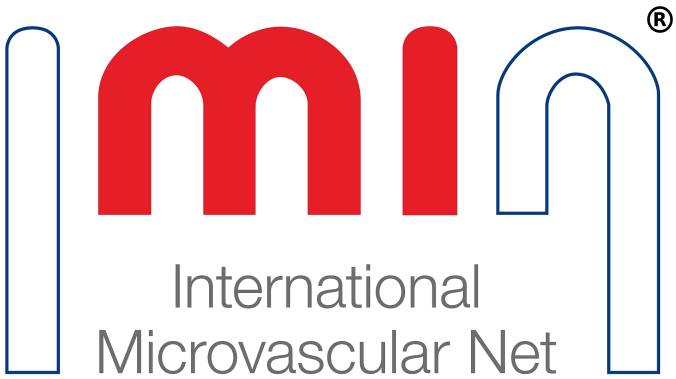
PROCEEDINGS
1ST INTERNATIONAL CONFERENCE



Editors
Michael A. Lang, PhD
Joshua D. Berka, NMD

Orlando, Florida USA - 24 September 2016

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ABSTRACT
Microcirculation research is on a path to establishment in mainstream medicine. An independent institution - International Microvascular Net (IMIN) - was founded in Brussels for the objective communication of modern 'Hightech Solutions'. Scientists and clinicians representing an array of disciplines collectively discuss the safety and efficacy of PEMFT. Research helps understand physiological mechanisms taking place at the microcirculatory level in health and disease. The approach includes the integration of traditional systemic physiological parameters, blood biomarkers, and variables such as microvascular permeability, leukocyte- and platelet-endothelial interactions and local blood flow measurements in addition to *in vivo* glycocalyx determinations. Translational physiology is in focus with the main questions related to treatment of ischemia and shock, primarily on mechanisms at the level of the microcirculation. Current research on the biophysics of micro- versus macrocirculation activation through a biorhythmically defined stimulus signal continues to advance the field in a measurable way. A review of developing diagnostic technology is provided to evaluate microcirculatory function. The evolution of PEMFT in science and medicine is traced and merges into an in-depth discussion of microcirculation as the cornerstone of life. The effects of dysfunctional circulation on cardiovascular health are defined as are several profound impacts on vascular pathology and chronic disease triggered by inflammation. Maintenance and sustenance of the structural integrity and optimal function of the arterial system is emphasized. Current PEMFT application as a clinical tool in Integrative Medicine is highlighted as is select clinical experience of its effects on vision.

Contact information:
Mr. Fred Unrath
International Microvascular Net
info@imin-org.eu
www.imin-org.eu

PROCEEDINGS OF THE 1ST INTERNATIONAL IMIN CONFERENCE
24 September 2016 - Orlando, Florida

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WELCOMING REMARKS

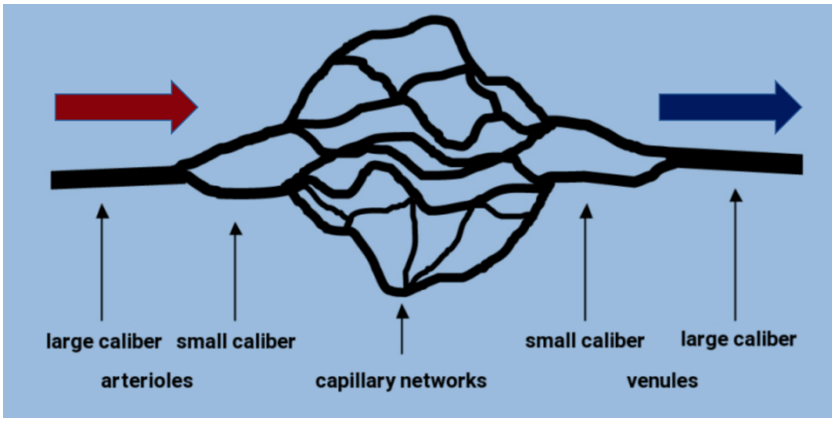
Ulises Baltazar, MD, FACS, RVT
Houston Methodist
Medical Office Building 3
16605 Southwest Fwy #505
Sugar Land, TEXAS 77479 USA

The mind is not a vessel to be filled, but a fire to be kindled
Plutarch, Greek biographer and essayist

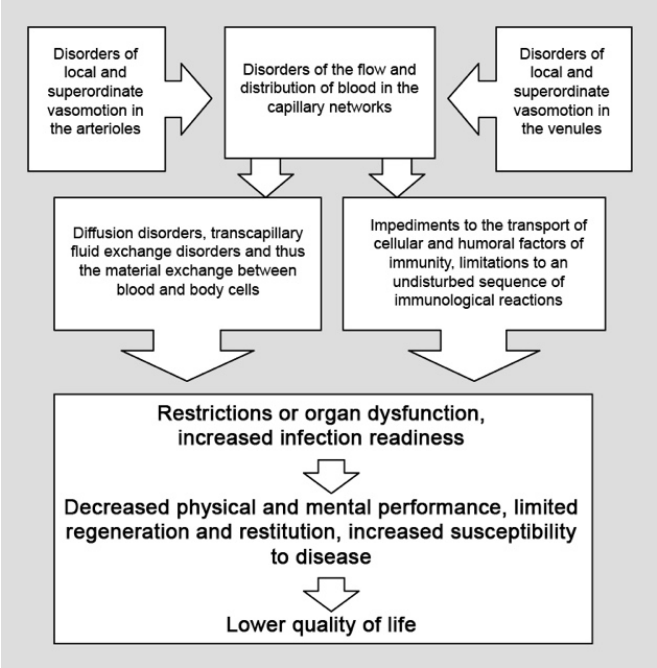
I extend a warm welcome to the first International Microvascular Net Conference in Orlando, Florida. Today research scientists, medical doctors, clinicians, chemists, biologists, philanthropists and visionaries in general have gathered to discuss the exciting field of microcirculation. This conference is not industry driven nor does it strive to achieve any commercial goals. It is a purely scientific event, hence the opening quote.

Electromagnetic fields are their own entities and can be manipulated to acquire their own specific characteristics. The Pulsed Electromagnetic Fields (PEMF) per se will be reviewed for these different parameters: wave form or signal; frequency; intensity; and clinical patient outcomes.

The transport phenomena of material exchange between blood and tissues and the first steps of cellular and humoral immune reactions are realized in the area of microcirculation, the area of the smallest blood vessels and lymphatics. Microcirculation is the area of human blood circulation (arterioles, capillaries, venules, initial lymph), the important functional part of the circuit. The efficiency of the nutritional and immunological benefits determines the functional state of organs and the body's defense mechanisms. Various pathological changes in the flow properties and conditions of the plasma-blood-cell mixture in the microvascular network can limit or interfere with the neural and humoral regulation of organ perfusion. This can result in reduced or impaired organ function and an increased susceptibility to inflammation and subsequent infection.



It is now generally recognized that a large number of microcirculatory disorders are based on clinical syndromes and their disease progression is accompanied by their own dynamics. Drug options for the treatment of microcirculation disorders are currently limited. As a result, the foci of urgently needed research are disorders of local and higher-level perfusion regulation (spontaneous, autorhythmic vasomotion of small-caliber arteriole sections and the neurologically and/or humorally controlled vasomotion of large caliber arteriole sections) and the distribution of the plasma-blood-cell mixture in the capillary networks. Causal drug treatment of many of these disorders is not known, rendering complementary, therapeutically effective treatment options of great importance. New research findings have shown that an effective non-pharmacological influence of impaired vasomotor processes is possible expanding the limited standard width of tissue perfusion to a complementary, therapeutically relevant extent.



Adequate organ blood circulation can be impaired by a number of diseases, e.g. blood loss, heart and lung diseases or vascular damage. Circulatory dysfunction is found in cases of different types of shock with a massive loss of blood pressure such as cardiogenic and septic shock. Microcirculatory dysfunctions are implicated for the high death rate among shock patients. It is possible to stabilize the macrocirculation using measures to raise blood pressure, diuresis or liquid substitution, but these do not necessarily stabilize the dysfunctional microcirculation. It is therefore of significant clinical interest to improve these patients' dysfunctional microcirculation in a targeted way, in particular because at present there are no promising medical treatment options. Research is underway to determine whether the functionally impaired microcirculation of intensive care patients with multi organ-dysfunction syndrome (MODS) can be improved with electromagnetic fields of low flux density with biorhythmically defined impulse configurations. This could demonstrate a possible approach to physical therapy for the treatment of the MODS patients' impaired microcirculation, which could be applied in a complementary manner as an alternative to previous medical measures having lower rates of success.

Physical vascular therapy aims to stimulate inadequate regulation of organ blood circulation so that the body's own mechanisms are able to rectify the microcirculatory dysfunction. The microcirculation is not only an important reservoir of blood, influencing blood pressure and supporting heat transfer, but is also responsible for the exchange of substances with tissue cells. It is also the location where the initial steps of immune reaction take place. The functional level of microcirculation and its range of regulation, the so-

called microcirculatory reserve, are thus decisive for the functionality and performance of the organs and immune defense.

It is now generally recognized that numerous diseases are due to microcirculatory dysfunction or that the progress of the disease is significantly influenced by the function of microcirculation. With regards to organ circulation, the most important microcirculatory regulation mechanism is the arteriolar vasomotion. In the large-caliber arteriole sections, there are receptors for neural controls and humoral substances for the supraordinate regulated vasomotion processes. In the small-caliber arteriole sections, which are connected immediately before the capillary networks, there are in contrast spontaneous, autorhythmic vasomotions with their own biorhythm. In cases of dysfunction or disease, both these vasomotion phenomena would not be in harmony with each other.

Medicinal therapy options are available for large-caliber arteriole sections. Locally regulated, spontaneous-autorhythmic vasomotion in the small-caliber arteriole sections, in contrast, cannot be influenced with pharmaceutical means. The options for treating microcirculatory dysfunctions are limited in this way. A physical energy transfer using a specific biorhythmically defined stimulus can however be used for therapy. New research findings have shown that an effective non-medicinal influence on dysfunctional vasomotor processes is possible, and that in this way the limited range of regulation in the tissue circulation can be expanded to a complementary/therapeutically relevant extent.

Physical vascular therapy has high levels of preventive, therapeutic and rehabilitative potential. Despite the great significance of the technology for prevention and the economic benefits resulting from it, physical vascular therapy has not yet been successfully established on a widespread basis. In order to change this first IMIN Conference was convened to explore the possibilities of the method and to disseminate the results of the studies at an international level.

INTERNATIONAL MICROVASCULAR NET (IMIN) GOALS AND VISION

Fred Unrath
President
International Microvascular Net
Gottlieb-Daimler-Strasse 80
72290 Loßburg, GERMANY

Microvascular High Tech Solutions

Modern medicine is increasingly recognizing the complex connections of the entire vascular system and focusing on the interplay between the large vessels and the microvessels in the peripheral circulation. Arteries and veins have been scientifically documented in basic research for many years. However, it is only recently that the significance of microvessels has been thoroughly investigated. These findings give rise to new hope for excellent therapeutic approaches for the entire vascular system. Thus it is now time to offer an international platform for the various findings and experience for a scientific exchange in this field. The time is ripe for the International Microvascular Net (IMIN).

Our Goals

The International Microvascular Net is the result of several years of discussions with renowned scientists with vast experience of the connections within the entire vascular system. We want to build a synergized international network for this knowledge, which is available in many places to document scientifically proven therapeutic approaches for the entire vascular system and, if necessary, also define new therapeutic approaches. At the same time, we are committed to getting such new procedure made refundable – the focus being that of a basic requirement. Together with competent scientists, we are supporting the definition of new standards at an international level for patient benefit and their awareness of reducing therapy costs.

Our Activities

We initiate collaborations and scientific studies with experts in microcirculation research. We consider clear definitions and terminology as well as inclusion of appropriate and acceptable collection and diagnostic procedures to be a basic prerequisite for achieving scientific consensus. By synergizing various therapeutic approaches, we are contributing to a further improved range of therapy offers in microcirculation. The knowledge of the significance of healthy microvessels for health and their interactions with arteries and veins is for us a vital prerequisite to move this field of medicine further into the spotlight of science, research and daily practice. For this reason, we fully support the dissemination of this knowledge. In addition, we are committed to establishing clear therapy structures and sequences in line with the definitions specified by World Health Organization: prevention (primary prevention), treatment (secondary prevention), and follow-up care (tertiary care). We coordinate EU-research projects and maintain contacts with international institutes and experts in the field of microcirculation research.

RESEARCH IN MICROCIRCULATION IN HEALTH AND DISEASE: AN OVERVIEW

Ivo Torres Filho, MD, PhD
U.S. Army Institute of Surgical Research
3650 Chambers Pass
JBSA Fort Sam Houston, TEXAS 78234 USA

Introduction

In this brief review the basic structure of the microcirculation is presented. Some relatively recent research findings made in this field will be also reviewed with regards to their impact on diseases or pathologies of clinical significance. In each process described below, the focus will be on cellular and vascular events. In many (if not all) cases a host of molecular events takes place simultaneously but they will not be reviewed due to the limited scope of this overview.

One of the reasons for convening in this conference is that for years the treatment of patients has been based on the recovery of systemic parameters like arterial blood pressure. Unfortunately, sometimes the patient dies despite this recovery. Perhaps we have been looking at the wrong parameter, i.e., the blood pressure was reestablished but the microcirculation remained shut down. Currently the best parameters to be monitored for the best outcome after some life-threatening emergencies are still unknown. Some answers may lie in the microcirculation! Similar statements may be true for the treatment of many diseases. Modulation of microvessel activity may be essential to alter the whole organ function.

The survival, integration and proper functioning of organs depends upon suitable transport and exchange of various molecules between the flowing blood and parenchymal cells. This continuous process takes place at the level of the microcirculation, and includes gases such as oxygen (O_2) and carbon dioxide (CO_2), nutrients, waste products, hormones as well as various molecules and cells linked to the immune response, inflammation and coagulation. Since the system is so deeply involved in nearly all physiological functions, it is not surprising that all pathologies (and potential treatments) will implicate one or more elements of the microcirculation.

Microcirculation – Structure and Function

The microcirculation includes the most distal part of the vascular system, typically comprising vessels with an internal diameter of less than 100 μm (Fig. 1). These microvessels (arterioles, capillaries, or venules - depending on anatomic features and direction of blood flow) form complex networks in most tissues (Popel et al. 2005). Several arterioles connect to many capillaries that drain to numerous venules. Many vessels are interconnected and the internal diameter of each input arteriole is variable. Therefore, local variables such as pressure, flow, oxygenation, and hematocrit, will vary depending on the balance of constrictive and dilating influences actuating on different arterioles. Moreover, rheological factors such as blood viscosity and leukocyte adhesion may play a role in local blood flow and O_2 distribution. Since the microcirculatory vessels are embedded within the organs, the communication between parenchymal tissue cells and the flowing blood is a critical function provided by the microcirculation. This exchange maintains cell survival and integration through processes that include passage of water, solutes, proteins, and even some blood cells through the microvascular wall. The microcirculation is involved in the transport of drugs and medications as well as in the control of temperature. The lymphatic vessels are also included in several microcirculatory studies.

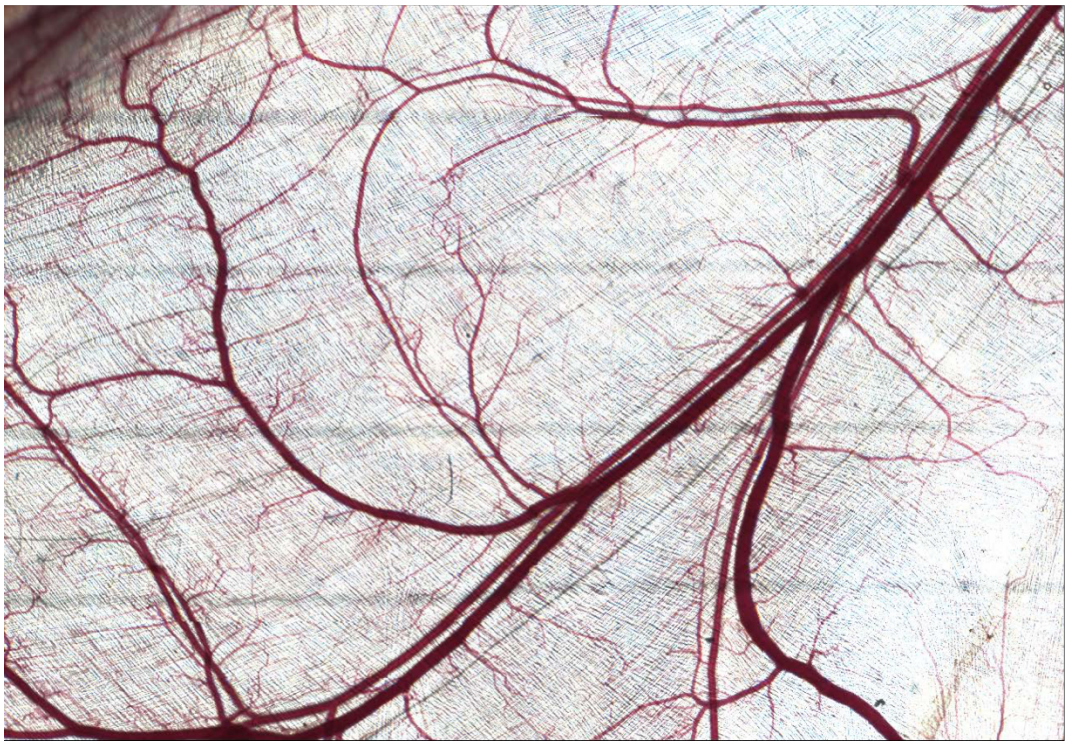


Figure 1. Microvascular network of the exteriorized cremaster muscle in an anesthetized rat. Reproduced with permission from Torres Filho et al. (2012).

Glycocalyx

The endothelial glycocalyx is a layer covering the lumen of the blood vessels. The glycocalyx protects and exerts several physiological functions related to permeability, flow, cell adhesion, and coagulation. The glycocalyx can be studied *in vivo* using microscopy imaging techniques. A compound (fluorescent Dextran) that does not penetrate the glycocalyx is injected into the bloodstream. The lumen of the vessel and the diameter of the fluorescent column are measured using the images; by comparing the difference between the two measurements, the glycocalyx thickness is established (Torres Filho et al. 2013). This thickness can decrease after hemorrhage (post-hemorrhage degradation or shedding).

These are several situations and diseases where the glycocalyx thickness has been shown to decrease or disappear (e.g., dialysis, high fat diets, hyperglycemia, diabetes, inflammation). The glycocalyx can also decrease following hemorrhage (post-hemorrhage degradation or shedding), both in humans and experimental animals. Treatment with solutions like lactated Ringer's or saline offers no improvement but plasma can allow the glycocalyx to recover (Torres et al. 2013; 2016a). This is important for situations when hemorrhages occur, e.g., car crash or soldiers' injuries on the battlefield. Which solution should be used (in case of hemorrhage) to recover the small vessels (microcirculation) as well as the arterial blood pressure?

Vasomotion and flowmotion

Vasomotion is the spontaneous cyclical variations in the lumen of vessels. These oscillations can have various frequencies but should not be confounded with different, unrelated phenomena such as heart rate. In the case of shock resulting from blood loss the vasomotion increased in animals treated with hypertonic saline solution both in vessels that had vasomotion before the treatment during hypotension and in vessels that did not (Torres Filho et al., 2001). The treatment that improved outcome in these animals also improved vasomotion. While cause and effect could not be precisely established in these experiments, these findings

deserve further investigation. Moreover, vasomotion occurs in normal healthy people and animals.

When diameter in a vessel changes, the flow produced downstream also changes. Changes in diameter are called vasomotion, while downstream changes are named flowmotion. In a recent study, diabetic ulcer patients treated with hyperbaric oxygen therapy (HBOT) showed improved condition of the ulcer and simultaneous changes in vasomotion/flowmotion activity (Fig. 2). The authors concluded that flowmotion dynamics may partly explain the positive effect of HBOT on the healing process of a diabetic ulcer (Balaz et al., 2016).

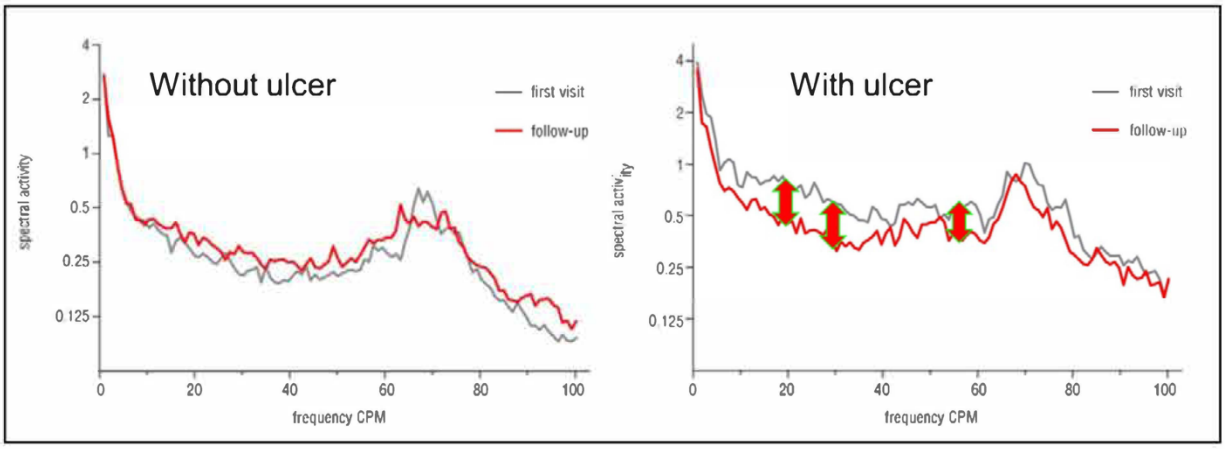


Figure 2. Hyperbaric oxygen therapy changes flowmotion dynamics that may be involved in the healing of ulcers in diabetic patients. Reproduced with permission from Balaz et al. (2016). Colors and arrows added for clarity and emphasis.

Thrombus formation *in vivo*

When the inside of a vessel is damaged using a laser, passing blood platelets immediately attach to the vessel wall (endothelium). It is a precursor to mitigate vessel perforation, i.e., the platelets form a clot. Since some of these platelets have been made fluorescent, they are easier to visualize, record and count. This experimental procedure allows *in vivo* testing of the functionality of platelets, and the efficacy of platelets that have been under various conditions of storage (different temperatures and periods of time). These techniques use a special microscope, and may help to find fluids to treat soldiers with hemorrhage on the battlefield (Torres Filho et al., 2016b).

Inflammation

Many steps of the inflammatory process occur at the level of the microcirculation. Leukocytes (white blood cells), as part of the defense mechanisms, intermittently roll along the inside wall of post-capillary venules and scan for bacteria, foreign particles, etc. Various other leukocyte activities have been described such as firm adhesion to endothelium and transmigration (Popel et al. 2005). The inflammatory process also includes changes in microvascular permeability, diameter and flow.

Oxygenation

Oxygenation can be studied through PO_2 (oxygen partial pressure) and SO_2 (oxygen saturation) measurements in the microcirculation. Vessel diameter and blood flow can also be measured in arterioles and venules allowing the determination of O_2 delivery and O_2 consumption. PO_2 measurements in normal tissues and human tumors have been made with techniques such as the phosphorescence quenching (Torres Filho et al., 1993). The PO_2 in certain areas within a tumor starts high but rapidly decreases, becoming very low over relatively small distances (Torres Filho et al., 1994). This is critical because when oxygenation is low (hypoxia) tumors become resistant to radiotherapy.

Moy et al. (2011) and Styp-Rekowska et al. (2007) measured SO_2 using different methodologies and achieved results that allowed relatively detailed maps of the SO_2 distribution in large areas of the microcirculation.

Human Microcirculation

Using non-invasive techniques such as orthogonal polarization spectral imaging and side stream dark field microscopy the human microcirculation (especially the sublingual mucosa) can be studied (Ward et al., 2010). Different situations have been examined such as septic shock, hemorrhagic shock, heart failure, and sickle cell disease. These methods have been extensively used in Europe but also in North and South America (Massey et al., 2016).

Summary

There are new methodologies for examining various microcirculatory functions *in vivo*. These data suggest that the modulation of the microcirculation can affect or improve the quality of life and in many circumstances mean the difference between life and death.

Disclaimer

The opinions and assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the U.S. Department of Defense. This study has been conducted in compliance with the Animal Welfare Act, the implementing Animal Welfare Regulations, and the principles of the Guide for the Care and Use of laboratory Animals, using protocols approved by the Institutional Animal Care and Use Committee of the U.S. Army ISR.

Acknowledgments

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MICROCIRCULATION IN THE FOCUS OF RESEARCH

Rainer C. Klopp, MD, PhD
Institut für Mikrozirkulation
Biomedizinischer Forschungscampus Berlin-Buch
Robert-Rössle Strasse 10
13125 Berlin-Pankow GERMANY

Introduction

Profound concepts of biomechanical regularities of circulatory blood flow are needed for physiological observations and their possible subsequent clinical inferences.

In consideration of blood circulation *in toto* a fundamental biophysical difference exists between the blood flow in vessels > ~100 μm diameter and those < 100 μm, which is defined by the Reynolds number (Re). The Reynolds number is dimensionless and describes the ratio of inertial forces to viscous forces in a flowing fluid. It quantifies the relative importance of these two types of forces for given flow conditions and is a guide to when turbulent flow will occur, as in blood for example:

$$\mathrm{Re} = \frac{v \cdot l}{\eta}$$

where v is the current speed, l the characteristic length and η the kinetic viscosity of the current's medium (blood).

A value of Re > 1 characterizes the macrocirculation (arteries and veins), while Re < 1 characterizes the microcirculation (arterioles, capillaries and venules). In the microcirculation blood changes its flow characteristics as a consequence of certain segregation phenomena of the plasma-blood cell mixture whereby the enormous peripheral flow resistance is overcome and a blood circulation is even possible.

In the macrocirculation a certain cardiac output (CO) is moved in the vasculature through the contraction force and myocardial contractibility of cardiac activity (Stroke Volume - SV, and Heart Rate - HR). The CO effects the necessary pressure differential between arterial (high pressure) and venous (low pressure) systems.

$$CO = SV \,.\, HR$$

The peripheral flow resistance and the elastomechanical behavior of the artery walls (in particular the aorta) dictate the blood flow characteristics and periodicity in the macrocirculation.

The microcirculation is functionally the most important part of the human circulation as the locus of material exchange with the tissue cells and the first site of immunoreactivity. The known fluid mechanics laws, derived from the Euler continuity equation, lose their validity in this area. Blood in the microcirculation is a mixture of plasma and cells of varying sizes that no longer approximates the behavior of a physical fluid but rather resembles bulk material on a conveyor belt.

Dysfunction or disturbances of the microcirculation contribute to a large number of illnesses. These microcirculatory limitations are either causal factors or contributory to the course of the disease. Disturbances in the microcirculation are often triggered by disturbances in the macrocirculation but show a repetitive tendency to develop with their own dynamic, often therapy resistant, substantial independence

from macrocirculatory events. For example, *Ulcus cruris* with stage III chronic venous insufficiency, circulatory disorders and necrotic formations with *Diabetes mellitus* Type II, and various chronic wound healing disorders.

A demand-oriented circulatory adaptation in response to diverse organ material exchange requirements is the most important prerequisite for a high human physical and mental performance capacity. Maintenance or regeneration of an efficient regulation of blood circulation to organs is therefore central to prophylactic and therapeutic measures. An optimal regeneration, restitution or healing progression is not possible without adequate participation of the microcirculation.

To understand the microcirculation's physiological laws impacting the local regulation of blood circulation in organs, their dysfunction and possible therapeutic options, several physicochemical, physiological, flow-mechanical and elastomechanical parameters need to be taken into consideration.

Aspects of current biophysical and physiological knowledge of the microcirculation

The flow area of the microcirculation encompasses the arterioles, capillaries and venules (Fig. 1). The wall architecture of the large caliber arterioles consists on the lumen side of a singular endothelial layer, the basal membrane and two to three layers of smooth muscle cells. The small caliber arterioles only have a single layer of smooth muscle cells at their disposal that become intermittently spaced towards the capillaries. A corresponding situation occurs in the small- and large-caliber venules. The capillary walls exist only of the lumen-surrounding endothelial sheath and basal membrane.

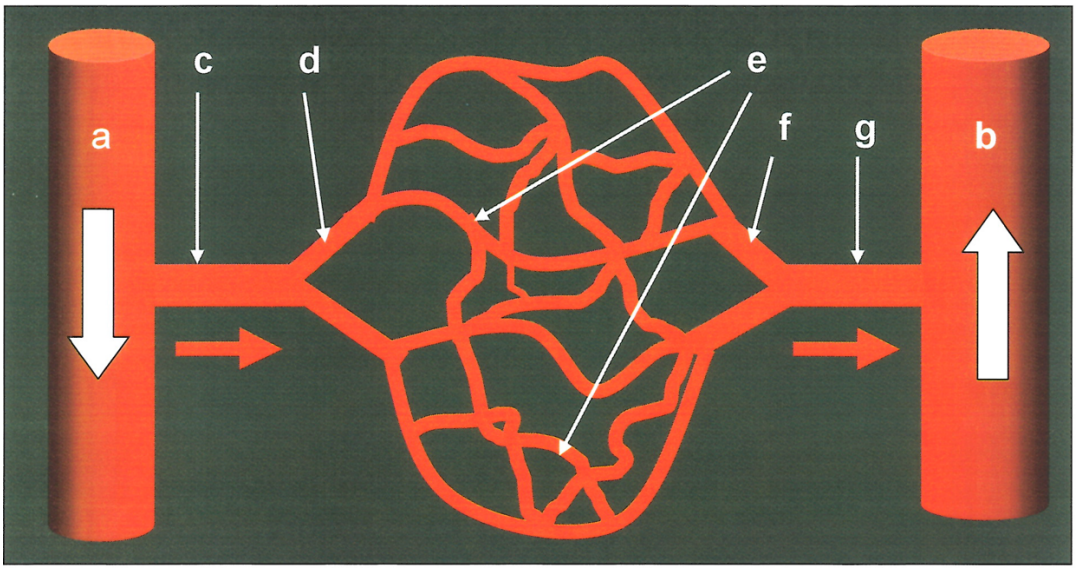


Figure 1. Schematic area of microcirculation between a small artery (a) and a small vein (b); large caliber arteriole branch (c), small caliber arteriole branch (d), capillary network (e), small caliber venule branch (f), large caliber venule branch (g).

The material exchange occurs in the capillaries. The blood plasma substrate transports nutrients in and metabolic end products are transported out. The transit pathway is the transcapillary fluid current along a capillary due to the interactions of hydrostatic and colloid osmotic pressures in the arterial and venous flanks of a capillary. Further, plasma factors of the immune system are also transported in the plasma. The hemoglobin in the erythrocytes are responsible for the exchange of blood gases (oxygen and carbon dioxide) due to their respective concentration gradients between blood and tissue cells. The paradigm of a

dysfunctional microcirculation is the disturbance of diffusion. To focus the consideration on this part of the material exchange, the diffusion law generally states:

$$\Delta m = D\frac{A \cdot \Delta c \cdot \Delta t}{\Delta x}$$ where m is mass, D the diffusion constant, A the area through which a diffusion takes place, c the concentration, t the time and x the diffusion path.

Of particular biological interest is the relationship between diffusion path and diffusion time, which cannot be simply inferred from the diffusion law. Solving the diffusion equation for D:

$$\Delta x \sim \sqrt[2]{\Delta t}$$

This means that a ten-fold increase in the diffusion path x results in a one hundred-fold increase of the diffusion time. This dependence of the diffusion time on the diffusion path is the biophysical cause for the varying capillary thicknesses of the different tissues corresponding to their material exchange requirements. Consequently, the disturbed microcirculation is in the first order a distribution disruption of the plasma-blood cell mixture in the capillary network.

For a principal consideration of current flow the simple assumption is made that blood behaves like a homogenous fluid (continuum mechanics). The flow stream Q is the Quotient of a flow volume ΔV over the unit of time Δt:

$$Q = \frac{\Delta V}{\Delta t} \qquad \left[\frac{\mu m^3}{\text{sec}}\right]$$

A prerequisite of any flow is the pressure differential Δp, and furthermore the flow resistance R must be considered (OHM law):

$$Q = \frac{\Delta p}{R}$$

The flow resistance R in a pipe is dependent on the radius r of the vessel, the overall length of the single vessel l_1, and of the quotients of the shear stress τ and the shear rate γ in the pipe diameter, resulting in:

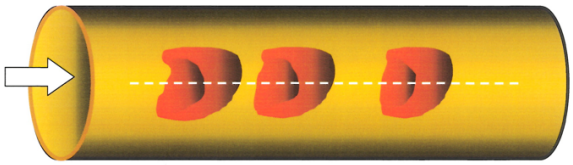
$$Q = \xi \frac{r^4 \cdot \Delta p}{\frac{\tau}{\gamma} \cdot \sum_{i=1}^{i=n} l_i}$$ where ξ = proportionality factor

This equation can strictly only be applied qualitatively because of the idealized acceptance of homogeneity of the blood as a circulation medium. Of eminent significance is the dependence of the flow stream Q on the Radius r of the vessel:

$$Q \sim r^4$$

Under the assumption that all dimensions remain constant, a doubling of the radius r means a 16-fold increase of the flow stream Q. A resultant increase in blood flow to the capillary network is commensurate with the increase in radius of the large caliber arterioles. Figure 2 illustrates an intravital microscopic observational example. As can be inferred from the above-mentioned flow equation, a lowering of the flow resistance is coupled to this circulation flow. The state of contraction in the large caliber arteriole segments is realized by neural or hormonal instructions to the smooth muscle cells in the microvasculature wall (formerly known as resistance vessels).

The full explanation for regulation of organ perfusion is not yet complete. A further biophysical law is to be considered to explain the segregation of the plasma and blood cells in microvessels < 100 µm.



Note that flow velocity of the circulation causes blood cells and plasma to move at differential speeds in the circulation, which causes their segregation.

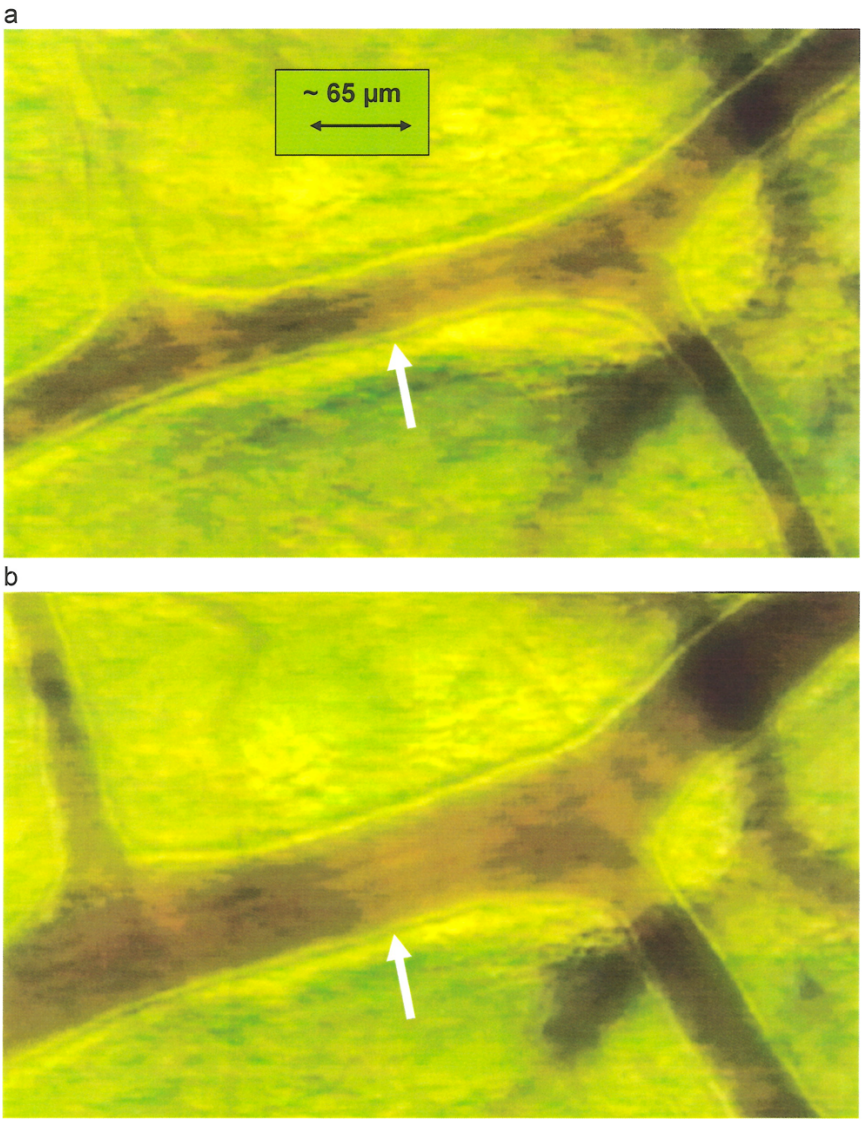


Figure 2. Intravital microscopic observational example of an intestinal arteriole (arrow) showing differential vasodilatation of the same microvasculature region at two separate observational points in time.

The particles with a higher kinetic energy (mass) in a fluid medium have, for physical reasons, a higher flow velocity. In the context of blood as a flow medium, those particles would be the blood cells, which are directed towards the axial current. The slower blood plasma moves preferentially in the peripheral currents. This separation of the plasma-blood cell mixture is more pronounced as the flow velocity of the blood increases.

The consequences of shear stress τ and shear rate γ for flow stream Q in the above-mentioned equation can be clarified by a simple experiment under idealized assumptions (Figure 3). Assume a fluid between two plates broken down in lamellae on surface A. The lower plate is motionless and only the upper plate moves through force F parallel to the fluid lamellae. Observations show that because of the differential effect of inter-lamellar frictional force F_R the individual lamellae are moved along at different speeds. A velocity gradient now exists $\Delta v/\Delta x$, mentioned above. The Newtonian friction law applied to solve F_R is as follows:

$$F_R = \eta^* A \frac{\Delta v}{\Delta x}$$

where η is the proportionality constant (material constant of the flowing medium, kinematic toughness-viscosity). Because the idealized assumptions of the flow medium are not strongly realized, a sham-viscosity η^* is used in the following viscosity equation, yielding:

$$\eta^* = \frac{\left(\frac{F_R}{A}\right)}{\left(\frac{\Delta v}{\Delta x}\right)} = \frac{\tau}{\gamma}$$

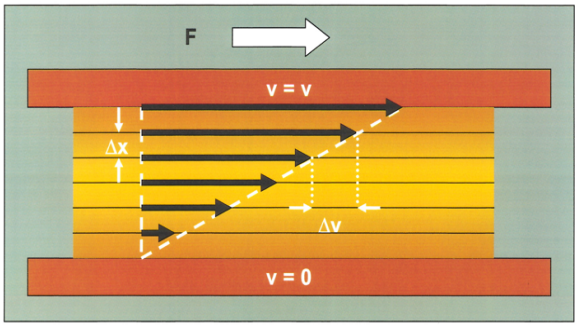


Figure 3. A flow profile in a flow-through pipe.

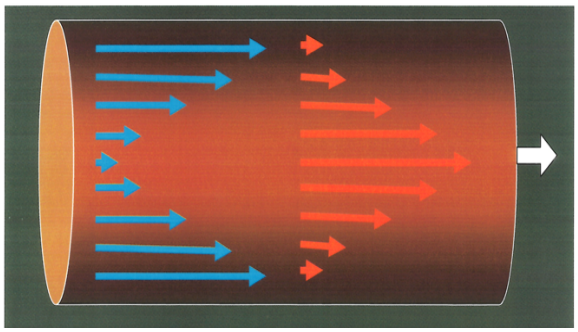


Figure 4. Shear stress τ and shear rate γ in pipe

The relationship of shear stress τ and shear rate γ is hereby clarified in the conditional equation of the flow stream Q of the blood. In a flow-through vessel the velocity of the flow medium v is highest when the frictional forces are lowest (in the axial current) and the opposite when the velocity is lowest and the frictional forces highest (at the vessel wall). The flow velocity also has an effect on the morphology of the red blood cells. The cell membrane displays certain plasticity characteristics (stiffness, rigidity) that are influenced by the momentary flow velocity. Figure 5 illustrates schematically that with increasing contributions of flow velocity blood becomes increasingly thinner.

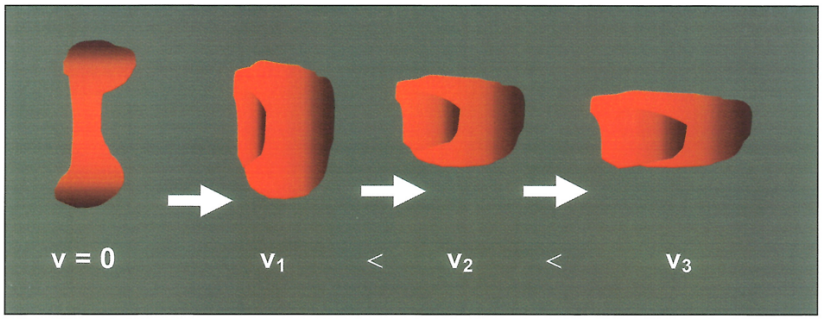


Figure 5. Schematic cross-sectional representation of red blood cells at varying flow velocities v.

The next consideration is the distribution of the plasma-blood cell mixture in the microvasculature, in particular the capillary network. Examination of the same organ microvasculature region at various activity levels of the supporting parenchymal cells reveals that all available capillary flow paths are not perfused with blood cells at all times (Fig. 6). During a resting phase of the organ few capillaries are perfused with blood cells. Longer diffusion pathways are tolerated. Metabolic requirements of the body cells and material exchange increase with activity, requiring shorter transportation pathways. At this stage a larger number of capillaries, which heretofore were predominantly perfused with plasma, transport red blood cells.

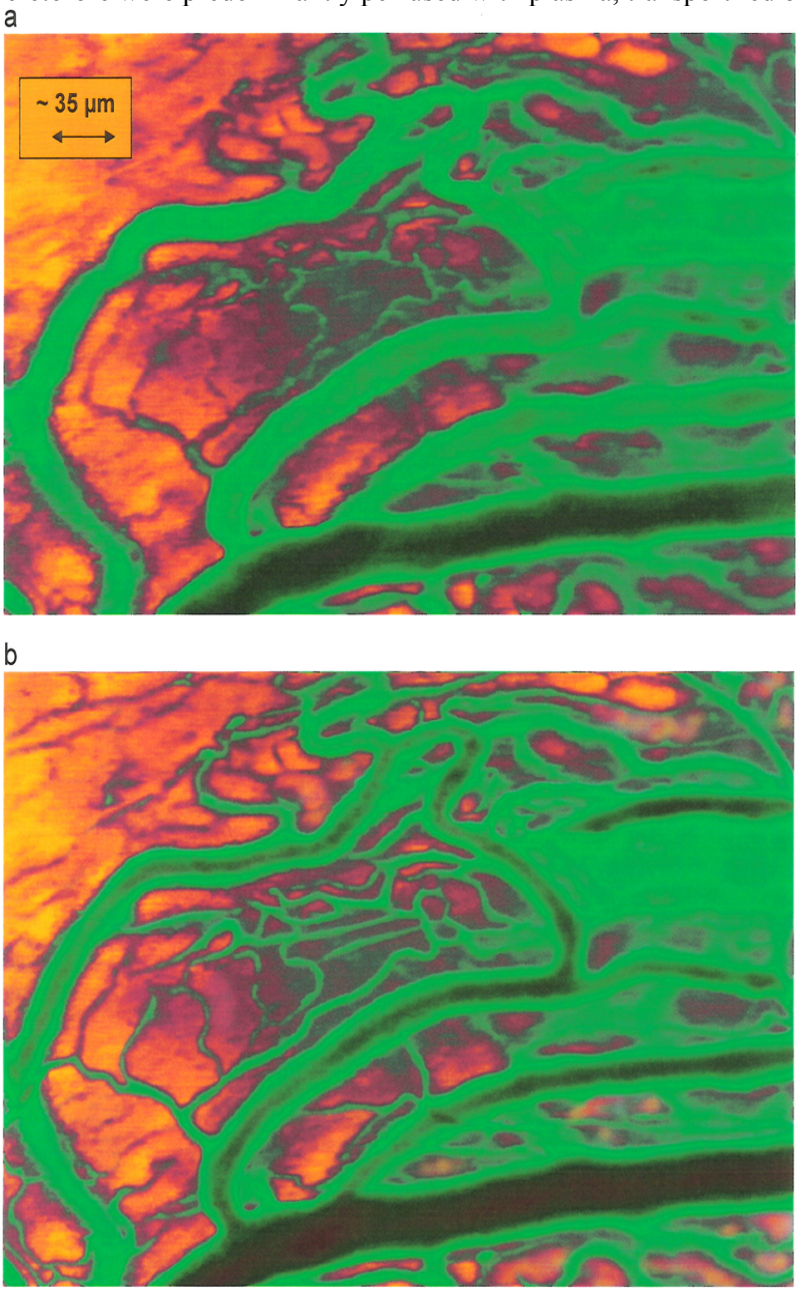


Figure 6. Variable distribution status of the plasma-blood cell mixture in the microvasculature network (a: resting phase, b: active phase) of the subcutis observed with intravital microscopy. Color correction of the original frames showing blood cell perfusion in green.

Figure 7 schematically illustrates the changes of the plasma-blood cell mixture distribution status in the capillary network.

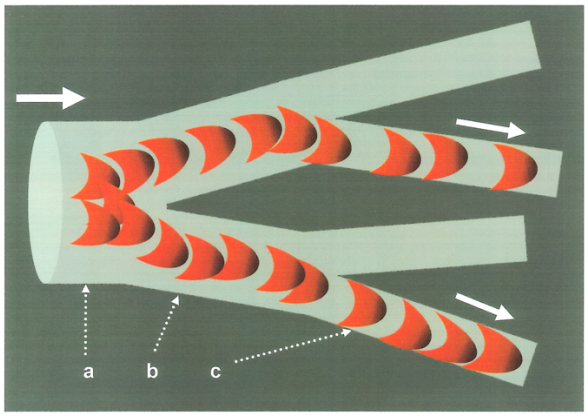


Figure 7. Schematic representation of the distribution of the plasma-blood cell mixture in the microcirculation (arterioles and capillaries); a. large caliber arteriole, b. small caliber arteriole branch; and, c. capillary branch.

The hydrostatic pressure differential of arterioles at a particular point in time is not the same in all capillary branches of a network entity. Red blood cells transported in the axial current of the arterioles are directed to the capillaries exhibiting the greatest pressure differential. The other capillaries are predominantly perfused by plasma. The capillary states switch continuously between predominantly blood cell and plasma perfusion. Independent thereof, a lesser number of network capillaries are perfused with blood cells in a resting organ with lower material exchange requirements, while an increase in organ activity level requires a greater need for material exchange and blood cells. The most important characteristic of a dysfunctional microcirculation is a distribution disturbance of the plasma-blood cell mixture in the capillary networks. The consequences are elongated distribution pathways.

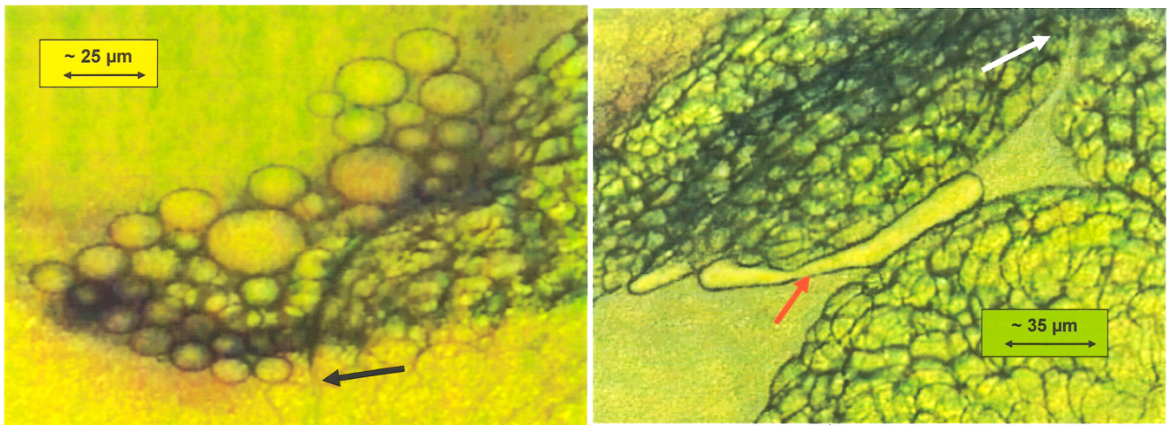


Figure 8. a (left). Observational example from intravital microscopy of the initial lymph flow exit of a fat droplet from the blood plasma of a venule into the extravasal space; b (right) example of the initial lymph movement of a fat-phase (red arrow) that developed from numerous fat droplets due to minimization of fluid surfaces to a lymph capillary (white arrow).

An undisturbed microcirculation is the prerequisite for an unobstructed course of the first steps of a cellular immune reaction. The first steps are as follows: the transport and arrival of white blood cells, the adhesion of white blood cells to the endothelium of the microvessel, and transmigration of the white blood cells into the tissue. Therefore, a connection exists between the functional state of the microcirculation and the immune reactions.

A large portion of the cellular immune reactions occurs in the venules. Figure 9 illustrates the mechanical flow problem of the transport of white blood cells through capillaries to the venular outflow. In

contrast to the red blood cells, the cumbersome and unshapely white blood cells must be pushed through the capillaries from behind by the red blood cells. At first the white blood cells transported from the small caliber arterioles block the capillary whereafter the following red blood cells build up a higher hydrostatic pressure. Once the pressure buildup is sufficient a movement of the white blood cells in the direction of the blood flow is enacted.

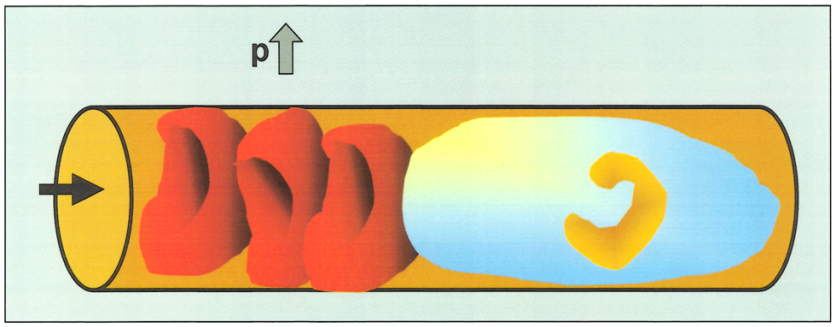


Figure 9. Schematic of white blood cell transport through a capillary.

Transmigration of white blood cells into the tissue in the context of an immune reaction occurs preferentially in the venules. Figure 10 shows the accumulation and partial adhesion of white blood cells from an intravital microscopy example.

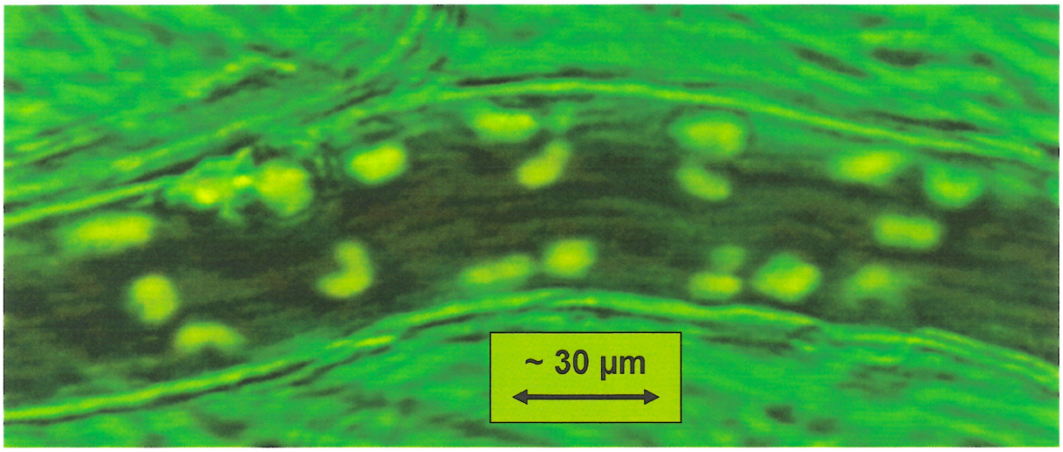


Figure 10. Accumulation of white blood cells in a venule and partial adhesion to the endothelium.

The physiological regulation mechanisms of organ perfusion are now in focus. The principal biomechanical flow relationship of the microvasculature's plasma-blood cell mixture (under idealized assumptions) was easily understandable whereas processes now become more complex.

The discussion now involves the perfusion regulation in large-caliber arteriole sections (cf. Fig.) Receptors are located in this region for neural and hormonal instructions for diameter adjustment that is realized through the contraction state of the smooth muscle cells in the vessel wall. This is called arterial vasomotion. This becomes an effective regulation agent because of $Q \sim r^4$. In the course of minutes to hours periodic diameter changes occur from which pressure gradients develop that effect a demand-oriented adaptation of the total perfusion volume in this vascular zone. The distribution and flow pathways of blood volume that reaches the narrowing small caliber arteriole branches and the subsequent capillary network is effected by a different, local mechanism. This regulation mechanism is not determined by central orders because this section of small caliber arterioles does not contain receptors for such neural or hormonal commands. The diameter changes of small caliber arterioles occur by autorhythmic contractile movements

of smooth muscle cells that surround these vessel sections in a single-layered and intermittent manner. This is referred to as spontaneous autorhythmic vasomotion, the most important localized regulation mechanism of organ perfusion because it is responsible for determining the segregation phenomena of the plasma-blood cell mixture. This local mechanism has therefore the deciding influence on the distribution of the plasma-blood cell mixture in the capillary networks (cf. Fig. 7). This mechanism is so effective that even central neural and hormonal influences on the large caliber arterioles can often under certain circumstances be overridden or compensated for. Explanation of the spontaneous autorhythmic vasomotion lies with the smooth muscle cells that phylogenetically belong to the oldest cells of the human organism and have conserved the characteristic of independent contraction in response to a physical stimulus. This capacity has been lost by other cells over the course of evolution.

The periodicity of vasomotion in the large caliber arterioles and the spontaneous autorhythmic vasomotion of the small caliber arterioles have differing biorhythms yet are in close physical proximity (cf. Fig. 1). From intravital microscopic observations under physiological flow conditions approximately 1 to 5 (median 3) vessel wall oscillations per minute can be discerned. Under illness conditions (e.g., an older patient with diabetic insufficiencies) oscillatory movements of the small caliber vessel wall are only discernible at greater intervals of multiple minutes coupled with reduced amplitudes. From these observations distribution disturbances of the plasma-blood cell mixture in the downstream capillary network are detected with the known effects of material exchange and immune reactions.

The mechanism by which the synchronization of the various biorhythms in the large- and small-caliber arterioles takes place is under current investigation. What is known is that this occurs under physiological flow conditions, and mainly under acute stress. The effect of an acute stress-mediated narrowing of the large caliber arteriole on the material exchange can be compensated for by an elevated frequency of the spontaneous vasomotion of the small caliber arterioles. This is not the case under chronic stress conditions. Under long-term stressor influences it is understood that the spontaneous autorhythmic vasomotion of continually narrowed large caliber arterioles can no longer sufficiently equalize the distribution of the blood in the capillary networks and sometimes reacts in an opposing manner. The consequences span from limitations of material exchange, functional reduction of support to the tissues, and cellular damage (necrosis, ulcerations) to cell death.

The spontaneous periodicities are initiated by the shear stress-dependent, endothelium-mediated arteriolar tone regulation. The state of contraction of the vessel wall smooth muscles is influenced by the released, highly diffusive Nitric Oxide (NO) that is formed in the endothelium (cf. Fig. 4). The endothelium is the central modulator of vascular functions. The endothelial lumen surface influencing shear stress τ releases a molecular enzymatic mechanism in the endothelial cells. This enables NO to have a relaxing effect on the smooth muscle cells from the activation of the soluble guanylyl cyclase.

Several therapeutic options are currently available for the treatment of vasomotor dysfunction. In the area of large caliber arterioles (with corresponding receptor stock) a successful medication-based treatment is possible (e.g., beta-receptor blockers). This achieves not only a diameter change of the arteriolar section with a corresponding effect on the pressure gradient and the distribution state of the blood, but also influences the related reduction of the peripheral flow resistance of the systemic blood pressure. A medication-based influence on the spontaneous autorhythmic vasomotion is not possible, because of the absence of corresponding receptors. A directed influence on the autorhythmic vasomotion periodicity is clearly only possible from an inherent natural stimulation by a corresponding physical stimulus. This is supported by more precise knowledge of the oscillation behavior of the small caliber arteriole vessel walls.

Figure 11 shows measurement results of the flow stream of small caliber arterioles with an extreme, high-resolution research method (measurement data collected at 20 ms intervals). The periodicity of stream flow Q_{RBC} is an expression of the oscillation behavior of the vessel wall, for which the contraction behavior

of the smooth muscle cells is relevant. A very similar oscillation curve is obtained from comparable measurements of the diameter of the microvasculature as a function of time. Every smooth muscle cell delivers a harmonic component that synchronizes with its amplitudes and frequencies to produce compound oscillations. Every compound oscillation exists of a base oscillation and harmonics. In this 'orchestra' of harmonics specialized cells (smooth muscle cells) exist that show the slightest oscillation frequency (base oscillation f_0). They function in essence as 'pacemaker' cells and transfer the oscillation progression to the next highest oscillation frequency f_1 (1st harmonic), which in turn transfers to another cell with the next highest oscillation frequency f_2 (2nd harmonic) etc., as illustrated in Figure 12.

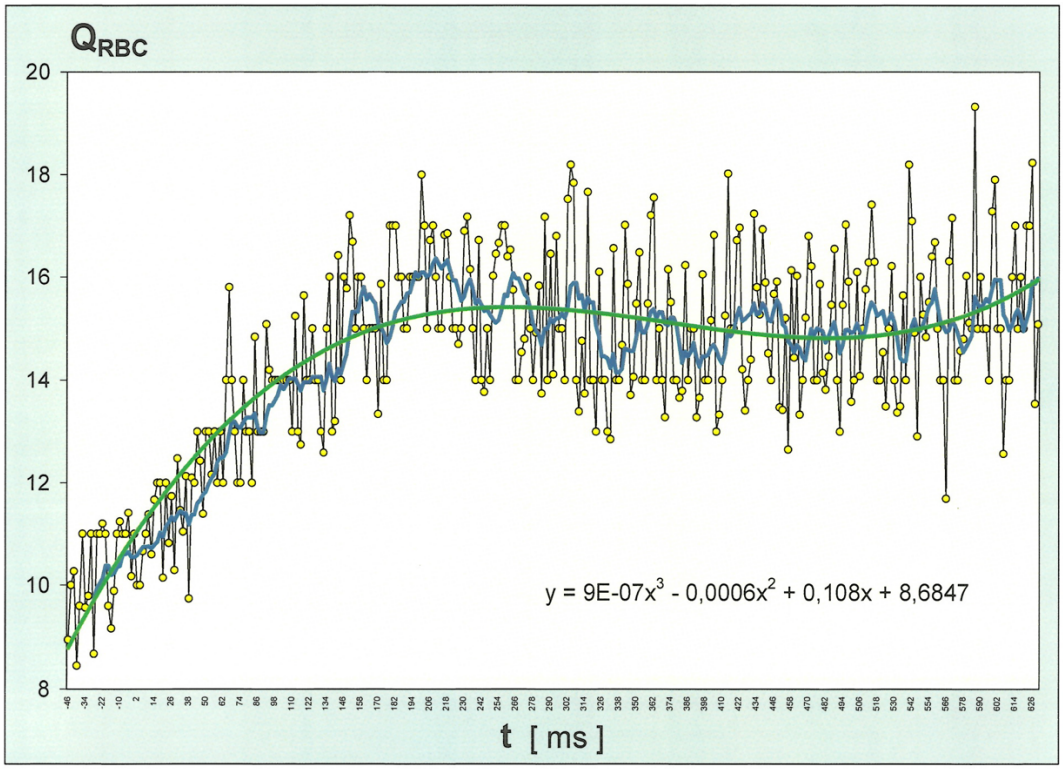


Figure 11. Biorhythmic behavior of the flow stream Q_{RBC} in a small caliber arteriole (extract of a measurement protocol). Ordinate: flow stream Q_{RBC} in relative values, abscissa: time (ms). Blue is sliding average, green is polynomial.

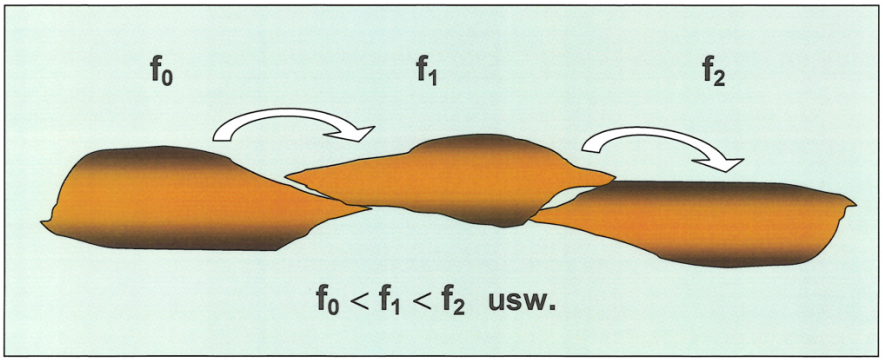


Figure 12. The development of harmonics (f_1 and f_2) excited through a base oscillation f_0 of the smooth muscle cells in the microvessel wall.

The elastomechanical behavior of the arteriolar vessel wall is the next consideration. A force *F* working on a vessel wall surface *A*, i.e., a stress $\sigma = F/A$, results in a length change Δl in reference to the original length l_0. Per Hooke's law of elasticity, the equation becomes:

$$\sigma \sim \frac{\Delta l}{l_0}$$

In the tension-extension diagram a comparatively small area of direct proportionality (Hooke's elasticity) is shown and a larger area of plastic distortion. The elastic restoring forces are less than the active processes (energy-dependent activities of the smooth muscle cells). Despite this an analysis can be made of the composite oscillation activity of a small caliber arteriolar vessel wall. The composite oscillation is broken down into its harmonic (sinusoidal) components (base oscillation and higher mode harmonics). For a periodic function *f(t)* with Period *T* the Fourier analysis produces:

$$f(t) = a_0 + \sum_{n=1}^{\infty} \left[a_n \cos\left(2\pi nt / T\right) + b_n \sin\left(2\pi nt / T\right) \right]$$

with

$$c_n = \sqrt{a_n^2 + b_n^2} \qquad \text{and} \qquad \varphi_n = arctg\left(a_n / b_n\right)$$

where c_n are the amplitudes and φ_n the phase constants.

The knowledge of these periodicities is thereby of significance for the understanding of the spontaneous autorhythmic vasomotion. Figure 13 provides the amplitude-frequency spectrum. The content of the defined A_{VM} area (broken line) is considered the functional level of vasomotion. This is how, for example, lesser oscillation amplitudes of the small caliber arterioles through restriction of the segregation phenomena between blood cells and plasma achieve a decline of the blood perfused capillaries and therefore an elongated diffusion pathway. The consequences are limitations of the material exchange and therefore limitations of organ functions.

In summary, the spontaneous autorhythmic arteriolar vasomotion is the most important regulation mechanism of organ perfusion. The shear stress-dependent, endothelium-mediated arteriolar tone regulation is only possible with fast flowing blood (microhemodynamic 'window' of an optimal material exchange-adequate perfusion regulation).

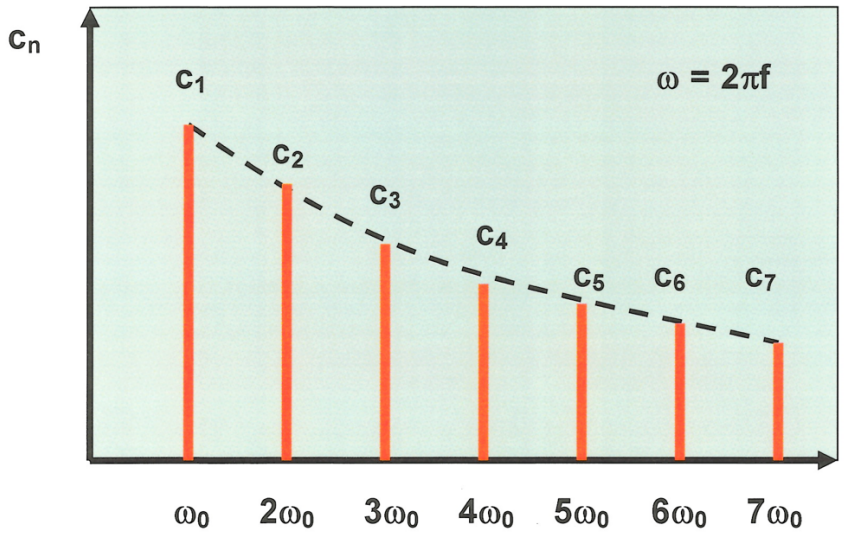


Figure 13. Amplitude frequency spectrum of a composite oscillation. Frequency of base oscillation ($\omega_0 = 2\ \pi f$) and harmonics $\omega_n = n\ \omega_0$ (with n=2,3,4...); c_n amplitudes; φ_n phase constants.

Further details of the performance regularity of the venous outflow from cellular functions, among other aspects, are not discussed here in the context of this topic. Klopp's book *Microcirculation* (2nd ed.) is currently in preparation to incorporate the enormous increase in knowledge in this field of the past 15 years.

The most important consequences of a disturbed microcirculation are finally summarized in Figure 14.

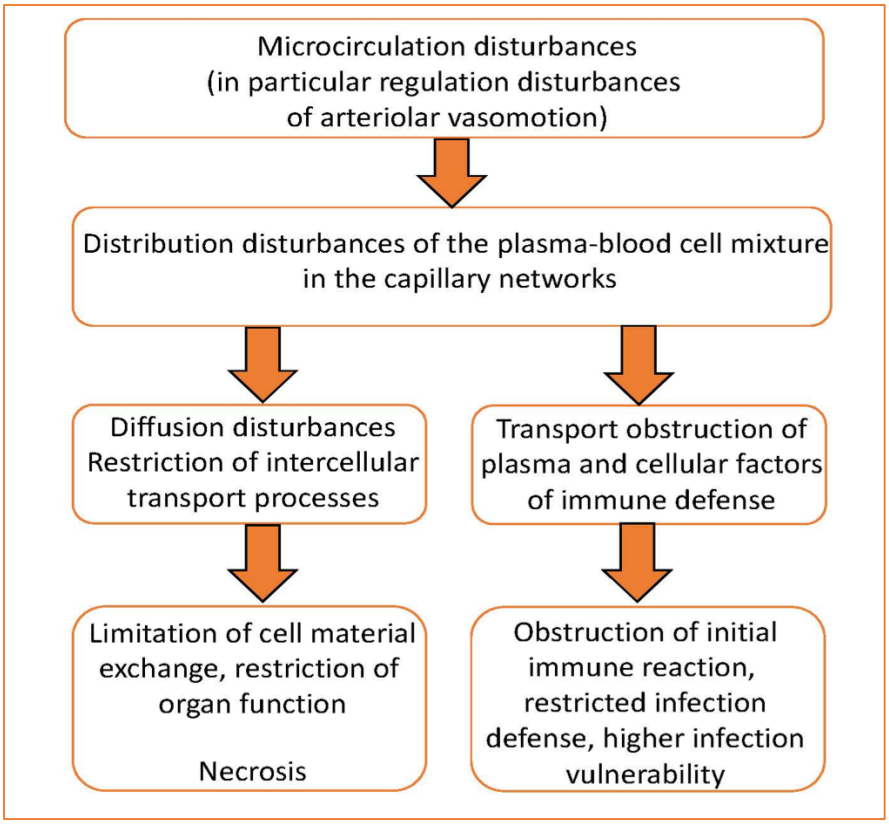


Figure 14. Consequences of a disturbed microcirculation.

A physical stimulation of the deficient spontaneous autorhythmic arteriolar vasomotion

The following concept is central to all clinical pathophysiological thinking: In the deficient state it is to stimulate bodily regulatory mechanisms via a suitable physiological stimulus to be able to by themselves clear the disturbance that has occurred. Such physiological stimulus must be recognized by the system as a stimulant.

As previously discussed a series of highly effective pharmacological therapy options are available for the large caliber arteriolar sections, that are not applicable for the small caliber arteriolar branches. This is the cause for numerous shortfalls of therapeutic success and therapy resistance.

The effective influence of various vascular medications, e.g., beta-receptor blockers, on macrocirculatory factors and some microcirculatory effects on large caliber arteriolar sections has in retrospect been known for a long time (Klopp et al. 2006; 2007). The importance of the local perfusion regulation through the small caliber arteriolar sections has only come to light in the last 10 to 15 years of intensive research. Because the spontaneous autorhythmic vasomotion is determined by a physical stimulus, the shear stress of flowing blood, it was advisable to search for a physical therapy option by which the inherent bodily regulatory factors in the deficient case would be stimulated externally. The end result of

these considerations was the analysis of the oscillation behavior of the small caliber vessel wall under physiological and pathological conditions (cf. Figs. 11, 12, 13).

The complexity of the physiological regulation processes in the small caliber arteriolar sections and the molecular-biological processes in the context of this treatise could only be discussed on a basic level. It could not be anticipated *a priori* that causal therapeutic effects through such a physical stimulation were achievable, but rather in the best case scenario an adjunctive treatment therapy would be discovered.

As carrier wave of a suitable stimulation signal both elastomechanical and electromagnetic waves were considered of which the electromagnetic wave ultimately prevailed.

Natural conditions were of significant importance for the establishment of the energy contributions that are transferred through the physical stimulation signal (transfer of much lower energy contributions from the shear stress-dependent, endothelial-mediated tone regulation of the small caliber arterioles). Very small energy contributions are sufficient for the endogenous regulation from the shear stress of flowing blood on the lumen side of endothelial surfaces and to provide the endothelial bio-catalytic converters (enzymes) the necessary activation energy for the molecular-biological processes to be lowered for the regulation to take place under physiological flow conditions. An effective physical stimulus of electro-magnetic flux density of ~100 μTesla was deemed sufficient.

The establishment of the appropriate signal configuration was determined by the results of the oscillation analyses of the natural physiological oscillation behavior of the arteriolar wall. With the help of an electromagnetic field as an energy carrier to the tissues the physical stimulus of the amplitude-, frequency-, and phase-modulated complex signal (composed of the sinusoidal harmonics) is transported in a specified frequency window of approximately 5 to 40 Hz.

As part of a placebo-controlled study of a biometrically defined sample of middle-aged male subjects exposed to mild chronic stress and mixed infections the representative characteristics of microcirculation in the abdominal subcutis were measured by way of high-resolution investigative methods after application of different electromagnetic alternating fields of the same flux densities and research conditions (Klopp et al. 2013d). As the imaging measurement method a laser Doppler vital-microscopic unit was used in a combined incident-transmitted light method with secondary computer-based image processing.

Measured values collected were: a) number of blood cell-perfused nodes in a defined tissue volume unit nNP (as measure of the state of distribution of the plasma-blood cell mixture of the microvascular network); b) venular oxygen saturation ΔpO_2; and, c) area under the envelope of the amplitude-frequency spectrum of the spontaneous arteriolar vasomotion A_{VM}. For the statistical analysis of the measured data the Wilcoxon rank sum test at the significance level $\alpha = 0.05$ was used.

The test equipment used was TD1: placebo-device, TD2-TD6: devices to elicit electromagnetic alternating fields of simple square-, triangular-, sawtooth-, sinusoidal- and amplitude-modulated sinusoidal oscillations, and TD7: device with amplitude-, frequency- and phase-modulated signal in accordance with physiological oscillatory behavior of small caliber vessel walls, a biorhythmically defined stimulation signal).

The treatments were administered under defined conditions in a 3-day interval twice daily for 10 minutes at 2-hour intervals. The measurement times of the daily data collection were: D0 - determination of initial values one day prior to start of study; D1, D2, D3 - immediately after the 2nd treatment of the corresponding day; D4 - determining the decline of characteristic changes after the end of treatments. Figures 15, 16 and 17 depict the obtained data.

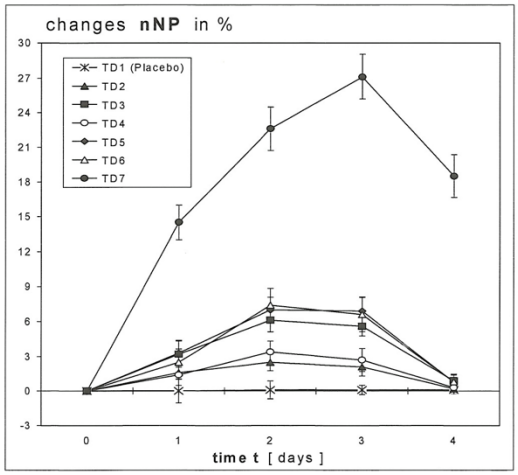


Figure 15. Measured values of the characteristic "number of blood cell perfused nodes in the defined network unit, nNP" (means and standard deviations) following application of test devices TD1-7.

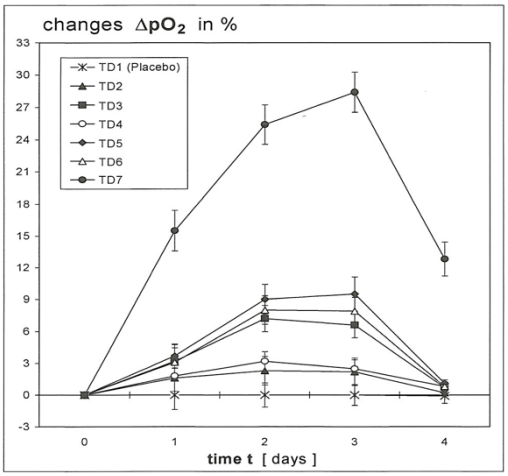


Figure 16. Measured values of the characteristic "venular oxygen saturation pO_2" (means and standard deviations) following application of the test devices TD1-7.

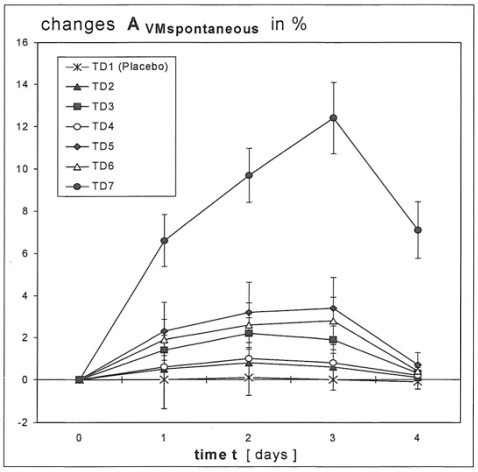


Figure 17. Measured values of the characteristic "area under the envelope of the amplitude-frequency spectrum of spontaneous arteriolar vasomotion A_{VM}" (means and standard deviations) following application of test device TD1-7.

The examinations showed that only a targeted, biorhythmically defined stimulus could affect arteriolar vasomotion and thus microcirculatory blood flow regulation in a therapeutically relevant manner and therefore was suitable for prophylactic and complementary-therapeutic use. TD 7 was the only test unit meeting this requirement, while the placebo device had no effect and TD2-TD6 effected only minimal changes.

In another placebo-controlled study Klopp et al. (2014) examined a biometrically defined sample of elderly patients with diabetes mellitus type II and wound healing disturbances to determine the extent to which a complementary application of a biorhythmically defined physical stimulus can contribute to the therapeutic treatment success of dysfunctional spontaneous arteriolar vasomotion. During the 27-day treatment period two subsamples were examined: a) control group of standard clinical treatment; and, b) test group standard clinical treatment and complementary adjuvant application of a biorhythmically defined physical stimulation signal.

As the imaging measurement method a laser Doppler vital-microscopic unit was used in a combined incident-transmitted light method with secondary computer-based image processing. The examined characteristics were: a) number of blood cell-perfused nodes in a defined tissue volume unit nNP (as measure of the state of distribution of the plasma-blood cell mixture of the microvascular network); b) venular oxygen saturation ΔpO_2; c) area under the envelope of the amplitude-frequency spectrum of the spontaneous arteriolar vasomotion A_{VM}; and, d) number of white blood cell adhesions in a defined venular inner wall surface A = 18,000 μm^2, nWBC/A (first stage of cellular immune reaction). For the statistical analysis of the measured data the Wilcoxon rank sum test at the significance level $\alpha = 0.05$ was used.

The adjuvant treatment during the 27-day period occurred at intervals of every 3 days (2 applications of 12 minutes with 2-hour intervals). The following measurements were taken under constant constraints of the immediate treatment day after the last daily treatment: D0 - determination of initial values prior to start of study; D3, D6, D9,...D27 - immediately after the 2nd treatment of the corresponding day. Measurement locus was a defined subcutaneous tissue region (corresponding to the wound region, ankle or foot area). Measurements were taken in the wound periphery (8mm from the wound edge). Figures 18-21 depict the obtained data.

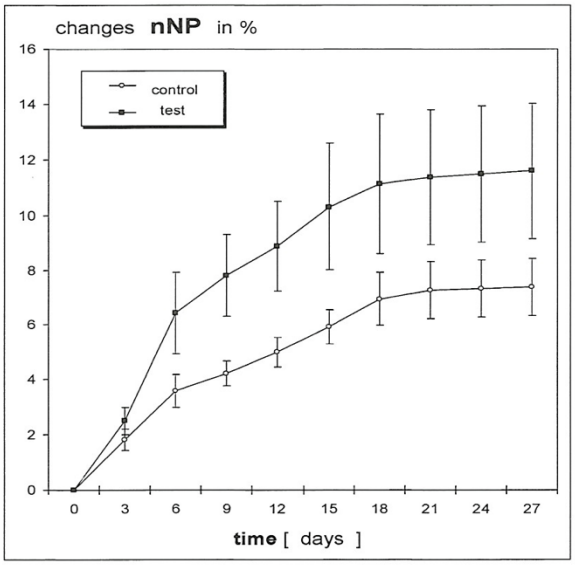


Figure 18. Measured values of the characteristic "number of blood cell perfused nodes in the defined network unit, nNP" (means and standard deviations).

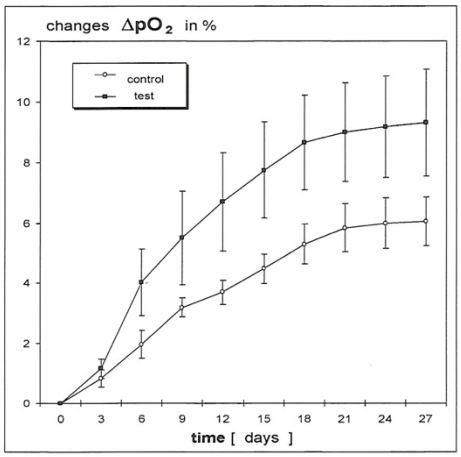


Figure 19. Measured values of the characteristic "venular oxygen saturation pO_2" (means and standard deviations).

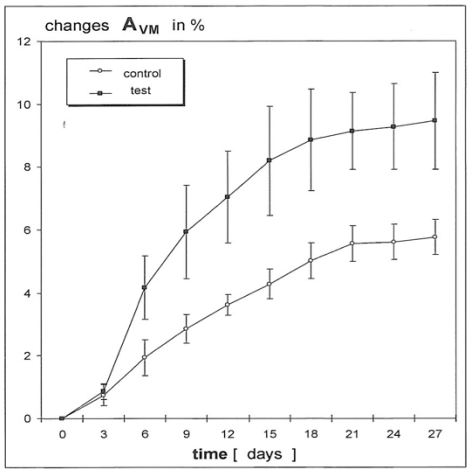


Figure 20. Measured values of the characteristic "area under the envelope of the amplitude-frequency spectrum of spontaneous arteriolar vasomotion A_{VM}" (means and standard deviations)

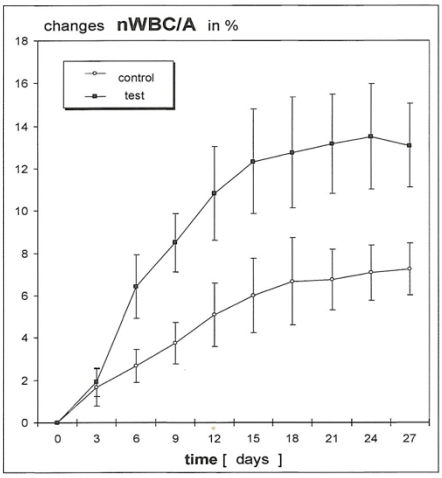


Figure 21. Measured values of the number of adhering white blood cells on a defined venular inner wall surface nWBC/A (means and standard deviations).

The planimetric investigation of the wound surface resulted in significant value differences between samples. On D27 the wound surface of the control group patients had shrunk by ~ 41% while the patients in the test group shrunk by ~ 64%. The obtained measurement data support an adjuvant application of a biorhythmically defined physical stimulus for optimal therapeutic treatment of material exchange under inadequate perfusion regulation and also for promising supplementation of prophylactic measures. These achieved research results and others (Klopp et al. 2013a; 2013b; 2013c; 2014; 2016) can be considered encouraging for the conduct of further investigations in this field.

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DIAGNOSTICS TO EVALUATE MICROCIRCULATORY FUNCTION

Thomas Derfuss
LEA Medizintechnik GmbH
Winchesterstrasse 2
35394 Giessen, GERMANY

Oxygen To See (O2C)

Oxygen To See (O2C) was introduced as a technology for microcirculatory assessment to determine adequate perfusion for tissue viability. It is a non-invasive diagnostic tool used to assess the oxygen supply in blood-perfused tissue. O2C provides various microcirculatory parameters for the assessment of tissue metabolism such as: 1) flow (relative blood flow); 2) SO_2ven (venous oxygen saturation of hemoglobin); and, 3) rHb (amount of regional hemoglobin – blood). O2C is based on the principle referred to as Tissue Photo Spectrometry (TPS). It is a combination of two principles: Laser Doppler Flowmetry and Tissue Spectrometry.

Laser Doppler Flowmetry

Measurement of the relative blood flow velocity is based on the Doppler frequency shift of illuminated laser light caused by moving erythrocytes. The depth selection in tissues such as skin, bone, and muscle lies between 200µm-15mm. The O2C can assess the blood flow in capillaries, arterioles, venules and smaller vessels whereas the conventional ultrasound can only do so in larger vessels.

Tissue Spectrometry

A white light is used to measure the oxygen saturation (SO_2) and relative amount of hemoglobin (rHb). The radiated light scatters and is absorbed in the tissue, which can be re-measured at the tissue surface. The erythrocytes change the color and intensity of the light. The absorption spectrum of the blood determines SO_2 whereas the amount of light absorbed by tissue determines rHb.

Measurements are taken using an optical probe with a recording time of 25ms. Correspondingly suitable sterile or non-sterile probes are available for different applications. Probes can be affixed to tissues using double-sided adhesive tapes or knots for a wet environment.

O2C Diagnostic Applications

a. Perfusion and oxygen saturation in the cortex

Walter et al. (2002) evaluated the O2C by measuring perfusion and oxygen saturation in the cortex region of the pig brain. Regional cerebral perfusion was measured with color microspheres and compared with the O2C results during cerebral perfusion pressure (CPP) decrease and reperfusion. The cerebral oxygen saturation measured using O2C was also compared with cerebral venous oxygen saturation.

b. Regional myocardial blood flow

Bierbach et al. (2012) validated O2C for the continuous measurement of regional myocardial blood flow (RMBF) in a porcine model. The probe was attached to the left ventricle anterior wall. Blood flow in the left anterior descending artery was reduced using an occluder clamped around the artery. O2C was used to compare RMBF using microspheres under various conditions such as baseline, baseline-flow,

reperfusion, and complete occlusion at both the epicardial and endocardial layers. Bierbach et al. (2012) were able to measure myocardial blood flow at different depths in the beating heart using the O2C.

c. Healing and non-healing wounds

A diabetic foot ulcer study was conducted by Beckert et al. (2004) using O2C. Measurements were made directly at the wound site at 2mm and 6mm depths on two consecutive days. Wounds were classified as healing and non-healing. The results showed that initial SO_2, rHb, Flow and Velocity were significantly lower in non-healing wounds compared to healing wounds. Therefore, the classification of healing wounds and non-healing wounds was possible as was early detection of ischemic conditions, giving better healing prognosis.

d. Lower limb ischemia

Jørgensen and Schroeder (2012) compared O2C results in patients with lower limb ischemia with their toe blood pressure. SO_2 and flow were determined with the lower limb in a horizontal, elevated position of 55cm whereas toe pressure was determined in a horizontal position only. In the elevated position the positive predictive value was 97% and the negative predictive value 68%. Some patients were investigated before and after 3 days of revascularization. A high predictive value of low SO_2 and significantly higher postoperative values after successful revascularization were observed.

e. Surgical flap monitoring

The field of Plastic Surgery can use the O2C for continuous monitoring of pedicle flaps and microvascular flaps (visible and buried flaps). The flap perfusion can be continuously monitored and assessed during operation and post operation to avoid flap loss and unnecessary revision.

Hölzle et al. (2010) monitored fasciocutaneous, osteocutaneous, myocutaneous and perforator flaps with O2C to define the critical values of success by comparing perioperative blood perfusion parameters. A rapid increase in rHb (>30%) indicated venous congestion whereas abrupt reduction in Flow and SO_2 indicated arterial occlusion.

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THE EVOLUTION OF PEMF THERAPY IN SCIENCE AND MEDICINE

Joshua D. Berka, NMD
Infinity Health Source
27520 Hawthorne Blvd, Suite 174
Rolling Hills Estates, CALIFORNIA 90274 USA

History of Electro-Magnetic Therapy

Humans have evolved and continue to evolve with the environment. Environmental factors such as weather, temperature, seasonal changes, and diurnal variations are important elements in our world and all intimately involved with electromagnetic energy. This Earth we live on generates a geomagnetic field that is crucial to survival of all biological systems on this planet. The inseparable relationship between energy and matter have always been of interest to scientists and has emerged as an invisible web that connects all of this world and the universe we live in.

Early Shamans, doctors, and scientists innately knew of this connection with nature and sought to use this force to influence our health. Magnetically charged lodestones were used to manipulate the flow of blood and ionic or charged particles within the body. In addition, acupuncture needles were used at specific points to stimulate the human biofield (referred to as qi) and influence blood flow.

Natural electricity and magnetism have also been used throughout recorded history for therapeutic purposes. Accounts from ancient Roman physicians (ca 47 AD) discuss the use of electric eels (torpedo fish) to treat a range of medical problems from gout to headaches and even musculoskeletal injuries. Applying a combination of electricity and magnetism is the cutting edge of emerging technologies such as Pulsed Electromagnetic Field (PEMF) Therapy that we have at our disposal to maintain and sustain health and treat disease.

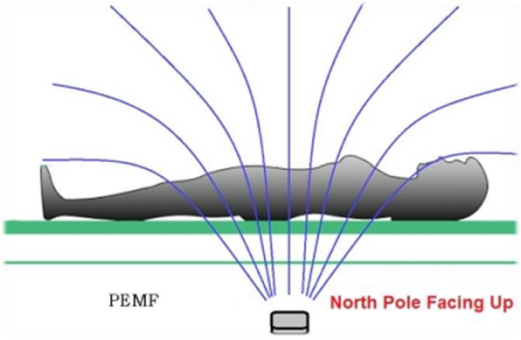

Figure 1. Pulsed Electromagnetic Field as a systemic therapy.

In the 1800's most of the discoveries relating electricity to magnetism were made by the early pioneers of our modern technical world (e.g., *Gauss, Weber, Faraday and Maxwell*). By the end of the 19th century, the electron was discovered and electro-magnetism was brought into the realm of science on the atomic level. By the 20th century, Albert Einstein showed that electricity and magnetism are not discrete phenomena, but different aspects of the same phenomenon. Not until after World War WII did scientists in Japan begin generating various electromagnetic wave shapes by changing electrical currents and

observing their physiological effects. This modality quickly moved to Europe and then forward to the United States.

In the 1970s Bassett et al. (1974) introduced at Columbia University Medical Center a new approach for the treatment of non-healing bone fractures and pseudarthroses that employed very specific bi-phasic, low frequency, electromagnetic signals. Public awareness also increased in the mid-1970s amidst reports of successful enhancement of the speed and endurance of race horses treated with electromagnetic fields.

The U.S. Food and Drug Administration cleared the application of electromagnetic fields for non-union and delayed union fractures based on the published work of Bassett et al. (1977; 1982). In 1987 the FDA cleared the use of pulsed electromagnetic fields for the treatment of pain and edema in superficial soft tissues. More recently the FDA cleared in 2008 a PEMF device using repetitive transcranial magnetic stimulation (rTMS) for the treatment of Major Depressive Disorder in adult patients who failed to achieve satisfactory improvement from prior antidepressant medication. The latest clearance by the FDA was in 2013 for the treatment of Migraine Headaches when applied during the prodrome or migraine aura.

While all these approvals were with high power PEMF devices, it is now commonly accepted that even weak or low power pulsed electromagnetic fields with the appropriate waveform are capable of initiating various beneficial biological processes leading to numerous applications in healthcare and medicine.

PEMF Therapeutic Effects & Clinical Applications

Table 1 describes many of the therapeutic effects and clinical applications of PEMF Therapy. A therapeutic modality like PEMFT can do so much because it is not a drug with one or two isolated mechanisms of action. PEMFT provides an activation energy that triggers innate, self-regulating mechanisms within the body. The most common manner in which PEMF works is through an inductive effect. PEMF influences charged particles within the body. The other more complex effect is that which occurs through resonance-activating molecules, cells, and tissues.

Table 1. Effects of PEMF through research and clinical practice (left column) and diseases that can benefit from PEMFT (right column).

Modulates inflammation	Cardiovascular related diseases
Reduces pain and edema	Diabetic related diseases
Improves blood flow	Eye diseases
Promotes tissue repair	Concussion/Traumatic Brain Injury (TBI)
Promotes tissue regeneration	Osteoporosis/Osteopenia
Improves wound care outcomes	Muscle atrophy
Improves neurological function	Arthritis
Improves cardiac function	Stroke rehabilitation
Reduces fatigue	Urinary Incontinence
Improves performance	Sleep disorders
Accelerates recovery	Seizures and Epilepsy
Enhances well-being	Neuro-degenerative diseases
Supports detoxification	Peripheral Neuropathy

For example, PEMF reduces or modulates inflammation and promotes repair by triggering a signaling compound in the body called nitric oxide (NO). There is a pro-inflammatory form of nitric oxide (iNOS) and two anti-inflammatory forms (eNOS and nNOS). Excess levels of the pro-inflammatory form cause chronic pain and many autoimmune and inflammatory diseases. The anti-inflammatory forms promote blood flow, oxygenation, growth and repair, and relaxation of blood and lymph vessels. Studies show PEMF promotes the anti-inflammatory forms of nitric oxide, which supports recovery, regeneration, and the modulation of inflammation. PEMF enhances the repair of bones and tissue by increasing the flow of blood

and lymph. The lymphatic system removes waste products and blood delivers oxygen and nutrients to the body's tissues and organs. PEMF enhances these systems, stimulating the growth of new blood vessels (angiogenesis) and bone, and speeds repair and recovery from injuries and wounds.

The resting potential of damaged and diseased cells is up to 80 percent lower than normal. This lowers metabolism and energy and makes the body more vulnerable to damage from disease-causing free radicals. PEMF raises the body's supply of circulating electrons, thus serving as a potent antioxidant to boost cellular energy. PEMF's antioxidant benefits, along with its proven ability to repair and regenerate tissue, make it a powerful anti-aging or healthy aging tool. Studies show that PEMF's effect on the nervous system dramatically improves neuropathies, insomnia, reduces the damage from strokes, and improves symptoms associated with multiple sclerosis.

Parameters of PEMF

The following parameters are integral to Pulsed Electromagnetic Field Therapy: waveform, frequency, intensity/flux density, timeline, delivery system.

PEMF Research

a. Preclinical studies

NASA research interests include physiological and molecular genetic effects of time-varying electromagnetic fields on human neuronal cells (Goodwin, 2003). Walther (2007) reported the results of his study that indicate that the exposure to weak, low-frequency pulsed electromagnetic fields is able to alter the gene expression of a limited number gene products in human mesenchymal stem cells and human chondrocytes. Regulated genes identified in Walther's study via gene chip analyses mainly affect cell metabolism and the cellular matrix.

Kafka et al. (2005) reports that the effects appear to be cell specific. There was no increased expression of genes known to be linked to cancer development nor inductions observed of mRNA levels related to other diseases in their study on MSCs and chondrocytes or in previous study on human osteoblasts. This study confirmed the data retrieved from several other trials where, so far, there is no evidence that low-energy pulsed electromagnetic fields may induce the development of malignant tumors (Feychting and Forssén, 2006; Johansen and Olsen, 1998; Loberg et al., 2000; Tynes and Haldorsen, 2003).

b. Bone Loss and Muscle Atrophy

Although studies on PEMF have been ongoing for more than 20 years, little is known about the molecular and cellular mechanisms involved in their beneficial therapeutic effects. In particular, the field energetics must be precisely defined and optimized for specific applications, such as frequencies, pulse shape, waveforms, amplitude, and spatial orientation (Byerly et al., 2005)

c. Chronic Degenerative Muscle and Musculoskeletal Disorders

The therapy administered in combination with traditional physiotherapy procedures reduces chronic lower back pain in the short term and may be effective in the long-term treatment of patients with osteoarthritis of knee (Gyulai et al., 2015).

d. Multiple Sclerosis Fatigue

In one pilot study (Piatkowski et al., 2009) it was demonstrated that a specific PEMF Therapy had a beneficial effect on MS-related fatigue. There was a statistically significant advantage for the treated patients after 12 weeks of daily use. In another open-label trial (Piatkowski et al., 2011) the positive effects of long-term PEMF use are both a safe and effective adjunctive treatment for MS-related fatigue.

e. Wound Healing

In wound healing studies the following therapeutic endpoints following PEMF Therapy could be

evaluated: inflammation of the perilesional skin; pain or neuropathy; diameter and depth of lesion; infection; PO_2 - PCO_2 percutaneous; metalloproteases; temperature and humidity; capillary changes; healing times; and, number of visits to the physician.

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MICROCIRCULATION: THE CORNERSTONE OF LIFE

Ulises Baltazar, MD, FACS, RVT
Houston Methodist Sugar Land Hospital
Medical Office Building 3
16605 Southwest Fwy #505
Sugar Land, TEXAS 77479 USA

Introduction

Traditional Chinese Medicine is built on a foundation of more than 2,500 years of medical practice that includes various forms of herbal medicine, massage, exercise, and dietary therapy, primarily used as a complementary alternative medicine approach and becoming increasingly prevalent in Western culture. A basic premise maintains that the body's vital energy (*chi*) circulates through channels (*meridians)* that have branches connected to bodily organs and functions. It emphasizes dynamic processes with little emphasis on anatomical structures. The theory was that blood motion made possible the interaction between Ying and Yang.

Hippocrates (460 BC-370 BC) of Kos, Greece is referred to as the Father of Modern Medicine after whom the Hippocratic Oath is named. The four humors of Hippocratic medicine are black bile, yellow bile, phlegm, and blood. He is credited with greatly advancing the systematic study of clinical medicine. He proposed that the liver and the spleen were the central organs within which blood was constantly produced and then traveled to the heart to be warmed or cooled by the air entering the lungs via the trachea.

Galen (129-216 AD) of Pergamum, Greece was a prominent acupuncture physician, surgeon, and medical researcher of antiquity. He influenced the development of anatomy, physiology, pathology, pharmacology and neurology as well as philosophy and logic. Galen's theory of the physiology of the circulatory system postulated that there were two kinds of blood: bright red carried by the arteries and dark red carried by the veins. He believed that it was the pulsations in the walls of the arteries that propelled the bright blood forwards; the darker blood carried by the veins was produced by the liver and the bright blood carried by the arteries was produced within the heart. Galen's concepts endured until William Harvey's 1628 published treatise *De motu cordis*.

Ibn al-Nafis (1213-1288) of Damascus was an Arab physician who first described the pulmonary circulation of the blood. He also performed several human dissections and was a prolific author of medical textbooks.

William Harvey (1578-1657) of Folkestone, England was the first physician known to describe completely and in detail from precursors of the theory the systematic circulation and properties of blood being pumped to the brain and body by the heart.

Michael E. DeBakey (September 7, 1908 – July 11, 2008) from New Orleans, Louisiana was an American surgeon and visionary who set the basis for the cardiopulmonary machine, which allowed for *in-* and *ex-vivo* open heart surgeries. This revolutionized the treatment of coronary artery disease as well as a myriad of other cardiac and vascular pathologies. DeBakey was Chancellor Emeritus of Baylor College of Medicine and Senior Attending Surgeon at Methodist Hospital in Houston, Texas.

Microcirculation

Wiernsperger and Bouskela (2003) described the microcirculation consisting of a dynamic "organized chaos" of empty-filled capillaries, fluxmotion, and metabolic, physical, humoral, and nervous mechanistic processes.

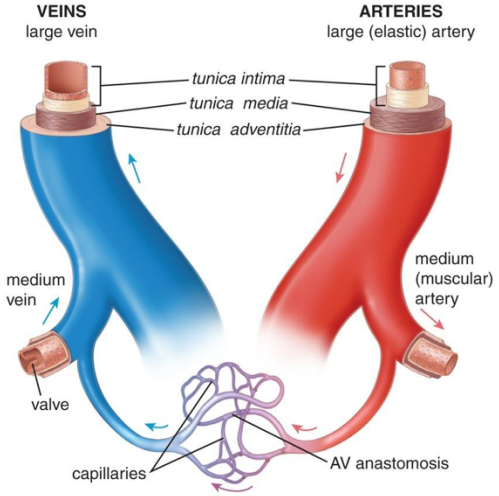

Figure 1. Endothelial barrier function (Yuan and Rigor, 2010). Arteries (red, right): Large (macrocirculation); Medium (Resistance) 50-100µm, 20-35mmHg; and Small (microcirculation) 5µm. Veins (blue, left): Large, CVP 2-6mmHg; Medium 3-100µm, 30mmHg; and, Venules 8-30µm, 12-15mmHg. Source: https://www.studyblue.com/notes/note/n/heart-blood-vessels-exam-4-final/deck/12865100.

Medium-sized arterial vessels regulate blood pressure. Small-sizes arterial vessels support the "nutritive structure", are of 5µm diameter, 15-20 capillaries, consist of a single endothelial cell layer as opposed to a basement membrane and their permeability varies from organ to organ (Wiernsperger and Bouskela, 2003).

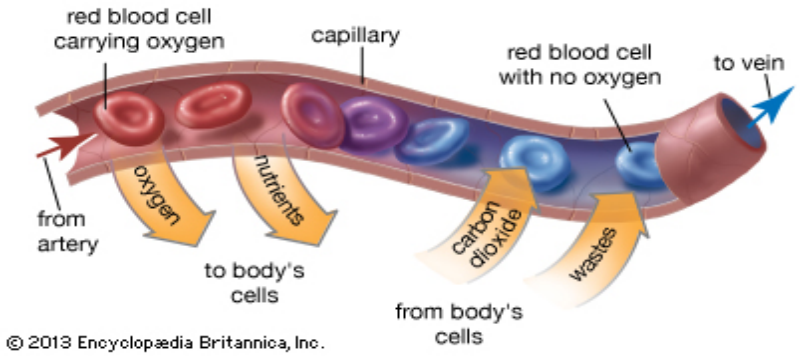

Figure 2. Capillary permeability: nutrient/waste and gas exchange. https://www.studyblue.com/notes/note/n/circulation-and-blood-pressure-regulation/deck/16648055.

The main role of capillaries is the exchange of gases (oxygen and carbon dioxide), nutrient transport and waste removal. The hydrostatic pressure at the arteriole-venule interface regulates vessel permeability varying from <3nm (tight or moderate) to >3nm (fenestration). The regulation of flow is dependent on the arteriolar myogenic response, veno-arteriolar reflex, and pre-capillary arteriolar vasomotion.

Arteriolar vasomotion is coupled with the unique role of Nitric Oxide (NO) in the control of blood flow (Pohl and De Wit, 1999). Endothelium-Derived Hyperpolarizing Factor (EDHF) is a substance and/or electrical signal that is generated or synthesized in and released from the endothelium. EDHF acts to hyperpolarize and relax vascular smooth muscle cells, which allows the blood vessel to expand in diameter (Pohl and De Wit, 1999). Slow-wave arteriolar contraction causes high amplitude (1-10 Hz) oscillations of membrane potentials (Intaglietta, 1990; Bartlett et al., 2000).

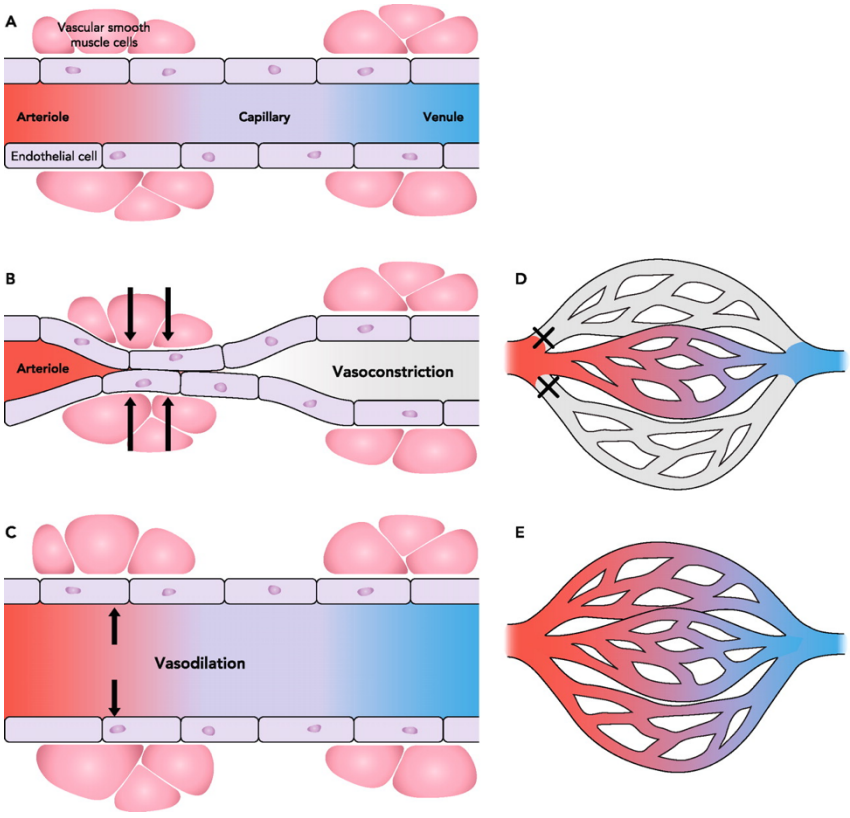

Figure 3. Capillary vasoconstriction and vasodilation (Kolka and Bergman, 2012).

Vasoconstriction is not necessarily bad. Large and medium vessels (macrocirculation) determine the blood volume. Capillaries (microcirculation) are regulated by perfusion. When this delicate balance is altered changes in any of the three main components of microcirculation occur. Pressures in the capillary bed change resulting in capillary hypertension and thus increased permeability triggering tissue edema with associated changes.

The Centers for Disease Control (CDC, 2015) reports the leading causes of death in USA as heart disease, cancer, chronic lower respiratory diseases, accidents, stroke, Alzheimer's disease, diabetes, influenza or pneumonia, nephritis, nephrotic syndrome or nephrosis, and suicide. At least nine of the causes involve pathological states at the microcirculation level.

Diabetes

Diabetes induces vessel wall sclerosis affecting the ability to distribute blood flow to the retina, renal cortex and peripheral nerve (McMillan, 1984). The veno-arteriolar reflex is lost. Capillary hypertension and hyperperfusion become shunt pathways. Capillary narrowing from thickening of basement membrane or Glycocalyx results (Wiernsperger and Bouskela, 2003). The arteriolar vasomotion is blunted as evidenced by 47% without and 82% with neuropathy that had slow-wave vasomotion affected. Functional

capillary density decreases in 50% of diabetic animals (Wiernsperger and Bouskela, 2003). Chronic hyperglycemia (advance glycation products) affects permeability. There is increased permeability in the kidney and retina.

Sepsis

An inflamed microcirculation is key in impaired homeostasis in sepsis coupled with decreased NO and iNOS production that triggers a blunted arteriolar myogenic response. This can result in a damaged or destroyed Glycocalyx (Asha et al., 2009). The arterioles become hyporesponsive. Perfused capillaries are reduced in number and venules are obstructed by sequestered neutrophils (Asha et al., 2009). Shunting occurs from arterioles to venules and the pO_2 gap ($mppO_2 \Delta vppO_2$) serves as indicator of the severity of shunting.

Heart disease, Stroke, Limb ischemia, Transplant

Ischemia is a reperfusion injury from oxidative stress with endothelial barrier damage. Reactive oxygen species are at the center of most pathological membrane changes (Yuan and Rigor, 2010).

Nerve compression

During nerve compression the arteriolar myogenic reflex is lost and capillary hypertension and edema result. Two peaks occur after injury: one week after radius and size increase but a decrease in number; and, after six weeks a frank proliferation (Yueming et al., 2013).

Pulsed Electromagnetic Field (PEMF)

There exists controversy in the literature regarding the effects of magnetic fields. Some studies demonstrate vasoconstriction after exposure to magnetic fields, yet vasodilation after exposure to PEMF is possibly a response to vasoconstriction.

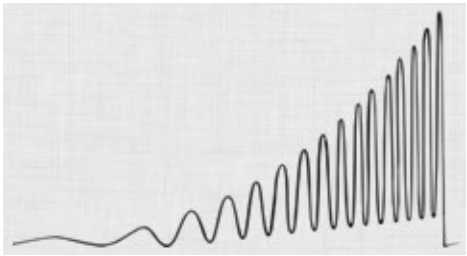

Figure 4. Proprietary PEMF wave form (10 Hz and 30 Hz).

Preliminary study

Individuals were exposed to PEMF in a Helmholtz coil configuration for 8 minutes (n=3) to a magnetic field of 3 to 5 gauss. The blood flow assessment consisted initially of a TCO_2 and duplex ultrasound. The results assessed in medium size arteries (not in the microcirculation) showed an increased blood flow of 12-151%. Assessing blood flow, perfusion and oxygen exchange at the capillary bed will be key to assess PEMFT effects.

Conclusion

It is interesting to note from a review of the history of biochemistry, physiology, pathology, pharmacology, etc., how advances and discoveries in these fields have not always been understood, nor immediately accepted. Time, effort, and further validation research have been pivotal in incorporating that knowledge into our daily practice. With a better understanding of the physiology and pathophysiology of microcirculation we have entered a new era in diagnosis and treatment of countless diseases. It has also opened the door for new approaches in the management and treatment of these conditions. Some options,

which in the past seemed irrational due to a lack of knowledge, have become viable treatment alternatives. One of these is, without a doubt, is the use of Pulsed Electromagnetic Fields. The plasticity to manipulate the pulses and the effects on microcirculation physiology make them a viable alternative. An array of research literature has begun to flood scientific journals. I believe that we are on the threshold of a new therapeutic era for microcirculation disorders and the pathology they trigger.

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DYSFUNCTIONAL CIRCULATION AND CARDIOVASCULAR HEALTH

Robert B. Chesne, MD, FACC
Centinela Hospital Medical Center
501 E Hardy St # 200
Inglewood, CALIFORNIA 90301 USA

Introduction

Cardiology has seen dynamic changes over the past 30 years with a greater emphasis on interventional technology. Dr. Andreas Grüntzig (Matthias et al. 2014) modified Dotter and Judkins (1964) techniques of transluminal angioplasty by adding a balloon to the Dotter catheters. In 1977 at the University Hospital in Zurich, Switzerland, Grüntzig successfully performed the first coronary angioplasty on an awake human. This new procedure was a mechanical revascularization of coronary arteries, which involves threading catheters with inflatable 'balloons' into the coronary artery to open blockage. Angioplasty rapidly replaced the need for coronary artery bypass surgery, an open-heart procedure with high risk factors. This marked the beginning of interventional cardiology and revolutionized medicine.

Since 1982 many advancements of intervention, including stent, atherectomy have progresses, and clinical practice now also includes interventional treatment for peripheral artery disease. Pulsed magnetic field induction of angiogenesis and improved cardiac function of surgically induced infarcted myocardium has also been shown in animal models (Yuan et al. 2010).

Statin investigation

Pharmaceutical therapies have also advanced over the past thirty years, assisting in the treatment of chronically ill patients. One of the major developments was the statin drug, a medication for lowering high cholesterol levels. In one double-blinded research trial with many patients enrolled we were able to discern quickly those patients in the placebo group from those on the investigative statin drug. Knowing that, the project was terminated on ethical grounds so that all patients could benefit from the therapy.

Increase of capillary bed filling with PEMF

There is an increasing interest in new technologies, i.e., antibody therapy for hypercholesterolemia, immunotherapy for cancer patients and in particular advancements in improving microcirculation through application of Pulsed Electromagnetic Fields (PEMF). Cardiovascular disease is the leading cause of death in the United States. This fact fuels the interest for even newer and more effective technology that is based on evidence. Evidence-based medicine is the application of methods of treatment and clinical decision making that have been rigorously tested by properly controlled, peer-reviewed research studies. It also encompasses a physician's clinical expertise, and, of course, the needs and preferences of the patient.

Small arteries (arterioles) deliver blood to metarterioles that form branches into capillary bed capillaries. The tunica media (middle layer) of a vessel contains few layers of muscle. It lies between the tunica externa and the tunica intima (elastic internal layer adjacent to the endothelium). To bypass the capillary bed, precapillary sphincters close and blood flows out of the bed in thoroughfare channel (Fig. 1). Vasomotion is the intermittent sphincter contraction/relaxation allowing capillary bed fill 5-10 times/min.

An increase in vasomotion improves cardiovascular health. PEMF therapy provides a biorhythmically-defined physical stimulation of insufficient spontaneous arteriolar vasomotion. Perfusion is thus increased

through this particular mechanism especially since 75% of the microcirculation has no response to medications.

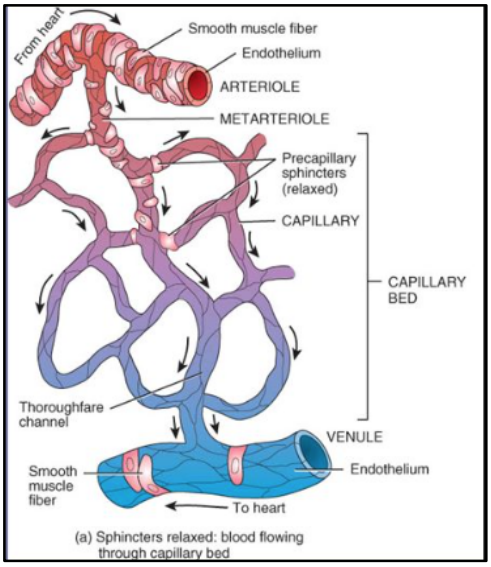

Figure 1. Mechanics of capillary bed filling.

Improving patient clinical outcomes

A dysfunction of the endothelium results in loss of the protective role of endothelium-derived relaxing factors, mainly nitric oxide (NO), which has prognostic significance in patients with coronary artery disease. Management of patients with persistent angina and no obstructive coronary artery disease continues to be a challenging area. Complete understanding of the mechanisms and factors responsible for coronary vasomotor adjustments will lead to advances in treatment. Expectations for the use of PEMF Therapy in practice include, but are not limited to, increased perfusion of myocardium (Patel et al. 2008), increased delivery of medications and elimination of metabolic waste (toxins) at the cellular level, treatment of polyneuropathies and erectile dysfunction (sign of CAD), wound healing, and increased multi-organ perfusion. An area of my practice that is of particular concern is the group of patients who describe persistent angina with no visible obstructive coronary artery disease as seen on angiogram. These patients are typically categorized as "Syndrome X." Improving microcirculation to the capillary beds within the heart could lead to improvement of Syndrome X symptoms. There is also an increase in patient interest in PEMFT for preventive measures.

Conclusion

PEMF technology provides high hopes for a more healthful future and will be influencing medical and preventative treatment for generations to come.

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INFLAMMATION EFFECTS ON VASCULAR PATHOLOGY AND CHRONIC DISEASE: PEMF THERAPY APPLICATION IN INTEGRATIVE MEDICINE

Sunil Pai, MD
House of Sanjevani
Integrative Medicine Health and Lifestyle Center
9001 Holly Avenue NE, Suite B
Albuquerque, NEW MEXICO 87122 USA

Introduction

Western medicine often treats symptoms of diseases with drugs and surgery while leaving underlying causal conditions untouched. Conventional medical treatment has classified over two hundred different 'itis' conditions, with over a dozen different types of medical specializations that treat these individually and symptomatically (Pai, 2016). Lowering inflammation through dietary and lifestyle changes along with use of natural anti-inflammatories is important, but perfusion of these factors has been limited due to chronic vascular pathology. Pulsed Electromagnetic Field (PEMF) Therapy has shown positive results in improving microcirculation, which is a key part in resolving chronic vascular pathology and chronic disease.

Inflammation

Inflammation is the triggering mechanism that makes many diseases worse (e.g., pulmonary diseases, cancer, cardiovascular diseases, Alzheimer's, diabetes, arthritis, autoimmune and neurological diseases).

Inflammation/flame/fire results in controlled and uncontrolled "itis" conditions of which there are over 200, e.g., Conjunctivitis, Rhinitis, Sinusitis, Gingivitis, Pharyngitis, Thyroiditis, Bronchitis, Esophagitis, Gastritis, Colitis, Vaginitis, Prostatitis, Arthritis, Bursitis, and Dermatitis. Symptomatic treatment of the "itis" conditions includes, for example, eye drops, nose sprays, mouthwash, hormones, inhalers, acid blockers, stool modifiers, antimicrobials, pain pills, and skin creams. These only treat the symptoms but not the underlying triggering mechanism of inflammation.

Potential sources of inflammation include: Food factors (grilled, fried, animal proteins, dairy; environmental pollutants and toxic agents (industrial chemicals, fuel, smog, heavy metals, chemotherapy), cigarette smoke; infections (bacteria, parasites, viruses); stress (low pH, hypoxia); ultraviolet radiation; alcoholic beverages.

Acute inflammation may be helpful for most conditions such as having a fever but chronic inflammation leads to chronic diseases such as osteoarthritis (hypertrophy and spurring of bone and erosion of cartilage); heart disease where fatty material deposits in vessels responding to inflammation thereby leading to narrowing and blocked arteries; Alzheimer's disease where protein plaques deposit in the brain causing language and memory impairment, and Crohns/ulcerative colitis having chronic inflammation to the colon leading to pain, bowel dysfunction and bleeding.

Peripheral Neuropathy

An integrative medicine evidence-based approach to peripheral neuropathy (neuritis) is now availing itself of PEMF Therapy (Pai, 2016). Neuritis is a common neurologic disorder resulting from damage to peripheral nerves. Its causes include diabetes/glucose intolerance (40-60% in 25 years), Rx drugs

(chemotherapy), toxic trauma (chemicals, ETOH), mechanical injury, nutritional deficiencies, infections, cancer, etc. Among these persistent hyperglycemia, oxidative stress, inflammatory, immune and microvascular mechanisms are important factors.

Endoneural vascular insufficiency

Endoneural vascular insufficiency is characterized by decreased NO production, impaired endothelial function, impaired Na+/K+-ATPase activity, and homocysteinemia. Ischemia related to endoneural and epineural vascular changes triggers nerve damage by thickening of blood vessel wall, which compromises endoneural blood flow and results in microvascular impairment. There is a decrease in peripheral perfusion in nervous tissue and skin (indicative of microvascular changes).

Improving inflammatory conditions

A vicious feedback cycle is created by chronic insults of inflammation coupled with a weak immune system: Peripheral neuritis triggers more inflammation thus reducing vascular flow, normal physiological functions, immune repairing mechanisms and increasing pain and dysfunction.

Solutions include eating an anti-inflammatory, plant-based diet; removal of food sensitivities (IgE, IgG4); and, reduction of inflammation through use of patented synergistic natural anti-inflammatory formula (i.e., Bosmeric-SR). Immunological response can be improved through the use of patented immune supportive therapy (i.e., Glucan 300 and Vitamin D3) and nerve conduction improvement from Benfotiamine, Alpha lipoic acid, and Acetyl-L-Carnitine.

With above recommendations, Peripheral Neuritis improves physiologically more than standard pharmacotherapy (Pai, 2016) but the full physiological improvement is directly related to a lack of effective delivery of phytonutrients, antioxidants, natural anti-inflammatory agents, immune cells and oxygen to these damaged and dysfunctional areas. PEMF therapy improves the microcirculation for all of the above to work optimally and thus is integral in optimizing outcomes.

PEMF Therapy Studies on Vascular Pathology and Chronic Diseases

PEMF Therapy studies have demonstrated significant improvement in microcirculatory characteristics such as capillary perfusion, venular flow or oxygen utilization (Bohn, 2013). By increasing microcirculation the penetration and increased efficacy of medications used to treat peripheral neuropathy improves (Bernát, 2013).

Various case-controlled, pilot- and placebo-controlled studies have shown the benefits of improved microcirculation including blood glucose response and utilization in organ tissue, immune response, physical rehabilitation response, wound healing, pain-free walking due to peripheral arterial disease, and decreased pain and neuropathy. (Klopp, 2013; Balogh, 2013; Rozsos, 2013; Miléder, 2013; Naudé, 2013; Kovács, 2013; Bernát, 2013).

A study (Csécsei, 2013) of 165 patients with difficult PN not well-controlled with medications who underwent five weeks treatment using a PEMF device daily for 25-30 minutes reported results of visual scale (VAS) with a 61% decrease in pain, improvement of the motor performance (25%), elimination of the associated depression (32%), and a significant improvement in the quality of life (75%).

General PEMF Therapy Recommendations

Hydrate prior to therapy session; better results with filtered and structured water (Pai, 2016). Medications/supplements should be administered one hour prior to PEMF Therapy to improve utilization and efficacy. Start low at lower intensity first. More intensity is not better but more frequency treatments. Twice daily or a few times weekly is generally better than a one-time session at higher intensity.

More chronic or severe diseases require a higher intensity and more frequent sessions. PEMF Therapy is considered synergistic before float tank therapy, massage, osteopathic and visceral manipulation and during and after acupuncture. For long-term PEMF Therapy, step down a few settings and increase weekly. By going back to baseline settings, one will be able to prolong benefits and prevent the possibility of tolerance.

PEMF Therapy recommendations (for Physicians who are licensed to treat patients with cancer)

Avoid full-body use during days of chemotherapy (wait one to two days after half-life is eliminated). PEMF Therapy at lower intensity than usual may be used for local area of concern with spot applicator with patients while on chemotherapy and during radiation therapy and is helpful post-radiation to regain capillary function and improve healing response.

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PEMF THERAPY AND VISION: SEEING THE DIFFERENCE

D. Todd Wylie, OD, FCOVD
Advanced Eyecare & Optical
412 E. 30th Avenue
Spokane, WASHINGTON 99203 USA

Introduction

By 2020, one third of the U.S. population will be over 60 years of age. My interests are in all areas of eye care, particularly in vision development and vision therapy, which has led me to believe there is more to eyesight than meets the eye. My other experience is with head trauma patients and nutrition.

My introduction to PEMF Therapy was through a female head trauma patient working for a government agency when her portable phone headset exploded on her head. This completely took out hearing in one ear and resulted in a concussive head injury. We provided some vision therapy and light therapy and examining near-point peripheral vision which gives a snapshot of the volume of information a person can process through the visual system. Progress was slow going until she came in for her third progress visit and her peripheral vision was 50% better. Startling difference after therapy progress had plateaued. When queried whether she had been doing anything differently patient replied she had done 5 PEMFT sessions. She also mentioned her neck and shoulders were feeling noticeably better as well. I had used PEMFT devices in the past in the office and microcurrents with macular degeneration.

An 84-year old male experienced vertigo over a one-year period and determined the vision system was not a contributing factor. After one PEMFT session he sat up, shook his head and claimed the world was no longer moving around the way it had for the past year. One week later he reported to have much more energy than he has experienced in a long time. After further investigation of the published research on PEMF Therapy, its effects made total sense for continued support for the visual system as well as overall health of the whole body.

The complexity of the capillary network of various organs in the human body is astonishing. The retina of the eye has over 2000 capillaries/mm^3 (Fig. 1). This same density of capillaries is also found in the heart, kidney, liver, adrenal glands ad the brain. These same organs will be discussed below with regard to photography of metabolically stressed retinal cells.

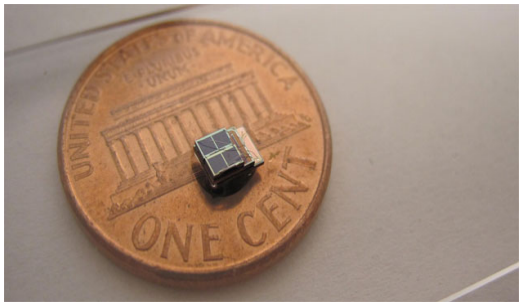

Figure 1. The microchip on the penny represents the scale of 2000 capillaries/mm^3.

Vision

With an ageing population come prevailing vision disorders of cataracts, glaucoma and macular degeneration. Treatment for cataracts these days is surgery, which does not constitute a major problem.

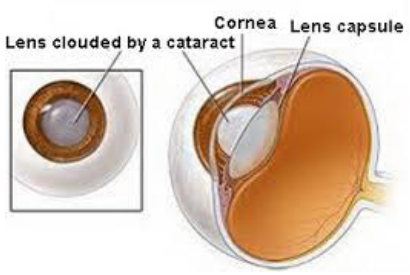

Figure 2. Lens clouding from cataract.

Cataracts

The lens in the eye is where cataracts take place. The lens is built like an onion with layer upon layer upon layer of cells that are spaced perfectly the right distance apart to allow the visible light spectrum to pass through. A cataract is where some of these cell layers start to separate or delaminate, which throws them out of synch. Light hits these layers and bounces or scatters with one of the first symptoms experiencing glare at night.

There is no direct blood supply to the lens. Some vessels are close such as the ciliary muscle, a ring of smooth muscle in the eye's middle (vascular) layer that controls accommodation for viewing objects at varying distances and regulates the flow of aqueous humor. It changes the shape of the lens within the eye but not the size of the pupil, which is carried out by the sphincter pupillae muscle and dilator pupillae. The aqueous fluid containing nutrients circulates around the lens and drains out behind the junction of the iris and the cornea.

It has been exciting to see macular degeneration and glaucoma improving with PEMF Therapy. We have also observed how quickly changes occur in the lens of the eye, which is avascular (without blood vessels).

Results in a 6-month period have shown 36 of 43 patients to have measurable improvement with over 90% to 20/20 vision with 10-20 PEMF Therapy sessions in 2-6 weeks. Several patients showed marked improvement after 10 PEMFT sessions.

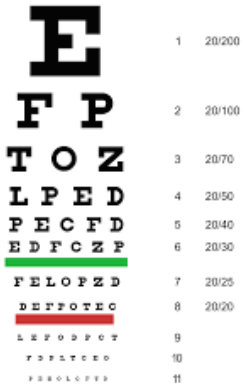

Figure 3. Eye chart showing vision acuity lines.

Case studies

1. A 60-year old male noticed blurry vision and on initial consult had 20/50 vision. A 20/40 vision capability qualifies for a surgical cataract removal procedure. After 10 PEMFT session he progressed from 20/50 to 20/25 and after an additional 10 sessions read the 20/20 line and the cataract had totally disappeared and the lens was completely clear. At the 2-month mark post-PEMFT he was still at the 20/20 line and cataract-free. Interestingly, not long thereafter he shared that he had 4 stents put in his heart for 95-90% blockage. He was not overweight, exercises but still had major clogging of arteries. Lens changes are an indication of your overall health and metabolic efficiency. This patient has been eating pork most every day of the week, which may have been a contributing factor to some of these other health issues.
2. A 62-year old female, super nearsighted, who would have benefitted from cataract surgery which would provide for a lesser prescription. She went from the 20/100 line to 20/50 with 10 PEMFT sessions. Her good eye went from 20/40 to 20/25 with another 10 sessions. Catching cataract patients with PEMFT before surgical intervention is required has shown dramatic results.
3. A 79-year old female patient with mild cataracts and vision of 20/30 improved a few letters after 10 sessions, and reported to have less arthritic feeling in her fingers and arms. Another 10 sessions improved her vision to 20/20 and her knees felt much better coupled with more energy, no depression and overall better feeling.

It should be noted that if a patient does not continue with the PEMFT the beginning cataracts do return over the next several months. Also, if the cataracts are operable then the probability of PEMFT alone reversing the cataracts is significantly lessened.

Macular degeneration

Recent research has shown that the blue end of the light spectrum is a higher energy level of light that tends to produce a physiological effect. With the common use of iPads and iPhone in our digital world and hours spent looking at the emitted blue-white light there are scientific questions to be answered regarding the effects of long-term exposure. A pigment develops in the lens of the eye once we are in our 20s that filters out some of the blue light spectrum to protect the back of the eye. Youth who now spend many hours on these devices have not yet developed this filter. There exist now interreflective coatings and filters in glasses that can help protect the eye from that exposure. This knowledge is in its infancy and additional studies and further education is needed. There are UV absorbing properties in intraocular lens implants but the upper blue light spectrum filtration is not yet addressed. Post-cataract surgery patients using these electronic devices are counseled to use glasses with the blue-light absorbing tint.

Glaucoma

Glaucoma is a disease that is the silent thief of vision. The vast majority of glaucoma patients have no idea they have it until it's quite advanced. On the very front of the optic nerve looking at the retina is a round disk. A fiber optic cable gathering the million nerve fibers that head back into the brain. Traditionally glaucoma was thought of as eye pressure. However, 50% of glaucoma patient have normal eye pressure yet have glaucoma or nerve damage. While pressure in and of itself is extremely important and needs to be controlled, the question is whether it is the sole cause of glaucoma. The mechanism of disease is that some of the million nerve fibers start to die. Pressure in the eye pushes on the tiny capillaries that nourish the nerve where it comes into the eye. However, there is also some evidence that shows glaucoma nerve damage starts back in the brain and moves toward the eye. It is quite evident that PEMF Therapy helps the microcirculation in a profound fashion and the eye is ripe for benefitting from that improved circulation.

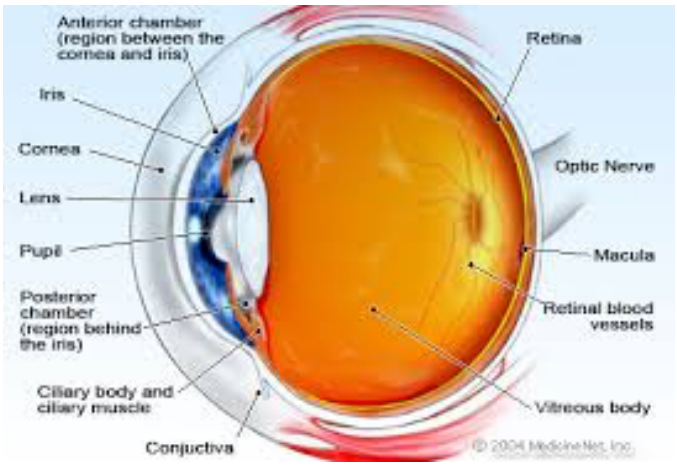

Figure 4. Anatomy of the eye.

Within a month of having a PEMF device in my office I already realized the benefits from having seen head trauma patients. The first patient, a 23-year old female, had a 24/7 headache for an entire year after severe head injury from a bicycle accident involving a car wreck and laying in a coma for a month. One day after her first PEMFT session she was texting her mom that her head did not hurt. Patient had also experienced zero short-term memory for the last year. After two weeks of PEMFT, the first glimpse of short-term memory materialized. After 40 PEMFT sessions she has experienced an occasional headache but at least a 95% reduction of the headache frequency of the past year and slow but steady short-term memory improvement was noted. Her age is her biggest ally because she smokes a pack of cigarettes daily and eats nothing but junk food. In spite of that her young age allows her body to continue healing. It would be interesting to know what PEMFT could do if her body was given proper nutritional fuel.

At about ten times the cost of a PEMF Therapy device the visual-evoked potential (VEP) instrument measures the electrical signal from the retina to the brain and the electroretinogram (ERG) the retinal activity response to light. It has been exciting to see objective documentation that vision is improving.

Dry macular degeneration

The retina in the back of the eye has the highest metabolic need of any tissue in the body. It is literally a sea of blood vessels. The macula is the pinpoint of sharpest light (black dot) with a million light receptors in that central part of the eye. As a person ages there is an increased probability for development of deposits within the retina called drusen. According to the American Academy of Ophthalmology (AAO) drusen occur naturally with age. They are believed to be a result of the eye's failure to eliminate waste products produced by the cells of the eye.

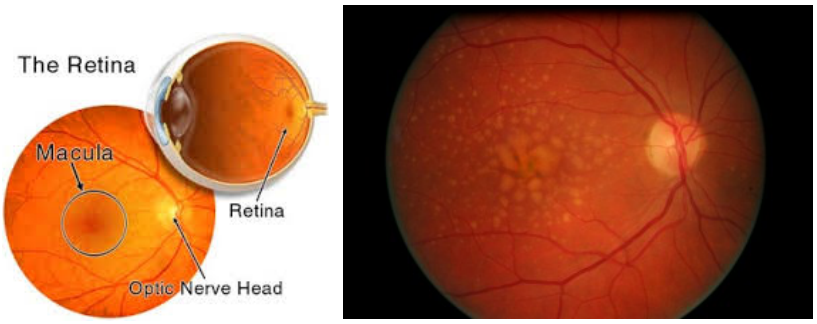

Figure 5. Retina (left) and drusen (right).

The exact relationship between degenerative macular disease and drusen is not clear. Scientists are uncertain whether drusen cause age-related macular degeneration (AMD) or whether AMD and drusen are caused by the same process but are otherwise unrelated. However, the presence of soft drusen is a sign of AMD according to the AAO (2016).

Drusen are the yellow lipid-deposit precursors to dry macular degeneration. PEMFT works on improving the venous side of the microcirculation as well, which allows the removal of waste products in the eye and filtration out of the body versus deposition. The macula has the highest metabolic need of the retina and serves as the canary in the coal mine to see changes take place.

An 86-year old male with normal tension glaucoma and macular degeneration was told by his medical eye doctor that there was nothing more that could be done and he should prepare himself to go blind. He had been doing several things for the past year and a half that slowed down the progression. We had many discussions about sleep habits and a sleep study was done as this was likely oxygen related. Unfortunately, his sleep study results were initially misread but later reinterpreted resulting in the diagnosis of needing more oxygen. The effect of grief from his wife's death made his condition worse and had physiological impacts. He received counseling and support that stabilized his condition. After two weeks of PEMFT using the sleep program his sleep pattern and eyesight started to improve. He was sleeping more soundly and when waking up no longer saw black blotches and squiggly patches dancing in his field of vision. This was now true for both the nights he used the sleep cycle and those he did not. He started seeing a slight improvement in overall vision. He then applied the local PEMFT applicator with three coils over his eyes and alongside his head. He got the most benefit from the lowest program setting. His system was so tenuous and the feedback instantaneous that any application of a higher power was too much.

This was a reminder that less is more. The body does not need to be hit with a 2"x4" board to show improvement. The PEMFT device is appreciated because it is such a low-level electrical activity that emits a pulsed electro-magnetic signal. It carries the message to the blood vessels and cells to help nitric oxide (NO) and vasomotion provide the signal that allows the body to do what it was designed to do. We often believe that more is better but this patient was a classic example that this paradigm does not always hold true.

Another case of an 84-year old male with dry macular degeneration who lives and fishes in Baja California, Mexico. The minimum vision required for an unrestricted driver's license is 20/40. The best he could see was the 20/70 line in the eye that had the worst macular degeneration and the 20/40 line with his better eye. On his first examination we made a visual evoked potential (VEP) measurement as baseline to document any change. With VEP, 3 milliseconds is the variability within a person. If they repeat the test the timing from retina to brain should not exceed 3 ms. A measurement above 3 ms is significant. The patient was encouraged to hydrate with 2 ounces of water every 30 minutes while awake. The intent is not to overhydrate but to provide the body with enough fluid to allow nutrients and oxygen to flow. A chronically dehydrated state is considered a significant contributor to dry macular degeneration due to increased electrolytes, salts, thicker blood, more difficult diffusion in the microcapillaries and definite interference with the transport of oxygen and nutrients. Fluid consumption of more than 8 ounces in one hour tends to pass right through us. We also started the patient on a commercially available nutrient supplement for macular degeneration. Eight PEMFT sessions were performed in 10 days resulting in two lines of vision improvement. His VEP in the good eye sped up by 9 ms and the worse eye by 6 ms.

Two months later the patient started the PEMFT sleep program. He started sleeping most nights for 8 hours for the first time in 35 years. His vision on the macro charts (Amsler Grid) were all good on the left eye. On the right eye the lower left corner was a real mess. Macular degeneration shows distortion or holes in the grid. Patient then spent a whole day doing heavy outdoor exertion and with one PEMFT session negated all the aches and pains from that exercise. His arthritis had been so bad that he needed to lean on a

cart in the grocery store and use a wheelchair in the airport. After one month of PEMFT he was taking the dogs for long walks.

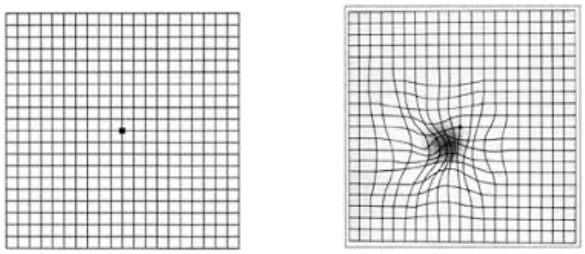

Figure 6. Amsler Grid of left eye and right eye.

Case study: Significant soft drusen in 71-year old female patient

This patient's visual acuity was fortunately not yet severely affected. She could see 20/30 line letters. If one of the large soft drusen deposits was directly under the foveal pit (green line) her visual acuity would likely be reduced to 20/80 or 20/100. With the amount and size of the drusen the prognosis was guarded. Patient commenced PEMF sessions twice daily for 7 months.

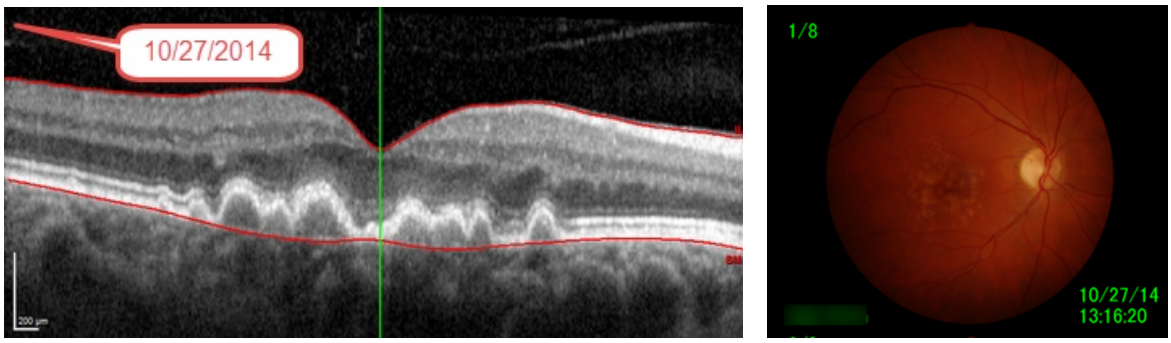

Figure 7a. Initial ocular coherence tomography (OCT) side profile showing large drusen surrounding center of macula.

Patient's visual acuity had improved to 20/20 with quite significant reduction in soft drusen deposits. Interestingly, her left eye did not change at all over this same period. She has additional medical history which could account for the discrepancy in eye to eye results. However, her outlook for improved quality of life has significantly increased.

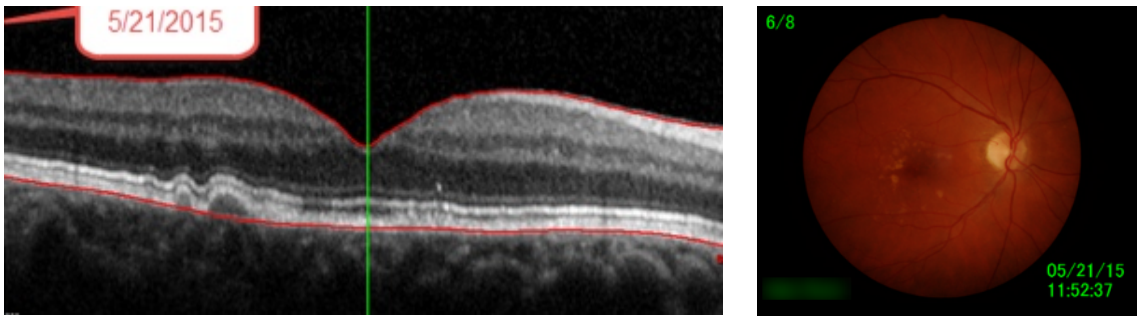

Figure 7b. Patient's OCT seven months after starting PEMFT.

Lipofuscin, the "wear and tear" pigment

Another way of assessing retinal health is by the ability to measure increasing deposits of lipofuscin. Increased amounts indicate retinal cells under metabolic stress. Lipofuscin is a yellowish pigment made of free radical damaged protein and fat. It contributes to drusen formation. Lipofuscin is also known to often contain sugars and metals (mercury, aluminum, iron, copper and zinc). Lipofuscin deposits are also found in the heart, kidney, liver, adrenal glands and ganglion cells in the brain, which are all organs of the body with the highest concentration of capillaries per cubic millimeter. Accumulation of lipofuscin is also implicated in Alzheimer's, Parkinson's, Amyotrophic Lateral Sclerosis and Chronic Obstructive Pulmonary Disease. Lipofuscin deposits can be seen in the retina and will fluoresce or glow under a particular wavelength of light.

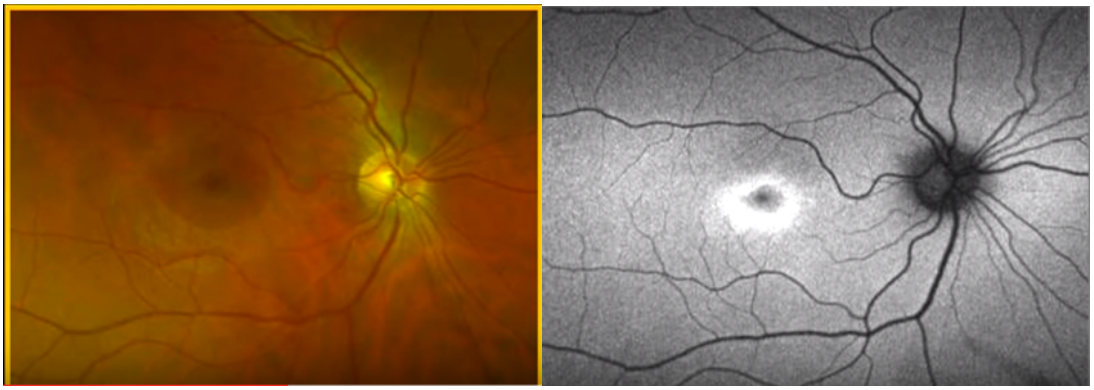

Figure 8. Hyper AF (increased autofluorescence) indicates cell dysfunction/stress. Left: normal appearance; Right: "sick"

Case study: Advanced macular degeneration in 65-year-old female patient

Patient had been diagnosed with AMD in the last 2 years. She had noticed a decrease in clarity of eyesight within the previous 2 months. Visual acuity was 20/40 right eye, 20/25 left eye.

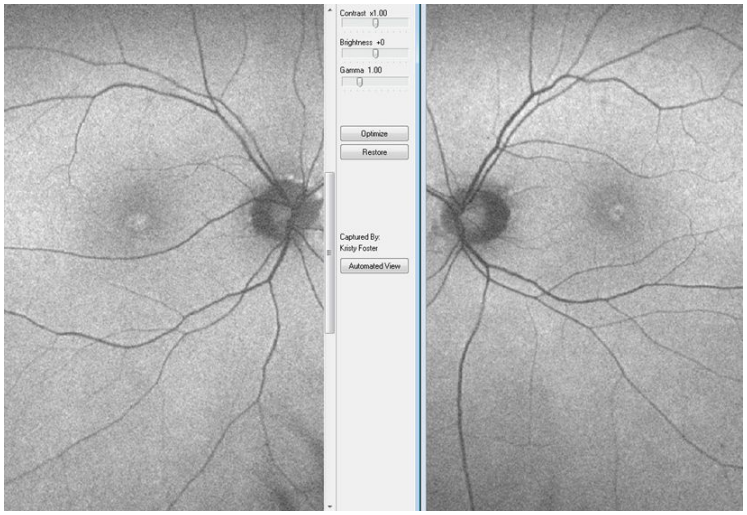

Figure 9. AF photos of right and left eye.

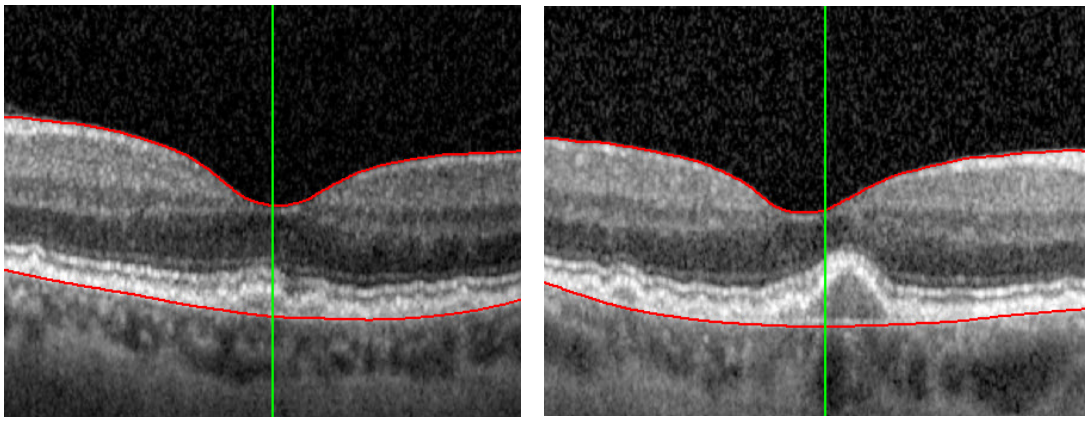

Figure 10. OCT of L eye (left) and R eye (right)

The patient began doing 3 PEMFT sessions in office per week. After 3 weeks and 9 PEMFT sessions patient noted, "I am seeing more clearly." Visual acuity in the right eye improved from 20/40 to 20/20 and left eye improved from 20/25 to 20/20. One additional observation of the effectiveness of PEMFT was after 2 more PEMFT sessions the patient unfortunately slipped at home, fell and broke a hand, toe and when her face hit the floor her glasses frame split her eyebrow requiring 6 stitches. After 4 more PEMFT sessions over the next 9 days she went to the doctor to have the stitches removed. Her physician did a double take and said, "The wound should still be red, I have never seen a wound heal so quickly!"

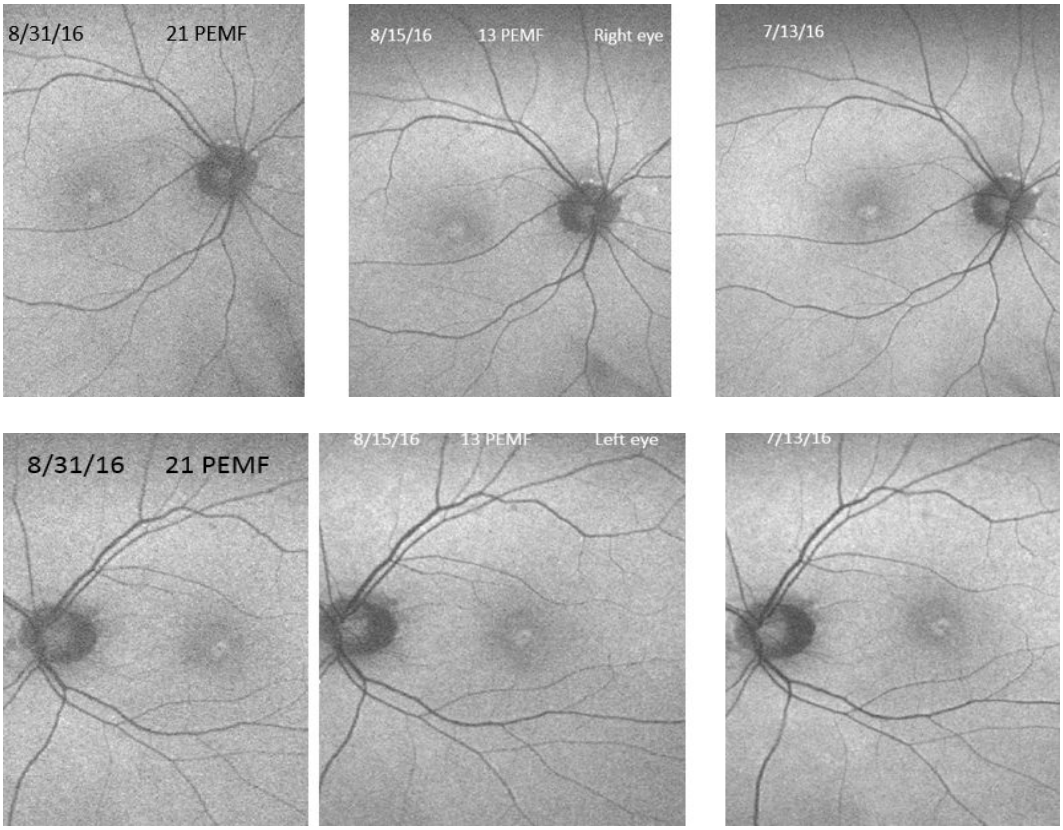

Figure 11a: AF photos over 6 weeks and 21 PEMFT sessions. R eye (top); L eye (bottom).

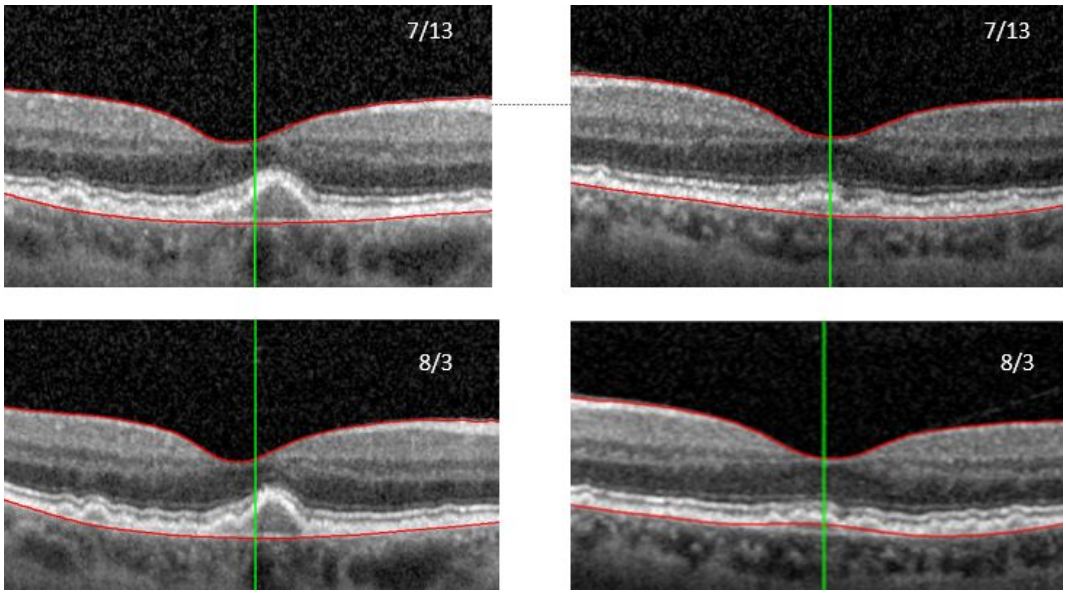

Figure 11b. OCT scans show very slight changes yet AF and visual acuity improvements noted. The patient is very pleased with her clearer eyesight.

In summary, the new AF technology is extremely helpful for finding retinal cells under metabolic stress. This early detection will allow for proactive treatment like PEMFT before cell death has occurred.

PEMF Therapy to date has not been shown to be helpful with wet macular degeneration, which does not leak blood but rather interstitial fluid. Vitamin C is the glue that holds cell membranes together. Several patients are now being treated with high quality Vitamin C supplements to see whether that will help seal some of the leaks.

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THE RULE OF THE ARTERY IS ABSOLUTE: MAINTAINING AND SUSTAINING STRUCTURAL INTEGRITY AND OPTIMAL FUNCTION

Carey Benenson Taussig, DO (MP)
Balance Point Therapeutics, LLC
1000 Cordova Place #360
Santa Fe, NEW MEXICO 87505 USA

Introduction

Dr. Andrew Taylor Still (1829 -1917) was a physician, surgeon, legislator, author, son of a preacher and the founder of Osteopathic medicine, a diverse and unique approach to traditional medicine that uses manual therapeutic techniques to release blockages in the body to support homeostasis. Dr. Still founded the world's first osteopathic medical school, The American School of Osteopathy, now named A.T. Still University, in Kirksville, Missouri. His teachings historically outline how to treat the human body effectively as a functional unit by removing the obstacles which block the fluidics and suppress the hemodynamics.

In a clinical setting the removal of blockages in the body by applying Osteopathic Manipulative Treatment (OMT) and/or Pulsed Electromagnetic Field Therapy (PEMFT) often succeeds in achieving and accelerating healing potential. If blood flow is enhanced systemically or locally tissues have the capability to restore and repair themselves because blood and lymphatic fluid carry the essential building blocks that support cellular metabolism. There exists scientific support from clinical studies demonstrating that certain OMT and PEMFT modalities have shown improvement in patients with certain ailments and disorders.

Osteopathic Medicine

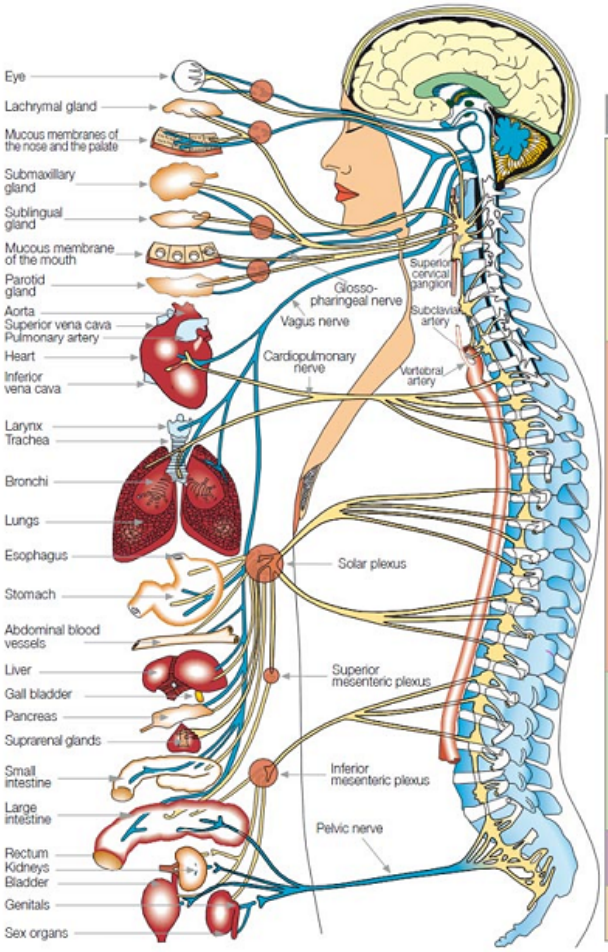
The tenets of Osteopathic Medicine promulgated by the American Osteopathic Association are as follows: 1) the body is a unit; the person is a unit of body, mind, and spirit; 2) the body is capable of self-regulation, self-healing, and health maintenance; 3) structure and function are reciprocally interrelated; and, 4) rational treatment is based upon an understanding of the basic principles of body unity, self-regulation, and the interrelationship of structure and function.

The key principle of Osteopathy maintains that the rule of the artery is absolute. Still (1908) stated “the artery is the river of life, health and ease and, if muddy or impure, disease follows.” The primary goal of Osteopathy is to remove the obstacle creating the blockage so that the artery can transport health to the source.

When pathology is diagnosed or a system presents lack of functionality, it is prudent to consider the interrelationships between the organs and the alignment of the associated vertebra. We know that the sympathetic drive of the organ stems from the ganglion in the spine. Therefore, if a vertebra is out of alignment or is lacking proper nourishment (blood flow and waste disposal), this may cause hypofunction of the organ in which the system is related.

Interrelationships in the body (Fig. 1) include the gut-brain connection (e.g., an embedded rib may cause vagal disruption and therefore trigger a lack of peristalsis due to potential sympathetic overdrive). In immunosuppressed patients assessment of D5-D9 or D12-L2 should be considered because 70% of immunity is generated by the gastrointestinal system. Surgical adhesions can also disrupt functionality by

inhibiting blood and lymphatic flow (i.e., scar tissue is fibrous and can pull connective tissue holding the organ out of alignment). Another example would be a history of whiplash that compromises the ability for the brain and nervous system to receive proper blood flow through the vertebral artery, which makes two ninety degree turns before entering the cranium and can be strained by such incident(s).



VERTEBRAE	AREAS AND PARTS OF THE BODY	POSSIBLE SYMPTOMS
CERVICAL		
C 1	• Back of the head	Headaches (including migraines, aches or pain at the back of the head, behind the eyes or in the temples, tension across the forehead, throbbing or pulsating discomfort at the top or back of head)
C 2	• Various areas of the head	
C 3	• Side and front of the neck	
C 4	• Upper back of the neck	Jaw muscle, or joint aches or pains
C 5	• Middle of neck and upper part of arms	
C 6	• Lower part of neck, arms and elbows	Dizziness, nervousness, vertigo
C 7	• Lower part of arms, shoulders	Soreness, tension and tightness felt in back of neck and throat area
DORSAL		
D 1	• Hands, wrists, fingers, thyroid	Pain, soreness, and restriction in the shoulder area
D 2	• Heart, its valves and coronary arteries	Bursitis, tendonitis
D 3	• Lungs, bronchial tubes, pleura, chest	Pain and soreness in arms, hands, elbows and /or fingers
D 4	• Gall bladder, common duct	
D 5	• Liver, solar plexus	Chest pains, tightness or constriction, asthma, difficulty breathing
D 6	• Stomach, mid-back area	Middle or lower mid-back pain, discomfort and soreness
D 7	• Pancreas, duodenum	Various and numerous symptoms from trouble or malfunctioning of:
D 8	• Spleen, lower mid-back	– Thyroid
D 9	• Adrenal glands	– Heart
D 10	• Kidneys	– Lungs
D 11	• Ureters	– Gall bladder
D 12	• Small intestine, upper/lower back	– Liver – Stomach – Pancreas – Spleen – Adrenal glands – Kidneys
LUMBAR		– Small and large intestines – Sex organs – Uterus – Bladder – Prostate glands
L 1	• Ileocecal valve, large intestine	
L 2	• Appendix, abdomen, upper leg	
L 3	• Sex organs, uterus, bladder, knees	Low back pain, aches and soreness
L 4	• Prostate gland, lower back	Trouble walking
L 5	• Sciatic nerve, lower legs, ankles, feet	Leg, knee, ankle and foot soreness and pain
SACRO	• Hip bones, buttocks	Sciatica, pain or soreness in the hip and buttocks
COXIS	• Rectum, anus	Rectal trouble

Figure 1. Interrelationships (retrieved from chiropracticnyc.com). 24 vertebrae in the spinal column protect the spinal cord made up of billions of nerves. Between each vertebra nerves emerge that lead to internal organs, muscles, ligaments, tendons and other parts of the body (Winsor, H. 1921).

Movement of lymph and blood

Osteopathic Manual Therapy provides relief of many symptoms related to pathological influence and has been scientifically proven to be effective even in cases of *Streptococcus pneumoniae* in nasally infected lab rats. Some OMT modalities include: cranial osteopathy, myofascial release, ligamentous strain, strain-counterstrain, functional release, energetic impulsing, muscle energy techniques, visceral manipulation and lymphatic drainage (Schooley, 1958; Chikly, 2005). The key goal of these therapies is to remove blockages in the body to liberate and enhance the movement of lymph and blood in support of auto-regulation. PEMFT provides an optimal integrative therapy because of its enhancement of blood flow.

Hodge (2012) demonstrated in a clinical study a reduction of *Streptococcus pneumoniae* after lymphatic manual therapy (LMT) performed on nasally infected rats to increase flow of lymphatic fluid that carries white blood cells to tag and combat infection. The study group received one lymphatic pump per second for 4 minutes over 8 days. Lungs were collected and examined showing a significant reduction in bacteria while the control group subjects were unable to clear their lungs.

Importance of PEMF Therapy

PEMFT enhances blood flow (passively in that patients are only required to lay on a mat) and produces cumulative results as an optimal supportive tool. This is especially noted when used over 6+ weeks and incorporates a sleep or nap mode where a lower frequency is applied over longer periods (called PEMFT naps) to more compromised patients.

The electro-magnetic field: The beginning and continuum

The electromagnetic field begins as an invisible electromagnetic signal (in a torus-shaped field) that comes from the embryonic protoplasm. The signal radiates and returns in waves as the embryo begins to recognize the difference between self and intrusion. This wave develops before the heart develops (lymphatic system develops at week 5, heart at week 7). As we live and breathe the hemodynamic flow consists of a spiraling motion through the vessels in a lemniscate pattern. Therefore, hemodynamics creates a field by stimulating an enzymatic cascade in the vessels.

The organs reference the axis of motion which are established in embryological development *in utero*. As the thoracic diaphragm descends in inspiration the motility of viscera continues to regenerate the field as do the ventricles in the brain that house the production of the cerebrospinal fluid (CSF) from the choroid plexus. The CSF spirals around the thalamus through the third ventricle before it descends into the fourth ventricle entering the aqueduct of Sylvius, again regenerating the field.

Vascularized bones and nerves

Treatment of dysfunction in the spine requires assessment of proper alignment of vertebrae and correction of any misalignments. It is essential to consider blood flow to the nerves that exit the vertebral foramen (Fig. 2) as well as the blood supply to the vertebra itself to release some of the more chronic strains that may be present. Inhibition of blood flow and venous drainage can often have a larger impact than facilitated blood flow (increased flow into an area).

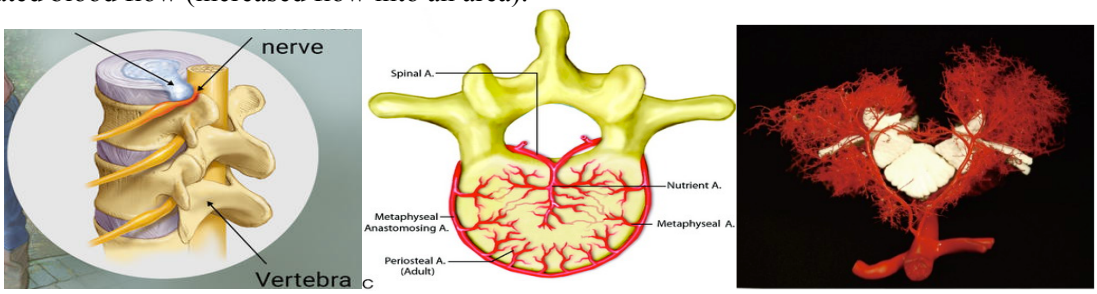


Figure 2. Vertebral anatomy, blood flow and microvasculature.

A 72-year old female suffering an acute herniation (T4/T5) reported relief once PEMF therapy was applied. Once the spasms had settled OMT was successfully applied in order to align the spine (through soft tissue techniques) to re-establish translation of the lines of gravity.

A 62-year old female was not a candidate for surgery given clear presentation of resonance imaging (i.e., no impingements, bulging discs or calcifications present). OMT could not reach the strain. A single PEMF therapy application allowed the patient to feel her toes for the first time in 20 years. OMT was then applied to facilitate improvement of strains in the connective tissue that was too rigid to move without discomfort in prior sessions.

Lyme disease linked to pathologies

Lyme disease is a systemic disease (Baranova et al., 2012; Halperin et al., 2012; 2013) that has challenged specialists by often presenting symptomatically like autoimmune disorders. Presentations include those of rheumatoid arthritis, cardiac disorders, Lupus, Alzheimer's Disease, Parkinson's, Lou

Gehrig's, Multiple Sclerosis, chronic fatigue, fibromyalgia, psychiatric disorders, neuropathies and neuralgias, and gastrointestinal disease and inflammation. Patients suffering from autoimmune disease comprise over 23.5 million cases in the U.S. Medical studies have linked several of these pathologies to Lyme disease.

The Center for Disease Control and Prevention (2013) reports Lyme disease as the number one vector-borne illness in the U.S., Canada, Europe and Japan. 30,000 cases reported in 2012 jumped to 300,000 in 2013.

The bacterium *Borrelia burgdorferi* (Bb) thrives without oxygen. The coil-shaped, anaerobic Bb burrows where oxygen and blood flow is inhibited (opportunistic pathogen). There have been few randomized clinical trials of treatment, so optimal choice of antibiotic or optimal duration of treatment are not known. In general, early Lyme disease in adults is treated with doxycycline (100 mg orally twice daily) or amoxicillin (500 mg orally three times daily for 20 to 30 days). There was a shortage of doxycycline in 2013 (CDC). PEMFT enhances oxygen transport to capillaries and thus may be considered an optimal tool (Dr. Dietrich Klinghardt, pers. comm.) in supportive therapies.

Table 1. Lyme disease timeline

1800s:	Diphtheria and Tuberculosis
1883:	Lyme first discovered in Germany by Alfred Buchwald
1976:	Lyme, Connecticut: children discovered with rheumatoid arthritis
1981:	Burgdorfer W et al. (1982) discover *Borrelia burgdorferi* (Bb)
1999:	Costerton JW et al. (1999) discover microbial biofilm (bacterial society)
2014:	Deer tick *Ixodes scapularis* and sheep tick *Ixodes ricinus* complex
Note:	5,300 years before present the Tyrolean iceman mummy Ötzi may hold the earliest evidence of Lyme disease (Keller et al., 2012)

OMT/PEMFT application to Lyme and Autoimmune disease

Digestion, detoxification and drainage are clinically examined in patients suffering from symptoms related to Lyme and autoimmune disease. OMT and/or PEMFT is applied to areas that channel the blood and support the detoxification potentials. The key areas assessed where therapies applied are: superior mesenteric artery, portal vein, and inferior vena cava. Through application of cranial osteopathic techniques more fluidic balance is achieved by aligning and opening the ventricles and venous sinuses. Drainage is improved by opening or stimulating the key areas linked to the lymphatic system: left clavicle, cisterna chyli, and inguinal lymph nodes. Endotoxins can often congest areas where the immune system is reliant. The mobility and potential of the thymus, spleen, and long and flat bones (bones rich in marrow) are also considered. The endocrine system needs balance to ensure optimal blood flow and venous drainage to and from the hypothalamus, pituitary and adrenal glands (HPA axis stabilization). The endocrine system also supports the potential of the parasympathetic nervous system and is linked to its limbic and involuntary functions. PEMFT application twice daily or 2-3 times per week at a minimum can help maintain results and help the patient passively clear deep congestion inhibiting the life force or circulatory system.

New Discoveries: The Brain

Ninety percent of Lyme patients in clinic present a history of head trauma. Injury to orbital/frontal areas triggers insomnia and restlessness. Studies from the University of Virginia have linked the immune system to social behavior and have connected the brain to the immune system as new vessels have been discovered (Filiano et al., 2016). The Glymphatic System was named by the University of Rochester presenting evidence that the glia creates a network of fluidic flow like the lymphatic system (Jessen et al. 2015).

Antibiotic resistance or Endotoxin/Toxic Load?

Capillaries comprise 74% of the circulatory system (vasodilation- and vasoconstriction-driven by a spontaneous vasomotion) and are non-responsive to commands from the endocrine system, CNS, or medications due to lack of striated muscle and receptor sites to receive the messages. The lymphatic system scans for pathogens in the capillary bed where the arterioles and venules interface (Fig. 3). Endotoxic or environmental toxic loads may congest these deep capillary beds that subsequently inhibit the function of the lymphatic and immune system. The influence and congestive qualities of the capillary bed biofilm may perhaps interfere with the body's ability to utilize and metabolize antibiotic interventions. OMT or PEMFT as tools that enhance blood flow in the circulatory system as a whole might prove these interventions as more effective.

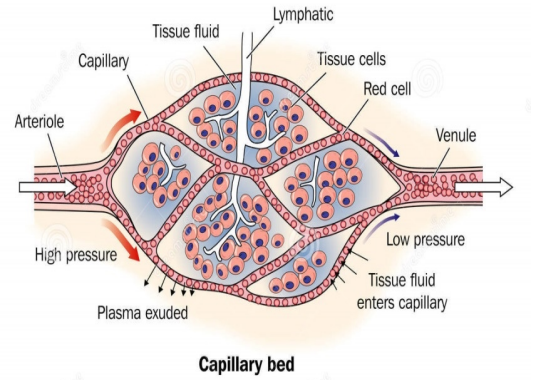


Figure 3. Capillary bed structure and function.

Influence of surgical adhesions/scars: PEMF Therapy Reboots the Hydraulics

Organs rely on lubrication from the interstitial fluid to glide properly with each compression and release of the thoracic diaphragm. Surgical adhesions and scars can influence the alignment of the organs in the abdomen and can potentiate a dryness surrounding the organs. The key immune dispatch centers that may be influenced by scar tissue lie in the intestines: Brunner's Glands (duodenum), Peyer's Patches (Ileum), and Appendix (Cecum). Just below the lumen in the intestinal wall at these sites a T-lymphocyte aggregation is present ready to dispatch if the flora of the biome shifts away from the norm or if a mass of antigens is detected. Intestinal epithelium monitors the mucosa for pathogens (Fig. 4).

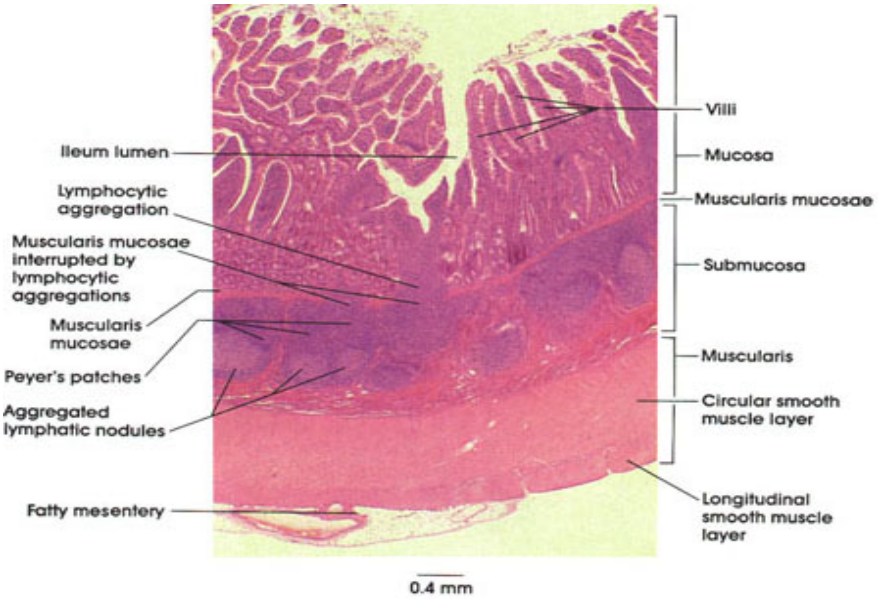


Figure 4. Intestinal cross-section.

Clinical applications and case studies

1. **Parietal Subdural Hematoma:** A 65-year old retired schoolteacher was left paralyzed on the left side from a subdural hematoma. Scar tissue presented challenges for cranial OMT therapy in addition to difficulties in repositioning the patient. One PEMFT session was applied to the right parietal lobe, which resulted in movement of patient's left side phalanges.

2. **Charcot's Foot:** Patient was diagnosed with softening of the cuboid bone with neuropathy and diabetic complications (Charcot's foot). This condition can often result in amputation. OMT and PEMFT were applied to the navicular bone and tibiotalar joint. The diagnosis was revised after 2 weeks since changes were sighted after new imaging was done.

3. **Multiple Sclerosis:** A 32-year old female diagnosed with multiple sclerosis was not responding to care and presented with increased weakness. Therapies applied included chemical/nutritional analysis (Lyme disease was suspected), and OMT through cranial osteopathy to encourage enhancement of venous flow in straight sinus. Techniques were applied to support nourishment of bone marrow and to open immune dispatch areas in abdomen. Results included a slowed degenerative pattern and an eventual pregnancy.

4. **Diabetes:** A 68-year old female with uncontrolled diabetes underwent PEMFT and OMT resulting in discontinuation of her insulin with simultaneously more energy, ability to exercise, and loss of weight.

5. **Multiple Chemical Sensitivities/Environmental Illness:** A 59-year old female presented with a history of extensive bone infection in the mouth. Her history included twenty traumatic dental surgeries and over 200 stitches in the forehead from a multi-vehicle accident. Diagnosis was slow healing, inability to get teeth, spinal cord injury and maxillary osteoma. Oxygen was prescribed for extreme multiple chemical sensitivities/environmental illness (MCS/EI) and electromagnetic field exposure (with documentation of electric smog). OMT was applied (standard care of facial bones) and PEMFT (2-3 times daily to cranium). Results included instant cessation of reactions with PEMFT application and no further need for oxygen was indicated. The MCS/EI was 80% resolved. Dental pain improved and patient proceeded with fitting for dentures within a week.

6. **Migraine:** A 60-year old female presented with **a** history of chronic migraines since her 30s. OMT sessions (1 x week) and PEMFT (daily for 4 weeks) were applied. Results included a migraine-free record for 102 consecutive days.

7. **Lyme Disease:** A 47-year old mother and her family received treatment with antibiotic/herbal applications for 18 months. The mother reported chronic lumbar back pain that was not relieved by OMT. Other symptoms included brain fog, joint pain, fatigue, which was particularly difficult for her as an athlete. She was unable to cope and plateaued in care. Applied therapies included OMT (primarily at mesenteric root) and PEMFT (twice daily) were applied. A cyst in lumbar spine (L2/L3) eventually resolved through surgery and congestion did not return. PEMFT helped patient avoid Herxheimer reaction (detoxification) that often followed from her OMT sessions. She successfully stopped her IV therapy and antibiotics and returned to athleticism, energetic nature, and stability. The son who presented with a long history of on and off viral activity (including mononucleosis), learning disabilities, and malaise, returned to functioning well in life. Now he is thriving in school and rides his bike and the daughter is a star basketball player.

Summary

The body has a phenomenal potential to heal itself once the correct channels are opened to provide nourishment and auto regulation capabilities to the tissues. If a patient's left clavicle is compacted at the

level of the sternoclavicular joint, the lymphatic system is not capable of draining at the level of the subclavian vein. If surgical adhesions and scar tissue are creating a dryness around the Glisson's capsule of the liver that depends on movement induced by the thoracic diaphragm to rotate around its three axes of motion, the parenchymal tissue cannot properly expand and retract to maintain optimal function of the liver itself.

Clinicians need tools to help support the whole organismal system. The focus needs to be on enhancing and inducing better fluidic flow. Promotion of optimal health occurs through enhancement of carrying building blocks the body requires to support cellular metabolism, ATP production, and cellular differentiation. OMT is an extremely effective tool and provides care to the most chronic patients. However, it remains challenging to find extensive OMT sessions nationally. PEMFT, however, is an optimal tool to help patients maintain what they have achieved in their care as well as continually opening channels of nourishment, drainage, and detoxification.

The body is a mechanism designed to self-repair. Many case studies and medical trials document the healing potential of the body if the natural pathways are supported. If adequately nourished, the entire body functions to maintain, repair and heal itself to the best advantage if its structures (Magoun, 1966). Change happens when we tune into what truly supports our existence.

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PANEL OF EXPERTS – AUTHOR BIOGRAPHIES

ULISES BALTAZAR, MD, FACS, RVT

Dr. Ulises Baltazar has vast experience treating venous insufficiency, varicose veins and venous stasis ulcers using laser, radio frequency, mechano-chemical ablation and surgery. Dr. Baltazar completed his medical education at La Salle School of Medicine in 1986. He finished his general surgery residency at the General Hospital of Mexico City followed by general surgery training at East Tennessee State University in Johnson City, where he was administrative chief resident and received the award for outstanding performance. He then finished a vascular and endovascular surgery residency at Baylor College of Medicine in Houston, Texas where he was again the administrative chief resident and received an award for his performance. Dr. Baltazar is certified by the American Board of Surgery in vascular surgery, is a Fellow of the American College of Surgeons and a member of the American College of Phlebology. He is also certified by the American Registry for Diagnostic Medical Sonography as registered vascular technologist and registered physician in vascular interpretation. Dr. Baltazar is a Vascular Surgeon at Methodist Hospital in Sugar Land, Texas.

FREDERIC UNRATH

Mr. Frederic Unrath is the Executive Director of the International Microvascular Net (IMIN). Mr. Unrath's extraordinary organizational skills and experience in marketing have paved the way for him to fulfill his role as a bridge builder. He has helped bridge the gap between medical device manufacturers and leading researchers to bring innovative technology to both public and medical circles. Fred has over 20 years of experience and has been involved in many research projects and developments of diagnostic systems and treatment modalities in the field of Microcirculation.

IVO TORRES FILHO, MD, PHD

Dr. Ivo Torres' research focus has played a significant role in our ability to understand physiological mechanisms in health and disease as it relates to microcirculation. By applying novel techniques and methods, he and his teams use various experimental strategies to investigate the pathophysiology of specific cardiovascular conditions and their treatment. He was one of the pioneers in the early research of vasomotion in a bat wing model. The main focus of his recent studies have been directed towards endothelial cell function, specifically on the glycocalyx structure and function *in vivo*. As part of the translational physiology research, his studies also focus on hemorrhagic shock, and factors that affect the local distribution of oxygen and blood flow. A key and unique component of the approach is to integrate traditional systemic physiological parameters, blood biomarkers, and microvascular variables such as; microvascular permeability, leukocyte-endothelial interactions, platelet-endothelial interactions, and local blood flow measurements in addition to *in vivo* glycocalyx determinations. With his extensive experience as research physiologist at the Damage Control Resuscitation Group as well as the US Army Institute of Surgical Research, Dr. Torres has held a key position in the United States Department of Defense research team.

RAINER C. KLOPP, MD, PHD

Dr. Rainer Klopp founded the Institute for Microcirculation in Berlin, Germany and is a leading researcher in the field of Microcirculation. He has over 120 scientific publications in scientific and clinical research and is the recipient of multiple scientific awards. Dr. Klopp has conducted world-renowned research in the fields of Biophysics, Cardiology, Angiology, Oncology, Internal Medicine and Dermatology. He is the founder of the Institute for Microcirculation in Berlin, Germany. Dr. Klopp was

commissioned by the International Society of Geriatrics to investigate non-invasive, non-drug alternatives to assist geriatrics with chronic conditions, reducing their need for pharmaceutical medications and medical treatments. He is also a holder of multiple patents and an innovator of technology in science and medicine.

THOMAS DERFUSS

Mr. Derfuss is an engineer in Giessen, Germany, and manages LEA Medizintechnik GmBH as Chief Executive Officer. He is the developer of the LEA O2C, a non-invasive diagnostic device for the measurement of microcirculation in the capillary-venous part of the vascular tree. The measurement method is a combination of the laser Doppler spectroscopy for determination of blood flow and the white light spectroscopy for determination of oxygen saturation and relative amount of hemoglobin in the tissue.

JOSHUA D. BERKA, NMD

Dr. Joshua Berka is certified as a Naturopathic Doctor, Diplomate of Acupuncture, and is a certified Functional Medicine practitioner. He has served as an educator and clinician both in the U.S. and abroad. Dr. Berka is also an adjunct faculty member of the Institute of Functional Medicine and has been an Integrative Medicine advocate for many years. His goal has been to build networks, supporting the process of bridging the scientific communities and medical disciplines in support of healthcare and wellness. He specializes in the use of PEMF and LASER Therapies in both clinical and home healthcare. Dr. Berka is a member of the Microcirculation Society in San Diego, CA. He serves as the medical director of Infinity Health Source and BEMER USA as well as board member of multiple organizations.

ROBERT B. CHESNE, MD, FACC

Dr. Robert Chesne is board certified in Internal Medicine and Cardiology. He is also involved in academic education in his position as Associate Clinical Professor of Medicine at University of Southern California School of Medicine and Director of the Coronary Care Unit at the Hospital of the Good Samaritan, Los Angeles, California. Dr. Chesne is dedicated to his clinical practice and teaching and has multiple scientific publications regarding vasculature conditions that have provided much support and insight to the research community. His involvement as Director of Cardiology and Chief of Staff at Centinela Freeman Hospital Medical Center has been a remarkable contribution. Dr. Chesne has also contributed his expertise and talent as the Director of Cardiology at the Tommy Lasorda Heart Institute.

SUNIL PAI, MD

Dr. Sunil Pai is a board certified Medical Doctor in Holistic Integrative Medicine. Dr. Pai completed his residency in Family Medicine at the University of New Mexico. He is certified by Dr. Deepak Chopra as a Primordial Sound Meditation Instructor and a Creating Health (Ayurveda Lifestyle) Instructor. He is also certified in Functional Medicine, Physiological Regulating Medicine, Medical Acupuncture and Neuro-Acupuncture through UCLA and Stanford University School of Medicine. Dr. Pai is the Vice President of the Neuro-Acupuncture Institute, a non-profit organization focused on teaching physicians neuro-acupuncture to treat pain conditions and neurological dysfunction such as stroke, Multiple Sclerosis, Parkinson's disease and traumatic brain injury. Dr. Pai is a Deacon of the House of Sanjevani Integrative Medicine Health & Lifestyle Center located in Albuquerque, New Mexico. As a nonprofit organization, they provide full service health education and Integrative Medicine services with emphasis on indigenous and natural medicines. Dr. Pai recently released his highly anticipated book, *An Inflammation Nation*, which describes the health benefits of plant-based diets and the use of natural anti-inflammatories for the prevention and treatment of chronic diseases and cancer.

D. TODD WYLIE, OD, FCOVD

Dr. Todd Wylie is board certified in Vision Development and Vision Therapy by the College of Optometry in Vision Development. His love for innovative technology has advanced his treatment methods in vision care and rehabilitation at his private practice in Spokane, Washington. Dr. Wylie is also the charter member of the Neuro-Optometric Rehabilitation Association. As a medical director of Advanced Eye Care

& Optical, Dr. Wylie's innovative vision care techniques truly delivered many remarkable results by his patients. Dr. Wylie thoroughly enjoys helping children and adults with vision-related learning disabilities, head trauma rehabilitation utilizing nutrition, PEMF therapy, and other treatment modalities to help improve eye health and wellness.

CAREY BENENSON-TAUSSIG, DO (MP)

Dr. Carey Benenson-Taussig is a certified graduate of the *Collège d'Études Ostéopathiques* and is affiliated with the *Swiss International School of Osteopathy (SICO)* as well as the *Canadian School of Osteopathy* in Vancouver, British Colombia. Dr. Benenson-Taussig specializes in Visceral Manipulation in her practice and is known for her work with the brain, Lyme disease, auto-immune disorders, and performs chemical and nutritional analyses. She is trained in the traditional philosophy of Osteopathy and has a Bachelor's degree in Mass Communication from Boston University. Dr. Benenson-Taussig enjoys public speaking both locally and internationally by offering her lectures on the healing potential of the human body according to classical Osteopathic principles as well as in the field of biodynamics. She also holds a weekly educational radio program, *Balance Point,* and is known for her achievements in her work with the brain and the immune system.