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Original Article

Contractile Responses of Murine Hearts Subjected to Different Modes of Motor Activity to Traumatic Brain Injury

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Abstract

For the first time ever, this research studied the response of stroke volume in animals to various modes of motor activity after a traumatic brain injury. The study showed a pronounced decrease in stroke volume (SV) the first day after modeling an open craniocerebral injury in rats of all age groups. At the same time, the smallest SV response to brain injury was observed in immature animals. After modeling a traumatic brain injury, it was found that the implementation of systematic dynamic exercises by animals of pre-senile agedoes not contribute to increase SV; a significant increase in SV after a traumatic brain injury is observed only in immature animals. It was revealed that limiting physical activity and the performance of isometric exercises after a traumatic brain injury restrain a natural increase in SV in immature rat pups and decrease SV in sexually mature and pre-senile animals.

Keywords: traumatic brain injury, stroke volume, modes of motor activity

Réponses Contractiles des Cœurs Murins Soumis à Différents Modes d'Activité Motrice à une Lésion Cérébrale Traumatique

Résumé: Pour la toute première fois, cette recherche a étudié la réponse du volume systolique chez les animaux à divers modes d'activité motrice après une lésion cérébrale traumatique. L'étude a montré une diminution prononcée du volume systolique (VS) le premier jour après la modélisation d'une lésion cranio-cérébrale ouverte chez les rats de tous les groupes d'âge. Dans le même temps, la plus petite réponse SV aux lésions cérébrales a été observée chez les animaux immatures. Après avoir modélisé une lésion cérébrale traumatique, il s'est avéré que la mise en œuvre d'exercices dynamiques systématiques par des animaux d'âge présénile ne contribue pas à l'augmentation du VS; une augmentation significative du VS après une lésion cérébrale traumatique n'est observée que chez les animaux immatures. Il a été révélé que la limitation de l'activité physique et la performance des exercices isométriques après une lésion cérébrale traumatique restreignent une augmentation naturelle du VS chez les jeunes rats immatures et diminuent le VS chez les animaux sexuellement matures et

préséniles.
Mots-clés: Lésion Cérébrale Traumatique, Volume Systolique, Modes D'activité Motrice

1. Introduction

Today, traumatic brain injury (TBI) remains one of the main problems in both domestic and foreign medicine. In the Russian Federation, death due to trauma ranks second, with mortality from severe TBI at 60-80% or more. TBI leads to structural and functional brain damage with motor and cognitive impairments of various degrees and prevalence rates. Studying the epidemiology of TBI is a necessary basis for organizing rational assistance to victims and developing adequate measures for the primary and secondary prevention of damage to the central nervous system (1).

Rehabilitation is an integral part of the treatment process in patients with TBI.

The absence of a rehabilitation stage of treatment condemns the patient and his relatives to a long and painful process of self-treatment, which sometimes ends with a severe disability or death for the patient.

Various modes of physical activity are widely used in rehabilitation measures.A number of authors have devoted their studies to the investigation of the laws of influence of various modes of physical activity on heart functions in ontogenesis (2-7). Moreover, a significant number of works has been carried out on the effects of enhanced motor activity on the heart functions of a mature organism, yet the peculiarities of the function of the heart in immature animals subject to various modes of motor activity have not been sufficiently studied (8, 9). Few works in the literature have studied the characteristics of changes in the function of the heart of a developing organism subjected to various modes of physical activity after suffering a brain injury are extremely rare. Thus, the current study aimed to investigate the indicators of the pumping function of the heart in rats exposed to various modes of motor activity after modeling a traumatic brain injury.

2. Material and Methods

White outbred laboratory rats aged 21-210 days were used in the experiments. The rats were categorized according to their anatomical and physiological characteristics, as proposed by V.I. Makhinko, V.N. Nikitin (1975). All work with laboratory animals was in compliance with the basic regulatory and ethical requirements for laboratory and other experiments with the participation of experimental animals of different species.

Traumatic brain injury was modeled according to the method described in the article by foreign scientists: Sleep deprivation exacerbates concussive head injury-induced brain pathology;neuroprotective effects of nanowired delivery of cerebrolysin with α-melanocyte-stimulating hormone.

The animals were concussed (cerebral edema) under anesthesia with etaminal (intraperitoneally 40-50 mg/kg). The surgical stage of anesthesia was determined by the absence of a corneal reflex in the animal. The scalp was shaved and treated with an aseptic solution. Then a median longitudinal incision (2 cm) was made in the right parietal region of it, and trepanation was performed with a cutter (2 mm lateral to midline). The dura mater was left intact. Aweight, a steel cylinder weighing 114.6 g, was dropped from a height of 20 cm along a guide tube, thereby striking the area of the trepanation window in the right parietal region of the brain. After injury, the skin of the animals was tightly sutured with surgical thread (0.2 mm), and the suture was treated with an antiseptic solution. Antibiotic therapy was carried out intramuscularly with a solution of gentamicin. With this weight and distance,

the right parietal region of the brain was exposed to 0.224 N.

Experiments with animals after modeling TBI were organized into three age groups. The first group included immature animals, i.e. from 21 to 51 days of age. The second group consisted of mature animals, from 70 to 100 days of age. The third group included pre-senile animals, from 180 to 210 days of age.

Within each age group, animals were divided into four subgroups. Each subgroup was subjected to its own established regimen of physical activity. Animals of the first subgroup (control) were kept in the usual conditions of the vivarium for 9-12 animals under unlimited motor activity (UPA). The second subgroup underwent enhanced motor regimen. The animals systematically and forcibly performed stepwise muscle swimming training (MST) increasing in time. The third subgroup of animals was limited in motor activity, i.e. hypokinesia (LMA). Animals of this group were subjected to daily hour-long restriction of physical activity by stretching and fixing the limbs on a special table. The fourth subgroup of animals was systematically subjected to the isometric exercise (IE) regimen. On the turntable, animals with fixed limbs hung upside down daily. The execution time gradually increased from 5 minutes on the first day up to about 2 hours at the end of the experiment.

To determine the SV, tetrapolar chest rheography was used (10). The differentiated rheogram was recorded in dynamics in anesthetized animals during natural respiration using an RPG-204 device.

To assess the significance of differences, standard student t-test values were calculated.

3. Results

3.1. Changes in SV in Immature Rats Exposed to Different Modes of Physical Activity After a Traumatic Brain Injury

As our studies show, stroke volume (SV) in control rat pups of 21 days of age was 0.051 ± 0.006 ml (Table 1). In the process of natural growth and development of these rat pups within 30 days, SV values increased by 0.111 ml and amounted to 0.162 ± 0.008 ml ($p<0.05$). Consequently, immature rat pups from 21 to 51 days of age had a natural age-related increase in systolic blood ejection values.

UMA rat pups aged 21 days had a SV equal to 0.049±0.009 ml. On the second day after modeling the traumatic brain injury (TBI), SV decreased to 0.034 ± 0.002 ml. This value was 0.015 ml less than the initial data ($p<0.05$). During the subsequent maintenance of these rat pups under conditions of unrestricted motor activity (UMA) for 30 days, SV significantly increased in comparison with the initial data and reached 0.137 ± 0.009 ml ($p<0.05$). This value was 0.088 ml more than the initial data ($p<0.05$). Consequently, immature animals that underwent TBI showed a slight increase in SV during the next 30 days of maintenance under unrestricted motor activity (UMA). However, comparing the values of SV of animals of control group and the UMA group at 51 days of age revealed a significant difference. According to the current data, SV in UMA animals was 0.023 ml less than that in control animals of the same age ($p<0.05$). Consequently, animals with TBI had a slight slowdown in the process of natural increase in SV. Most likely, this is due to a violation of the autonomic regulation of the heart function as a consequence of TBI in these animals.

In immature rat pups of the MST group aged 21 days, SV was 0.053 ± 0.007 ml. On the second day after modeling the traumatic brain injury, SV was 0.028 ± 0.004 ml. This value was 0.025 ml less than the initial data ($p<0.05$). In performing dynamic swimming exercises over the next 30 days, SV in these rat pups significantly increased. Enhanced motor regimen (MST) by the age of 51 days caused an increase in SV by 0.126 ml compared with the initial data ($p<0.05$). Consequently, it can be argued that in immature animals that had undergone a craniocerebral injury at

21 days of age, performing the subsequent stepwise-increasing dynamic exercises in the form of swimming contributed to a significant increase in stroke volume.

In immature rat pups of the LMA group at 21 days of age, SV was 0.052 ± 0.008 ml. On the second day after modeling the TBI, SV was 0.031 ± 0.003 ml. This value was 0.021 ml less than the initial data (p<0.05). With an hour-long restriction of physical activity daily, stretching and fixing the limbs on a special table for 30 days in these rat pups revealed that SV increased compared with the initial data by 0.074 ml and amounted to 0.126 ± 0.004 ml (p<0.05). This value was 0.037 ml less than the SV of animals in the control group (p<0.05). Therefore, it can be argued that in immature animals that have undergone traumatic brain injury, the subsequent 30-day restriction of motor activity restrains the natural age-related increase in stroke blood volume.

In immature rat pups of the IE group aged 21 days, SV was 0.050 ± 0.006 ml. On the second day after modeling the TBI, SV was 0.029 ± 0.005 ml,a value 0.021 ml less than the initial data (p<0.05). Starting from the age of 21 days after suffering a TBI, over the next 30 days, the animals were tightly fixed on a turntable and gradually accustomed to hanging upside down (antiorthostasis). The performance of systematically increasing isometric exercises for 30 days led to an insignificant increase in SV. Thus, by the age of 51 days, SV in these animals was 0.115 ± 0.007 ml, which was 0.065 ml more than the initial data (p<0.05). However, this value was 0.046 ml less compared to the SV of animals of the same age in the control group (C) (p<0.05). Consequently, the performance of isometric exercises after TBI leads to a significant inhibition of the natural age-related increase in SV.

The results of this study indicate that after a traumatic brain injury, the most favorable mode of physical activity for immature rat pups is the performance of dynamic exercises in the form of systematic swimming. Restriction of motor activity and performance of isometric exercises after TBI significantly restrain the natural age-related increase in the SV of immature animals.

Table 1. Changes in SV in immature rats exposed to different modes of physical activity after a TBI

Motor activity regimen	n (number of animals)	SV (ml)		
		day 21 (initial)	day 21 (after trepanation)	day 51 (experiment)
C	9	0.051 ± 0.006		0.162 ± 0.008
UMA	11	0.049 ± 0.009	0.034 ± 0.002	0.137 ± 0.009
MST	10	0.053 ± 0.007	0.028 ± 0.004	0.179 ± 0.005
LMA	12	0.052 ± 0.008	0.031 ± 0.003	0.126 ± 0.004
IE	9	0.05 ± 0.006	0.029 ± 0.005	0.115 ± 0.007

3.2. Changes in SV in Mature Rats Exposed to Different Modes of Physical Activity after TBI

In mature control animals aged 70 days, SV was 0.221 ± 0.004 ml (Table 2). In the process of natural growth and development of animals, SV gradually increased, and by the age of 100 days SV reached 0.238 ± 0.006 ml (p<0.05). The difference between the initial values of SV in these animals by days 70 and 100 of age was 0.017 ml (p<0.05). Consequently, sexually mature rats from 70 to 100 days of age had a slight increase in their SV.

The UMA rats aged 70 days had an SV equal to 0.225 ± 0.007 ml. On the second day after modeling the TBI, the SV in these animals decreased to 0.191 ± 0.003 ml,a value 0.034 ml less than the initial data (p<0.05). During the subsequent maintenance of UMA rats for 30 days, SV did not change significantly. By day 100 of age, the SV of these animals was 0.223 ± 0.007 ml,a

value 0.002 ml less than the initial data. Consequently, in control animals who had a TBI at 70 days of age and were kept in the UMA regimen until 100 days of age, SV values remainedat approximately the same level, i.e. there was no increase in their SV.

In mature rats of the MST group aged 70 days, SV was 0.220 ± 0.006 ml. On the second day after modeling TBI, the systolic blood ejection was 0.195 ± 0.007 ml,a value 0.025 ml less than the initial data (p<0.05). After suffering a craniocerebral injury and in the process of dynamic swimming exercises within 30 days, the rats showed a significantly increased SV. Enhanced motor regimen (MST) by day 100 of age caused an increase in SV by 0.039 ml compared to the initial data (p<0.05). Consequently, in mature animals that had undergone TBI at the age of 70 days, the subsequent systematic performance of dynamic exercises led to a significant increase in SV. In contrast to all other studied groups, these animals had an increase in SV. Systematic performance of dynamic exercises after a traumatic brain injury contributes to an increase in systolic blood volume values.

At 70 days of age, in mature rats of the LMA group, the SV was 0.224 ± 0.008 ml. On the second day after modeling TBI, SV was 0.192 ± 0.004 ml, a value 0.032 ml less than the initial data (p<0.05). With the daily restriction of physical activity for 30 days in these rats, SV decreased in comparison with the initial data by 0.020 ml and amounted to 0.204 ± 0.008 ml (p<0.05). Therefore, in animals with TBI, the subsequent restriction of motor activity (LMA) from 70 to 100 days of age causes a significant decrease in SV.

In mature animals of the IE group aged 70 days of age, SV was 0.223 ± 0.005 ml. On the second day after modeling TBI, the SV in these animals was 0.194 ± 0.006 ml,a value 0.029 ml less than the initial data (p<0.05). Starting at 70 days of age after suffering TBI, the animals were hung upside down on aturntable for the next 30 days (antiorthostasis). The performance of systematically increasing isometric exercises by these animals for 30 days led to a significant decrease in SV. By 100 days of age, SV was 0.197 ± 0.003 ml, which was 0.026 ml less than the initial data (p<0.05). Consequently, performing isometric exercises after a TBI leads to a significant decrease in SV.

Summarizing the above, it can be stated that modeling TBI at 70 days of age led to a decrease of about 0.025-0.030 ml (p<0.05) in SV in all examined groups of animals. However, subsequent regimens of motor activity within 30 days did not equally affect the indices of systolic SV. The most favorable regimen of physical activity for mature rats with TBI was dynamic exercises in the form of systematic swimming. This regimen, in contrast to all others, contributed significantly to an increase in SV in mature animals. Restriction of motor activity and performance of isometric exercises after TBI significantly reduced SV.

Table 2. Changes in SV in mature rats exposed to different modes of physical activity after a traumatic brain injury

Motor activity regimen	n (number of animals)	SV (ml)		
		day 70 (initial)	day 70 (after trepanation)	day 100 (experiment)
C	12	0.221 ± 0.004		0.238 ± 0.006
UMA	10	0.225 ± 0.007	0.191 ± 0.003	0.223 ± 0.007
MST	9	0.22 ± 0.006	0.195 ± 0.007	0.259 ± 0.005
LMA	9	0.224 ± 0.008	0.192 ± 0.004	0.204 ± 0.008
IE	11	0.223 ± 0.005	0.194 ± 0.006	0.197 ± 0.003

3.3. Changes in SV in Presenile Rats Exposed to Different Modes of Physical Activity after TBI

In control animals aged 180 days, SV was 0.237 ± 0.009 ml (Table 3). In the process of natural growth and development in these animals, SV gradually increased, reaching 0.258 ± 0.006 ml by the age of 210 days (p<0.05). The difference between the initial values of SV in these animals and those of days 180 and 210 of age was 0.021 ml (p<0.05). Consequently, the rats showed a slight increase in their SV in the course of natural activity from 180 to 210 days of age.

The UMA rats aged 180 days had an SV equal to 0.234 ± 0.006 ml. On the second day after modeling TBI, the SV in these animals decreased to 0.206 ± 0.008 ml,a value 0.028 ml less than the initial data (p<0.05). During the subsequent maintenance of these rats for 30 days, SV significantly decreased. By day 210 of age, the SV of these animals was 0.219 ± 0.005 ml,a value 0.015 ml less than the initial data (p<0.05). Consequently, in control animals who had TBI at 180 days of age and were kept in the UMA regimen until 210 days of age, the values of SV decreased. A natural insignificant increase in SV was not observed in these animals.

In rats of the MST group aged 180 days, SV was 0.236 ± 0.004 ml. On the second day after modeling TBI, the systolic blood ejection was 0.209 ± 0.005 ml,a value 0.027 ml less than the initial data (p<0.05). With dynamic swimming exercises after suffering a craniocerebral injury within 30 days in these rats, SV did not change significantly. Enhanced motor regimen (MST) by day 210 of age caused an increase in SV by 0.230 ml compared to the initial data (p<0.05). Consequently, in presenile animals with TBI at the age of 180 days, the subsequent systematic performance of dynamic exercises did not cause an increase in systolic SV.

At 180 days of age in rats of the LMA group, SV was 0.238 ± 0.001 ml. On the second day after modeling TBI, the SV was 0.207 ± 0.009 ml,a value 0.031 ml less than the initial data (p<0.05). With daily restriction of physical activity for 30 days in these rats, SV decreased in comparison with the initial data by 0.027 ml and amounted to 0.211 ± 0.007 ml (p<0.05). Therefore, in animals with TBI, the subsequent restriction of motor activity (LMA) from 180 to 210 days of age caused a significant decrease in SV.

In animals of the IE group aged 180 days of age, SV was 0.223 ± 0.005 ml. On the second day after modeling TBI, the SV in these animals was 0.204 ± 0.006 ml,a value 0.029 ml more than the initial data (p<0.05). Starting at 180 days of age after suffering TBI, the animals hung upside down on the turntable for the next 30 days (antiorthostasis). The performance of systematically increasing isometric exercises by these animals for 30 days led to a significant decrease in SV. By 210 days of age, SV was 0.196 ± 0.008 ml, which was 0.037 ml less than the initial data (p<0.05). Consequently, performing isometric exercises after a traumatic brain injury leads to a significant decrease in stroke volume.

The results indicate that modeling of a TBI at 180 days of age led to a decrease of about 0.0030 ml (p<0.05) in SV in all examined groups of animals. However, the subsequent modes of physical activity within 30 days had a multidirectional effect on SV. The most favorable regimen of physical activity for animals with TBI was dynamic exercises. In these animals, SV did not undergo significant changes, remaining approximately at the level of the initial values. Restriction of motor activity and performance of isometric exercises after TBI significantly reduced SV.

Table 3. Changes in SV in presenile rats exposed to different modes of physical activity after a traumatic brain injury

Motor activity regimen	n (number of animals)	SV (ml)		
		day 180 (initial)	day 180 (after trepanation)	day 210 (experiment)
C	12	0.237 ± 0.009		0.258 ± 0.006
UMA	11	0.234 ± 0.006	0.206 ± 0.008	0.219 ± 0.005
MST	10	0.236 ± 0.004	0.209 ± 0.005	0.228 ± 0.004
LMA	11	0.238 ± 0.01	0.207 ± 0.009	0.211 ± 0.007
IE	9	0.233 ± 0.005	0.204 ± 0.006	0.196 ± 0.008

4. Discussion

On the second day after modeling an open TBI, rats of all age groups showed a pronounced increase in heart rate. This is believed to be due to the combined damage of both frontal lobes and the brain stem by increasing edema, which reveals an increased activity of the dopaminergic system and a tendency to increase in the activity of the peripheral (adrenaline) link of the sympathetic system. In case of damage to the two main central regulatory structures of the sympathetic nervous system (frontal lobes and brainstem), the response to TBI proceeds mainly in the peripheral type with an increase in adrenaline levels and a decrease in the norepinephrine/epinephrine ratio (NE/EP) (11). The regulation of the central link of the sympathetic system is carried out through the interaction of the frontal lobes with the noradrenergic pontine center (A5 and A6 nuclei). The peripheral link of the sympathetic system also has its own central regulatory center located in the medulla oblongata (adrenergic C1 nuclei) and under the inhibitory control of the locus coeruleus (LC)) (12). It can be assumed that such an arrangement of the regulatory center determines its greater safety in case of injury due to the more rare primary damage to the medulla oblongata or its incompatibility with life. Therefore, in surviving animals with trunk injuries, damage to the central link is more likely, and therefore, the response to trauma occurs through activation of the peripheral link of the sympathetic system, as was noted in the examined sample of animals.

The conducted studies showed that after a TBI, the most favorable regimen of physical activity for immature rat pups is dynamic exercises in the form of systematic swimming. In our opinion, this fact is explained as follows. Against the background of natural processes occurring in the developing organism of rat pups, dynamic muscle training at earlier stages of postnatal development causes significant changes in the heart itself and the mechanisms of its regulation. First, myocardial hypertrophy develops at a significant rate. Second, muscle training, organized at earlier stages of postnatal development, significantly alters the sympathetic and parasympathetic influences as well as their ratio in the regulation of the pumping function of the heart. Muscle training also contributes to the faster maturation of intracardiac regulatory mechanisms.

Limited physical activity and isometric exercises after a traumatic brain injury maintained the heart rate at an increased level in all age groups of animals and also significantly restrained the natural age-related decrease in the heart rate of immature animals. It is likely that with isometric loading, a minimal change in muscle length occurs, and at the same time its tone increases. Muscle tension for a longer period of time in comparison with dynamic exercises causes a compression of the vessels (arteries) of the muscles; thus, their resistance increases. In this case, only certain muscle groups are involved, and external work is not performed. The oxygen demand during this exercise is proportional to the mass of the muscles involved and is usually moderate. However, these needs cannot be met by increasing blood flow, as local vasodilation is limited by mechanical compression of the resistive vessels by the isometrically contracting muscle, and therefore blood flow in the working muscle may actually decrease. Muscle perfusion is maintained by an increase in blood pressure, which is mediated by a reflex arc originating in the contracting muscle, which leads to an increase in systemic vascular resistance even with moderate exercise. Along with this, there can be a decrease in SV and the development of an excessive reaction from the heart rate to isometric load.

Thus, in contrast to isotonic exercise, isometric exercise poses increased demands on the systolic function of the heart in the form of a significant increase in pressure load. In our opinion, when the animal is fixed upside down on the turntable, an increase in cerebral edema occurs, which aggravates the traumatic damage to the trunk and frontal lobes of the brain. At a glance, this study revealed the following conclusions:

1. The study showed a pronounced decrease in SV on the first day after modeling an open craniocerebral injury in rats of all age groups. At the same time, the smallest SV response to brain injury was observed in immature animals.

2. Systematic dynamic exercises do not contribute to an increase in SV of pre-senile animals after modeling TBI. A significant increase in SV after a TBI is observed only in immature animals.

3. Limitation of physical activity and performance of isometric exercises after a TBI restrain a natural increase in SV in immature rat pups, and in sexually mature and pre-senile animals cause a decrease in stroke volume.

Authors' Contribution

Study concept and design: B. I. V.
Acquisition of data: I. S. R.
Analysis and interpretation of data: T. L. Z
Drafting of the manuscript: I. Kh. V.
Critical revision of the manuscript for important intellectual content: L. I. V.
Statistical analysis: B. I. V.
Administrative, technical, and material support: I. S. R.

Ethics

All work with laboratory animals was in compliance with the basic regulatory and ethical requirements for laboratory and other experiments with the participation of experimental animals of different species.

Conflict of Interest

The authors declare that they have no conflict of interest.

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