

The Effect Of A Non-Transdermal Surface Patch On Mitochondrial Function

By Frank Shallenberger, MD, Homer Nazaran, Ph.D.

Abstract

Background

This investigation will examine the effect of applying a commercially available non-transdermal surface patch containing amino-acids (proteins) on ATP production, substrate utilization, and strength. The manufacturer of this product claims the benefits of using the LifeWave™ Energy Enhancer patches include: a) increased energy, b) increased stamina, and c) increased performance.

Methods

This 2-week placebo controlled single-blind research study will measure respiratory oxygen uptake and carbon dioxide production under both resting and exertional conditions before and after application of the LifeWave™ Energy Enhancer patch. The data obtained will then be analyzed by a computerized program (Bio-Energy Testing®) to determine the following metabolic parameters: Maximum aerobic ATP, maximum ATP from fatty acid metabolism, resting ATP, resting ATP from fatty acid metabolism, and maximum aerobic work.

Results

Application of the LifeWave™ Energy Enhancer patch produced a significant increase in maximum aerobic ATP, maximum ATP from fatty acid metabolism, resting ATP, and maximum aerobic work. There was no significant effect on resting ATP from fatty acid metabolism.

Conclusions

Application of the LifeWave™ Energy Enhancer patch has significant metabolic effects which confirm the manufacturer's claim that it increases energy, stamina, and performance. These findings provide a rationale for using the patch in conditions in which increased metabolic performance is desired.

This investigation will examine the effect of applying a commercially available non-transdermal surface patch (LifeWave LLC, Suwanee GA) containing amino-acids (proteins) on ATP production, substrate utilization, and strength. The manufacturer of this product claims the benefits of using the LifeWave™ Energy Enhancer patches include: a) increased energy, b) increased stamina, and c) increased performance; all within 20 minutes of application.

The membrane of the patches is made of a non-porous polyethylene with an acrylic adhesive; therefore, nothing is directly transferred from the patch into the body (see attached report from MVA Scientific Consultants). Within the patches is a combination of amino acids, water, oxygen, and organic substances bound to a polyester substrate and all compounds are recognized as safe (FDA 21 CFR) (LifeWave information brochure).

The theoretical basis for the mechanism of action is through frequency modulation and resonant energy transfer. Simply, the protein combination contained within the patches interacts with the naturally occurring magnetic field of the human body. The manufacturer suggests that the application of the patches to the skin (exposing the patch to the naturally occurring magnetic field of the body) causes the contents of the patch to vibrate (resonant energy transfer) and transmit a signal to the cells (frequency modulation with biological energy field). Through signal transduction, the cells interpret the signal initiated from the patch stimulating an increase in fatty acid metabolism.

The implication for a non-pharmacologic method of stimulating ATP production, and specifically fatty acid utilization, are great. Therefore, the purpose of this investigation is to evaluate the short-term regular use of the LifeWave™ Energy Enhancer patches on the following metabolic parameters: Maximum aerobic ATP, maximum ATP from fatty acid metabolism, resting ATP, resting ATP from fatty acid metabolism, and maximum aerobic work.

Methods and Procedures

This research study was conducted by Frank Shallenberger, MD and The Nevada Center, Inc., a general medical clinic located at 1231 Country Club Dr., Carson City, NV 89703. Prior to any data collection, all study procedures were thoroughly explained by an investigator and each subject provided written consent to participate in the study.

Subjects

The subjects include 30 men and women between the ages of 18 and 65 years. Criteria for participation in this study include: a) being able to complete all test protocols; b) being free of chronic illnesses; c) not taking any medications that may alter metabolism; and d) being a non-smoker. All participation is voluntary in nature. Subjects were paid \$200 upon completion of their arm of the study.

Recruitment of subjects will occur throughout northern Nevada and the surrounding communities as a result of applications sent to the patient data base of The Nevada Center, Inc. Subjects may or may not be patients of The Nevada Center, Inc.

Bio-Energy Testing®

The Bio-Energy Testing® protocol uses an FDA approved pulmonary gas analyzer and computerized ergometer (Medical Graphics Corporation, 350 Oak Grove Parkway, St. Paul, Minnesota 55127 U.S.A.) that analyzes oxygen to carbon dioxide conversion rates and work in watts, a bio-impedance body fat analyzer (Omron Healthcare, Inc., 1200 Lakeside Drive, Bannockburn, Illinois 60015), a heart rate monitor, (Polar Electro Inc. 1111 Marcus Avenue, Suite M15, Lake Success, NY 11042-1034), and computer software (Bio-Energy Testing, LLC, 1231 Country Club Dr. Carson City, NV, 89703) to determine a subject's mitochondrial efficiency. By that is meant, how much ATP a subject's mitochondria are capable of producing, and what percentage of substrate is fat or glucose.

Almost all of the oxygen that is consumed in the human body is consumed in the mitochondria to produce energy. Although a small percentage is used as part of the oxidative burst of the activated immune system and also as part of the P450 detoxification systems in the liver, as long as the subject's immune system is not actively fighting an infection, and as

long as there is no acute toxicity, it can be safely assumed that in a fasting individual all oxygen consumed is being consumed in the mitochondria.

Thus, ATP can be measured as a function of oxygen uptake as follows:



Thus when fatty acids are metabolized by oxygen, there is a ratio of 5.6 (130/23) molecules of ATP produced per molecule of oxygen consumed. By measuring oxygen consumption, the amount of ATP being produced can be easily determined by multiplying this amount by 5.6.

In the case of glucose, there is a ratio of six molecules of ATP being produced per molecule of oxygen being consumed (36/6). By measuring oxygen consumption, the amount of ATP being produced can be easily determined by multiplying this amount by 6.

The ratio of glucose metabolism to fatty acid metabolism is a linear relationship, and can be determined by the ratio of CO_2/O_2 .

Thus, the Bio-Energy Testing® software can determine at any point in time how much ATP is being produced, and what percentage is being produced from fatty acids and from glucose.

ATP produced from anaerobic production is not measured because all determination of oxygen consumption is stopped as soon as lactic acid threshold is reached. This point can be determined by the point at which the ratio of CO_2/O_2 suddenly accelerates above 1.0.

These determinations are made in the morning after an overnight fast. The first measurements are taken while the subject is resting in a reclined position for eight minutes at his predetermined resting heart rate. The subject then exercises on a cycle ergometer using a ramping protocol that is determined by his age and level of fitness. All measurements are stopped when the subject reaches his lactic acid threshold. This form of analysis can be used to determine a patient's mitochondrial functional dynamics, including:

- 1) Total Resting ATP production (resting metabolism).
- 2) Resting ATP production from fatty acid metabolism.
- 3) Maximal ATP production from fatty acid metabolism.
- 4) Maximal aerobic ATP production (aerobic capacity).
- 5) Maximal aerobic work.

Study Design

This was 2-week placebo controlled single-blind research study. Each subject reported to The Nevada Center, Inc. for a total of three (3) visits. The first visit included an explanation of what is involved in the Bio-Energy Testing® testing procedure, an orientation with the laboratory equipment, and the initial test. The remaining laboratory visits involved subject testing and will be referred to as a testing session. Each testing session was approximately 1 hour in duration and testing sessions were separated by 1-week (7 days). Tests were performed in the morning, and subjects were asked to avoid foods and beverages (except for water) and all forms of mental or physical exertion on the morning of testing.

Week 1 Testing Session: The week 1 testing session served as the baseline measurement for the study. Following this test, the subject was instructed regarding the correct placement on the skin of the LifeWave patches as directed by the product manufacturer (Figures 1-2). When the patches were positioned correctly, the subject was then given a placebo set of LifeWave patches, and was instructed to begin a daily application of these patches.

Week 2 Testing Session: The week 2 testing session served as the placebo effect measurement for the study. The test was performed while the subject was wearing the placebo LifeWave patches. Following this test, the subject was given an active set of LifeWave patches, and was instructed to begin a daily application of these patches as directed by the product manufacturer (Figures 1-2). The subject was blinded to which patches are placebo and which are active. Both placebo and active patches were identical in appearance.

Week 3 Testing Session: The week 3 testing session served as the active effect measurement for the study. The test was performed while the subject was wearing the active LifeWave patches. Following this test, the subject was given a copy of all three testing results and a check for \$200. The subjects was not advised as to what patches were active or placebo until the completion of the study.

Follow-up Consultation: An investigator contacted each subject 7 days following the week 3 testing session via telephone or e-mail (at the discretion of the subject) to inquire about any perceived residual effects from the patches.

Treatment Patches

The efficacy of the LifeWave Energy Enhancer patches is the primary focus of this study. The nonporous membrane of the patches is made of polyethylene and one side of the patch is coated with an acrylic adhesive (Figure 1). When applied to the surface of the skin, there is no direct transfer of material from the patch to the body (non-transdermal).

A single patch has a centralized blister pocket 32mm in diameter encompassed by an edge approximately 4.5mm wide for a total diameter of 41mm. The blister pocket of a patch contains a synthetic fiber disc 28mm in diameter and all of the compounds used in the composition of the patches are recognized as safe (FDA 21 CFR).

The synthetic fiber disc is composed of a polyester substrate matrix containing a combination of amino acids, water, oxygen, and organic substances. A patch has either a brown color (glucose patch) or a white color (glycerin patch). Patches are worn in pairs and applied bilaterally over one of four possible anatomical landmarks with the white patch worn on the right side of the body and the brown patch worn on the left side of the body (Figure 2).

Each subject was instructed to wear a pair of patched (brown & white) every day of both the treatment and the placebo cycles, and to be sure to apply the patches at the same locations for the duration of the study. To clarify, each subject was provided a diagram similar to Figure 2 labeling the location and date of patch application. Further, each subject was instructed how to apply the patches and the exact anatomical locations of patch application was identified on each subject's body. For the duration of each treatment cycle, subjects were instructed to consume a minimum of two liters of water each day because the

patch manufacturer suggests an enhanced efficacy of the patch with this minimum volume of fluid consumption.

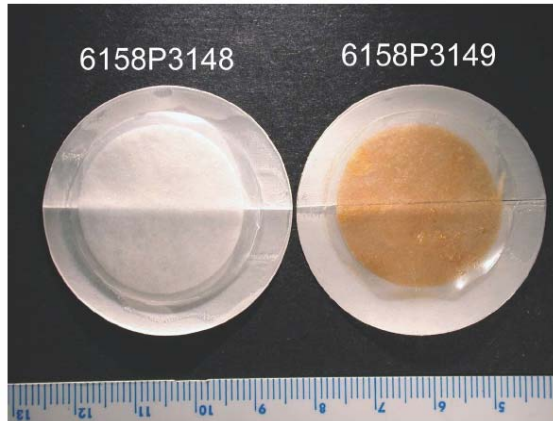


Figure 1. LifeWave Energy Enhancer patches: White (glycerine) patch (left); and brown (glucose) patch (right).

Source: MVA Report, Nov 2004



Figure 2. The four possible bilateral anatomical locations for patch placement.
Source: LifeWave Information Brochure

Source of Treatment Patches

For this study, LifeWave Products, LLC (Suwanee, GA) provided the LifeWave™ Energy Enhancer patches and the placebo patches. The placebo patch was designed to have all of the physical appearance characteristics of the LifeWave patch.

Statistical Analysis

For each of the 5 sets of responders, we are testing the null hypothesis that the means of the response variable are the same across the 3 groups (or times as Base, Control and Active) versus the alternative hypothesis that at least 2 of the 3 means are different. To test these hypotheses, we use the General Linear Mixed Model Analysis which is a generalization to the Analysis of Variance for repeated measures over group. When the group effect is significant, further testing using the Tukey post-hoc procedure is employed to see where the differences lie. The significance level of 0.05 is used for all tests.

1. *Effect of Energy Patches on Maximal Aerobic Work Responders*

There is a significant difference in the mean FF for the 3 groups (p -value = 0.0032). From the Tukey post-hoc procedure, the Active mean FF (mean = 91.7) is significantly

higher than the Base mean FF (mean = 77.0, p-value = 0.0031) and the Control mean FF (mean = 80.8, p-value = 0.0197).

2. Effect of Energy Patches on Total Resting ATP Production Responders

There is a significant difference in the mean MF for the 3 groups (p-value = 0.0443). From the Tukey post-hoc procedure, only the Active mean MF (mean = 99.3) is significantly higher than the Base mean MF (mean = 85.5, p-value = 0.0373).

3. Effect of Energy Patches on CF (Resting ATP Production from FAT) Responders

There is a significant difference in the mean CF for the 3 groups (p-value = 0.0002). From the Tukey post-hoc procedure, the Base mean CF (mean = 60.1) is significantly lower than the Control mean CF (mean = 80.7, p-value = 0.0042) and the Active mean CF (mean = 91.6, p-value = 0.0001).

4. Effect of Energy Patches on FBF - Maximal Aerobic ATP Production from Fat Responders

There is a significant difference in the mean FBF for the 3 groups (p-value = 0.0048). From the Tukey post-hoc procedure, the Active mean FBF (mean = 131.8) is significantly higher than the Base mean FBF (mean = 90.8, p-value = 0.0050) and the Control mean FBF (mean = 100.2, p-value = 0.0204).

5. Effect of Energy Patches on EQ - Maximal Aerobic ATP Production Responders

There is a significant difference in the mean EQ for the 3 groups (p-value = 0.0001). From the Tukey post-hoc procedure, the Active mean EQ (mean = 121.6) is significantly higher than the Base mean EQ (mean = 94.2, p-value < 0.0001) and the Control mean EQ (mean = 106.5, p-value = 0.0194).

Results

Application of the LifeWave™ Energy Enhancer patch produced a significant increase over placebo in maximum aerobic ATP, maximum ATP from fatty acid metabolism, resting ATP, and maximum aerobic work. There was no significant effect on resting ATP from fatty acid metabolism. There were no significant side effects from the patch.

Discussion

This study demonstrates a statistically significant improvement from the LifeWave™ Energy Enhancer patch in responders in all metabolic markers except resting fatty acid metabolism. In some cases very dramatic improvements were noted. These results coincide with other performance related studies using the patch. The implications are that the patches would be valuable in a selected subset of individuals seeking improved metabolic performance and/or help with weight control.

However, it is important to note that not all subjects responded to the patch application. Specifically:

1. Maximum aerobic work improved in 50% of subjects.
2. Maximum aerobic from fatty acid metabolism improved in 36% of subjects.
3. Maximum aerobic ATP improved in 46% of subjects.

4. Resting ATP improved in 23% of subjects.
5. Resting ATP from fatty acid metabolism improved in 40% of subjects.

A possible explanation for a failure to improve in the non-responders may be patch location variability. It may be that there is a certain amount of individual variation in the locations of patch placement that will be effective.

Another reason may be that diet was not controlled for. The carbohydrate content of the diet during the 4-5 days before an CO₂/O₂ evaluation has been shown to skew the CO₂/O₂ ratio such that in a resting state glucose metabolism becomes greater than fatty acid metabolism. This latter fact may explain why there was no consistency found in the responders regarding resting fatty acid metabolism, while there was consistency in exertional fatty acid metabolism.

References

- American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescription. 7th ed. Philadelphia, PA: Lipincott Williams & Wilkins, pp. 10-18, 2006.
- Brown, R. S. Patch permeability. Report No. MVA6158, MVA Scintific Consultants, November 23, 2004.
- Chernoff, R. Nutritional support in the elderly. Geriatric Nutrition: The Health Professional's Handbook (2nd ed.). Gaithersburg, MD: Aspen Publishers, 1999.
- Katch, F. I., E. D. Michael, and S. M. Horvath. Estimation of body volume by underwater weighing: description of a simple method. *J. Appl. Physiol.* 23: 811-813, 1967.
- Kline, G. M., J. P. Porcari, R. Hintermeister, P. S. Freedson, A. Ward, R. F. McCarron, J. Ross, and J. M. Rippe. Estimation of VO₂max from a one-mile track walk, gender, age, and body weight. *Med. Sci, Sports Exerc.* 19:253-259, 1987.
- LifeWave Products, LLC. Product information brochure. LifeWave Product, LLC, 1000 Peachtree Industrial Blvd, Suite 6-321, Suwanee, GA, 30024.
- Lohman, T. G. Applicability of body composition techniques and constants for children and youths. *Exerc Sport Sci Rev.* 14:325-357, 1986.
- National Research Council. Food and Nutrition Board. Washington, DC: National Academy of Sciences, National Academy Press, 1989.
- Salamone, L. M., T. Fuerst, M. Visser, M. Kern, T. Lang, M. Dockrell, J. A. Cauley, M. Nevitt, F. Tyavsky, and T. G. Lohman. Measurement of fat mass using DEXA: a validation study in elderly adults. *J. Appl. Physiol.* 89:345-352, 2000.
- Wilmore, J. H. A simplified method for determination of residual lung volumes. *J. Appl. Physiol.* 27:96-100, 1969.

- (1) Wilson TM, Tanaka H. *Meta-analysis of the age associated decline in maximal aerobic capacity in men: relation to training status*. Am. J. Physiol. Heart Circ. Physiol. Vol. 278: 829-834, 2000
- (2) Trounce I, Byrne E, Marzuki S. *Decline in skeletal muscle mitochondrial respiratory chain function: possible factor in ageing*. Lancet. 1989 Mar 25;1(8639):637-9.
- (3) Hagen TM, Ingersoll RT, et al: *Acetyl-L-carnitine fed to old rats partially restores mitochondrial function and ambulatory activity*. Proc Natl Acad. Sci. USA 1998, August 4; 95 (16):9562-6.
- (4) Trifunovic A, Wredenberg A, et al. *Premature ageing in mice expressing defective mitochondrial DNA polymerase*. Nature. 2004 May 27;429(6990):417-23.
- (5) Speakman JR, Talbot DA, et al. *Uncoupled and surviving: individual mice with high metabolism have greater mitochondrial uncoupling and live longer*. Aging Cell. 2004 Jun;3(3):87-95.
- (6) Dean W. *Biological Aging Measurement*. 1988, second edition, The Center for Biogerontology, Los Angeles, CA.
- (7) Caldwell SH, Chang CY, Nakamoto RK, Krugner-Higby L. *Mitochondria in nonalcoholic fatty liver disease*. Clin Liver Dis. 2004 Aug;8(3):595-617.
- (8) Duchen MR. *Mitochondria in health and disease: perspectives on a new mitochondrial biology*. Mol Aspects Med. 2004 Aug;25(4):365-451.
- (9) Beal MF. *Mitochondria, oxidative damage, and inflammation in Parkinson's disease*. Ann N Y Acad Sci. 2003 Jun;991:120-31. Review.
- (10) Krieger C, Duchen MR. *Mitochondria, Ca²⁺ and neurodegenerative disease*. Eur J Pharmacol. 2002 Jul 5;447(2-3):177-88. Review.
- (11) Wenzel U, Nickel A, Daniel H. *Increased carnitine-dependent fatty acid uptake into mitochondria of human colon cancer cells induces apoptosis*. J Nutr. 2005 Jun;135(6):1510-4.
- (12) Lesnefsky EJ, Hoppel CL. *Ischemia-reperfusion injury in the aged heart: role of mitochondria*. Arch Biochem Biophys. 2003 Dec 15;420(2):287-97. Review.
- (13) Lamson DW, Plaza SM. *Mitochondrial factors in the pathogenesis of diabetes: a hypothesis for treatment*. Altern Med Rev. 2002 Apr;7(2):94-111. Review.
- (14) Lusk G. J.Biol. Chem., 59, p41 1924.

- (15) Cheney PR, Davidson M, et al., *Bicycle ergometry with gas exchange analysis and neuropeptide responses to exercise in chronic fatigue syndrome*. Albany, New York.
- (16) Daly J. *The ventilatory response of exercise in CFS*, The Third Annual Conference on Chronic Fatigue Syndrome and the Brain, Bel-Air, California, April 24-26, 1992.
- (17) Stevens SR. *Using exercise testing to document functional disability in CFS*. Journal of Chronic Fatigue Syndrome, Vol. 1: No. ¾, p 127-9, 1995.
- (18) Wasserman K, Hansen J, Sue D, et al. *Principles of exercise testing and interpretation*. Third Addition., Lippincott Williams & Wilkins, Baltimore, MD, 1999.
- (19) Shigenaga MK, Hagen TM, Ames BN. *Oxidative damage and mitochondrial decay in aging*. Proc. Natl. Acad. Sci. USA, Vol. 91, 10771-78, Nov. 1994.
- (20) Hagen TM, Liu J, et al. *Feeding acetyl-L-carnitine and lipoic acid to old rats significantly improves metabolic function while decreasing oxidative stress*. Proc Natl Acad Sci USA. 2002 Feb 19; 99:1870-5.
- (21) Liu J, Atamna H, Kuratsune H, Ames BN. *Delaying brain mitochondrial decay and aging with mitochondrial antioxidants and metabolites*. Ann N Y Acad Sci. 2002 Apr;959:133-66.
- (22) Milne AC, Potter J, Avenell A. *Protein and energy supplementation in elderly people at risk from malnutrition*. Cochrane Database Syst Rev. 2005 Apr 18;(2): CD003288. Review.
- (23) Wengreen HJ, Munger RG, West NA, Cutler DR, Corcoran CD, Zhang J, Sassano NE. *Dietary protein intake and risk of osteoporotic hip fracture in elderly residents of Utah*. J Bone Miner Res. 2004 Apr;19(4):537-45.
- (24) Waldmann A, Koschizke JW, Leitzmann C, Hahn A. *Dietary intakes and lifestyle factors of a vegan population in Germany: results from the German Vegan Study*. Eur J Clin Nutr. 2003 Aug;57(8):947-55.
- (25) Vognild E, Elvevoll EO, Brox J, Olsen RL, Barstad H, Aursand M, Osterud B. *Effects of dietary marine oils and olive oil on fatty acid composition, platelet membrane fluidity, platelet responses, and serum lipids in healthy humans*. Lipids. 1998 Apr;33(4):427-36.
- (26) Cartwright IJ, Pockley AG, Galloway JH, Greaves M, Preston FE. *The effects of dietary omega-3 polyunsaturated fatty acids on erythrocyte membrane phospholipids, erythrocyte deformability and blood viscosity in healthy volunteers*. Atherosclerosis. 1985 Jun;55(3):267-81.
- (27) Corps AN, Pozzan T, Hesketh TR, Metcalfe JC. *cis-Unsaturated fatty acids inhibit cap formation on lymphocytes by depleting cellular ATP*. J Biol Chem. 1980 Nov 25;255(22):10566-8.

- (28) Dement WC. *The Promise Of Sleep*. 1999 Dell publishing, 1540 Broadway, NY, NY 10036.
- (29) Van Cauter E, Plat L, Leproult R, Copinschi G. *Alterations of circadian rhythmicity and sleep in aging: endocrine consequences*. *Horm Res*. 1998;49(3-4):147-52. Review.
- (30) Sturis J, Polonsky KS, Mosekilde E, Van Cauter E. *Computer model for mechanisms underlying ultradian oscillations of insulin and glucose*. *Am J Physiol*. 1991 May;260(5 Pt 1):E801-9. Review.
- (31) Altman J. *Weight in the balance*. *Neuroendocrinology*. 2002 Sep;76(3):131-6. Review.
- (32). Gerver WJ, De Bruin R, Delemarre VD, Waal HA, Aldewereld B, Theunissen P, Westerterp KR. *Effects of discontinuation of growth hormone treatment on body composition and metabolism*. *Horm Res*. 2000;53(5):215-20.
- (33) Mahler H, Cordes E. *Biochemistry*. Harper and Row, NY, 1966, p 525-553. ambient oxygen reference p. 22.
- (34) Schwela D. *Air pollution and health in urban areas*. *Rev. Environ Health*. 2000 Jan-Jun; 15 (1-2): 13-42.
- (35) Ferrand Robson, DDS. Lecture. Orthomolecular Health-Medicine, Feb 27-29, 2004, San Francisco, California.
- (36) Stevenson KJ. *Measurements of carbon monoxide and nitrogen dioxide in British homes using unflued heating or cooking appliances*. *Tokai J Exp Clin Med*. 1985 Aug;10(4):295-301.
- (37) Howell J, Keiffer MP, Berger LR. *Carbon monoxide hazards in rural Alaskan homes*. *Alaska Med*. 1997 Jan-Mar;39(1):8-11.
- (38) Kelley JS, Sophocleus GJ. *Retinal hemorrhages in subacute carbon monoxide poisoning. Exposures in homes with blocked furnace flues*. *JAMA*. 1978 Apr 14;239(15):1515-7.
- (39) Viebahn R, Rilling S. *The Use Of Ozone In Medicine*. Revised edition, December, 1994. Biologica Medicina, 2937 NE Flanders St., Portland, OR 97232.
- (40) Pangborn, J, Baker S. *Autism: effective biochemical treatments*. Available from the Autism Research Institute, 4182 Adams Ave., San Diego, CA 92116, p280.
- (41) Martinez RM, Saponaro A, Dragagna G, Santoro L, Leopardi N, Russo R, Tassone G. *Cutaneous circulation in Raynaud's phenomenon during emotional stress. A morphological and functional study using capillaroscopy and laser-Doppler*. *Int Angiol*. 1992 Oct-Dec;11(4):316-20.

- (42) Meerson FZ, Arkhipenko IuV, Rozhitskaia II, Kagan VE. *Damage to the Ca²⁺-transport system of cardiac sarcoplasmic reticulum during emotion-pain stress*. Biull Eksp Biol Med. 1981 Apr;91(4):405-6.
- (43) Hasegawa R, Daimon M, Toyoda T, Teramoto K, Sekine T, Kawata T, Watanabe H, Kuwabara Y, Yoshida K, Komuro I. *Effect of mental stress on coronary flow velocity reserve in healthy men*. Am J Cardiol. 2005 Jul 1;96(1):137-40.
- (44) Bacon SL, Ring C, Hee FL, Lip GY, Blann AD, Lavoie KL, Carroll D. *Hemodynamic, hemostatic, and endothelial reactions to psychological and physical stress in coronary artery disease patients*. Biol Psychol. 2005 June 13.
- (45) Berg D, Berg L.H., and Couvaras J. *Is CFS/FM due to an undefined hypercoagulable state brought on by immune activation of coagulation*. Accepted for presentation: American Association Chronic Fatigue Syndrome, Oct, 98.
http://www.hemex.com/publications/csf_fm_hyperstate.php
- (46) von Ardenne M. *Oxygen Multi-Step Therapy*. George Thieme Verlag Publishing, January 1, 2000.
- (47) Irrcher I, Adhietty PJ, Joseph AM, Ljubicic V, Hood DA. *Regulation of mitochondrial biogenesis in muscle by endurance exercise*. Sports Medicine, 2003;33(11):783-93.
- (48) Brechue WF, Pollock ML. *Exercise training for coronary artery disease in the elderly*. Clin Geriatr Med 12: 207-229, 1996.
- (49) Radzewitz A, Miche E, et al. *Exercise and muscle strength training and their effect on quality of life in patients with chronic heart failure*. Eur J Heart Fail 4: 627-634, 2002.
- (50) Colcombe SJ, Erickson KI, Raz N, et al. *Aerobic fitness reduces brain tissue loss in aging humans*. J Gerontol A Biol Sci Med Sci 58: M176-M180, 2003.
- (51) Cooper CE, Vollaard NB, et al. *Exercise, free radicals, and oxidative stress*. Biochem Soc Trans 30: 280-285, 2002.
- (52) Shallenberger, F. *Is Your Patient Exercising Too Hard To Be Healthy?* Townsend Letter For Doctors, August-September, 2004.
- (53) Navarro A, Gomez C, Lopez-Cepero J, Boveris A. *Beneficial effects of moderate exercise on mice aging: survival behavior, oxidative stress, and mitochondrial electron transfer*. Am J Physiol Regul Integr Comp Physiol. 286: R505-R511, 2004.
- (54) Sastre J, Pallardo FV, Vina J. *The role of mitochondrial oxidative stress in aging*. Free Radic Biol Med. 2003 Jul 1;35(1):1-8.
- (55) Lee HC, Wei YH. *Mitochondrial alterations, cellular response to oxidative stress and defective degradation of proteins in aging*. Biogerontology. 2001;2(4):231-44.

(56) Wei YH, Lu CY, Lee HC, Pang CY, Ma YS. *Oxidative damage and mutation to mitochondrial DNA and age-dependent decline of mitochondrial respiratory function*. Ann N Y Acad Sci. 1998 Nov 20;854:155-70.

(57) Levine SA, Kidd PM. *Antioxidant Adaptation – Its Role In Free Radical Pathology*. 1985, Biocurrents Division, Allergy Research Group, 400 Preda St., San Leandro, CA 94577.