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Evidence of efficacy for the VADOplex® intermittent pneumatic compression system (foot impulse technology) for peripheral arterial occlusive disease (PAOD)

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Independent expert opinion on the following:
Evidence of efficacy for the VADOplex® intermittent pneumatic compression system (foot impulse technology) for peripheral arterial occlusive disease (PAOD)

Ladies and Gentlemen,

In the following, I am submitting an independent expert opinion on evidence of efficacy for the VADOplex® intermittent pneumatic compression system (foot impulse technology) for the indication of peripheral arterial occlusive disease (PAOD).

1. Summary

Intermittent pneumatic compression (IPC) is a manifest and established therapy option for improving the treatment results in patients with peripheral arterial occlusive disease.
The physiological basis has been examined in detail and the evidence for the application in this range of indications has been confirmed for more than ten years.

IPC proves to be at least equivalent to controlled treatment with movement exercises and significantly superior to uncontrolled movement therapy.
The quality of life for patients with PAOD in the lower limbs can be verifiably improved.

In regards to the effectiveness, the application of intermittent compression by means of impulse technology is superior to other forms of application.

2. The VADOplex® intermittent pneumatic compression system with foot impulse technology

The VADOplex® system is an intermittent compression system using foot impulse technology.
An intermittently pneumatically filled cuff generates mechanical compression in the area of the vascular network in the foot or hand. Pressure is built up as a very fast impulse. The

process and character of the resulting compression correspond to the typical, physiological pressure pattern during movement, thus during walking for the foot. Pressure is applied exclusively in the area of the foot (or hand). There is no compression of the ankle region and lower leg or forearm.
The system constitutes an established application of intermittent pneumatic compression.

3. Basis of the effect of intermittent pneumatic compression therapy in patients with peripheral arterial occlusive disease (PAOD)

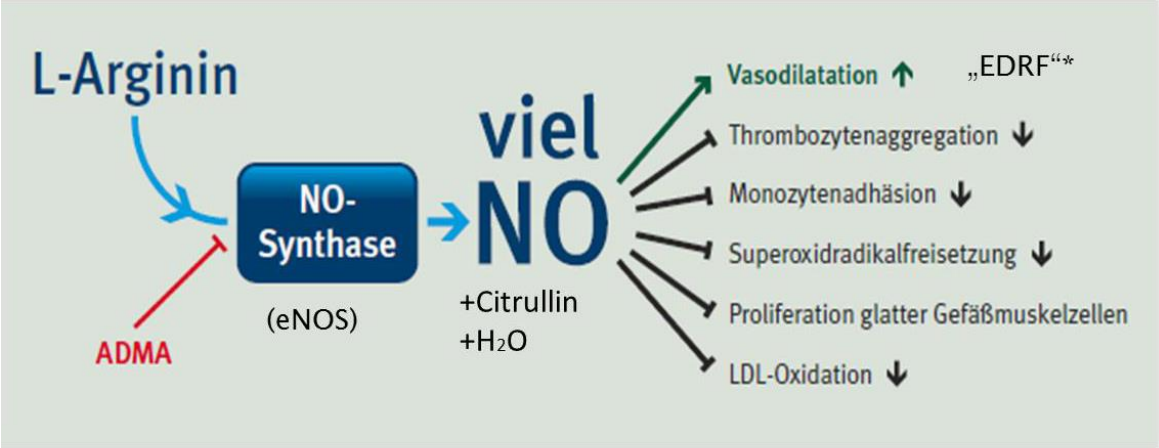
3.1. Regarding the general physiological basis: The role of nitrogen monoxide (NO; also Endothelial Derived Relaxing Factor EDRF) and its synthesis and release in the vascular wall

Movement exercises constitute an established conservative treatment basis for peripheral arterial occlusive disease.
The main features of the effectiveness of this treatment approach are found in the general physiology of the vascular system.
It is known that any acceleration of blood flow in the vascular system due to the effect of corpuscular fluids on the surfaces (here the blood on the vascular wall) leads to an increased shear effect on the endothelial surfaces [2,10,11,14,24,26].
There is a non-linear relationship between the ateriovenous pressure gradient on the one hand and the transcutaneous oxygen partial pressure in the tissue on the other hand [2,10,24]. This makes the role of the flow rate of blood in the vessels particularly significant, since the gradient affects this relationship exponentially [24].
In the physiological consequence, it can therefore be noted that any shear loading on the inside of the vascular wall leads to a direct release of NO from the endothelial tissue [2,10,17,18].

The fact that arterioles and venoles work as a functional unit within the scope of the physiological effects and the regulation of the microcirculation processes is also significant [2,3,10,11,33]. The regulatory effect of circulation unfolds on the overall complex of arteriole and venole [2,3,10,11,14,15,17-19]. Influences on the venous endothelial tissue, which can be triggered by movement but also by intermittent compression, produce assured arterial effects [15,17-19,33]. NO produced in the venous endothelial tissue is also transferred to the neighbouring arterial vessels by diffusion in this process. Such a comprehensive effect is definitely proven [2,3,10,14,15,17,19,26,33].

3.2. Overview of the physiological effects

The nitrogen monoxide (NO) released by the endothelial tissue of the vascular wall under shear stress was identified as Endothelial Derived Relaxing Factor EDRF (Nobel Prize for Medicine 1998; Figure 1).



ADMA: Asymmetrisches Dimethylarginin (wirkt hemmend)

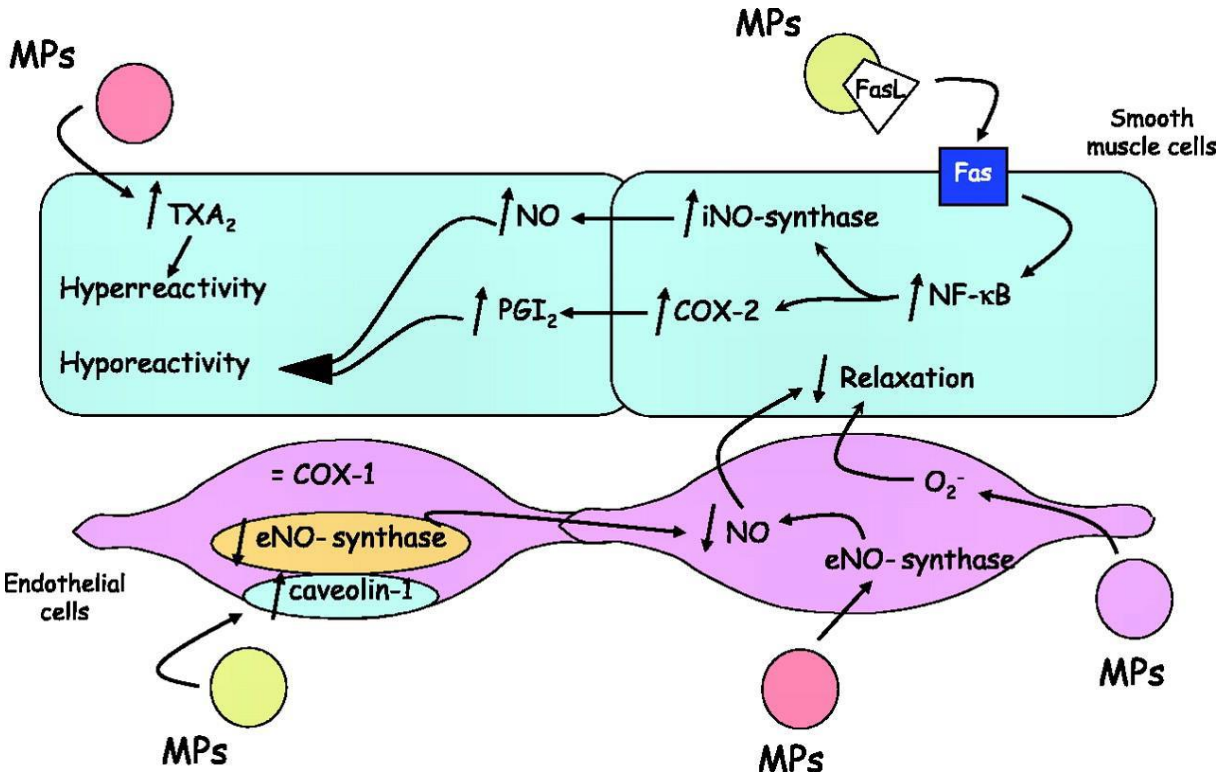
*Furchgott, Murad und Ignarro: Nobelpreis für Medizin 1998

L-Arginin	L-arginine
ADMA	ADMA
NO-Synthase	NO synthase
(eNOS)	(eNOS)
viel NO	much NO
+Citrullin	+Citrulline
+H_2O	+H_2O
Vasodilation	Vasodilation
Thrombozytenaggregation	Platelet aggregation
Monozytenadhäsion	Monocyte adhesion
Superoxidradikalfreisetzung	Superoxide radical release
Proliferation glatter Gefäßmuskelzellen	Proliferation of vascular smooth muscle cells
LDL-Oxidation	LDL oxidation
„EDRF“	“EDRF”

Figure 1: Simplified overview of the effect of nitrogen monoxide (NO; EDRF)

NO exhibits a relatively short half-life in tissue, which is influenced by a number of local factors (metabolic activity) and mechanisms [11,19,20].
Overall NO production is controlled by a number of regulatory processes. The average half-life of the substance in tissue is specified at about 9 seconds; this is a significant factor which contributes to preventing a substance accumulation and therefore an excessive effect [8,12,22,24,26,30-32].

The highly complex processes on the vascular wall and the interaction of effects and substances on the endothelial tissue and muscle cells have been comprehensively described already [11,12,22,24,26,33].
Figure 2 provides an overview of the typical assured effects and actions in the physiological context.



Legend:
MPs: mcicroparticles
COX: Cyclooxygenase
eNO synthase: endothelial nitrogen monoxide synthase
iNO synthase: inducible nitrogen monoxide synthase
FasL: Fas Ligand
Red circles: Platelet mcicroparticles
Violet circles: endothelial mcicroparticles
Green circles: leukocytic mcicroparticles

Figure 2: Overview of the processes on the vascular wall (muscle cell and endothelial tissue) [from: Martinez MC, Tesse A, Zobairi F, Andriantsitohaina R. Shed membrane microparticles from circulating and vascular cells in regulating vascular function. Am J Physiol Heart Circ Physiol. 2005 Mar;288(3):H1004-9.]

4. Clinical significance and classification of the scientific results

As previously described, an increased endothelial shear effect, for example due to a higher venous flow rate, consistently leads to the release of larger quantities of EDRF and increased effects on microcirculation [9,16,22,30,31].

The application of isolated impulse compression (a short, sharply increasing compression impulse which is typical for the Vadoplex® system and forms the foundation of the method) causes brief respective episode of hyperaemia, the individual duration of which is specified at approximately 20 seconds in the literature [1,5,7,21,22].

Repeated compression triggers the effect repeatedly [1,5,22].

As expected, this mechanism can be inhibited by cooling or elevating the limb, since the effect is weakened by the reduced venous inflation [5,22].

Therefore both fundamental research and clinical results confirm that intermittent pneumatic compression (IPC) has a significant and reproducible effect on the arterial component of microcirculation.

In the clinical outcome, IPC by means of impulse systems is more efficient than without impulse application [23].
Overall, any type of sufficient IPC is suitable for improving the symptoms of PAOD (at the limb level) [4,21,27,29].
This applies for both the lower [1,4,5-7,21,23,29] and the upper limbs [27].
A significant influence on the quality of life of patients has been reported [4].

The existence of fundamentally confirmed evidence was already recognised in 2002 by a systematic review of the method: “It is evident that an intermittent pneumatic compression program appears promising and may be used in patients with severe peripheral arterial disease who are not candidates for revascularization using surgery or percutaneous angioplasty.” [21]

Since then the quality of the statements has further improved based on newly presented data, consistently and clearly supporting the previous insights [4,23,27,29].

5. Conclusion and outlook

Intermittent pneumatic compression (IPC) is a manifest and established therapy option for improving the treatment results in patients with peripheral arterial occlusive disease [23,29].
IPC proves to be at least equivalent to controlled treatment with movement exercises and significantly superior to uncontrolled movement therapy [4].

Furthermore, there are indications that adequate intermittent compression therapy in diabetic patients with diabetic angiopathy and polyneuropathy can also develop a positive influence on the sensitivity of the foot in addition to the circulation situation [28].

The quality of life for patients with PAOD in the lower limbs can be verifiably improved [4].
In regards to effectiveness, the application of compression with impulse technology is superior to other forms of application [14].

[signature]

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6. Bibliography

[1] Abu-Own A, Cheatle T, Scurr JH, Coleridge Smith PD. Effects of intermittent pneumatic compression of the foot on the microcirculatory function in arterial disease.
Eur J Vasc Surg. 1993 Sep;7(5):488-92.

[2] Arnal JF, Dinh-Xuan AT, Pueyo M, Darblade B, Rami J. Endothelium-derived nitric oxide and vascular physiology and pathology.
Cell Mol Life Sci. 1999 Jul;55(8-9):1078-87. Review.

[3] Buga GM, Gold ME, Wood KS, Chaudhuri G, Ignarro LJ. Endothelium-derived nitric oxide relaxes nonvascular smooth muscle.
Eur J Pharmacol. 1989 Feb 14;161(1):61-72.

[4] Chang ST, Hsu JT, Chu CM, Pan KL, Jang SJ, Lin PC, Hsu HC, Huang KC. Using intermittent pneumatic compression therapy to improve quality of life for symptomatic patients with infrapopliteal diffuse peripheral obstructive disease.
Circ J. 2012;76(4):971-6.

[5] Delis KT, Labropoulos N, Nicolaides AN, Glenville B, Stansby G. Effect of intermittent pneumatic foot compression on popliteal artery haemodynamics.
Eur J Vasc Endovasc Surg. 2000 Mar;19(3):270-7.

[6] Delis KT, Nicolaides AN, Labropoulos N, Stansby G. The acute effects of intermittent pneumatic foot versus calf versus simultaneous foot and calf compression on popliteal artery hemodynamics: a comparative study.
J Vasc Surg. 2000 Aug;32(2):284-92.

[7] Delis KT, Nicolaides AN, Wolfe JH, Stansby G. Improving walking ability and ankle brachial pressure indices in symptomatic peripheral vascular disease with intermittent pneumatic foot compression: a prospective controlled study with one-year follow-up.
J Vasc Surg. 2000 Apr;31(4):650-61.

[8] Drexler H, Hornig B. Endothelial dysfunction in human disease.
J Mol Cell Cardiol. 1999 Jan;31(1):51-60. Review.

[9] Esper RJ, Nordaby RA, Vilariño JO, Paragano A, Cacharrón JL, Machado RA. Endothelial dysfunction: a comprehensive appraisal.
Cardiovasc Diabetol. 2006 Feb 23;5:4.

[10] Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine.
Nature. 1980 Nov 27;288(5789):373-6.

[11] Furchgott RF, Cherry PD, Zawadzki JV, Jothianandan D. Endothelial cells as mediators of vasodilation of arteries.
J Cardiovasc Pharmacol. 1984;6 Suppl 2:S336-43. Review.

[12] Feelisch M, te Poel M, Zamora R, Deussen A, Moncada S. Understanding the controversy over the identity of EDRF.
Nature. 1994 Mar 3;368(6466):62-5.

[13] Fleming I, Busse R. NO: the primary EDRF.
J Mol Cell Cardiol. 1999 Jan;31(1):5-14. Review.

[14] Ignarro LJ, Buga GM, Wood KS, Byrns RE, Chaudhuri G. Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide.
Proc Natl Acad Sci U S A. 1987 Dec;84(24):9265-9.

[15] Ignarro LJ, Byrns RE, Buga GM, Wood KS. Endothelium-derived relaxing factor from pulmonary artery and vein possesses pharmacologic and chemical properties identical to those of nitric oxide radical.
Circ Res. 1987 Dec;61(6):866-79.

[16] Ignarro LJ, Byrns RE, Buga GM, Wood KS, Chaudhuri G. Pharmacological evidence that endothelium-derived relaxing factor is nitric oxide: use of pyrogallol and superoxide dismutase to study endothelium-dependent and nitric oxide-elicited vascular smooth muscle relaxation.
J Pharmacol Exp Ther. 1988 Jan;244(1):181-9.

[17] Ignarro LJ, Buga GM, Chaudhuri G. EDRF generation and release from perfused bovine pulmonary artery and vein.
Eur J Pharmacol. 1988 Apr 27;149(1-2):79-88.

[18] Ignarro LJ, Buga GM, Byrns RE, Wood KS, Chaudhuri G. Endothelium-derived relaxing factor and nitric oxide possess identical pharmacologic properties as relaxants of bovine arterial and venous smooth muscle.
J Pharmacol Exp Ther. 1988 Jul;246(1):218-26.

[19] Ignarro LJ. Endothelium-derived nitric oxide: actions and properties.
FASEB J. 1989 Jan;3(1):31-6. Review.

[20] Ishii K, Chang B, Kerwin JF Jr, Huang ZJ, Murad F. N omega-nitro-L-arginine: a potent inhibitor of endothelium-derived relaxing factor formation.
Eur J Pharmacol. 1990 Feb 6;176(2):219-23.

[21] Labropoulos N, Wierks C, Suffoletto B. Intermittent pneumatic compression for the treatment of lower extremity arterial disease: a systematic review.
Vasc Med. 2002 May;7(2):141-8. Review.

[22] Maiorana A, O'Driscoll G, Taylor R, Green D. Exercise and the nitric oxide vasodilator system. Sports Med. 2003;33(14):1013-35. Review.

[23] Manfredini F, Malagoni AM, Felisatti M, Mandini S, Lamberti N, Manfredini R, Mascoli F, Basaglia N, Zamboni P. Acute oxygenation changes on ischemic foot of a novel

intermittent pneumatic compression device and of an existing sequential device in severe peripheral arterial disease.

BMC Cardiovasc Disord. 2014 Mar 31;14:40.

[24] Mitchell JA, Förstermann U, Warner TD, Pollock JS, Schmidt HH, Heller M, Murad F. Endothelial cells have a particulate enzyme system responsible for EDRF formation: measurement by vascular relaxation.

Biochem Biophys Res Commun. 1991 May 15;176(3):1417-23.

[25] Murad F, Ishii K, Förstermann U, Gorsky L, Kerwin JF Jr, Pollock J, Heller M. EDRF is an intracellular second messenger and autacoid to regulate cyclic GMP synthesis in many cells.

Adv Second Messenger Phosphoprotein Res. 1990;24:441-8.

[26] Murad F, Waldman S, Molina C, Bennett B, Leitman D. Regulation and role of guanylate cyclase-cyclic GMP in vascular relaxation.

Prog Clin Biol Res. 1987;249:65-76. Review.

[27] Rifkind JM, Nagababu E, Dobrosielski DA, Salgado MT, Lima M, Ouyang P, Silber HA. The effect of intermittent pneumatic compression of legs on the levels of nitric oxide related species in blood and on arterial function in the arm.

Nitric Oxide. 2014 Aug 31;40:117-22.

[28] Rosales-Velderrain A, Padilla M, Choe CH, Hargens AR. Increased microvascular flow and foot sensation with mild continuous external compression.

Physiol Rep. 2013 Dec 19;1(7)

[29] Sheldon RD, Roseguini BT, Laughlin MH, Newcomer SC. New insights into the physiologic basis for intermittent pneumatic limb compression as a therapeutic strategy for peripheral artery disease.

J Vasc Surg. 2013 Dec;58(6):1688-96.

[30] Taddei S, Ghiadoni L, Virdis A, Versari D, Salvetti A. Mechanisms of endothelial dysfunction: clinical significance and preventive non-pharmacological therapeutic strategies.

Curr Pharm Des. 2003;9(29):2385-402. Review.

[31] Waldman SA, Murad F. Biochemical mechanisms underlying vascular smooth muscle relaxation: the guanylate cyclase-cyclic GMP system.

J Cardiovasc Pharmacol. 1988;12 Suppl 5:S115-8. Review.

[32] Warner TD, Schmidt HH, Murad F. Interactions of endothelins and EDRF in bovine native endothelial cells: selective effects of endothelin-3.

Am J Physiol. 1992 May;262(5 Pt 2):H1600-5.

[33] Vallance P, Patton S, Bhagat K, MacAllister R, Radomski M, Moncada S, Malinski T. Direct measurement of nitric oxide in human beings. Lancet. 1995 Jul 15;346(8968):153-4.

7. Experience of the expert
As of November 2015

Name:	Dr.med. Thomas Eberlein
Date of birth:	13.12.1967
School education:	
09/1974 - 07/1984	Secondary modern school
09/1984 - 07/1986	School-leaving certificate (university entrance diploma)
Vocational training:	
1989 – 1991	Pre-clinical studies at Humboldt University Berlin - D
1991 - 1995	Clinical studies at the medical faculty of Dresden Technical University - D
Professional occupation and qualifications:	
1995 - 1997	Medical occupation at a dermatology practice in Plauen - D
1997 – 1998	Assistant in the department for peripheral vascular surgery at Zurich University Hospital - CH (manager: Professor Dr. med. U. V. Brunner)
01/1998	Graduation as doctor of medicine at the medical faculty of Dresden Technical University - D
1998 –1999	Assistant at the clinic for dermatology at the medical faculty of Dresden Technical University - D (director: Professor Dr. med. M. Meurer)
09/1999 to 10/2001	Occupation as dermatologist and allergist at a practice in Plauen - D
06/2000	Acquisition of the technical qualification “specialist for dermatology and venerology”
06/2001	Acquisition of the additional qualification “allergist”
02/2001 to 12/2004	Special consulter / lecturer / medical-scientific manager at Kammerlander Consulting – Embrach / Zurich - CH
08/2006	Certified expert “wound management” for TÜV CERT Austria
02/2011	Affiliation with the College of Medicine and Medical Science, Arabian Gulf University, Manama, Bahrain
furthermore	Chief medical manager academy ZWM Embrach – CH; lecturer for various continuing education projects in wound management in German-

	speaking Europe; medical-scientific management of various project groups Board member of Deutsche Wundakademie, Hamburg - D Managing Editor of the journal “Wound Medicine”, the International Wound Journal for Clinical and Health Economics Research and Applications (Elsevier)

Associations and federations:

Since 2003	Member of the “Gesellschaft deutschsprachiger Lymphologen (GDL)” Long-term membership in various German-language wound associations

Scientific activities:

- Since 2000: Extensive publication activities in a wide variety of technical gazettes focusing on “wound management”
- Co-author of volume 5 “Wundversorgung” of the “Manuale zur Pharmazeutischen Betreuung” of the Bundesapothekerkammer (Federal Pharmacy Chamber)
- Co-author of the book “Manual der Wundheilung” (Eds. Th. Wild and J. Auböck)
- Co-author of the book “Krankenhaus- und Praxishygiene” (Eds. A. Kramer and O. Assadian)
- Since 2000: More than 720 presentations, thereof over 170 national and international convention presentations in German and English
- Planning, implementation, controlling, evaluation and publication of various clinical application observations and studies in the field of “wound management”