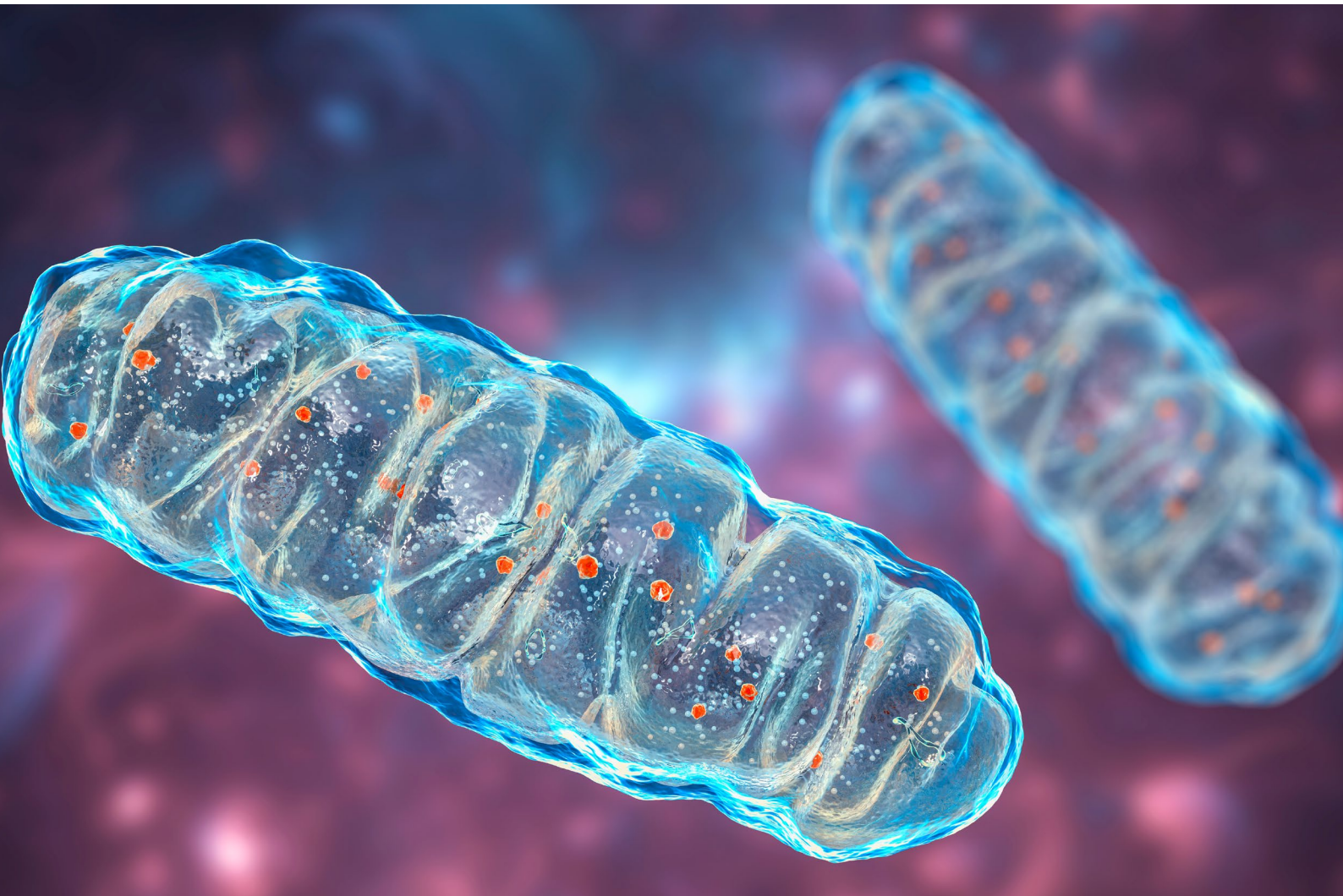


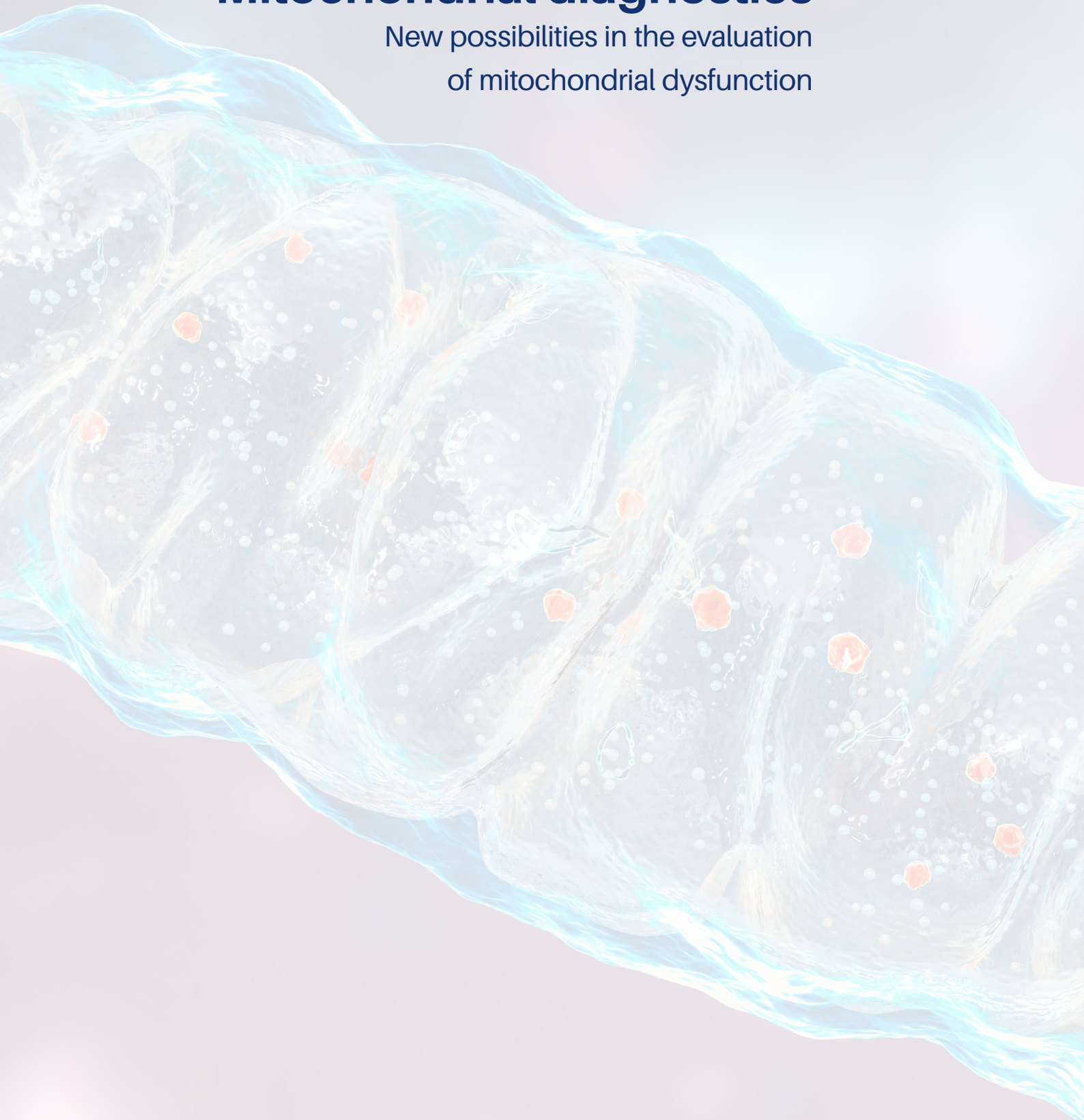
Mitochondrial diagnostics




New possibilities in the evaluation
of mitochondrial dysfunction

Mitochondrial diagnostics

New possibilities in the evaluation
of mitochondrial dysfunction



- 
- Mitochondria are widely known as the power-plants of almost all living beings. Additionally, mitochondria execute a variety of functions essential for proper cell function. Since they are responsible for a wide array of tasks within the cell, the requirements for appropriate diagnostics and subsequent therapy are equally challenging.

New possibilities in the evaluation of mitochondrial dysfunction

Mitochondrial dysfunctions are becoming an increasingly prevalent issue in modern society. Neurological, metabolic, cardiological, and oncological diseases are frequently associated with mitochondrial dysfunction. Whether it occurs as the cause of various illnesses (especially chronic diseases) or because of modern Western lifestyle, mitochondrial dysfunction has a significant impact on our lives. Since mitochondria are primarily responsible for energy production, dysfunction notably affects performance. Tissues with high energy demands, such as the nerve, heart, and muscle cells, are particularly reliant on adequate energy supply from mitochondria. Besides energy production, they are responsible for a wide array of crucial tasks and play important roles in almost every metabolic process [1, 2].

For diagnosing mitochondrial dysfunction, we employ a modern, robust, and, above all, functional mitochondrial analysis which aligns with the current progress in mitochondrial research. This allows for the identification of disturbances and the subsequent addressing of the root causes of mitochondrial dysfunction. Moreover, it facilitates the development of targeted and effective therapies.

MITOCHONDRIOPATHY

Acquired mitochondriopathy or mitochondrial dysfunction must be differentiated from genetically caused primary mitochondriopathy.

Primary mitochondriopathy arises from mitochondria malfunction due to hereditary gene mutations impacting energy metabolism enzymes. These gene mutations can occur in both nuclear DNA and mitochondrial DNA, existing from birth. Given the potential variability in affected enzymes, symptoms vary widely, resulting in diverse clinical presentations.

Mitochondrial dysfunction, on the other hand, constitutes an acquired form of mitochondriopathy, meaning it is not caused by an individual's hereditary genetic mutations..

MITOCHONDRIA

Mitochondria serve as the energy powerhouses of all living organisms. These cell organelles, typically ranging from 1-5 μm in size, are distributed in different densities across nearly every cell in the body, depending on their energy needs. For instance, individual heart, liver, and brain cells can contain between 2,000 and 100,000 mitochondria each, while cells like erythrocytes or keratinocytes contain no mitochondria at all.

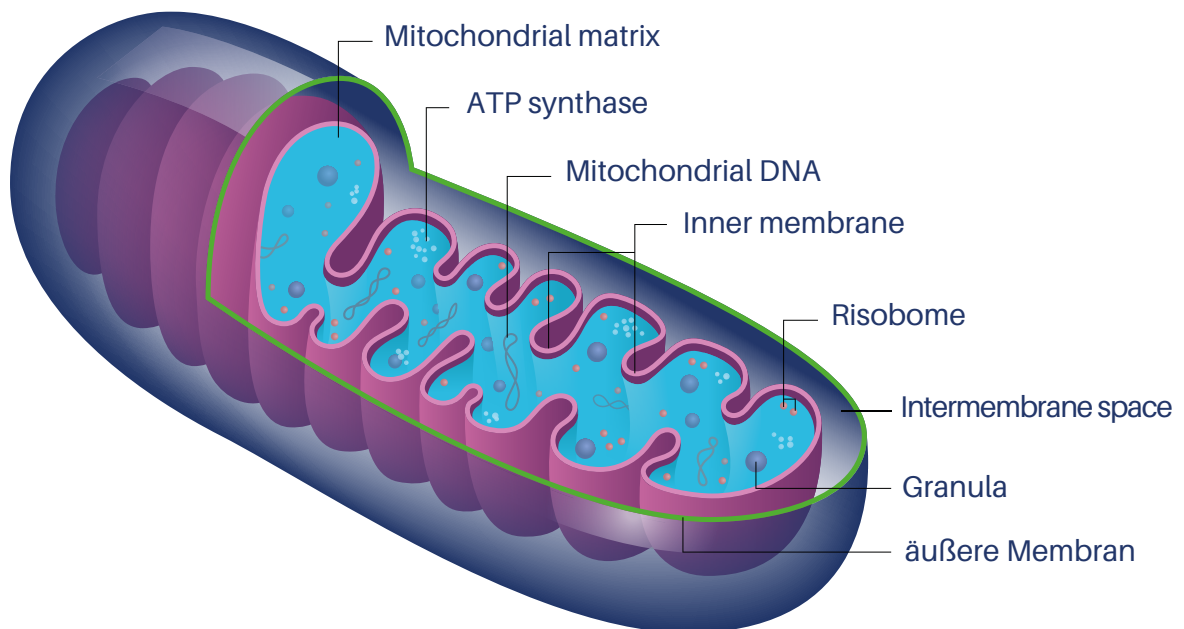


Fig. 1 Structure of a mitochondrion.

Mitochondria are composed of both an inner and an outer membrane, with the outer membrane serving as a barrier between the mitochondrion and the cytoplasm. The inner membrane is intricately folded, creating a vast surface area for numerous biochemical processes. Here, complexes I through V of the respiratory chain are located. Enclosed by the inner membrane is the mitochondrial matrix, where enzymes responsible for the citric acid cycle and β -oxidation are situated. Both membranes, inner and outer, contain transport proteins facilitating the movement of metabolites and other substances in and out of the mitochondrion. Notably, the inner mitochondrial membrane exhibits significantly lower permeability compared to the outer membrane [3].

Respiratory chain

The respiratory chain, also known as the electron transport chain (ETC), plays a crucial role in cellular respiration by shuttling electrons through different complexes. These complexes reside on the inner mitochondrial membrane. As electrons move through this chain, energy is released, which is harnessed to create a proton gradient across the inner membrane. While complexes I to IV facilitate electron transfer, complex V, known as ATP synthase, generates energy in the form of ATP [3].

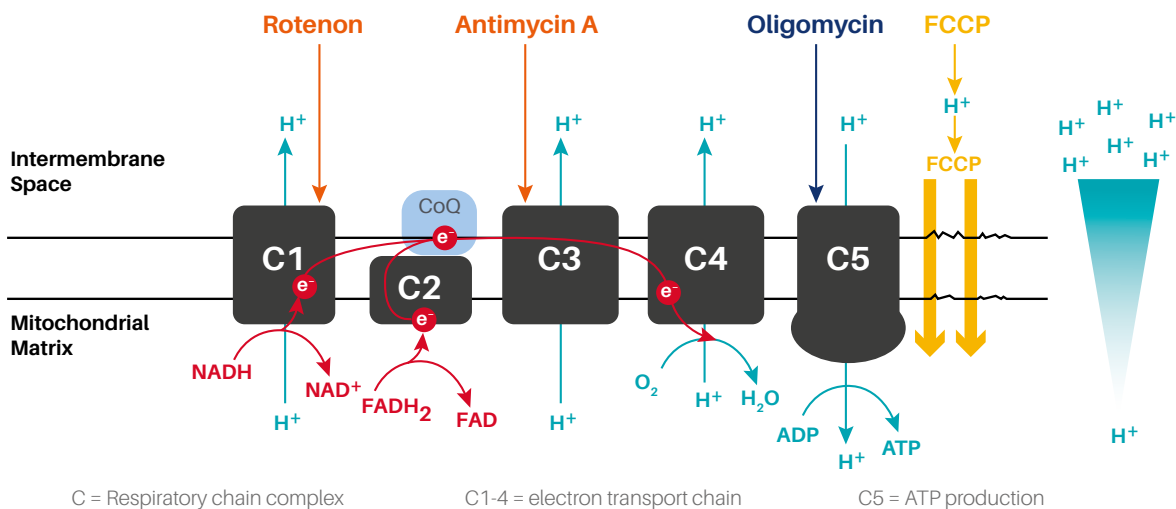


Fig. 2 Graphical representation of the respiratory chain. Complexes I to IV comprise the electron transport chain, while complex V (ATPase) is responsible for the production of ATP. To assess oxygen consumption rates, cells undergo exposure to various inhibitors sequentially, including oligomycin, FCCP, rotenone, another proprietary inhibitor identified through in-house studies, and antimycin A. These inhibitors target different complexes within the respiratory chain.

The transported electrons originate from the upstream energy metabolism. NADH and FADH₂ serve as electron carriers. These take up the electrons during the citrate cycle and transfer them to complexes I and II of the respiratory chain. The electrons are then transferred via coenzyme Q10 and complex III to complex IV. There they are transferred to molecular oxygen and water is produced. The transport of electrons generates energy, which is used by complexes I, III and IV to pump H⁺ ions from the matrix into the intermembrane space. As a result, H⁺ ions accumulate in the intermembrane space and a proton gradient is created along the inner mitochondrial membrane. This means that significantly more protons (H⁺ ions) are localised on the side of the intermembrane space. Due to the large difference in concentration, the protons tend to flow back through the ATPase into the matrix. The resulting energy is utilised by the ATP synthase to generate ATP from ADP [3].

When this system malfunctions, the body's capacity to produce sufficient amounts of energy diminishes, resulting in a decrease in performance. On an average day, healthy adults convert each ADP molecule in their body into ATP roughly 3000 times, totalling an ATP production of approximately 70 kg.

BHI - The bioenergetic health index

Many complex and chronic diseases are associated with mitochondrial dysfunction. New findings indicate that defects in the respiratory chain also play a role in SARS-CoV-2 infection [4]. The capture of the bioenergetic health index (BHI) is therefore of particular importance. With the help of the BHI, it is possible to determine the performance of the mitochondria with regards to energy production. The result then enables a precise assertion about the mitochondrial health of the examined cells [5].

THE MEASURING PRINCIPLE

The principle of BHI is based on the measurement of oxygen consumption rates in peripheral blood mononuclear cells (PBMCs) [5]. For the measurement, white blood cells are isolated from the patient's blood and their mitochondrial oxygen consumption is then determined under defined test conditions. For this purpose, the complexes of the mitochondrial respiratory chain are inhibited with several chemical substances [6]. At the same time, various parameters are determined which, taken as a whole, allow a prognostic statement to be made about the health of the mitochondria.

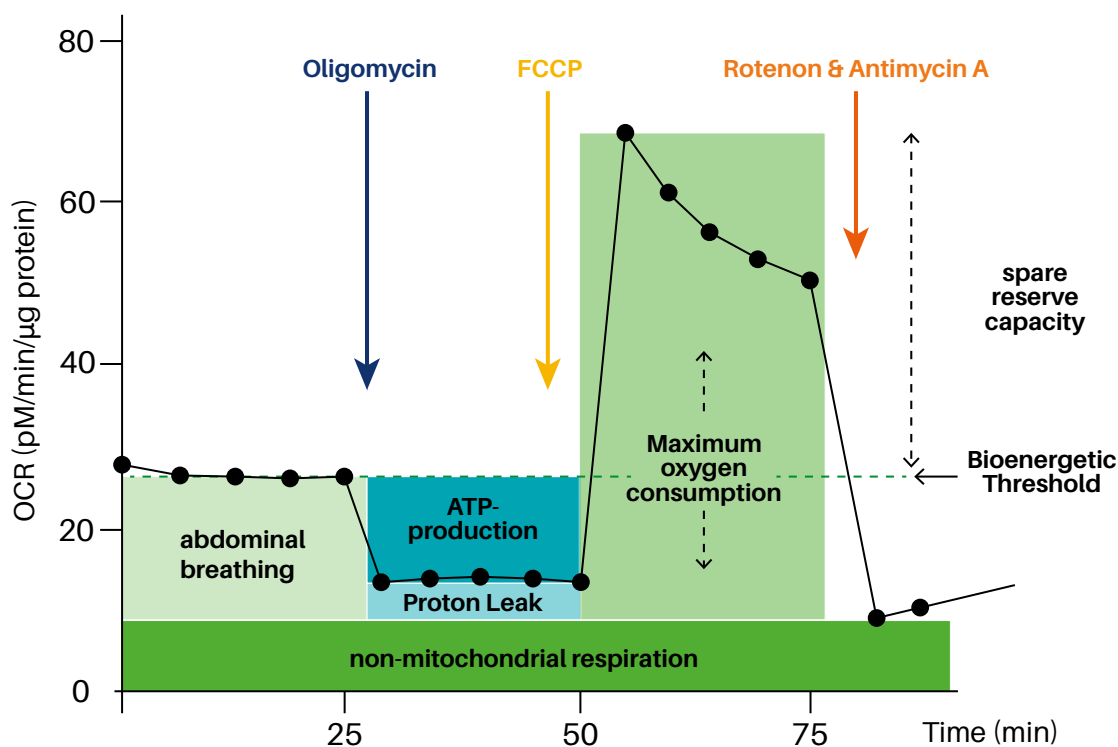


Fig. 3 Once the basal oxygen consumption rate of the PBMCs is measured, oligomycin is used to block the respiratory chain. The remaining oxygen consumption rate enables the determination of the proton leak extent. Mitochondrial ATP production is then calculated by subtracting the basal respiration from the proton leak. Next, the maximum respiration is assessed by introducing FCCP. The difference between this value and the basal respiration represents the reserve respiratory capacity. To distinguish between oxygen consumption inside and outside the mitochondria, additional inhibitors are applied to completely block the respiratory chain. This reveals the oxygen consumption rate outside the mitochondria (also known as nonmitochondrial respiration).

The initial measurement of oxygen consumption rate includes **basal respiration** and non-mitochondrial respiration. Basal respiration reflects the energy needed for fundamental cellular functions and comprises oxygen consumption for mitochondrial ATP production and proton leak [5].

Subsequently, the **mitochondrial ATP production** is determined by inhibiting the enzyme ATPase with oligomycin. This inhibits proton transport by the ATPase, leading to a decrease in the cell's oxygen consumption. The drop in oxygen consumption indicates proton leak, while the remaining rate represents the proton leak. The proton leak represents the protons that diffuse back from the intermembrane space and are not used for ATP synthesis [5, 6].

The **reserve respiratory capacity** is then measured, derived from the difference between maximum respiration and basal respiration. FCCP (carbonyl cyanide-p-trifluoromethoxyphenylhydrazine), a decoupling agent, is introduced for this purpose, enabling the measurement of maximum possible respiration. This capacity indicates how the ATP production of the examined mitochondria responds to an increase in energy demand [5, 6].

Additionally, alongside ATPase inhibition, the inhibitors rotenone and antimycin A target complexes I and III of the respiratory chain, entirely halting oxygen consumption by mitochondrial processes. This measurement focuses on oxygen-consuming processes occurring outside the mitochondria, also known as **non-mitochondrial respiration**. These processes are prooxidative, driven by the activation of prooxidative and proinflammatory enzymes, thereby posing a risk of mitochondrial damage. Elevated non-mitochondrial respiration adversely affects the BHI [5, 6, 7].

Through the recording of various parameters, the BHI offers insights into the following cell states and processes:

- The mitochondrial condition of the cells
- Levels of oxidative/nitrosative stress within the cells
- Cellular oxygen consumption
- Mitochondrial efficiency
- Availability of mitochondrial reserve capacity for energy production

The new Biovis BHI Plus

Precision in the laboratory process

The BHI Plus tests are conducted utilizing state-of-the-art Seahorse-XF Pro analysers, surpassing the effectiveness of our previous devices due to their enhanced precision and sensitivity. We've also opted to increase the number of replicates, further elevating the accuracy of our measurements. Additionally, the utilization of additional inhibitors enhances the inhibitory effect of previously used inhibitors, enabling even more precise determination of individual parameters.

- Latest generation of devices
- Additional replicates
- Additional inhibitors

Data-based formula optimisation

In a study involving 183 treated volunteer samples, we examined mitochondria under oxidative stress conditions similar to those described by Chacko et al. To achieve this, cells were subjected to induced stress in an in vitro setting, followed by an analysis of its impact on various parameters such as ATP production, proton leak, reserve respiratory capacity, and non-mitochondrial respiration. By assessing the effect of stress on these individual parameters, we adjusted the weighting of BHI parameters accordingly. This led to the development of a new formula, enhancing the significance of the BHI.

- Adjustment of parameter weighting based on in vitro data from our study
- Introduction of a new formula to enhance informative value

Automated evaluation algorithm

The vast dataset produced by the study was employed to train an algorithm, aiding in the objective and data-driven analysis of the data. This innovative approach enables the automatic detection and reporting of outliers, facilitating the swift and reliable identification of incorrect measurements. As a result, human verification is supported, enhancing the overall accuracy and efficiency of the process.

- Objective AI analysis
- Automatic identification of incorrect measurements
- Assistance for human verification

THE PROTON LEAK AND UCPS

It has been discovered that the induction of stress has little to no impact on proton leak, according to our own data, suggesting that proton leak may not exert as significant an influence on mitochondrial health as previously believed. Proton leak refers to the number of protons passing through the inner mitochondrial membrane that are not utilized for ATP production. Uncoupling proteins (UCPs) represent one potential pathway for protons to traverse the membrane. The body can enhance this leakage of protons by incorporating UCPs into the membrane [8]. This phenomenon has been observed during thermogenesis and in well-trained athletes [9, 10]. For instance, the thyroid hormone T3 influences UCP expression, thereby affecting energy metabolism and thermogenesis in brown adipose tissue [11]. UCPs also play a crucial role in the cell's redox signalling pathways. Activation and deactivation of UCPs can regulate electron transfer at the respiratory chain complexes, consequently impacting the generation of superoxide oxygen [12].

Previously, considerable emphasis was placed on the proton leak in the calculation of the BHI. The leakage of protons served as an indicator of an inefficient electron transport chain, leading to diminished ATP production. While this perspective remains fundamentally valid, it is challenging to discern whether proton leak arises from pathological or physiological processes mediated by UCPs. Therefore, preference is now given to other parameters in the calculation, such as ATP production. This approach enables a much more detailed mapping of clinical symptoms..

Causes of a “poor” BHI Plus

- Deficiency in cofactors
- Oxidative stress
- Aging processes

Emphasis on oxidative stress

Typically, reactive oxygen species (ROS) and reactive nitrogen species (RNS) arise from various metabolic processes. At low, “normal” levels, they regulate various physiological processes as signalling molecules. The issue arises when ROS or RNS production is excessively high and/or the antioxidant detoxification function is insufficient.

Possible reasons for increased radical formation:

- High exposure to environmental toxins/heavy metals
- Drug intake
- Chronic inflammation
- Chronic stress
- lack of sleep / poor sleep

Radicals are highly reactive compounds that can promote the formation of toxic intermediate products (e.g., hydrogen peroxide, peroxynitrite, etc.).

An excessive flood of radicals harbours a high risk of damage to mitochondrial DNA (mtDNA) in particular. The ring-shaped mtDNA is localised in the mitochondrial matrix and is highly susceptible to damaging reagents. In addition, the increase in radicals inhibits enzyme activity, particularly that of the respiratory chain, and increases the permeability of the inner mitochondrial membrane. Increased permeability of the inner membrane in turn favours the release of cytochrome C into the cytosol, a cytotoxic substance that ultimately causes apoptosis (cell death). Consequently, the mitochondrion or cell is no longer available for ATP production. This loss of energy leads to numerous symptoms, which are often associated with physical exhaustion, lethargy, and fatigue.

Mitochondrial dysfunctions can both trigger and accompany various diseases, including:

- Chronic fatigue syndrome (CFS)
- Long-COVID
- Burnout
- Depressive moods
- Neurodegenerative diseases (Alzheimer's disease, Parkinson's disease)
- Lack of concentration
- Metabolic syndrome (diabetes, hypertension, obesity)
- Cardiovascular diseases

Effects on the BHI Plus and interpretation

The BHI Plus provides valuable insights into mitochondrial health, allowing for prognostic assessments. It evaluates both the efficiency of ATP generation and the mitochondria's ability to meet increased energy demands. This dual evaluation helps identify the presence of mitochondrial dysfunction and guides treatment decisions, including therapy selection and duration.

An optimal BHI Plus is indicated by sufficient ATP production and reserve capacity alongside low values for non-mitochondrial respiration, suggesting proper mitochondrial function.

Conversely, evidence of mitochondrial dysfunction arises when there is insufficient ATP production and reserve capacity, combined with elevated values for non-mitochondrial respiration. Inflammation or oxidative stress, characterized by high concentrations of ROS and RNS, contribute to increased non-mitochondrial respiration. Consequently, ATP synthesis and reserve respiratory capacity decrease, leading to cellular energy depletion.

Further mitochondrial markers

In addition to the BHI Plus, additional markers can be analysed to gain a more comprehensive understanding of cellular and mitochondrial health.

mtDNA/nDNA ratio

mtDNA/nDNA ratio: Mitochondrial dysfunction can stem not only from inefficient ATP production but also from a reduction in mitochondrial biogenesis. The ratio of mitochondrial DNA (mtDNA) to nuclear DNA (nDNA) aids with the determination of the number of mitochondria per cell. Physiologically, the number of mitochondria decreases with age [2]. However, metabolic, or neurodegenerative diseases often coincide with a decrease in mitochondrial number. A low mtDNA/nDNA ratio suggests a reduced number of mitochondria per cell.

Nrf2

Nrf2 (nuclear factor erythroid 2-related factor 2) serves as a transcription factor and acts as a marker for mitochondrial and cellular defence against ROS [13]. However, an elevated Nrf2 level can indicate both oxidative stress and the body's antioxidant counter-regulation. To ensure clear differentiation, lipid peroxidation (perOx) and 8-OH-deoxyguanosine should also be assessed simultaneously.

	Optimal state	Protection, antioxidant capacity of Nrf2	Protection, but with caution	Oxidative stress
perOx	-	-	↑↑	↑↑
Nrf2	-	↑↑	↑↑	- / ↑
8OH-DG	-	-	-	↑↑

Tab. 1 Differentiation of Nrf2 in combination with perOx and 8-OH-deoxyguanosine..

PGC-1 α

PGC-1 α (Peroxisome Proliferator-Activated Receptor Gamma Coactivator-1Alpha) is a transcriptional coactivator known for stimulating mitochondrial biogenesis and respiration. It plays a significant role in neutralizing ROS by regulating the expression of various ROS-detoxifying enzymes, including SOD2 and GPX1. In this context, a high PGC-1 α level is considered a positive physiological response [14]. Conversely, a decrease in PGC-1 α indicates a disruption in the signalling pathway, which could stem from a lack of essential substrates or an excess of substances blocking the process. Increasing mitochondrial biogenesis can be achieved through PGC-1 α . Hence, PGC-1 α serves as a promising therapeutic target. Causes of PGC-1 α deficiency include:

- Lack of necessary substrates
- Excessive substances blocking the process

Rhodanase

Rhodanase, also known as thiosulfate sulphurtransferase or sulphur transferase, is a mitochondrial enzyme responsible for the transmission of sulphur groups (thiol groups). It plays a crucial role as a sulphur donor in the formation of iron-sulphur clusters, especially in the third complex of the respiratory chain. Iron-sulphur clusters are complex formations of iron and sulphur that serve as important cofactors in various reactions that are carried out by enzymes. These include enzymes from the citrate cycle and respiratory chain (aconitase, NADH dehydrogenase, succinate dehydrogenase and cytochrome C reductase) [20].

Larger range of values enables the selection of suitable therapies

While most BHI values were previously between 1.5 and 2.0, the value spectrum of the BHI Plus has now been extended to 0.3 to 3.3. The wide range of values enables a better depiction of the clinical symptoms. The BHI Plus is a dynamic index that is made up of various parameters. Depending on the level of the BHI Plus, a prognosis for the duration of therapy and the selection of suitable types of therapy can be derived. With a slightly reduced BHI Plus, interventions of 1 - 3 months are usually sufficient. In the case of severely reduced BHI Plus values, the necessary therapies are often very lengthy (over 1 year).

IHHT for BHI Plus values > 1.5

To enhance the number and efficiency of mitochondria, Interval Hypoxia-Hyperoxia Therapy (IHHT) has proven to be a potentially effective intervention. The duration, frequency and intensity have to be decided individually. For patients with a BHI Plus ranging from 1.5-2.2, therapy should be combined with anti-oxidative supplementation, for example, depending on the findings. However, IHHT is also suitable for athletes who already exhibit adequate mitochondrial function but still desire improvement.

Medical effects:

- Improves the oxygen supply to the cells and mitochondria
- Degradation of damaged mitochondria → mitochondrial biogenesis is stimulated
- Intact mitochondria become more efficient
- Improve microcirculation
- Dilation of the blood vessels → antihypertensive effect, improves the blood flow
- Angiogenesis is stimulated by the increase of the vascular growth factor VEGF
- Mental and physical performance increases
- Improve the immune system
- Optimisation of stress resilience



IHT for a reduced BHI Plus value in the range of 1.3 to 1.5

In the case of a BHI Plus value, which indicates impaired mitochondrial function, intermittent hypoxia therapy (IHT) has proven to be a possible effective intervention to activate mitochondrial performance. Here too, the duration, frequency and intensity must be decided on an individual basis.

Medical effects:

- Regeneration of the mitochondria: positive changes in the respiratory chain
- Increased production of the transcription factor HIF-1 α in almost every tissue (hypoxia-inducible factor), which induces health-promoting processes in the body (optimisation of capillarisation, erythrocyte formation, promotion of glucose transport and -metabolism, increase in neurotransmitter formation, improvement in antioxidant capacity)
- Recovery ability: accelerated onset of regeneration after exercise
- Performance: improved concentration and memory, longer physical endurance
- Quality of sleep: restorative effect in the morning, reduces sleep disorders and the number of nighttime visits to the toilet
- Stress tolerance: reduced stress perception, better general feeling

Ozone treatment or CO₂ baths for inadequate mitochondrial performance and BHI Plus values of < 1.3

In the case of a very deficient BHI Plus value, treatment with ozone or CO₂ baths has proven to be effective. The duration, frequency and intensity should be decided on an individual basis.

Medical effects:

- Disinfectant and anti-inflammatory effect
- Virucidal, fungicidal and bactericidal
- Promotes blood circulation
- Vasodilator
- Performance-enhancing
- Pain-relieving
- Detoxifying
- strengthens the immune system
- Induction of all enzymes involved in oxygen metabolism

Other therapeutic interventions

The causes of a reduced BHI Plus Index can be both an altered ATP production and reserve respiratory capacity as well as increased non-mitochondrial respiration. However, a combination of several causes is common. Basically, the therapy consists of improving the quality or quantity of the mitochondria and reducing non-mitochondrial respiration. This is achieved by promoting mitochondrial biogenesis, e.g. via PGC-1, increasing their activity and oxidative defence capacity, e.g. via Nrf2, and stabilising the cell membrane. Possible therapeutic interventions are listed below depending on the indication:

Activate mitochondria:

creatine
coenzyme Q10
vitamin B2
vitamin B3
vitamin B6
vitamin B12
magnesium

Improve oxidative defence:

curcumin
selenium
coenzyme Q10
vitamin B12
vitamin C
vitamin D
vitamin E - mixed tocopherols
NAC or glutathion

Improve ATP production:

coenzyme Q10
vitamin B1
vitamin B2
NADH
vitamin B3
vitamin C
magnesium
melatonin
alpha lipoic acid
glutamine
taurine

Improve mitochondrial biogenesis:

if necessary, iron and sulphur (in case of deficiency)
L-arginine
leucine
Endurance training
resveratrol
carbs reduction
intermittent fasting

Activate Nrf2:

curcuma
green tea extract
resveratrol
OPC

Increase PGC-1 α :

endurance training
carbs reduction

Stabilize cell membrane:

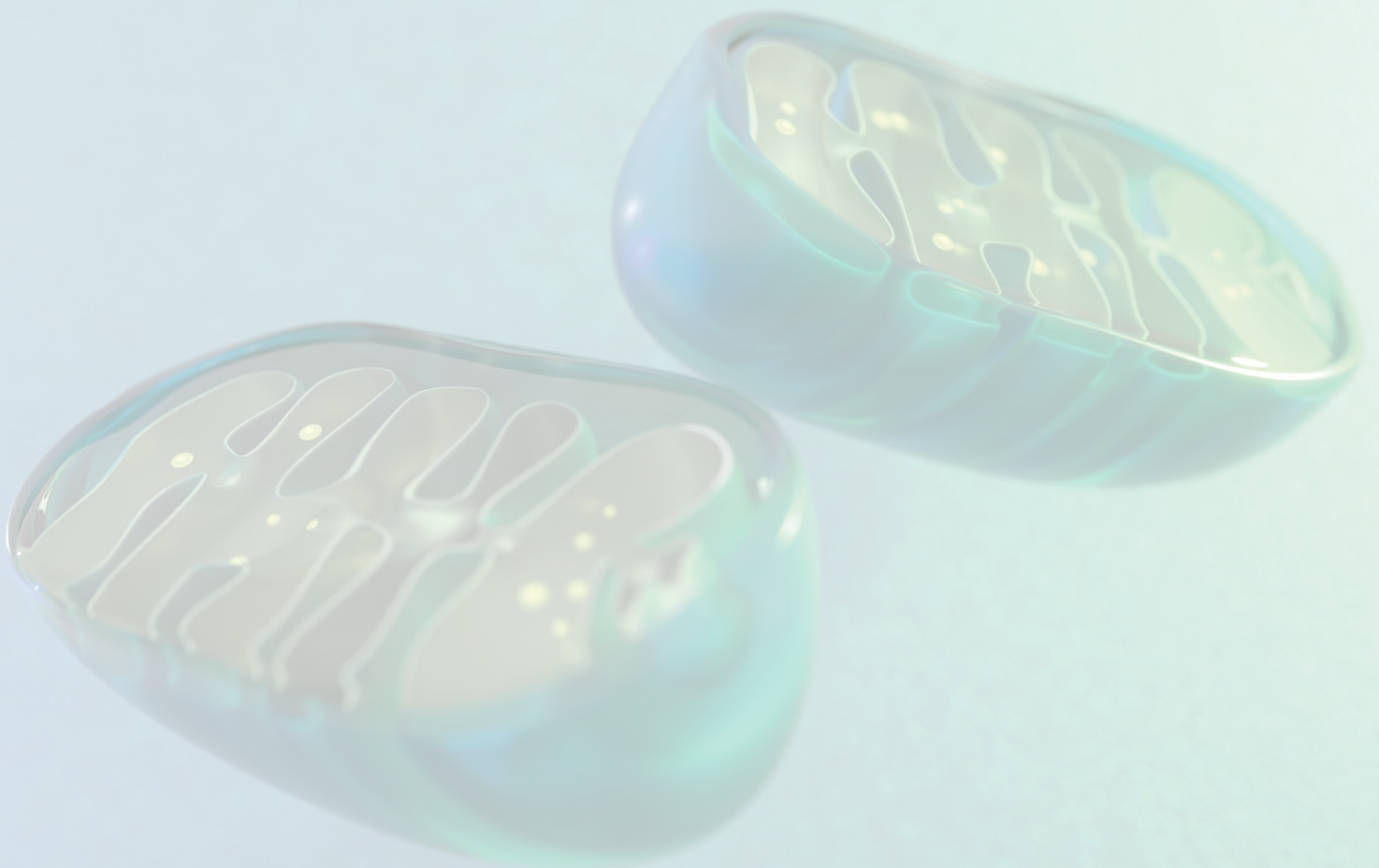
vitamin E - mixed tocopherols
L-carnitine
EPA and DHA
phospholipids

Effect on measurement parameters

Various factors can affect the measurement parameters of the BHI Plus both positively and negatively and should therefore be avoided before blood collection. For example, exercise on the day before the sample collection or certain medications can influence the result (usually negatively). The intake of antioxidant substances, on the other hand, can have a positive effects. It is therefore important to consider certain aspects when interpreting the results.

The following should be considered:

- Oxidative stress has a negative effect on mitochondrial performance [16]
- Exercise triggers short-term oxidative stress, which is necessary to achieve a training effect [17, 18]
- In the long term, exercise has a protective effect against oxidative stress [19]
- Some antibiotics such as amoxicillin and cefazolin trigger oxidative stress [20]
- Anit-oxidative therapy improves mitochondrial performance [21]



Mitochondrial diagnostics at a glance:

- E328** BHI Plus
- E335** Complementary Biomarkers to clarify causative factors
- E336** mt/n DNA
- E337** PGC-1 α
- E338** Nrf2
- E339** Rhodanese
- E330** Mitochondrial Activity
- E332R** Mitochondrial O₂-Radikal Formation

Additional investigations

Oxidative stress

- E320** Profile Nitrosative Stress + Mitochondria
- E325** Profile Nitrosative Stress
- E340** Nitrotyrosine
- E400** Nitrophenylacetic Acid in Urine
- E350** Citrulline im Urine
- E360** Protein S100
- E370** Protein S100 Stress Test
- E380** LDH and LDH-Isoenzymes
- E390N** Lactat/Pyruvat Ratio

Oxidativer Stress

- E210** Profile Oxidative Stress
- E220** Profile Antioxidants
- E230** Profile Glutathione Metabolism
- E240** Lipid Peroxidation
- E250** Antioxidant Capacity
- E255** Thiol Status
- E260** 8-Hydroxydesoxyguanosin
- E290** Glutathione Peroxidase
- E301** Superoxide Dismutase Mn
- E305** Ox. LDL

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© biovis Diagnostik MVZ GmbH

biovis Diagnostik MVZ GmbH

Brüsseler Str. 18

65552 Limburg-Eschhofen

Tel.: +49 6431 21248 0

Fax: +49 6431 21248 66

info@biovis.de

www.biovis.de