Advanced Wound Care

Using VasoActive Therapy

A multi-faceted approach that reverses some of the worst aspects of chronic[SM], non-healing wounds through physiology.

A Powerful Weapon For A Difficult Battle[SM]

VASOACTIV®
BIOMEDICAL TECHNOLOGIES

This is a wound therapy unlike any you have seen before.

It will:

Restore Circulation
Mitigate Inflammation
Reduce Oxidation
Improve Microvascular Perfusion
Increase Oxygen Uptake
Strengthen Angiogenesis
Block Complement Activation
Facilitate Collagen Formation
Help Develop Granulation Tissue

The VAT 200 is a Circulation Assistance Device that uses sequential neuromuscular stimulation to contract skeletal muscles from distal to proximal, increasing venous return, preload, stroke volume and cardiac output. The resulting blood flow has many direct benefits to the patient and through endothelial mechanotransduction, can affect the patient's blood chemistry by raising or lowering many vasoactive substances. In the next few pages, you will see the physiological principles on which VasoActive Therapy (VAT) is based.

Additionally, you will see several case studies where VAT was successfully used to treat severely compromised wounds.

Endothelial dysfunctional and wound-healing capabilities

The Endothelium plays a major role in ulcer and wound healing.

The endothelium is the largest organ in the body, equivalent in size to approximately six tennis courts. It exerts control over an array of synthetic mechanisms, all of which serve to maintain vascular tone and blood fluidity and provide homeostasis in the event of intimal injury. Thus, the endothelium has a prominent role in angiogenesis, lipoprotein metabolism, capillary transport, vasomotion, vascular structure, and in the general mediation of interactions between circulating blood and the vessel wall. In presiding over this range of vascular functions and responding to a local environment, the endothelium produces a formidable array of agents that influence vascular tone and structure, as well as the interaction of the vessel wall with circulating blood elements.

Normally the endothelium functions as an inhibitor, placing constraints on smooth muscle contraction, platelet aggregation, vascular smooth muscle growth, thrombosis, and monocyte adhesion.

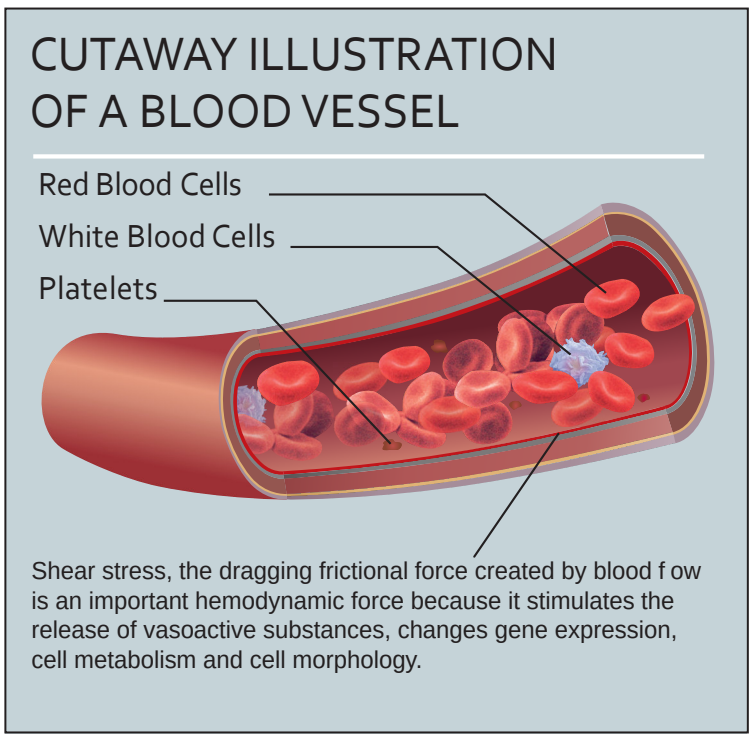
Functions of the Endothelium

Maintains vascular smooth muscle tone
Regulates angiogenesis,cell proliferation
Mediates inflammatory and immune responses
Regulates vascular permeability
Regulates thrombolysis
Regulates leukocyte adhesion
Regulates platelet adhesion and aggregation
Regulates lipid oxidation

A surprising and powerful ally in the fight against Diabetic Ulcers and other non-healing wounds: Laminar Shear Stress

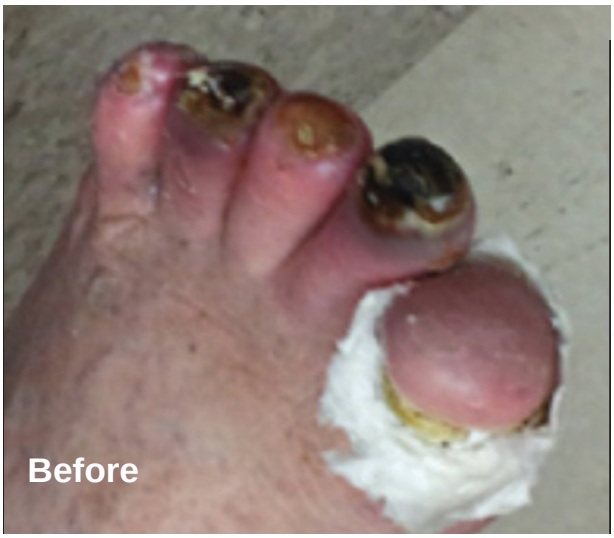
The Hemodynamic Basis of Vascular Health

The mechanism by which the endothelium up-regulates some substances (NO, prostacyclin) and downregulates others such as vascular cellular adhesion molecules (VCAM), and inter-cellular adhesion molecules (ICAM) is largely mechanical: laminar shear stress from blood flow creates a frictional force on the endothelium, triggering the process of mechanotransduction which elicits paracrine and autocrine responses. Areas of the endothelium receiving higher levels of shear stress produce an athero-protective result while areas of low shear produce a pro-atherosclerotic effect. More broadly stated, higher levels of shear stress move the vascular system toward homeostasis and low levels move it toward dysfunction.

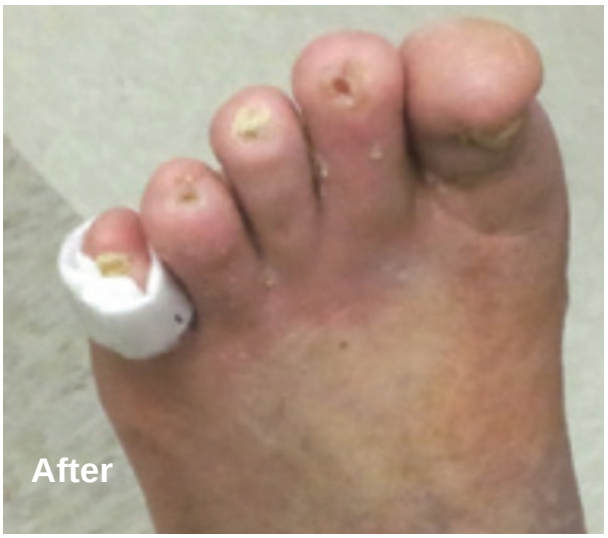


Shear stress, the dragging frictional force created by blood f ow is an important hemodynamic force because it stimulates the release of vasoactive substances, changes gene expression, cell metabolism and cell morphology.

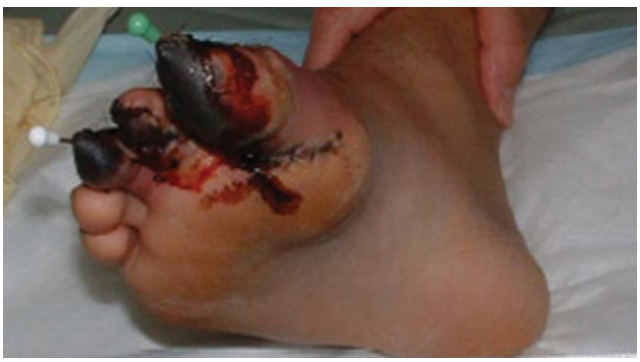
Endothelial dysfunction contributes to delayed healing in several respects, most notably through ischemia and hypoxia. Oxygen is crucial to the process since it is essential for the formation of collagen, the basic building block of granulation tissue. A gradient of oxygen from the wound to the periwound area is the strongest stimulus for angiogenesis necessary to form capillaries in any new tissue formed. Increased oxygen also increases the killing capacity of white blood cells, essential to handling the wound bacteria burden. VasoActiv Therapy promotes vasodilation and brings elevated levels of blood and oxygen to the wound area while elevating wound-periwound oxygen pressure gradients.

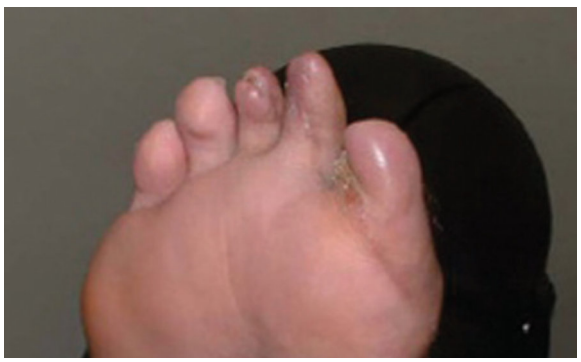


Leg cool to touch, Poor color, Poor capillary refill, three gangreneous toes, $TCPO_2$ of 1, No sensation, Facing amputation.



Leg warm to touch , Good color, Good capillary refill, NO gangreneous toes, $TCPO_2$ of 28, Sensation partially restored, No amputation





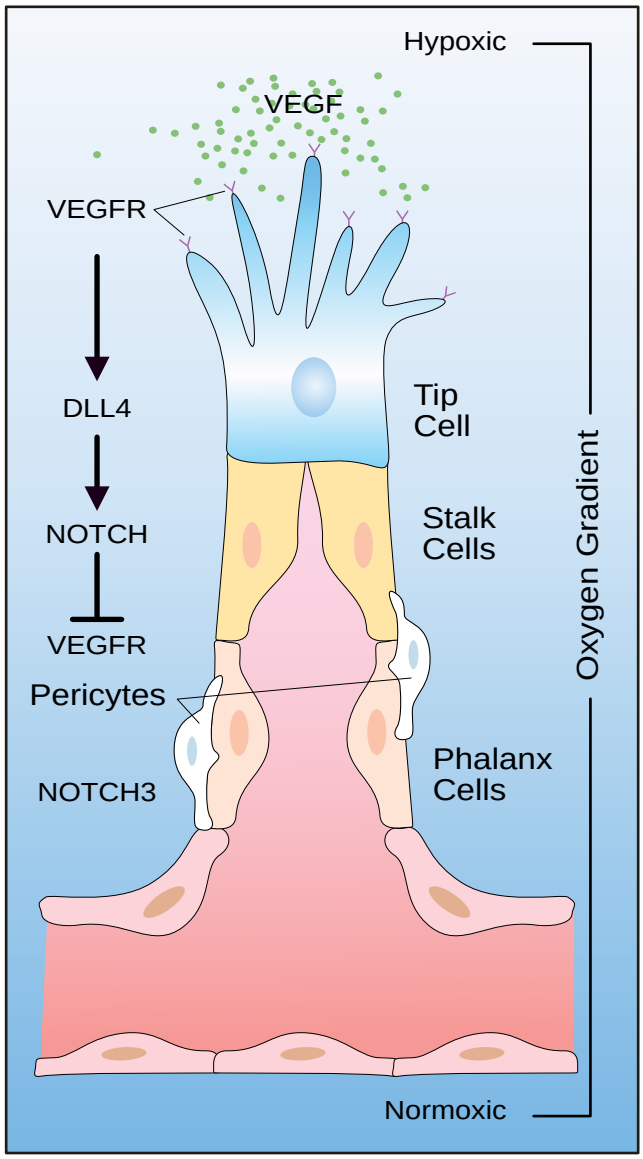
Traumatic lawnmower amputation of three toes on right foot. Reattachment surgery failed with subsequent infection and gangrene. Five months of VasoActiv Therapy (VAT) and concomitant wound therapy resulted in salvage of all toes and full function.

The NOTCH Pathway Coordinates Angiogenic Sprout Development

The Notch signaling pathway plays a key role in coordinating multiple aspects of endothelial behavior during vessel patterning and thus in shaping the formation and remodeling of the vascular network.

Angiogenic sprouting and development are triggered by growth factors and chemokines that stimulate the endothelial cells to break out of their stable position in the vessel wall and jointly coordinate sprouting, branching, and new lumenized network formation.

Each new sprout eventually connects with adjacent sprouts via the tip cell to form a continuous lumen and thus establish flow in the new vascular loop Flow-dependent tissue oxygenation finally downregulates paracrine VEGF-A production, and thus helps establish a quiescent state for the new vessels.



1. In tip cells, VEGF stimulates DLL4/NOTCH signaling via VEGF-R2, thereby inhibiting tip cell formation and inducing VEGF-R1 expression in the endothelial cells downstream. Astrocyte-derived SDF-1 acts as an additional chemoattractant, activating CXCR4 in tip cells.

2. In stalk cells, predominance of VEGF-R1 and activation of Tie-2 by Ang-2 secreted from the tip cell lead to proliferation and survival.

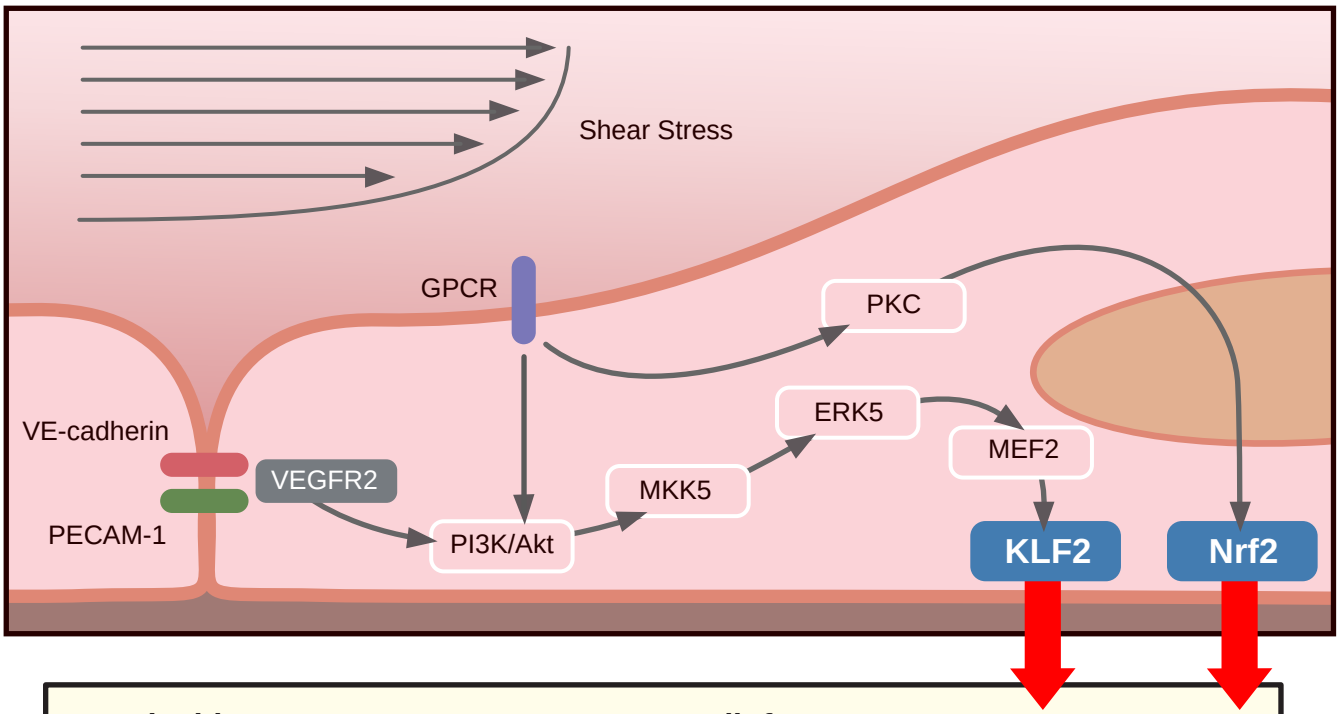
3. Platelet-derived growth factor receptor (PDGFR)—pericytes are attracted to the growing sprout by PDGF-B, released from tip cells. Interaction of recruited pericytes with endothelial cell—derived Jagged-1 induces the expression of Notch3 and activation of an autoregulatory loop that further enhances Notch3 activation, thereby promoting pericyte survival, investment, vascular branching, and induction of smooth muscle cell (SMC) genes.

4. Transforming growth factor (TGF)-produced in endothelial cells further induces SMC differentiation and pericytes-derived Ang-1 binds to and activates the Tie-2 receptor on endothelial cells, stimulating vessel maturation and stabilization.

VasoActive Therapy (VAT) promotes the angiogenic process through increased blood f ow which raises the oxygen gradient, providing a strong stimulus for vascular sprouting. Both VEGF and NOTCH are upregulated through VAT-stimulated shear stress.

KLF2 and Nrf2 Form a Powerful Healing Team

Krüpple-Like Factor 2 (KLF2) is a vasculoprotective transcription factor that plays a key role in maintaining endothelial cell homeostasis and quiescent phenotype. KLF2 negatively regulates NF-jB and activating transcription factor 2 (ATF2), thereby inhibiting endothelial expression of proinflammatory mediators and adhesion molecules. KLF2 up-regulates thrombomodulin and down-regulates plasminogen activator inhibitor-1 (PAI-1), thereby increasing antithrombotic properties of ECs. Nuclear factor (erythroid-derived 2)- like 2 (Nrf2), like KLF2, possesses strong vasculoprotective properties. Nrf2 directs the expression of a set of antioxidant genes which contribute to the healing process. The chart does not include superoxide dismutase or glutathione peroxidase which are upregulated by VAT in a KLF2 and Nrf2-independent manner.



Antioxidant

↑ HOX-1, heme oxygenase 1
GST, glutathione S-transferase
NQO1, NAD(P)H quinone oxidoreductase 1
SQSTM1, sequestosome 1
TRX1, thioredoxin 1
EPHX1, microsomal epoxide hydrolase 1
GCG, c-glutamylcysteine synthase

↓ NOX2, NAD(P)H oxidase 2
NOX4, NAD(P)H oxidase 4
XO, xanthine oxidase

Antiinf ammatory

↑ ENOS, endothelial nitric oxide synthase

↓ NF-κB, nuclear factor kappa B
AP-1, activator protein 1
VCAM1, vascular cellular adhesion molecule 1
E-selectin (CD62E)

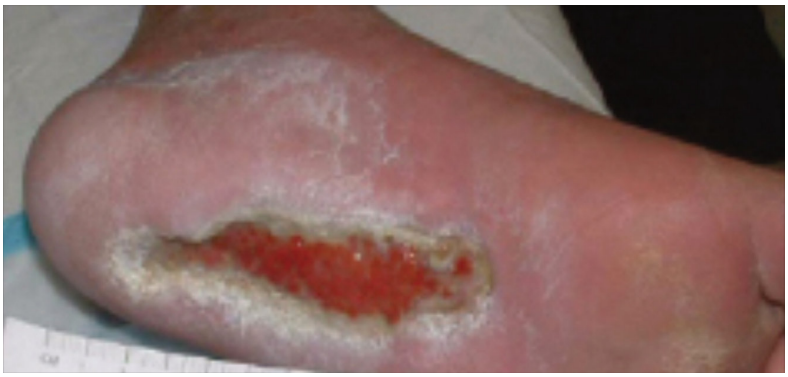
Vasodilatory

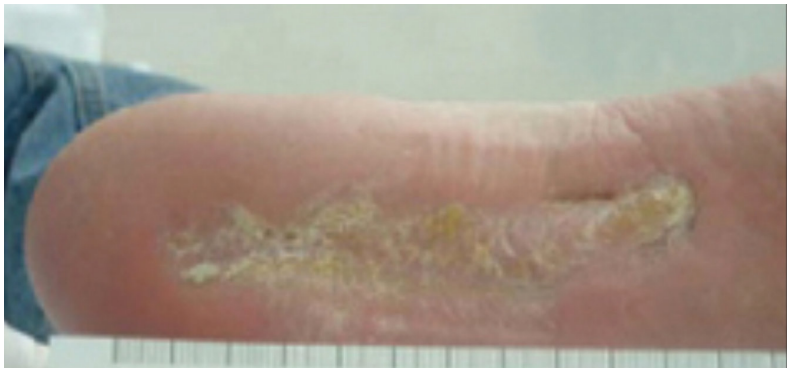
↑ ENOS, endothelial nitric oxide synthase
CNP, C naturiuretic peptide
ASS, argininosuccinate synthase

↓ ET1, endothelin

Chistiakov DA, Orekhov AN, and Bobryshev YV, Ef ects of shear stress on endothelial cells: go with the f ow, *Acta Physiol* 2017, 219, 382–408

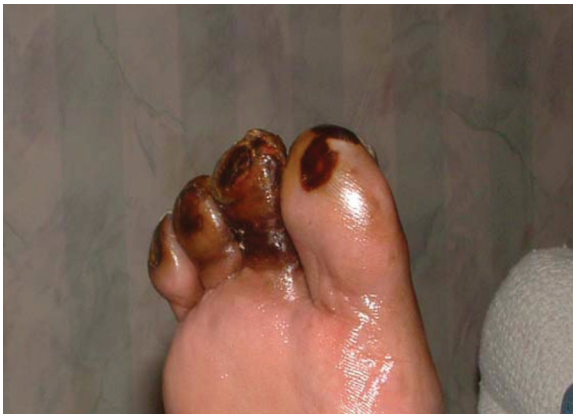
VasoActive Therapy (VAT) promotes the angiogenic process through increased blood f ow which, through mechanotransduction, increases both KLF2 and Nrf2, leading to the upregulation or downregulation of nineteen vasoactive substances, moving all of them toward a wound healing phenotype.

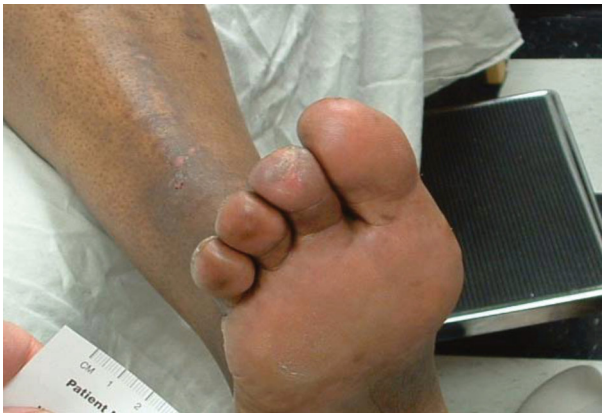




A 59 year old white male at onset of gas gangrene. He was scheduled for urgent amputation. Received wide surgical debridement followed by VAT and standard wound care.

Patient reached 100% granulation of the wound on day 85. Five days later, his gangrene was completely resolved. He regained his weight bearing and walking ability and the wound was completely closed.



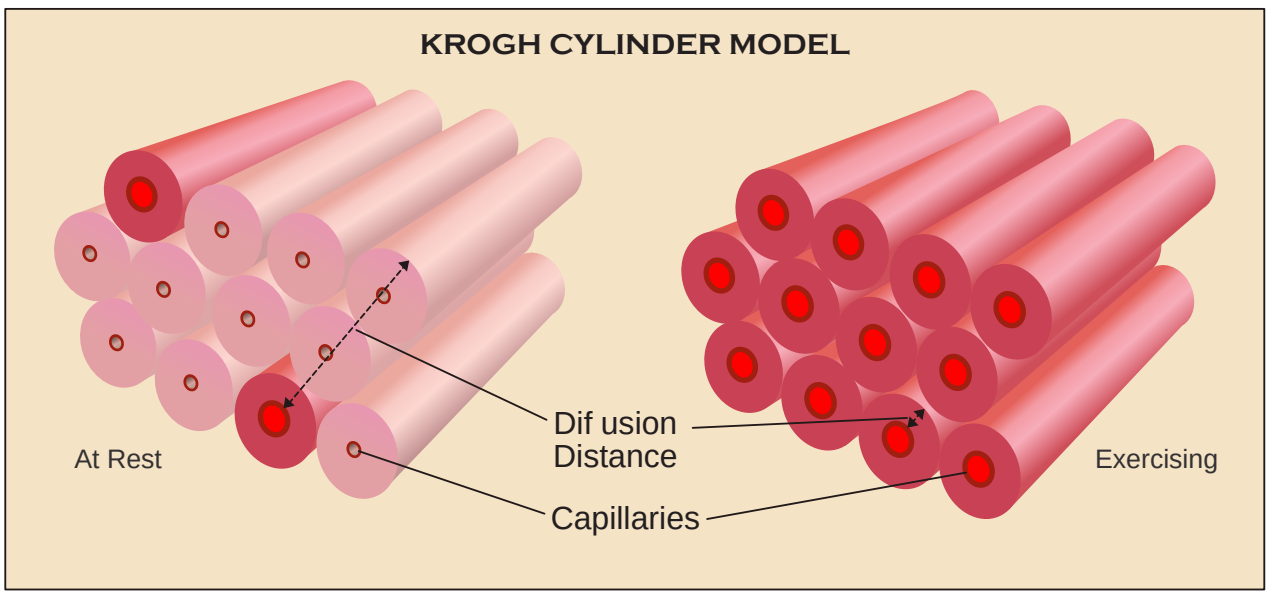


63 year old barber with previous left below knee amputation, with gangrene and flatline toe waveforms on the right, offered amputation of his right leg. Treatment with VAT and conservative management resulted in complete resolution of the gangrene and normal toe waveforms.

Tissue pO_2 and Perfused Capillary Density

In resting tissue, the number of open capillaries is relatively small because the need for oxygen delivery and carbon dioxide removal is relatively small. However if the tissues begin working or consuming greater amounts of oxygen, the number of open capillaries normally increases. As additional capillaries open, smaller and shallower Krogh cylinders form resulting in much more efficient oxygen delivery and carbon dioxide removal to meet the increased metabolic need. The number of open capillaries within a specific volume of tissue is called perfused capillary density (PCD). PCD changes as metabolic needs chang, increasing as metabolic need increases and decreasing as metabolic need decreases, such as when muscles start or stop working.

The body's ability to open and close capillaries is the key to maintaining homeostasis in any type of tissue.

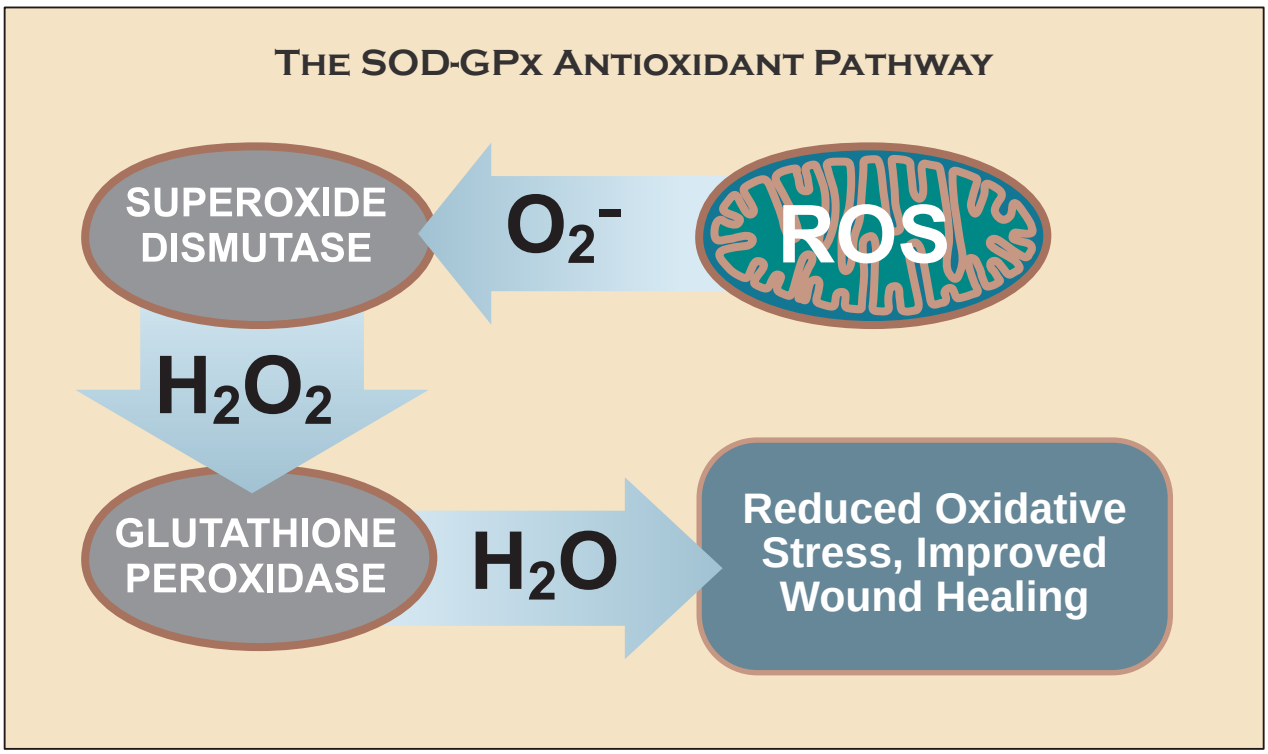


VAT is based upon neurostimulation of muscles causing contractions...in other words, it's involuntary exercise and generates physical responses similar to those from regular physical exercise. By squeezing the veins with sequential, overlapping distal to proximal contractions, VAT will elevate blood flow in the macrocirculation, The microcirculation, however, is different--it will create it's own flow in response to metabolic demand. When exercise, or VAT is commenced, the microcirculation will become perfused within 4 seconds with nearly all capillaries flowing and diffusion distances shortened as shown in the illustration. Of course, surface area available for transfer is greatly expanded and oxygen uptake will increase as much as 200%

VasoActive Therapy (VAT) promotes tissue perfusion through increased blood f ow which shortens dif usion distances, increases surface area and elevates oxygen uptake. all of which moves the patient toward timely wound healing.

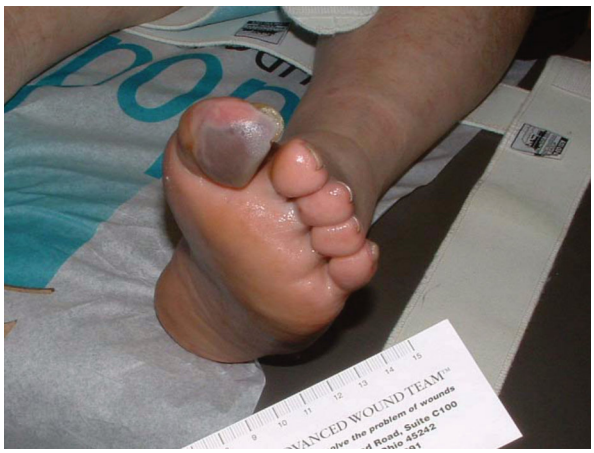
Shear-Stress Activated Antioxidant Pathways

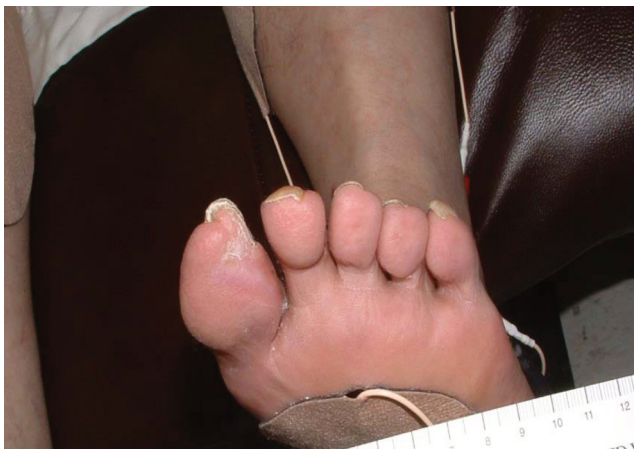
Wound healing is a well-tuned biological process, which is achieved via consecutive and overlapping phases including hemostasis, inf ammatory-related events, cell proliferation and tissue remodeling. Several factors can impair wound healing such as oxygenation defects, aging, and stress as well as deleterious health conditions such as infection, diabetes, alcohol overuse, smoking and impaired nutritional status. Growing evidence suggests that reactive oxygen species (ROS) are crucial regulators of several phases of healing processes. ROS are centrally involved in all wound healing processes as low concentrations of ROS generation are required for the f ght against invading microorganisms and cell survival signaling. Excessive production of ROS or impaired ROS detoxif cation, however, causes oxidative damage, which is the main cause of non-healing chronic wounds.



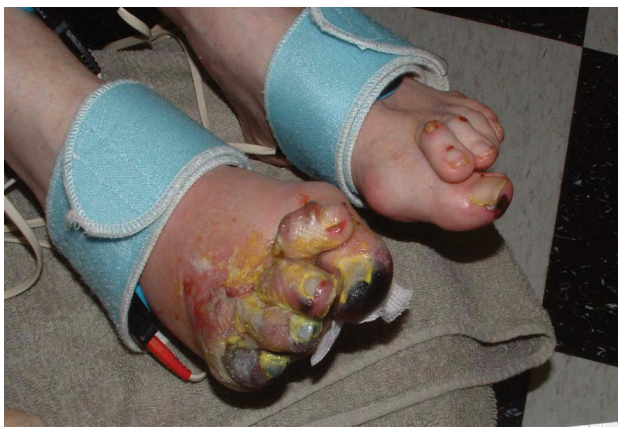
While the Superoxide Dismutase-Glutathoine Peroxidase pathway is the best known and perhaps most effective antioxidant pathway, shear stress and mechanotransduction can upregulate an extensive list of genes with antioxidant properties. These substances include NAD(P)H (nicotinamide adenine dinucleotide phosphate oxidase), menadione oxidoreductase, Heme Oxygenase 1, cyclo-oxygenase 2, (COX2), nitric oxide, thioredoxin reductase, ferritin (heavy and light chains) glutathione-S transferase, g-glutamyl cysteine synthase, microsomal epoxide hydrolase, glucose-6-phosphate dehyd-rogenase, cyto-chrome P450 1A1 and cytochrome P450 1B1,

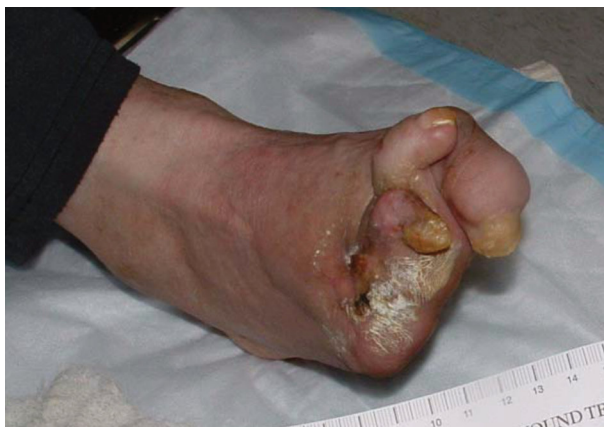
VasoActive Therapy (VAT) promotes the angiogenic process through increased blood f ow which, through mechanotransduction, increases levels of SOD (types 1, 2, and 3), glutathione peroxidase and many other vasoactive substances which move the patient toward wound healing.





60 year old white male with thromboembolism to distal foot during femoral stent placement, with loss of toe waveforms. Subsequently, developed infection and gangrene. Was able to return to work in 2 weeks. Normal waveforms returned in 3 weeks with VAT and concomitant standard wound care. Complete resolution and healing was reached in five months, with full return to normal function.





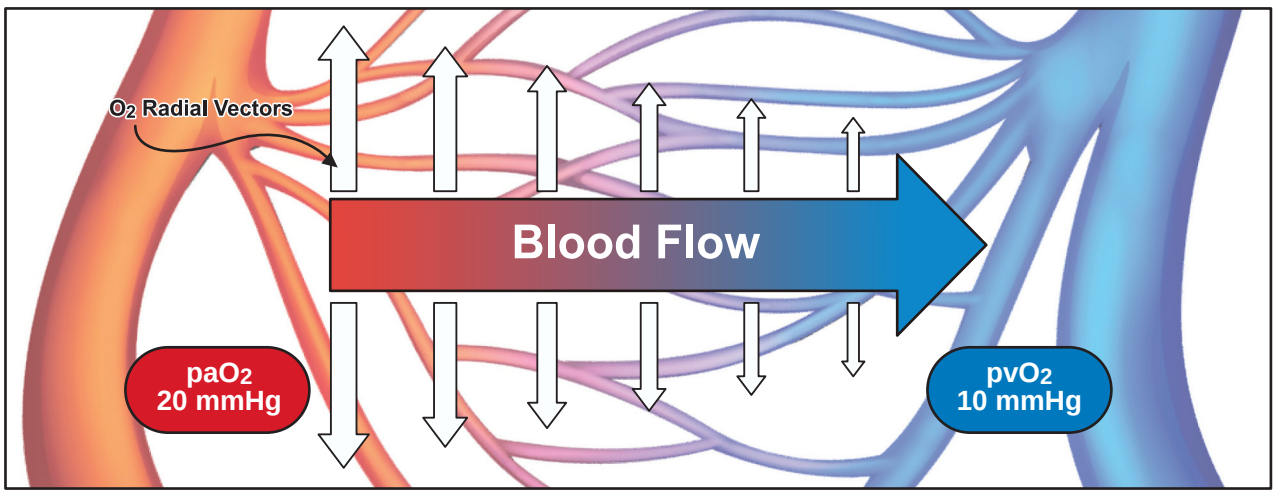
A 58 year old white female with thromboembolic event to right foot secondary to rheumatoid arthritis and vasculitis with subsequent infection and gangrene. Was offered a below knee amputation. VAT started, with concomitant wound therapy. Patient returned to work two weeks later. Reached resolution in 8 months, with loss of two lateral toes, but retention of full premorbid function.

Capillary Pressure Gradients Affect O_2 Transport, Perfusion

Chronic wound patients typically have compromised circulation as a causative or contributing factor in their delayed healing pattern. Their lower blood flow leads to reduced pressure gradients across the capillary beds. This not only reduces O_2 and CO_2 transport, across the endothelium, but impairs the ability of the RBCs to enter and pass through the capillary.

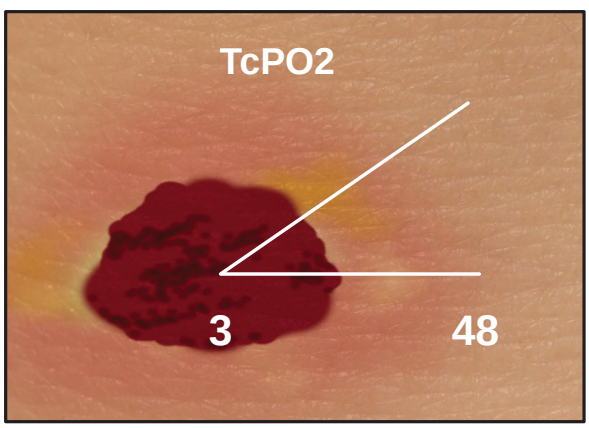
RBCs are larger in diameter than the capillaries and must deform through curling or folding in order to pass through. In good health this is not a problem, but in many disease conditions, such as diabetes, RBCs become stiff and have difficulty deforming.

The extra hydraulic pressure produced by increased flow serves to "push" the cells through the capillary. Additionally, that pressure and shear stress contribute to RBC deformability as do both nitric oxide and prostacyclin, which are increased by VAT.



Oxygen Pressure Gradients Affect Angiogenesis, Tissue Formation

The American Diabetic Association in 1999, following a Diabetic Foot conference in Boston, issued a consensus statement that said, "the strongest stimulus for angiogenesis in diabetic foot ulcers is the oxygen pressure gradient between the wound and the periwound area." *(Kahn, ADA 1999)* VasoActive Therapy will gradually raise periwound oxygen levels and, following behind, the wound as angiogenesis takes place.



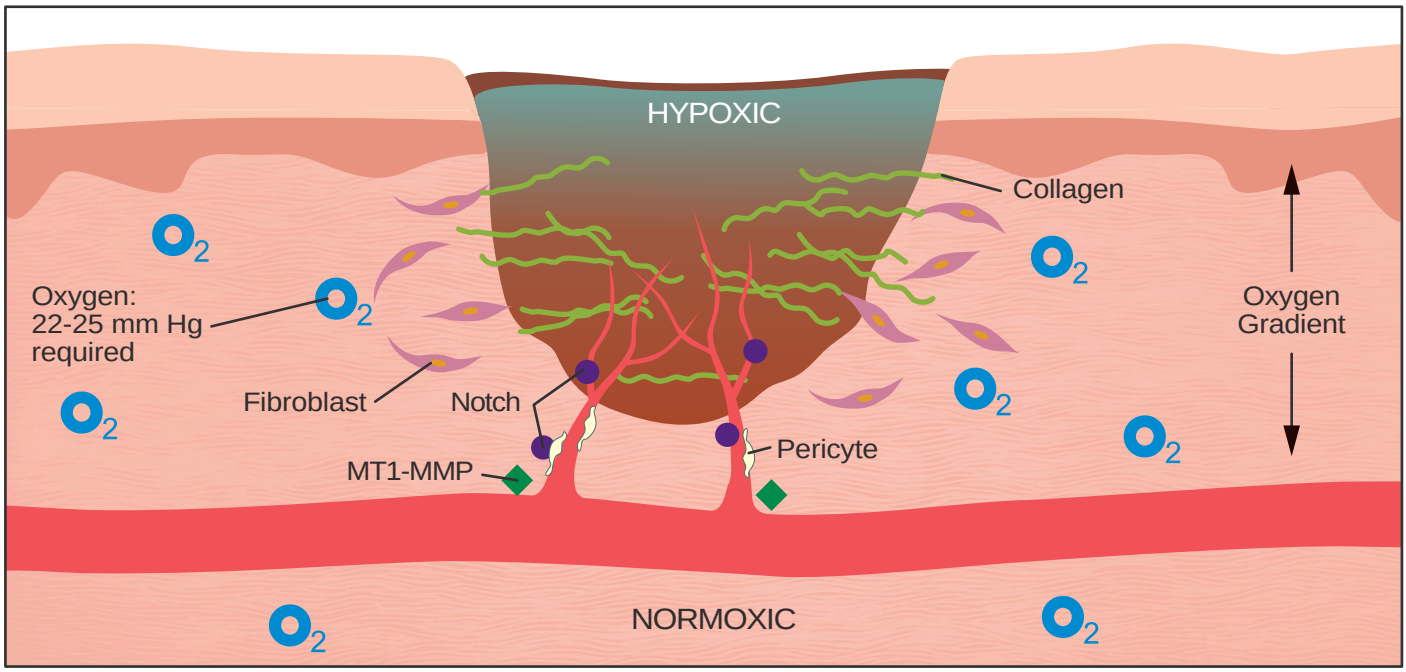
VasoActive Therapy (VAT) promotes the angiogenic process through increased blood f ow which raises the capillary pressure gradient for improved transfer as well as wound-periwound oxygen gradients to stimulate angiogenesis.

VAT Helps Deliver Oxygen, Enable Collagen Hydroxylation

Mitochondrial respiration is responsible for more than 90% of O_2 consumption in humans. Cells utilize O_2 as the final electron acceptor in the aerobic metabolism of glucose to generate ATP which fuels most active cellular processes such as during wound healing. Increased energy demand of the healing tissue leads to a hypermetabolic state wherein additional energy is generated from oxidative metabolism increasing the O_2 demand of the healing tissue. Oxygen powers ATP generation for tissue repair.

The collagen hydroxylation process requires molecular oxygen, consequently, collagen may fail to mature if there is an insufficient supply of oxygen to the tissue. Collagen deposition proceeds in direct proportion to pO_2 across the entire physiologic range, from zero to hundreds of mm Hg. The minimum level of pO_2 for collagen to form is 20-25 mm Hg. Angiogenesis is directly proportional to pO_2 in injured tissues.

All developing vessels require a net or sheath of extracellular matrix, mainly collagen and proteoglycans, to guide tube formation and resist the pressures of blood flow. Conditions for collagen deposition and polymerization can be created only if molecular O_2 is available to be incorporated into the structure of nascent collagen by prolyl- and lysyl hydroxylases.



VAT helps provides the threshold level of pO_2 for collagen to form, thus providing the scaffolding necessary for the development of granulation tissue. Shear-dependent NOTCH directs the development, budding and growth of new capillaries. NOTCH 3, produced by pericytes in response to shear stress, is the rate-limiting factor in that process. Endothelial cells initiate blood vessel growth and invade the extracellular matrix (ECM). Membrane type-1 matrix metalloproteinase (MT1-MMP), upregulated by shear stress, facilitates this process then translocates to promote ECM cleavage. MT1-MMP promotes vessel formation, and is clearly required for initiating new blood vessel growth. In addition, MT1-MMP is required for EC tubulogenesis and lumen formation.

VasoActive Therapy (VAT) promotes the formation of collagen by raising tissue oxygen levels above the threshold below which collagen will not form. The additional O_2 also boosts mitochondrial performance and promotes angiogenesis.

	Day 1		Week 4		Week 8	
Patient	Baseline	End TX	Baseline	End TX	Baseline	End TX
1.	1	3	3	8	-	-
2.	0	2	3	8	5	35
3.	12	24	18	29	-	-
4.	21	36	32	48	54	63
5.	27	27	-	-	-	-
6.	7	21	24	36	-	-
7.	40	46	48	52	-	-
8.	1	6	2	14	-	-
9.	35	45	-	-	-	-
10.	47	56	-	-	48	60
11.	28	46	-	-	-	-
12.	53	60	-	-	-	-
13.	3	31	-	-	-	-
14.	60	65	-	-	-	-
15.	13	21	-	-	-	-
16.	21	23	-	-	-	-
17.	36	46	-	-	46	51
18.	15	32	-	-	-	-
19.	1	1	-	-	-	-
20.	28	37	-	-	-	-
21.	30	34	-	-	-	-
22.	23	25	-	-	-	-
23.	4	16	-	-	-	-
24.	40	47	-	-	-	-
25.	22	62	-	-	-	-

VasoActive Therapy Elevates Tissue Oxygen Levels

48% Average tissue oxygen improvement in one treatment

487% Increase in tissue oxygen levels following twelve treatments of 45 minutes each, spread over 4 weeks.

Cost of an Amputation?

In a study by the VA, amputation costs include hospital, surgeon, anesthesiologist, pre and post operative care, prosthetics, physical therapy, occupational therapy, revision surgeries, pressure ulcers on stumps and glutes, depression counseling, home health visits, potential stay in a nursing home, prescriptions, mobility equipment (power chair, etc.). Together, these costs add up to over $150,000. Care over the lifetime of the amputee can easily double this figure.

VasoActive Therapy (VAT) uses overlapping neuromuscular stimulation at 16 places distributed on the legs. The contraction impulses are sequential, from distal to proximal at quarter-second intervals. This neuromechanical circulation increases blood flow toward the heart, thereby increasing venous return, preload, stroke volume, and blood pressure. VAT, thus, increases blood flow and shear stress.

Shear stress, through mechanotransduction, revives the autocrine and paracrine processes. Davies, Berk, Pan, Malek, Traub and others have cataloged dozens and dozens of vasoactive substances that are flow dependent. Under conditions of normal, physiological flow, substances are increased that are mostly anticoagulent, antiinflammatory, vasodilatory, antiapoptotic, and anti-adhesive, and can change endothelial cells to a quiescent phenotype. Low shear rates reverse most of these processes.

VasoActive Therapy℠

A Powerful Weapon For The Difficult Battle Against Chronic Wounds℠

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