Journal of Clinical and Experimental Neuroimmunology

Pingel, et al. J Clin Exp Neuroimmunol 2021, 6:4

Review Article Open Access

The Development of Contractures in Cerebral Palsy and Stroke: Pathophysiological Approaches

Pingel J[1]*, Harrison A[2], Korbo L[3] and Bartels EM[3]

[1]*Department of Neuroscience, Health and Medical Sciences, University of Copenhagen, Denmark*

[2]*Department of Biomechanics and Pathobiological Sciences, Health and Medical Sciences, University of Copenhagen,Denmark*

[3]*Department of Neurology, Copenhagen University Hospital, 2400 København, NV, Denmark*

[*]**Corresponding author** Dr Pingel J, Department of Neuroscience, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark, Tel: +45 20606199; E-mail: jpingel@sund.ku.dk

Received date: May 21, 2021; **Accepted date:** June 04, 2021; **Published date:** June 11, 2021

Abstract

The aim of this review is to elucidate the underlying processes that cause muscle contractures arising in connection with brain injury. We have chosen to compare brain lesions that occur early in life in the developing brain, as in cerebral palsy (CP), or brain lesions that occur late in life to the adult brain, as in stroke. It is generally recognized that deterioration of muscle function and motor skills occurs at different rates depending on whether the injury to the brain happens to the developing or the adult brain. We document structural as well as both physiological and functional changes in muscle contractures after brain injuries in both the developing- and the adult brain. Finally, we discuss the implication of these new findings in relation to diagnostics and therapy.

Keywords: Cerebral palsy; Carotid stenosis; lesions; Hypercholesterolemia; Contractures

Introduction

Lesions to the central nervous system regardless of whether the lesion occurs early in life, as in CP [1], or late in life, as in stroke [2], have some common complications e.g. contracture development. We define the term 'contracture' as being increased muscle stiffness [3]. Causes of CP include anoxia, epilepsy, occult infection, inflammation, brain trauma [4], whilst known risk factors for a stroke include hypertension, hypercholesterolaemia, carotid stenosis, cigarette smoking, excessive alcohol use, insulin resistance, and diabetes mellitus [5].

Muscle contractures result in a reduction in the range of movement and a dislocation of joints due to increased resistance of the passive elastic elements in the muscle and surrounding tissue [3]. Muscle contractures are therefore very debilitating complications to central nervous lesions, preventing normal daily activities, causing pain, reduced mobility, and often reduced social participation [6]. Why and how contractures develop is still not entirely clear. We have recently argued that the lack of a pathophysiological explanation of contracture development is due to involvement of multiple factors in a complex network of tissues, stimuli, and regulatory factors that define tissue homeostasis [3]. In the following we will outline what is known in CP as a representative for brain damage to the developing brain and in stroke as a representative for brain damage to the adult brain.

Possible Causes for Occurrence of Contractures

It has generally been assumed for decades that spasticity is a major cause of contracture development, being defined as "a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motoneuron syndrome."[7], the theory being that spasticity maintains muscles in a shortened position and thus causes the development of contractures. However, several recent studies have shown that increases in the passive stiffness of the joints occurs prior to development of spasticity and that contractures still develop even in situations when spasticity has been effectively abolished or at least diminished by sectioning of the dorsal roots (Dorsal Rhizotomy) [8,9]. Unfortunately, there is at present no effective therapy for muscle contractures, although considerable efforts are being put into various forms of physical therapy [10]. Since there is a growing body of evidence that indicates that spasticity alone does not cause contracture development, a couple of new theories regarding contracture development have been proposed.

One hypothesis for what causes the increased passive stiffness in the muscle is that the amount of intramuscular connective tissue increases. Booth and colleagues (2001) have reported an increased fraction of collagen seen in CP muscles compared to healthy muscles, and the fraction was highest in the most severe cases [11]. In children with CP all present collagen types were increased, as was the number of fibroblasts per unit volume, and increased collagen fibrils organized in cables were seen [12]. Lieber and Fridén (2019) also found such perimysial cables in children with cerebral palsy. These cables can be expected to result in a structural change of the extra-cellular matrix, most likely adding to the stiffness of a given muscle [13]. The physical work required to counteract a higher stiffness would over time make it harder to contract the muscle cells and could lead to muscle waste [14].

Another hypothesis as to what causes muscle contractures in cerebral palsy is based on impaired muscle growth. There is a growing body of evidence suggesting that reduced growth of muscles in infants with cerebral palsy may cause the development of contractures acting through muscle changes causing muscles to shorten [15,16].

However, in stroke patients the development of contractures must have a different cause since the muscles are already fully developed.

This illustrates that one cannot directly compare the consequences of injuries that occur in the adult brain and the developing brain. Besides stroke being the fourth-leading cause of death, stroke is also the leading cause of functional impairment [17]. Malhotra and colleagues (2011) showed that 25 stroke patients out of 30 (83%) developed signs of contracture in their upper limbs ~ 10 month post stroke [18].

A third hypothesis favours contracture development in stroke (and CP) as being the cause of immobilization/denervation of a muscle. Immobilization causes muscle atrophy and loss of muscle strength. One study showed that two weeks of immobilization using plaster cast of Paris in a neutral position caused a loss of 7% of the muscle mass and 10% of muscle strength [19]. However, these changes are fully reversible. Muscle denervation, however, causes more severe changes to the muscle. Four weeks of denervation has been shown to result in a muscle loss of 80%-90% in the affected leg when compared to the contralateral control side in rats [20,21].

However, both CNS lesions may have a specific window of opportunity in which it may be possible to change the development in muscle tone and further spasticity and contracture. In this review, we want to add another factor to the current discussion on contracture development and open up for new hypotheses and theories regarding contracture formation both in patients who suffer a developmental CNS lesion as well as those who are affected in adulthood.

The Importance of Calcium during Contracture Development

Children with cerebral palsy

Children exposed to deprivation of oxygen during birth (birth asphyxia) exhibit total serum calcium and ionic calcium levels at birth that are linked to the severity of asphyxia, e.g. lower concentrations of both total serum and ionic calcium at birth is associated with increased severity of hypoxic ischemic encephalopathy [22]. The question remains, however, if this condition sets serum calcium at too low a level for life or at least during early development. This could partly explain the findings of Nakano and colleagues (2003) in which a third of a studied group of CP subjects showed an abnormal calcium metabolism defined as serum calcium <8.5 mg/dl; serum phosphate <2.6 mg/dl or serum alkaline phosphatase >260 U/l when looking at bone mineral density (BMD) [23]. However, there are no studies published that report the electrolyte values for a large cohort of CP subjects (New South Wales Management Guidelines, 2018: (https://www.health.nsw.gov.au/aod/Pages/nsw-clinical-guidelines-opioid.aspx)).

Furthermore, vitamin D deficiency is found in a high proportion of children with CP, but this may often be caused by the use of antiepileptic medicine which can affect the vitamin D metabolism and ultimately result in a decrease of bone density [24]. One study showed that antiepileptic medicine induced disturbances of bone metabolism, which were often accompanied by a fall in 25(OH)D, hypocalcemia, secondary hyperparathyroidism, and increased bone turnover [24].

Another study observed that adults with CP had an abnormal calcium metabolism and lower BMD, which was significantly correlated to treatment with anti-epileptics [23]. An abnormality in electrolytes in the cerebrospinal fluid in CP could be another factor worth considering [25]. However, despite the recognition of volumetric differences in critical regions of the brain being related to a child´s gestational age at birth, research is currently limited concerning any clear correlation between specific neuromotor abnormalities and these volumetric measurements [26]. Recently, it was concluded that neuroimaging, whilst capable of providing an insight into the region and severity of cerebral injury, and if detected early enough providing a window of opportunity for neuroprotection, is still in need of further research and development [27].

Other studies, looking at electrolytes in saliva in CP subjects, have found lower saliva sodium and flow rate [28,29]. Sodium is linked to flow rate, so the flow rate is most likely the cause of the lower sodium. Potassium, on the other hand, is higher than in healthy individuals, and is not linked to flow rate. The total saliva protein and electrolyte concentration are higher in CP than in healthy subjects, giving a higher saliva osmolality. The authors suggest that CP subjects have an impaired ion exchange in the saliva glands, giving rise to a hypo-hydration condition [28]. At the muscle tissue level recent findings have shown that the expression of gene targets involved in calcium handling and muscle signaling are significantly different from the expression levels in typically developed children [30]. The same study showed structural abnormalities of the basement membrane of the muscle cell, which lead the authors to conclude that the basement membrane might be a crucial factor of the muscular abnormalities experienced by children with CP [30].

Stroke Patients

In patients with both ischemic and hemorrhagic strokes the systemic electrolyte levels are changed [31]. Indeed, it has been shown that out of 110 stroke patients, more than 40% of the patients had abnormal sodium levels, more than 30% of the patients had an abnormal potassium levels, and more than 30% had abnormal chloride levels [31]. In a study by Panda and co-workers (2019) acute stroke patients were also found to have lower mean serum sodium (71% being hyponatraemic) and lower mean serum calcium (48% being hypocalcaemic), but no difference in serum chloride or potassium were found compared to healthy subjects [32]. In addition, it has been reported that hemorrhagic stroke results in a number of changes, including Na+/K+/2 Cl−co-transporter expression affecting an increase in CSF secretion [33]. Recent evidence suggests that Ca^{2+} dysregulation is a common underlying phenomenon in the pathophysiology of muscle atrophy caused by hypoxia, sepsis, cachexia, sarcopenia, heart failure, dystrophy and spinal cord injury [34]. Moreover, we suggest that stroke should be included in this list of pathologies since it is very likely that the calcium regulation in the muscle is disturbed in stroke patients. Recent findings also revealed that the gene expression of Myostatin and collagen type 4 was significantly downregulated in stroke patients when compared to healthy control subjects. This indicates a compensatory reaction of the muscle towards muscle weakness, reduced muscle growth and/or muscle atrophy [35]. The same compensatory reaction of muscles has also been observed in individuals with CP [35].

Hubbard and colleagues (2018) offer another explanation for possible impaired ion exchange in both cerebral palsy and stroke. These authors suggest that aquaporin-4 channels (AQP4) very likely play a crucial role in the pathology of stroke since the AQP4 channels are located at the perivascular astrocytic end-feet and hence the control of brain water balance and edema [36]. However, whether AQP4 channels may play a role in the pathology of CP is yet unclear.

Diagnostic Techniques

It is important that any diagnostic tool is quick and easy to use, as well as being non-invasive and pain-free. To this, it is also vital that diagnostic tools provide accurate information about structural, metabolic and functional properties of the subject´s muscles. One such promising diagnostic tool that matches all the requirements mentioned is multi-frequency bioimpedance (mfBIA). This is a tool for assessing static muscle structure and metabolism [37-40]. It´s use in a number of studies has helped identify aspects of muscle injury as well as muscle health [41-48]. Indeed, the relation between its parameters and muscle health are well-documented [37,41-45]. Recently it was used successfully for the assessment of muscle injury and subsequent recovery in athletes [42,43], as well as with CP subjects, in which several mfBIA parameters were found to differ significantly between individuals with CP and those of healthy controls. These changes in mfBIA parameters are to such an extent that some correlate significantly with the severity of CP, as assessed using the GMFCS scale [49]. The technique has also been applied on skeletal muscles in stroke when assessing muscle mass [50]. The authors used the mfBIA device to calculate a skeletal muscle index (SMI) standardizing by height squared (kg/m^2), and they observed that a low SMI index at the onset of ischemic stroke is an independent predictor of walking function [50].

Whilst a static assessment of a subject´s musculature is valuable, it is equally important that their muscles be assessed whilst functional. Movement and the electrical signals of active muscles have long been assessed by means of surface electromyography (sEMG) [51]. Indeed, it has been said that sEMG has as its strongest feature the fact that it is relatively easy to use, but this also represents its greatest weakness [52]. Over the years, many have attempted to address the complex sEMG issues of sampling rate, noise and interference, as well as the specific issues of causative, intermediate and deterministic factors, which affect recorded signals from active muscles, making it difficult and complex to interpret [53]. Recent technological advances, however, have paved the way for a more readily useable clinical tool in the form of acoustic myography (AMG) [51]. This wireless, stable, quick and easy to use technique lends itself specifically to the assessment of patients with musculoskeletal complaints during daily activities [54].

To this end a recently published reference data set not only serves to illustrate the reproducibility and ease of this technique in the clinic, it also provides data with which to compare and assess individuals with musculoskeletal problems [14]. Recently the use of this diagnostic tool for the functional assessment of muscles in CP subjects revealed that they use a higher degree of spatial summation (more fibres recruited) to maintain the same speed during treadmill exercise when compared to healthy matched control subjects [55]. Using this novel technique, the authors were able to conclude that individuals with CP tend to recruit more muscle fibres than healthy controls during periods of exercise, a finding that goes a long way to explaining, in part, the observation that CP subjects suffer from premature fatigue when exercising [55].

Discussion

The method has so far not been applied on stroke patients, but it may have great potential in this patient group during rehabilitation. Of course, being able to assess muscle contractures in subjects with either damage to the developing brain or injury to the adult brain is important, but it is also essential that one can monitor the effects of for example changes in the dosage of medication and, most importantly, the effects of therapy in such subjects. To this end mfBIA lends itself to the static assessment of muscular changes, that is to say measurements made pre-exercise over a period of time by way of assessing structural as well as both metabolic changes in muscle contractures as a result of damage to the developing brain or injury to the adult brain. In contrast, AMG as a diagnostic tool lends itself to the assessment of functional changes in muscle contractures in such subjects. It is often these functional changes that form the basis of quality of life assessments, determining the ability of subjects to look after themselves, to master daily tasks and to interact with their surroundings, and to this end the recently published reference data set for AMG is important [14]. However, functional assessment of therapeutic interventions is also necessary in this connection, and here AMG can most likely be a great help.

Following a stroke there is an opportunity to alleviate the development of contractures and other complications, and regain function both in the upper and lower limbs [56,57]. In contrast, cerebral palsy is often diagnosed much later, mostly at the age between 12 to 24 months in high-income countries. In low resource countries, children with CP are mostly diagnosed as late as 5 years after the brain lesion has occurred [58]. The question with regard to CP is then, if the window of opportunity to act has been missed or whether investment in early detection and preventive methods may be beneficial or even curative concerning development of contractures. Although we are dealing with a young developing brain, it may still be possible to learn from the new interventions applied in stroke treatment.

A possible non-invasive method well suited for measurements on infants would be multi-frequency bioimpedance, focusing mostly on the centre frequency parameter, which has the potential to reveal even small changes in muscle tension [46,47]. Indeed, as a technique multi-frequency bioimpedance has already proved itself useful in adult CP subjects.

Conclusion

Although CP and stroke lead to similar disabilities like contractures, there are differences in the site of damage in the brain, differences between the developing brain and an adult brain, as well as differences in the homeostasis when the injury happens. The similarities are occurrence of contractures, although not to the same extent and with different time for onset, structural changes of muscle, proprioception deficits, disturbance in ion transport homeostasis, but both conditions can be anoxia, occult infection and inflammation related. Both conditions are variable in severity, probably related to the degree and extent of known contributing factors. When assessing the condition, stroke is monitored from the appearance and treatment starts soon after the injury, while it may take years before CP is diagnosed and treated. If CP was diagnosed as early as stroke, the outcome might be reversible or at least much less severe.

References

1. Mathewson MA, Lieber RL (2014) Pathophysiology of muscle contractures in cerebral palsy. Phys Med Rehabil Clin N Am 26(1): 57-67.
2. O'Dwyer NJ, Ada L, Neilson PD (1996) Spasticity and muscle contracture following stroke. Brain. 119 (Pt 5):1737-49.

3. Pingel J, Bartels EM, Nielsen JB (2016) New perspectives on the development of muscle contractures following central motor lesions. J Physiol. 595(4):1027-1038.
4. Colver A, Fairhurst C, Pharoah PO (2014) Cerebral palsy. Lancet. 383(9924):1240-9.
5. Hankey GJ. (2017) Stroke. Lancet. 389(10069):641-54.
6. Graham HK, Rosenbaum P, Paneth N, Dan B, Lin JP, Damiano DL, et al. (2015) Cerebral palsy. Nat Rev Dis Primers. 2:15082.
7. W. LJ. Symposium synopsis. (1980). In: Feldman R G, Young R R, Koella W P, editors Spasticity: Disordered Motor Control. 185-204.
8. Tedroff K, Lowing K, Astrom E (2015) A prospective cohort study investigating gross motor function, pain, and health-related quality of life 17 years after selective dorsal rhizotomy in cerebral palsy. Dev Med Child Neurol. 57(5):484-90.
9. Tedroff K, Lowing K, Jacobson DN, Astrom E (2011) Does loss of spasticity matter? A 10-year follow-up after selective dorsal rhizotomy in cerebral palsy. Dev Med Child Neurol. 53(8):724-9.
10. Kalkman BM, Bar-On L, O'Brien TD, Maganaris CN (2020) Stretching Interventions in Children With Cerebral Palsy: Why Are They Ineffective in Improving Muscle Function and How Can We Better Their Outcome? Front Physiol. 11:131.
11. Booth CM, Cortina-Borja MJ, Theologis TN (2001) Collagen accumulation in muscles of children with cerebral palsy and correlation with severity of spasticity. Dev Med Child Neurol. 43(5):314-20.
12. Smith LR, Pichika R, Meza RC, Gillies AR, Baliki MN, Chambers HG, et al (2019) Contribution of extracellular matrix components to the stiffness of skeletal muscle contractures in patients with cerebral palsy. Connective tissue research. 62(3):287-298.
13. Lieber RL, Friden J (2019) Muscle contracture and passive mechanics in cerebral palsy. J Appl Physiol. 126(5):1492-1501.
14. Bartels EM, Korbo L, Harrison AP (2020) Novel insights into cerebral palsy. Journal of muscle research and cell motility. 41(2-3):265-267.
15. Gough M, Shortland AP (2012) Could muscle deformity in children with spastic cerebral palsy be related to an impairment of muscle growth and altered adaptation? Dev Med Child Neurol. 54(6):495-9.
16. Smith LR, Lee KS, Ward SR, Chambers HG, Lieber RL (2011) Hamstring contractures in children with spastic cerebral palsy result from a stiffer extracellular matrix and increased in vivo sarcomere length. J Physiol. 589(Pt 10):2625-39.
17. Ovbiagele B, Goldstein LB, Higashida RT, Howard VJ, Johnston SC, Khavjou OA, et al. (2013) Forecasting the future of stroke in the United States: a policy statement from the American Heart Association and American Stroke Association. Stroke. 44(8):2361-75.
18. Malhotra S, Pandyan AD, Rosewilliam S, Roffe C, Hermens H (2011) Spasticity and contractures at the wrist after stroke: time course of development and their association with functional recovery of the upper limb. Clin Rehabil. 25(2):184-91.
19. Pingel J, Moerch L, Kjaer M, Langberg H (2009) The influence of training status on the drop in muscle strength after acute exercise. Eur J Appl Physiol. 106(4):605-11.
20. Ma J, Shen J, Garrett JP, Lee CA, Li Z, Elsaidi GA, et al. (2007) Gene expression of myogenic regulatory factors, nicotinic acetylcholine receptor subunits, and GAP-43 in skeletal muscle following denervation in a rat model. J Orthop Res. 25(11):1498-505.
21. Dow DE, Cederna PS, Hassett CA, Kostrominova TY, Faulkner JA, Dennis RG (2004) Number of contractions to maintain mass and force of a denervated rat muscle. Muscle Nerve. 30(1):77-86.
22. Mahajan K. SB, Chandwani C., Singh V (2020) Correlation of Total Serum Calcium and Ionic Calcium Levels with Severity of Birth Asphyxia. Indian Journal of Public Health and Development. 11(03).
23. Nakano H, Aoyagi K, Ohgi S, Akiyama T (2003) Factors influencing metacarpal bone mineral density in adults with cerebral palsy. J Bone Miner Metab. 2003;21(6):409-14.
24. Gröber U, Kisters K (2012) Influence of drugs on vitamin D and calcium metabolism. Dermatoendocrinol. 4(2):158-66.
25. Ito M, Konishi Y, Okuno T, Nakano Y, Yamori Y, Hojo H (1979) Computed tomography of cerebral palsy: evaluation of brain damage by volume index of CSF space. Brain Dev. 1(4):293-8.
26. Panigrahy A, Barnes PD, Robertson RL, Back SA, Sleeper LA, Sayre JW, et al. (2001) Volumetric brain differences in children with periventricular T2-signal hyperintensities: a grouping by gestational age at birth. AJR Am J Roentgenol. 177(3):695-702.
27. Shimony JS, Lawrence R, Neil JJ, Inder TE (2008) Imaging for diagnosis and treatment of cerebral palsy. Clin Obstet Gynecol. 51(4):787-99.
28. Santos MT, Guaré RO, Leite MF, Ferreira MC, Durão MS, Jardim JR (2010) Salivary osmolality in individuals with cerebral palsy. Arch Oral Biol. 55(11):855-60.
29. Siqueira WL, Rodrigues Santos MT, De Oliveira E, Nicolau J (2007) Comparison of electrolyte concentrations in whole saliva of individuals with and without cerebral palsy. Quintessence international. 38(4):301-6.
30. Pingel J, Kampmann ML, Andersen JD, Wong C, Døssing S, Børsting C, et al. (2021) Gene expressions in cerebral palsy subjects reveal structural and functional changes in the gastrocnemius muscle that are closely associated with passive muscle stiffness. Cell Tissue Res. 384(2): 513-526.
31. Alam MN, Uddin MJ, Rahman KM, Ahmed S, Akhter M, Nahar N, et al. (2012) Electrolyte changes in stroke. Mymensingh Med J. 21(4):594-9.
32. Panda M SP, Mandal MK, Mohapatra AK, Dany (2019) Altered Serum Electrolyte Status in Acute Stroke Patients in Western Odisha, A Predictor of Syndrome of Inappropriate ADH (SIADH) or Cerebral Salt Wasting Syndrome (CSWS). Journal of Clinical and Diagnostic Research 13(1):10-13.
33. Karimy JK, Zhang J, Kurland DB, Theriault BC, Duran D, Stokum JA, et al. (2017) Inflammation-dependent cerebrospinal fluid hypersecretion by the choroid plexus epithelium in posthemorrhagic hydrocephalus. Nat Med. 23(8):997-1003.
34. Agrawal A, Suryakumar G, Rathor R (2018) Role of defective Ca(2+) signaling in skeletal muscle weakness: Pharmacological implications. J Cell Commun Signal. 12(4):645-59.
35. Pingel J. PC, Petersen Tw., Nielsen Jb (2021) Cerebral Palsy and Stroke—Early and Late Brain Lesion Present Differences in Systemic Biomarkers and Gene Expression Related to Muscle Contractures. World Journal of Neuroscience. 11(01):34-47.
36. Hubbard JA, Szu JI, Binder DK (2018) The role of aquaporin-4 in synaptic plasticity, memory and disease. Brain Res Bull. 136:118-29.
37. Ivorra A (2003) Bioimpedance monitoring for physicians: an overview. Centre National de Microelectronica, Barcelona. 11:17.
38. Jaffrin MY (2009) Body composition determination by bioimpedance: an update. Curr Opin Clin Nutr Metab Care. 12(5):482-6.
39. Kalvoy H, Martinsen OG, Grimnes S (2008) Determination of tissue type surrounding a needle tip by electrical bioimpedance. Annu Int Conf IEEE Eng Med Biol Soc. 2008:2285-6.
40. Matthie JR (2008) Bioimpedance measurements of human body composition: critical analysis and outlook. Expert Rev Med Devices. 5(2):239-61.
41. Nescolarde L, Yanguas J, Lukaski H, Alomar X, Rosell-Ferrer J, Rodas G (2013) Localized bioimpedance to assess muscle injury. Physiol Meas. 34(2):237-45.
42. Nescolarde L, Yanguas J, Lukaski H, Alomar X, Rosell-Ferrer J, Rodas G (2015) Effects of muscle injury severity on localized bioimpedance measurements. Physiol Meas. 36(1):27-42.
43. Nescolarde L, Yanguas J, Lukaski H, Rodas G, Rosell-Ferrer J (2014) Localized BIA identifies structural and pathophysiological changes in soft tissue after post-traumatic injuries in soccer players. Annu Int Conf IEEE Eng Med Biol Soc. 2014:3743-6.
44. Nescolarde L, Yanguas J, Medina D, Rodas G, Rosell-Ferrer J (2011) Assessment and follow-up of muscle injuries in athletes by bioimpedance: preliminary results. Annu Int Conf IEEE Eng Med Biol Soc. 2011:1137-40.

45. Gupta D, Lis CG, Dahlk SL, King J, Vashi PG, Grutsch JF, et al. (2008) The relationship between bioelectrical impedance phase angle and subjective global assessment in advanced colorectal cancer. Nutr J. 7:19.
46. Bartels EM, Andersen EL, Olsen JK, Kristensen LE, Bliddal H, Danneskiold-Samsoe B, et al. (2019) Muscle assessment using multi-frequency bioimpedance in a healthy Danish population aged 20-69 years: a powerful non-invasive tool in sports and in the clinic. Physiol Rep. 7(11):e14109.
47. Bartels EM, Sorensen ER, Harrison AP (2015) Multi-frequency bioimpedance in human muscle assessment. Physiol Rep. 3(4):e12354.
48. Harrison AP, Elbrond VS, Riis-Olesen K, Bartels EM. (2015) Multi-frequency bioimpedance in equine muscle assessment. Physiological measurement. 36(3):453-64.
49. Pingel J, Harrison A, Von Walden F, Hjalmarsson E, Bartels EM (2020) Multi-frequency bioimpedance: a non-invasive tool for muscle-health assessment of adults with cerebral palsy. J Muscle Res Cell Motil. 41(2-3):211-219.
50. Abe T, Iwata K, Yoshimura Y, Shinoda T, Inagaki Y, Ohya S, et al. (2020) Low Muscle Mass is Associated with Walking Function in Patients with Acute Ischemic Stroke. J Stroke Cerebrovasc Dis. 29(11): 105259.
51. Harrison AP (2018) A more precise, repeatable and diagnostic alternative to surface electromyography- an appraisal of the clinical utility of acoustic myography. Clin Physiol Funct Imaging. 38(2):312-25
52. De Luca CJ, Kline JC (2012) Influence of proprioceptive feedback on the firing rate and recruitment of motoneurons. J Neural Eng. 9(1):016007.
53. Hermens HJ, Freriks B, Disselhorst-Klug C, Rau G (2000) Development of recommendations for SEMG sensors and sensor placement procedures. J Electromyogr Kinesiol. 10(5):361-74.
54. Harrison AP, Danneskiold-Samsøe B, Bartels EM (2013) Portable acoustic myography a realistic noninvasive method for assessment of muscle activity and coordination in human subjects in most home and sports settings. Physiol Rep. 1(2):e00029.
55. Pingel J, Andersen IT, Broholm R, Harder A, Bartels EM, Bülow J, et al. (2019) An acoustic myography functional assessment of cerebral palsy subjects compared to healthy controls during physical exercise. J Muscle Res Cell Motil. 40(1):53-58.
56. Veerbeek JM, van Wegen E, van Peppen R, van der Wees PJ, Hendriks E, Rietberg M, et al. (2014) What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. PloS one. 9(2):e87987.
57. Pollock A, Baer G, Campbell P, Choo PL, Forster A, Morris J, et al. (2014) Physical rehabilitation approaches for the recovery of function and mobility following stroke. Cochrane Database Syst Rev. 2014(4):CD001920.
58. te Velde A, Morgan C, Novak I, Tantsis E, Badawi N (2019) Early Diagnosis and Classification of Cerebral Palsy: An Historical Perspective and Barriers to an Early Diagnosis. J Clin Med. 8(10):1599.