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REVIEW ARTICLE

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Whole Body Periodic Acceleration: "Passive Exercise" for Parkinson's disease

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The important benefits of exercise in the prevention and treatment of chronic diseases have long been recognized. However, exercise participation such as brisk walking at least 30 minutes a day for five days a week as recommended by the American Heart Association is accomplished in less than 10% of the adult American population.[1] For patients with chronic conditions such as Parkinson's disease (PD), compliance is even lower. Patients with PD are usually elderly, often sedentary, and frail, with the afflictions of cardio-vascular and rheumatologic diseases and therefore incapable of exercising. Further, the fear of falling, freezing of gait, and impaired economy of gait (small stepping distance) associated with PD interfere with walking.[2 3 4] Therefore, there is a place for technology that would provide similar benefits to exercise without requiring voluntary movements. Such a technology, called Whole Body Periodic Acceleration (WBPA) that is administered with a motorized platform called Exer-Rest® (NIMS, Miami FL), increases release of the same beneficial substances into the circulation and to the same extent as exercise.[5 6] Further, both exercise and WBPA elevate levels of Brain- and Glial-Derived Neurotrophic Factors within in the brain, e.g., BDNF and GDNF, respectively that ameliorate neurological abnormalities.[7] WBPA does not produce caloric burn, weight loss or increased muscle mass as does exercise, but WBPA does not increase oxidative stress or inflammatory substances that are potentially deleterious effects of strenuous but not moderate exercise.[8]

WBPA is a non-invasive, drug-free, safe, well-tolerated procedure that involves repetitive movement of a subject who lies flat on a mattress placed on top of a motorized platform. The movements occur about 140 times per minute over a travel distance of about 5/8" (Figure 1). This procedure provides an unusual but not uncomfortable sensation that may be perceived as horseback riding or jumping on a trampoline while lying flat. By adding small pulses to the circulation as the body is repetitively accelerated and decelerated, WBPA increases pulsatile shear stress to the inner lining of blood vessels (endothelium), thereby stimulating the activity of endothelial located beneficial genes. One such gene is endothelial nitric oxide synthase (eNOS) that catalyzes the conversion of the circulating amino acid, L-Arginine, into nitric oxide (NO). Through this process, small amounts of NO are released into the circulation with attendant potent anti-inflammatory, vasodilator, anti-arteriosclerotic, neurotransmitter and antioxidant properties of both normal subjects and diseased patients.[9] The failure to detect NO in the body until the 1990s was hampered by its rapid breakdown within 4 seconds of arrival into the circulation and the lack of a sensitive method of analysis. Since overcoming such technical difficulties, over 115,000 scientific papers regarding NO have been published in the medical literature. Robert F. Furchgott, Louis J. Ignarro and Ferid Murad were jointly awarded The Nobel Prize in

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Physiology or Medicine 1998 "for their discoveries concerning nitric oxide as a signalling molecule in the cardiovascular system."

Figure 1. A subject lying on the motorized platform that delivers Whole Body Periodic Acceleration (WBPA). The footboard fixes the feet with shoes onto it to prevent slippage while the platform is moving.

WBPA sessions of 30-45 minutes duration are comparable to 30-45 minutes of moderate exercise insofar as release of nitric oxide into the circulation, an exercise challenge that cannot be met by most healthy individuals, let alone patients with PD. After three to four consecutive sessions, carryover effects appear to last 24-48 hours. For treatment of chronic diseases such as PD, similar to drugs, treatment is lifetime and access to WBPA therapy needs to be available within a home or group long-term health-care facility.

WBPA meets FDA and Common Market regulatory requirements and its administration has been cleared as an aid to improve circulation, relieve aches and pains, relax muscles, reduce morning stiffness and increase joint mobility. Recently, the regulatory bodies of the European Common Market and Canada allowed the following additional indications for its use: (1) as an aid to diminish pain and reduce morning stiffness in patients with Fibromyalgia; (2) as an aid to accelerate recovery from Delayed Onset of Muscle Soreness (DOMS); (3) as an aid to improve the circulation in patients with Peripheral Arterial Disease (PAD); and (4) as an aid to improve the circulation in patients with Coronary Artery Disease (CAD).

Typical questions regarding the effectiveness of WBPA for PD include when can improvement be detected, what constitutes improvement and how long does it last. In 16 patients with moderate to severe PD with an average duration of disease of 9 years on optimal drug therapy, about 2/3 showed improvement after a 10 day course of WBPA (A. Lieberman, M.D., personal communication). I have observed improvement in motor symptoms in 70% of about 50 PD patients after a single or multiple WBPA treatments. Improvement is generally recognized by both the patient and/or the healthcare provider immediately after the first treatment. It most often includes greater flexibility, less shuffling gait manifested by longer strides, diminution or complete elimination of freezing of gait should this be present, better turning and balance control, stronger and more distinct articulation of speech if this has been affected, and improved facial appearance. Wheelchair bound patients may be able to rise unaided to the standing posture and take steps although their gait is far from normal. Tremor of the hands may decrease, but in some instances it may increase particularly if there was a marked reduction in muscle rigidity following the WBPA treatment. These beneficial effects last about eight hours after the first treatment and then gradually dissipate so that by 24 hours the symptoms are the same as before the first WBPA treatment. However, if WBPA treatments are administered for three or four consecutive days and then discontinued, carryover relief of symptoms can last 24-48 hours. Longer interruptions of treatments, just like with cessation of drugs, will cause return to the pre-treatment status. If WBPA treatments do not produce any improvement of PD features after five consecutive daily treatments, it is unlikely that effectiveness can be achieved, although athero-sclerotic complications arising from a sedentary life style associated with NO deficiency can be ameliorated.[8 10]

The beneficial effects of WBPA in PD can be attributed in part to the increased release of nitric oxide into the circulation that reduces oxidative stress, inflammation and mitochondrial dysfunction present in PD but the rapid onset of relief of symptoms suggests that other mechanisms might play a significant role.[11 12 13] Research studies in animals treated with WBPA have shown that increases of BDNF and glial-derived neurotrophic factor GDNF in the brain to the same extent as values achieved with exercise.[7] It is of interest that BDNF has reached the mainstream of lay reporting as published in Newsweek magazine in January 2011, "Can You Build A Better Brain?"[14] The writer characterizes BDNF: "Greater cognitive capacity comes from having more neurons or synapses, higher levels of neurogenesis (the creation of new neurons, especially in the memory-forming hippocampus), and increased production of compounds such as BDNF [brain-derived neurotrophic factor], which stimulates the production of neurons and synapses." It has been found that both BDNF and GDNF are deficient in

neurons that release dopamine, a molecule necessary to counteract the manifestations of PD. Such deficiency hinders the capacity of these neurons to release adequate amounts of dopamine.[7] [15] The keystone of clinical management of PD involves administration of L-Dopa and related compounds as replacements for dopamine, but side-effects are common. BDNF and GDNF have the potential to lessen these side-effects as well as promoting rapid clinical effects in PD observed with administration of WBPA.

Motor disorders present in PD have been attributed to basal ganglia dysfunction from the loss of nigral cells with resultant dopamine deficiency. They include bradykinesia, rigidity, and resting tremor. Bradykinesia is a complex phenomenon with many different components where many of them are dopamine responsive, but some are not. Bradykinesia refers to slowness, akinesia is the absence of expected movement, and hypokinesia refers to small movements. The concept of akinesia can include the feature of slow reaction time because the movement does not occur when expected. Bradykinesia leads to difficulties with several motor tasks, often beginning with handwriting deterioration and then extending to all activities of daily living. It is the main factor leading to the difficulty with balance and gait, often listed as the fourth principal motor feature of PD.

Bradykinesia appears to be a loss of motor energy such that movements are not given the full motor command that they require. For attempting rapid movements, larger movements should be faster, but patients tend to have the same velocity for all movements. This requires more time to accomplish the movement. If the patients used the same kinematics that they generate for a large movement to make a small movement, then the small movement would be normal. Hence, the problem is often not what the patients can do, but what they actually do. Moreover, patients sometimes do not even realize that they are under-scaling. For example, it is common with speech that they do not know that their voices are soft. This suggests a matched deficit in the sensory system to the hypofunction in the motor system. If the motor command and the sensory feedback from the movement are matched, then the patient would not realize that there is a problem.[16]

Rigidity is as an increased resistance to passive movement of a limb that is felt as a constant resistance persisting throughout its range of passive motion. There are two basic elements in parkinsonian rigidity: (1) hypertonia, which is an increased resistance of the joint to passive movement; and (2) uniformity of the resistance or ‘‘lead-pipe’’ resistance, in which the mechanical resistance stays relatively constant across the range of joint motion.[17] Clinical observations of muscular strength measures are consistent with excitation contraction and relaxation uncoupling. When patients are off medication, their reduction in strength is significantly greater in extension than flexion. The extensor weakness is primarily due to decreased tonic activation of the extensor muscles and not to muscle coactivation. Muscle relaxation time was much more prolonged than was force generation time or active force return time. The increase in relaxation time and the decrease in extensor strength both correlated with changes in clinical status. Finally, changes in extensor torque is correlated with the time to actively return force, suggesting that reduced strength is related to a reduced ability to generate rapid contractions in some patients with PD.[18]

Although the vast majority of research regarding PD therapy has focused on the central nervous system abnormalities, the clinical manifestations of PD reside in skeletal muscle abnormalities. Rare skeletal muscle complications of PD include the “dropped head” and “bent spine” phenomenon. Histologic examination of biopsied skeletal muscle in such a series of 19 patients revealed necrotizing or inflammatory myopathies in ten and myopathy with mitochondrial abnormalities in nine.[19] Genetic mutations associated with the etiology of familial PD are consistent with widespread mitochondrial dysfunction that may accompany such entities and also may predispose to sporadic PD. Mutations of PINK1, Parkin and DJ-1 mutations in some cases of PD leads to loss of mitochondrial protective effects both in the brain and skeletal muscle cells.[11] [20] [21] [22] Therefore, motor abnormalities such as bradykinesia and freezing of gait present in PD might wholly or in part be directly related to skeletal muscle disease itself as demonstrated by Shtifman et al.[23]in DJ-1 null mice, a form of experimental PD. In these mice, excitation-contraction uncoupling in the skeletal muscle is reflected by a two-fold increase of resting, cytoplasmic $[Ca^{2+}]$ ($[Ca^{2+}]_i$) and a decreased depolarization-evoked Ca^{2+} release. Such abnormalities are reversed by resveratrol, a mitochondrial activator that stimulates eNOS to increase NO.[24] WBPA administered for one hour to conscious rats significantly increased neuronal nitric oxide synthase (nNOS) in the cardiomycyte as well as nitrosylated protein in cardiac tissue indicating that nNOS was responsible for producing NO in the myocardium.[25] Presumably, nNOS increased as a result of signaling from eNOS activation in the endocardium since nNOS is not stimulated by pulsatile shear stress as delivered with WBPA. Further, acute administration of WBPA increases nNOS in the sarcolemmal membrane of conscious

mice. In mice with intrinsically altered Ca^{2+} and Na^{+} homeostasis due to dystrophin deficiency, WBPA ameliorates the intracellular Ca^{2+} and Na^{+} overload in skeletal muscle and improves strength (Jose Rafael Lopez, M.D., Anesthesia Department, Brigham & Women's Hospital, Boston MA, personal communication). WBPA also accelerates recovery of Ca^{2+} overload in mice after eccentric exercise due to downhill running, a model for Delayed Onset of Muscle Soreness (DOMS). Here, the salutary effect of WBPA on $[Ca^{2+}]_{rest}$ appears to be mediated by an increase in NO generation, since the NOS blocker, L-NAME, eliminated the effect of WBPA on $[Ca^{2+}]_{rest}$ after EC.[26] Taking all these observations together might explain the rapid onset of action of WBPA in improving the symptoms of bradykinesia and minimization in freezing of gait as a function of improving excitation coupling and relaxation of skeletal muscle in PD. However, before this can be taken as fact, more basic and clinical research studies are warranted.

Approximately 40% of PD patients have chronic pain that is often overlooked or dismissed by practitioners as related to PD. In a minority, pain becomes its most distressing symptom. Pain is due to multiple causes which may be rendered more severe by major depression that occurs in 20-40% of PD patients. WBPA has a role to play here since nitric oxide has analgesic properties that are several-fold greater that over-the-counter drugs and major depression is marked by BDNF deficiency that is helped by certain anti-depressive drugs that increase serum BDNP.[27 28 29 30]

PD patients on average are about 30% physically less active than healthy individuals of comparable age. This may lead to major complications and symptoms associated with a sedentary life style.[31] In this respect, WBPA can be considered a "passive exercise modality."[32] In addition to increasing beneficial substances into the circulation such as nitric oxide and signaling increase of neurotrophic factors, WBPA passively moves all major joints of the body a total of 6,300 times during a 45 minute treatment session.

The potential benefits of WBPA in sedentary PD patients are similar to those produced with exercise since both modalities increase nitric oxide, BDNF and GDNF.[7 9 33 34] These benefits include (1) prevention and treatment of arteriosclerosis that leads to coronary artery disease, stroke, and peripheral vascular disease; (2) arrest of osteoporosis; (3) improved cognitive function; (4) prevention and treatment of depression; (5) improved sleep; (6) decreased constipation; (7) decreased fatigue; (8) improved functional motor performance; (9) improved drug efficacy; and (10) optimization of the dopamine producing neurons.[36]

In my experience, WBPA can diminish the abnormal, involuntary movements associated with long-term treatment of PD with dopamine replacement drugs as well as the peripheral edema that occurs in 5-15% of PD patients.[36]

In conclusion, WBPA has a strong scientific basis as ancillary therapy to combat the clinical manifestations of Parkinson's disease as an ancillary tool to pharmacologic replacement therapy.

DISCLOSURES

Marvin A. Sackner is a member of the Board of Directors of NIMS, Inc., and the company that markets WBPA as the Exer-Rest®. He holds approximately 3.1% of the shares and receives no financial compensation. The comments and opinions expressed in this paper reflect solely his own comments and opinions not those of NIMS, Inc.

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