Chapter 5
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Chronic Infrasound Impact is Suspected of Causing Irregular Information via Endothelial Mechano-transduction and Far-reaching Disturbance of Vascular Regulation in All Organisms

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ABSTRACT

Famous researchers have long recognized the connection between vibration, energy, and information.
Albert Einstein and *Max Plank* in particular classified all energy transfers as *oscillations*. With the current findings on *endothelial mechano-transduction*, we can come closer to understanding the complex regulation of vital functions of life by mechanical forces. The undisturbed course of essential functions such as growth, blood pressure regulation, inflammatory sequence, and embryogenesis is bound to the absence of externally transmittable forces *and* endothelial integrity.
The recognition of various endothelial cell structures *as mechano-sensors* is simultaneously important for understanding vital regulations. The endothelial cell itself, which corresponds to a *viscoelastic "tensegrity model*", is a mechano-sensor that adapts *beat to beat* to the current conditions in the blood flow in alignment with the effect of various physical forces.
Numerous endothelial mechano-sensors are identified, whereby the conserved structures of PIEZO channels for all organisms - from bacteria to mammals - have an outstandingly important role in numerous life processes, the decoding of which is still far from complete.
The present knowledge sheds new light on the importance of *low frequencies*. The endothelial cytoskeleton identified now as a low-pass filter, offers the possibility for *mechano-transduction*. There is strong evidence that parts of the energy transmission of low-frequency oscillations become irregular information at the

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endothelial level that interferes with the autochthonous control of the *microcirculation*. Recent studies confirm the importance of a balance of the NO metabolism due to a synchronized release *at the right time, in the right place, and with the right quantity*. Misinformation, caused by external forces, must inevitably lead to an increase in *oxidative and oscillatory stress*, the main reason for a loss of endothelial integrity with inflammation diseases like atherosclerosis. This could indicate the long-sought pathophysiological way in which *infrasound* and *vibration* can exert a stressor effect at the cellular level. Noise-exposed citizens, who live near infrastructures such as *biogas installations, heat pumps, block-type thermal power stations*, and *bigger industrial wind turbines* (IWT's), show worldwide mainly a symptomatology associated with microcirculatory disorder.
Marine ecosystems, but also insects, appear to be particularly at risk from increasing emissions of very low frequencies. There is evidence for the increasing incompatibility of ever lower frequencies for all organisms and therefore for *whole biodiversity.*

Keywords: Mechano-transduction; endothelial cytoskeleton; infrasound; oscillatory and oxidative stress; biodiversity.

1. INTRODUCTION

Endothelium health is essential to the regulation of physiological vascular functions. Because of the critical capability of endothelial cells (ECs) to sense and transduce chemical and mechanical signals in the local vascular environment, their dysfunction is associated with a vast variety of vascular diseases and injuries, especially atherosclerosis and subsequent cardiovascular diseases [1]. The vascular endothelium serves as an interface between the blood and the tissue. This layer of cells is increasingly recognized as a critical component of vascular health. The endothelial regulation of vasodilation and contraction, vascular permeability and inflammation, and immune signaling is critical to vascular health, which in turn is pivotal to our survival [2].

1.1 Structure, Components, and Regulation of the Microcirculation System in Mammals

The flat endothelial cells line all the mammal's vessels (including lymph vessels) as its largest organ. Responsible for the entire transport of energy- and substrate metabolism as well as for many vital functions, they have a very large surface area (approx. one football field, respectively four to five tennis courts in an adult) [3,4]. The endothelial cell corresponds in its structure to a somatic cell and is specified for its diverse tasks, whereby the respective vessel (capillary vessel, artery), as well as the type of tissue (splanchnic area, kidney, brain), is responsible for its further specification [5]. It differs in shape, expression, surface, and staffing of receptors of the adrenergic system [4]. According to their ultrastructure, endothelial cells are differentiated, depending on their organ-specific substructure, into various types of continuous, fenestrated, and discontinuous endothelium. The circulatory system is self-contained in a combination of vessels - connected in series and in parallel - in which, by *Ohm's law*, the total resistance decreases with each

additional parallel connection [5,4]. By regulating the resistance via the upstream arterioles, we physiologically find laminar flows with uniform velocity, strictly bound to the vessel size, in the capillary network. This is a crucial precondition for the diverse and vital tasks of the microcirculation [5,6]. In contrast, we find chronic oscillatory stress, a strong causal factor for atherosclerosis, at vascular branches and stronger curves of medium and larger vessels [4]. One of the main tasks of microcirculation is to adapt vascular blood flow to current needs [3,7]. The functional vessel density (FVD) in resting muscle is about 25% of the total vessel density (TVD). Conversely, this also means that blood flow can be increased by a multiple [8]. The compensatory capacity of the capillary network is thus many times higher than that of the "macrocirculation". Under physical strain, so-called *capillary recruitment* according to Moore and Fraser [9] begins by lowering the vascular resistance of upstream arterioles, resulting in a significant increase in the nutrient exchange surface and a decrease in the distance between two capillaries with a consequently reduced diffusion distance for oxygen and nutrients [4]. The regulation of local blood flow (so-called vasomotor function) is extremely complex and "orchestrated" [7,4]. It is controlled by intrinsic and extrinsic factors (e.g., autonomic nerve system and vasoactive hormones, e.g., *adrenaline*, *vasopressin*, *angiotensin*, *serotonin*) which modulate intrinsic activity [3], dependent also on vessel size and the distribution of adrenergic receptors to a given organ [4].

One basis for *intrinsic* regulation is the *Bayliss effect* [10]. Blood flow is kept constant: If blood flow increases, vasoconstriction occurs, if blood flow falls, vasodilation occurs [4]. A second basis is *metabolite factors* according to the classical theory, in which local hypoxia leads to an increased release of vasodilatory active substances (e.g., *NO*, *ATP*, *prostaglandins*), causing an increase in local blood flow [4]. Accumulating metabolites such as *lactate*, *hydrogen ions*, *potassium, and adenosine* maintain this effect [3]. One of the most important and mainly responsible prerequisites for *NO bioavailability* is the *classical laminar shear stress response* due to mechanical forces according to Chien [11]. NO is triggered classically by blood flow causing a mechanical change at the endothelial cell membrane and formed from its precursor L-arginine via NO-synthetase (*NOS*) [4]. NO mediates vascular relaxation by activation of the soluble guanylate cyclase (sGC) which catalyzes the conversion of guanosine triphosphate (GTP) into 3'-5'-cyclic guanosine monophosphate (cGMP) [4].

The latter is extraordinarily typical for microcirculation, but one of the least explained phenomena: *vasomotion*.

Vasomotion was first observed in the classic example of a bat vein and described as rhythmic contractility that accelerates blood flow forward through fine and synchronized pulsations [12]. The causes and control of these have not yet been fully elucidated [4]. The current state of knowledge is that *vasomotion* depends *on the integrity of the endothelium* and serves to optimize nutrient support [13]. *Vasomotion* can be directly observed *in vivo* with SDF-video microscopy. Quote from Aalkjaer C. Mulvany MJ [13] in cap. 1.3, page 7: "*Perhaps the only feature related to vasomotion which is agreed by everybody is that an oscillation of the smooth muscle cell membrane potential is the background for the oscillation of the*

individual smooth muscle cell tone and also for the synchronization of the smooth muscle cells […] *This strongly suggests that* [Ca^{2+}] *in the smooth muscle cells is also oscillating in a synchronized manner— and this is indeed the case*. […]". There is deeper insight in the original article [13, 4].

The extent of endothelial involvement in clinical syndromes is immense, as are the potential factors that can influence *microcirculation* in both positive and negative ways. The most important potential influences arise from vital functions such as oxygen and nutrition supply, growth, embryogenesis, blood coagulation, immune regulation, etc. The main causes of dysfunction are those that can disrupt the integrity of the *endothelium*, in particular, an *excess of oxidative and oscillatory stress* [4].

Table 1. The different possible effects of Nitric Oxide as protective, regulatory, and deleterious

***Protective effects*:**
• Antioxidant
• Inhibits leucocytes and platelet adhesion
• Protects against toxicity and peroxidation
Regulatory effects:
• Vascular tone
• Cell adhesion
• Vascular permeability
• Neurotransmission
• Bronchodilation
• Inflammation regulation
• Regulation of renal function
Deleterious effects
• Inhibits enzymatic function
• Induces DNA damage
• Induces lipid peroxidation
• Increases susceptibility to radiation, alkylating substances, toxic metals
• Depletes reservations of antioxidants

1.2 Redox System Homeostasis

Crucial for both, synchronized blood flow regulation and the maintenance of vascular health, is the adequate release of *NO* with the right amount, right quantity, at the right place, and at the right time [14]. *As a strong antioxidant*, *it plays a decisive role in the homeostasis of the entire redox metabolism with interruption of lipid peroxidation and therefore decrease of aggressive free oxygen radicals* (*ROS*) [14,15] Table 1 [4]. As free radical (in a gaseous state), it can diffuse freely through the membranes. The vascular effects of NO are presented *as vascular protective*, *regulatory, or deleterious* [13,16]. How the reaction turns out, depends according to Laurindo F. et al. [14] on several factors. According to these authors, the unfavourable properties usually are associated with *excessive* NO production, the *protective NO effects are* attributed to a steady and *for the specific situation adequate NO production* [4]. Not only NO, but also its *three isoenzymes* of endothelial NO-Synthetase are involved in redox signaling pathways. Depending

on the kind of isoenzymes and surrounding conditions, they have likewise either protective effects or such that are deleterious as shown in Table 1 [4, 17,18,19].

After the Original Tab. 1 in Wink AA. Mitchell J (1998) chemical biology of nitric oxide: insights into regulatory, cytotoxic, and cytoprotective mechanisms of nitric oxide, Radiation Biology Branch, National Cancer Institute, Bethesda, MD, USA from Book Free Radical Biology & Medicine, Vol. 25, Nos. 4/5, pp. 434-456, 1998. Published by Elsevier Science Inc. 0891-5849/98 $0.00 1.00 reference Fig. 1 Page 435.

Chronic exposure to low sound frequencies (IFLN) will inevitably increase the effects of inadequate NO release. In a study from 2022 [20] the results demonstrated that the vascular endothelium is *the* target tissue of ILFN and NO is an effector of the ILFN-mediated increase in cutaneous blood, which can explain the increase of cutaneous blood flow in *short term* impact and the decrease in longer impact. A further result is that the *vestibular-sympathetic nervous system* has *limited effects* on the increase of cutaneous blood flow (demonstrated with *wavelet-transform spectrum analysis*) [20].

In sum, the dependence of an adequate *NO* provision on *auto regulated* physical forces leads to a sensitivity to external stressors that would be capable of leading to *irregular mechanic transduction* and *inadequate NO supply*. More details on the whole theme are in articles from [14,15,16,21,22].

In the area of microcirculation, further vasodilating substances play a decisive role. Vascular segments in arterioles respond to *endothelial autacoids* such as *angiotensin, serotonin, and eicosanoids* [5] and to *agonists* such as *acetylcholine, bradykinin, or substance P* as well as to *transmural pressure changes*. They do this not as isolated entities, but in a *coordinated manner*. This is attributed to the *Endothelium-derived-hyperpolarising-factor* (*EDHF*) [14,4]. *EDHF* has a long-distance effect, as its locally triggered formation can also trigger a rectified vascular response up and downstream. The calcium-dependent activation of potassium efflux by *EDHF* is followed by *hyperpolarisation* with the transmission of electron transfer within the vessel wall via the *gap junctions* and without loss of time [23,4]. The transmission reaction is comparable to *a school of fish*, very fast and synchronized [8]. The possibilities of *micro tactile* stimulation compared to triggering via acetylcholine, were experimentally tested and confirmed [8,4].

1.3 Inflammation and Fibrosis Homeostasis

All sequential series of reactions here depend on the *integrity* of the endothelium and involve the *endothelial cytoskeleton*. Since it is a *vital endothelial function*, the complex process of inflammation can be disrupted at any level according to Suthahar [24]. In line with its high relevance to the topic of our work, we present a more detailed description to show how sensible the whole process, e.g., *for mechanic stress*: An inflammatory response is essential as a physiological defense mechanism against, e.g., *bacteria, viruses, injuries*. The point of no return is the *diapedesis of leucocytes*. The further course leads in the favourable case to a

restitution ad integrum, in the unfavourable to *chronic inflammation* with *fibrosis*, *defect healing*, and *possible organ damage* [4].

Important works on the state of the science come from Ley et al. [25] and Serhan et al. [26], related work in particular from Nussbaum and Sperando [27] and [3,28]. According to Ley [25], the orderly process in all phases is crucial for its outcome. Here is presented the undisturbed course [4]:

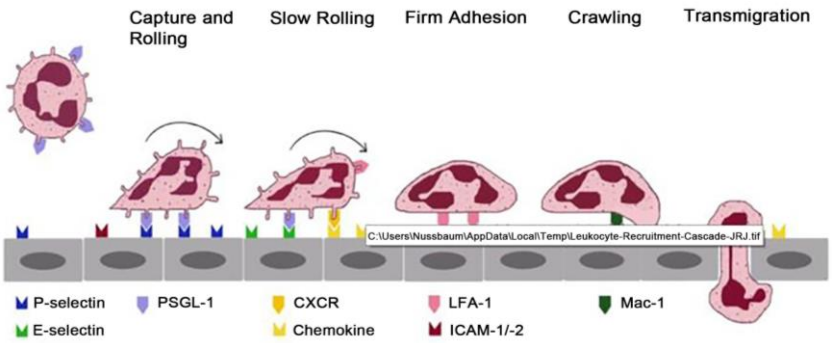

Fig. 1. *Original description*: Schematic overview of the leukocyte recruitment cascade using the example of a neutrophil leaving a postcapillary venule. Capture and rolling are mediated by the interaction of selectins with PSGL-1 on the neutrophil surface. During rolling, the neutrophil is activated by chemokines presented on inflamed endothelium leading to firm adhesion through binding of neutrophil integrins (LFA-1 and Mac-1) to endothelial adhesion molecules (e.g., ICAM-1 and -2). Upon firm adhesion, the neutrophil spreads and begins to crawl along the endothelial lining in search of an appropriate site for transmigration. States of leucocytes diapedesis: Capture and rolling, Slow rolling, Firm adhesion, Crawling, Transmigration source [27] Nussbaum, C., Sperando, M. (2011): Innate immune cell recruitment in the fetus and neonate. J Reproduction. Immunol 2011; 90(1): 74-81. (IF 2, 966). Page 2 Fig. 1 With permission

The circulating leukocytes move *passively* in the bloodstream. In the *postcapillary venules*, local changes near sites of inflammation in the hemodynamics lead to a reduced blood flow rate [4]. This increases the likelihood of leukocytes coming into contact with endothelia. The endothelium is in an *activated state* for a few hours and expresses *adhesion molecules* that lead to leukocyte binding. The "*slow rolling*" of leukocytes is also made possible by another inducible endothelial *E-Selectin*, which is based on a partial activation of *Integrins* on the leukocytes [25] (compare Fig. 1) [4]. The actin cytoskeleton is also actively involved in this process. Further chemokines, partly from the endothelium and partly from the extracellular space (*ECR*), activate tight binding and then amoeboid passage of leukocytes into the *ECR*. Selective changes in permeability (gate- keeper-function of the endothelial cell) allow cellular components such as neutrophils and monocytes, to move from the intravascular space to the *ECR.* More details of the sequences in

leucocyte diapedesis are presented in standard works [3,27]. There is an intensive interplay between endothelial secreted mediators, *cytokines* and such of the ECR [3,24,4].

Anti-inflammatory signals such as *corticosterone* mitigate the severity and limit the duration of the early phase [24].

In summary, the process of inflammation is a complex interplay between a temporally and spatially defined process of mutual influence and activation between factors of the intra- and extra-vascular space [4]. At the center of the process is the adequate *gate-keeper function* of an endothelium in an *integrity state.* After diapedesis of the leucocytes, an orderly process depends on the *absence of increased oscillatory and oxidative stress*, to lead *to a restitution ad integrum*. In the other case, defect healing can occur due to a shift of the equilibrium in the direction of *chronic inflammation and fibrosis*. In clinical medicine, shifts to chronic inflammation and the prevention of themselves play a big role [23,4].

The standard works by Buckley et al. [29] and Serhan et al. [26] describe the sequences after the leukocyte diapedesis: Appropriate "*checkpoints*" and "*stop signals*" prevent further leukocyte entry. *Lipoxins*, *Resolvins, and Prostaglandins* act in an active *pro-resolving process* [4]. This paves the way for the migration and differentiation of monocytes to phagocytosis, for the chemokine gradient normalization (which allows the leukocytes to undergo *apoptosis*), and for exiting the tissue via the draining lymphatic vessels. Failure of such regulatory mechanisms can lead to a state of *chronic inflammation*, causing continuous tissue damage and progressive fibrosis. The central role of the endothelium in the inflammatory process explains the necessary immobilization of infected areas and the need to *avoid external pressure* on the infected area. A classic example is chronic heart failure by "*remodeling*" of the heart [24,4].

At heart, *immunocompetent myofibroblasts* and factors of the *ECR* actively modulate the development of initially *perivascular and later progressive fibrosis*. Starting points can be the development of myocarditis into a chronic form, state after myocardial infarction, and/or *chronic mechanic pressure load on the h*eart (systemic high pressure or pulmonary hypertension) [4]. The consequence is an *increase in diffusion distance, a decrease in capillary density*, an impaired electroconductive system with cardiac arrhythmia, and disruption of angiogenesis, leading again to a deteriorated substrate and oxygen supply with a self-reinforcing process: *a vicious circle* [24,4].

1.4 Hemodynamic Forces

Physiologically physical forces constantly act on the organism, e.g., *gravidity, pressure, shear stress, vibration*. The major ones come from the blood flow itself and are tangential forces (e.g., *laminar shear stress*) or stretching forces (e.g., *pulsatile distention*) according to Fernandes, C.D. et al. [6] and Mazzag et al. [30]. As described above, *internal oscillatory stressors are physiologically limited by*

vessel size, which is a critical factor in maintaining vital functions [6,4]. The regulation of several vital cellular processes via *mechano-transduction* and signaling networks including growth, differentiation, migration, angiogenesis, and apoptosis, is essential [3,6]. During morphogenesis, *shear stress* directs the formation of the vascular tree according to Hahn and Schwartz [31]. Changes in shear stress determine *instantaneous vasomotor* changes that are regulated on a "*beat-to-beat*" basis [6,4] to maintain *constant laminar stress* and optimize the conductance artery flow distributive function. In consequence, disturbed flow can have deleterious effects on embryogenesis. At the same time, it is important to rely on sufficient NO release [6]. An overview of the different effects of shear stress is given in Fig. 2 [4].

The integrity of the vascular endothelium plays a decisive role in the origin of atherosclerosis, which is the precondition of cardiovascular diseases like myocardial infarction, stroke, and aneurysm. Endothelial cells "orchestrate" the different roles of monocytes, macrophages, and smooth muscle cells and their interactions through local expression and secretion of signaling molecules. This means that the activated vascular endothelium is *the* essential driver of atherosclerosis, which induces a proinflammatory and proatherogenic phenotype in response to *disturbed flow* [22]. Recent studies confirm the decisive role of a disturbed flow for the endothelial activation for flow-induced inflammation and leucocyte recruitment as well as a crucial involvement of the mechanosensitive PIEZO-1 channels (Fig. 1 in [22], on page 3). The results show an increase in oxidative stress in areas of disturbed flow with an increase in oxLDL, which in turn acts as an additional proatherogenic factor.

1.5 Tensegrity Structure of the Endothelial Cytoskeleton

The *viscoelastic structure* of the endothelial "tensegrity"-structure offers the foundation for mechano-transduction of forces. The term "tensegrity" was coined by R. Buckminster Fuller [32], architect of the geodesic dome, where *discontinuous compression and continuous tension* were used to achieve the highest possible stability combined with lightness. Additional anchorage points are used to transfer mechanical forces to the individual compression and tension elements [33,4]. The equivalents at the endothelial cell level are the *three intercommunicating networks of protein filaments* and their anchor points:

Actin filaments as the elastic part, serve to maintain the cell shape by forming a ring under the cell membrane [33] with a communication network to flow sensors (*mechano-sensors*) and membrane focal adhesion points (*FAS*) — the "*anchor points in the tensegrity model*"— as well as the intercellular *gap junctions* (*CCAP*) [33,4]. According to Dudek et al. [34], over 80 actin-binding proteins are critical participants in the generation of *tensile forces.* The original article [33] provides a deeper insight into this complex topic. In response to contractile stimuli, *actin- and myosin filaments* form membrane-bound, parallel-organized units, called "*stress fibers*" that stimulate the sliding of myosin along the actin filaments. This leads to an increase in intracellular tension and thus cell contraction according to Wang et al. [35] and Lee et al. [36]. The closing and opening of the paracellular gaps in response to inflammation, ischemia, and invading substances (*gate-keeper-*

function) are essential according to Patrick Belvitch et al. [37]. Actin filaments also make up the so-called *microvilli*. These contain a central bundle of *actin filaments*, also anchored to the cytoskeleton. Microvilli are found in various organs (e.g. intestine) where they have mainly resorptive properties [4].

Microtubules constitute the compression element with pressure-resistant hollow rods, consisting of *α*- and *β-tubulin* [33]. They are connected to the *ECR* by integrins (*transmembrane proteins*) and support the cellular structure in communication with actin filaments and intermediate filaments as well as the formation of spindles for mitosis [4].

1.6 Mechanical Force Transmission via "Biophysical" Mechano-Transduction

The observation that many processes take place much faster than the *mechano-chemical* pathway via *gene expression* and *protein synthesis* would allow (namely a minimum of some seconds), led to intensive research in the "tensegrity" structure and to the definition of the "*biophysical pathway*" [4]. This relies on direct physical links between *specific mechano-sensors of the endothelial surface and cytoskeleton elements*. It allows cells to transfer mechanical stimuli over long distances and very importantly, a *spatially heterogenic excitation to transform information into a desired reaction* [35,4]. Crucial work with important relevance to our work is the research on the dynamics and distribution of transmission in response to "*noisy flow*" from Bori Mazzag et al. [38] and Mazzag B, Gouget C, Hwan Y, Barakat AI [30]. By "noisy" flow, the authors mean an "*oscillating or turbulent flow* under *conditions with random fluctuations in the flow properties of pressure and velocity*", Quote Mazzag, Barakat 2010 on page 912 [38].

Predecessors in the exploration of the "biophysical pathway" in the early 2000s were Wang et al. [11] and Davies et al. [39]. Significant works have been contributed in this context by Helmke et al. [40], Hsu, H. J., Lee, C.F, Locke, A. et al. [41]; Hwang, Y., Gouget, C. L. M and Barakat, A. I. [42].

To better understand the dynamics of force transmission via cytoskeletal filaments, several mathematical models have been developed. The authors Mazzag and Barakat present an overview (possibilities and limitations) in [30,4].

The Temporal Network Model, as presented in [38] and [30] is based on a viscoelastic structure of a tensegrity model, to develop insight into "noisy" flow transmission and to define, which transmission structures are sensible to "noisy" flow. This model is shown in Fig. 3 [4].

The results show that the amplitude of the *oscillations* in the "noisy" flow will be answered *more strongly than its duration*. Another significant implication is that *FAS* (Focal adhesion points - equal anchoring points to *ECR*), due to their high sensitivity to noise, are prime candidates for acting as cellular "Noise detectors" [38,4].

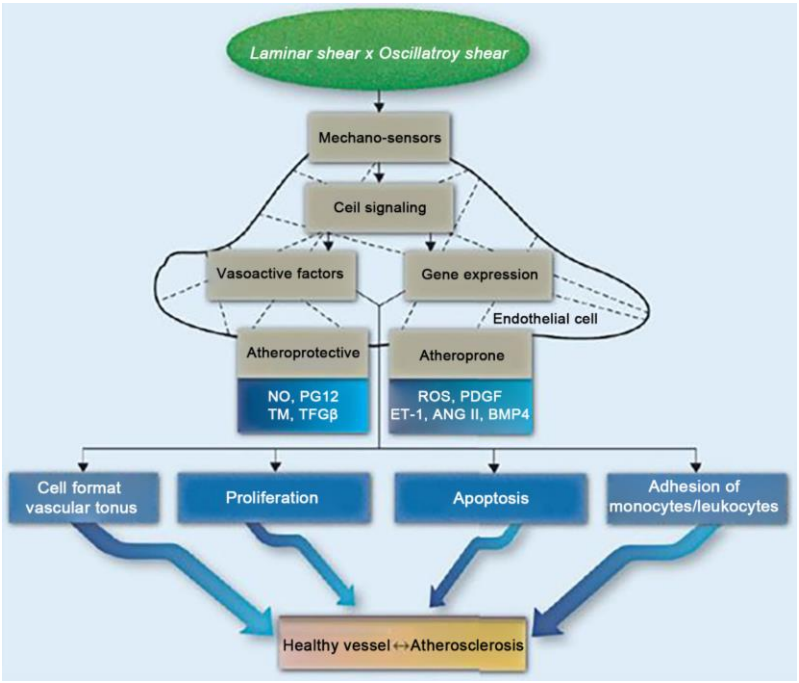

Fig. 2. Original description: Different effects of laminar and oscillatory shear on cell function and atherosclerosis. The *dotted lines* represent the endothelial cell cytoskeleton. Laminar and oscillatory shear forces are recognized in endothelial cells by mechano-sensors and the mechanosignals initiate signaling cascades that regulate the production of vasoactive factors, and the balance between these factors. While laminar shear stimulates the production of atheroprotective factors, oscillatory shear stimulates the production of atherogenic factors and the balance of these factors determines the vessel's tendency to stay healthy or to develop atherogenic plaques. PGI2, prostacyclin; TM, thrombomodulin; TGFb, Transforming Growth Factor beta; PDGF, Platelet-Derived Growth Factor; ET-1, Endothelin-1; BMP4, Bone Morphogenetic Protein 4. Adapted from Jo H, Song H, Mowbray A. Role of NADPH oxidases in disturbed flow- and BMP4-induced inflammation and atherosclerosis. Antioxid Redox Signal 2006; 8: 1609-19. Overview over the different effects of laminar and oscillatory shear stress on cell function and atherosclerosis. Original source [6] Fernandes CD, Araujo Thaı's S, Laurindo FRM, Tanaka LY. Hemodynamic Forces in the Endothelium. Mechano-transduction to Implications on Development of Atherosclerosis. In: ENDOTHELIUM AND CARDIOVASCULAR DISEASES. Vascular Biology and Clinical Syndromes. Edited by Protasio L. DA Luz. Peter Libby Antonio C. P. Chagas. Francisco R. M. Laurindo. Publisher: Mica Haley. Sao Paolo. (2018) ISBN 978-0-12-812348-5 Cap. 7 Fig. 7.3, p 90. With permission

A summary assessment follows in Mazzag, B. [30] with further developments of models, e.g., for the spatial distribution of mechanical forces during transmission such as the Spatial-temporal network Model. According to the authors [30], there were important contributions from the original articles from [42] and Mazzag and Barakat (2011) as well as Mazzag et al*.* (2003).

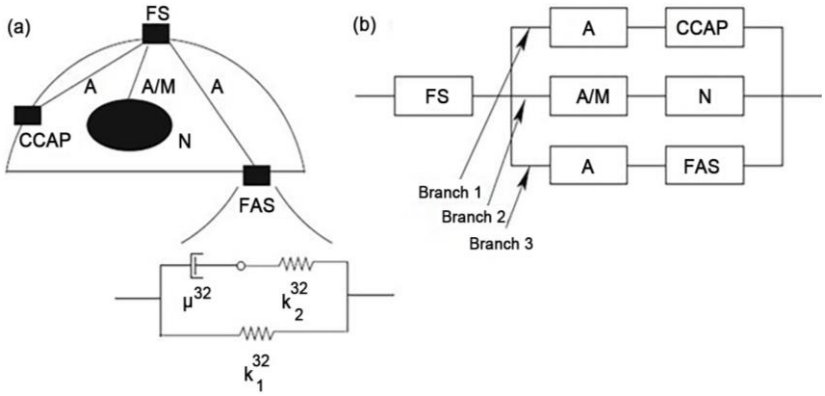

Fig. 3. *Original description*: Schematic representation of an EC consisting of a mechano-sensor (MS), cytoskeletal elements (either actin stress fibers (a) or microtubules (M)), a nucleus (N), cell-cell adhesion proteins (CCAP), and focal adhesion site (FAS). The inset shows a TPMM (or Kelvin body) representation and the viscoelastic parameters for FAS. The superscripts '32' on the parameters indicate that this element is the second element on the third branch (see text). (b) Branching network representation of the EC components in panel A. Each cell component corresponds to a TPMM, coupled to other components according to the diagram shown. Actin stress fiber and CCAP connected in series are referred to as Branch 1, actin stress fiber/microtubule in series with the nucleus is Branch 2, and actin stress fiber in series with the FAS is Branch 3. (a) Schematic representation of an endothelial cell consisting of a flow-sensor (FS), cytoskeletal elements actin filament (a) or microtubules (b) and the connections (N), (CCAP), (FAS). (b) Mathematical representation. Source [30] [38]: Temporal Network Model Fig. 1 *Bori Mazzag*, *Cecile L. M. Gouget*, *Yongyun Hwang* and *Abdul I. Barakat* [30] Cap. 5. Page 98 [38] Mechanical Force Transmission via the Cytoskeleton in Vascular Endothelial Cells. In Endothelial Cytoskeleton. *Editors* Juan A. Rosado and Pedro C. Redondo Department of Physiology, University of Extremadura Cáceres, Spain. With permission

In summary, *the results provide a strong frequency dependence of force transmission with the definition of a threshold value for actin filaments* (*more sensible*) *and microtubules*.

Another issue for the authors was the saturation behavior when the signal persists and an explanation, as to why the natural frequencies, generated by organs of the organism itself, do *not* lead to a long propagation of transmission. We cite the authors Mazzag and Barakat 2014 on page 107 [30]:

"*In the case of oscillatory forcing*, *the deformation-related stress as in the case of constant forcing exhibits an initial transient before it eventually saturates to a time-periodic steady-state response*. *Importantly the saturation amplitude of the deformation-related stress at the nucleus is found to be strongly dependent on the forcing frequency*. *Figs. 3D and 3E illustrate the saturation amplitude of deformation-related stress at the nucleus as a function of forcing frequency for transverse and axial forcing*, *respectively* [4]. *In both the axial and transverse directions*, *a low-frequency* (<0.1 *Hz*) *mechanical stimulus is transmitted to the nucleus without decay in its amplitude*, *whereas a high-frequency mechanical stimulus undergoes significant decay in amplitude*. *This implies that individual stress fibers act as low-pass filters of mechanical forcing*. *Interestingly*, *transverse motion exhibits a much broader filter width than axial motion: the filter width for transverse motion extends to f* ~ 1000 *Hz whereas the one for axial motion extends to only f* ~ 1 *Hz*" […] (Remarks: citation italic letters) [4].

Second important quoting *on page* 101 [30,4]:

"*As already described*, *oscillatory flow has been reported to induce EC dysfunction and to correlate with the development of early atherosclerotic lesions*. *Therefore*, *we also investigated the response of the simple networks described in the previous paragraph to oscillatory flow*. *The results revealed that the peak deformation* (*defined as the largest deformation within a period after the asymptotic time-periodic behavior is attained*) *of each of the structures in the network* (*mechano-sensor*, *actin stress fibers*, *microtubules, and nucleus*) *is strongly frequency-dependent*. *At sufficiently low oscillatory frequencies*, *the peak deformations match those for constant forcing; however*, *above a threshold frequency*, *the peak deformations drop significantly*. *The analysis demonstrated that this threshold frequency is in the range of* 10−5 - 10−4 *Hz for microtubules and* 10−3 - 10−2 *Hz for actin stress fibers*, *suggesting that stress fibers can effectively transmit force over a wider frequency range*." "[…]." [Remarks: Italic letters from me].

Research by Na et al*.* [43] experimentally compared the velocity of mechano-transduction via the *bio-physical* and *mechano-chemical* pathways (*growth factor and gene expression*). The authors used comparable physical exposures for Infrasound (0.3 Hz), duration of 30 s, and sound pressure of 1.8 Pa (studies with 1.8 Pa up to about 20 Pa). The most important results were the confirmation that the speed was 40 times faster than by mechanical-chemical means (confirming the above results), namely 300 ms (milliseconds). Beyond this, the findings were that the "*Stress-Induced Src Activation depends on Integrin Activation*, *Substrate Stiffness*, *Prestress, and F-Actin Integrity*" [43], quoting from Na et al*.* on page 1. Remarks: in italic letters (from me) [43,4].

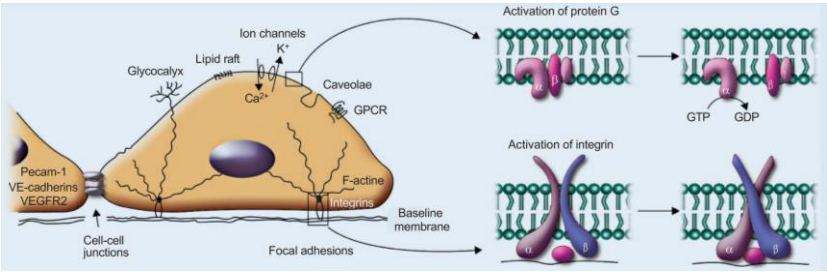

Fig. 4. O*riginal description*: Endothelial cell mechano-sensors. Location of mechano-sensors such as cytoskeleton, integrins, cell-cell junctions, caveolae, lipid rafts, cell surface glycocalyx, G protein-coupled Receptors (GPCR), and ion channels. While mechano-sensors in the apical region (lumenal) are activated directly by shear stress (such as G proteins), the cytoskeleton (represented by actin fibers, F-actin) is responsible for transmitting forces to the mechano-sensors at the basal region of endothelial cells (such as integrins). G protein activation occurs due to local changes in plasma membrane fluidity, therefore directly due to shear stress and independent from an agonist, causing hydrolysis of GTP into GDP. On the other hand, the structure of mechanosensitive integrins is changed from inactive to active when submitted to shear stress, possibly due to the transmission of the mechanical force to the cytoskeleton. In active conformation, integrins have a higher affinity for cognate proteins in the extracellular matrix. Mechano-sensors of the endothelial cell (status 2019) source 5 Fernandes CD, Araujo Thaı's S., Laurindo FRM, Tanaka LY. Hemodynamic Forces in the Endothelium. Mechano-transduction to Implications of Development of Atherosclerosis. In: ENDOTHELIUM AND CARDIOVASCULAR DISEASES. Vascular Biology and Clinical Syndromes. Edited by PROTASIO L. DA LUZ. PETER LIBBY ANTONIO C. P. CHAGAS. FRANCISCO R. M. LAURINDO. Publisher: Mica Haley. Sao Paolo (2018) ISBN 978-0-12-812348-5. Cap. 7 Fig. 7.2, p. 89. With permission.

1.7 The Mechano-Sensors of the Endothelial Cell

According to [6] the cytoskeleton itself is a mechano-sensor. On the side facing the vessel (luminal), mechano-sensors are especially the *glycocalyx*, *integrins*, *cell-cell junctions* (*CCAP*), *caveolae*, *lipid rafts*, *G-protein coupled receptors, and ion channels*. They are activated according to their location via *shear stress* [6] (Fig. 4) [4]. According to the author in [6], *endothelial mechano-sensors* are altered in their microenvironment by shear stress and can activate intracellular signaling pathways in this new formation. The fluidity of *microdomains* in the plasma membrane is altered [6]. This leads according to [6] to a spatial rearrangement of various proteins and thus to the activation of signaling pathways. The *transmission of forces* takes place via the three intercommunicating networks of the cytoskeleton to the basal region of the cytoskeleton (e.g., Integrins) [6,30,38,4].

One of the most important mechano-sensors is the *glycocalyx* [3,6] Fig. 4). In critically ill patients the extent of the *glycocalyx* damage (so-called *shedding*) correlates with the severity of disease and mortality [3,44,45].

As identified to date, mechano-sensors are presented in Fig. 4 (status 2019).

1.8 PIEZO-1-Channels

Additional recently defined endothelial mechano-sensors, the *PIEZO-1 channels*, have been established *as a sensory system of internal organs* by the *receptors for pressure and vibration in all vessels*. Due to the great importance of their breakdown, Ardem Patapoutian received the Nobel Prize in Medicine in 2021. According to Rode et al*.* [46], Piezo-1 is responsible for flow-sensitive, non-inactivating, non-selective cationic channels which *depolarize* the membrane potential: Ca^{2+} permeable Piezo-1 channels are activated by physical force on the cell membrane (compare Fig. 5) [4]. PIEZO-1 senses the whole body's physical activity to reset cardiovascular homeostasis and enhance performance. They are critical for *lymphogenesis* and *homeostasis* and are important *shear stress mechano-sensors* [47]. PIEZO channels are crucial in all multicellular organisms, *i.e.*, *also invertebrates such as flies and vertebrates* (*fish*) [48]. A schematic representation of an embedded PIEZO-1 channel is shown in Fig. 5 [4].

Further studies have now identified a pivotal role for PIEZO channels, e.g. Feng et al. [49], on the importance of the Piezo-1 channel for the *alignment and migration of endothelial cells, formation of capillary networks, the endothelial regulation of inflammation, and neuronal development* [4]. The work confirms the central role of PIEZO channels from bacteria to mammals in the mechano-transduction processes. According to Feng et al. [49], a variety of ion channels in eukaryotic cells can sense various forms of mechanical force, whereby most MS candidates (*the TRP channel* in particular) are activated not only by *mechanical stimuli* but also by *chemicals, temperature, osmolarity, and heat* (> 27–34°C). *Voltage dependence* of the opening mechanism is intended to protect against overstimulation according to Feng et al. [49], first described by Coste [50,4].

According to Feng, we have a "new age of research on the pathological and physiological processes associated with mechano-transduction […]" quote Feng et al. [22] on page 16.

2. NOISE, SOUND AND INFRASOUND

In the International Classification of Diseases (ICD-10) (2010), published by the World Health Organization (WHO), "Noise exposure" (item W42) is listed under the heading of "*Exposure to inanimate mechanical forces*" (items W20- W49) [51]. Indeed, airborne propagating pressure waves (*i.e.*, sound) permeate the *viscoelastic tissue* of biological organisms as *external mechanical forces* [4].

In the more recent ICD-11 (2020), additional Extension Codes (Section X) have been established, and "noise exposure" (item XE7Y1) now falls under the

categories of “External causes/Exposure to another mechanism” [52]. The condition “*Vertigo from infrasound*” (item T75.2 in the ICD-10) under the heading “Effects of vibration” now falls under the category of “Other specified effects of vibration” (item NF08.2Y) [4].

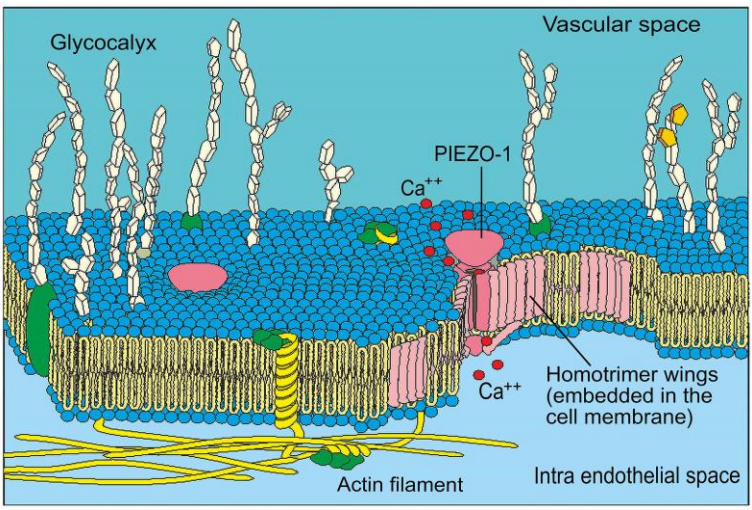

Fig. 5. Schematic presentation of a PIEZO-1-channel, embedded in the endothelial cell membrane with a triggered Ca^{2+}-inflow. The actin ring (intra-endothelial) is indicated. The wings are moved by mechanical forces on the membrane and release the channel in an opening movement. Blue/Yellow: endothelial biomembrane with lipid bilayer structure. Schematic presentation of a PIEZO-1-channel

Infrasound is defined as sound with a frequency below 20 Hz. Low-frequency noise (IFLN), not clearly defined, according to DIN 45680, draws the line at 125 Hz. The lower the frequency, the greater the wavelength. Infrasound can only be minimally dampened and is less attenuated by propagation through the atmosphere as well as through roofs and walls than the audio spectrum [4]. For example, sound propagation in the air with a wavelength of 0,1 Hz is about 3,3 km (standard condition 20 degrees Celsius), and that of 1000 Hz is about 34 mm. Infrasound is generated by heavy-moving masses as well as by resonance phenomena/vibration. Its exposure can be occupational or residential, and can be emitted from natural (e.g., earthquakes) or technical sources (trains, airplanes, occupational or residential sources). The emitters differ in frequency, sound pressure P (Pa), time/effect profile (impulsiveness), and duration [4]. According to increasing numbers and size of IWT rotors, therefore complaints increase especially [53]. The *larger the rotor, the lower the emitted frequency*. Infrasound of IWTs is meanwhile with big parts in the range of 0,1 Hz to 10 Hz according to [54,55]. Its infrasound emission is impulsive in the *effect/time profile* according to Roos W., Vahl, C.F. [55] and Vanderkooy, J. [56], as shown in Fig. 6 [4].

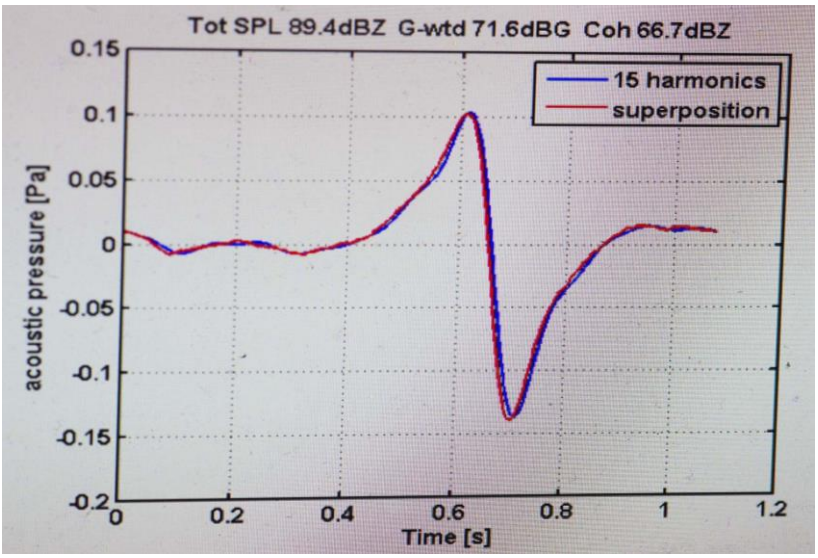

Fig. 6. An infrasonic pulse extracted from the emission of a wind turbine. The fluctuations of sound pressure measurable near a wind installation usually contain noise, *i.e.* irregular sound events of different origin. Noise removal is possible by averaging the sound pressure over a large number of mast-blade passages (here 4100), which reveals their common element (red line). The red peak thus visualized from the time sequence coincides with the blue peak, which shows the fundamental pulse as reconstituted in the frequency domain from 15 (very sharp) harmonic lines by Fourier analysis. The result is the coherent fundamental peak of this turbine of 0.9 Hz frequency, accordant to 1.08 seconds required per blade passage. Extracted infrasonic pulse of a wind turbine showing the relation between sound pressure (P) and time (s). Original source 56 corresponding to Fig. 7 Vanderkooy[1] J, Mann[2], R Measuring Wind Turbine Coherent Infrasound Department of Physics and Astronomy 1, Department of Computer Science 2 University of Waterloo, Waterloo, ON, Canada, N2L3G1 jv@uwaterloo.ca, mannr@uwaterloo.ca Date posted: 2. October 2014. With permission

The physical laws of wave theory apply to the propagation of sound, e.g., as longitudinal or transverse waves and with different velocities of propagation (in fluid medium about three times as fast as in gas) [4]. The propagation behavior depends on the various elastic media, whether liquid, gaseous, solid, or a mixture thereof; the same applies to *the viscoelastic organism*. Since *sound is a mechanical wave, the propagation can be refracted, reflected, interfered with, and can be transmitted* [57,4]. The propagation of a wave is a *transport of energy*, but not a transport of material. During propagation, particles are set into *oscillation*. Furthermore, in indoor spaces of buildings, interferences of airborne sound pressure and *structure-*

borne sound are possible, which can lead also to relevant amplifications or attenuations of the total impacting sound [58].

The vertical design of today's large wind turbines inevitably leads to infrasound being emitted, especially when passing the mast; the following applies: the longer the rotor blades, the lower the frequency in Hz of this emission. Technical solutions with a horizontal design could be significantly less affected here [4].

The following applies to Hydroacoustics: At around 1480 m/s, sound travels much faster in the ocean than in the air, where it travels at around 340 m/s under normal conditions. The speed of sound increases with *temperature, pressure, and salinity*. A sound wave travels through the elastic medium of water as a longitudinal pressure wave and can only end at a larger land mass. Accordingly, the effects of *repeated, impulsive low-frequency pressure waves* on *all marine life* are particularly far-reaching and impact all marine life. Given the importance of *mechanosensory systems for all living creatures*, we must assume *that marine mammals in particular are in life-threatening danger*. Chronic impact with deep frequencies not only affects their orientation, which often takes place over long distances via *low-frequency sounds* but also their *vital functions* such as e.g*., energy and substrate supply, homeostasis of the redox system, and embryogenesis*. All in all, there is a great danger for our marine mammals, but also for the health of fish and other marine creatures.

3. THE HYPOTHESIS

3.1 The Difference from Current Thinking

The possible pathophysiological pathway of a cellular stressor effect of infrasound, based on endothelial mechano-transduction, was first published in 06/23 [4]. This was made possible by the research results of the last 15 years on the control of vital life functions through endothelial mechano-transduction e.g. [3,6,30,38,19].

Everybody accepts that impacts on the organism are not depending on perception. Why not here? This question has already been asked in 2007 [59]. By exposure to *noise in low-frequency ranges,* many health disorders or manifest clinical symptoms cannot be explained with purely audio-vestibular perception or involvement of certain brain structures [60]. Since around 2015, the author noticed that many complaints worldwide raised by the residential situation. They correspond to functional microcirculatory disorders according to reduced and uncoordinated *NO-bioavailability*.

These are especially signs of *disturbed and inadequate support* with *nutrients and oxygen,* e.g., dizziness, school *performance disorder, fatigue, tinnitus, muscular weakness, and headaches*. With chronic exposure, symptoms occur such as *increased blood pressure, cardiac arrhythmia, breathing disorders, immune deficiencies, and late-onset epilepsy* [59]. In a second step, a working hypothesis has been developed that tested the prerequisites for a direct stressor effect on *both*, the *endothelial cell level and* the *technical side*. The results, available to date

from epidemiological studies, experimental and animal experimental studies, were included in the considerations.

In a third step, the currently available literature on molecular endothelial physiology and pathophysiology has been reviewed with respect to the possibility of mechano-transmission of mechanic forces if outgoing from an *extern-acting stressor.* The identification of PIEZO-1 channels in 2021 as important mechano-sensors for sound and vibration strengthened the evidence for our hypothesis. The extensive literature on pathohistological findings in occupational exposure to infrasound from the 1980s [59], later from the 2000s on exposure of residents to wind turbines [61], and the reassessment of these findings were included.

A so-called perception threshold, which was defined by the sound pressure level that is just audible at the respective low frequency, *cannot* be an effect threshold on cellular structures according to the current state of science.

3.2 The Hypothesis Is Based on the Evidence for:

- Noise is a mechanical force, therefore subject to physical laws;
- The existence of numerous mechano-sensors for sound and vibration at the membrane/endothelial level with newly identified, in particular endothelial PIEZO-1-channels, is state of the science;
- Mechano-transduction of mechanical forces is crucial for many vital vascular regulations;
- The mechanical transmission of forces via the structures of the endothelial cytoskeleton is state of the science;
- The *micro tactile* excitability of endothelial cells with rapidly propagated conduction up and downstream has been scientifically proven.

3.3 The Hypothesis in Detail

- Noise, when it affects organisms, is under *certain conditions in frequency, sound pressure, effect/time profile, and duration*, able to change the physiological laminar flow situation in the capillary bed in the sense of an *oscillatory environment*. In this case, the transition of mechanical forces might take place in an uncontrolled manner;
- In consequence, vasomotor functions and in particular *vasomotion* could be disturbed;
- The expected effects of chronic impact could lead to a chronic inadequate nutrient supply and therefore to a shift of *equilibria to disequilibria*, especially for the redox systems and for the *responses to inflammation* processes.

4. EVALUATION OF The HYPOTHESIS

The first basic condition that applies to our hypothesis is the question, of whether exposure to “Noise”, in the sense of an oscillatory stressor, causes an oscillatory field in the capillary bed in turn.

4.1 Positive Support for Evidence

The evidence for this is supported by the responsiveness of endothelial mechano-sensors for external influences such as gravity, pressure, swelling, and noise [3, 6, 30, 38, 49] as well as the micro tactile excitability of endothelial cells [5]. There is also evidence that infrasound interacts with cell metabolism and leads to perivascular fibrosis in *Infrasound induces coronary perivascular fibrosis in rats* according to Lousinha [62]. Similar findings are presented in [63,64,65]. Empiric data in experimental studies show clear indications that exposure to IFLN leads to a *ROS increase* [66,22,49]. Positive evidence also indicates the study of Chaban et al. [67] and very noteworthy, the direct cell effect is shown in *the Effect of infrasound on the growth of colorectal carcinoma in mice* [68]. In clinical medicine, there are currently considerations about the possible benefits of i*nfrasound* in the therapy of human colon carcinoma. High evidence for a direct cell and membrane effect are the results of the review of Roos, W and Vahl, CF [55], which focus on the evidence for the interaction of cellular structures, resp. sensible membrane structures, in a stress reaction. A possible disturbance of microcirculation is discussed. A positive evaluation in this direction is also the *metanalysis* from Dumbrille, A. et al. [69]: This evaluation results in the causality of *adverse health effects (ADHs)* and the stressor in all "*Bradford Hill criteria*". Reported adverse effects on animals revealed not only stress reactions but also negative effects on *fertility, development, and reproduction* [70]. About *the Bradford-Hill criterion dose-response*, analyses showed a demonstrable deterioration in *mental performance* from residents, living within 1.4 km of wind turbine(s) to those living outside this radius [71]. Increased complaints occurred when the frequencies approached lower frequencies (0.2 Hz in the example mentioned) [72].

Positive evidence for the frequent occurrence of atrial fibrillation is presented in the "*nurse cohort study*" [73]. My statement here: The development of atrial fibrillation in the absence of hypoxemia corresponds with structural changes and therefore conditions for disturbances of the electromechanics and also with the observations of increased diastolic intracellular Ca^{2+} plus levels under IFLN [55,22,18].

4.2 Reassessment of Pathohistological Findings

Research [59] on the symptomatology of occupationally with IFLN confronted groups in the 1980s showed *wall thickening of vessels*. According to the authors, animal studies showed *abnormal amounts of fibrosis/collagen in the trachea, lungs, and pleura*; *damaged (sheared) tracheal and bronchial cilia*; *fused actin-based microvilli of tracheal and bronchial brush cells*. *Thickening of the pericardial wall has been observed in occupationally exposed persons to ILFN* [59] and in persons living in the vicinity of large IWT plants [61] as a specific alteration. Fig. 7 shows *pericardial wall thickening* in chronic occupationally exposed persons in the eighties (so-called *Vibroacoustic Syndrome* "VAD-syndrome") in comparison to non-exposed.

Fig. 8 is the presentation of a *non-exposed* bronchial epithelium of a rat in comparison to an *exposed* one in Fig. 9. The figures show the changes in the microvilli (actin) before and after exposure. The interpretation of these findings suggests a shift in the homeostasis of the redox system toward chronic inflammation and fibrosis.

4.3 Possibly Negative Support for Evidence

The choice of sound pressure levels (SPL) in dB in experimental studies is often higher than expected from IWT's installations.
Objection:

a) The SPL in dB(A) can only map airborne noise in the frequency part of hearing (compare cap. 2).
b) The effect of the steady drip when living near emissions must be considered as a strong factor [74], the exposure time in reality often can be (also for sensitive groups) 24/7 hours/a day. In contrast, the time in animal experimental studies is limited for practical reasons. A similar applies to the higher sound pressures in the context of occupational exposure: Here, the times of exposure are limited; sensitive groups have no access.
c) *However*, *the decisive factor is that the frequency of Noise was not recognized in its significance* (e.g., the use of 8 Hz in Chaban et al. [67]. *There is strong evidence, that in approaching increasingly lower frequencies and thus the 1:1 transmission threshold for especially actin fibers, less sound pressure is required for endothelial mechano-transduction*. Added to this: *The behavior* of sound propagation in the viscoelastic organisms differs in that way, that decodable information about the low-pass filters becomes conceivable (compare cap. 2) [30,38,43].

Exemplum Poulsen-Study [75]: As a result, he found no statistically significant association between exposure to infrasound and the incidence of cardiovascular diseases. A relativization of the study took place by the author himself (e.g., a study on relatively little IWT's).

4.4 Evaluation of Computational Studies

Important parts of the statements from Mazzag and Barakat 38 and 2014 Mazzag et al. 30 are based on computational models. As already mentioned, the authors themselves refer to possible limitations and results.

Quote from authors [30] on page 96: "*Therefore*, *models need to be validated to the extent possible against experimental data*. *It is only after such validation is performed that mathematical models can potentially fulfil their promise of providing powerful and predictive tools for studying the dynamics and spatiotemporal organization of mechanically-induced responses in cells*".

My statement: Several predecessors [35,41,42,43] have done essential preparatory work over years with high evidence; the whole process of mechano-transmission is highly dynamic with numerous pathways interlocking. Computational models are necessary to achieve the best possible approximation of dynamic processes to improve understanding of cellular mechano-transduction. The further work from Na [43] as an experimental study is one of the required experimental studies, which confirms the mathematical models. Studies in this direction have *not* taken place on infrasound-emitting technical sources.

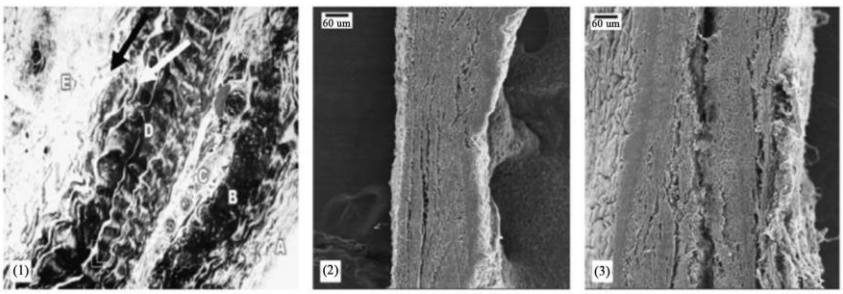

Fig. 7. *Original description*: Light microscopy (100×)—VAD patient pericardium, with pericardial sac on right. Five (instead of the normal three) layers are identifiable: (A) mesothelial, (B) internal fibrosa, (C) loose tissue, (D) external fibrosa, and (E) epipericardium. The loose tissue is rich in vessels. No inflammatory cellularity was identified in any of the five layers. In both fibrous layers, wavy collagen bundles are visible, however the wave length of fibres in layer B (internal fibrosa) is smaller than that in layer D (external fibrosa). Taking together the increased amount of collagen bundles, in wavy, accordion-like arrangements, with different orientations in relation to each other, and with more than one elastic fibre accompanying the bundles at seemingly perpendicular angles (seen through electron microscopy, not shown), seems to suggest a pneumatic-like structure, designed to absorb abnormally large external forces. Similarly, this functional arrangement also explains why there is no diastolic dysfunction, despite the thickened pericardial walls. (2) SEM of non-VAD patient pericardium. Normal three layers are visible: mesothelium (white arrow), fibrosa (black arrow) and epipericardium. (3) SEM of VAD patient pericardium. Fibrosa has split into two halves (arrows) that sandwich a newly formed layer of loose tissue (L). Note that the scale in both (2) and (3) is the same. The wavy form of collagen bundles is a mechanically energy-efficient method to deal with the movement that the fibrosa must constantly undergo to follow the rhythm of the cardiac cycle. Similar to an accordion, collagen bundles will extend and contract in diastole and systole, respectively. However, during an episode of sudden and violent tachycardia (common in VAD patients), this rhythm can be greatly increased (up to 200 beats per minute, in a matter of seconds) and the mechanical stress imposed on the MC monolayer may threaten its structural integrity. One of the functions of the loose tissue layer must certainly be blood and nutrient supply to this much larger organ. Remarks: ultrastructure micrographs, obtained with scanning (SEM) and transmission (TEM) electron microscopy. Pericardial wall in exposed and non-exposed persons 1) exposed (Light microscopy) 2) non-exposed (SEM) and 3) exposed (SEM) [59] Alves-Pereira M., Branco C. (2007) Vibroacoustic disease: biological effects of infrasound and low-frequency noise explained by mechano-transduction cellular signalling http://www.sciencedirect.com/science/article/pii/S0079610706000927. Page 11 Fig 2. With permission

4.5 Additional Extrinsic Regulation of Microcirculation

The influence of the extrinsic part on vasomotor function via the *autonomic nervous system* is the variable part that strongly depends on the individual ability to compensate for stress factors. It`s an additional influencing factor that is probably the reason why people in the same environment do *not react in the same way in* their symptomatology. The following can be expected when comparing a *short-term stressor load with a permanent one*: After an individual period, the compensation possibilities of biological systems *are exhausted.*

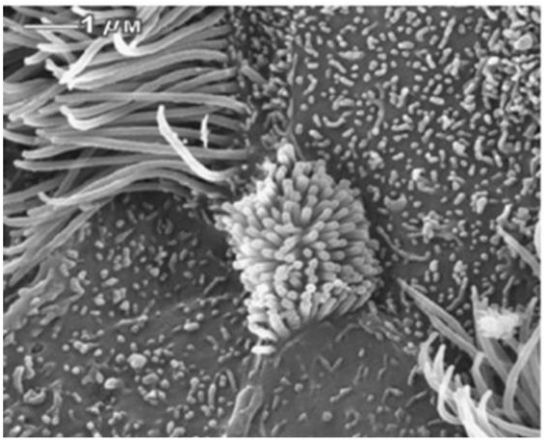

Fig. 8. *Original description* (SEM) Non-exposed bronchial epithelium. The BC in the center of the image exhibits a tuft of microvilli that are individually identifiable, uniformly distributed, and sprouting upward into the airway. Surrounding the BC are SC with microvilli of different sizes. Tufts of cilia featuring vesicles are also visible. No sheared, shaggy, or wilted cilia are visible SEM). No oedema is present. *BC* (*brush cells*), *SC* (*Secretory cells*). Rat bronchial epithelium, exposed to 2160 h of continuous IFLN

4.6 Proposed First Research and Methods

For further confirmation, we propose an experimental design with a determined number of infrasound-exposed test persons in comparison to non-exposed subjects. The positive group is exposed to *a defined infrasound stressor in frequency, sound pressure p in (Pa), time/effect profile (impulsiveness), and duration*. The design is double-blinded, in on/off design under the SDF-video-microscopy technique, examining the *sensible vasomotion and the flow characteristics* via the oral mucosa. Corresponding *animal experiments are conceivable* about the assessment of direct vasomotor changes under infrasound (e.g. in hamsters via the cheek). The indications of changes in animal behavior as well as reproductive behavior in *vertebrates* and *non-vertebrates* would be a meaningful addition and extension of further scientific clarification.

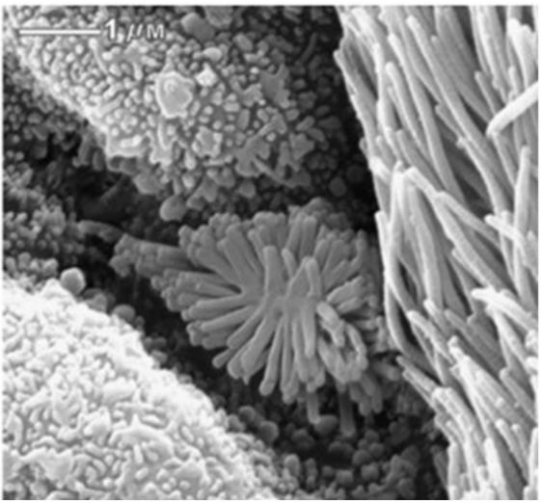

Fig. 9. *Original description* (SEM) Rat bronchial epithelium exposed to 2160 h of continuous ILFN. A *BC* is in the center of the image. Its *microvilli* are not sprouting upward and, instead, have fused, forming a central indentation that seems to be spreading outward. The prominent *SC* that surround the *BC* are swollen forming deep valleys at the intercellular junctions. SC microvilli are very irregular. Ciliary vesicles are visible. *Ultrastructure micrographs were obtained with scanning* (*SEM*) *and transmission* (*TEM electron microscopy*. *BC* (*brush cells*), *SC* (*Secretory cells*). Rat bronchial epithelium, exposed to 2160 h of continuous IFLN

4.7 Importance of Our Research

Vascular health is strictly combined with *NO bioavailability*. Of great importance for its maintenance, is the classification of possible damaging environmental factors. The particularly sensitive population groups *must be the bench*. Our hypothesis can help to define sensitive stages for mechano-transmission of deep frequencies of “Noise”. Emissions of very low sound frequencies from technical emitters endanger the health not only of humans but of all living organisms. This represents a potential danger to the livelihoods of all organisms, which need to be urgently classified and, if necessary, avoided.

5. ESTABLISHED METHODS TO ASSESS AND VISUALIZE MICROCIRCULATORY PROCESSES

The microcirculation can be visualized *in vivo* on newborn babies via the skin, and on adults via the oral mucosa [3]. Changes, especially in *vasomotion*, can be detected immediately and are reproducible. Appropriate techniques are video microscopy techniques such as *SDF* (*side stream dark field*) imaging. A better visualization of the microcirculation *in vivo* has become possible [76]. The

microcirculation in the context of diseases can be visualized and quantified immediately after exposure to the stressor, as well as in its absence. Parameters that are be specifically observed, include:

- *The intact vasomotion in the first order*
- *An instantaneously changing in vasomotion under a defined stressor effect*
- *The functional blood vessel density* (*FVD*) (*mm/mm*^{2})
- *The red blood cell flow velocity* (*RBCV*)
- *The number of perfused capillaries* (*N/A*) (*n/mm*^{2})
- *The capillary vessel diameter* (*DM*)
- *The glycocalyx thickness in nm* (*conceivable for further research projects*)

6. PROPOSED RESEARCH AVENUES AND QUESTIONS REGARDING TARGET

- Under which defined conditions does noise with certain properties, affect the *endothelial mechano-transduction* of signals at the cellular level (e.g. membrane components, cytoskeleton) and/or the cell-cell interaction?
- Which mechano-sensors, defined structures, are specifically sensitive? Which role do PIEZO-1 channels?
- Which sound pressure is required at a certain frequency to obtain a transfer response? Based on this: Below which frequency does a *particular danger for all living organisms exist (so-called cut-off frequency*)?
- Which specific role do resonance effects?
- What is the specified role of PIEZO-2 channels for the perception of deep frequencies?
- Which parameters can be determined to demonstrate the emerging imbalance of the redox system and at the same time distinguish the aggravation of atherosclerosis in its causes?

7. CONCLUSIONS AND REQUIREMENTS

For the first time, the symptoms of chronically infrasound-exposed humans and animals can be classified pathophysiologically in a coherent hypothesis. This has been made possible by recent advances in the knowledge of endothelial mechano-transduction, essential as a vascular function of vital character in response to mechanical forces. Crucial cellular processes such as growth, differentiation, migration, angiogenesis, redox homeostasis, and inflammation, are simultaneously dependent on mechanical forces *and* the integrity of the endothelium.

Normally, the flow of microcirculation is laminar and not variable. Persistent changes in shear stress patterns, particularly oscillatory flow, have been associated with decreased bioavailability of NO, an increase in reactive oxygen species (ROS), higher lipoprotein oxidation rates, increased endothelial apoptosis, pro-atherogenicity, chronic inflammation, and possible development of cancer. With the crucial basics of mechano-transduction, there is now strong evidence with obvious indicators for a possible interaction of infrasound, esp. with *deep frequencies and impulsive character*, as have, e.g., IWTs or heat pumps.

The elucidation of the strong dependency on mechano-transduction from the frequency of “Noise” and the identification of actin filaments and microtubules as “low-pass filters”, support our hypothesis. In this way, the propagation of sound waves in the viscoelastic organism could become decodable information. Regeneration, as would occur with a one-time or infrequent exposure, could not take place with chronic impact. Initially, dysfunctions of the orchestrated vasomotor system are to be expected, with prolonged exposure then anatomically recognizable organ damage. Important in this context are the structural changes that tend to be self-reinforcing, as described in the example of remodeling of the heart. Consequently, the increasing loss of endothelial integrity with continued exposure to a stressor, even in sensitive phases (e.g. pregnancy, inflammation), means a major risk of dysregulation of vital life functions. Based on current research, it will be possible to define low frequencies below a certain cut-off frequency as dangerous for all living organisms. Many scientific questions remain to be answered, but there is sufficient evidence to suggest that as precautionary measurements, further technologies, involving very low frequencies and/or impulsive emissions with potential impact on living organisms, should be better avoided until all issues are scientifically resolved. The possible effects on insects, which have not been clarified yet, could be of great importance, e.g., for biodiversity and co-affection of pollinators and thus nutrition. If the number of technical installations emitting ultra-low frequencies continues to increase, we recognize a potential major threat to the *entire biodiversity on land, in water, and even underground* through chronic vibration stress e.g. the affected *edaphon*. What will that mean for affected landscapes, especially forests?

Inner organs are sensitive to sound and vibration. The current state of knowledge on mechano-transduction together with known oscillatory and oxidative stress effects, points in the direction of our hypothesis and should be the reason for immediate precautionary actions and further research, based on this hypothesis.

DISCLAIMER

For the author, there are no conflicts of interest. The author would like to clarify that: Alternative forms of renewable energy such as industrial wind turbines are considered as valuable additions at suitable locations. The same is valid for biogas installations, heat pumps, and block-type thermal power stations. The data reported herein have been scrutinized under one, and only one agenda, that of pure scientific inquiry. There are no commercial, financial, or professional agreements.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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1. Bellut-Staeck UM. Microcirculation and its importance for all life. Subtitle: Current findings on the vital functions of endothelial cells. In Series Titles: Essentials. Publisher Springer Berlin, Heidelberg; 2022.
2. Bellut-Staeck UM. Impairment of the endothelium and disorder of microcirculation in humans and animals exposed to infrasound due to irregular mechano-transduction: Journal of Biosciences and Medicine. 2023; 11(6). DOI: 10.4236/jbm.2023.116003

Any other remarkable point(s): She is a Conservationist.

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