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# Dynamic Properties of Skeletal Muscle Contraction in Rats with Diabetes

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## Abstract

The study was conducted on 20 white nonlinear male rats, which were divided into 2 groups of 10 animals each. Rats in the first group were used as control. Rats in the second group were induced type I diabetes by intraperitoneal (i.p.) administration of streptozotocin (65 mg/kg). Diabetes in rats was confirmed by the presence of hyperglycemia. For the establishment of nociceptive pain sensation, mechanical nociceptive test and tail-flick test were conducted in rats. Further animals were anesthetized by i.p. administration of Nembutal (40 mg/kg). The study of dynamic properties of muscle contraction was performed under conditions of the tibia muscle activation by using the modulated stimulation of efferent n. tibialis. Streptozotocin (STZ) was injected in rats; as a result, the blood glucose level was increased by 4.4 times ( $p \leq 0.001$ ). Pain sensitivity in diabetic rats was suppressed, indicating the development of peripheral neuropathy. In rats with diabetes, biomechanical parameters of tibia muscle contraction such as the maximum force of contraction, the speed of maximum force of contraction, the retention time of maximum force of contraction and integrated power of muscle contraction (it is calculated on the total area of the received force curves) were violated. This prevents adequate implementation motor neuron pools muscular system, which will have significant consequences in accurate positional movements.

**Keywords:** skeletal muscle, contraction, diabetes, neuropathy

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## 1. Introduction

The damages of the peripheral nervous system in patients with diabetes mellitus are recorded in 40–60% of cases and manifests itself in the form of diabetic polyneuropathy. The incidence of

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diabetic polyneuropathy increases with age and duration of diabetes mellitus [1]. According to recent data, in the last 10 years, in young patients with type 1 diabetes, an increase in the incidence of diabetic polyneuropathy from 24.2% to 62.9% has been observed [2]. Diabetic neuropathy correlates with a high risk of cardiovascular complications [3, 4]. Patients with diabetic polyneuropathy are also at risk for the formation of trophic ulcers that do not heal for a long time and often lead to amputating a limb [5–7]. In the USA, 15% of all patients with diabetes will develop foot ulcers [8].

Mortality due to diabetes mellitus, complicated by diabetic polyneuropathy, remains high in all countries of the world, regardless of their socioeconomic status [3]. Patients with diabetic polyneuropathy often require outside help, which, of course, is reflected on the quality of their life [9, 10].

Metabolic, vascular and immune theories were proposed to explain the pathogenesis of diabetic polyneuropathy [11]. Independent causes of the risk of this serious complication of diabetes mellitus are age, male gender, unsatisfactory control of the level of glycaemia, elevated lipid levels in the blood, height, overweight and obesity, and insulin treatment [12–16]. Thus, the pathogenesis of diabetic polyneuropathy is multifactorial. It includes the increase of mitochondrial production of free radicals due to hyperglycemia-induced oxidative stress [1]. A number of other factors affect the activity of neurons, mitochondrial function, permeability of membranes and endothelial function. These include the activation of polyol aldose reductase pathway [17], activation of poly(ADP ribose) polymerase [18], and modified Na<sup>+</sup>/K<sup>+</sup>-ATPase pump function [19].

In diabetic polyneuropathy, autonomic, motor, large fiber and small fiber nerve functions are attacked [20]. The most frequent variant of defeat of peripheral nervous system at a diabetes is distal symmetric sensorimotor neuropathy [21]. As a rule, this complication occurs in a few years from the onset of the underlying disease [22]. This form of diabetic polyneuropathy develops slowly (chronically), the first symptoms (numbness and paresthesia) occur in the lower extremities, sometimes unilateral [23]. Distal symmetric sensorimotor neuropathy is the cause of the development of chronic neuropathic pain syndrome. Pain is the reason for 40% of patient visits in a primary care setting, and about 20% of these have had pain for more than 6 months [24]. In this form of neuropathy, poorly myelinated and thin nonmyelinated fibers are affected in various combinations. In most cases, at the onset of the disease, the neurological deficit is caused by the damages to fine fibers. Symptoms of their damages are manifested by burning or shooting pain, hyperalgesia, paresthesia, disturbances of pain and temperature sensitivity, ulceration of the feet and a decrease in pain sensitivity from the internal organs. With the defeat of myelinated (thick) fibers, there is a violation of deep and vibrational sensitivity, and a decrease or loss of tendon reflexes.

Diabetic polyneuropathy affects both type 1 and type 2 diabetes patients, although specific differences exist in the underlying pathobiology, pathology and clinical expression of the disease [25]. In type 1 diabetes patients, diabetic polyneuropathy is more rapid and severe.

The nerve conduction study is a reliable and objective diagnostic method to evaluate the diabetic polyneuropathy treatment response [26]. Although a nerve conduction study is regarded as the

gold standard in clinical research, it is not useful in clinical practice because it is time-consuming, requires special devices and trained examiners, and has no general consensus regarding its criteria, even after multiple investigations [27]. That is why the experiments on the rats give us possibility to investigate the mechanisms of diabetic polyneuropathy development, to evaluate the quality of treatment, and to propose the new approaches to diagnostic and treatment of diabetic polyneuropathy.

In isometric conditions, analysis of registered effort developed by the muscle due to frequency-modulated stimulation of its nerve is the qualitative indicator of the level of neuro and myopathy pathological processes.

Phenomenological approach in the analysis of pathological processes that influence the mechanical properties of the muscle makes it possible to establish important relationships between the real macroscopic parameters of the muscle state, such as the strength, length and level of efferent activity. Frequently, the analysis of pathological changes in muscle dynamics is sufficient for the analysis of central regulatory processes, both motor activity and pathological state of the organism as a whole.

The dynamics of contractile component is determined by the delicate interaction of motor neuron pools that appeared in the muscle through the activated motor neuron and the activation of actin and myosin myofilaments interactions. Dependence of muscle force response on value, duration of applied stimulation (force-velocity for the initial site) and on time of achievement and retention of the stationary state of the contractile process makes possible to track the level of pathological processes development that affect the mechanisms of positioning in muscle dynamics. These processes play a huge role in the accurate positional movements of hands and fingers, even minor violations in the control system of these movements lead to serious domestic and physiological problems.

The rapid excitement of contractile apparatus, in the process of prolonged activation of muscle fibers, usually undergoes a slow and stable modification, which can partly be due to the phosphorylation of the so-called light chains of myosin located in the neck of the bridge. A slower dephosphorylation process under conditions of prolonged uninterrupted activation of the muscle fiber causes stable phosphorylation of myosin, which, apparently, increases the mobility of the bridges or changes their orientation. Analysis of amplitude-velocity changes of activated muscle's force response makes it possible to assess the influence of developing pathology on these processes. One of the most effective and widely used methods to identify the dynamic systems' levels pathologies is to determine the reaction in responses to the harmonic input effects of different velocity ranges of increase stimulating irritations.

## **2. Dynamic properties of skeletal muscle contraction in rats with diabetes**

### **2.1. Methods of experiment conduction**

The study was conducted on 20 white nonlinear laboratory male rats, which were divided into two groups of 10 animals each. The rats in the first group were used as control. Rats in

the second group were induced type I diabetes by administration of streptozotocin (STZ) (65 mg/kg, i/p). Diabetes in rats was confirmed by the presence of hyperglycemia. On the 28th day of experiment, glucose loading test was conducted for the confirmation of diabetes presence. For the establishment of pain sensation, mechanical nociceptive test was conducted in rats (Randall-Selitto analgesiometer test) [28]. Also heat-induced rat tail-flick latency was determined as a measure for nociceptive pain [29].

Animals were anesthetized (Ketamine (100 mg/kg “Pfizer”, USA), and tracheotomy and connection to lung ventilator were performed. In the area of the popliteal fossa, musculus gastrocnemius was isolated and cut down to be attached to the force sensors. Further, the animal was fixed in a stereotaxic machine with the head, pelvis and extremities rigid fixation system. Nerve that innervate musculus gastrocnemius was fixed on a bipolar platinum wire electrode for further electrical stimulation. The parameters of stimulation signals were programmed. The skin edges (hind legs) around the incision were sutured to the machine tool and formed trays with the muscle and nerve and were filled with liquid paraffin. Heart rate and ECG amplitudes were monitored during surgery and experiments [30].

Before stimulation of the spinal cord, the ventral root muscle was connected to a load that did not stretch it because of unilateral mechanical limiter, and only shortening of the muscle was possible. After activation, the isometric growth of the force began until the muscular effort reached the external load, after that the isotonic shortening of the muscle started.

In the initial stage of the shortening, it was possible to distinguish a near-linear part of motion due to velocity measurement at which it was possible to establish the empirical dependence of the contraction rate on the level of isotonic loads. The pathological processes that occurred during the development of diabetic polyneuropathy modulated the muscular response registered by us. The level of this modulation was a qualitative characteristic of residual physiological disorders both at the neuropathic and at the myopathy level of pathology development. The statistical analysis of the data was conducted in the program Statistica 8.0. To approximate this empirical dependence, several analytic approaches were selected.

As a modulating component, a stimulating signal of different amplitudes and times characteristics was used and regarded as an input effect, and the output signal was the first harmonic of the muscle-developed effort and the subsequent realization of the modulated stimulation pool.

## **2.2. The analysis of electro-physiological parameters used in work as indicators of pathological processes development during diabetic polyneuropathy**

### *2.2.1. The changes in time of muscle force response beginning caused by a single stimulation pool*

Time between first and second mitotic response that was caused by successive stimulation with fixed meaning between them (2000 ms). This indicator makes it possible to assess the presence or absence of pathologies (neuropathy or myopathy) during the initial stages of

the study, and to correct the algorithm of further investigation whether pathological changes are present.

### *2.2.2. The changes in time of muscle force response beginning caused by 10 consecutive stimulation pools with 10 s relaxation time between them*

When the intensity of stimulation changes, the temporal parameters of the stimulation pools conduction in axon do not remain constant. The investigation of changes of time delays of impulses conduction with an increase number of stimuli makes it possible to assess the level of pathological changes in the neuromuscular preparation with prolonged, static reactions of the muscular system. High-frequency stimulation of peripheral afferents that form monosynaptic contacts with motor neuron causes an effective summation of successive action potentials and stable depolarization of the cell membrane. In this case, the pulse frequency is determined by the average level of membrane depolarization and increases with rise of frequency stimulation. During the development of pathological processes associated with diabetic polyneuropathy, the use of stimulation without relaxation of the corresponding long transsynaptic activation of motor neurons causes adaptive time decrease of stimuli conduction. Change in this parameter is the marker of pathological processes presence in the neuromuscular preparation while applying stimulation signals close to physiological parameters.

We analyzed several basic biomechanical parameters during studying the myotonic response of the muscle. These parameters are universal markers that show the presence of biomechanical disturbances caused by factors of different nature.

Changes in each of described biomechanical parameters is an indicative marker of the dysfunction presence in the excitation-response chain of both the neuromuscular preparation and the state of the organism as a whole.

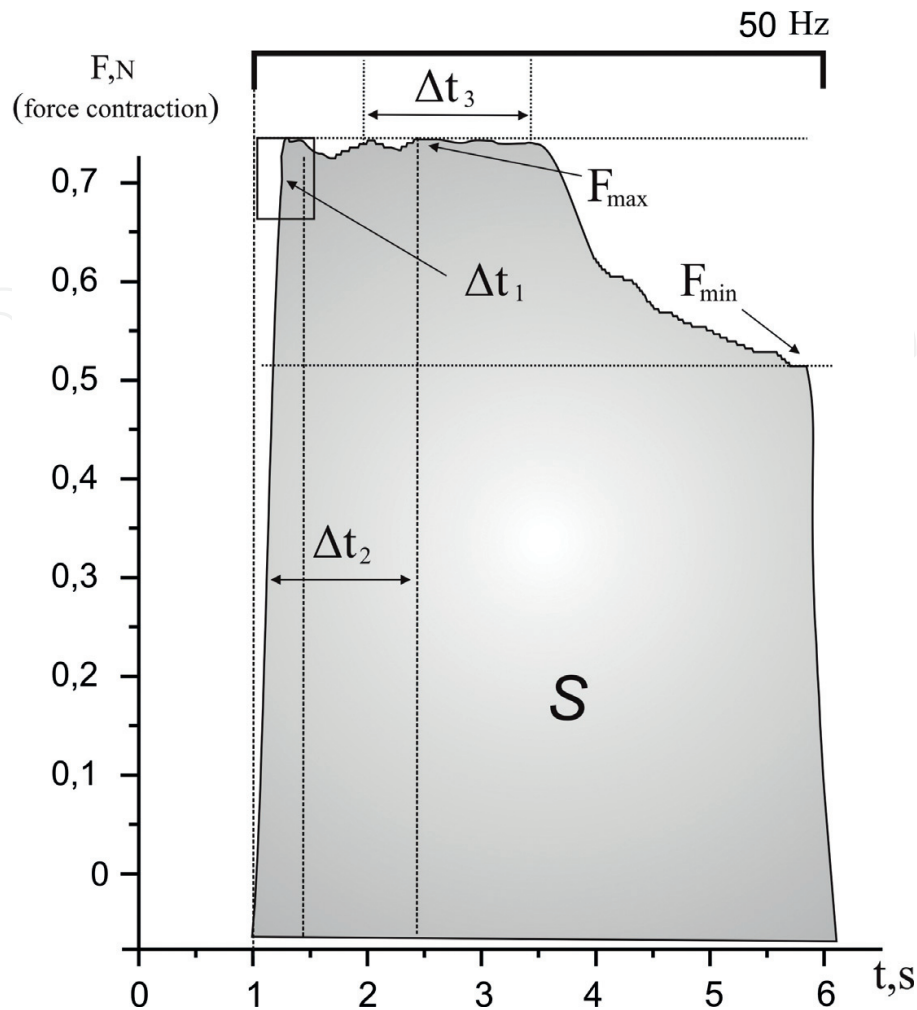
We have designated the investigated segments of biomechanical responses for more favorable description of the changes in the obtained curves (**Figure 1**).

### *2.2.3. The changes in time to reach maximum force response*

The maximum force generation on which the active muscle is capable is an important indicator for fast, ballistic, nontargeted movements (**Figure 1**— $\Delta t_1$ ). The changes of this indicator show the level of physiological dysfunction of neuromuscular preparation when it implements the maximum power tasks.

### *2.2.4. The changes in time of achievement of stationary state of contraction, with the use of modulated stimulation signal*

The stationary state of the active muscle is a temporal area of the contractile activity of the muscle tissue without the presence of a significant trend in one or the other direction, during the activation of the muscle (**Figure 1**— $\Delta t_2$ ). Physiologically, the stationary state of the active muscle is the level of muscle force production that corresponds to the physiological state of the



**Figure 1.** Schematic representation of analyzed biomechanical parameters of muscles gastrocnemius contraction using a modulated stimulation signal.

neuromuscular preparation at this moment. The time of its establishment is a time of adaptation processes passage in the muscle during its activation by stimulating pools, to select the optimal amplitude-strength characteristics of the contracting muscle in order to realize the incoming stimulations with the least deviations from the CNS tasks.

#### 2.2.5. The changes in time of stationary state retention, with the use of modulated stimulation signal

The retention of stationary state is an indicator of adaptability of the muscular system to a new state of the neuromuscular system, altered by a pathological action (**Figure 1**— $\Delta t_3$ ). In some cases, we could record relatively stable periodic changes in the level of stationary state at the applied pulse activity frequency, but without significant dependencies of these fluctuations to the level of pathology development or methods of drug administration. We consider the presence of oscillations at the phases of stationary state retention is a consequence of individual differences in the muscular system of experimental laboratory animals.

#### *2.2.6. The changes in time of maximum contraction force generation*

This marker is an indicator of the general dysfunction of the muscular system, index of decrease (with pathologies development) of the maximum possible force response (**Figure 1**— $F_{\max}$ ). The change in this parameter can be related either to a violation in the neuronal component or to the myofibrillar components of the studied pathology. The dysfunction of this parameter can also be associated with a violation of the integrity of the signals that generate motor neurons in the synaptic current, and as a result, the violation of the summation of the transmembrane currents occurred in accordance with the internal membrane properties. That influences the pathological transformation of the sequence of action potentials that trigger a muscle contraction that causes the maximum force response.

#### *2.2.7. The changes in minimum contraction force generation*

This data show the maximum pathological changes caused by the pathological process during analyzing changes in contraction of each successive contractile act (**Figure 1**— $F_{\min}$ ). This marker is the main indicator of muscle dysfunction while performing simple one-joint movements. The phenomenological analysis of it makes possible to establish the presence of cause-effect relationships between the level of decrease in biomechanical activity of muscles, the basic mechanical parameters of movements and the level of development of the pathological process. The accuracy of such conclusions is enhanced due to multiple repetitions of these stimuli and stimulation time increase.

#### *2.2.8. The changes in integrated power of muscle contraction*

The integrated power is subtracted from the total area of force curves (**Figure 1**— $S$ ) and is an indicator of the overall capacity of the muscle with the use of applied stimulation pools. Analysis of this value makes it possible to evaluate the mechanisms of the formation of muscular activity in the equilibrium system, in the force-external load system, that is, a physiological analogue of the working capacity of the muscular system as a whole.

#### *2.2.9. The changes in fatigue processes of the neuromuscular preparation accompanied by diabetic polyneuropathy*

In condition of 1 and 2 Hz, unrelaxed stimulation of the analysis of fatigue processes development was made, which makes it possible to evaluate the development of fatigue in different time ranges. Fatigue evaluation was calculated by time intervals with achievements of 50 and 30% force responses, with stimulation irritations. It should be noted that in control, the change of this data had a long time frame, which complicated the description of fatigue processes development during pathology. Therefore, for more precise description of results, the change in control values was considered 100%, and while analyzing the data, the percentage difference was described.



### 2.2.10. Analysis of fusion index

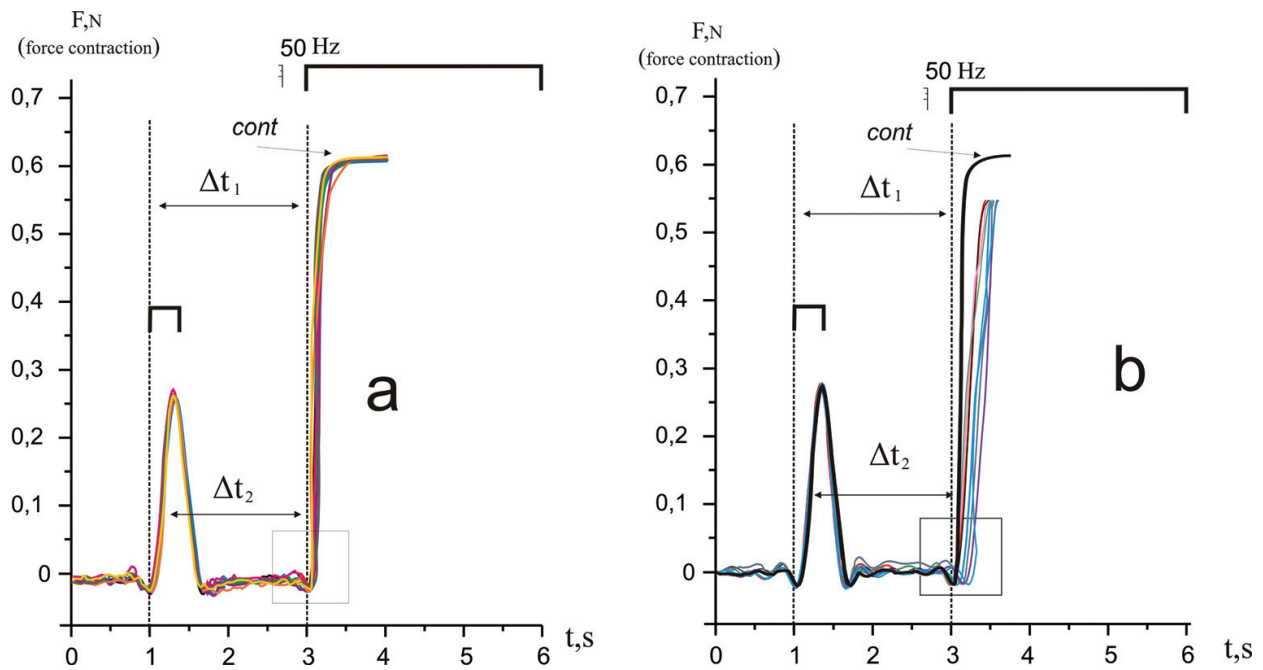
To analyze the dynamics of real movements, we considered the peculiarities of the transformation of segmental and descending activity during the development of polyneuropathy. An important role in the realization of the motor function belongs dedicated to asymmetric nature of the muscle reactions as a result of increase in the level of incoming efferent activity. In our work, almost all movements are relatively simple and are provided with straight pattern of motor neuron populations. Since motor neurons directly control muscle contraction, the nature of the transformation of activity coming to them from multiple sources is largely predetermined by the peculiarities of muscle dynamics. The significant inertia of muscle contraction during the development of the pathological process requires motor neurons to have such dynamic properties that could compensate for the insufficiently high-speed parameters of muscle contraction. Thus, the slowdown of smooth tetanus appearance can be used as another parameter to describe the dynamics of pathologies development. We investigated the transition of active muscle force response from the state of the unfused tetanus to the fused one. We had also analyzed the time variation between the peaks of the force response and their maximum force. Two above-described parameters are important for the transition of the active muscle from the state of unfused tetanus to the fused one. The analysis of their changes shows us the peculiarities of dysfunction generation by individual motor units, and the consistent nature of their activation provides the possibility of smooth regulation of the force developed by the whole muscle.

## 3. Electrophysiology

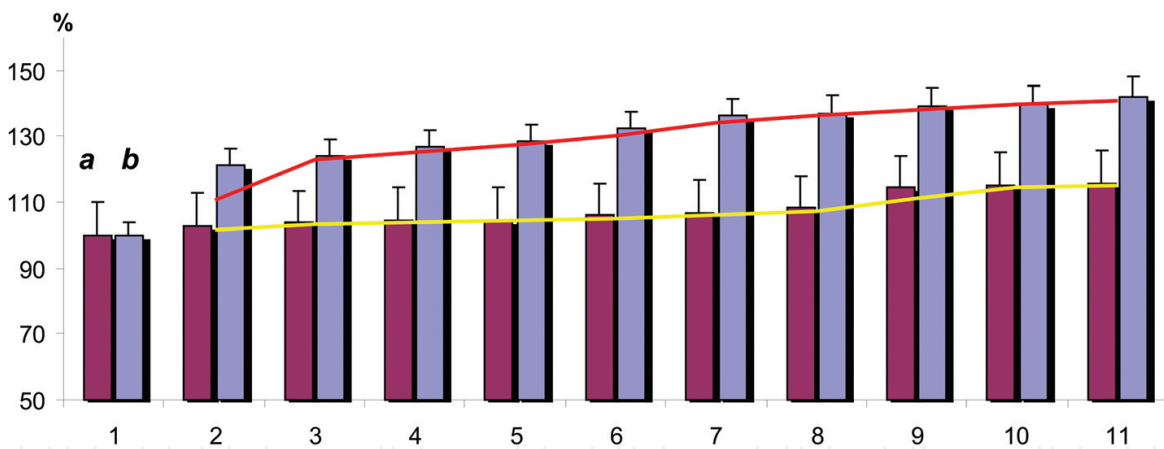
STZ was injected in rats on 28th day of experiment; as a result, blood glucose level was increased by 4.4 times ( $p \leq 0.001$ ). On the 14th and 28th day of development of diabetes, the threshold of pain sensitivity increased by 26.4% ( $p < 0.05$ ) and 95.86% ( $p < 0.01$ ), accordingly, by comparison to an initial level (before STZ injection). Therefore, pain sensitivity in diabetic rats was suppressed, indicating the development of peripheral neuropathy.

Force response of musculus gastrocnemius in rats with diabetic polyneuropathy caused by single stimulation pool with frequency of 50 Hz showed that time of the force response beginning increased by 119.34% with stimulation through the nerve (**Figures 2 and 3**). It should be noted that time of force response in the condition of direct stimulation through the muscle did not change.

The time of force response beginning increased from 121.25% at the first run till 142.27% at the tenth run in case of 10 consecutive stimulation pools usage (**Figures 1 and 3**). It was concluded the presence of neuropathic changes associated with the impossibility of generation of 10 consecutive stimulation pulses without significant physiological disturbances of myopathy origin.



**Figure 2.** The change in time of muscle force response in rats with diabetic neuropathy caused by 10 consecutive irritation pools by modulated electrostimulation with 50 Hz frequency. The relaxation time is 10 s. Cont—control;  $\Delta t_1$ —time between two consecutive stimulation pools;  $\Delta t_2$ —time of muscle force response beginning; a—direct stimulation of the muscle, rat with diabetic neuropathy; b—stimulation through the nerve, rat with diabetic neuropathy.

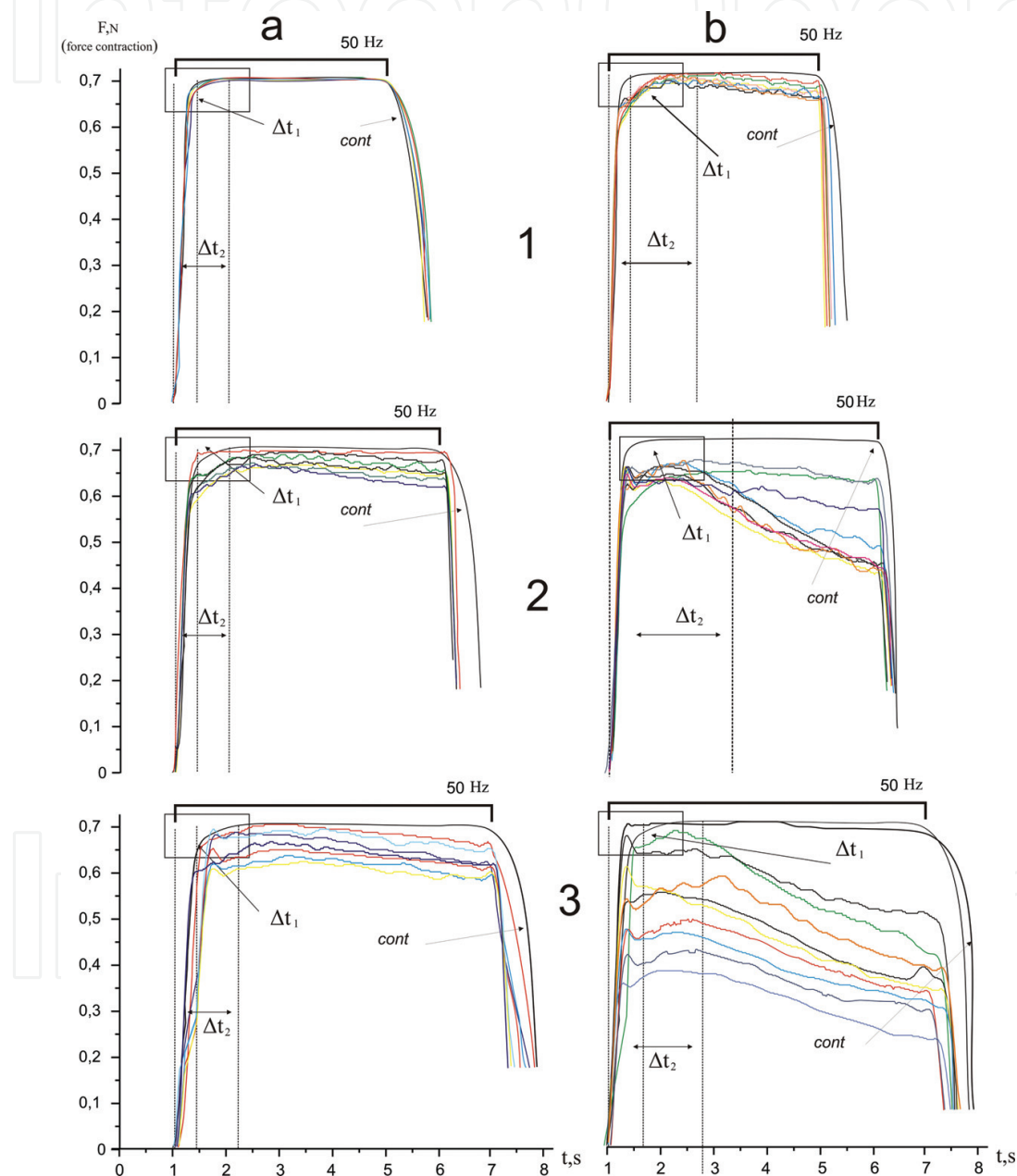


**Figure 3.** The change in time of muscle force response in rats with diabetic neuropathy caused by 10 consecutive irritation pools by modulated electrostimulation with 50 Hz frequency. The relaxation time is 10 s. The meanings are represented as percentages from control values considered as 100%. 1—control values; 2–11—consecutive irritation pools; a—direct stimulation of the muscle; b—stimulation through the nerve.

It was shown that the diabetic polyneuropathy leads to significant dysfunctions during stimulation signal transfer to effector. When the parameters of stimulation signal approach to the physiological level, the dysfunction of neuromuscular activity increases till the level that is capable to disturb the overall dynamics of the contractile process.

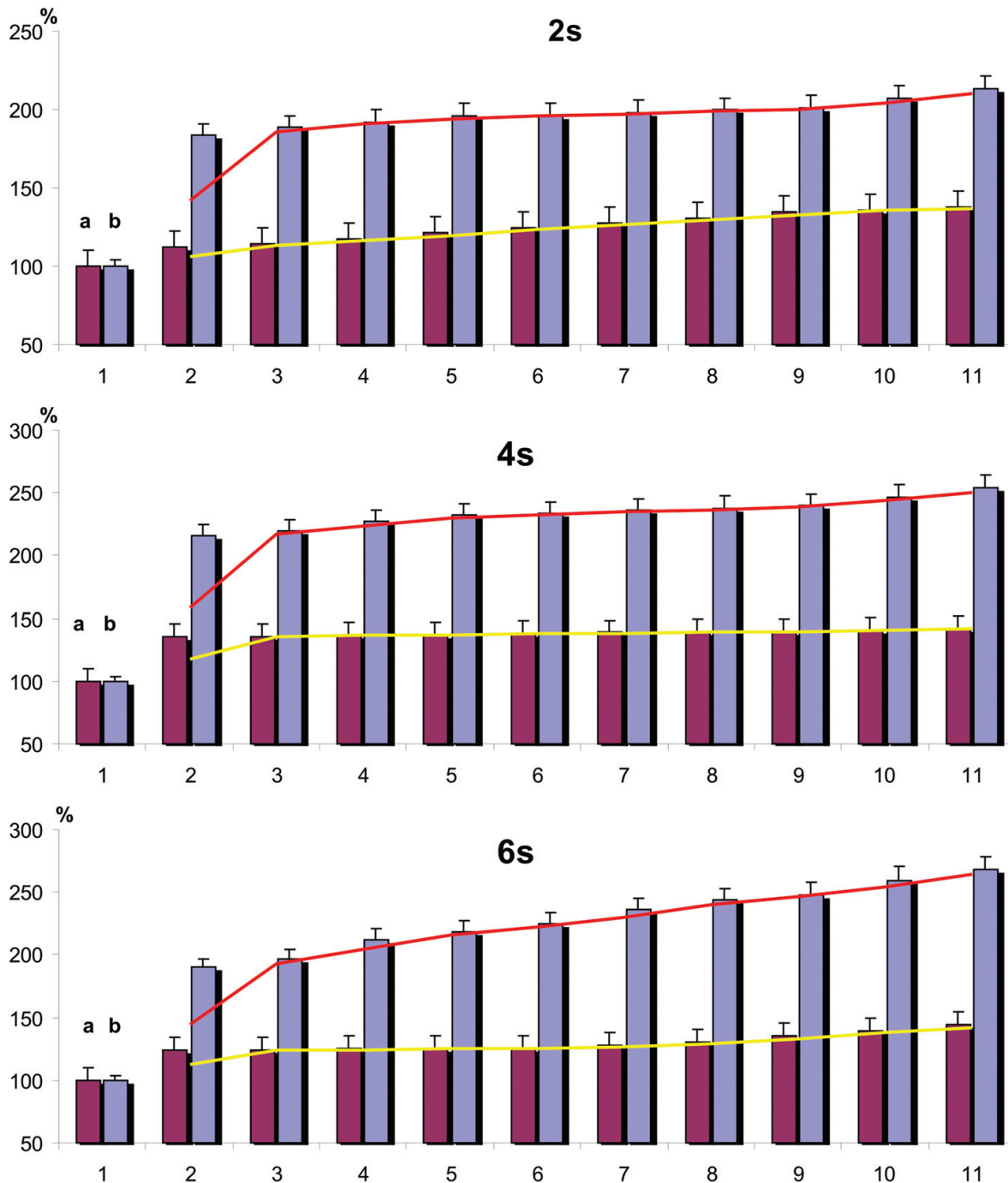
Thus, the use of streptozotocin increases time of force response, which is an adequate criterion for the presence of neuropathy in rats with diabetic neuropathy.

As a result, amplitude-force changes in the muscle response were revealed (**Figure 4**), both compared to control or to direct muscle stimulation. It should be noted that the presence of clearly expressed fluctuation changes in the phase of stationary state retention in rats with diabetic polyneuropathy with stimulation through the nerve.



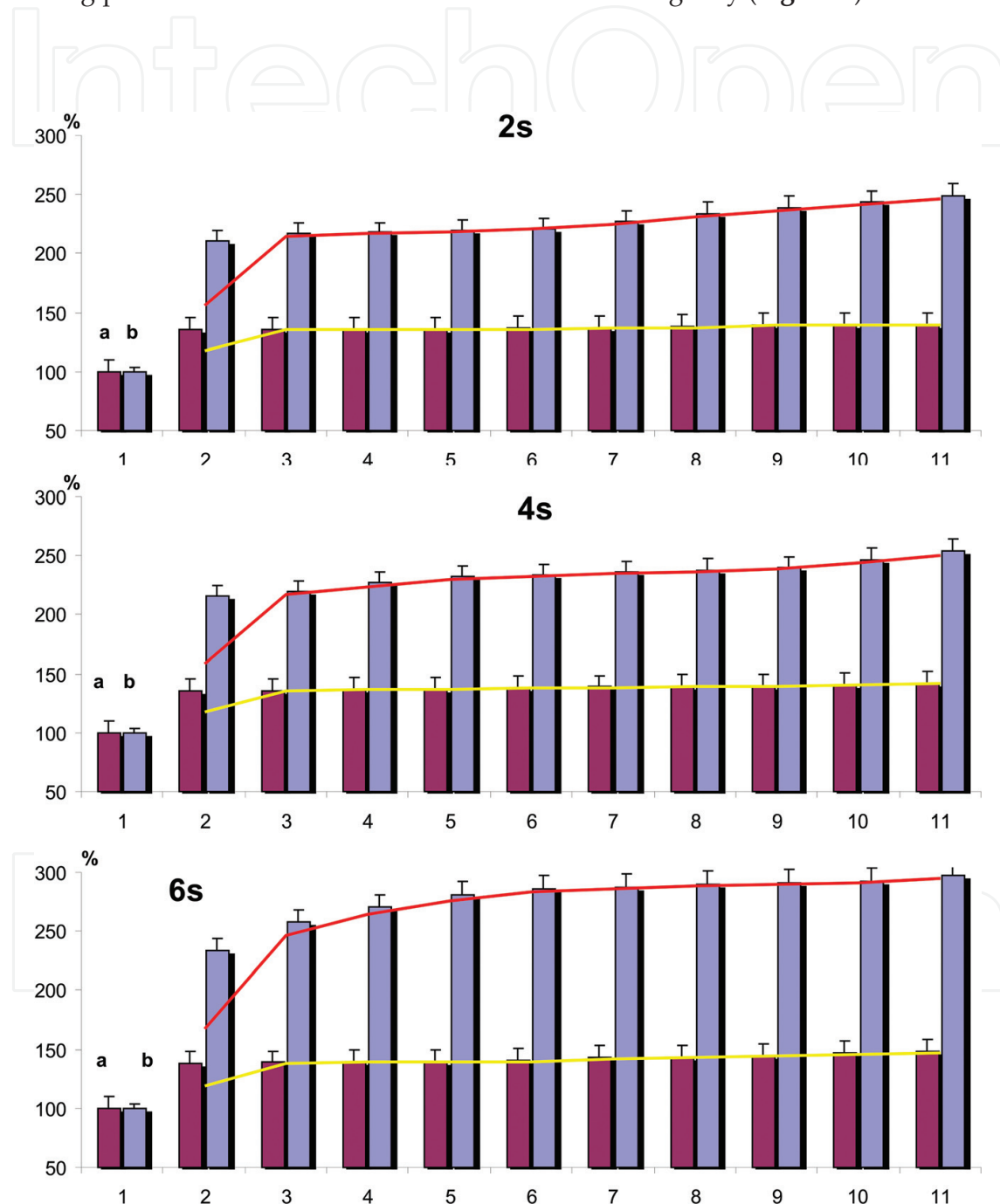
**Figure 4.** The changes in the dynamic parameters of musculus gastrocnemius contraction in rats with diabetic polyneuropathy, stimulated by modulated electrostimulation with 50 Hz frequency and duration of 2, 4 and 6 s. The relaxation time is 10 s. a—direct stimulation of the muscle; b—stimulation through the nerve; 1, 2, 3—stimulation time 2, 4 and 6 s, respectively; Cont—control,  $\Delta t_1$ —phase of the maximum force response,  $\Delta t_2$ —phase of stationary state of contraction.

The change in time of maximum force reach (**Figure 5**) caused by 10 consecutive stimulation pools modulated by electrostimulation with 50 Hz frequency and duration of 2 s was 183.41% at the first and 213.27% at the tenth run, respectively. When stimulation time was increased till 4 and 6 s, the data were 188.49% (1), 243.47% (10), 188.49% (1) and 243.47% (10), respectively.

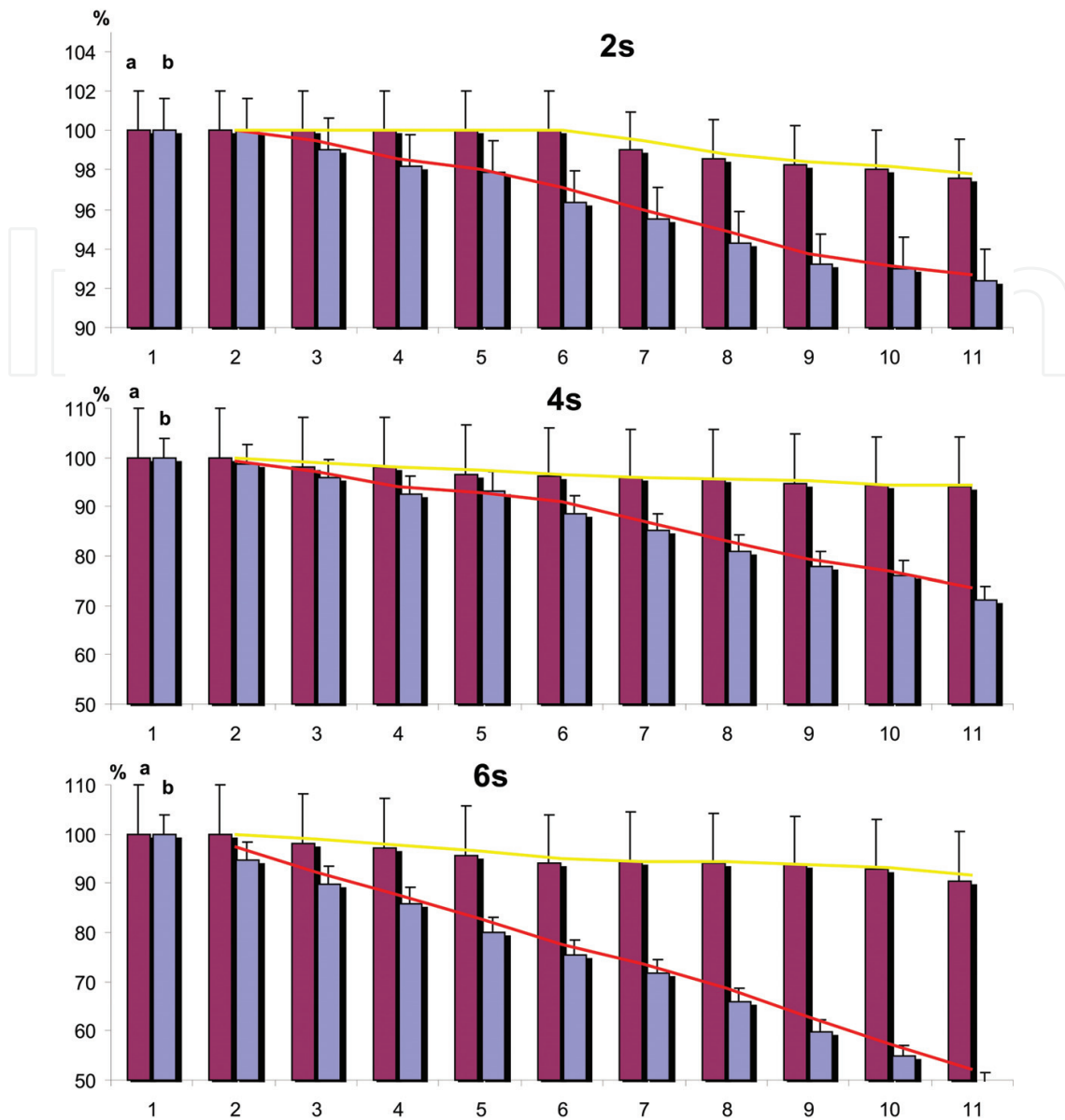


**Figure 5.** The change in time of maximum force reach by musculus gastrocnemius in rats with diabetic polyneuropathy caused by 10 consecutive stimulation pools with electrostimulation with 50 Hz frequency and duration 2, 3 and 4 s. The relaxation time is 10 s. The meanings are represented as percentages from control values considered as 100%. 1—control values; 2–11—consecutive irritation pools; a—direct stimulation of the muscle; b—stimulation through the nerve.

The time of stationary state reach by musculus gastrocnemius in rats with diabetic neuropathy by stimuli for 2 s showed that the time increased from 211.34% at the first till 249.14% at the tenth run corresponding (Figure 6). When stimulation time was increased till 4 and 6 s—215.64% (1), 253.78% (10) and 234.12% (1) 297.66% (10), respectively. At the same time, the time of stationary state retention also decreased linearly as with the increase in the number of stimulating pools and with an increase in the stimulation longevity (Figure 7).



**Figure 6.** The change in time of stationary state reach by musculus gastrocnemius in rats with diabetic polyneuropathy caused by 10 consecutive stimulation pools with electrostimulation with 50 Hz frequency and duration 2, 4 and 6 s. The relaxation time is 10 s. The meanings are represented as percentages from control values considered as 100%. 1—control values; 2–11—consecutive irritation pools; a—direct stimulation of the muscle; b—stimulation through the nerve.



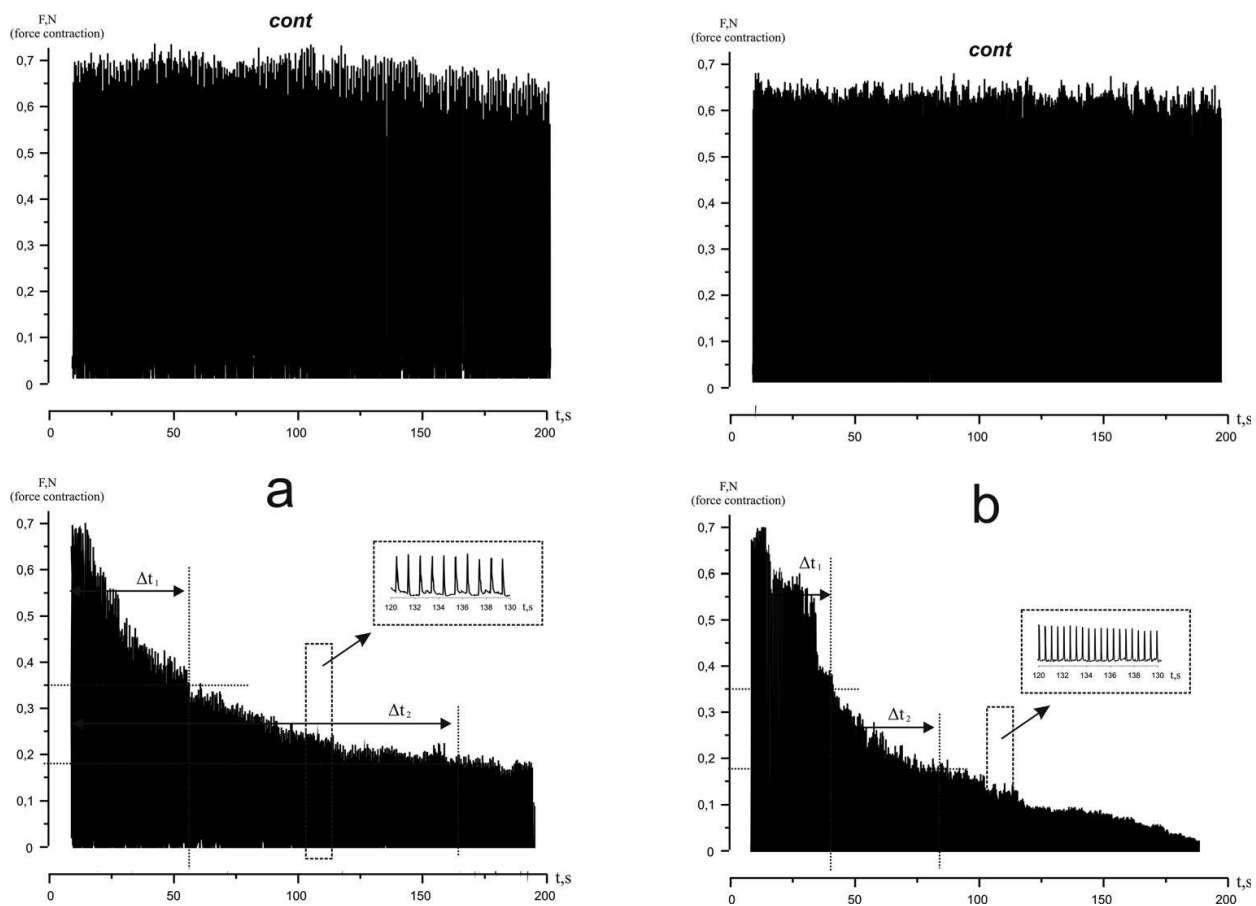
**Figure 7.** The change of integrated power of musculus gastrocnemius in rats with diabetic polyneuropathy caused by 10 consecutive stimulation pools with electrostimulation with 50 Hz frequency and duration 2, 3 and 4 s. The relaxation time is 10 s. The meanings are represented as percentages from control values considered as 100%. 1—control values; 2–11—consecutive irritation pools; a—direct stimulation of the muscle; b—stimulation through the nerve.

The changes in the maximum and minimum force of muscle contraction in rats with diabetic neuropathy caused by 10 consecutive stimulation pools with modulated electrostimulation with 50 Hz frequency and duration 2, 4 and 6 s were analyzed. The decrease in the maximum force was found from 99.34% at first run till 91% at tenth run, as well as decrease in the minimum force response was found from 99% (1) till 90.78% (10). The changes in these indicators with increasing stimulation duration up to 4 s were as follows: 98.71% (1) to 78.58% (10) and 97% (1) to 51.8% (10) for the maximum and minimum force, respectively. Increase in stimulation up to 6 s: 97% (1) to 51.8% (10) and 91.18% (1) to 65.34% (1) for the maximum and minimum force, respectively.

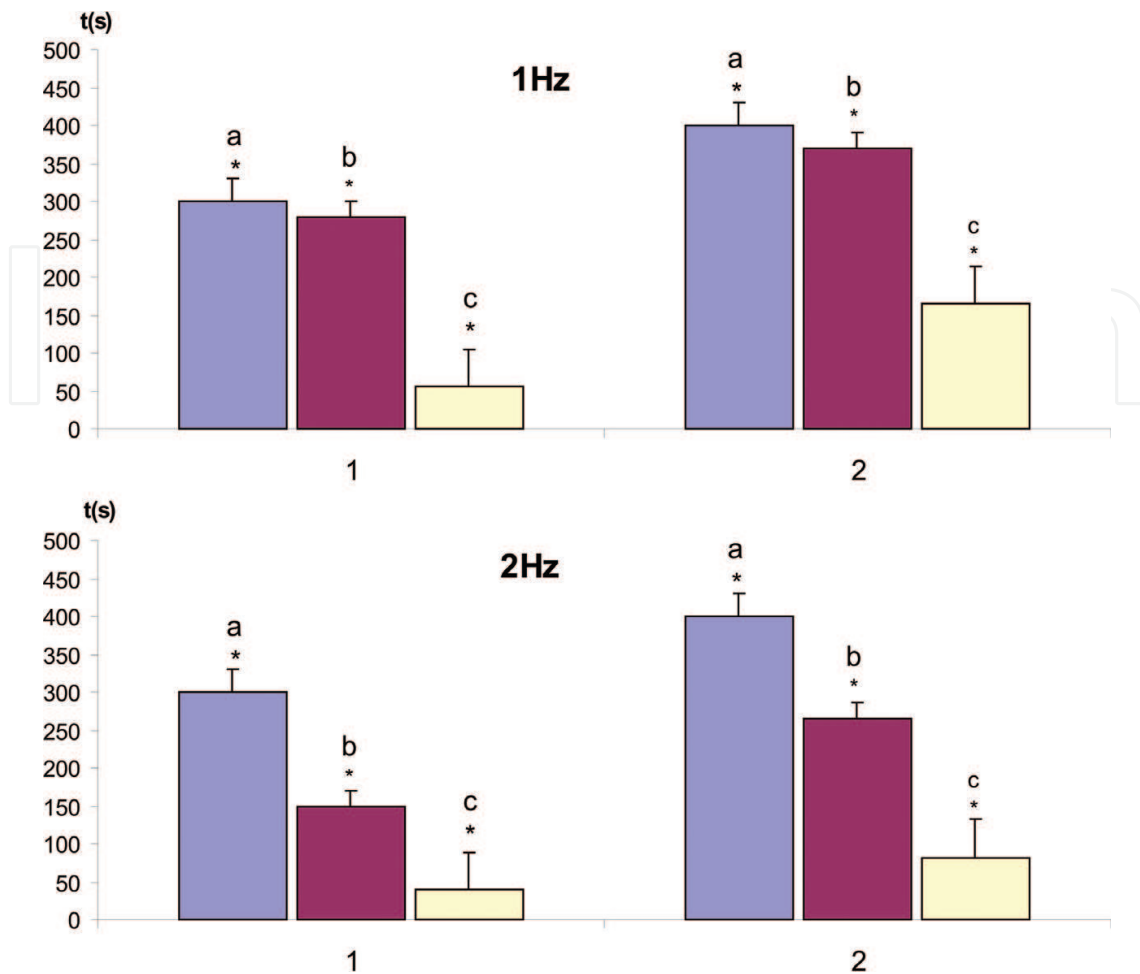
Integrated power in rats with diabetic polyneuropathy showed a slight decrease from 100% at the first run to 92.37% at the tenth run with stimulation duration of 2 s. More significant changes were recorded at 4 and 6 s stimulation from 98.7% (1) to 71.16% (10) and from 94.71% (1) to 49.6% (10), respectively.

Based on the obtained data, it could be concluded that with the development of diabetic neuropathy for all 10 consecutive stimulation pools, the formation of a stable muscle response in the phases of the maximum force retention (and stationary state) does not occur. The dynamics of amplitude-force formation had a clear tendency to reduce the stabilization time of the constant power characteristics.

Biomechanical curves showed that prolonged stimulation with 1 and 2 Hz frequency (**Figure 8**) decreased the maximum force response of the muscle throughout the period of stimulation. Stimulation of 2 Hz caused the development of rapid fatigue processes, and the maximum change in muscle power productivity occurs on 1 min of force parameters registration (**Figures 8 and 9**). If we continue stimulation in the same way, after 150 s, the muscle passes into a state of complete nonexcitability (**Figure 10**).



**Figure 8.** Curves of musculus gastrocnemius force generation caused by unrelaxed stimulation by electrostimulation with 1 Hz (a) and 2 Hz (b) frequency.  $\Delta t_1$ —time of force reduction by 50% compared to the initial level;  $\Delta t_2$ —time of force reduction by 30% compared to the initial level.

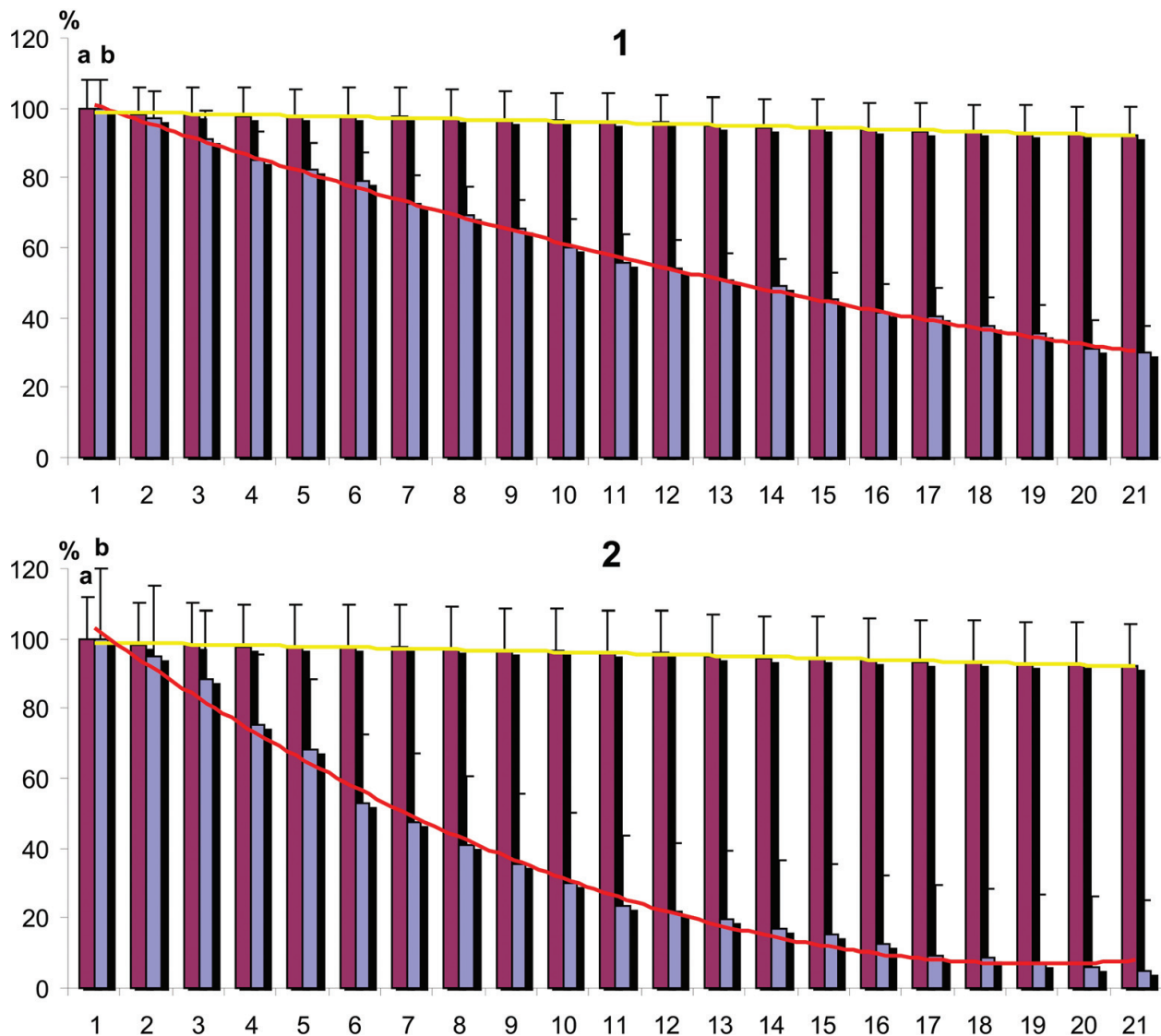


**Figure 9.** Time of musculus gastrocnemius force reduction in rats with diabetic neuropathy by 50% (1) and 30% (2) compare to initial level caused by unrelaxed stimulation by electrostimulation with frequency 1 Hz and 2 Hz. a—control; b—direct stimulation of the muscle; c—stimulation of the muscle through the nerve; 1—time of force reduction by 50% compared to the initial level; 2—time of force reduction by 30% compared to the initial level.

The time of muscle contraction force reduction during diabetic polyneuropathy by 50% was 55 and 39 s, respectively. The time of muscle contraction force reduction by 30% was 165 s at 1 Hz and 82 s at 2 Hz (**Figure 9**).

Thus, it can be assumed that the conversion of the depolarization current to the impulse frequency of the outgoing motor neuron during the development of these pathological processes is a linear process of the development of fatigue with the absence of rapid adaptation by a constant frequency stimulus. The registered parameters during fatigue process development were similar to the processes of motor neuron impulse frequency changing caused by severe pathological disorders of the neuromuscular preparation. The transformation of depolarization current into the pulse frequency in this case is a nonlinear process, most likely connected with numerous pathological processes in organism. The absence of both initial and subsequent adaptation of the induced fatigue process can be associated with processes of inactivation of Ca channels located in the initial axon segments.



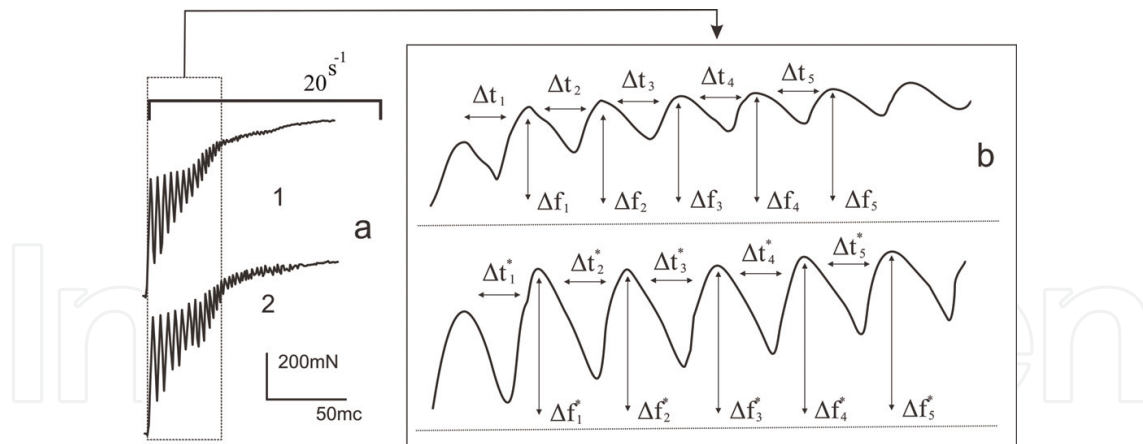


**Figure 10.** Musculus gastrocnemius maximum force reduction in rats with diabetic neuropathy compared to the initial level caused by unrelaxed stimulation by electrostimulation with 1 Hz and 2 Hz frequency and duration of 200 s. The meanings are represented as percentages from control values considered as 100%. a—control; b—rat with diabetic neuropathy; 1–21—consecutive irritation pools.

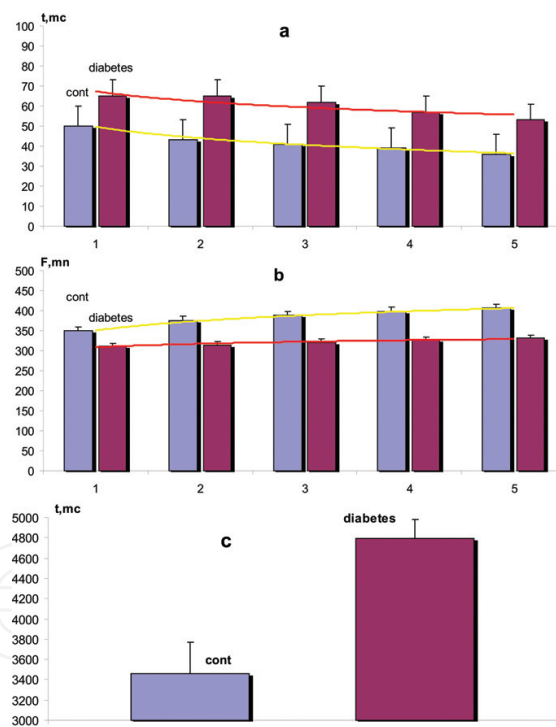
Maximum force contraction during diabetic neuropathy decreased from 97% till 30% with stimulation of 1 Hz and duration of 200 s (**Figure 11**).

With stimulation of 2 Hz and duration of 200 s, the maximum force contraction of musculus gastrocnemius in rats with diabetic neuropathy decreased significantly from 95 to 5%, respectively (**Figure 10**).

Time between the development of the maximum force response decreased by 65 min during first unfused tetanus till 53 min during the fifth contraction (**Figures 10**). The change in peaks force is 311 mN at the first contraction and 331 mN at the fifth contraction of the unfused tetanus. The time for establishing of fused tetanus caused with stimulation of 20 Hz and 6 s duration was 4789 ms. In control this time was 3456 ms (**Figure 12**).



**Figure 11.** The changes in musculus gastrocnemius maximum force response development at five first peaks of the unfused tetanus caused by stimulation with 20 Hz frequency in rats with diabetic neuropathy. a—it is the general view of the muscle force response caused by stimulation with 20 Hz frequency, for 6 s control (1), rats with diabetic neuropathy (2); b—five consecutive peaks of the tetanus; \*—indicated parameters of the investigated rats;  $\Delta t_1$ – $\Delta t_5$ —time of force response development 1–5 consecutive reductions;  $\Delta f_1$ – $\Delta f_5$ —the force of consecutive peaks of the first contractions of musculus gastrocnemius.



**Figure 12.** The changes in time between the development of the maximum force response (a), force (b), during the first five contractions of unfused tetanus and the time of its establishment (c), stimulation with 20 Hz frequency of the control (cont) and diabetic (diabete) rats. 1–5—consecutive irritation pools.

#### 4. Conclusions

To form macroindicators of neuromuscular activity during the development of diabetic polyneuropathy numerous complex, nonlinear nonstationary processes occur. The influence of

pathological factors on these processes leads to either complete dysfunction of these parameters or their desynchronization. As a result, the whole muscle as a dynamic system is not able to adequately implement the pool of neural activity getting from the central nervous system. The nature and level of these dysfunctions is linearly related to the level of pathological processes development, the analysis of which at present can be carried out exclusively at the phenomenological level. Despite new experimental approaches in studying microlevel of neuromuscular regulation, traditional electro-physiological models with usage of neuromuscular preparation in vivo are still important. Such studies should be conducted not only to obtain accurate quantitative analysis of the pathologies of muscle dynamics but also to study the totality of the central processes involved in the regulation of muscle contraction.

In condition of diabetic polyneuropathy development, differences in the response of the muscle to frequency changes indicate that to determine the contractile properties of the muscle, it is important to know not only the current values of the force response and activation intensity but also the history of changes in these parameters. The consequence of above-described dysfunction of the neuromuscular complex is the need of motor neurons to generate powerful dynamic discharge components to resume the error-free operation of the muscular system. Thus, at the same levels of the stationary state of the efferent command, an increase in the duration of the preceding dynamic component not only slows down the transition to a new equilibrium force but also leads to decrease in the maximum force response. The mechanokinetic curves showed the changes in the implementation of complex stimulation programs during the development of polyneuropathy. The analysis of dynamic properties of various parts of the motor system gives an idea of the presence of changes in the dynamics of complex movements associated with the precision positioning of joints and the ability of the system to correct the descending motor commands by adaptation processes in the central neurons.

Usage of static characteristics “stimulation signal-reduction force” to analyze the pathological processes during diabetic polyneuropathy development will lead to incomplete picture of pathology development. For an adequate understanding and analysis of these changes, a multifaceted experimental approach is needed with the possibility of simultaneous monitoring of various biomechanical parameters with different amplitude-time intervals and a labile system of external stimulation. Only in this case it becomes possible to trace the changes in the reaction of neuromuscular preparation to stimulation that are responsible for the development of ballistic precision positional movements, the analysis of which will be a critical factor in concluding the level of development of pathologies in diabetic polyneuropathy.

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