for the HDT bed rest regime.

Ultrastructural changes of myofibrils were observed in all the subjects on the 60th, as well as on the 120th day of hypokinesia; intensity of those changes lacking considerable correlation with duration of exposure. Destructive changes in myofibrillar apparatus (disruption of myofibrils, Z-line "streaming", striation disturbance, lysis of the whole sarcomeres and their parts) have been earlier observed under conditions of gravitational unloading [115,116,117]. Krippendorf & Riley [1992] think that, that in animals post microgravity changes in myofibrils are not consequences of the gravitational unloading itself, but of fiber readaptation to 1g environment after gravitational unloading. Our observation do not confirm that assumption. In the course of hypokinesia muscle samples were obtained from the subjects, who have not changed their body position; and quantitative analysis revealed that considerable increase in volume density of damaged myofibrillar areas was observed, already, by the 60th day of hypokinesia.

At the same time, on the total, changes in volume density of myofibrils turn out to be rather small at the background of considerably decreased muscle fiber sizes confirming that in the course of hypokinesia, absolute volume of myofibrillar apparatus changes proportionally to alterations in fiber sizes. At the same time, data, derived from the ultrastructure examination of myofibrillars in human m. soleus indicate, that by the 120th day of hypokinesia volume density of myofibrillars have been observed to be significantly (approximately by 10%) reduced in comparison with the initial level (Mazin et al, 1999 in press).

Size dynamics of rat muscle fibers in "slow" and "fast" extensors was followed under the long term suspension conditions [49]. Thirty day suspension have induced decrease in fiber size of m. soleus: type I – by 69%, type II – by 62%. After 90 days of suspension, type I fiber sizes have not significantly altered in comparison with the 30 day level, and type II fibers were found to be less than control only by 42%. After 14 day suspension CSA of type I fibers in m. gastrocnemius medialis was decreased by approximately 30%, and was not found to be considerably altered by the 90th day of exposure. Fiber sizes of type 2A, that were reduced by 29% by the 14th day of suspension, were observed to decrease only by 12% in comparison with the control values by the 90th day of exposure.

Thus, simulation studies have revealed that:

- under hypokinesia conditions calf muscle fibers (especially that of m. soleus) atrophy more intensively than thigh muscle fibers;
- at the first stage of the atrophy (by the 60th day of exposure), in ankle and knee joint extensors fibers of both types experience, on the average, similar decrease in size;
- further pattern (by the 120th day of exposure) differs in extensors of the ankle and knee joints: in calf muscles slow fibers are further reduced in size, CSA of fast fibers does not change in comparison with the 60th day level; in m. vastus lateralis size of slow fibers experience only slight changes by the 120th day of exposure, while atrophy of fast fibers becomes more marked as compared to the 60th day level;
- under hypokinesia conditions, muscle fiber atrophy is accompanied by increased occurrence of disrupted ultrastructural integrity of myofibrils, which is not related to changed body position after cessation of exposure;
- under hypokinesia conditions, reduction in muscle volume turns out to be less pronounced than decrease in their fiber size, which is, probably, due to elevation of non-contractile muscle components in the course of exposure.

Naturally, it is impossible to completely simulate effects of all the biomechanical factors of weightlessness under conditions of HDT hypokinesia. If considerable decrease of mechanical load could be successfully achieved, then the model fails to simulate complete support unloading: reaction of the support is only redistributed over the whole body surface. To evaluate contribution of that factor it is necessary to utilize dry immersion model (Fig.11) [125,126], which provides degree of mechanical unloading comparable to that under HDT bed rest conditions, and lacks support stimulus.

Fig.11. Dry immersion simulation study

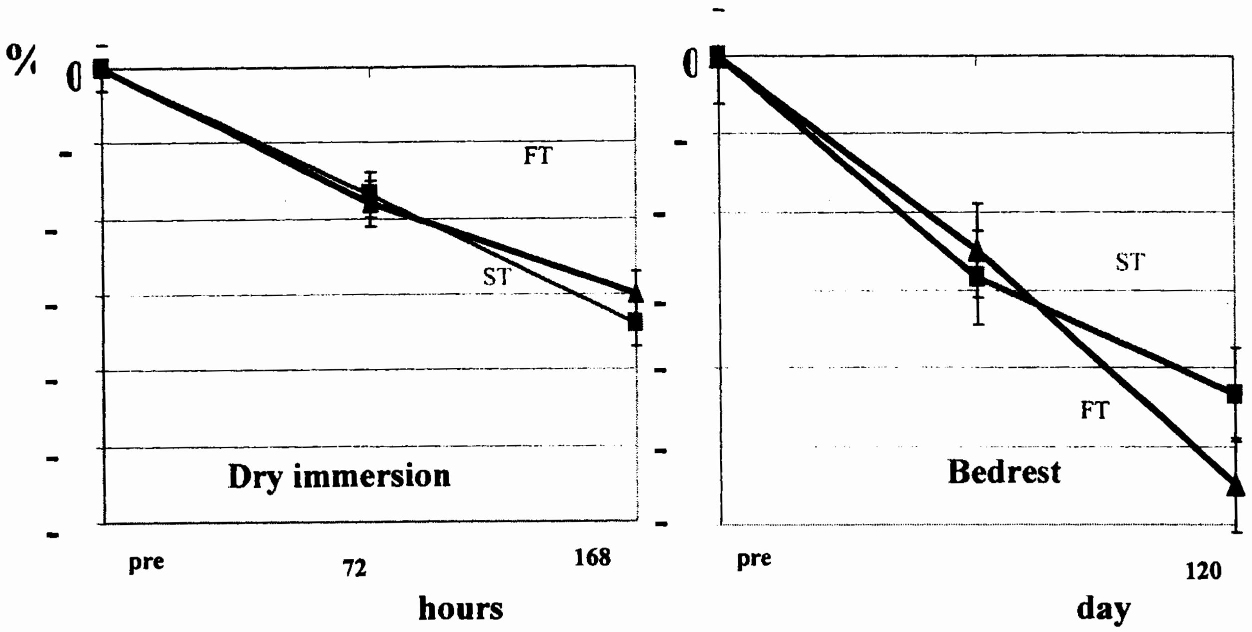


Fig.12. Relative changes of ST and FT fiber size during dry immersion and bed rest dexposures.

The obtained data are evident of some decrease in m. vastus lateralis fiber size already by the 3rd day of dry immersion; the decrease becomes rather large (up to 18%) after the 7th day of exposure (Fig.12) [123].

In the course of immersion decrease in both types of fiber sizes is accompanied by reduction of body weight. It is known that during immersion decrease of body weight is mostly due to dehydration of the organism. However, in the present study individual variability of weight loss was not correlated with variability in fiber CSA, indicating different mechanisms of those processes. It should be emphasized that similar atrophy intensity of that muscle under HDT bed rest conditions is reached only after the 30th day of exposure, or even later. Judging by the data from the American investigations 7 day hypokinesia have not induced alterations in fiber size of m. vastus lateralis (Dr. Siconolfi, private communication). A the same time, after 7 days of immersion decrease in fiber size was similar to that observed after short term space flight [23]. As dry immersion differs from HDT bed rest only by complete simulation of supportless environment, characteristic for the actual weightlessness, it is quite likely, that elimination of support is one of the triggering factor, inducing hypogravitational muscle atrophy. The hypothesis was supported by data, obtained in the joint

Soviet-Cuban studies, where artificial support device improved the muscle properties in cosmonauts [35]

That hypothesis is also confirmed by rat studies. For instance, muscles of rats, exposed for 18.5 days to weightlessness on board of "Kosmos-936" [41] satellite, were compared to on-ground control animals, and to animals, subjected to in-flight centrifuging at 1g acceleration. Weightlessness has induced a decrease in CSA of m. soleus fibers: in type 1 by 40-45%, in type 2 – by 30% (Fig.13). Atrophy of m. gastrocnemius medialis, m. quadriceps, m. tibialis anterior, and EDL has been far less marked. In centrifuged animals fiber sizes of the most studied muscles were close to control values.

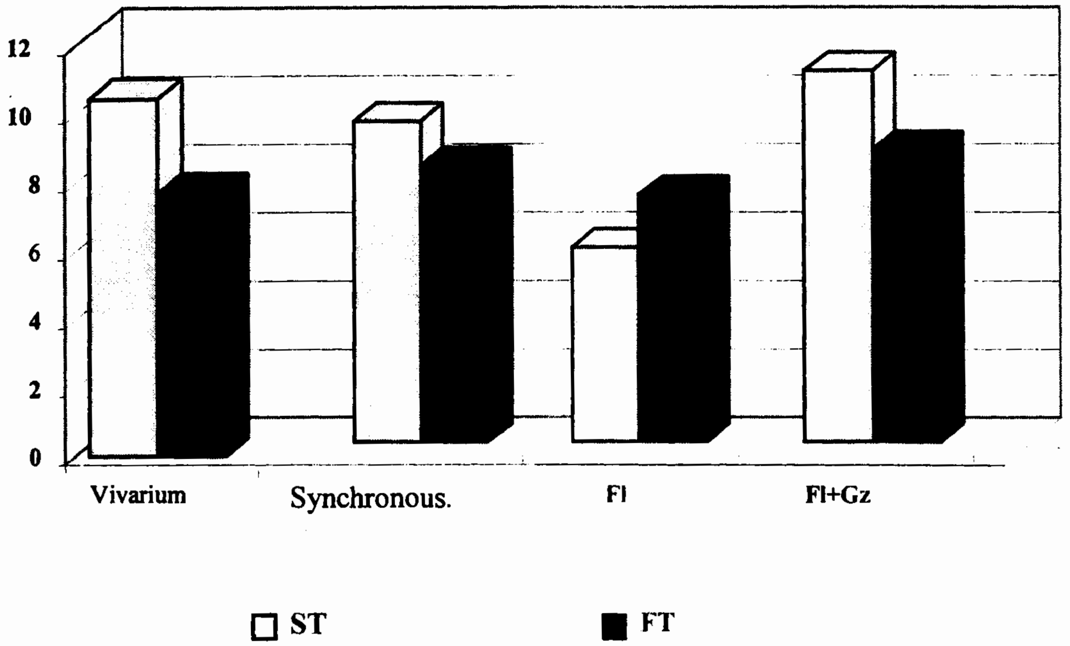


Fig.13. Soleus fiber size changes in rats exposed to spaceflight (FL) and spaceflight, combined with Gz- acceleration on-board biosatellite (Fl+Gz) KOSMOS-936.

In work by Ilyina-Kakueva and Kaplansky [50] it was shown that at the background of 14 day hindlimb suspension daily cessation of suspension for two hours (i.e., support loading) resulted in inhibition of fiber atrophy in m. soleus; suspension induced reduction in CSA of type 1 fibers by 50%, and of type 2 – by 47%, and support loading has reduced decrease to 29% and 22%, accordingly.

Our study [96] utilized model by Stump et al.[128], which enabled to create support loading for one of the rat' limb at the background of hindlimb suspension. In that case, development of the atrophy in m. soleus fibers have been completely prevented. It is interesting that immobilization of ankle joint in the neutral position, in its turn, neutralized countermeasure effect of support loading. One of the suggestions, explaining the obtained data, is that anti-atrophy effect of support is mediated by the active loaded contractions of the postural muscle, in that case.

Motor unloading was usually evaluated in studies, utilizing system of countermeasure physical exercises at the background of simulated weightlessness. In 49 day HDT bed rest study application of physical exercises and electrostimulation have enabled to slightly decrease muscle fiber atrophy, predominantly in type I [42]. At the same it, atrophy development in the course of 30 day HDT bed rest failed to be affected by physical exercises mainly of the locomotor nature (running on a treadmill) [74].

We have also studied effect of physical exercises on muscle structure in the course of 120 day HDT bed rest [29]. Application of monthly alternating local loads ("Cybex" dynamometer), directed at training strength, force-velocity and endurance properties, as well as passive stretching of leg and back muscles, resulted in practically preventing atrophy in fibers of both types in m. gastrocnemius lateralis.

During the first 2 months of 370 day HDT bed rest, when training in group A (performing physical exercises since the 21st day of hypokinesia) consisted predominantly of resistive exercises with little contribution of locomotor exercises, size of type I fibers in that group have decreased less than in control group (without countermeasure physical exercises) [76,78]. By the 120th day of hypokinesia, when training in group A consisted of running and resistive exercises of increased volume and intensity, performed, firstly, once a day, then twice a day, size of "slow" fibers was not different from the initial level, and size of type II "fast" fibers have even increased.

By the 180th day of hypokinesia, application of single training sessions of predominantly locomotor nature (complemented by resistive training with bungee- cord) resulted in a little increase of slow fiber sizes, and in reduction of hypertrophy in fast fibers of type II in group A. At the same time, in group B, subjected to 120 day hypokinesia without countermeasures, rehabilitation program (slowly increasing volume of low intensive training) failed to decrease the degree of the atrophy level, and its intensity has even increased.

After 240 days of hypokinesia, increased volume of training (2 times a day) resulted in considerable size reduction of both fiber types in group A. At the same time, in group B, application of single training sessions with predominantly running exercises (according to the regular on-board program) resulted in restoration of the initial sizes in fibers of both types.

By the 300th day of the study, in group A application of bicycle training resulted in restoration of the initial size in fast fibers, and a little reduction of the atrophy in slow fibers. In group B, at that stage having trained at resistive device, and then being subjected to passive muscle stretching, sizes were noticeably reduced in fibers of both types.

At the final stage of the study, application of special running training in group A was accompanied by restoration of the initial CSA in slow fibers. By the end of the study, sizes of the fast fibers comprised 85% from the initial level.

In spite of the intensive training program at the final stage of the study, subjects of group B failed to restore the initial level of sizes in fibers of both types /76,78/.

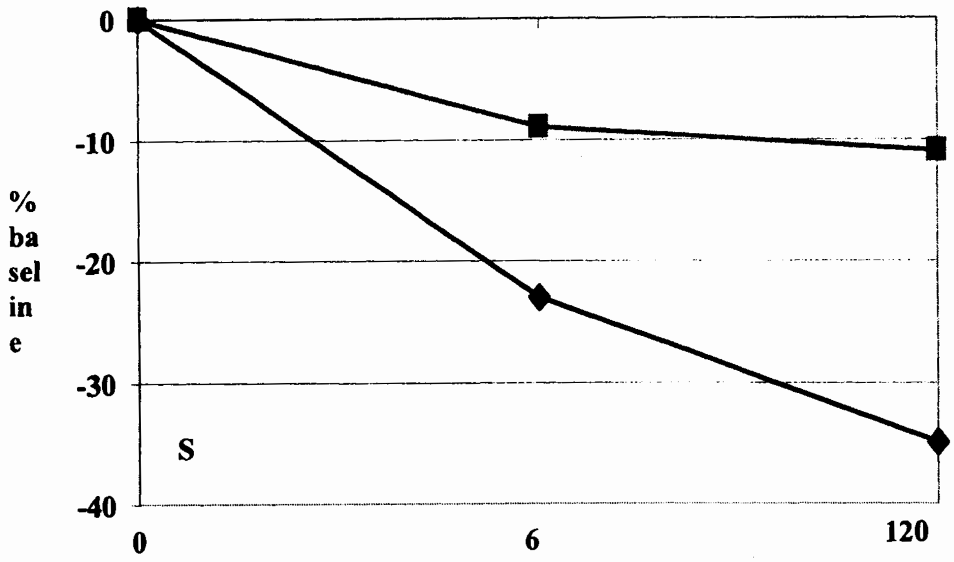


Fig.14. ST fiber size changes during female bed rest with and without «MIR-type» training square – bed rest + training, rhombs – pure bed rest

Changes of type 1 fiber CSA in females, performing countermeasure physical exercises in the course of hypokinesia, were far less marked than in the control group (Fig.14). This study practically has not revealed any countermeasure effect of physical training on type 2 fibers. Physical training enabled to compensate gravitational unloading effects both in animal, and in human studies. In suspended rats support loading or physical training, as a rule, resulted in decreased atrophy both in fast fibers, and in slow fibers (at least, for the muscles, performing predominantly postural function). Study of the countermeasure effect of electrostimulation of submaximal intensity at the background of 30 day human hypokinesia, revealed predominant inhibition of the slow fiber atrophy /22/. Earlier, similar results were obtained, analyzing changes in fiber sizes of the subjects, performing physical exercises at the background of 370 day HDT bed rest /76,78/.

The obtained data show that type 1 fiber atrophy in m. vastus lateralis was considerably prevented by application of the "Penguin" loading suit [9] , (Fig.15,16).

Fig. 15. Exercise session with PENGUIN suit

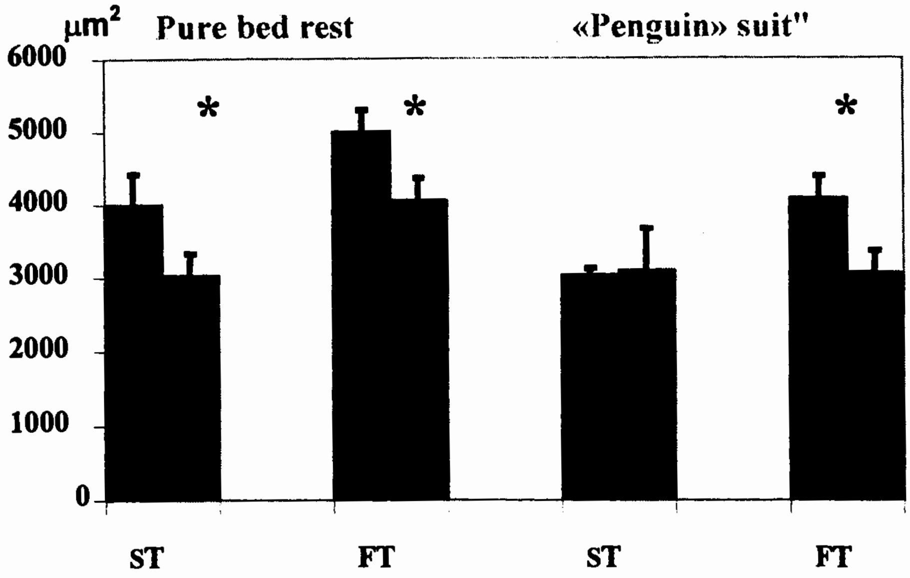


Fig. 16. M. vastus lateralis fiber cross-sectional area after bed rest with and without PENGUIN training.

It is likely, that even little volume of training against external resistance (resistive training) is able to prevent type 1 fiber atrophy in the course of HDT bed rest. A number of authors have observed that in the course of hypokinesia application of resistive training prevents fiber atrophy, and decrease in protein synthesis [7]. Probably, resistive training is able to compensate deficiency of muscular mechanical loading.

A number of rat studies, **reviewed** by M. Falempin and Y. Mounier [24], indicate that the main physiological factor, inducing atrophy, is deficiency of the so called "loaded" contractions (see later). Application of non-loaded contractions fails to prevent atrophy. Thus, observed in our study efficiency of resistive ("loaded") muscle contractions for prevention of the atrophy may be considered as an indirect evidence of the positive effect of resistive muscle activation (for the posture-tonic muscles – mechanical loading) in maintenance of muscle fiber size.

It is supposed that specific feature of the resistive, or loaded contractions is that it is impossible to completely reduce muscle length (as in isotonic contraction), resembling passively stretched muscle.

It was shown repeatedly that passive stretching can decrease the atrophy intensity, and change protein metabolism in m. soleus of "suspended" limb [Goldspink, 1970]. In suspended rats marked anti-atrophy effect of stretching was similar to that induced by physical training [79].

A number of experimental studies have examined hypothetical conception of physiologic and cellular mechanisms that mediate effect of decreased contractile activity on the structure of skeletal muscle fibers, analyzing contribution of both central neural and hormonal mechanisms, and of the intrafiber self regulation mechanisms.

It is known that muscle contractile activity considerably affects hormonal regulation of the metabolism via proprioceptive apparatus. There is certain ground to suppose that decrease in anabolic hormone level, increase of glucocorticoid content, and of tissue sensitivity to glucocorticoids, in a certain degree, may be mediated by the structural and metabolic effects of microgravity.

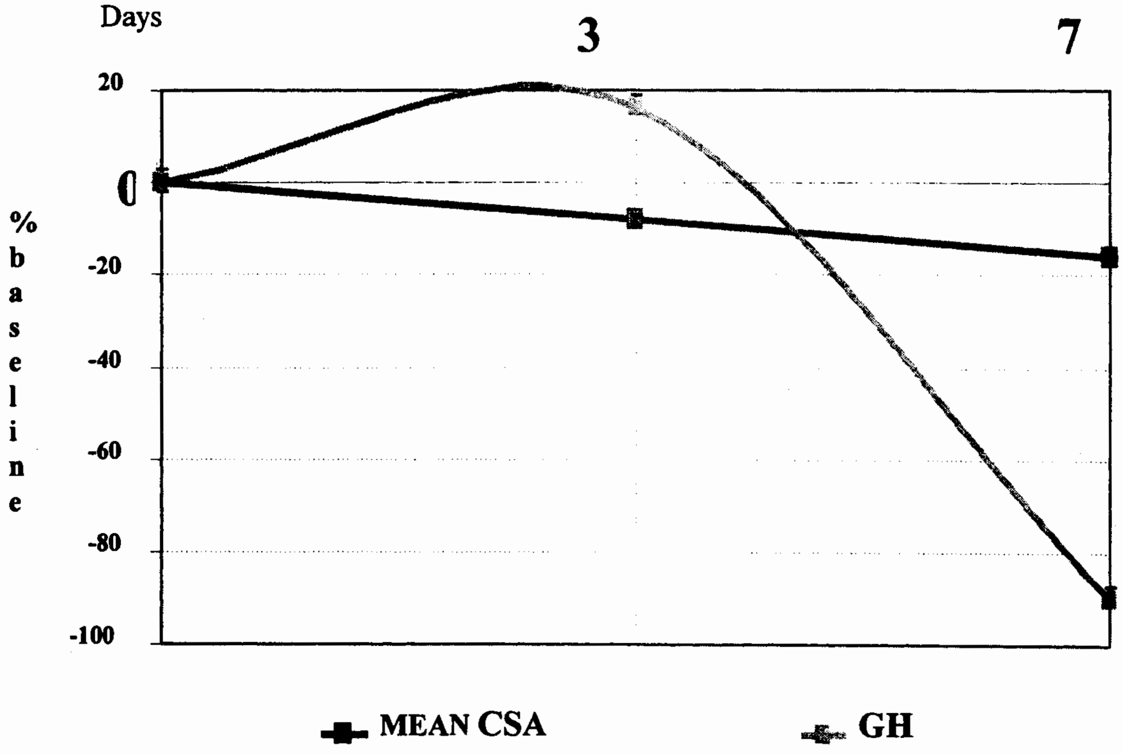


Fig.17 Relative changes of growth hormone and m. vastus lateralis ST fiber size levels in the course of dry immersion.

A number of authors think that under microgravity conditions decrease of growth hormone level induces decrease in protein synthesis, and, accordingly, decrease in muscle fiber sizes [33, and others]. Our studies failed to expose significant alterations in level of growth hormone during bed rest [81]. Similar results were simultaneously obtained in the course of hypokinesia studies of shorter duration [91]. At the same time, considerable reduction of muscle fiber sizes was observed in the course of hypokinesia (see above). The dynamics of growth hormone levels and fiber atrophy development appeared to be quite different in dry immersion study (Fig.17)

Chronic injection of the recombinant growth hormone failed to induce considerable changes in fiber sizes of suspended rats [54] (Fig.18). Development of the atrophy changes in m. soleus was greatly hampered by joint action of growth hormone and support loading, application of growth hormone failing to considerably modify effect of support loading. The same is true for the thyroid hormones, studied in the same work.

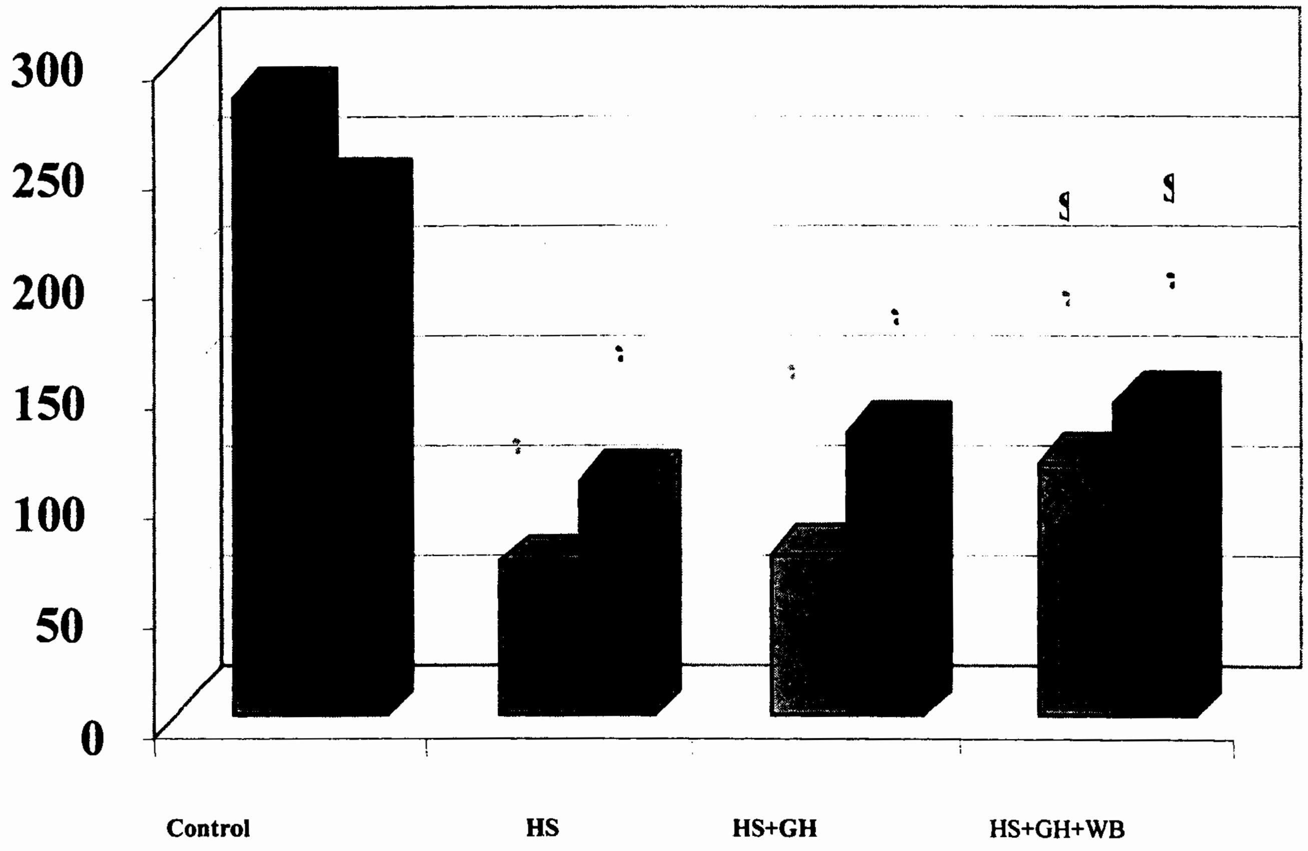


Fig.18. Growth hormone (GH) and weightbearing (WB) effects on soleus in hindlimb suspended (HS) rats. Light bars – ST fibers; dark bars – FT fibers;

Therefore, obtained data do not afford ground for considering alterations in the growth hormone level to be the cause of development of hypogravitational muscle atrophy.

Decrease in contractile activity of skeletal muscle fibers is accompanied by structural and functional changes in motoneurons. That is confirmed by the partial denervation of muscles in animals after biosatellite flights, and in humans after hypokinesia, as well as by changes in structural and metabolic parameters of motoneuron bodies in the anterior horn of rat spinal cord after exposure to actual microgravity [110, 2,3, 112,113]. Disorders of innervation may themselves cause atrophic, or other changes in muscle fibers. Ultrastructural study of rat neuromuscular synapses revealed signs of their morphologic reorganization after 13 – 14 day exposure to weightlessness (biosatellites "Kosmos-1667, 1887", and SLS-2 project). Area of synaptic contact was decreased because of the partial destruction of presynaptic structures (axone terminals). There were observed exposed parts of postsynaptic membrane, axoplasm lightening in presynaptic terminals, destruction of the axoplasm fragments, sometimes, total [8, 112, 48]. Similar changes, though considerably less marked, were observed also in m. gastrocnemius medialis. The described above changes are manifestations of developing denervation. At the same time, it is known that under microgravity conditions atrophy mechanisms (in particular, proteolysis mechanisms) greatly differ from the mechanisms of denervation atrophy [Henriksen et al., 1990].

In connection with all the aforementioned, an attempt was made to experimentally evaluate contribution of changed neuromuscular transmission into genesis of hypogravitational atrophy of skeletal muscles. However, under suspension conditions chronic stimulation of the central nervous system failed to considerably affect m. soleus atrophy [50].

Judging by some data, chronic decrease of the contractile activity results in accumulation of high energy phosphates. Peroral application of the analogue of **creatine β-guanidin propionic** acid (β-GPA) enabled to induce chronic deficiency of high energy phosphates, simulating metabolic consequences of chronic loading of such an intensity, which can not be attained by natural training. Application of β-GPA prevented changes in oxidative potential of muscle fibers at the background of suspension (see later). The results of the study allowed to suppose that accumulation of the high energy phosphates (as a result of fiber disuse) may stimulate changes in oxidative catabolism. However, it turned out, that application of β-GPA did not decrease reduction of rat muscle fibers during suspension [92,93,94,95,97].

As for the anabolic effects of resistive activities, some authors believe they are associated with the changes in sarcoplasma and its cytoskeleton (Goldspink, 1999). Few authors observed the changes in sarcoplasma permeability for macromolecules under conditions of real and simulated microgravity [87 and Shenkman et al, 2000 in press].

Thus, study of the mechanisms of muscle fiber atrophy under condition of actual and simulated microgravity showed that:

- under hypokinesia conditions, muscle atrophy has not been accompanied by stable and significant decrease of growth hormone blood concentration;
- even short-term dry immersion results in markedly decreased m. vastus lateralis CSA of both fiber types; usually, similar decrease is observed at later stages of HDT bed rest. That observation, as well as an analogous degree of muscle fiber atrophy, revealed after space flights of similar duration, enables to regard lack of support to be one of the main biomechanical factors, inducing development of hypogravitational atrophy in muscle fibers;
- most likely, lack of support also triggers decrease in plasma level of growth hormone, however, experimental and literature data do not afford ground for directly connecting physiological mechanism of hypogravitational atrophy development in muscle fibers, and decreased level of growth hormone;
- application of locomotor and resistive exercises enables to prevent MB1 atrophy under hypokinesia conditions.

4. Changes in myosin phenotype and in excitation contraction coupling under microgravity conditions

Changes in ratio of fast and slow (light chain) myosin isoforms in rodent muscles was observed for the first time after 18 day biosatellite flight [101,114]. Increased ratio of fast isoforms of myosin light chains in m. soleus, and in some other muscles was found after 7 day flight, already [101,105]. Joint Russian/American investigations revealed similar marked changes in light, as well as in heavy myosin chains after 13 –14 day flights [108]. In those investigations alterations of myosin phenotype were manifested at morphological level, as well: postflight decrease in ratio of slow type fibers, and increase in ratio of fast fibers was observed in rat m. soleus, and in some other muscles [39,40, 43,47].

Study of Rhesus monkeys, exposed for 12 –14 days to microgravity, has also revealed considerable decrease in percentage of slow type fibers in m. soleus, and in m. vastus lateralis [118]. That phenomenon was confirmed by American counterparts, who, using the same material, applied immunohistochemical staining, based on the binding properties of antibodies specific for the various isoforms of myosin heavy chains [Bodine-Fowler et al., 1994].

Changes in fiber ratio were also observed in ground-based suspension rat studies. It is interesting, that under conditions of long term suspension dynamics of alterations in fiber ratio is somewhat different from dynamics in fiber size changes. In the course of 90 day suspension decrease in percentage of m. soleus slow fibers did not reach plateau, though it was constantly declining to 50% [49].

Along with changes in myosin phenotype, exposure to gravitational unloading results in considerable changes in excitation contraction coupling (ECC) of muscle fibers. Russian authors have observed those changes in all the three units of ECC: at the level of Ca-dependent sensors of action potential, in Ca transport system via membranes of sarcoplasmic **reticulum,** and as a part of troponin-tropomyosin myofibrillar complex. Thus, St. Petersburg authors have revealed that 14 day suspension of rats induced more acute, than in control animals, decrease of the amplitude of the single isometric **tension** in m. soleus, isolated in Ca-free environment [1]. In that study, in Ca-free and in Ringer solution post suspension m. soleus demonstrated similar tolerance to fatigue, evoked by a series of tetanic **tensions,** though fatigue tolerance of control m. soleus was considerably reduced in Ca-free environment. The authors think that Ca deficiency acutely decreases sensitivity in Ca-dependent sensors of action potential to repeated stimulation, that after suspension can be compensated by hypothetical abundance of the intrafiber Ca (evidently, diffusing from the sacrolemma). That concept was indirectly confirmed in another series of studies, where isolated control, and post suspension m. soleus had slow Ca channels blocked by **Verapamil.**

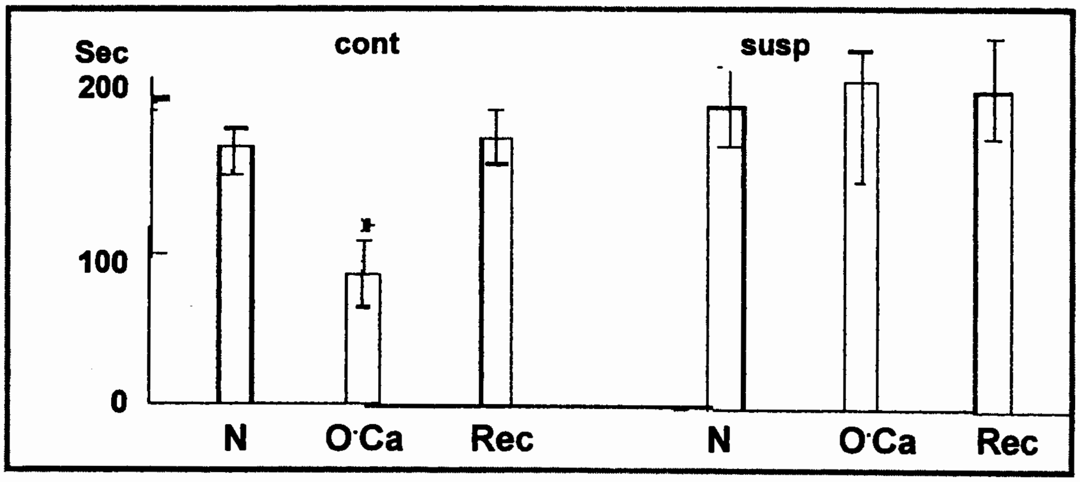


Fig. 19 Isolated soleus fatigue development under normal conditions and in Ca-free media

In control m. soleus series of tetanic tensions in Verapamil environment induced marked increase in fatigability similar to that, demonstrated in Ca-free environment. However, after suspension fatigability in Verapamil environment has also increased (in contrast to Ca-free environment). Thus, results obtained in those series of investigations indicate that 1) decrease in Ca affinity of Ca-dependent sensors of action potential, and 2) accumulation of the intrafiber Ca (more marked under tension), sustain fatigue tolerance of fibers even in Ca-free environment.

Study of Ca-transport properties of rat sarcoplasmic reticulum showed that after 40 days of suspension rate of Ca transport via SR vesicle membranes increases in m. soleus by 31%, in m. gastrocnemius lateralis by 58%, and in m. vastus medialis by 52% [127]. After restoration of support loading acute decrease in rate of Ca transport via SR membranes was observed in m. gastrocnemius homogenate in 4 hours, already. More gradual decrease of that parameter was observed in m. soleus for the 14 day rehabilitation period after cessation of gravitational unloading.

Changes in Ca-binding properties of myofibrillar apparatus were observed in rat muscles after biosatellite flights (joint Russian-French studies): shift of the "Ca/ isometric contraction" curve indicated decreased Ca affinity of myofibrils [37]. That phenomenon was accompanied by the corresponding decrease of slow, and increase of fast protein isoforms of troponin-tropomyosin complex [104,106].

5. Performance, capillarization, and energy potential of muscles under conditions of gravitational unloading

One of the most significant consequences of exposure to microgravity is profound decrease in muscle performance.

After the long term space flight the cosmonauts (n=4) had their isometric performance of knee joint extensors decreased more than by 50%; indices of glycolytic energy supply were a little (insignificantly) increased, and rate of aerobic energy supply, practically, was not altered [135].

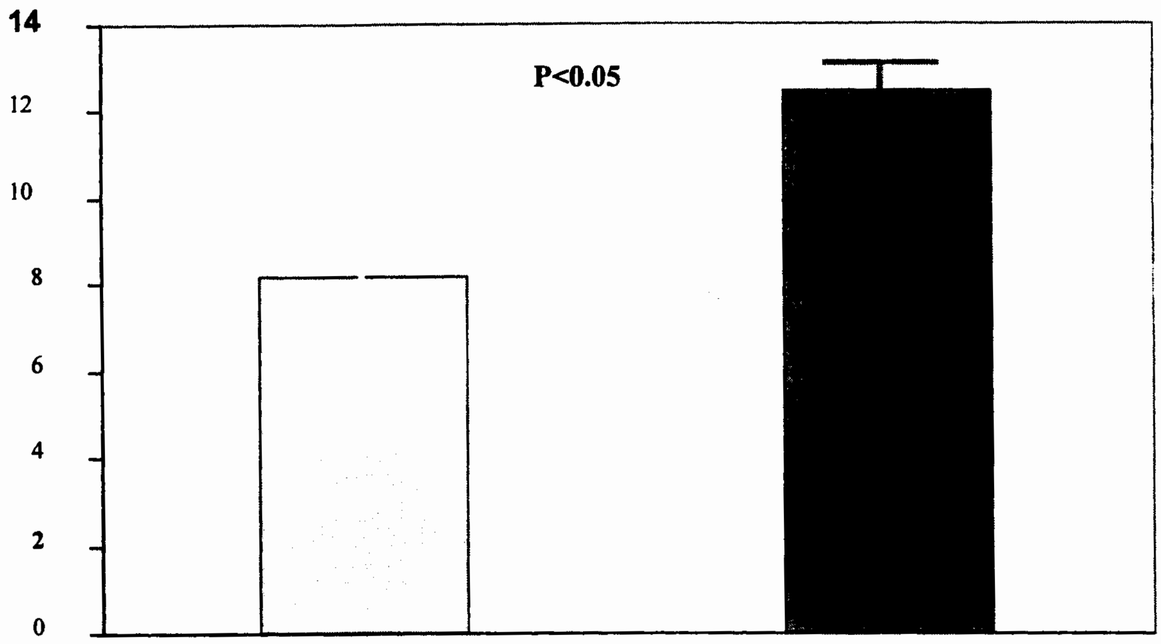


Fig.20. ATP depletion (per force-time integral) during sustained contraction in cosmonauts spent more than 30 days on-board MIR station.

Evaluation of the local performance of calf extensors in cosmonauts after the long-term flights, have revealed its considerable decrease at the background of stable aerobic energy supply, some increase in anaerobic energy production, and deeply reduced efficiency of ATP depletion during muscle contraction.

Thereby, considerably decreased performance of calf extensors during submaximal isometric tension should not be regarded as consequence of changed aerobic energy supply after the 6-month space flight.

Studies, dealing with nature of performance decrease in cosmonauts, have been complemented by simulation experiments. Physiological cost of the submaximal bicycle exercise, usually evaluated by heart rate changes, persistently increased in the course of hypokinesia, which is in agreement with the results of earlier studies [Kakurin et al, 1968]. At the same time, by the 60th day of exposure none heart rate changes were observed in "Penguin group" through the whole exercise.

Sixty day exposure to HDT bed rest without countermeasures resulted in increased lactate level in capillary blood, on the average, by 1.5 times in comparison with the pre-exposure level by the 5th and 30th minutes of test, and by the 3rd minute post test. At the same time, in subjects, wearing "Penguin" suit, lactate level **at those time points of test** was not different from the pre-exposure level (Fig.21,22). By the 120th day of exposure, blood lactate level was similar to that, obtained by the 60th day of hypokinesia at **all time points**.

Evidently, increase in physiological detectors of the exercise cost indicates decreased maximal aerobic performance of humans after hypokinesia.

Among the factors, determining muscular performance, are usually mentioned structural and metabolic parameters of the skeletal muscle transport and utilization system for oxygen and substrates: capillary supply and oxidative potential.

Earlier, incremental test, performed after HDT bed rest and spaceflight, have revealed decrease in **maximal oxygen consumption**, and in **maximal aerobic power**, level of heart rate and lactate concentrations having not been altered [18,25,111].

Nearly all the studied in that sense models of gravitational unloading induce increased capillary density in muscle. For instance, 7 –14 day space flight of rats [19,20], HDT bed rest of Rhesus monkeys [45] resulted in increased capillary density at the background of stable, or a little decreased number of capillaries per one fiber. All the authors are unanimous that that effect is induced by the muscle atrophy, which is more intensive than decrease in capillary number. Our data show, that after long-term space flights decrease in capillary number per fiber in m. vastus lateralis of the cosmonauts have been quite small.

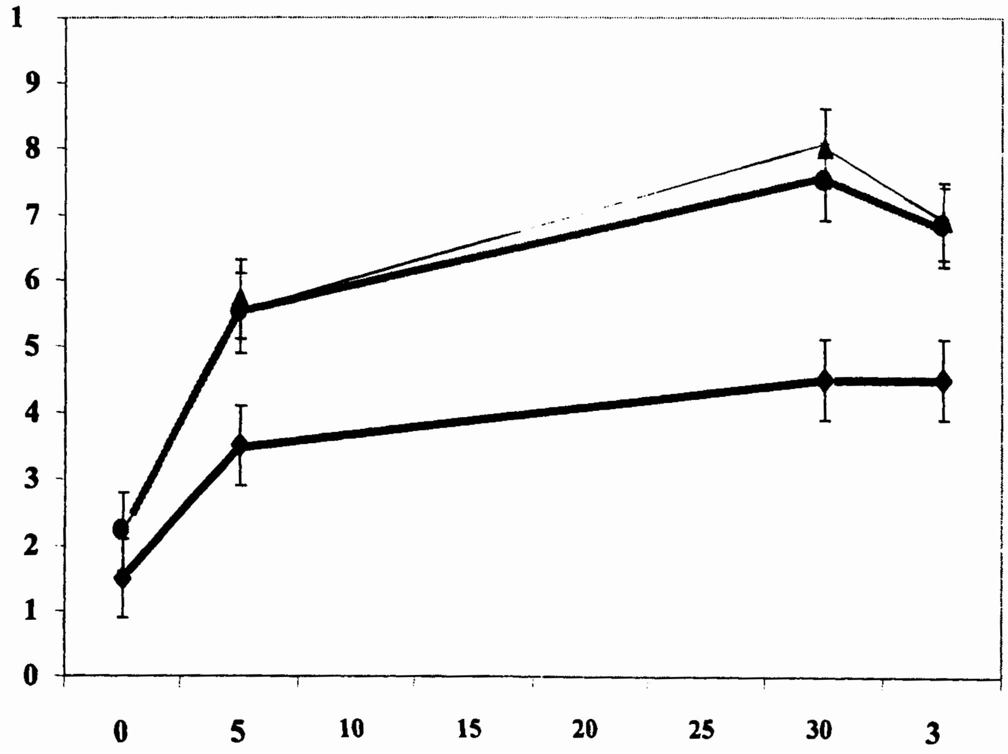


Fig.21. Blood lactate (mM/l) levels during the 30 min cycle submaximal standard supine test in the course of 120-day bed rest (pure bed rest group) (Rhombs – pre, circles – 60 days, triangles – 120 days)

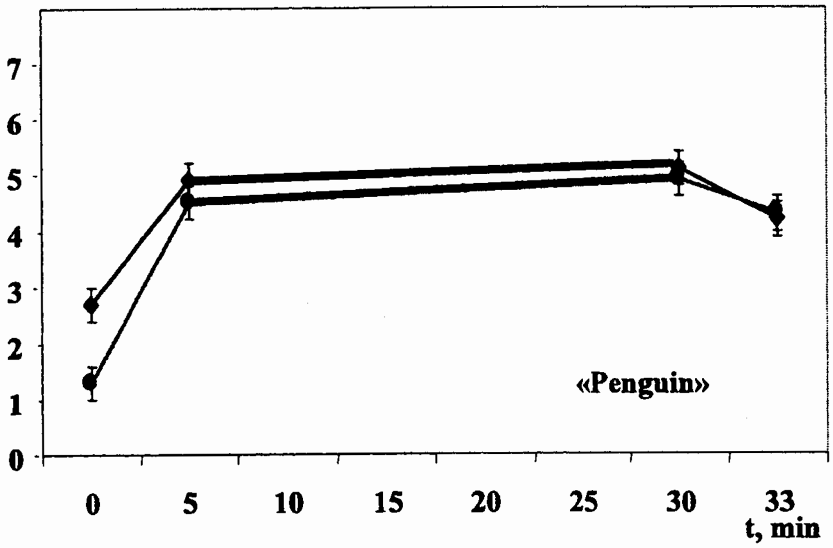


Fig.22. Blood lactate levels during the cycle submaximal standard supine test in the course of 60-day bed rest (Penguin-wearing group) (circles – pre, rhombs – 6- days)

At the same time, after 11 day space flight decrease in capillary number per fiber was especially marked in astronauts' m. vastus lateralis [23].

In cosmonauts, considerable decrease in capillarization level could be prevented by an application of countermeasures, in particular, by physical training, and regular sessions of lower body negative pressure (LBNP). Capillary growth with increased volume blood flow have been shown earlier (see above) [Hudlicka et al, 1982, and other works]. Thus, there is every ground to believe that, at least, physical training, resulting in increase of volume blood flow in skeletal muscles, could prevent reduction in capillarization level of the cosmonauts in the course of long-term space flight. That conception can be examined in lacking countermeasure Rhesus monkey studies of the space flight effects on muscle capillarization level, and in microgravity simulation studies, utilizing physical training.

Two series of Rhesus monkey studies revealed considerable reduction of capillary number (for more than 20%) in antigravity extensor muscles of upper and lower limbs in space-flown animals, and lack of such changes in control animals [122]. Those results are in agreement with the earlier data, obtained from weightlessness-exposed rats [19-20].

Thus, actual weightlessness results in pronounced decrease in capillary number, and to increased (or constant) capillary density. Judging by results from the Rhesus studies, without countermeasures, that decrease should be rather considerable in humans if they do not use countermeasures. In that case, dynamics of changes, their dependence on biomechanical factors, and efficiency of physical countermeasure may be followed in ground-based studies.

The first series of female studies, without application of physical exercises in the course of HDT bed rest, exposed a little reduction (by 10.2%) in capillary number per fiber by the 60th day of hypokinesia; and approximately the same level on the 120th day. At the same time, capillary density has considerably increased by the 120th day of the study. In second series of female studies, with application of physical exercises, by the 60th day of HDT bed rest capillary number per fiber was significantly higher in comparison with the initial level (about 20%); considerable changes in capillary density were not observed [81].

In the course of HDT bed rest application of physical exercises enabled not only to maintain capillary number at the initial level, but even to somewhat increase it. The obtained data confirm hypothesis that regards physical training as the cause for low capillary atrophy in the Russian cosmonauts in comparison the American astronauts119,124].

At the same time, for disclosing role of supportlessness in muscle capillarization changes under weightlessness conditions, HDT bed rest studies should be complemented by the data, derived from dry immersion studies. After 3 day of dry immersion capillary number per fiber demonstrated only a little tendency to decrease, and capillary density has increased. By the 7th day, number of capillaries per fiber was similar to that, observed on the 4th day of dry immersion, and capillary density exceeded that, found on the 3rd day.

The described data do not allow to consider decrease in capillarization level, observed in the cosmonauts and astronauts, as well as in the Rhesus monkeys, exposed to actual weightlessness, and in the rats, exposed to actual and simulated weightlessness, to have been induced by one of the aforementioned biomechanical microgravity factors. Decrease in muscle blood flow may be one of the causes of reduction in number of muscle capillaries under weightlessness conditions [McDonald et al, 1992]. Contribution of biomechanical factors, inducing decrease in blood flow, requires further study.

Thus, under actual microgravity conditions changes in capillary supply of the human and Rhesus antigravity muscles have been found to be more intensive in comparison with changes, observed in ground-based simulation studies. Under actual or simulated microgravity conditions, decrease in a number of capillaries in skeletal muscles, as a rule, does not result in decreased capillary density, and, consequently, in impaired morphological background for the oxygen and energy substrates transport to muscle fiber mitochondria. Therefore, it can not be cause of decline in physical performance.

Exercise physiology considers an oxidative potential, i.e. ability of tissue to aerobic energy production, to be one of the most important factors, determining muscular performance (see above).

Space flight and suspension induce considerable decrease in oxidative capacity of muscles, which was demonstrated in space-flown rats [26,27,16,86]. The decrease can be caused by not only increased interstitial muscle space [Martin et al, 1979, Kandarian et al, 1981], but also by changes in fiber ratio: reduction in oxidative type I fibers, and elevation in type II fibers, affecting muscle oxidative potential as a whole. At the same time, postflight decrease in rat m. soleus oxidative capacity per mass unit of mitochondria protein, revealed by the Russian authors, is a quite noticeable fact [16]. Under conditions of gravitational unloading nature of that phenomenon may be related to changes in qualitative content of phosphorylating mitochondria components.

It is also important, that results of the joint Russian-American [10], and Russian-French [19,20] studies have exposed considerable changes in pattern of mitochondria distribution inside m. soleus fibers: volume density of mitochondria (and, correspondingly, activity of oxidative enzymes) increases (or does not change) in the center of fiber, and decreases at its periphery, in subsarcolemmal area.

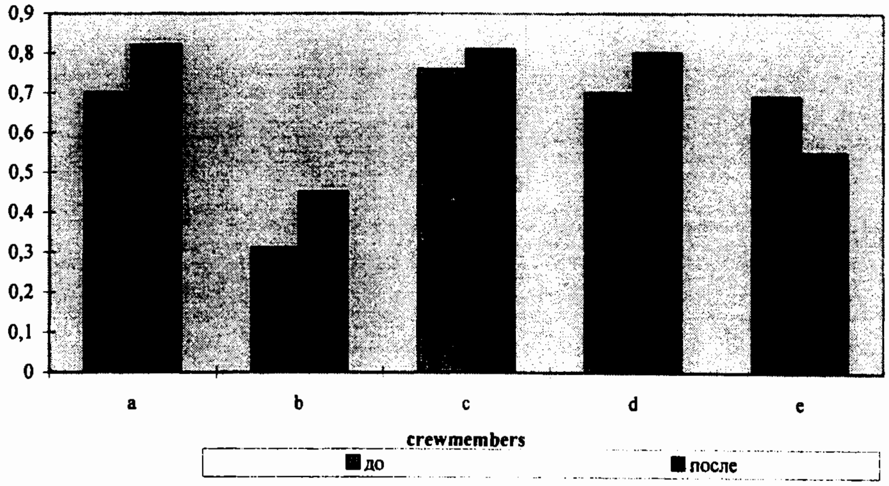
Data, derived from human HDT bed rest studies, somewhat disagree with results of animal studies. After 49 day HDT bed rest the Russian authors have observed small decrease in activity of m. soleus oxidative enzymes (visual evaluation of histochemical samples) [42]. Our results show that by the 60th day of bed rest, activity of succinate dehydrogenase (SDH) have been found to be markedly decreasing in fast fibers of m. gastrocnemius lateralis; by the 120th day, it have returned to the initial level in fast fibers, while manifesting significant decrease in slow type I fibers [76,78]. Later, when subjects started program of physical training at the background of hypokinesia, oxidative potential was restored to the initial level; however, after the 240th day it was found to be decreasing, and by the 300th day it comprised 75 – 77% from the initial. By the 365th day of hypokinesia oxidative activity reached plateau at the level of 82 – 85% from the initial. Changes were rather similar in fibers of both types.

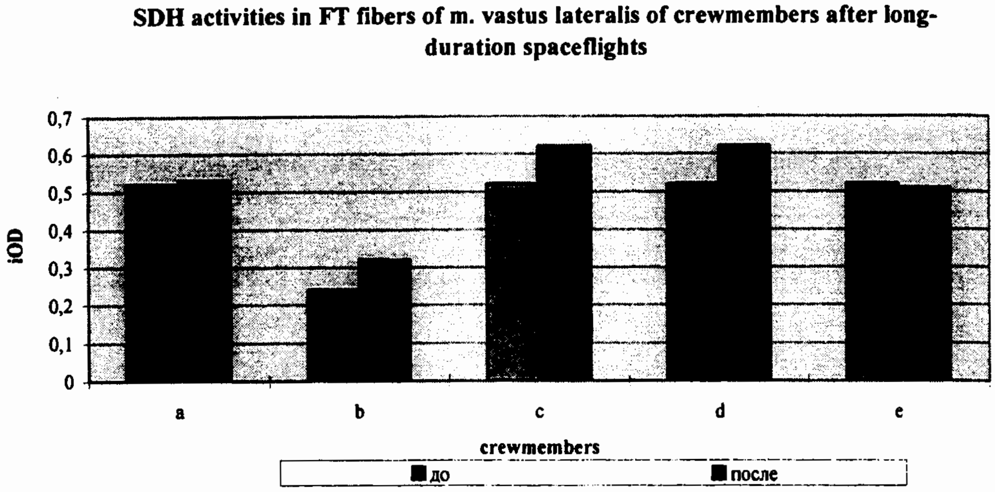
In muscle fibers of the most cosmonauts postflight SDH activity was elevated in comparison with the preflight level; in three cosmonauts SDH activity was increased in both fiber types (Fig.23). Decrease of enzyme activity, approximately by 20%, was observed only in cosmonaut E.[119,124]

In m. vastus lateralis fibers decrease in activity of mitochondrial enzymes was also observed under HDT bed rest conditions [13,14,25, and other works]. Comparison of the results from the present study with **reference data** suggests that unexpected increase in SDH activity, induced by space flight, was caused by countermeasure training. That concept was confirmed by data, derived from comparison of individual values for SDH activity with the volume of countermeasures. Of all the examined cosmonauts, only E (who had decreased postflight SDH activity) performed not more than 50% of the recommended volume of physical training.

If we assume that weightlessness induces only small decrease in human fiber SDH activity (according to results from short term weightlessness exposure studies) [23], then, large volume of physical training can really cause increase in SDH activity. That concept was examined in Rhesus monkey study without countermeasures, aimed at revealing weightlessness effects on the muscle oxidative potential [11,122].

SDH activities in ST fibers of m. vastus lateralis in crewmembers after long-duration spaceflights





SDH activities in FT fibers of m. vastus lateralis of crewmembers after long-duration spaceflights

Fig.23. SDH activities in crewmembers before and after long-duration spaceflights with countermeasures.

In both series of studies we have not found significant in-flight changes in activity of SDH and НАДН-TR in Rhesus m. soleus fibers; in one Rhesus maximal respiration of mitochondria in skinned fibers of m. soleus have not differed from the control level. Those results fully agree with the earlier data, derived from rat m. soleus in similar studies [Chi et al, 1992, and other works]. At the same time, lack of changes in concentration of enzymes, along with substantial reduction of fiber volume, indicate considerable decrease in content of enzymatic molecules, proportional to decrease in the total protein content.

Quantitative ultrastructural analysis showed some postflight decrease in volume density of mitochondria only in subsarcolemmal area of Rhesus m. soleus fibers. That data fully agree with the results, earlier obtained from rat studies. For instance, it was shown that in space-flown rats mitochondria volume density, and activity of mitochondria enzymes were redistributed from periphery to center [115]. The present study for the first time revealed tendency to reduction in volume density of subsarcolemmal mitochondria after exposure to space flight conditions.

In spite of the total small changes of mitochondria density in m. soleus fibers, more detailed investigation of m. soleus mitochondria populations have disclosed a pronounced tendency to decreased number of mitochondria profiles per CSA unit, and to increased average area of mitochondria profile only in space-flown animals. It could be suggested that the observed changes have been meant to reduce diffusion surface of mitochondria apparatus in relation to decrease in volume of muscle fiber.

In space-flown Rhesus monkeys maximal respiration of mitochondria in skinned fibers of m. vastus lateralis was considerably decreased in comparison with cage controls; indices in the capsule group were a little reduced as compared to cage control animals. In m. vastus lateralis activity of oxidative enzymes (especially in type II fibers), and volume density of mitochondria were found to be substantially decreased in space-flown, and in capsule animals (Table 8.) [11].

Table 8. SDH activity in Rhesus monkey m. vastus lateralis

N	FT fibers		ST fibers	
Space flight	Preflight	Postflight	Preflight	Postflight
484	0,186±0,003	0,159±0,004*	0,468±0,013	0,442±0,010
357	0,266±0,006	0,206±0,005*	0,632±0,014	0,592±0,015
Capsule controls	0,301±0,07	0,143±0,008*	0,425±0,050	0,406±0,030
Cage controls	0,206±0,003	0,189±0,010	0,512±0,020	0,466±0,020

Decrease of the oxidative potential in predominantly locomotor muscle may be connected with the total reduction in fiber contractile activity both after exposure to weightlessness, and after restraint (probably, 1g environment mostly affects locomotor muscles in comparison with postural antigravity muscles, though gravitational loading prevents considerable decrease in their functional activity).

Under HDT bed rest conditions decrease of human performance is also attributed to changes in oxygen utilization by muscle mitochondria, i.e., to decrease in oxidative potential. Among other objectives, that female study has been following dynamics in mitochondria apparatus to reveal changes of m. gastrocnemius medialis oxidative potential after 60 day HDT bed rest (Table 9).

Table 9. Volume density of mitochondria, lipid droplets and bilaminary components in slow-twitch fibers of m. gastrocnemius medialis before and after 60 day female HDT bed rest

	Mitochondria	Bilaminary components	Lipid droplets
Subsarcolemmal area			
Before	4,40 ± 0,43	0,02 ± 0,01	0,39 ± 0,08
60 days	2,68 ± 0,34*	0,09 ± 0,03*	1,35 ± 0,28*
Central area			
Before	2,81 ± 0,46	0,02 ± 0,02	0,31 ± 0,10
60 days	2,65 ± 0,40	0,16 ± 0,09	0,84 ± 0,25

The present study has for the first time disclosed decrease in volume density of subsarcolemmal mitochondria after the long term human hypokinesia. Increase in volume density of lipid droplets was also observed after hypokinesia; similar phenomenon in human m. soleus was reported earlier [36]. It is likely that accumulation of intrafiber lipids have been caused by decreased level of lipid oxidation under conditions of gravitational unloading [6].

Thus, various numerous studies have revealed that

- under conditions of gravitational unloading, decrease of the oxidative potential in fibers of tonic slow musculature, on the whole, occurs proportional to decrease in volume of the fiber contractile apparatus, preliminary observations testifying for the tendency towards reconstruction of the very spatial organization of mitochondrial apparatus, aiming at reduction of diffusion surface of mitochondrion membrane;
- in most cases, fibers of those muscles reveal tendency towards predominant decrease in mitochondria volume density, and in activities of oxidative enzymes per volume unit in subsarcolemmal area;
- in most cases, gravitational unloading induced tendency towards decreased oxidative potential per volume unit in predominantly locomotor muscles, the fact allowing to suggest realization of some other pattern of adaptation to hypogravity conditions in those muscles.

6. CONCLUSION

The numerous studies performed in Russian laboratories described not only the main phenomena related to the muscle plasticity under conditions of actual and simulated weightlessness, but some physiological and cellular mechanisms underlying these phenomena.

There is no doubt that the development of different muscle events under these conditions is caused by changes in muscle functioning, which are determined in turn by changes of motor control mechanisms, induced by alterations in afferent input signals. The authors of the review have tried to make a schematic overview (Fig.24} of the hypothetical mechanisms of these changes.

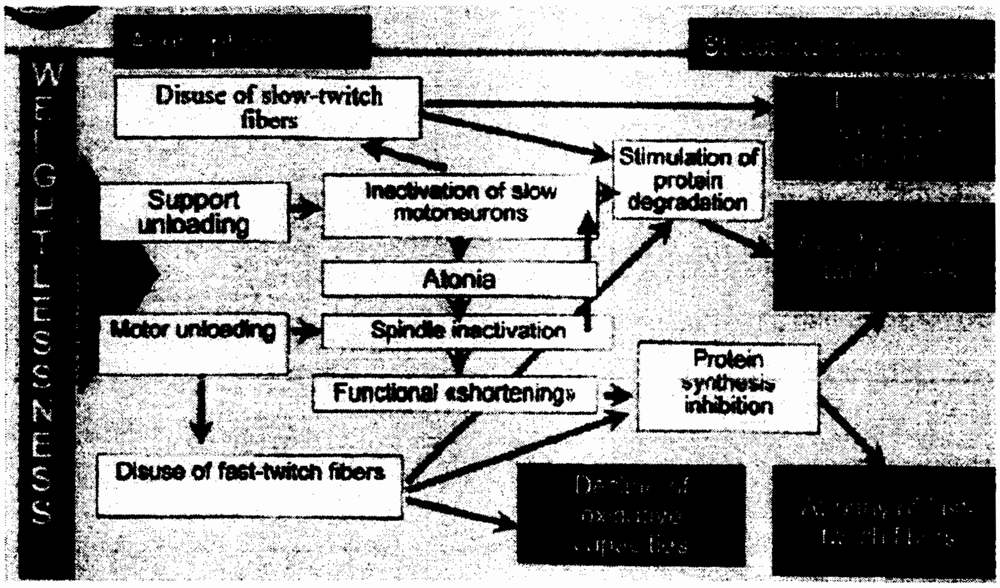


Fig.24. Physiological mechanisms of muscle adaptation to microgravity (hypothesis) (I.B.Kozlovskaya, B.S.Shenkman)

The hypothetical scheme supposes that the main trigger input for the changes in muscle tonic system is withdrawal of support. The elimination of support stimuli leads to inactivity of tonic "small" motoneurons, which in turn causes the acute drop of muscle tone (measured as muscle stiffness) [51,68]. These events underlies the acute decline in voluntary contractile properties. The mentioned prolonged relaxation induces the proprioceptive deprivation and apparent "passive shortening" of the antigravity muscle. It is known that shortening inhibits the aminoacid incorporation, i.e. protein synthesis in muscle. The continuous disuse of slow-twitch fibers leads to increased proteolysis, changes in myosin isoform expression patterns and decline in muscle oxidative capacities.

The adaptation of phasic system to unloading is less known update. The deprivation of loaded motor activities may be the main trigger for this process. It seems evident that in phasic muscle fibers decline in oxidative potential is more profound than that in tonic muscles. The monkey studies revealed that structural parameters of these muscles were more sensitive to limitation of amount of movement than tonic ones.

The aforementioned data and theoretical considerations became the physiological basis for the Russian countermeasure system, elaborated for the long-duration missions on-board MIR station [72]. The system is based on several physiological principles, formulated on the basis of data, obtained in the course of numerous on-board, pre- and post flight and on-ground simulation studies, performed in Russian laboratories. Among these principles are:

- support loading;
- resistive activity of antigravity muscles, performed in natural form (loaded running)
- increase of proprioceptive and support afferent input;

The usefulness of these principles were confirmed not onle in experimental studies but also in the practice of countermeasure performing by Russian crewmembers.

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REPORT

Results of the Studies of the Effects of Space Flight Factors on Human Physiological Systems and Psychological Status, and Suggestions of Future Collaborative Activities Between the NSBRI and the IBMP

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