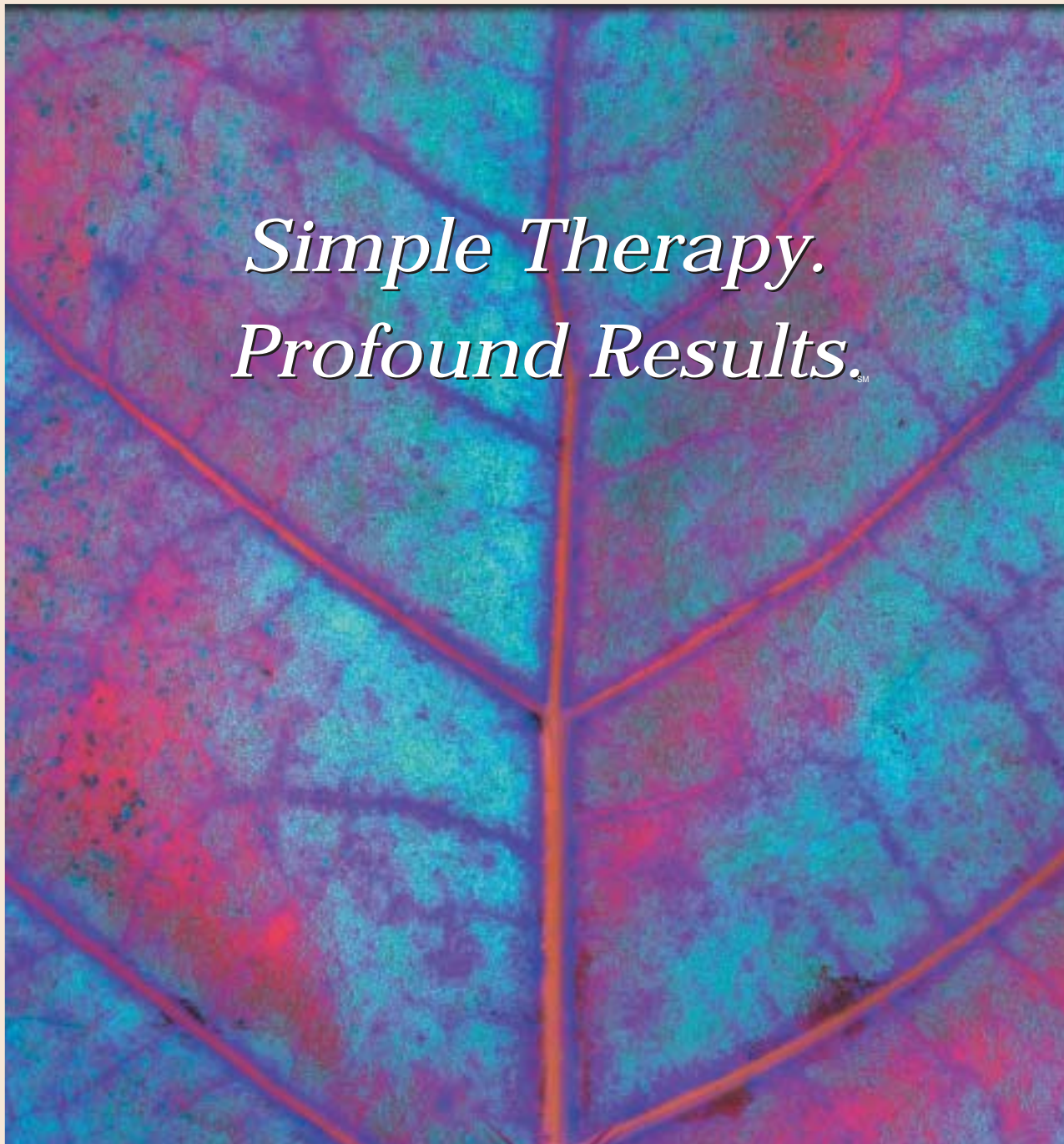


FLOW-MEDIATED THERAPEUTICS™

*Simple Therapy.
Profound Results.*SM



The postulated effects of

Vaxxon Flow-Mediated Therapy (FMT)™

Activation of Muscle Pump
through Neuromuscular Stimulation

Upregulated Metabolism

Increased Local Temperature
Increased Local Metabolites
Increased Capillary Recruitment
Increased Transcapillary Exchange
Increased O₂ Capture

Upregulated Lymphatic Drainage

Reduction of Edema
Reduction of Inflammation
Increased Immune Response

Increased Blood Flow Leading to:

Increased Tissue Oxygen
Increased Pressure Gradients*
Increased Cyclic Stretch
Increased Laminar Shear Stress

*1. Pressure gradient across capillaries: increases filtration and absorption

*2. Tissue oxygen pressure gradient between wound and periwound areas: increases angiogenesis and healing

Flow-Mediated Endothelial
Mechanotransduction

Angiogenesis
Increased Vasomotion
Reduced A-V Shunting
Reduced Ischemia
Reduced Hypoxia
Reduced Claudication
Improved Bone Healing
Improved Wound Healing

Increased Prostacyclin Increased Nitric Oxide

Increased Vasodilation
Improved Vascular Tone
Increased Arteriogenesis
Increased Angiogenesis
Increased RBC deformability
Deactivation of Polyol Pathway
Decreased Platelet aggregability
Decreased Monocyte adhesion
Decreased Thrombosis
Decreased Apoptosis
Decreased Intimal Hyperplasia
Decreased Stenosis, Restenosis

Simple Therapy Profound Results

The Vaxxon Treatment System upregulates blood flow through neuromuscular activation of the muscle pump (see chart, opposite). The increased flow generates elevated levels of laminar shear stress which, through mechanotransduction, results in an amazing cascade of biological and physiological events which are not yet fully understood, but which hold promise of great benefit to people suffering from the effects of endothelial dysfunction and cardiovascular-related problems.

*Also known as: Flow-Mediated Vascular Therapy (FMVT), Flow-Mediated Cardiovascular Therapy (FMCT), Flow-Mediated Nitric Oxide Therapy (FMNOT), Flow-Mediated Oxygen Therapy (FMOT), Flow-Mediated Microvascular Therapy (FMMT), Pressure Gradient Therapy (PGT)

Flow-Mediated Therapy: Nutritive Blood Flow and Tissue Oxygenation

Ischemia plays a significant role in a wide variety of disease states. The most common treatment for ischemia is to upregulate blood flow through the administration of systemic or topical vasodilators. The Vaxxon Vascular Treatment System approaches the problem from a different direction: using strategically placed treatment pads, the system generates ionic impulses to activate the muscle pump through neuromuscular stimulation to increase circulation in the treated area. This process is called Flow-Mediated Therapy™ (FMT™) and is a physical medicine modality which works directly and mechanically to elevate blood flow.

The chart, below, shows the immediate and cumulative effects of FMT™ on twenty-five diabetic patients as shown by transcutaneous oximetry readings taken on the dorsum of the foot. Readings were taken before and after each treatment for eight weeks.

Patient	Day 1		Week 4		Week 8	
	Baseline	End TX	Baseline	End TX	Baseline	End TX
1. RH	1	3	3	8	-	-
2. EH	0	2	3	8	5	35
3. MM	12	24	18	29	-	-
4. VW	21	36	32	48	54	63
5. SB	27	27	-	-	-	-
6. ED	7	21	24	36	-	-
7. JF	40	46	48	52	-	-
8. WG	1	6	2	14	-	-
9. RG	35	45	-	-	-	-
10. BH	47	56	-	-	48	60
11. KH	28	46	-	-	-	-
12. DH	53	60	-	-	-	-
13. RJ	3	31	-	-	-	-
14. BK	60	65	-	-	-	-
15. JR	13	21	-	-	-	-
16. HL	21	23	-	-	-	-
17. JM	36	46	-	-	46	51
18. RM	15	32	-	-	-	-
19. MN	1	1	-	-	-	-
20. JN	28	37	-	-	-	-
21. AO	30	34	-	-	-	-
22. AS	23	25	-	-	-	-
23. WT	4	16	-	-	-	-
24. DW	40	47	-	-	-	-
25. NW	22	62	-	-	-	-

The University of Oklahoma Health Science Center, Oklahoma City, OK, Clinical Study, 1999, Unpublished

48%

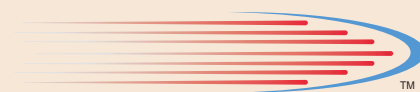
Average tissue oxygen tension improvement after **one FMT** treatment.

58%

Average tissue oxygen tension improvement in **baseline** in 4 weeks, measured **before FMT** treatment.

157%

Largest tissue oxygen tension improvement in **baseline**, 8 weeks, measured **before FMT** treatment.



Flow-Mediated Therapy
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SM

...an inadequate vascular supply fails to provide the inducers, substrates, and oxygen necessary for wound healing.

Strauss, M.B., Problem Wounds: How to Promote Healing, Prevent Recurrence. Consultant, 11/01/2000

Hypoxia plays a critical role in wound healing since it impairs collagen synthesis and prevents fibroblast proliferation and migration.

Harkless, et al, Podiatry Today, 2000, 1045-7860

Investigators have consistently shown that a sufficient oxygen supply to tissue is critical to the healing process and the avoidance of wound infection.

Physiologic effects of tissue oxygenation on wound healing. Whitney JD. Heart Lung. 1989 Sep;18(5):466-74.

One risk factor for amputation stands high above all others in terms of both risk and prevalence. This is hypoxia. Local tissue hypoxia, as measured transcutaneously, imparts a 161-fold increased likelihood of lower extremity amputation in diabetic patients.

Reiber GE, Pecoraro RE, Koepsell TD: Risk factors for amputation in patients with diabetes mellitus. Annals of Internal Medicine 1992;117:97-105.





Oxygen is needed for the hydroxylation of proline and lysine, and at tissue levels below 20 mmHg, collagen synthesis stops. Collagen lysis continues, however, and wounds may actually dehisce in a hypoxic wound environment.

Black J. Tissue Oxygen Perfusion and Pressure Ulcer Healing, Plastic Surgical Nursing, 03/2000



Beyond its role as a nutrient and antibiotic, O₂ may support vital processes such as angiogenesis, cell motility, and extracellular matrix formation.

Gordillo GM, Sen CK, Revisiting the essential role of oxygen in wound healing. Am J Surg. 2003 Sep;186(3):259-63

Flow-Mediated Therapy™ and Oxygen in Wound Healing And Infection

It is a fundamental clinical observation that wounds do not heal in tissue that does not bleed, and they almost always heal in tissue that bleeds extensively. Continuous supply of oxygen to the tissue through microcirculation is vital for the healing process and for resistance to infection. Evaluation of tissue perfusion and oxygenation is important in all types of wound patients. Monitoring systems should measure the hemodynamic situation and the ability of the cardiovascular system to deliver an adequate volume of oxygen to meet the metabolic demands of the peripheral tissue. Oxygen therapy may be beneficial in situations where the nutritive flow and oxygen supply to the healing tissue are compromised by local injury, and particularly if anaerobic infection is present.

It can be concluded that adequate delivery of oxygen to the wound tissue is vital for optimal healing and resistance to infection. Assessment of perfusion and oxygenation is essential for the wound patient, as well as the treating personnel. During wound healing the continuity and function of the damaged tissue are re-established. This is only possible through a restoration of the microcirculation and thereby the nutrition to the tissue. The main component of the nutrition is oxygen, which is critically important for healing a wound by production of granulation tissue and for ensuring resistance against infection.

Gottrup F., Oxygen in wound healing and infection., World J Surg. 2004 Mar;28(3):312-5

Physiologic effects of tissue oxygenation on wound healing.

Researchers have documented the importance of oxygen as a substrate during tissue healing. Development of knowledge in this area is primarily based on studies conducted in animals with limited studies of tissue oxygen tensions in human beings. However, investigators have consistently shown that a sufficient oxygen supply to tissue is critical to the healing process and the avoidance of wound infection.

Whitney JD., Heart Lung, 1989 Sep;18(5):466-74

Flow-Mediated Therapy: Metabolic Response and Capillary Function

FMT™ uses strategically placed treatment pads to deliver sequential ionic impulses which pass through the body, or an extremity. The pads are positioned 180° from each other in groups of up to 8 pairs. These ionic impulses upregulate blood and lymphatic circulation in the treated area through neuromuscular stimulation of the muscle pump, and by upregulating the metabolic process.

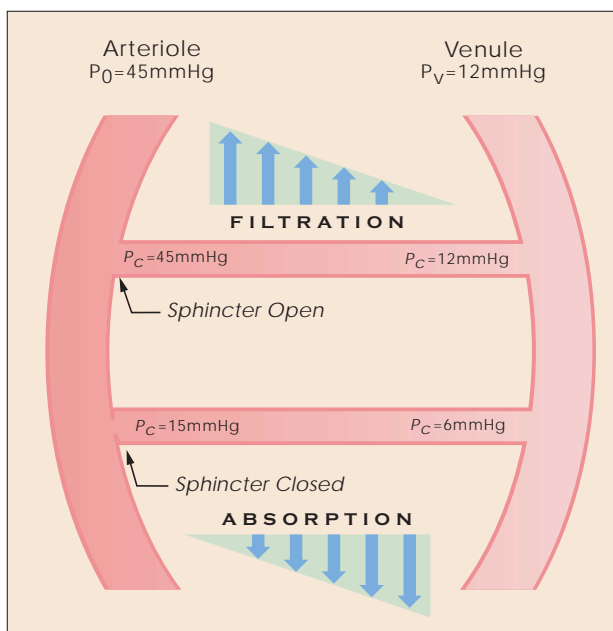
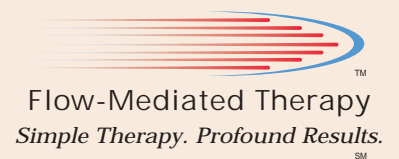
FMT™, like voluntary exercise, increases local metabolism with parallel increases in local temperature and levels of local metabolites: adenosine, potassium, lactic acid, bradykinin and others. These, subsequently, give rise to vasodilation and capillary recruitment. Under these conditions, capillary surface area and transcapillary transfer are greatly increased. The combination of increased PCO_2 , temperature and acidity, promotes the release of O_2 from haemoglobin allowing skeletal muscle to increase its O_2 extraction as much as 300 percent.

The Cardiovascular System, Aaronson PI, Ward, JP Blackwell Publishing, 1999, p. 62

Vasomotion

The chief mediator of vasomotion is tissue oxygenation. Increased levels of tissue oxygen trigger more periods of blood flow and each flow period is of longer duration.

Guyton's Textbook of Physiology, 8th Edition, p232



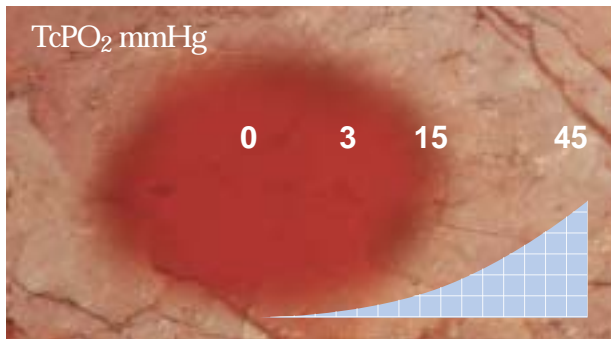
Hydrostatic Force ($P_C - P_i$)

There are many chronic wound patients who do not respond to antibiotics simply because the antibiotics never reach the wound.

FMT™ may help. At three-second intervals, the Vaxxon System stimulates skeletal muscle contractions. These contractions trigger elevated pulsatile blood flow thereby elevating capillary hydrostatic pressure and raising the pressure gradient across the capillary beds, which increases filtration.

The higher filtration rate elevates delivery of oxygen, nutrients and, if used, systemic medication. Both increased angiogenesis and capillary recruitment can shorten diffusion distances to improve uptake by muscle tissue.

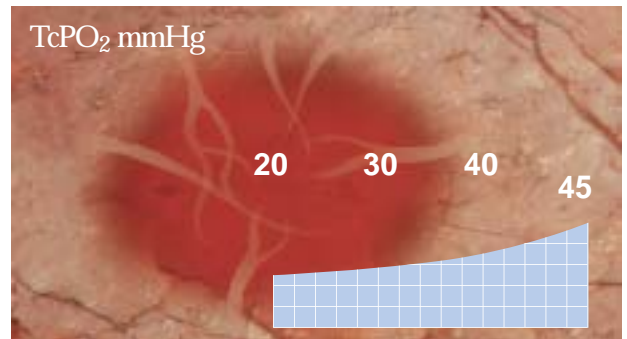
Flow-Mediated Therapy And Pressure Gradients



The body senses the pressure gradient between the ischemic wound and the periwound tissue resulting in angiogenic signaling factors which begin the process of neovascularization.

Angiogenesis occurs most rapidly when it proceeds from a high oxygen tension to a low one and from a low-lactate environment to a high one. The data suggest that **angiogenesis is proportional to the gradient of PO₂ from capillary to wound space**. Therefore, restoration of PO₂ to normal or supranormal levels enhances not only epithelialization, fibroplasia, collagen deposition, and bacterial killing, but also capillary proliferation and advancement into the wound space.

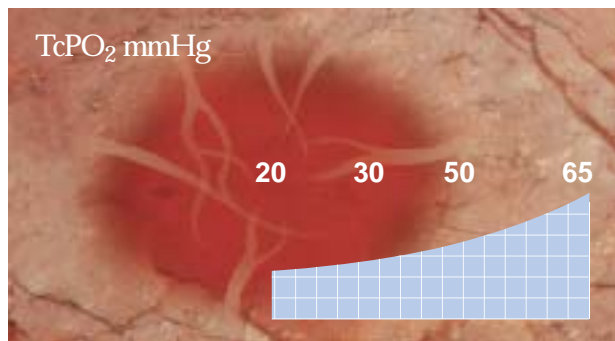
Stone JA, Cianci P, The Adjunctive Role of Hyperbaric Oxygen Therapy in the Treatment of Lower Extremity Wounds in Patients With Diabetes, Diabetes Spectrum, Vol 10-2, 1997, 118-123



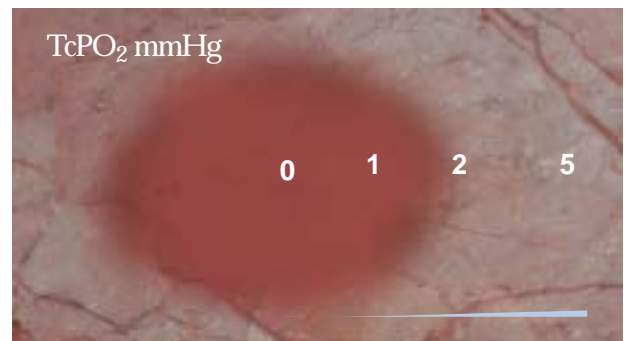
As new capillaries begin to bud and develop, the TcOP₂ in the wound begins to rise. Collagen synthesis will occur only when the TcPO₂ rises above 30.

A number of studies have demonstrated the critical role of angiogenesis for successful wound repair. Vascular disruption leads to a hypoxic zone in the healing wound. In this dynamic process, angiogenesis is vital for the delivery of oxygen, nutrients, and growth factors necessary to initiate the synthetic processes of wound healing. These data support the theory that hypoxia-driven angiogenesis is critical for ECM formation and remodeling . . .

Steinbrech DS, Longaker MT, Mehrara BJ, Saadeh PB, Chin GS, Gerrets RP, Chau DC, Rowe NM, Gittes GK. Fibroblast response to hypoxia: the relationship between angiogenesis and matrix regulation., J Surg Res. ,1999 Jun 15;84(2):127-33.



As new capillaries begin to bud and develop, FMT continues to elevate the periwound TcPO₂ to maintain the pressure gradient, thereby continuing the angiogenic and healing processes.



In the hypoxic patient, there is little or no pressure gradient. The body sees no hypoxia localized to the wound, does not begin the angiogenic response: the wound becomes chronic.

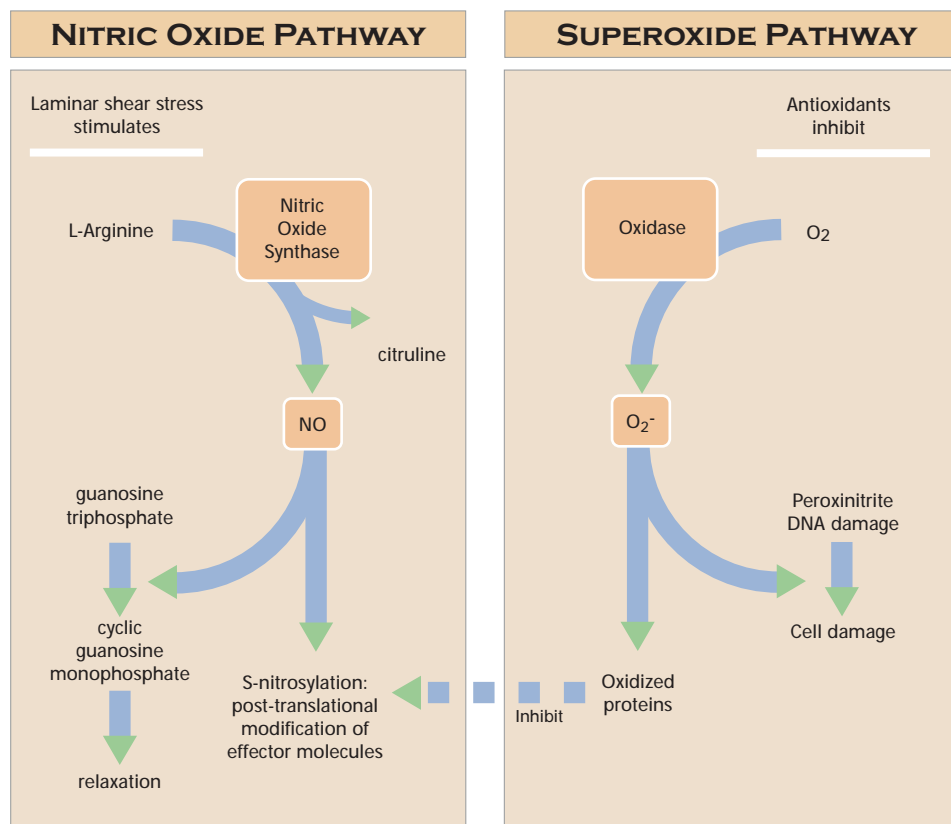
Flow-Mediated Therapy: Mechanotransduction, Prostacyclin and Nitric Oxide (NO).



“Shear stress is the most potent physiological stimulus for NO production in endothelial cells . . . shear stress stimulated NO production by 10-fold to 30-fold above static levels.” *

Endothelial cells play a critical role in vascular homeostasis by performing many functions. They sense and integrate hemodynamic and hormonal stimuli and effect alterations in vascular function through the secretion of various mediator proteins and molecules. As a result of these properties, endothelial cells modulate biological processes related to the blood vessel wall, including regulation of the permeability of plasma lipoproteins, adhesion of leukocytes, and release of antithrombotic factors and growth factors, changes gene expression, cell metabolism, and cell morphology. Impairment of these endothelial cell-mediated processes has been postulated to play a central role in the pathogenesis of atherosclerosis and other vascular complications.

Endothelial cells experience three primary mechanical forces: pressure, created by the hydrostatic forces of blood within the blood vessel; circumferential stretch or tension; and laminar shear stress (LSS). LSS appears to be a particularly important hemodynamic force because it stimulates the release of vasoactive substances, most notably **nitric oxide (NO)** and **prostacyclin**.*



An editorial in The New England Journal of Medicine, November 11, 2004, cites the success in a recent trial treating nitroso-redox imbalance in congestive heart failure with antioxidants and exogenous NO donor drugs.** Using FMT to upregulate **endogenous** nitric oxide, oxygen, and prostacyclin, along with adjunctive antioxidant therapy, offers a means of addressing these same problems. The nitroso-redox imbalance, along with endothelial dysfunction and the reduced deformability of erythrocytes are implicated in a wide variety of disease states which may be helped through FMT and adjunctive antioxidant therapy.

Copyright © 2004, John M. Owen Adapted from Hare, JM

* Traub O, Berk BC: Arteriosclerosis, Thrombosis, and Vascular Biology, 1998;18:677-685.

** Hare, JM. Nitroso-Redox Balance in the Cardiovascular System, NEJM, 11/11/2004

Much ado about NO - nitric oxide in the body

Naomi Freundlich, Harvard Health Letter, Oct, 1993

Nature has a way of reminding us of the value of simplicity. Consider nitric oxide (NO): although it is nothing more than the coupling of our atmosphere's two most abundant gases, there is growing evidence that it is one of most important and versatile chemical messengers in the body.

NO helps regulate blood flow and penile erections, fights infections, and is essential for long-term memory. If researchers can figure out how different cells make NO and how it interacts with other substances to carry out its myriad functions, this knowledge could lead to innovative treatments for ailments as varied as hypertension and impotence.

A big breakthrough came in 1987 with the discovery that EDRF is actually NO. This finding explained why nitroglycerin and other organic nitrates relieve the pain of angina and heart spasms: the body breaks them down into NO, which then helps to dilate blood vessels. NO's ability to act as a messenger between the endothelium and smooth muscle cells is now causing researchers to look at the compound's role in hypertension, atherosclerosis, and reperfusion injury. In healthy individuals, NO helps prevent blood clots by keeping platelets from clumping together and adhering to vessel walls.

Fluid flow stimulates nitric oxide in osteoblasts

NO has been shown to be a potent factor in bone maintenance and remodeling by inhibiting osteoclast resorptive activity and stimulating osteoblast proliferation . . . osteoblasts contain a constitutively present NOS isoform capable of generating NO at nearly 20 times the maximal rates previously reported for cytokine stimulation.

Johnson DL, McAllister TN, Frangos JA, Fluid flow stimulates rapid and continuous release of nitric oxide in osteoblasts. Am. J. Physiol. 271 (Endocrinol. Metab. 34): E205-E208, 1996



Critical Influence of NO

Wound healing of the skin represents a highly ordered process of important tissue movements that aims for a rapid closure of the wound site and a subsequent regeneration of the injured tissue. . . it has become evident that the diffusible, gaseous molecule nitric oxide (NO) participates in the orchestration of wound healing. NO critically influences macrophage, fibroblast, and keratinocyte behaviour within the intercellular communication network during repair.

Nitric oxide drives skin repair: novel functions of an established mediator. Frank S, et al, Kidney Int. 2002 Mar;61(3):882-8

NO Regulates Collagen Production

NO released through iNOS regulates collagen formation, cell proliferation and wound contraction in distinct ways in animal models of wound healing. .

Role of nitric oxide in wound repair. Witte MB, Barbul A., Am J Surg. 2002 Apr;183(4):406-12

Important Element in Wound Healing

Since its discovery almost 20 years ago, NO has proven itself as an important element in wound healing. This review highlights many of the important aspects of nitric oxide in wound healing, including a review of the basic biology of nitric oxide, its role as part of the cytokine cascade and as a promoter of angiogenesis, as well as its more recently elucidated role in apoptosis

Nitric oxide and wound healing. Rizk M, Witte MB, Barbul A., World J Surg. 2004 Mar;28(3):301-6

Critical level of endogenous nitric oxide

The results of a preliminary retrospective study suggest that nitric oxide production is reduced in the nonhealing diabetic wound, and that topical therapy is effective only when wound nitric oxide production deficiency is corrected. In addition, the data suggest that below a critical level of endogenous nitric oxide production, diabetic ulcer repair may not be achieved.

The nitric oxide connection: hyperbaric oxygen therapy, becaplermin, and diabetic ulcer management. Boykin JV Jr. Adv Skin Wound Care. 2000 Jul-Aug;13(4 Pt 1):169-74





Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy.

Diabetic neuropathy is associated with risk factors for macrovascular disease and with other microvascular complications such as poor metabolic control, dyslipidaemia, body mass index, smoking, microalbuminuria and retinopathy. Studies in human and animal models have shown reduced nerve perfusion and endoneurial hypoxia. Arterio-venous shunting also contributes to reduced endoneurial perfusion. These vascular changes strongly correlate with clinical defects and nerve pathology.

Vascular endothelium is particularly vulnerable, with deficits in the major endothelial vasodilators, nitric oxide, endothelium-derived hyperpolarising factor and prostacyclin. Together, this complex of interacting metabolic factors accounts for endothelial dysfunction, reduced nerve perfusion and function. Thus, the evidence emphasises the importance of vascular dysfunction, driven by metabolic change, as a cause of diabetic neuropathy, and highlights potential therapeutic approaches.

Cameron NE, Eaton SE, Cotter MA, Tesfaye S., *Diabetologia*. 2001 Nov;44(11):1973-88.

* Veves A, King G., "Can VEGF reverse diabetic neuropathy in human subjects?" *J Clin Invest*. 2001,May;107(10):1215-8.

**Vinik, AI, Address to 18th International Diabetes Federation Congress, Paris 2000

Flow-Mediated Therapy: Diabetic And Non-Diabetic Neuropathy

Peripheral polyneuropathy is a common complication of diabetes that can clinically affect 30% of all diabetic patients and is the most common form of diabetic neuropathy. The main histologic changes of diabetic polyneuropathy are loss of myelinated and unmyelinated fibers and segmental demyelination. Hyperglycemia, which has emerged as a major risk factor for the development of diabetic neuropathy, may affect the peripheral sensory nerves through several mechanisms. Several of the current hypotheses are:

First, the increased flux through the polyol pathway may lead to intracellular sorbitol accumulation and, potentially, to osmotic increase or changes in the NAD/NADH ratio induced by the flux through the aldose reductase pathway. These changes can cause direct neuronal damage or decrease neuronal blood flow, indirectly leading to peripheral nerve hypoxia.

Second, the activation of protein kinase C (PKC) in response to increased diacylglycerol levels via the de novo synthesis pathway can affect the Na, K⁺ ATPase, and other enzymes that are important for maintaining cellular membrane potential and nerve conduction. In addition, PKC activation can induce vasoconstriction and reduce neuronal blood flow.

Third, the auto-oxidation of glucose causes increased production of reactive oxygen species and the formation of advanced glycation end products (AGEs) by nonenzymatic glycation of proteins. AGEs then bind to a cell-surface receptor and cause activation of the NF- κ B, which is associated with endothelial dysfunction and reduced nerve blood flow.

Finally, diabetes impairs the hepatic β -6 desaturation of dietary linolenic acid to γ -linolenic acid and results in reduced synthesis of vasoactive prostanoid in the vasa nervorum. This defect leads to reduced endoneurial blood flow and nerve hypoxia.*

Each of these models includes ischemia/hypoxia as the terminal path to neuropathy. It is postulated that FMT, by elevating circulation, reverses ischemia/hypoxia to provide the oxygen and nutrients needed for neuronal regeneration and remyelination.

Flow-Mediated Therapy: Neuropathy™

A Lancet editorial in 1994 said that all we can do for neuropathy is make the diagnosis and commiserate with the patient. We have found new windows into its recognition, and have opportunities for not only treating but also potentially reversing the disorder. Wouldn't it be a shame if we failed to recognize it when it was right there under our noses?"

FMT Results:

FMT technology has demonstrated in clinical trials, the ability to reduce both diabetic and idiopathic neuropathic pain while improving sensation and simultaneously helping patients to reduce or eliminate palliative drug use.

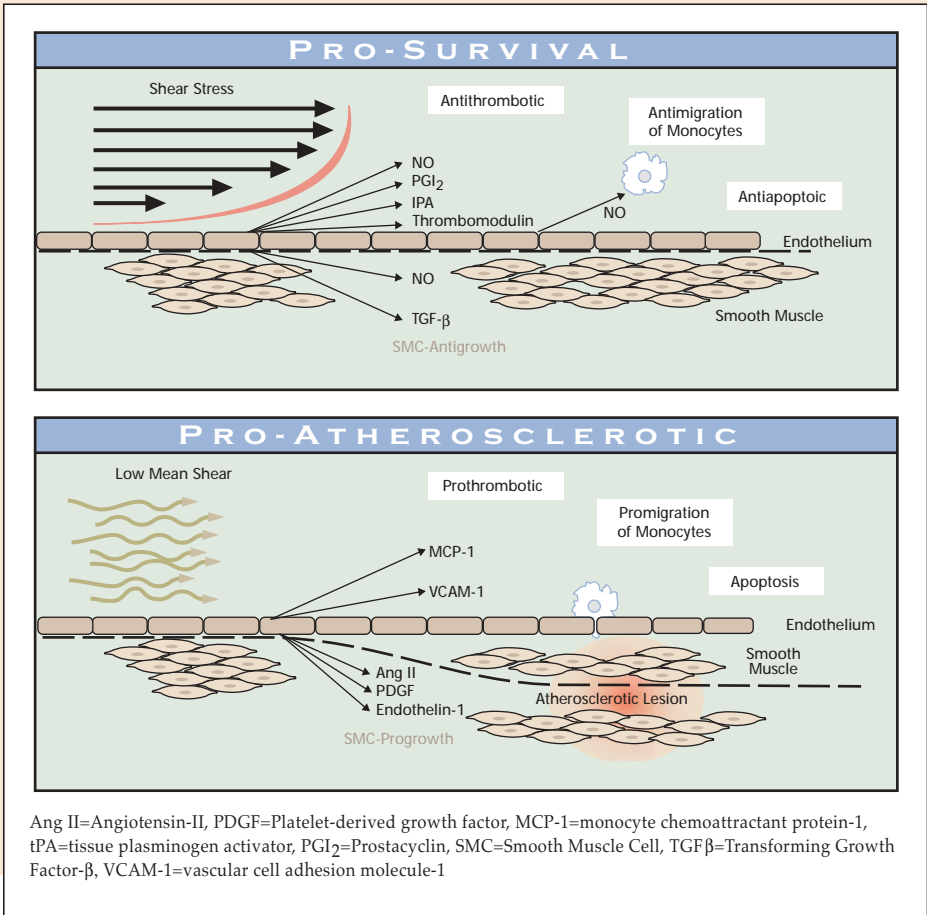
Ambulation and ADLs were improved, claudication was reduced or eliminated.

The cost of neuropathy in type 1 diabetes is \$1.3 billion and the cost in type 2 diabetes is \$17.5 billion, according to a survey conducted in 2001. Since neuropathy occurs in 59% of people with type 1 diabetes and 49% of those with type 2 diabetes.

Gordois A, Scuffham P, Shearer A, Oglesby A, Tobian JA. The health care costs of diabetic peripheral neuropathy in the US., Diabetes Care. 2003;26:1790-1795

*"An urgent need exists to develop new therapeutic approaches that will improve nerve function in diabetic patients"**





Flow-Mediated Therapy
Simple Therapy. Profound Results.

Mechanisms by Which Endothelial Cells Transduce an Atheroprotective Force

Oren Traub; Bradford C. Berk, Arteriosclerosis, Thrombosis, and Vascular Biology. 1998;18:677-685.

Shear stress has direct influences on the pathogenesis of atherosclerosis via regulation of endothelial cell function and integrity. Shear stress influences many of the processes relevant to development of the atherosclerotic lesion, including secretion of growth factors, regulation of coagulation, and transmigration of leukocytes. Regulation of these processes is proposed to occur via shear-activated endothelial cell signal-transduction pathways that involve primary mechanotransducers.

Further elucidation of the mechanisms of shear stress-mediated signal transduction and its alteration with these risk factors will greatly advance our understanding of atherosclerosis.

Arteriogenesis: role of nitric oxide

Prior BM, et al, Endothelium. 10(4-5):207-16 2003

Arteriogenesis is an important process for adapting the pre-existing circuit of vessels into functional collateral conduits. Evidence has shown that arteriogenesis is regulated by nitric oxide (NO), angiogenic factors and shear stress. NO significantly impacts vasomotor tone to enhance conductance of the newly recruited collateral arteries. NO-mediated increases in vascular conductance allows for greater collateral dependent blood flow to the tissue. NO production is also critical to the efficacy of therapeutic arteriogenesis achieved by delivery of exogenous angiogenic growth factors. The critical role of NO in therapeutic arteriogenesis is independent of NO-mediated changes in vascular conductance. Improvement of NO production and signaling may improve endothelial cell function.



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