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Review Article

Muscle Electrostimulation for the Treatment of Peripheral Arterial Disease. A Review of the Physiological Aspects of Muscle Adaptation and the Possibilities for Treatment of Intermittent Claudication. Science or Fiction?

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Abstract

Purpose: Peripheral Arterial Disease (PAD) is a major cause of death and disability, greatly influenced by the modern western way of living. The use of Electrostimulation (ES) for the treatment of patients with Peripheral Arterial Disease (PAD) is not a novel concept. It has been studied for many years and various aspects of the method have been researched. Many possible advantages exist but have not been confirmed with solid findings.

Method: We performed a search in the literature to evaluate the results and see if they can be applied in everyday medical practice. We tried to categorize findings in different categories, based on the physiological concepts of muscle adaptation.

Results: Results were neither disappointing nor enthusiastic. Initial enthusiasm is followed with skepticism because the available data are not very cogent and with heterogeneity.

Conclusion: Further research must be conducted as to make clear if it is a method that can be applied in general for patients with PAD in the initial phase of disease treatment, when limb viability is not threatened.

Keywords: Electrostimulation; Peripheral arterial disease; Intermittent claudication

Introduction

Peripheral Arterial Disease (PAD) is the most common result of atherosclerosis, with a prevalence of 20% in population over 60 years old. At 2010, 200 million people worldwide were diagnosed with PAD [1]. Smoking, Diabetes Mellitus, Dyslipidemia, Hypertension, Hyperhomocysteinemia and race are considered the main prevalent factors for the manifestation of PAD [2].

The first and most characteristic symptom of PAD is intermittent claudication, defined as pain in the lower leg, calf or hip, with or without muscle cramping caused by inadequate blood flow to the lower limbs. Pain is severe with a burning sensation, forcing the patient to stop walking. After a brief rest, pain ceases and the patient walks pain-free again. Pain depends on the level of disease localization. Distance to claudication is characteristic of the progression of the PAD and helps in the categorization of the patients with clinical criteria and the help of symptom intensity [3]. The use of Ankle Brachial Index (ABI), defined as the result of the division of the systolic blood pressure in the ankle, divided by systolic blood pressure in the arm is a reliable, reproducible method of patient categorization [4].

About half of the patients with PAD are asymptomatic. From the other half, about 40-45% present with intermittent claudication and the remaining 5% present with Critical Limb Ischemia (CLI). The 5-year outcome is stable disease in about 70-80% of the patients, worsening claudication in about 10-20% and disease progression to Critical Limb Ischemia (CLI) or amputation in 0, 5-1% of the patients [5].

Treatment for PAD is either conservative or surgical, depending on symptoms severity. Smoking cessation, anti-platelet therapy, statin and lipid lowering therapies, serum glucose level optimization in diabetics, hypertension treatment in hypertensive, cilostazol prescription and exercise therapy are the suggested conservative treatment measures [4]. When disease progresses, significant functional impairment begins, lifestyle limiting disability arises or limb viability is threatened, surgical treatment in the form of endovascular therapies or open surgical treatment is recommended [4,6].

Of all treatment options, the one with greater controversy is exercise therapy. Due to major cardiovascular comorbidities, patients with PAD cannot always follow an aerobic exercise plan, mostly based on walking. The type of aerobic exercise, resistance training or not, intensity and duration cannot simply be decided as the most appropriate or not [7]. It has been proven that strict adherence to

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a training protocol under guidance can achieve significant benefits and increase time and distance to claudication [8]. For these patients electrostimulation appears as an alternative exercise method, due to its ability to induce muscle activity without demanding significant cardiovascular load. It has been proven to increase oxygen supply to ischemic muscle fibers, even without changes in micro vascular permeability and so improves capillary perfusion and optimizes oxygen consumption [9]. These changes in the ischemic muscles help in the improvement of the walking distance and in the reduction of the muscle fatigue and lactic acid concentration.

But what if we could reproduce exercise with the use of electrostimulation? One would hardly disagree that it appeals ideal for patients with PAD to be able to use electrostimulation as an adjunctive treatment option, especially for those unable or unwilling to exercise. We tried to review the literature to verify the benefits of trans-cutaneous electrostimulation as an alternative to exercise treatment for patients with PAD.

Methods

Google Scholar and PubMed databases were used to search for articles in English language. Terms 'electrical stimulation', 'intermittent claudication' and 'peripheral arterial disease' were used. A total of 348 articles turned out. Of these, 41 were included in this review, since they were clinical trials and studies about PAD in lower limbs and electrostimulation. The results of our study focus mainly on the following categories.

Results

The effect of ES on muscle composition

The composition of skeletal muscles differs as there are different types of muscle fibers, each one with different characteristics. There are two main types of fibers and a third one with intermediate characteristics. The slow reacting fibers, called slow twitching or type I, are mostly found in muscles performing slow and long contractions. The majority of muscle fibers are fast reacting, the so called fast twitching fibers or type II, mostly found in muscles with fast reaction and short contractions. Main differences between type II and type I are the larger amount of glycolytic enzymes found in type II fibers, the larger amount of mitochondria in type I and the less extensive blood supply network in type I fibers. All these differences serve the different metabolic requirements of each fiber. Type II fibers are further divided in three subgroups. Type IIA, which are relatively resistant to fatigue and have high oxidative and glycolytic capabilities, type IIB which are sensitive to fatigue but with large glycolytic capabilities and type III with intermediate characteristics [10].

Application of electrical current in skeletal muscles has been proven to cause changes in muscle composition, mostly an increase in the absolute number of mitochondria in type II fibers which further converts them to type I [11,12]. In laboratory experiments in rabbits, electrostimulation of skeletal muscles stimulated an increase in capillarization and reduction of glycolytic enzymes [13]. A more interesting finding of the same study was the detection of the sequence of the changes in muscle fibers. Type IIB fibers convert to type IIA and then to type I. In animal studies with long term electrical stimulation of gastrocnemius muscles, total transformation to type I fibers was achieved after 76 days [14]. It is safe to say that at least in animals, electrostimulation increases the oxidative profile of the muscles with a simultaneous reduction of the glycolytic activity, thus making them more resistant to fatigue [15].

In patients with PAD, a higher proportion of type II fibers in skeletal muscle composition are detected [16]. In these patients the predominance of the type II muscle fibers is considered a limiting factor in the working ability of the muscles and not only the limited oxygen supply. This finding can also adequately explain the early onset of fatigue during exercise in claudicants. This leaves a therapeutic opportunity for the use of electrotherapy in patients with PAD, with the scope of muscle transformation.

Augmentation of capillarization and oxidative capacity

In vivo studies [12,15,17] conclude that increase in muscle capillarization and oxidative enzyme activity occur in different times. In endurance training, muscles adapt to the increased training load by an initial increase in their oxidative capacity, a result of increased oxidative enzyme activity and mitochondrial volume density [18]. On the other hand, Eggington, et al. proved that long term electrical stimulation of fast twitching glycolytic fibers increases capillary density first and then oxidative enzyme activity [17].

Skorjans. et al. studied the effects of low frequency chronic electrostimulation (10 Hz for 50 days) in rabbits' tibial muscles [13]. They concluded that concerning capillaries per fiber proportion, capillary expansion occurred as soon as the second day whereas increase in mitochondrial enzyme activity occurred in the eighth day. After that period, it was evident that energy supply in muscle fibers was oxidative and no longer glycolytic. Peak capillarization occurred 3 weeks after ES, although mitochondrial enzyme activity continued to increase. According to the authors this was a proof that increase in oxygen supply precedes structural changes in muscle metabolism. Huddlicka, et al. studied rabbit skeletal muscles stimulated at 10 Hz frequency for 8 hours per day [19]. Initial findings after 2 days were an increase in capillarization rather than oxidative conversion of the fibers. After the 4th day capillarization reached plateau whereas with the continuation of the treatment muscles fibers turned oxidative. In other studies, same writers confirmed that muscles treated with ES, after 28 days had all their muscle fibers turned to oxidative and also that capillary proliferation is an early step in ES muscles. This was accompanied with reduction of fatigue in fast twitching fibers after a short period of stimulation [20,21].

Interesting findings were reported by Tsang, et al. [11] in a study where patients with P.A.D were submitted to ES of flexor muscles in the ankle, for 20 minutes, 3 times a day for 4 weeks in total. Authors reported a significant increase in muscle functional performance. However, after therapy cessation, performance of the muscles recessed to its initial levels.

Differences between electrostimulation and exercise

Chronically trained muscles adapt to exercise by two means: Hypertrophy and capillary formation. This brings an increase in absolute capillary number and capillary density, which further increases oxygen supply and perfusion, leading to increased oxidative aerobic capacity [11,13].

Capillary growth that is observed in chronically trained muscles is caused by either metabolic or mechanic factors [22]. Ongoing

muscle contractions cause lactic acid accumulation which together with tissue hypoxia increases the acidic environment in the muscle. Oxidative enzyme activity and mitochondrial activity are increased as an adaptation to the acidic cellular environment. Angiogenesis has been proven to be directly related (proportionally) to the degree of tissue hypoxia [16]. On the other hand, increased blood flow and the shearing stress produced in the capillary wall have also been related with capillary growth [23]. Interestingly, similar findings have been reported in chronically electro stimulated muscles [11].

Decrease in oxygen perfusion in circulating blood of working muscles, leads to increased endothelial cell mitoses in muscle capillaries. Vascular Endothelial Growth Factor (VEGF) acts as a catalyst. Huddlicka, et al. treated rabbit fast-twitching muscles for more than two days with electrostimulation. Findings included correction of PO_2 levels and maintenance of capillary proliferation with occasional increases in VEGF proportion. More importantly, high levels of VEGF were measured after 14 days in chronically electrostimulated muscles. Authors hypothesized that transient hypoxia is the possible mechanism that explains the increase in VEGF levels [24].

Another possible mechanism of capillary growth, through endothelial cell proliferation, is the increased capillary shearing stress, a consequence of increased blood flow and turbulence [17,24,25].

Chronic electrostimulation in fast-twitching muscles causes effects similar to endurance training [26]. In endurance training, intense aerobic exercise recruits glycolytic muscle fibers, (type II and IIB fibers) compared to electrostimulation which recruits all types of muscle fibers but with different and asynchronous order [17,24]. Type II fibers are recruited first and that leads to improved early resistance to fatigue [16].

Huddlicka, et al. reported that in endurance training, new capillary formation is more efficient in oxidative fibers [27]. This comes in contrast to findings from chronic electrostimulated muscles, in which capillary formation is more evident in glycolytic fibers, which are innervated by large neuron axons and are the ones mostly activated during ES [15]. These findings led to the foundation of the following theory. In chronic ES muscles, capillary density increases but muscle fiber diameter is reduced, in contrast to the changes provoked by endurance training. This increases oxygen diffusion in the stimulated muscles, as distance from capillaries to cells decreases, making the activation of the oxidative enzyme system more efficient.

In a study by Jawad, et al. electrostimulation of the lower limbs provided 24% increase in arterial blood velocity and 370% in total microcirculation blood velocity, compared to mechanic compression [28]. Yilmaz, et al. in their study noted a significant increase in anterior tibialis artery blood velocity, after peroneal nerve ES [29]. This also proves an increase in blood velocity but the correlation to angiogenesis as a direct result of it has not been studied thoroughly and therefore not proved.

Difference in electrostimulation frequency. Aim high or low?

Increased capillarization as a direct effect of ES frequency has been studied in rabbits' fast twitching muscle fibers. Writers came into conclusion that both high and low frequency ES application leads to an increase in capillary density with the only difference being in the early stimulation period [27].

Application of ES with a frequency lower than 20 Hz triggers muscle fatigue tolerance through the stimulation of muscle resistance. It has been noted that muscles stimulated with 10 Hz current, increase their oxidative aerobic capacity, through the increase of Type I fibers, thus leading to increased vascularization [30]. Currents between 5-10 Hz, cause muscle vibration which also activates circulation. At frequencies higher than 20 Hz muscles contract tetanically.

This makes rest intervals inevitable, otherwise ES application becomes uncomfortable. It has been reported that electrical current frequency is directly related to muscle fatigue [31].

The difference in the effect caused by the application of various ES frequencies in muscle fibers has been proved in a study of continuous ES in rabbit fast twitching muscles [32]. Continuous ES at 10 Hz caused individual contractions and continuous increase in blood flow. This effect however did not cause interruptions in blood flow. When stimulated with 40 Hz current, muscles contracted tetanically, producing perfusion pressure higher than the systematic. In another study, same writers reported a significant increase in capillary density in rabbits' muscle groups' electrostimulated at 10 Hz frequencies. Increase was obvious after 4 days and double after 28 days. When the same muscle groups were electrostimulated at 40 Hz, increased capillary density was obvious after the 28th day of treatment. That led to the conclusion that both frequencies led to capillary density growth but the 40 Hz frequency produced the effect at only a later stage [27].

Conclusion

The effect of ES in ischemic muscles has not been studied systematically and thoroughly, therefore literature is scarce with controversial findings. From total failure to total success and from surprise to disappointment findings vary and are coped with skepticism. *In vitro* laboratory findings are not always verified by *in vivo* studies and vice versa. Furthermore, not many clinical studies have been conducted and of those that we came up with during our research most are with a small number of patients. Many parameters in electrical current applied, muscle groups targeted, patient categories and characteristics, *in vivo* and *in vitro* studies differ and make studying of the phenomenon and its' application difficult. Safe results cannot be extracted and that makes further interpretation of the results concluded difficult. Furthermore, adaptation to everyday practice is controversial and not widely accepted as a treatment method by the medical community. The idea behind ES application in patients with PAD seems ideal. Low cost, ease of application and wide unsupervised usage are questionless advantages. In our review of the literature we cannot totally confirm nor reject the method of ES as an adjuvant method of treatment for patients with PAD. Further studies with more focus on clinical findings and solid laboratory results must be conducted as to more objectively evaluate the method.

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