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THE EFFECTS OF INTENSIVE TENS THERAPY ON MUSCLE BLOOD BIOMARKERS AND ACTIVITIES OF DAILY LIVING IN HAEMORRHAGIC STROKE PATIENTS

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Abstract— Hemorrhagic strokeis a highly debilitating condition with several rehabilitations' problems. Transcutaneous Electrical Nerve Stimulation (TENS) has long been an indispensable tool in stroke rehabilitation. Thus, this study aimed to discern the effects of TENS, specifically intensive TENS therapy for 2 weeks, on a motor-impaired haemorrhagic stroke patient's recovery, on top of 6 weeks of conventional physiotherapy. We want to elucidate the effect of TENS and conventional physiotherapy on serum Creatine Kinase and serum Troponin T. Our outcome measures were serum Creatine Kinase, serum Troponin T, and modified Barthel Index scores. This was a pre-post convenient sampling controlled interventional study, conducted in the Hospital UniversitiSains Malaysia, with 10 control subjects and 10 TENS-therapy subjects.The intervention group underwent both intensive TENS therapy and conventional physiotherapy for 2 weeks, then 4 weeks of conventional physiotherapy. The control group underwent 6 weeks of conventional physiotherapy.All three outcome measures of each participant were measured before and after 2 weeks of intensive TENS therapy and 6 weeks of conventional therapy. Results indicated that serum Creatine Kinase and serum Troponin T were relatively unaffected by 2 weeks of intensive TENS therapy and 6 weeks of conventional physiotherapy (serum CreatineKinase: $p = 0.521$) (serum Troponin T: $p = 0.632$). The same also applied to 6 weeks of conventional physiotherapy alone (serum CreatineKinase: $p = 0.572$) (serum Troponin T: $p = 0.921$). On the contrary, modifiedBarthelIndexscorecomparisonsdidshowsignificantincreases in interventiongroup ($p = 0.040$) as comparedtocontrolgroup. This study currently acts as a pilot study and the results of this study, which demonstrated no change in blood biomarkers but improved activity of daily living scores in haemorrhagic stroke patients, shall be treated as preliminary results for future research on intensive TENS therapy.

Keywords: Barthel Index, activities of daily living, Haemorrhagic stroke, creatine kinase, Transcutaneous electrical nerve stimulation (TENS), Troponin

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1. Introduction

The International Classification of Diseases - 11 (ICD-11) defines stroke as the presence of acute neurological dysfunction[1]. This dysfunction is a result of either ischemia or haemorrhage; it can be sensory or motor in nature or both, and this is determined by imaging or pathology[2].Haemorrhagic stroke can occur due to direct trauma and damage to intracerebral blood vessels, or due to spontaneous bursting or leaking of cerebral blood vessels secondary to an acute hypertensive crisis, or a vascular malformation such as an aneurysm or arteriovenous malformation (AVM).Because of their contrasting etiologies and pathophysiologies, both subtypes of stroke have opposing management principles. However, the clinical result is almost similar: loss of blood circulation to the part of the brain distal to the site of vascular insult, death of the cerebral cells in the involved region, and ultimately loss of neurological function of that cerebral region[3, 4,5].

Transcutaneous electrical nerve stimulation, or TENS, encompasses delivering pulses of electrical current to the skin of a patient via a device, with the goal of inducing the production of nerve impulses in afferent nerves under the skin. A battery-powered, hand-held device generates the electrical current and passes through conductive pads to reach the skin. The procedure is non-invasive, and the strength (amplitude) of the electricity given can be increased or decreased to achieve a balance between painful overstimulation of the muscles and overt lack of stimulation. One can also modulate the frequency, duration and pattern of electrical current pulses, depending on the patient's clinical rehabilitative needs. Three different techniques of TENS are regularly used: conventional TENS (low amplitude, high frequency), acupuncture-like TENS (high amplitude, low frequency) and intense TENS (high amplitude, high frequency) [19,20, 21].

Conventionally, TENS aims to alleviate different forms of chronic pain. Lately, due to increasing evidence of its benefit to motor impaired patients, more and more recovery centres began adopting TENS in their rehabilitation regimes for stroke patients. With its relatively economical price, convenience and ease of handling, TENS would be a boon to any motor recovery programme.

Studies as early as 1984 demonstrated increases in muscle protein biomarkers Creatine Kinase and Troponin post-exercise [22, 23]. As most forms of traditional physiotherapy are essentially exercise-based, an important question arises: What is the significance of these biomarkers in exercise?

CK has long been a general marker of muscle damage, found in the cytoplasm and mitochondria of cells with high-energy demand such as skeletal and cardiac muscles[23, 24, 25]. Chronic stroke patients are common victims of cachexia and muscle wasting, especially without proper rehabilitation and physical therapy. The decrease in their muscle mass can be reflected through the decrease in serum CK compared to non-ill people [28]. Thus, it is for these reasons that we wish to use CK to monitor a stroke sufferer's progress through physiotherapy with and without TENS.

There are two known isoforms of cardiac Troponin, Troponin I and Troponin T. Both isoforms are elevated specifically in the presence of cardiac injury [25]. The phenomenon of post-exercise Troponin release was first hinted at in a 1987 study on post-exercise muscle enzyme changes, where a small percentage of subjects were found to have increased Troponin levels despite having no history of cardiac disease [23]. Several factors have been identified to predispose to higher post-exercise Troponin, but some studies also show conflicting evidence: underlying cardiovascular or renal disease, higher exercise intensity, less training experience, late sampling and low assay sensitivity. Among the factors with conflicting associations are age and exercise duration [29, 30, 31,32].

TENS has already shown various physical benefits to a stroke patient's rehabilitation in the aspects of spasticity and paresis. However, no study has yet objectively measured the effect of TENS on muscle growth in the form of biomarkers, nor measure any improvements it might have on activities of daily living. The concept of TENS improving muscle growth in motor-impaired haemorrhagic stroke patients is that repeated efferent peripheral nerve stimulation and the resultant repeated muscle contraction will act as a form of repeated exercise, causing increased muscular strength. This would explain why TENS complements conventional physiotherapy. This premise was first explored by Azman and Azman in 2017, though their focus was more on direct electrical muscle stimulation, they acknowledged that the same concept can be applied to TENS [43].

In this study, we studied the suitability of intensive TENS therapy for chronic stroke patients by measuring the changes in 3 outcomes: activities of daily living via modified Barthel index, skeletal muscle improvement via serum Creatine Kinase, and cardiovascular disease risk via serum Troponin T.

3. Methodology

This study is a pre-post convenience sampling single-blinded controlled interventional study, conducted in the Department of Neurosciences and Rehabilitation Medicine Unit, Hospital UniversitiSains Malaysia. The study population includes outpatient haemorrhagic stroke patients with motor impairments in Hospital UniversitiSains Malaysia, from November 2020 to March 2021.

We used non-probability convenience sampling method to recruit subjects for our study. We recruited 20 haemorrhagic stroke patients with half of the participants in the intervention group and the other half in the control group. Unfortunately, 1 of the 10 interventional subjects decided to withdraw from the study due to health issues, while another 3 subjects were lost to follow up.

We interpreted changes in serum Creatine Kinase as a representation of changes in muscle mass, and changes in serum Troponin T as a measure of future cardiovascular disease risk. Once subjects were recruited, we used the modified Barthel Index of Activities of Daily Living (MBI) to assess the activities of daily living of each subject.

The TENS was delivered using a Miutar Mini massager machine unit with two conductive pads that stimulate the lower arm of the subject's affected side (spastic or paresis). Electrical stimulation was given in bursts with each pulse having a pulse width of 230 microseconds, at 115 Hz for 15 minutes per session. Intensive TENS therapy was implemented by administering TENS for 20 minutes a day, Sunday through Thursday (5 days a week) for 2 consecutive weeks for a total of 10 sessions. After each session, we assess patients for any potential side effects of TENS application such as skin irritation from the adhesive and chest pain for possible cardiac effects.

All subjects from both groups underwent 6 weeks of conventional physiotherapy, once a week, which constitutes different physical exercises and therapies specific to their motor impairment, including stationary cycling, heat therapy, and limb strengthening exercises. The intervention group underwent both intensive TENS therapy and conventional physiotherapy for 2 weeks, then 4 weeks of conventional physiotherapy. The control group underwent 6 weeks of conventional physiotherapy. The control group were not given sham stimulation as conventional physiotherapy also includes occasional TENS therapy, which most patients are already accustomed to. The reason we implemented only 2 weeks of intensive TENS therapy is to see the long-lasting physiological benefit of 2 weeks of intensive TENS therapy, in addition to the 6 weeks of conventional physiotherapy in a hemorrhagic stroke sufferer's rehabilitation

plan. After the completion of 6 weeks intervention (6 sessions in total), we reassessed all subjects for their activities of daily living and took their blood again for comparison and analysis with the baseline values.

We used descriptive statistics to better consolidate the data we collected: the subjects' modified Barthel Index scores, their serum Creatine Kinase and serum Troponin T levels before and after intervention. We used paired T test and repeated measures ANOVA to compare the mean differences between the two groups. Within this study, 'significant' refers to significance with $p < 0.05$. We used box-plot and Shapiro-Wilk test to make sure there are no outliers and the data distributed normally for each group. The data was analysed with SPSS version 24.

4. Results

After going through our inclusion and exclusion criteria, 20 subjects were successfully recruited into our research, with a total of 4 dropouts as stated earlier, 3 from the intervention group and 1 from the control group. Themean (SD) age of our research subjects was 54.75 (13.94) years, with 8 (50.0%) ofthem being male and 8 (50.0%) of them female.

In this study, pre-intervention modified Barthel Index scores of all haemorrhagic stroke subjects average at 60.31.Intervention subjects reported a higher amount of improvement in modified Barthel Index scores relative to control subjects, with their average modified Barthel index score increasing from 42.86 to 53.57, a statistically significant increase ($p = 0.047$). The increase in index score sismostly in the categories of Self-dressing (3 subjects) and Bowel control (3 subjects). None of the subjects reported worsening in ADL scores. As a comparison, control subjects reported some but not significant change in activities of daily living before and after the study, with their modified Barthel Index scores reflecting this at ameagre increase from 73.90 to 75.00 score ($p = 0.347$).

In the control group, thelevelof serum Creatine Kinase only marginally increased from 100.67 U/L on average, to an average of 102.33 U/L, which is statistically insignificant compared to the control group'spre-CK levels ($p = 0.874$).In the intervention group, serum Creatine Kinase level decreased from 100.57 U/L to an average of 74.86 U/L post-intervention ($p = 0.385$). However, this is due to an outlier result of one of the subjects having a decrease in post-intervention serum Creatine Kinase of 186 U/L, without which the average serum Creatine Kinase difference is an increase of only 1.0 U/L ($p = 0.900$), a highly insignificant result.

Compared with pre-intervention levels, the serum Troponin T levels in the intervention group maintains from 10.91 ng/L, to 10.65 ng/L post-intervention. This is statistically not significant ($p = 0.815$).Similar to the intervention group, the average level of serum Troponin T in the control group remains relatively insignificant and stagnant from 6.82 ng/L to 7.58 ng/L after 6 weeks ($p = 0.498$).

Compared to changes in serum Troponin T ($p = 0.815$) and serum Creatine Kinase ($p = 0.385$), the increase in modified Barthel index scorepre- andpost-ITT in the intervention group is statistically significant ($p = 0.047$).

Table 4.8: Pairedsamples T test for Control Group

Paired Samples Test

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
PreCK - PostCK	-1.67	30.46	10.15	-25.08	21.74	-.16	8	.874
PreTropT - PostTropT	-.75	3.19	1.06	-3.20	1.70	-.71	8	.498
PreBI - PostBI	-1.11	3.33	1.11	-3.67	1.45	-1.00	8	.347

Table 4.9: Paired samples T test for Intervention Group

Paired Samples Test

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
PreCK - PostCK	25.71	72.68	27.47	-41.50	92.93	.94	6	.385
PreTropT - PostTropT	.27	2.92	1.10	-2.43	2.97	.25	6	.815
PreBI - PostBI	-10.71	11.34	4.29	-21.20	-.23	-2.50	6	.047

Analysis via repeated measures ANOVA demonstrated no significant differences between pre and post serum Creatine Kinase ($p = 0.321$) and serum Troponin T levels ($p = 0.520$) of control and intervention groups. However, modified Barthel Index score comparisons do show significant increases in intervention subjects ($p = 0.029$).

5. Discussion

Our results suggest that haemorrhagic stroke patients utilizing Intensive Tens Therapy show significant improvement in their modified Barthel Index scores. The increase in scores is most significant in the categories of Self-dressing and Bowel control. Although TENS application can explain improvement in ability to comb and brush their teeth (fine motor control), it does not adequately explain bowel control improvement. TENS was not applied on S3 - S5 dermatome areas, thus this finding might be coincidental,

secondary to prolonged self-training. Nonetheless, a possible indirect connection for future research cannot be denied.Among 8 out of the 10 control subjects have no change in modified Barthel Index score after 6 weeks of conventional physiotherapy. However, 5 out of 7 intervention subjects have increased modified Barthel Index scores after 2 weeks of intensive TENS therapy, in addition to the 6 weeks of conventional physiotherapy.

There appears to be no significant difference in serum Creatine Kinase levels before and after Intensive TENS Therapy among haemorrhagic stroke subjects. This demonstrates that Intensive TENS therapy does not significantly improve muscle mass. In fact, there is decreased serum CK post-intervention in 3 out of 7 (42%) of the intervention subjects. Kang, Jeon and Lee in 2015 demonstrated that TENS does not positively improve muscle fatigue, by showing that there is no significant change in serum CK level before and after 20 minutes of TENS stimulation. Our study, although applied in a longer period of time of 2 weeks with 20 minutes of TENS in each session, appears to support their findings.

Among haemorrhagic stroke subjects receiving conventional physiotherapy, our study does not show any significant difference in serum Creatine Kinase. Furthermore, 5 out of 10 (50%) of the control subjects actually have decreased serum Creatine Kinase levels after 6 weeks of physiotherapy. We may infer that Creatine Kinase may not be a good measure of muscle improvement in our study due to the relatively low intensity exercises compared to previous studies [24]. Perhaps, the exercises experimented upon in previous studies, which focused on the effect of significant strenuous exercises on biomarker changes in normal functioning subjects, are of sufficient magnitude to demonstrate CK increases, while the stressors involved in physiotherapy and intensive TENS therapy are of a relatively milder nature in motor-impaired individuals.

There does not appear to be any significant difference in serum Troponin T levels among haemorrhagic stroke subjects before and after Intensive TENS Therapy. The absence of significant change in the serum cardiac Troponin levels before and after intervention displayed that intensive TENS therapy does not adversely affect cardiac cells in anyway.Serum cardiac Troponin T levels also show no significant difference before and after 6 weeks of conventional physiotherapy in haemorrhagic stroke patients without Intensive TENS Therapy. As is the case with serum Creatine Kinase, the low exercise intensity nature of physiotherapy and intensive TENS therapy may be the contributing factor to the lack of significant serum Troponin T level increase. As an extension of this hypothesis, the involvement of only peripheral muscles, anatomically distant from the heart, may also explain the absence of an effect on the cardiac muscles.

Modified Barthel index scores show significant improvement as compared to Creatine Kinase and Cardiac Troponin. This would imply that, in regards to monitoring a haemorrhagic stroke patient's response to TENS use, and more specifically Intensive TENS Therapy, activities of daily living is a better indicator of motor improvement compared to Creatine Kinase. In fact, the lack of significant change in serum Creatine Kinase both in the control and intervention groups pragmatically eliminates it as a measure of muscle improvement post-conventional physiotherapy and TENS in the short term.Furthermore, the lack of significant difference in serum Troponin T levels highlight the safety of Intensive TENS Therapy with regards to the heart in haemorrhagic stroke patients. Better activities of daily living scores attained from physiotherapy-level exercise do not translate to worsening cardiac-related morbidity in future.

6. Conclusion and Future Recommendations

6.1 Conclusion

This study currently acts as a pilot study for future research on intensive TENS therapy and the precise settings for optimum rehabilitation results. The results of this study shall be treated as preliminary study results for research to come.

As reflected by the modified Barthel Index scores, intensive TENS therapy is undeniably an important element in any haemorrhagic stroke patient's recovery plan. This new therapy modality is also not debilitating or stressful to the heart, as evidenced by the lack of change in serum Troponin T.

In contrast, serum CK is not a reliable measure of a person's skeletal muscle recovery through rehabilitation, regardless of the use of TENS. This can be observed through the lack of change in serum CK, even in patients going through conventional physiotherapy alone.

6.2 Limitations of this Study

One impertinent limitation of this study resulting in skewing of the results is due to its small sample size. Compounded by the low incidence of haemorrhagic stroke as compared to ischemic stroke, this results in a shrunken sample size for this study.Another limitation is that we did not have the resources to investigate for the presence of neuromuscular diseases in this study. Doing so would have allowed us to analyze and factor in the effect of neuromuscular disease on the post-intervention change in serum Creatine Kinase.

6.3 Recommendations for Future Research

One proposed suggestion would be to increase the duration of intensive TENS therapy on participants and observe the changes in both biomarkers and activity of daily living (ADL) scores. A longer study may reveal better results in ADL scores, and even more significantly, may even show a different result in terms of the biomarker changes. In a similar note, future research can also involve the same duration of both intensive TENS therapy as well as conventional therapy, instead of a shorter duration intensive TENS therapy.Furthermore, increased funding might have allowed for studying the effects of conventional physiotherapy on both stroke as well as neuromuscular diseases.

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7. References

[1] World Health Organization, 2018. International classification of diseases for mortality and morbidity statistics (11th Revision). Retrieved from https://icd.who.int/browse11/l-m/en

[2] Sacco, R., Kasner, S., Broderick, J., Caplan, L., Connors, J., Culebras, A., Elkind, M., George, M., Hamdan, A., Higashida, R., Hoh, B., Janis, L., Kase, C., Kleindorfer, D., Lee, J., Moseley, M., Peterson, E., Turan, T., Valderrama, A. and Vinters, H., 2013. An Updated Definition of Stroke for the 21st Century. Stroke, 44(7), pp.2064-2089. doi.org/10.1161/STR.0b013e318296aeca

[3] Lindsay, K., Bone, I. and Lindsay, K., 2010. Neurology and Neurosurgery Illustrated (5th Edition). Elsevier Health Sciences.

[4] FitzGerald, M., Gruener, G. and Mtui, E., 2012. Clinical neuroanatomy and neuroscience. Saunders/Elsevier.

[5] Waxman, S., 2017. Clinical neuroanatomy. 28th ed. McGraw-Hill Education.

[6] Feigin V. L. et al, 2018. Global, Regional, and Country-Specific Lifetime Risks of Stroke, 1990 and 2016. New England Journal of Medicine, 379(25), pp.2429-2437.

[7] Ministry of Health Malaysia, Health Facts, 2009. Health Information Centre, Planning and Development Division

[8] Paolucci, S., Antonucci, G., Grasso, M., Bragoni, M., Coiro, P., De Angelis, D., Fusco, F., Morelli, D., Venturiero, V., Troisi, E. and Pratesi, L., 2003. Functional Outcome of Ischemic and Hemorrhagic Stroke Patients After Inpatient Rehabilitation. Stroke, 34(12), pp.2861-2865.

[9] Chu, C., Chen, Y., Chen, C., Chen, C., Chang, H., Chang, C. and Pei, Y., 2020. Functional Recovery Patterns of Hemorrhagic and Ischemic Stroke Patients Under Post-Acute Care Rehabilitation Program. Neuropsychiatric Disease and Treatment, Volume 16, pp.1975-1985.

[10] Kim, Y., 2018. Rehabilitation After Hemorrhagic Stroke: From Acute to Chronic Stage. Stroke Revisited, pp.219-231.

[11] Perna, R. and Temple, J., 2015. Rehabilitation Outcomes: Ischemic versus Hemorrhagic Strokes. Behavioural Neurology, 2015, pp.1-6.

[12] Dadlani, R. and Agrawal, A., 2017. Intracerebral Hemorrhage: Issues in Rehabilitation. Hemorrhagic Stroke - An Update.

[13] Kitago, T. and Ratan, R., 2017. Rehabilitation following hemorrhagic stroke: building the case for stroke-subtype specific recovery therapies. F1000Research, 6, p.2044.

[14] Winstein, C., Stein, J., Arena, R., Bates, B., Cherney, L., Cramer, S., Deruyter, F., Eng, J., Fisher, B., Harvey, R., Lang, C., MacKay-Lyons, M., Ottenbacher, K., Pugh, S., Reeves, M., Richards, L., Stiers, W. and Zorowitz, R., 2016. Guidelines for Adult Stroke Rehabilitation and Recovery. Stroke, 47(6).

[15] Kristensen, H., Tistad, M., Koch, L. and Ytterberg, C., 2016. The Importance of Patient Involvement in Stroke Rehabilitation. PLOS ONE, 11(6), p.e0157149.

[16] Hankey, G., 2017. Stroke. The Lancet, 389(10069), pp.641-654.

[17] Thomas, L., French, B., Coupe, J., McMahon, N., Connell, L., Harrison, J., Sutton, C., Tishkovskaya, S. and Watkins, C., 2017. Repetitive Task Training for Improving Functional Ability After Stroke. Stroke, 48(4), pp.e102-e103.

[18] de Sousa, D., Harvey, L., Dorsch, S. and Glinsky, J., 2018. Interventions involving repetitive practice improve strength after stroke: a systematic review. Journal of Physiotherapy, 64(4), pp.210-221.

[19] Sluka, K., 2007. TENS, Mechanisms of Action. Encyclopedia of Pain, pp.2406-2409.

[20] Johnson, M., 2007. Transcutaneous Electrical Nerve Stimulation: Mechanisms, Clinical Application and Evidence. Reviews in Pain, 1(1), pp.7-11. doi: 10.1177/204946370700100103

[21] Banerjee, G. and Johnson, M., 2013. Transcutaneous electrical nerve stimulation (TENS): A potential intervention for pain management in India?. Indian Journal of Pain, 27(3), p.132.

[22] Apple, F., Rogers, M., Sherman, W., Costill, D., Hagerman, F. and Ivy, J., 1984. Profile of creatine kinase isoenzymes in skeletal muscles of marathon runners. Clinical Chemistry, 30(3), pp.413-416.

[23] CUMMINS, P., YOUNG, A., AUCKLAND, M., MICHIE, C., STONE, P. and SHEPSTONE, B., 1987. Comparison of serum cardiac specific Troponin-I with creatine kinase, creatine kinase-MB isoenzyme, tropomyosin, myoglobin and C-reactive protein release in marathon runners: cardiac or skeletal muscle trauma?. European Journal of Clinical Investigation, 17(4), pp.317-324. doi:10.1111/j.1365-2362.1987.tb02194.x

[24] Baird, M., Graham, S., Baker, J. and Bickerstaff, G., 2012. Creatine-Kinase- and Exercise-Related Muscle Damage Implications for Muscle Performance and Recovery. Journal of Nutrition and Metabolism, 2012, pp.1-13. doi:10.1155/2012/960363

[25] Palacios G., Pedrero-Chamizo R., Palacios N., Maroto-Sánchez B., Aznar S., González-Gross M.,

EXERNET Study Group, Biomarkers of physical activity and exercise. Nutr Hosp. 2015; 31(Supl. 3):237-244

[26] Steinhagen-Thiessen, E. and Reznick, A., 1987. Effect of Short- and Long-Term Endurance Training on Creatine Phosphokinase Activity in Skeletal and Cardiac Muscles of CW-1 and C57BL Mice. Gerontology, 33(1), pp.14-18.

[27] Lee, E., Fragala, M., Kavouras, S., Queen, R., Pryor, J. and Casa, D., 2017. Biomarkers in Sports and Exercise. Journal of Strength and Conditioning Research, 31(10), pp.2920-2937. doi: 10.1519/JSC.0000000000002122

[28] Rosalki, S., 1998. Low Serum Creatine Kinase Activity. Clinical Chemistry, 44(5), pp.905-905.

[29] Eijsvogels, T., Hoogerwerf, M., Maessen, M., Seeger, J., George, K., Hopman, M. and Thijssen, D., 2015. Predictors of cardiac Troponin release after a marathon. Journal of Science and Medicine in Sport, 18(1), pp.88-92. doi:10.1016/j.jsams.2013.12.002

[30] Gresslien, T. and Agewall, S., 2016. Troponin and exercise. International Journal of Cardiology, 221, pp.609-621. doi:10.1016/j.ijcard.2016.06.243

[31] Eijsvogels, T., Fernandez, A. and Thompson, P., 2016. Are There Deleterious Cardiac Effects of Acute and Chronic Endurance Exercise?. Physiological Reviews, 96(1), pp.99-125. doi: 10.1152/physrev.00029.2014

[32] Aengevaeren, V., Hopman, M., Thompson, P., Bakker, E., George, K., Thijssen, D. and Eijsvogels, T., 2019. Exercise-Induced Cardiac Troponin I Increase and Incident Mortality and Cardiovascular Events. Circulation, 140(10), pp.804-814.

[33] Everett, B., Brooks, M., Vlachos, H., Chaitman, B., Frye, R. and Bhatt, D., 2015. Troponin and Cardiac Events in Stable Ischemic Heart Disease and Diabetes. New England Journal of Medicine, 373(7), pp.610-620. doi: 10.1056/NEJMoa1415921

[34] Sze, J., Mooney, J., Barzi, F., Hillis, G. and Chow, C., 2016. Cardiac Troponin and its Relationship to Cardiovascular Outcomes in Community Populations – A Systematic Review and Meta-analysis. Heart, Lung and Circulation, 25(3), pp.217-228. doi: 10.1016/j.hlc.2015.09.001

[35] Roos, A., Bandstein, N., Lundbäck, M., Hammarsten, O., Ljung, R. and Holzmann, M., 2017. Stable High-Sensitivity Cardiac Troponin T Levels and Outcomes in Patients With Chest Pain. Journal of the American College of Cardiology, 70(18), pp.2226-2236. doi: 10.1016/j.jacc.2017.08.064

[36] Eggers, K., Jernberg, T. and Lindahl, B., 2019. Cardiac Troponin Elevation in Patients Without a Specific Diagnosis. Journal of the American College of Cardiology, 73(1), pp.1-9. doi: 10.1016/j.jacc.2018.09.082

[37] Skadberg, Ø., Kleiven, Ø., Bjørkavoll-Bergseth, M., Melberg, T., Bergseth, R., Selvåg, J., Auestad, B., Greve, O., Dickstein, K., Aarsland, T. and Ørn, S., 2017. Highly increased Troponin I levels following high-intensity endurance cycling may detect subclinical coronary artery disease in presumably healthy leisure sport cyclists: The North Sea Race Endurance Exercise Study (NEEDED) 2013. European Journal of Preventive Cardiology, 24(8), pp.885-894. doi: 10.1177/2047487317693130

[38] Patten, C., Lexell, J. and Brown, H., 2004. Weakness and strength training in persons with poststroke hemiplegia: Rationale, method, and efficacy. The Journal of Rehabilitation Research and Development, 41(3A), p.293-312.

[39] Norris, J., Hachinski, V., Myers, M., Callow, J., Wong, T. and Moore, R., 1979. Serum cardiac enzymes in stroke. Stroke, 10(5), pp.548-553.

[40] James, P., Ellis, C., Whitlock, R., McNeil, A., Henley, J. and Anderson, N., 2000. Relation between Troponin T concentration and mortality in patients presenting with an acute stroke: observational study. BMJ, 320(7248), pp.1502-1504. doi: 10.1136/bmj.320.7248.1502

[41] Apak, I., Iltumur, K., Tamam, Y. and Kaya, N., 2005. Serum Cardiac Troponin T Levels as an Indicator of Myocardial Injury in Ischemic and Hemorrhagic Stroke Patients. The Tohoku Journal of Experimental Medicine, 205(2), pp.93-101. doi:10.1620/tjem.205.93

[42] Suleiman, H., Aliyu, I., Abubakar, S., Isa, M., El-Bashir, J., Adamu, R., Ibrahim, M. and Yusuf, R., 2017. Relationship of cardiac Troponin and creatine kinase-MB fraction at admission in acute ischemic stroke and outcome in a Tertiary Hospital in Nigeria. Ann Trop Pathol; 8(2):61-64

[43] Azman, M. and Azman, A., 2017. The Effect of Electrical Stimulation in Improving Muscle Tone (Clinical). IOP Conference Series: Materials Science and Engineering, 260, p.012020.

[44] Kang, D., Jeon, J. and Lee, J., 2015. Effects of low-frequency electrical stimulation on cumulative fatigue and muscle tone of the erector spinae. Journal of Physical Therapy Science, 27(1), pp.105-108.

[45] Ng, S. and Hui-Chan, C., 2007. Transcutaneous Electrical Nerve Stimulation Combined With Task-Related Training Improves Lower Limb Functions in Subjects With Chronic Stroke. Stroke, 38(11), pp.2953-2959. https://doi.org/10.1161/STROKEAHA.107.490318

[46] Mahmood, A., Veluswamy, S., Hombali, A., Mullick, A., N, M. and Solomon, J., 2019. Effect of Transcutaneous Electrical Nerve Stimulation on Spasticity in Adults With Stroke: A Systematic Review and Meta-analysis. Archives of Physical Medicine and Rehabilitation, 100(4), pp.751-768.