PEMF And Effects On Endothelial Cells For Wound Healing

PEMFs may provide unique research opportunities in the field of wound healing by boosting endothelial cell development and enhancing the endothelium's healing response, according to the findings

The clinical benefits of pulsed electromagnetic fields (PEMF) have been demonstrated, however the mechanism of action is unknown. The current study looked at the effect of PEMF on angiogenesis, a process that is crucial for effective tissue healing. PEMF boosted the tubulization (sevenfold) and proliferation (threefold) of endothelial cells in vitro. PEMF cultures' media displayed a similar stimulatory effect, but heat denaturation stopped it.

Furthermore, conditioned media induced proliferative and chemotactic alterations in human umbilical vein endothelial cells and fibroblasts, but not in osteoblasts. A fivefold rise in fibroblast growth factor beta-2 (FGF-2) was discovered in angiogenic protein screening, as well as lesser increases in other angiogenic growth factors (angiopoietin-2, thrombopoietin, and epidermal growth factor). Northern blot examination revealed an increase in FGF-2 transcription, and PEMF was suppressed by a FGF-2 neutralising antibody.

PEMF exposure boosted angiogenesis by more than threefold in vivo. PEMF enhances angiogenesis predominantly through boosting endothelial FGF-2 release, resulting in paracrine and autocrine alterations in the surrounding tissue, according to the findings. PEMF may play a role in therapeutic angiogenesis, according to these studies.

PEMF technologies have been demonstrated to be effective as an adjuvant therapy for the treatment of both delayed-union fractures1 and chronic wounds.

These relatively simple devices deliver short bursts of electrical current in wounded tissue without causing heat or interfering with nerve or muscle function using an external, non-invasive PEMF. Increased understanding of PEMF therapy's mechanism of action has recently allowed for technological advancements, resulting in low-cost, disposable PEMF devices.

PEMF therapy has been expanded to cover the treatment of postoperative pain and edoema in both outpatient and home settings3 thanks to these devices, giving physicians a more adaptable tool for patient management.

Poor presentation and, in many cases, insufficient comprehension of the scientific basis of action hindered the early development of PEMF technology and its evolution over the last century. Plastic and reconstructive surgeons, on the other hand, were early adopters of the therapy and pioneers in creating what is now a major and rigorous body of knowledge on the mechanism of action, alongside their basic science colleagues.

The history, development, and eventual transformation of a marginal therapy into a technology that, if it lives up to its potential, will become a standard part of surgical care and may lead to other, more significant therapies for a variety of acute and chronic conditions are described in this review.

Many of the benefits of Pulsed Electro-Magnetic Field ("PEMF") therapy have been demonstrated in over 2,000 university-level, double-blind medical studies conducted in a variety of countries using various PEMF therapy devices. By the mid-nineteenth century, some of the beneficial effects of PEMF therapy had been demonstrated. In the early 1900s, the first commercially available low-power PEMF devices hit the market.

These were employed in healing and cellular health research and experiments. They were sold to both consumers and physicians as medicinal gadgets. Around 1975, the first commercially available high-power PEMF devices hit the market. They concentrated on bone, muscle, nerve, tendons, ligaments, and cartilage health, as well as pain reduction and cellular and tissue regeneration.

PEMF therapy for medical purposes has been approved in a number of nations across the world. In 1979, the US Food and Drug Administration approved the use of PEMF devices for non-union bone fracture healing, urinary incontinence and muscle stimulation in 1998, and depression and anxiety in 2006.

The use of PEMF devices for migraine headaches has been approved in Israel. PEMF devices are legal in Canada for a variety of applications. PEMF therapy has been approved by the European Union for a variety of applications, including healing and recovery from damage, degeneration, and the treatment of pain associated with these illnesses.

PEMF Therapy's Main Advantages

PEMF therapy relieves pain linked with trauma from accidents, sports injuries, surgeries, and burns, as well as pain related with disease and degeneration, according to clinical evidence.

PEMF therapy heals these diseases in a number of ways at the same time, including mechanical, chemical, electrical, and magnetic processes within the body's cells.

Siskin and Walker published an overview of clinical findings on soft tissue damage in 1995. They found no negative effects and found the following favorable effects:

- Pain is lessened.
- Inflammation is reduced, and range of motion is increased.
- Improved functional recovery time
- Muscle loss after surgery is reduced.
- Increased ligament tensile strength
- Skin wounds heal more quickly.
- Capillary formation is improved.
- Nerve regeneration is accelerated.
- Tissue necrosis has been reduced.

Nitric Oxide Production and PEMF Therapy

Nitric oxide is produced by many cells in the body, but it is especially crucial in the regulation of blood flow by the vascular endothelium. Blood flow and other vascular processes can be harmed by abnormal nitric oxide production, which occurs in a variety of illness situations.

Nitric oxide is one of the few known gaseous signalling molecules, and it's even more unique because it's a radical gas. It is an important biological messenger in vertebrates, and it plays a role in biological processes.

The research "Evidence-Based Use of Pulsed Electromagnetic Field Therapy in Clinical Plastic Surgery" was published in the Aesthetic Surgery Journal in March/April 2009, and it highlights the advancement in the understanding of the physiological effects of PEMF therapy on cells and tissues.

PEMF was found to affect the production of growth factors in studies, and researchers began to focus on enzyme systems with well-defined calcium (Ca2+) dependence. Researchers began looking at the effects of electrical and PEMF signaling on intracellular Ca2+, specifically Ca2+ binding to calmodulin (CaM), in the mid-1990s, based on the understanding that CaM-dependent cascades were involved in tissue repair.

The Ca/CaM-dependent nitric oxide cascades, which are crucial in tissue repair, have been the focus of current research of the PEMF transduction route. The effectiveness of PEMF

is now understood to function inside this system. PEMFs alter the kinetics of calcium binding to calmodulin. Calcium/calmodulin (Ca/CaM) then activates numerous distinct isoforms of nitric oxide synthase (NOS). Long-lived inducible nitric oxide synthase produces a high amount of nitric oxide when an injury occurs (iNOS).

In this cascade, tissue levels of nitric oxide persist, and the presence of this free radical for an extended period of time is proinflammatory, which explains the leaky blood vessels that accompany pain and swelling. Endothelial and neuronal nitric oxide synthase isoforms (eNOS and nNOS, respectively) generate nitric oxide in brief bursts that relax blood and lymph arteries instantly.

These brief bursts of nitric oxide also result in the formation of cyclic guanosine monophosphate (cGMP), which stimulates the creation of growth factors. iNOS is not dependent on CaM, but the constitutive or cNOS (eNOS or nNOS) cascade is dependent on Ca/CaM binding.

As a result, therapies that can speed up Ca/CaM binding should have an impact on all stages of tissue repair, from acute pain and swelling to blood vessel expansion, tissue regeneration, and remodelling. This mechanism has been offered as a working model for PEMF treatments, as seen in the diagram below.

Various nitric oxide synthase (NOS) enzymes biosynthesize nitric oxide, also known as 'endothelium-derived relaxing factor,' or 'EDRF,' from L-arginine, oxygen, and NADPH. Dr. Richard E. Klabunde discusses how the enzyme nitric oxide synthase produces nitric oxide from the amino acid L-arginine (NOS). Constitutive NOS (cNOS; type III) and inducible NOS are the two types of NOS found in endothelial cells (iNOS; type II).

In addition to endothelial NOS, there is a neural NOS (type I) that acts as a transmitter in the brain and various nerves of the peripheral nervous system, such as non-adrenergic, non-cholinergic (NANC) autonomic nerves that innervate penile erectile tissues and other specialised tissues in the body to cause vasodilation.

Nitric oxide is used by the endothelium (inner lining) of blood arteries to signal surrounding smooth muscle to relax, resulting in vasodilation and increased blood flow. Nitric oxide is continuously generated by cNOS in the blood arteries under normal conditions. When the endothelium is intact, cNOS activity is Ca/CaM dependent and results in vascular relaxation.

The other isoform of endothelial NOS, iNOS, does not require calcium for activation. iNOS activity is quite low under normal circumstances. Bacterial endotoxins or cytokines like tumour necrosis factor (TNF) and interleukins promote the activation of iNOS during

inflammation. The amount of nitric oxide produced by iNOS during inflammation may be 1,000 times more than that produced by cNOS.

Mechanisms That Occur Within Cells

Nitric oxide is extremely reactive (with a lifetime of a few seconds) but diffuses freely across membranes, owing to the strong affinity of superoxide anion for nitric oxide. In addition to its tissue-damaging actions, superoxide and its derivatives can have vasoactive properties; the superoxide anion has another trait that makes it particularly significant in cardiovascular pathology and pathophysiology.

With its unpaired electron, the superoxide anion bonds to nitric oxide, which also possesses an unpaired electron, relatively quickly. Because nitric oxide is a potent vasodilator, the interaction between superoxide and nitric oxide efficiently scavenges the molecule, lowering its bioavailability.

Vasoconstriction, increased platelet-endothelial cell adhesion, platelet aggregation and thrombus development, increased leukocyte-endothelial cell adhesion, and morphologic changes in blood vessels, such as cell proliferation, are all consequences of this.

Nitric oxide also binds to haemoglobin (found in red blood cells) and guanylyl cyclase (present in vascular smooth muscle cells and most other cells in the body). When vascular endothelium produces nitric oxide, it quickly diffuses into the bloodstream, where it binds to haemoglobin and is broken down. It also diffuses into the endothelium-adjacent vascular smooth muscle cells, where it binds to and activates guanylyl cyclase.

This enzyme catalyses the dephosphorylation of GTP to cGMP, a second messenger involved in a variety of cellular processes, including smooth muscle relaxation signalling.

Because cGMP plays such an important role in nitric oxide-mediated vasodilation, drugs that inhibit the breakdown of cGMP (cGMP-dependent phosphodiesterase inhibitors) are used to improve nitric oxide-mediated vasodilation, especially in penile erectile tissue, in the treatment of erectile dysfunction. Increased cGMP possesses anti-platelet and anti-aggregatory properties.

PEMF therapy affects various transduction pathways, including the Ca/CaM-dependent nitric oxide cascades, as shown in the research above. Tissue healing is aided by CaM-dependent cascades. The endothelial and neuronal nitric oxide synthase isoforms (respectively eNOS and nNOS) generate nitric oxide in brief bursts that can relax blood and lymph arteries by changing the calcium-binding kinetics to calmodulin (intracellular

Ca2+/CaM). Nitric oxide, as a highly reactive gaseous molecule, is a suitable transitory paracrine (between nearby cells) and autocrine (inside a single cell) signalling molecule having direct and indirect vascular action, such as:

- Indirect vasodilation by blocking vasoconstrictor influences
- Anti-thrombotic effect - inhibits platelet adhesion to the vascular endothelium
- Anti-inflammatory effect - inhibits leukocyte adhesion to the vascular endothelium; scavenges superoxide anion
- Anti-proliferative effect - inhibits smooth muscle hyperplasia

PEMF therapy can successfully help improve conditions and diseases associated with vasoconstriction (e.g., coronary vasospasm, elevated systemic vascular resistance, hypertension), thrombosis due to platelet aggregation and adhesion to vascular endothelium, inflammation due to upregulation of leukocyte and endothelial adhesion molecules, and vasculitides due to upregulation of leukocyte and endothelial adhesion molecules

Nitric oxide is involved in synaptic plasticity and memory functions, as well as modulating the immunological response to infection (see diagram above). Nitric oxide is used by the endothelium (inner lining) of blood arteries to signal surrounding smooth muscle to relax, resulting in vasodilation and increased blood flow. The oxygen consumption rises in tandem with the increase in blood flow. PEMF therapy has been shown to effectively enhance blood flow and provide muscle relaxation, possibly due to improved muscle tissue oxygenation.

PEMF And Effects On Endothelial Cells For Wound Healing

Wound healing is a multi-step, interactive, and dynamic process that involves the complete closure of the injured skin area. Hemostasis, cellular proliferation, inflammation, angiogenesis, matrix synthesis and remodeling, and the creation of granulation tissue are all steps of the process.

The wound healing process evolves through a succession of events that represent attempts to restore the normal tissue's anatomical structure and function. The development of new vasculature by angiogenesis is one feature of wound repair that has always been deemed vital for optimal healing.

The creation of innovative treatments requires an understanding of the right sequence of molecular and cellular events that occur during wound healing. Previous research has shown that pulsed electromagnetic fields (PEMFs) can change the structure of cell

membranes and diversify the permeability of different ion channels, as well as the potential of cellular membranes.

PEMFs have been proposed to have a direct effect on protein synthesis and increase the creation of extracellular matrix proteins that regulate gene transcription at the molecular and cellular levels. Furthermore, past research has revealed that various types of electrical stimulation, such as direct current, mixed electromagnetic fields, and PEMFs, may alter angiogenesis in vivo and in vitro.

Studies on rat models showed that short-duration PEMFs appear to facilitate and increase the quality of skin wound healing. However, further research is needed to determine the best properties of PEMFs to ensure a faster and more successful wound healing process. PEMFs may also influence many membrane receptors and induce endothelial cells to secrete a variety of growth factors in vivo and in vitro, including vascular endothelial growth factor, connective tissue growth factor, and endothelial nitric oxide synthase.

PEMFs have been shown to reduce hypoxia-induced apoptosis in human umbilical vein endothelial cells (HUVECs) in vitro, as well as increase tube formation, migration, and proliferative abilities. PEMFs have been used to improve wound healing in both experimental and clinical settings for many years.

Hydroxytyrosol (HTY), also known as 3,4-dihydroxyphenylethanol, is a bioactive alcoholic ortho-diphenol that is one of the hydroxyaromatic components of secoiridoids. HTY appears to be antioxidant and antibacterial, with positive effects on the cardiovascular system and in a variety of human disorders, according to a growing body of experimental, clinical, and epidemiological evidence.

HTY upregulates heme oxygenase-1 expression via increasing the nuclear accumulation and stabilization of nuclear factor erythroid 2-related factor 2, which leads to vascular endothelial cell wound repair, which is important in the prevention of atherosclerosis, according to Zrelli et al. Scoditti et al. found that inhibiting matrix metalloproteinase-9 and cyclooxygenase-2 inhibited inflammatory angiogenesis in cultured endothelial cells, suggesting that dietary polyphenols may play a preventive role in atherosclerotic vascular disease and cancer.

However, the precise action of HTY on endothelial cells has remained unknown until now, particularly when combined with PEMF treatment.

Endothelial cells appear to be an ideal system to explore when constructing a wounding and healing model for PEMF studies. The current study looked at the effects of

combining HYT and PEMFs on HUVEC function, as well as their impact on HUVEC proliferation and migration in primary cultures.

Under the influence of different doses of HYT and PEMFs on HUVECs, the expression of functional parameters such as migration, viability, and apoptosis, as well as gene expression of protein kinase B (Akt), mechanistic target of rapamycin (mTOR), transforming growth factor (TGF)-1, and p53, were investigated.

PEMFs may provide unique research opportunities in the field of wound healing by boosting endothelial cell development and enhancing the endothelium's healing response, according to the findings.

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