CURRENT AND PRIOR RESEARCH PROJECTS – PRINICIPAL INVESTIGATOR – Dr. HN Mayrovitz

TITLE: Skin Firmness and Skin Water: Measurement Repeatability and Relationships Assessed in Young and Older Women

SUMMARY: Assessments of skin mechanical properties including skin fibrotic and elastic characteristics could potentially be a useful way to detect skin changes that accompany the insidious progression of pathological changes or those related to normal age-related changes associated with various age-related changes. We hypothesize that skin hydration when measured in the upper dermis and deeper will in fact directly correlate with skin elasticity. To test this hypothesis, we plan to locally measure certain skin water parameters and assess the mechanical properties of the skin noninvasively. These measurements are: tissue dielectric constant (TDC) which assesses the skin-to-fat water content, stratum corneum (SC) electrical capacitance which assesses SC water content, and skin mechanical property measurements will be made using the Elastimeter and Fibrometer devices to properly assess the validity of this hypothesis. Measurements will be collected from 70 Caucasian females (35 females age 18-30 and 35 females above the age of 45) to evaluate the proposed relationships for each age group. Four measurement sites on the right side of the face will be marked along with two sites on the neck and two sites on the right forearm. Measurements will be made at each site by touching the skin with four different small sensors for about 10 seconds each and will be done 5 times. In addition, a Co-investigator in this study will ask a series of questions designed to detect certain skin properties which may affect the values that are measured. The entire protocol will take about 30 minutes. Regression analysis will be used to test the hypothesized inverse relationship between mechanical skin stiffness as measured by Elastimeter or Fibrometer and TDC values as indices of local tissue water.

TITLE: Quantitative assessment of the effect of topical skin cooling as a modality to help manage patients with breast cancer treatment-related lymphedema (BCRL): A pilot study

SUMMARY: The current standard of care in the treatment for BCRL is Complete Decongestive Therapy (CDT). CDT is comprised of manual lymphatic drainage massage (MLD), compression wrapping, skin care and exercise. This study seeks to measure and otherwise evaluate the impact of adding cooling of the breast and arm as a component of CDT to women with BCRL. The use of cooling is routinely used in the clinic of the co-investigator (CI) with the qualitative observation of tissue softening (stiffness reduction) and also edema reduction facilitations. The purpose of this study is to quantitatively measure the potential effects of such cooling administered prior to MLD. The specific hypothesis being tested in this pilot study is that topical cooling of the affected area prior to MLD reduces tissue stiffness thereby facilitating the effectiveness of MLD and that cooling also decreases tissue water in the edematous arm, chest or breast. This hypothesis will be tested by measuring the direct effects of skin cooling on changes in edematous tissue stiffness and tissue water content in 30 women who will have been referred for BCRL treatment to the CI's clinic (Total Lymphedema Care). All of these clients will be normally receiving pre-MLD cooling. To evaluate the physical effect of cooling, tissue stiffness will be evaluated by a hand-held device that records the force required to indent the skin 1.3 mm. This device is called a fibrometer (FIB) since it is designed to assess tissue fibrosis. Tissue water will be assessed by measuring the tissue's dielectric constant (TDC) at a frequency of 300 MHz using a hand-held device that touches the skin for about 10 sec. At a frequency of 300 MHz, TDC is a good index of water content within the target tissue. In addition arm girth (GIRTH) and skin temperature (TSK) will be measured. All measurements, FIB, TDC, GIRTH and TSK will be made prior to cooling, immediately after completing the cooling process and at the end of the MLD process during a single client visit. . In addition a series of questions will be asked of the client related to the cooling experience and their perceived symptoms and their range of motion (ROM) will be assessed using a goniometer prior to cooling, after cooling and after MLD. This measurement and evaluations process will be done on the subjects 1st visit and repeated on the subject's 2nd and 5th visits for a total of three measurement sessions. The accumulated data will be used to assess the physical changes attributable to the cooling process and on the changes over the five visits.

TITLE: Investigation of glycosylation effects on skin-to-fat tissue water content in persons with diabetes mellitus assessed by skin tissue dielectric constant (TDC)

SUMMARY: It has been estimated by the International Diabetes Foundation that there are about 285 million people around the world living with diabetes and that approximately one third of this population undergo some form of skin manifestations. While patients with type I diabetes are more likely to suffer from autoimmune related lesions, patients with type II diabetes are more prone to cutaneous infections. Ultrasound research shows that diabetic patients have thinner skin and less subcutaneous fat compared to age-matched control subjects, which supports the idea that such biophysical changes may alter the skin-to-fat tissue water content which can then alter skin functions. Literature further supports the idea that the excess supply of glucose leads to non-enzymatic chemical reactions between the carbonyl group of glucose and amino acids of proteins and this glycation of structural and regulatory proteins plays a key role in the pathogenesis of diabetic skin complications such as diabetic ulcer or diabetic foot syndrome. However it is not clear whether the changes in tissue water content affect normal skin maintenance. Since the glycosylation of structural proteins strongly adheres glucose molecules to the protein, a plausible hypothesis is that diabetic persons with higher HbA1c values will have less tissue water content compared with persons with lower HbA1c values. Thus, our main goal is to determine the correlation between skin-to-fat tissue water as measured by tissue dielectric constant (TDC) and HbA1c amongst patients with diabetes. This study may be viewed as a pilot investigation of the possible correlation between these two important parameters.

TITLE: Quantifying the relationship between skin water and skin stiffness

SUMMARY: Prior work has suggested that differences in dietary water intake may affect skin water and skin mechanical properties but this concept is does not have firm scientific underpinnings. If the underlying suggestion were true then one would expect that independent of specific amounts of water intake there would be a measurable relationship between skin water and skin mechanical properties. It is our specific hypothesis that skin stiffness, as measured by indentation methods, is in fact correlated with skin water as measured by tissue dielectric constant (TDC) values. The goal of this research is to test this hypothesis by making appropriate measurements in a young adult population. We believe that the outcome of this research study will help uncover such possible fundamental interactions thereby extending our understanding of skin physiology and setting the stage for further discoveries. The working hypothesis will be tested by making a series of non-invasive forearm skin measurements on the forearm and face of 120 young adults divided equally by gender. The measurements are designed to determine skin water and skin stiffness. Skin water is assessed by measuring tissue dielectric constant (TDC) at depths of 0.5 mm (TDC5) and 2.5 mm (TDC25) at a standardized site on the forearm and on the face. At these same sites skin stiffness is measured by determining the indentation force needed to indent skin 0.3 mm using an Elastometer (ELS) and to 1.3 mm using a Fibrometer (FIB). These skin measurements take about 3.5 minutes in total. In addition, subject weight and total body fat percentage (TBF%) and total body water percentage (TBW%) are measured by having each subject stand on a scale for about 30 seconds. So the entire experimental time will be five minutes or less during a one time session. Data analysis and interpretation will be based on regression analysis of tissue water parameters (TDC5 and TDC25) and skin mechanical properties (ELS and FIB) with body composition parameters (TBF% and TBW%) as possible covariates.

TITLE: Effects of Heat-Induced Skin Blood Flow Changes on Skin Water Parameters

SUMMARY: Skin heating is associated with skin blood vessel vasodilation and increased skin blood flow. We hypothesize that such vasodilation should be associated with an increase in the amount of fluid filtered from the capillaries distal to the arteriolar vasodilation and that the subsequent increase in interstitial fluid is dependent on the amount of the blood flow increase. To test this hypothesis we plan to locally heat the skin, measure the blood flow produced and noninvasively measure parameters to assess the skin water changes. These measurements are: 1) tissue dielectric constant (TDC) which assesses the skin-to-fat water content, 2) stratum corneum (SC) electrical capacitance which assesses SC water content and 3) transepidermal water loss (TEWL) that assesses water loss from the skin. Measurements will be done in both sexes (35 male and 35 female with age-range of 18-35 years) since the literature indicates gender differences in skin blood flow and skin water content. Skin heating will be produced by a topically applied 20 mm disk that will cause skin to be heated to 40°C for 12 minutes. Blood flow during this time is monitored via a laser Doppler method. The target measurement site is the dominant anterior forearm 6 cm distal to the antecubital crease. Tissue water parameters will be measured prior to heating, immediately after heat removal and at 2-minute intervals for 12-minutes post-heating. The protocol, including initial set-up, subject acclimation and measurements will take about 45 minutes. The hypothesized dependence of tissue water on induced blood flow will be tested by regression analysis. Gender differences in measured parameters will be tested with independent T-tests with a p-value <0.05 accepted as significant.

TITLE: Evaluating the Utility of the Tissue Dielectric Constant Method as a Rapid Clinical Office Test for Early Lymphedema Detection in Patients Surgically Treated for Breast Cancer

SUMMARY: Our main goal is to determine the utility of using skin tissue dielectric constant (TDC) measurements in a clinical environment that will permit the rapid identification of early stage lymphedema. Lymphedema is swelling of an extremity caused by a blocked or damaged lymph system; this can lead to long-term physical, psychological, and social problems. Since TDC values are directly related to the local tissue water we hypothesize that such measurements made prior to a patients breast cancer surgery and at normal office follow-up visits after, will permit the early detection of subclinical lymphedema.

To test this hypothesis, 100 women diagnosed with unilateral breast cancer (who will be treated surgically by the collaborating investigator surgeon) will have multiple evaluation sessions with the surgical investigator allowing for TDC assessment over time. The first evaluation session will be prior to their surgery. After their surgery, evaluations will occur every 3-6 months for up to 3 years during the patients' normal follow-up visits. During each session, single TDC measurements will be made at two sites on each arm with a small, non-invasive, skin sensor (10 seconds/measurement) at 8 cm above and 6 cm below the antecubital fossa. Site girth, body weight and water percentage will also be determined. The entire measurement procedure per visit will take less than 5 minutes thereby being a feasible clinical measurement set in a busy surgical office. The TDC values and arm girths will be analyzed and compared to clinical signs of edema and to patient reported symptoms.

TITLE: Quantitative assessment of static magnetic field (SMF) effects on skin water and mechanical properties

SUMMARY: Prior work has shown that a SMF produced by a magnet can alter skin blood flow and change blood vessel tone. Further a SMF has been reported to reduce experimentally induced edema in an animal model and contrastingly to increase vascular permeability in an experimental tumor model. Based on these and other observations we believe that in addition to SMF affecting tissue water features in altered or abnormal states that there is likely to be an effect on normal skin water properties. Given the fairly wide use of magnets in a host of conditions we believe that the possible extent of such effects needs to be investigated. But beyond that issue, such an investigation is viewed as one directed toward a fundamental uncovering of the possible interaction of a SMF with viable normal tissue. Thus, the working hypothesis is that a SMF will alter measurable features of skin water and related aspects of skin mechanical properties. Specifically that application of SMF will reduce tissue water and thereby alter the indentation resistance of the tissue. This hypothesis will be tested by making a series of non-invasive forearm skin measurements prior to SMF and again after skin exposure to a SMF for an interval of 30 minutes. The measurements are designed to determine changes in skin water and skin stiffness. Skin water changes will be assessed by measuring transepidermal water loss (TEWL), stratum corneum capacitance (SCC) and tissue dielectric constant (TDC). Skin stiffness will be assessed by measuring the indentation force needed to indent skin 0.3 mm using an Elastometer (ELM) and to 1.3 mm using a Fibrometer (FIB). It is planned to conduct these measurements on 50 volunteer subjects during a single session lasting about 60 minutes. Data analysis and interpretation will be based on pre-post test analyses with the main intervention being the placement of an active magnet on forearm skin with a simultaneously placed sham magnet placed on the contralateral forearm skin.

TITLE: Efficacy of Osteopathic Manipulative Therapy (OMT) for Lower Extremity Edema Assessed via Measurements of Tissue Dielectric Constant and Girth

SUMMARY: Osteopathic Manipulative Treatment (OMT) is a hands-on approach to diagnosis and management of patients with a wide array of diseases. In this study we aim to evaluate the effectiveness of an OMT protocol on lower extremity edema. We aim to test the hypothesis that OMT is an effective therapy for management of lower extremity edema. Efficacy will be determined by analyzing changes in tissue dielectric constant (TDC) values which are indices of skin-to-fat water as measured at the leg section with the greatest initial edema and on foot dorsum and also by girth changes also measured at the leg section with greatest initial edema. These measurements will be made prior to OMT start, after an initial part of the OMT sequence, and at the end of the full OMT sequence. Participants in this study will be patients who are referred to Dr. Boesler for treatment of lower extremity edema secondary to congestive heart failure. Assessments of efficacy will be evaluated in this initial study on the basis of a single OMT session as administered to a planned 40 patients. The main research component of this study is the quantitative assessment of OMT effectiveness based on TDC and girth measured values.

TITLE: Characterizing Dielectric Properties of Malignant and Non-Malignant Skin Lesions

SUMMARY: The current gold standard for the diagnosis of skin cancers is histopathologically based using biopsied material. However some new non-invasive methods may offer additional and potentially beneficial improvements in this diagnostic process. One such methodology, yet to be evaluated in this context, is a portable hand-held device that quantifies the tissue dielectric constant (TDC) of skin. Our purpose is to compare TDC values among normal skin and benign and malignant lesions and gain an understanding of the fundamental relationship between the properties of healthy and pathogenic skin, as there is no known literature regarding these fundamental relationships. Subjects will be patients who present at the Dermatology Clinic for skin evaluations. Following patient evaluation, appropriate patients will be advised of the research study and interested patients will receive a full explanation of the study. After signing of an approved informed consent the approximate center of the lesion will be marked with a surgical pen and photographed with a digital camera with a scale included in the image. An anatomically corresponding site on normal skin will also be so marked but not photographed. Thereafter temperature and TDC measurements will be done at the lesion and contralateral sites. Temperature will be measured first followed by TDC measurements to a depth of 2.5 mm then to a depth of 0.5 mm. The measurement set will take about 5 minutes to complete. It is planned to recruit sufficient subjects to achieve at least 10 malignant lesions with biopsy determined diagnoses of basal cell carcinoma, 10 of squamous cell carcinoma and 10 of melanoma.

TITLE: Effect of Handedness on Measured Blood Pressure

SUMMARY: Literature has provided us with information stating that the systolic blood pressure (SBP) in the right arm is greater than that of the left arm[1-5]. There is yet to be a study to determine if, and how, the handedness of an individual may contribute to this phenomenon[6, 7]. Arm girth, local tissue water, arm fat or muscle percentages are among physiological factors that may cause differences when comparing the measured dominant versus the non-dominant arm's SBP. It is also possible that the internal vascular pathways account for observed differences [1-5]. It is our plan to investigate this phenomenon by using a technique to measure the BP of both arms simultaneously [4, 8-9] in persons who are left-handed (L-H) and who are right-handed (R-H). In addition we will be making measurements related to the physical features of the arms including arm girth, arm water and arm fat. It is our plan to recruit 50 R-H and 50 L-H volunteers of either gender for these measurements. The underlying hypothesis to be tested is that the SBP will be greater in the dominant arm as opposed to being just greater in the right arm. Our planned subjects will be drawn from university faculty, staff and students.

TITLE: Assessment of Skin Tissue Water in Persons with and without Diabetes Mellitus

SUMMARY: Although it is well documented that the diabetic condition is often associated with changes in skin blood vessels and blood flow, there is a surprising dearth of basic information as to possible changes in biophysical properties of the skin itself. Very recent findings based on ultrasound measurements suggest that persons with diabetes have thinner skin (epidermis + dermis) and also less subcutaneous fat than age-matched persons without diabetes. The implications of these new findings with respect diabetes-related complications such as dry skin, reduced skin microcirculation and impaired wound healing, are as yet unclear. However, the findings suggest that such structural changes may alter the skin-to-fat tissue water content, which then directly or indirectly affects one or more skin functions. Data that indirectly bears on this hypothesis indicates that stratum corneum water content and transepidermal water loss in persons with diabetes does not significantly differ from age-matched non-diabetic controls. However, such measurements provide no information as to the water content of the dermal or subcutaneous tissues. Thus, the goal of this research is to determine if skin-to-fat tissue water of persons with diabetes differs from that of persons without diabetes. Because the reported structural changes include both a skin thinning and less subcutaneous fat a suitable hypothesis as to whether a greater or lesser tissue water will be demonstrated in persons with diabetes can not be a priori made. This is so since skin thinning per se would tend to decrease water content whereas fat loss would tend to increase relative skin-to-fat tissue water since water content of fat is low. Thus the present research may be viewed as a seminal study in which the fundamental skin tissue water features of persons with diabetes will be determined and compared to features of persons without diabetes. The method to be used to assess skin tissue water is based on non-invasive measurements of the tissue dielectric constant (TDC). This method has successfully been used to evaluate localized tissue water in arms and legs of healthy subjects, in patients with breast cancer and in persons with lymphedema.

TITLE: Facial Skin Tissue Water Assessed by Tissue Dielectric Constant: Dependence on Nerve Territory and Posture

SUMMARY: There are differences among skin stratum corneum and biophysical parameters within facial regions. For example skin blood perfusion of cheek skin is greater than in forehead skin whereas cheek transepidermal water loss (TEWL) is less than for either forehead or chin. Since TEWL and perfusion differences affect skin tissue water content we hypothesize that regional property differences cause regional differences in local facial tissue water (LFTW). This concept is consistent with the fact that skin territories of forehead, cheek and chin are differentially innervated by trigeminal nerve branches that contain substance-P, which can contribute to facial and skin edema. Although edema is not targeted in this investigation, it is plausible that physiological innervation differences cause differences in normal LFTW. Another important physiological questions relates to the effect of posture on LFTW distribution. When a person is lying supine, gravitational forces act mainly perpendicular to the plane of the lying surface. When sitting, gravitational forces act vertically thereby causing force differentials to be experienced at forehead, cheek and chin. Based on such physical differences we further hypothesize that LFTW changes are differentially effected in supine and upright positions. Thus our goal is to quantitatively characterize the distribution of facial skin tissue water among the three differently innervated facial regions and determine the effect of posture on this distribution. To accomplish this, LFTW will be determined non-invasively in 40 male subjects using a tissue dielectric constant method that has been successfully used previously to assess local tissue water in other skin areas

TITLE: Foot Volume Estimation from Simple Metric Measurements

SUMMARY: The purpose of this research is to develop a simplified method to estimate foot volume that would be useful to clinically assess edema volume and its change without the need for using water displacement methods. At present, leg edema and its change can be adequately estimated by measuring leg circumferences and using these circumference values in a mathematical model known as a truncated frustum model. However, there is no metric-model counterpart that allows for estimating foot volume. Since, edema of the foot often occurs in persons with conditions that cause leg edema, health care providers and therapists have no simple method to estimate total lower extremity limb volume changes. Moreover, there are some conditions in which the edema is localized to the foot. The gold standard for measuring foot volume is water displacement, but this method is not one that can be routinely applied efficiently. Thus the specific aim of this research is to develop a mathematical algorithm that can be used to estimate foot volume based on foot measurements obtained with simple measurement tools such as a tape measure or calipers

TITLE: Low Intensity Pulsed Magnetic Fields as a Method to Increase Skin Blood Flow

SUMMARY: Previous work has demonstrated the potential for increasing skin blood flow as a result of the use of pulsed electromagnetic energy in the form of pulse modulated radiofrequency excitation. Such pulsed electromagnetic field (PEMF) methods are currently FDA approved for the use in the treatment of pain and edema and are cleared for the use as adjunct therapy in the treatment of skin ulcers of various types.
The original devices were physically large, with large applicator coils and maximum applied peak-to-peak magnetic fields of about two Gauss. In part, the large physical size was required by the need for providing a large peak power to the coil to produce the level of magnetic field then thought to be necessary to achieve the positive effects. Based on certain theoretical considerations, it has been postulated that magnetic field strengths much lower than those originally used could produce similar effects. If true, devices could be developed that are much smaller physically and thus pave the way for portable and “wearable” modes of delivering therapeutic PEMF. Inroads toward this end have been taken by at least one commercial organization (IVIVI Technologies Inc) that has developed a device that delivers PEMF energy that is less than 5% of that previously used. It is theorized that the much lower field strength needed to produce positive effects results from using a pulse width (PW, 2000 μs) and pulse repetition frequency (PRF, 5 Hz) that near-optimally matches and couples energy to certain postulated physiological targets. Although there is some theoretical basis and some recent empirical evidence to support this concept, there has been no systematic study of the effects on blood flow. Since changes in blood flow are fundamental to our understanding of the involved physiological mechanisms and clearly impact on many of the previous and future applications, the need to study this aspect is crucial. Thus one goal of this proposed research is to determine if, and to what extent, the newly configured low amplitude PEMF modulates skin blood flow in normal human subjects. This will be studied using the currently configured PW and PRF combination in 20 healthy volunteers. A second goal is to investigate the significance of different PRF and PW parameter values with respect to their effects on skin blood flow. The significance of the PRF aspect derives from the fact that there are a number of intrinsic physiological processes, related to blood flow, that operate below 5 Hz. Because of this fact, it is possible that using PRF values in the range of 1-4 Hz will more efficiently couple energy to corresponding receptors, resulting in greater blood flow effects. This aspect will be studied in a second group of 20 healthy subjects. The significance of the PW factor is that it is a determinant of the amount of spectral energy that is available for coupling into the tissue. A larger PW corresponds to more low frequency energy. Thus, by increasing the PW a greater blood flow effect may result. This aspect will be studied in third group of 20 healthy subjects.

TITLE: Local Tissue Water Changes in Lymphedematous Arms and Thorax of Women with Breast Cancer Treatment-Related Lymphedema: Short-term Effects of Therapy Using a Sequential Compression Therapy Device: A Pilot Study

SUMMARY: Automated sequential compression devices of different types have been reported to provide benefit in treating persons with limb lymphedema. These devices have been compared to the effectiveness of complete decongestive physiotherapy (CDP) and also have been used in conjunction with CDP. Most devices consist of multiple contiguous chambers that encircle the limb with the chambers sequentially inflated and then deflated simultaneously. Another approach, recently introduced, uses sequential compression patterns that may more closely emulate the pattern that is used in manual lymphatic drainage (MLD), an integral component of CDP. This device (Flexitouch), which is an FDA cleared device for lymphedema therapy, has several important features that differ from classical automated sequential compression approaches. One relates to the magnitude, pattern and timing sequences of the compression-release cycles. These are significantly different than classical sequential compression approaches in that the pressures are shorter acting and have significantly lower magnitude applied pressure pulses. Another major difference is its automated preparation phase in which the truncal region downstream from the lymphedematous limb is first treated under the physiological principle that such clearing is efficacious and will permit greater lymph drainage during the subsequent drainage cycle. This concept of clearing remote regions to facilitate drainage is in accord with experimental findings in animals in which thoracic compression facilitated peripheral lymph transport. However, the impact of this truncal clearance with respect to changes in tissue water in arm or truncal sites has not as yet been scientifically evaluated in patients with lymphedema. The investigation and elucidation of this aspect is important to the furtherance of our fundamental understanding of the lymphedematous condition and the factors that help ameliorate its impact on patients. Thus, the main goal of this research is to compare the effect of this new form of sequential Flexitouch compression therapy (hereafter referred to as FT) on local tissue water when FT is used with and used without the truncal compression component. The underlying hypothesis is that, because of fluid clearance associated with preparatory truncal compression, there will be differences in tissue water changes between the two modes of FT. Such differences are hypothesized to be expressed as a greater reduction in local arm tissue water and a greater change in truncal tissue water when the truncal component is used.

TITLE: Short-term Effects of a Sequential Compression Device (Flexitouch®) on Leg Skin Blood Flow

SUMMARY: Automated sequential compression devices of different types have been reported to provide benefit in treating persons with limb lymphedema1-8 and lower extremity skin ulcers9, 10. Most devices consist of multiple contiguous chambers that encircle the limb with the chambers sequentially inflated and then deflated simultaneously. Another approach, recently introduced, uses sequential compression patterns that may more closely emulate an optimal pattern of cyclical compression. This device (Flexitouch®), which is an FDA cleared device for treatment of lymphedema and lower extremity leg ulcers, has several important features that differ from classical automated sequential compression pumps. Of particular significance is this device's magnitude, pattern and timing of the compression-release cycles. These are significantly different than classical sequential compression pumps in that the pressures are shorter acting and have significantly lower magnitude pressure pulses. Because the main focus for the use of this device has been for treating patients, the underlying physiological impacts that potentially accompany its use have not been studied thereby limiting knowledge and insight into its mechanism of action. In considering potential physiological affects of this form of low pressure sequential dynamic compression, the principal investigator believes that at least part of the demonstrated positive outcomes achieved with the use of Flexitouch® relates to its impact on skin blood flow. Specifically, it is hypothesized that the cyclical dynamic pressures associated with Flexitouch® application promotes an augmentation in skin blood flow possibly related to endothelial cell release of vasodilating substances in response to the gentle massage-like compression cycles. The main purpose of this research is to test this hypothesis. A secondary goal is to assess possible changes in tissue water and properties that may accompany this form of dynamic compression.

TITLE: Analysis of Effects of Low Level Laser Therapy on Fibrosis Parameters in Patients with Breast Cancer Treatment-Related (BCRL) Upper Extremity Lymphedema: A Pilot Study

SUMMARY: One of the complications of lymphedema is the development of fibrosis in which the skin and underlying tissues of lymphedematous regions become hardened. One consequence of this form of fibrosis is that it makes it much more difficult to treat the underlying lymphedema since the fibrosis encapsulates fluid and otherwise reduces the efficiency of manual lymphatic drainage therapy (MLD) to remove excess fluid. A recent paper1 and various anecdotal reports have suggested that the use of low level laser therapy (LLLT) may act to 'break-up' fibrosis and otherwise soften fibrotic regions of tissue. If true this would represent a significant advance in the treatment of lymphedema. One commercial device has recently been cleared by the FDA for use in persons with arm lymphedema arising from breast cancer related treatment. Although this device is incorporated as a treatment tool in some centers in conjunction with standard treatment protocols, a scientific assessment of its impact on fibrosis remains essentially absent from the literature. The reason in part is because suitable quantitative measurements of its effect have not been done. The purpose of the present pilot research study is to quantify possible effects of this LLLT device on fibrotic tissue, as it is already used in clinic, by analyzing data obtained from two noninvasive biophysical measurements made on the skin prior to and after the application of the LLLT device. These measurements, which will assess the local tissue water and the local tissue hardness of fibrotic tissue before and after LLLT treatment, will thus provide the needed quantitative basis to judge the potential utility of this mode of treatment.

TITLE: Assessment of the utility of changes in the arm skin tissue dielectric constant (TDC) as an early indicator of lymphedema in women surgically treated for breast cancer

SUMMARY: This research aims to determine whether early detection of increased skin tissue fluid, assessed via measurements of the tissue dielectric constant (TDC), can be used as a predictor of subsequent clinical development of lymphedema in women who are at-risk for developing lymphedema. The TDC is directly related to tissue water content and is measured noninvasively using a small sensor that touches the skin for about 10 seconds. Subjects will be 120 women who have been recently diagnosed with unilateral breast cancer. TDC measurements will be made prior to their surgery and at 3, 6, 12, 18 and 24 months post surgery during their routine follow-up visits with their breast surgeon who is also a co-investigator. We hypothesize that such TDC measurements will permit the early detection of subclinical lymphedema. During each session, duplicate TDC measurements will be made on the forearm and biceps of the at-risk and contralateral arm. Arm girth at the sites will also be measured as a secondary index of possible lymphedematous changes. Further, because there is some possibility that body weight and composition (water and fat percentages) may be involved in the triggering of breast cancer related lymphedema (BCRL), body weight, whole body water and fat percentages, and arm segmental fat and muscle percentages will be determined using the method of bioimpedance. This requires the subject to stand on a scale while gripping two handles. The entire measurement procedure will take about 5 minutes thereby being a feasible clinical measurement set in a busy clinical office. Also, during each visit the patient will be evaluated for clinical signs of edema using standard clinical assessment and they will complete a questionnaire as to their perceived lymphedema-related symptoms. Changes in at-risk arm TDC values, arm girths and body composition parameters will be tracked and compared with the clinical assessments and perceived symptoms. The primary test of the underlying hypothesis will be based on the extent to which patients who develop clinical lymphedema also have a clear elevation in their TDC values at some time prior to the clinical diagnosis. If the hypothesis proves to be correct then physicians will subsequently be able to initiate lymphedema treatment early, before the onset of clinically detectible symptoms. Thus, Changes in TDC values may become an early marker for lymphedema.

TITLE: Reactive Hyperemia of Skin Blood Flow: A Study of the Effects of a Permanent Magnet and its Polarity

SUMMARY: Commercial claims for the efficacy of static magnets for pain relief, or other salubrious effects, have sometimes implied, or averred, that the magnets influence blood flow. However, in the few studies that report evidence of magnet-related reduction of pain, edema, or sympathetic diabetic neuropathy, the question of magnet-related enhancement of blood flow has not been addressed. While some studies have documented the influence of pulsed electromagnetic fields on skin blood perfusion and others have suggested an effect of static magnetic fields on blood vessels in experimental situations, no systematic evaluation of the effects of permanent magnets on human skin has shown a change in microcirculation. Indeed, we and others have reported the lack of effect of static magnets on resting blood flow in normal human skin and an absence of an effect on the blood flow reduction induced by the peripheral sympathetic nervous system. While the weight of existing evidence indicates no effect on normal or unperturbed tissues, there remains the possibility that there are magnet effects in perturbed systems. That is, it has been speculated that the therapeutic effect of an imposed field (EMF or PEMF) depends upon the initial state of the tissue, and that circulatory perturbed tissue responds differently than normal tissue. In an attempt to clarify this issue, the effect of magnets with a surface field of about 1000 Gauss were used to determine if they would modify the pattern of vasoconstriction produced by the "inspiratory gasp reflex." This reflex, triggered by a rapid and deep inspiration, induces a significant transient reduction in skin blood flow. Results showed no significant effect of permanent magnets on the vasoconstriction response under these conditions. However, the possibility that magnets might influence the vasodilatory potential has not been systematically investigated. From a clinical standpoint, a magnet-related augmentation in the vasodilatory capacity would be of great interest, since many conditions present with symptoms of reduced blood flow. This vasodilatory capacity can be assessed by examining parameters of the hyperemic blood flow response following an interval of prior blood flow deprivation 17, 18. An additional aspect of the potential interaction of permanent magnets with blood circulation is related to the polarity of the magnet that is placed in contact with the target tissue. The commercial literature is full of statements to the effect that polarity is a key factor in obtaining sought after therapeutic results. Yet, we know of no scientific evidence that indicates a pole-related dependency in human magnet-related effects. Because of this dearth in data related to this claim, we feel it important to include a consideration of polarity in the present research, so that its validity may be scientifically addressed via the following specific aims.

1. To test the hypothesis that the field of a permanent magnet, applied before and during an interval of occlusion-induced blood flow reduction to a finger, will result in a greater post-occlusion blood flow response (reactive hyperemia) than with no magnetic field applied.
2. To test the hypothesis that the reactive hyperemia will be dependent on which pole of the magnet faces the skin in which the response is being measured.

To test these hypotheses, dorsal skin blood flow will be continuously measured in middle fingers of both hands of volunteers by laser-Doppler methods, while fingers are serially exposed to either two sham magnets, a sham magnet and the positive pole of a magnet or a sham magnet and the negative pole of a magnet. For each magnet-sham combination, a four-minute blood flow deficit will be produced simultaneously in both fingers using vascular cuffs around the base of the fingers. Cuffs will be deflated simultaneously and resultant hyperemic responses recorded. Parameters of the hyperemic response to be used as a basis of comparison are (1) its maximum amplitude, (2) the area under the hyperemic curve and (3) the response recovery time. In addition, possible magnet-related effects on the temporal pattern of blood flow will be examined using spectral analysis methods.

TITLE: Investigation of Effects of Permanent Magnets on Sympathetic Reflex Control of Skin Blood Circulation

SUMMARY: Many clinical conditions are associated with varied forms of altered peripheral neurovascular control of blood vessels. Perhaps the most widely recognized are diabetes mellitus (Mayrovitz & Larsen, 1994,1996a; Lim et al., 1999, Caballero et al., 1999; Stansberry et al.; 1999; Bornmyr et al. 1999; Kilo et al., 2000,) and Raynaud's phenomenon (Popivanov et al., 1999; Edwards et al. 199a&b; Bertuglia et al., 1999). The altered neural reflex sometimes promotes exaggerated vasoconstrictive responses, thereby causing exaggerated blood flow decrements in response to normal stimuli, as in some persons with Raynaud's phenomenon, or causing decreased vasomotor tone, as is thought to be the case in peripheral neuropathies in some patients with diabetes.

In the work proposed here, the initial goal is to investigate the possibility that permanent magnets may modify digital blood vessel vasoactivity in a way that is potentially useful to favorably alter neurovascular deficits in conditions such as those noted above. Although the main emphasis is to characterize magnetic related neurovascular response modifications in normal persons, a subset of persons with known peripheral deficits will also be studied.

The basis for this research concept in part resides in recent work that reported that application of static magnetic fields, as may be produced by permanent magnets, may in fact alter the vasoactive state of arteriolar vessels. Thus, Okano et al., (1999) reported an effect of a static electromagnetic field on skin microcirculation in rabbit ears by observing magnet-related changes in blood vessel vasomotion (a rhythmical and often spontaneous variation in microvessel diameter). An ear chamber was used, and the ear vasculature was exposed to static fields ranging from 10 to 100 Gauss for 10-minutes and changes in vasomotion patterns were assessed under vasoconsticted and vasodilated states induced respectively by infused norepinephrine (NE) or acetylcholine (ACh). The results suggested that the presence of the field altered the vasomotion patterns such that both the NE and ACh induced vasomotion were blunted. In a related study, in which the same experimental design and magnet were used, magnetic field exposure caused either an increase or a decrease in vasomotion within 10 seconds of field activation without pharmacological alteration of vascular tone (Ohkubo and Xu, 1997). These results have been interpreted to be consistent with the concept that a static magnetic field effect that causes vasodilation associated with high vascular tone and vasoconstriction associated with low vascular tone.

If permanent magnet therapy could be shown to be a modality that could easily and noninvasively modulate peripheral neurovascular responses, then there would appear to be a large potential clinical application. However, prior to assessing such magnetic therapy in patients, it is essential to determine whether permanent magnets do in fact affect vascular-sympathetic responses in humans.

We therefore propose to investigate this question using standardized sympathetic-vascular perturbations that cause vascular responses in paired tissue regions, one of which is exposed to the field of a permanent magnet, and one that is simultaneously exposed to a corresponding sham device. The principal quantitative assessment of responses, and hence the characterization of any possible relation between magnet and sympathetic response, will be via laser-Doppler blood perfusion measurements made simultaneously at the magnet and sham tissue sites. This initial research work is to be done on normal young (< 50 year old) and more mature (>=50 year old) male and female adult volunteers and also on a sub-set of persons with known peripheral vascular disturbances.

TITLE: Assessment of Local Tissue Water Changes Accompanying Manual Lymphatic Drainage (MLD) of Patients with Lymphedema

SUMMARY: The main goal of this research is to determine the effect of a single session of manual lymphatic drainage therapy (MLD) on local tissue water in limbs of persons being treated for limb lymphedema. The underlying hypothesis is that following a single MLD treatment, local tissue water will be measurably reduced and that such reductions may not be demonstrable by simple limb girth measurements alone as is current practice. A secondary goal is to determine the effects of MLD treatment on the mechanical properties of the tissue. Study participants will be persons (male or female) who will have been diagnosed with limb lymphedema (upper or lower extremities) and who will have been referred by their physician to a lymphedema treatment clinic for MLD therapy. Local tissue water, skin temperature, limb girth and tissue properties at a site of maximum observable limb edema will be noninvasively assessed before and after an MLD treatment session. In subjects with bilateral lymphedema, measurements will be made on one limb – the one with the greatest estimated lymphedema. In subjects with unilateral lymphedema, measurements will be made on the affected limb. Changes in tissue water, tissue properties and limb girth (pre-to-post treatment) will be used to assess effects of MLD therapy.

Lymphedema with associated arm swelling following surgical and/or radiotherapy for breast cancer is a major complication experienced by 20-30% of women breast cancer survivors. Incidence depends on several cofactors and the nature of the primary treatment, with incidence rates of 10% to over 40% reported for radical mastectomies combined with radiotherapy. About 70% of women who will experience lymphedema complications do so within three years of treatment but new cases continue to develop at about 1% per year . The impact of this chronic condition, which grows worse without treatment, is multidimensional and may include loss of self esteem, depression, chronic pain, severe mobility limitations and predisposition to serious limb infections. Lower extremity lymphedema is a complication of gynecological surgery in women and prostate surgery in men.

Therapy, in the form of manual lymph drainage (MLD), compression and exercises, when used as a part of complete decongestive physiotherapy, is useful for some persons to prevent the condition's progression and in some cases to partially reverse significant lymphedema already present. Preventative measures9 are also available but, the efficacy of these when in fact used is unknown. Presently, assessments of MLD therapy rely on measures of limb volume or girth changes. However, these changes are time consuming and may not be readily detected until substantial changes have occurred. As a result, possible modifications to therapy may be delayed. We believe that if there were an earlier indicator of therapy effectiveness this would be beneficial to both patient and therapist.

Thus the main goal of the proposed research is to determine the utility of a simple, rapid, noninvasive test that might allow for this earlier detection of local tissue water changes. This test has recently been shown to be an indicator of the presence of lymphedema in post-mastectomy women but has not been evaluated as an indicator of early tissue water changes associated with MLD. As previously noted, and elaborated upon in the Methods sections, the main test is based on the measurement of parameters sensitive to local tissue water, which is quite different than changes that might occur in the whole limb. We believe these measurements, in addition to providing data needed to accomplish our main goal, will also reveal important aspects about the lymphedema features via both the tissue water and the tissue property evaluations..

TITLE: The Effect of Sex Hormones on Tissue Water Content and Skin Blood Flow: Implications for Therapy of Premenopausal Women with Postmastectomy Arm Lymphedema

SUMMARY: Lymphedema with associated arm swelling following surgical and/or radiotherapy for breast cancer is a major complication experienced by about 30% of women breast cancer survivors. Incidence depends on several cofactors and the nature of the primary treatment, with incidence rates of 10% to over 40% reported for radical mastectomies combined with radiotherapy. Although about 70% of women who will experience lymphedema complications do so within three years of treatment, new cases continue to develop at about 1% per year. The impact of this chronic condition, which grows worse without treatment, is multidimensional and may include loss of self esteem, depression, chronic pain, severe mobility limitations and predisposition to serious limb infections. Therapy, in the form of manual lymph drainage, compression and exercises, when used as a part of complete decongestive physiotherapy is useful for some persons to prevent the condition's progression and in some cases to reverse significant lymphedema already present.

When this condition occurs in premenopausal women, a likely added complicating factor is a sex hormone related increase in interstitial fluid volume. We believe that one manifestation of this is to cause hormone-dependent increases in skin, dermal and subdermal water thereby exacerbating the edema of the lymphedematous limb in a cyclic fashion. Data on these effects in skin is absent from the literature. However, if true, it implies that optimal compression and exercise therapy might be tailored to the cyclical changes in limb edema. It is also likely that increased interstitial tissue water affects skin blood flow due to internal compressive effects on microvessels in a way similar to edema. This may partly account for cyclic changes in skin blood flow and vascular reactivity in premenstrual women.

If our hypothesis is correct, such cyclic changes in tissue water would not be restricted to women with lymphedema, but should be present in most premenopausal women. Because this concept is new, and there is no information in the literature to allow for an estimation of the magnitude of this effect, it is our initial objective to test our hypothesis by determining the cyclical changes in tissue water content, volume and skin blood flow in normal limbs of premenopausal women.

Our main hypothesis is that, compared to the early follicular phase, tissue water content will rise during the ovulation and luteal phases of the menstrual cycle coincident with the normal rise in estrogen, with a further rise in tissue water occurring in the mid-follicular phase coincident with the normal rise in both estrogen and progesterone. It is our plan to test this hypothesis by quantitatively measuring skin-to-subcutaneous water content and arm volume at these three strategic time points during the menstrual cycle. At these same times, the levels of estrogen, progesterone and testosterone and skin blood flow will also be determined.

A demonstration of the hypothesized changes would provide a firm foundation for the development of rationally based new or modified therapeutic strategies for treating lymphedematous limbs in premenopausal women. Without this initial study of normal limbs, investigations of lymphedematous limbs would not be scientifically based. Thus, we believe that this study has the potential to provide significant new information relevant to this widespread condition and lay the foundation for further targeted work. In addition to its potential relevance to lymphedema, this study will provide a basic physiological characterization of the relationship between hormone changes and tissue water content in normal premenopausal women.

A second objective of this research is to compare tissue water content of pre- and postmenopausal women and its relationship to skin blood flow. Since hormonal levels are low in postmenopausal women (without hormone replacement therapy, HRT) and hormone temporal variations are small by comparison with premenopausal women, tissue water and its possible effects can economically be made between these groups at one time point corresponding to low values of estrogen and progesterone. The significance of this pre- versus postmenopausal comparison relates to the dearth of quantitative information on the role of hormones in age-related changes in skin moisture and blood flow. These are factors that are linked to a variety of skin conditions, and in the case of persons with lymphedema, the development of infection and retardation of wound healing.

TITLE: Forearm Skin Tissue Water Assessed by Tissue Dielectric Constant: Spatial Variation

SUMMARY: Previous work has demonstrated the potential utility of using noninvasive measurements of the tissue dielectric constant (TDC) as an indicator of local skin tissue water to assess lymphedema and other changes in local tissue water. The anterior forearm is a particularly useful measurement target since upper extremity lymphedema often initially manifests itself by an increase in forearm TDC in patients who develop the condition. However, since previous measurements on the forearm have been restricted to a single standardized site located six cm distal to the antecubital space, it is completely unknown the extent to which forearm TDC values depend on the specific site measured. Knowledge of the potential anatomical variations in arm TDC values would aid in assessing the normal pattern of expected variations if the measurement is used clinically at sites other than the standardized site previously characterized. Thus the goal of the present research is to provide such reference data by characterizing the pattern of variation as determined by multiple TDC measurements on the forearms of 30 healthy young adult females. Females are to be used since the frequency of upper extremity lymphedema is predominantly a female issue.

TITLE: Effect of Changes in Skin Vascular Volume and Blood Flow on Skin Dielectric Constant

SUMMARY: The goal of this investigation is to determine the extent to which skin vascular volume and skin blood flow affects the tissue dielectric constant (TDC) of the skin. The TDC is an important non-invasive measure and indicator of skin tissue water and is used as an index of changes in local skin tissue water in conditions such as lymphedema and patients with breast cancer (1-7). Because skin vascular volume and blood flow vary among patients and also vary in the same patient at different times, it is important to determine if and to what extent these factors impact the TDC measurement. Information bearing on this issue will be determined in this study by increasing and decreasing skin vascular volume and by modifying blood flow and determining the effect of such changes on the measured values TDC. Blood volume of the forearm will be increased by inflating a standard blood pressure cuff around the bicep to a pressure of 50 mmHg for four minutes. Blood volume will be decreased by supporting the subject's arm above heart level for five minutes. All procedures and measurements will be done with subject supine. Each maneuver will also modify skin blood flow which will be measured with the non-invasive laser Doppler method. The acclimation, setup and measurement sequence will require one subject visit lasting about 60 minutes. A total of 40 subjects will be recruited for participation in this research study.

TITLE: Local Tissue Water Variations Among Different Races Measured via Tissue Dielectric Constant

SUMMARY: The purpose of this investigation is to quantitatively determine local skin tissue water (STW) via measurements of skin tissue dielectric constant (TDC) in five distinct racial groups; Asian Indians, Hispanic, Blacks, Whites, and Asians. The main purpose of these measurements is to characterize the distribution of TDC among these groups, to determine if skin variations or other differences among the groups result in significant variability in STW as determined via TDC measurements. A second purpose is to determine if local tissue water is quantifiably related to the whole body fat and water percentages as determined using whole body bioimpedance measurements. We will be assessing the TDC in three areas bilaterally; anterior chest, anterior forearm, and posterior medial malleolus region. We will be using two probes that measure to different depths: 2.5 mm and 5.0 mm. Both will be used to assess the TDC in the subclavicular region (anterior chest wall) and the anterior forearm (antecubital fossa). Only the 2.5mm probe will be used to assess the posterior medial malleolus region. Whole body water percentage will be determined via bioimpedance measurements. All measurements will be taken with the patient in the supine position. Set-up, patient acclimatization and measurements will take approximately 30 minutes to complete. We plan to recruit 100 subjects to participate in the study consisting of 10 males and 10 females from each of the above mentioned groups. All data and consent forms will be stored in separate locked cabinets in room 1313 of the Terry building.

TITLE: Localized Tissue Water Content of Male Arms Assessed by Tissue Dielectric Constant (TDC) Measurements

SUMMARY: One in eight females in the USA will develop cancer in her life time but the incidence of male breast cancer is much lower and has been estimated as 1.06 per 100,000 men. Because of the relatively rarity of male breast cancer the potential complications such as post-surgical lymphedema have not been well studied. Further, there is essentially no reference data describing the normal amounts and variations of arm tissue water in males. This absence of reference data makes it difficult to determine what levels of tissue water differences between at-risk and contralateral arms constitutes a complication of breast cancer related treatment including surgery and radiation. The worldwide variation of male breast cancer resembles that of breast cancer in women, with higher rates in North America and Europe and lower rates in Asia.

The mean age at diagnosis for men with breast cancer is 67 years, which is approximately 5–10 years older than the average age at diagnosis for women. As in breast cancer in women, the incidence of breast cancer in men has increased, approximately about 26% over the past 25 years. Male and female breast cancers share many common risk factors such as advancing age, family history, BRCA2 gene mutation, and obesity. However others are male specific that include the following conditions. Klinefelter Syndrome which is a condition occurring in men with a XXY genotype, Androgen receptor mutation in which the androgen receptor suffers a change in structure and proper function, CYP17 mutations leading to pseudohermaphroditism, Cowden syndrome which is characterized by multiple tumor growths and predisposition to certain cancers, mutations in CHEK2, a gene which is activated in response to DNA damage, increased endogenous estrogen levels, and other testicular disorders.

Other factors linked to cancer in general include increased alcohol intake and exposure to estrogens via diet and household products. Owing to the rarity of male breast cancer, few epidemiological or clinical trial data are available. Therefore, our understanding of the disease comes from studies of female breast cancer that might be painting an inaccurate picture when it comes to contributing factors, age at presentation, evaluation and treatment strategies. Recent studies show that gender -related differences do exist, therefore, epidemiological and clinical trials are needed to clearly delineate the specifics of breast cancer in males. Men and women may respond differently to therapeutic interventions, drug regimens and their undesirable side effects probably exist. One such effect is the development of lymphedema after a patient undergoes breast surgery. In the USA, the incidence of cancer-associated lymphedema occurs in up to 75% of cases, depending on tumor type.

Lymphedema once present tends to get progressively worse without treatment and can result in physical deformity, discomfort, pain, loss of mobility, skin breakdown and infection with an overall significant negative impact on the patient's health and well being. As such, interventional therapy is best when initiated as early as possible. This underscores the need for research efforts to detect its presence as early as possible. Prior work has utilized biophysical measurements to establish normal ranges of reference values that could serve to help detect changes in tissue water in females. The purpose of the present research is to develop reference ranges specifically for males. The anticipated utility of such a reference data set is its potential use in the early detection of sub-clinical lymphedema in males diagnosed with breast cancer and to be treated with surgery and or radiation therapy.

TITLE: Skin Tissue Water as a Determinant of Transepidermal Water Loss (TEWL)

SUMMARY: Previous work has demonstrated the utility of using noninvasive measurements of the skin's tissue dielectric constant (TDC) as an index of local skin tissue water. Another widely used skin assessment test measures transepidermal water loss (TEWL) that is an index of water flux from skin to the environment. TEWL is most often viewed as being mainly dependent on the integrity of the epidermal stratum corneum (SC) barrier function. The investigators believe that TEWL is also importantly affected by the relative tissue water content within the epidermal-dermal-subcutaneous fat compartment. If true this concept would alter the current view on the interpretation TEWL and related information. The main goal of this research study is to test this hypothesis. TDC, TEWL and an SC water content index will be non-invasively measured at 17 anatomical sites to provide the wide range of parameter values needed to test the hypothesized relationship. The data so obtained will also be useful to independently characterize the normal anatomical variations in these important assessment measures and serve as future reference for subsequent clinical and research related undertakings by us and others. Because of known differences in male-female skin thickness (16) this seminal study will initially investigate only females to avoid unnecessary confounding effects. Thus it is planned to evaluate 30 female volunteers of various ages each of whom will be evaluated during one measuring session. It is estimated that the full protocol, including initial set-up, subject acclimation and the full measurement set will take less than 60 minutes.