

Clonus: definition, mechanism, treatment

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ABSTRACT

Clonus is involuntary and rhythmic muscle contractions caused by a permanent lesion in descending motor neurons. Clonus may be found at the ankle, patella, triceps surae, wrist, jaw, biceps brachii. In general, clonus may occur in any muscle with a frequency of 5-8 Hz and the average period of oscillations of the ankle clonus is approximately 160–200 ms. Plantar flexion (PF) comprises 45% of the period, dorsiflexion (DF) comprises 55% of the period. The first beat is always longer, with the time shortening in continuing beats and becoming stable in the 4th or 5th period. The exact mechanism of clonus remains unclear. Two different hypotheses have been asserted regarding the development of clonus. The most widely accepted explanation is that hyperactive stretch reflexes in clonus are caused by self-excitation. Another alternative explanation for clonus is central generator activity that arises as a consequence of appropriate peripheral events and produces rhythmic stimulation of the lower motor neurons. The durations of clonus burst were found longer than the durations of Soleus medium-latency reflex (MLR). There is a similarity in their nature, although the speed and cause of the stretch of triceps surae differ in the MLR and the clonus, and there is a sufficient period of time for group II afferents and for other spinal mechanisms to be involved in the clonus, together with Ia afferents. Clonus can be treated by using baclofen, applying cold, botox or phenol injections.

Key words: botulinum toxin, spasticity, upper motor disorder, gait disorder

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INTRODUCTION

Clonus is involuntary and rhythmic muscle contractions caused by a permanent lesion in descending motor neurons and it is usually considered to be a result of oscillations in the group Ia spinal stretch reflex (Figure 1). Clonus is accompanied by spasticity and other findings of reflex excitability (1). Spasticity is defined as an increased resistance to stretching caused by disorders involving the upper motor neurons, and clonus is characterized by exaggerated brain stem and spinal reflexes resulting in increased muscle tone and involuntary spasms. Although closely linked, clonus is not seen in all patients with spasticity (2). Clonus does not occur if the muscle is excessively hypertonic (2). Any mechanism or pharmacological drug suppressing increased reflexes and muscle tone is also prone to block the clonus (2). Severe clonus can interrupt sleep and prevent the transfer capability of the patient and result in fatigue that can decrease work performance of an individual (3). It can also interfere with the posture and gait of the patient (4). Clonus can also occur in normal individuals. The plantar flexion power is low in normal individuals (5). Clonus may be found at the ankle, patella, triceps surae, wrist, jaw, biceps brachii (6-8). Jaw jerk is due to supranuclear lesion of the trigeminal nerve and it may occur in Amyotrophic Lateral Sclerosis (6). Wrist clonus in patients with hemiplegia was notably described in lectures published in 1883 by the French neurologist Jean-Martin Charcot, who called the phenomenon “provoked trepidation”, the patients, on raising the paralyzed arm, often experience trembling similar to that which

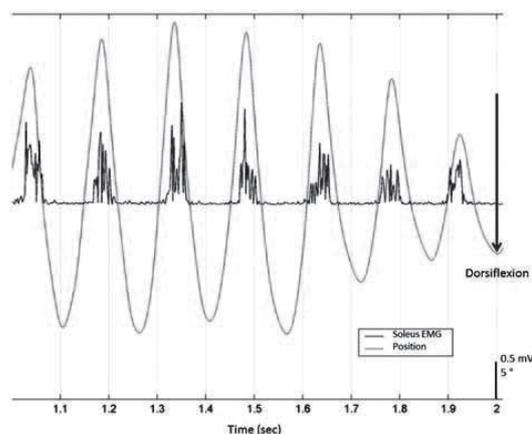


Figure 1. Ankle clonus Soleus rectified EMG and position of the ankle are displayed superimpose. Soleus muscle activity can be seen after ankle dorsiflexion

occurs in the lower limb under like circumstances (7). But the wrist-phenomenon, provoked or spontaneous, is much more uncommon. In general, clonus may occur in any muscle with a frequency of 5-8 Hz and the average period of oscillations of the ankle clonus is approximately 160–200 ms (9). Plantar flexion (PF) comprises 45% of the period, and dorsiflexion (DF) comprises 55% of the period (9). It has been shown that the duration of the dorsiflexion was 88.63 ± 10.83 ms, and the duration of the PF was 71.75 ± 6.73 ms (9). The DF and PF comprised $55.17 \pm 3.9\%$ and $44.83 \pm 3.9\%$ of one clonus beat, respectively (9). The first beat is always longer, with the time shortening in continuing beats and becoming stable in the 4th or 5th period. Measured the refractory period only in the triceps surae muscle is 90-100 ms. This period may differ for other muscle groups with different central stretch reflex organizations, thereby resulting in different maximum clonus frequencies (9). In order to reach an understanding of clonus, it is essential to consider not only reflex path length but also muscle contraction and relaxation times, muscle load, muscle spindle activity and central excitability, all of which play a role in clonus (7,9). Dimitrijevic et al. have shown that clonus occurred in the presence of a lesion involving a large portion of the lateral corticospinal tract (2). This observation was based on the histopathological evaluation of specimens from patients with a lesion in the central nervous system (CNS). They reported that the frequency of clonus was constant in each muscle and the frequency of clonus did not show a tendency toward a change over time (2). Rapid onset exteroceptive stimulations in sufficient intensity can induce clonic discharge in the muscle and not only via type Ia afferent fibers (9). Painful stimuli and cold are the leading cutaneous stimuli giving rise to and sustaining clonus. The cutaneous stimulation of the unaffected side can also produce clonus. The stimulations causing polysynaptic flexor or extensor reflexes are susceptible to produce clonus via nonspecific descending facilitations produced by the “Jendrassik” maneuver. The stimuli activating these pathways can stop clonus (5). Clonus may even occur in the absence of any movement in the extremity. The amplitude of clonus induced and sustained by stretch can decrease and become attenuated over time. Cutaneous sti-

mulation triggered by scratching skin over the muscle will provide sufficient input to the spinal cord to maintain the amplitude of clonus (2). Bernhard and Therman showed that proprioceptive inputs generated with the movement of the limbs trigger rhythmic discharges from the motor units in decerebrate cats (10).

Gottlieb and Agarwal showed that pharmacological agents increasing the discharge from stretched muscle fibers could produce clonus in healthy individuals. They reported that clonus in normal individuals shares common features with those in spastic patients and possesses a limited band of frequency, and it is independent from the loading on the extremity (11). Struppler observed these findings using iv succinylcholine injection, and Marsden, Meadows, and Hodgson used IV adrenalin injections (12,13).

CLONUS MECHANISM

The exact mechanism of clonus remains unclear. Two different hypotheses have been asserted regarding the development of clonus. The most widely accepted explanation since the pioneering studies by Denny-Brown (1928-1929) is that hyperactive stretch reflexes in clonus are caused by self-excitation (14). Szumski et al. observed that a few beats of clonus occurred after tendon tap in the wrist flexors and clonus was sustained by the "Jendrassik" maneuver. They concluded that the spindles involved in clonus were abnormally sensitive and dynamic fusimotor neurons were important motor neurons involved in eliciting clonus (2). Szumski and Hagbarth showed the discharge of Ia afferent fibers before clonic bursts on electromyographi (EMG) and these discharges were not activated during muscle contraction. They concluded that muscle spindles were stretched during muscle relaxation and repeated oscillatory movement elicited EMG activity (5). Janell et al. reported that clonus would not be elicited if reflex responses were not generated against a stretch (3). Rack et al. observed that the frequency of soleus EMG activity could be regulated by loading and loaded oscillatory movements in spastic patients, and they concluded that self-sustaining oscillation of stretch reflex pathway resulted in clonus. In spastic subjects, motoneuron firing threshold may decrease to a level in which the spindle afferent output eli-

cited during muscle lengthening is now sufficient to reach threshold for motoneuron firing (16). This shift in threshold can be thought of as an effective increase in the feedback gain since the same amount of afferent input in the spastic case will result in higher motoneuron activation than in a normal threshold level (17,18). According to control theory, instability may arise in a system with a high feedback gain and significant delays, conditions both present in the ankle muscles of spastic subjects (13). Hidler et al have clearly shown that both movement frequency and EMG burst frequency can be altered, and so we can only speculate that the loads used in the mentioned studies were not sufficient to perturb the system onto a different limit cycle orbit (19). Clonus was of shorter duration when more muscles were activated. In contrast, clonus was persistent when EMG activity was largely confined to the synergistic triceps surae muscles (20).

Iansek found a linear relationship between the frequency of clonus and the distance between spinal cord and the muscle. Mathematically, reflex oscillation latency was found to be predominant in determining frequency, and if there was a central spinal pacemaker, it would predict the frequency of clonus regardless of the length of the reflex pathway (21). The findings that are parallel to pure peripheral self-re-excitation mechanisms are preferably coupled with high reflex arc gain (shift in threshold of motoneuron activation). Possible factors involved in the regulation of clonus frequency are length of reflex arc; the frequency of clonus can increase with the decrease in activation latency of Ia afferent fibers; factors such as the mass and viscosity of the muscles can affect the frequency of clonus by changing the activity latency of spindle relaxation (21). The idea that central mechanisms may be involved was not adopted in observations where clonus was attributed to peripheral mechanisms. The frequency of clonus changed by changing the mechanical load on the joint. The rhythmic oscillations occurring in stretched muscles in some animal preparations are assumed to be analogous to clonus, and these oscillations were inhibited by the blockade of peripheral afferent fibers (22). Unsuccessful utilization of the signals from muscle spindles and Golgi tendon organs complicates imaging and regulation of muscle length

and power and autogenic reflex pathways play a major role in motor control in humans (4,23,24). The stretch reflex is a primary autogenic reflex and the negative feedback arc is the first line of active resistance when the body interacts with the environment. In normal conditions, the gains in reflex pathways were shown to be minimal. The functional behavior of the reflexes changes significantly with increasing excitability of motor neurons. It is believed that clonus with rhythmic or oscillatory contractions could occur in distal limbs where there is a change in the excitability of CNS associated with concurrent neurological disorders and when there is an increased tendency toward instability (2,4,23).

Hidler et al. hypothesized the coexistence of both conditions for the occurrence of clonus: reflex pathway delay (involving distal extremity muscles, displaying slow twitch properties), and increasing motor neuron excitability (decrease in motor neuron excitability threshold). These two phenomena disrupt the stability of motor neurons. The high incidence of orderly motor unit recruitment in human skeletal muscles that, due to spinal trauma, are under no voluntary control from higher centers suggests that spinal systems also dominate the stereotyped excitation of human motoneurons during clonus. Thus, any changes in spinal neuron excitability, synaptic inputs, or muscle properties due to injury were appropriate to preserve an orderly pattern of motor unit recruitment, as found during voluntary contractions of muscles innervated from the level of injury (12,13). Orderly recruitment of motor units during clonus is ordered by size of unit excitability. Afferent activity from the previous contraction and the level of spinal excitation were adequate to recruit most of the units during every contraction but were insufficient to increase their firing rates. None of these peripheral or spinal factors were sufficient to markedly disrupt the recruitment order of pairs of motor units during clonus (4).

The reason for this lengthened delay in spasticity may be the sensitivity of muscle spindles or changes in the passive features of the muscle. Increase of viscoelasticity of passive tissues enlarges the clonus receptive area (shaded); that is, it increases the amount of combinations of motor unit pool threshold and gain that will result in clonus

(24). Cook et al. showed that ankle dorsi-flexor remained reactively silent during the emergence of clonus, and the blockade of the peroneus communis nerve did not affect the amplitude and duration of oscillation (25).

The character of the input-output relationship in motor neurons can be defined by the Gaussian cumulative distribution function. Accordingly, the synaptic current scale is linearly correlated with the spindle firing rate. The functional pattern of motor neurons is determined by both motor unit recruitment and modulation rate. The single major reason for the delay in the generation of the monosynaptic reflex arc is neural conduction time in the reflex pathway. The delays in the "negative feedback" pathway possess a destabilizing effect on the behavior of the system. The frequency of oscillation decreases with increasing conduction delay (1).

Another reason for the delay in the reflex pathway is the contractile features of the muscle. These delays are caused by Ca dynamics, myofilament cross bridges, elasticity of the muscle fibers, and tendon compliance. In pathological conditions, slow-twitch muscle fibers can be replaced by fast-twitch muscle fibers. The input-output behavior in the muscle is similar to that in low pass filtering. Low pass filtering in the muscle or the delays in the reflex pathway due to conduction delays will affect reflex stability (24).

It is believed that clonus and spasticity share a common pathway; therefore, their co-occurrence on most, if not all, occasions is not surprising. The neuroaxial lesions such as stroke or spinal cord injury result in a net inhibition in segmental neurons. The balance of synaptic input to the motor neurons would change in favor of net excitation. It was reported that the muscle was continuously active due to on-off signal during rotational movement, and high tonic activity can be responsible for this condition. The oscillatory behavior observed in clonus is similar to closed arc oscillations seen in negative feedback control encompassing high feedback gains accompanied by significant delays.

Hagbarth et al. recorded medial gastrocnemius Ia afferent muscle spindle discharges during clonus caused by the stretch before muscle stretch and not during muscle activation. While spindle activity is expected during muscle stretch, the

observation of muscle spindle activation in medial gastrocnemius is not surprising during clonus elicited by fast stretch of PF; however, it was suggested that this would not be proven if spindle activation directly elicited or maintained clonus. No positive correlation was found between the number and frequency of power and spindle discharges following clonic EMG bursts. They reported that hyperexcitability of the stretch reflex is not centrally related for certain (26).

If repeated muscle stretch and the resulting muscle spindle activation elicit clonus, tibialis anterior muscle spindle activity and subsequent EMG activity should have been formed in a pattern following the activity of medial gastrocnemius. Hagbarth et al. did not record this from the tibialis anterior (26). Janell et al. suggested that the synchronous discharge of muscle spindle afferents of antagonistic muscles would be unlikely during DF-PF of the ankle joint, although muscle spindle activation was not measured directly (3).

When synchronous activation of plantar flexors and tibialis anterior during clonus was demonstrated, the inconsistency with the origin of the stretch reflex was not taken into consideration. Cook et al reported tibialis anterior EMG activity synchronous with PF that could not be eliminated by tibialis anterior nerve blockade, and they concluded that the observed tibialis anterior EMG activity could have been caused by cross-convergence due to PF (27). In addition, successive plantar-dorsiflexion EMG was not observed during clonus. They concluded that antagonistic activity was not necessary to elicit clonus and it was attributed to the repeated reflex stretch of plantar flexors. According to the results of the stimulation data, the investigators ruled out tibialis anterior and supported repeated stretch reflex as the cause of clonus (1). Cook et al. provided alternative explanations, suggesting that the activity observed in tibialis anterior was not caused by plantar flexors, but may have been caused by incomplete nerve blockade (19).

Hidler and Rymer observed tibialis anterior EMG activity synchronous with soleus and medial gastrocnemius activity during clonus, and they attributed tibialis anterior EMG activity to shortening reaction. The shortening reaction is defined as the EMG response in the shortened muscle commonly observed in patients with Parkinson's

disease. The shortening reaction in the ankle has been rarely observed in patients with first motor syndrome (12%) and the rate was uncommonly compared to disabled subjects (23).

Attempts have been made to change the frequency of clonic oscillatory burst patterns in order to test the stretch reflex and central oscillatory theories. If clonus correlates with the stretch, externally applied motion frequency affects the frequency of clonus. Rack et al. observed rhythmic EMG activity with various frequencies in response to ankle loading (16). Hidler and Rymer reported that the increase in the applied moment loading produced a greater stretch on the plantar flexors, and this resulted in early EMG response with higher frequency (1). It was reported that clonus could be re-established (reset) with the stimulation of the soleus H-reflex in the time frame between two successive clonic beats (28). Peripheral events are estimated to regulate afferent output, and such observations are commonly reported. On the other hand, there is no sufficient evidence to suggest that clonic EMG was only caused by the recurrent stretch reflex. The observation of oscillatory EMG activity in the absence of synchronous repetitive peripheral inputs supports the role of oscillatory neurons in the spinal cord that can be activated by many afferent events (19).

Another alternative explanation for clonus is central generator activity that arises as a consequence of appropriate peripheral events and produces rhythmic stimulation of the lower motor neurons (9). Walsh reported that clonic EMG frequencies of plantar flexors remained unchanged (14). In their study, Dimitrijevic et al. evaluated clonus EMG records, ankle angle, and pressure applied to the soles, and they investigated whether the silent period between two beats of clonus was caused by loading on the spindles or by the central refractory period (2). The attempts failed to change the frequency of clonus. The refractory period was approximately 100 msec and the excitatory period was approximately 60 msec, and accordingly cyclic changes in centrally regulated excitability constitute the basis for clonus and determine its frequency. They indicated that periodicity could be modified only for a short period by Ia inputs while transforming from the refractory period to excitatory period (2). According

to Dimitrijevic, the central generator is a transistor providing a functional organization, and it is made up of segmental reflex activity influenced by peripheral, propriospinal, suprasegmental mechanisms, proprioceptive volleys from the limb, and the movement of the muscle and parts of the limb. The features of the central generator include cyclic, regular activation at a fixed phase (2).

Brune and Schenck examined H-reflex volleys between two clonic bursts and reported a refractory period between EMG bursts. They attributed the cessation of motor neuron activity at the beginning of the silent period to the refractory state of the motor neurons with the inhibition of Renshaw cells after firing and lack of stimulation from spindle afferents at the rest of the period (29). Strupler, Burg, and Erbel suggested that recurrent inhibition produced by Renshaw cells and autogenic inhibition by Golgi afferents played a role in the refractory phase of the motor neurons and not only spindle unloading (30). Nathan measured the refractory period only in the triceps surae muscle (90-100 ms). He proposed that this period may differ for other muscle groups with different central stretch reflex organizations, thereby resulting in different maximum clonus frequencies (31). Wachholder and Altenburger showed that the latency of the first clonic beat was same as the stretch reflex. This time relationship did not persist in sustained clonus. Therefore, they expressed that clonus was triggered by the stretch and rhythmic discharge was maintained by the central factors (32).

The characteristic feature of clonus is synchronous motor discharge. It was reported that synchronous discharge occurred despite the input from asynchronous spindles to the clonus, muscle geometry, and the contribution of peripheral muscle factors such as the relaxation rate of the muscle (31). This indicates that the reflex is rigidly controlled over time and in the spatial extent in the motor unit pool. It was asserted that the discrepancy between peripheral factors and synchronized motor unit response indicates that central mechanisms play a major role (3,5). It was reported that peripheral input is essential for the re-activation of cyclic bursts and the overall activity is controlled by spinal mechanisms. The intermittent discharge of clonus is suggested to be caused by the periods of refractoriness, which

is due to the inhibition of motor neurons and/or interneurons. The prolonged period of refractoriness is caused by Renshaw cells.

The results of Janell et al. and Walsh support the interaction between many peripheral events and central mechanisms to elicit clonus (3,33). Despite the lack of an input that would produce a stretch in the muscles, bilateral clonic EMG activity was prominent in the proximal and distal limbs in the standing position without bearing weight. Clonus has been observed in the hamstring muscles following the development of clonus in the vastus medialis, vastus lateralis, and rectus femoris muscles while loading in the standing position and clinically after clonus in the ankle. The co-activation of the muscles between the limbs may have played a role after spinal cord injury, but the co-activation of antagonistic muscles in the same limbs also point to the convergence of the interneurons. A synchronous and bilateral muscle stretch in agonist and antagonist muscles seems unlikely (3).

TREATMENT OF CLONUS

Clonus can be treated by using baclofen, applying cold, botox or phenol injections (7, 9, 34-37). Several studies in the literature have reported that centrally active antispastic drugs do not have significant effects on clonus; however, some studies have shown that baclofen has more dramatic effects than other drugs. Tizanidine selectively blocks group II pathways, which have a role in spasticity but has no effect on clonus (38-41). In a study by Bassett and Lake on patients with upper motor neuron lesions, spasticity and clonus both decreased with the application of wet towels wrapped in crushed ice and with submergence in cold water (42). Measurable functional improvement has been reported in association with decreased spasticity after cold application. Knutsson who studied the kinematics of spastic gait before and after cold application, reported that a decrease in spasticity of antagonistic spastic plantar flexors paralleled an increase in the late oscillation phase during dorsiflexion (43). Hedenberg on the other hand, tested upper extremity functions of patients with hemiplegia before and after submergence in cold water and after cold application and noted significant improvements in functional capacities (44). Dimitrijevic et al. reported no

changes in clonus frequencies with cold application (2). Miglietta showed that the longer the period of cold application, the longer it took for clonus to recur. The average periods of recurrence of clonus observed after 10, 20, and 30 minutes of cold application were 28 (range, 15 to 45 minutes), 48 (range, 10 minutes to 2 hours), and 85 minutes (20 minutes to 6 hours), respectively (40,45). Cold application induced prolonged inhibitory effects on clonus. In response to cryotherapy, Boyraz et al. showed persistence of H and T reflexes with prolonged latencies, as well as decreases in the stimulation threshold and H/M ratio, but with a marked inhibitory effect on clonus. There is a persistence of ankle clonus inhibition even after a cooled muscle has returned to body temperature. This phenomenon could be explained by an increase in the threshold of the nerve fiber and/or a relatively prolonged refractory period. The prolonged effect of the cold supports the presence of spinal neuroplasticity and adaptation in individuals with neurologic impairments (35). Thevenon showed that clonus affected the first metatarsal, since it was selectively triggered by extension of the first metatarsophalangeal joint. To treat clonus, they applied injecting botulinum toxin into the peroneus muscles but failed. To stop clonus through selective neurotomy of the gastrocnemius and soleus, Thevenon performed neurotomy of the branches of the superficial fibular nerve that innervated the peroneus brevis and peroneus longus. After the surgery, clonus of the first metatarsal was no longer observed (35). Botulinum toxin has a role in treating ankle clonus in neurological patients, where it interferes in gait and may improve walking speed and level

of dependence on others (33). The treatment of clonus and spasticity may be obtained by using centrally and peripherally effective mechanisms simultaneously.

Clonus was considered to be a common presentation of the intrinsic oscillation of the spinal neural network after a reduction in sensorial input related to loading and chronic loss of supraspinal input. The spinal networks can be activated by numerous stimulations including interventions during voluntary movements, nociceptive synapses, and cutaneous synapses. Due to the presence of limited motor pools to elicit voluntary movements after severe spinal cord injury, the attempts mostly result in generalized motor patterns. In most cases with spinal cord injury, chronic unloading occurs not only as a result of the absence of supraspinal input, but also due to a lack of stepping and standing. Synchronous oscillatory motor output could be a re-organization of the neural network as a response to chronically changing afferent and supraspinal inputs, and therefore the same stimulus before injury did not cause the activation of the entire network. It must be investigated as to whether repetitive afferent information regarding stepping would re-modify the clonic motor firing pattern. Better results in the treatment of clonus and spasticity may be obtained by using centrally and peripherally effective mechanisms simultaneously.

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