Mitochondrial Therapies in Heart Failure

Albrecht von Hardenberg and Christoph Maack

Abstract

The current therapy for patients with stable systolic heart failure is largely limited to treatments that interfere with neurohormonal activation. Critical pathophysiological hallmarks of heart failure are an energetic deficit and oxidative stress, and both may be the result of mitochondrial dysfunction. This dysfunction is not (only) the result of defect within mitochondria per se, but is in particular traced to defects in intermediary metabolism and of the regulatory interplay between excitation-contraction coupling and mitochondrial energetics, where defects of cytosolic calcium and sodium handling in failing hearts may play important roles. In the past years, several therapies targeting mitochondria have emerged with promising results in preclinical models. Here, we discuss the mechanisms and results of these mitochondria-targeted therapies, but also of interventions that were not primarily thought to target mitochondria but may have important impact on mitochondrial biology as well, such as iron and exercise. Future research should be directed at further delineating the details of mitochondrial dysfunction in patients with heart failure to further optimize these treatments.

Keywords

Calcium • Energetics • Heart failure • Mitochondria • Reactive oxygen species

Contents

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1 Introduction

The current evidence-based (pharmacological) therapy for heart failure acts by modulation of neurohormonal systems, such as the renin–angiotensin–aldosterone and the sympathetic nervous systems (Ponikowski et al. 2016). Since these therapies are limited by hemodynamic side effects like not only hypotension and bradycardia, but also electrolyte disturbances or renal dysfunction, there is a need for novel drugs without these disadvantages (Gheorghiade et al. 2016). Mitochondrial therapies are one promising option for such hemodynamically neutral drugs. However, the development of such drugs is challenging, and the most prominent impediments are the lack of specific mitochondrial targets and the difficulties of delivering the respective agent to the mitochondrial compartment (Szeto and Schiller 2011).

Similar as diabetes and neurodegenerative diseases, heart failure is a secondary form of mitochondrial dysfunction. In contrast to primary mitochondrial diseases, secondary dysfunction is acquired and not caused by a primary genetic defect of the mitochondrial synthesis machinery or respiratory chain complexes (Smith et al. 2012). Mitochondria are ubiquitous in mammalian cells, but targeted mitochondrial therapies preferentially act on cells with high mitochondrial content such as cardiac or skeletal myocytes, which comprise ~30–40% of mitochondria. Nevertheless, due to mitochondria's ubiquity, mitochondrial therapies are feasible in many different indications. In general, mitochondrial therapies aim to improve disease burden rather than to achieve complete recovery, since they have an impact on common damaging disease pathways (Smith et al. 2012). As pointed out by Wallace et al. (2010) and McKnight (2010), however, our limited understanding of bioenergetics underlies the so-far disappointing progress in the development of treatments targeting metabolism and mitochondria. Therefore, we should place mitochondrial diseases and their therapeutics into a broader context of organismal and cellular bioenergetics (McKnight 2010; Wallace et al. 2010). Accordingly, a better understanding of intermediate metabolism and redox biology in the cardiovascular system and in particular, of mitochondrial bioenergetics may avoid previous failures such as vitamins, whose lack of benefit in cardiovascular diseases may be related to non-specific targeting and potentially paradoxical effects on redox biology at higher doses (Münzel et al. 2015).

In the following, we will provide an overview of the development and progression of mitochondrial dysfunction in heart failure and introduce different mitochondrial therapy strategies.

2 Mitochondrial Biology and Regulation

The heart consumes about 6 kg of ATP per day for pumping 10 tons of blood through the vascular circulation of the body (Marín-García 2012). Excitation-contraction coupling is the main consumer of ATP in the heart: about 2% of the cellular ATP is consumed per heart beat (Balaban 2002). Such efficient energy utilization was facilitated by the endosymbiosis of an alphaproteobacterium to an eukaryotic progenitor cell 4 billion years ago. The proteobacterium survived until today in form of mitochondria and enables the highly effective way to use oxygen (O_2) to produce ATP from food molecules, increasing the efficiency of glycolysis from 2 to 30 molecules of ATP (Lane and Martin 2010). However, the cost of this increase in efficacy by aerobic bioenergetics is the generation of reactive oxygen species (ROS), against which a whole battery of anti-oxidative enzymes are installed to prevent oxidative stress. If under pathological conditions, production of ROS overwhelms the anti-oxidative capacity, oxidative stress occurs that may contribute to the development and progression of heart failure (Dai et al. 2011b; Nickel et al. 2015).

Mitochondria have an outer (OMM) and an inner membrane (IMM) (Zick et al. 2009). Invaginations of the IMM form the cristae where the complexes of the respiratory chain assemble to respiratory "supercomplexes" or "respirasomes" (Cogliati et al. 2016; Gu et al. 2016). The cristae formation increases membrane surface and thereby enhances the capacity of oxidative phosphorylation (OXPHOS). Therefore, dense cristae formation is typical for mitochondria in highly energy-demanding tissues. Central to the cristae and respirasome formation is cardiolipin (CL), a phospholipid that is uniquely expressed in mitochondria, and in particular, on the IMM (Paradies et al. 2010).

OXPHOS regenerates ATP at the electron transport chain (ETC) (Mitchell and Moyle 1967). NADH and $FADH_2$, the main products of the Krebs Cycle, deliver electrons to the ETC, inducing sequential redox reactions which induce proton translocation across the IMM, establishing a proton gradient (ΔpH) which together with the electrical gradient ($\Delta\psi_m$) constitutes the proton motive force ($\Delta\mu_H$) (Fig. 1). This $\Delta\mu_H$ is the driving force for ATP production at the F_1F_o-ATP synthase (Balaban 2009). The Krebs cycle is fueled by energetic intermediates primarily from fatty acids as substrates (70%), and to a lesser extent glucose (30%), lactate and amino acids. In principle, however, the metabolic pathways of these different fuels are interwoven to a net of redundancy, variability, and effectiveness (Taegtmeyer 2007).

Cardiac workload and thus ATP consumption changes constantly and requires rapid and efficient adaptation of energy supply to demand. Two major regulators of oxidative phosphorylation are Ca^{2+} and ADP (Maack et al. 2007; Cortassa et al.

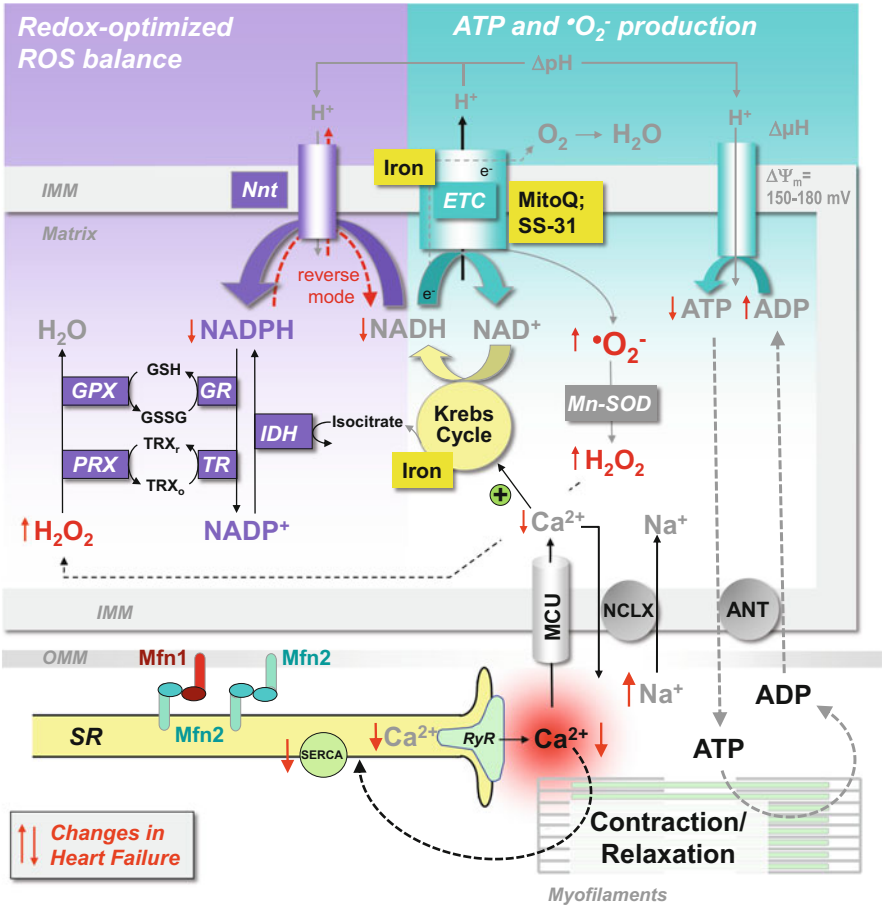

Fig. 1 Mechanisms of mitochondrial energetics and their regulation through ADP and Ca^{2+}. The points of intervention of mitochondria-targeted therapies (MitoQ, SS-31, iron) are highlighted in *yellow*. *Nnt* nicotinamide nucleotide transhydrogenase, *Mn-SOD* Mn^{2+}-dependent superoxide dismutase, *PRX* peroxiredoxin, *GPX* glutathione peroxidase, $TRX_{r/o}$ reduced/oxidized thioredoxin, *GSH/GSSG* reduced/oxidized glutathione, *TR* thioredoxin reductase, *GR* glutathione reductase, *MCU* mitochondrial Ca^{2+} uniporter, *NCLX* mitochondrial Na^+/Ca^{2+} (and Li^+) exchanger, *ANT* adenine nucleotide translocator, *RyR* ryanodine receptor, *SR* sarcoplasmic reticulum, *SERCA*, SR Ca^{2+} ATPase, *Mfn* mitofusin, *IMM* inner mitochondrial membrane, *OMM* outer mitochondrial membrane, $\Delta\mu_H$ proton motive force

2009). When ATP consumption increases, such as during β-adrenergic stimulation, ADP stimulates ATP production at the F_1F_o-ATP synthase, which slightly dissipates $\Delta\mu_H$ and accelerates electron flux along the ETC (Brand and Murphy 1987). This increased electron flux oxidizes NADH and $FADH_2$ (Fig. 1). At the same time, β-adrenergic stimulation increases the amplitude and frequency of cytosolic Ca^{2+} transients, facilitating the accumulation of Ca^{2+} in the mitochondrial matrix, where

Ca^{2+} stimulates Pyruvate dehydrogenase (PDH) and rate-limiting dehydrogenases of the Krebs cycle (isocitrate- and α-ketoglutarate dehydrogenases) to increase the rate of NADH and $FADH_2$ regeneration (Fig. 1). Thus, the balance of ADP-induced acceleration of respiration and Ca^{2+}-induced stimulation of the Krebs cycle maintains a constant redox state of NADH/NAD^+ and $FADH_2$/FAD and thus, a sufficient electron reserve to generate ATP (Nickel et al. 2013).

Already under physiological conditions, superoxide (O_2^-) is produced at complexes I and III of the ETC, which is rapidly dismutated to H_2O_2 by the Mn^{2+}-dependent superoxide dismutase (Mn-SOD) (Fig. 1). H_2O_2 is then eliminated by several enzymes (such as glutathione peroxidase and the thioredoxin/peroxiredoxin system) that require NADPH, which in turn is regenerated by three enzymes that derive their substrates from the Krebs cycle, such as isocitrate dehydrogenase, malic enzyme and the nicotinamide nucleotide transhydrogenase (Nnt) (Ying 2008) (Fig. 1). Therefore, mitochondrial Ca^{2+} uptake is not only required to adapt energy supply to demand, but also to regenerate the NADPH-coupled anti-oxidative capacity to prevent excessive emission of H_2O_2 from mitochondria (Kohlhaas et al. 2010).

3 Pathophysiology of Heart Failure: Focus on Mitochondria

In patients with heart failure, an energetic deficit can be detected in vivo, leading to the well-known concept of the heart as an "engine out of fuel" (Neubauer 2007). A reduction of the myocardial phosphocreatine (PCr) to ATP ratio, measured non-invasively by ^{31}P-MR spectroscopy, is an indicator of energy shortage predicting an adverse outcome of heart failure patients (Neubauer et al. 1997). Starling et al. (1998) observed an inverse correlation between ATP content and pulmonary wedge pressure. The decline of myocardial ATP was primarily associated with diastolic rather than systolic dysfunction (Starling et al. 1998). Increased energetic demand and/or energetic mismatch (Gorski et al. 2015) are supported by different experimental heart failure models, such as hypertension (Eirin et al. 2014a), pacing (Marín-García et al. 2001), and transaortic constriction (Patten and Hall-Porter 2009).

Two important aspects of the energy starvation concept, however, are presently incompletely resolved. First, the underlying reasons for the energetic deficit are unclear. Several studies ranging from 50 years ago at the National Institutes of Health (NIH) (Chidsey et al. 1966; Sobel et al. 1967) to more recent studies (Cordero-Reyes et al. 2014; Holzem et al. 2016) have suggested that the electron transport chain function per se is not impaired in failing versus nonfailing hearts, although conflicting data exist (Sharov et al. 2000). Instead, substrate metabolism, i.e., the capacities of glycolysis and fatty acid oxidation to provide acetyl-coenzyme A to the Krebs cycle, and also Krebs cycle activity per se – responsible for the production of NADH and $FADH_2$ from acetyl-coenzyme A, appear to be impaired in failing hearts (Nickel et al. 2013; Cordero-Reyes et al. 2014). Second, it is unclear as to how far the energetic deficit – mostly monitored by decreased PCr levels – actually contributes to the contractile deficit per se and the progression of

heart failure (through induction of maladaptive remodeling), or whether the energetic deficit may rather impair only cardiac function under maximal exertion, as discussed in more detail previously (Nickel et al. 2013). In fact, in mice that are completely deficient of PCr, no impairment of cardiac function at baseline or after myocardial infarction could be observed, while maximal cardiac output in response to β-adrenergic stimulation or the recovery of cardiac function from ischemia was slightly reduced (Lygate et al. 2013). These data argue against a maladaptive role of a deficit of the final currency of energy, i.e., ATP, for cardiac dysfunction. In contrast, the mentioned defects of substrate metabolism may rather result in the accumulation of metabolic intermediates that can become toxic and/or induce maladaptive signaling in their own right (Chatham and Young 2012; Nickel et al. 2013).

One important consequence of the changes in intermediary metabolism is oxidative stress. In patients with heart failure, oxidative stress occurs in the plasma and LV myocardium and correlates with LV dysfunction (Belch et al. 1991; Maack et al. 2003). Increased levels of ROS can deteriorate Ca^{2+} handling (Xu et al. 1997; Zweier and Talukder 2006; Maack et al. 2009), cause arrhythmias (Akar et al. 2005; Wagner et al. 2013), and induce hypertrophic signaling (Ago et al. 2008; Erickson et al. 2008), apoptosis, and necrosis (Halestrap 2005; Biasutto et al. 2016). Ca^{2+} calmodulin kinase II (CaMKII) activation through a ROS-dependent pathway led to increased Ca^{2+} leak of the sarcoplasmic reticulum (Viatchenko-Karpinski et al. 2014). But oxidative stress in cardiac myocytes can be either adaptive (Zhang et al. 2010) or maladaptive (Dai et al. 2011b), depending on its source, timing, and quantity.

Besides NADPH oxidases and other enzymes, one major source of ROS is mitochondria. In a dog model of heart failure, excessive production of O_2^- at complex I is transformed to H_2O_2 and (via the Fenton reaction) hydroxyl radicals (Ide et al. 2000). Besides an increase in ROS *production*, decreased ROS *elimination* is another key contributor to mitochondrial oxidative stress (Nickel et al. 2014). In the failing heart, defects in Ca^{2+} homeostasis result in smaller amplitudes and slower velocities of cytosolic Ca^{2+} transients (Bers 2006), which deteriorate mitochondrial Ca^{2+} uptake to stimulate key enzymes of the Krebs cycle (Kohlhaas and Maack 2013). Furthermore, increased cytosolic Na^+ concentrations, as observed in heart failure, accelerate mitochondrial Ca^{2+} export via the mitochondrial Na^+/Ca^{2+} exchanger (Maack et al. 2006; Liu and O'Rourke 2008) (Fig. 1). Under physiological conditions, microdomains between the sarcoplasmic reticulum (SR) and mitochondria mediate efficient mitochondrial Ca^{2+} uptake (Kohlhaas and Maack 2013). During systole, very high Ca^{2+} concentrations in the immediate vicinity of the ryanodine receptors (RyRs) of the SR in close juxtaposition to mitochondria and the mitochondrial Ca^{2+} uniporter (MCU) allow uptake of Ca^{2+} into mitochondria despite the relatively low affinity of the MCU for Ca^{2+} (Kohlhaas and Maack 2013). These microdomains are controlled by tethering proteins between the SR and mitochondria, among which mitofusin (Mfn) 1, located on the OMM, and Mfn2, located on both the OMM and the SR, play important roles (de Brito and Scorrano 2008; Chen et al. 2012). In animal models of heart failure, decreased

expression of Mfn1 and Mfn2 may deteriorate the well-organized spatial pattern of mitochondria within cardiac myocytes, but potentially also the SR-mitochondrial Ca^{2+} microdomain (Goh et al. 2016; Maack 2016). Finally, the open probability of the MCU is reduced in mitochondria from human failing hearts (Michels et al. 2009).

Together, these data indicate that in heart failure, decreased mitochondrial Ca^{2+} uptake during cardiac workload transitions impairs the Ca^{2+}-induced stimulation of the Krebs cycle and thereby, the regeneration of NADH and NADPH, required for energy production and the anti-oxidative capacity (Nickel et al. 2014). One important consequence of this energy supply-and-demand mismatch is oxidation of NADH, which favors the reverse mode of the mitochondrial nicotinamide nucleotide transhydrogenase (Nnt) during elevated cardiac workload, which oxidizes NADPH and therefore dissipates the anti-oxidative capacity (Nickel et al. 2015). The depleted NADPH-coupled anti-oxidative capacity is then overwhelmed by ROS production by NADH-coupled respiration at the ETC. This imbalance appears to be a core mechanism of oxidative stress during pressure-overload induced heart failure, since in animals that lack a functional Nnt, no oxidative stress and less systolic dysfunction or premature death occurred (Nickel et al. 2015).

According to the concept of "redox-optimized ROS balance" (R-ORB), Aon et al. (2010) proposed that "mitochondria have been evolutionarily optimized to maximize energy output while keeping ROS overflow to a minimum by operating in an intermediate redox state" (Aon et al. 2010). This implies that the optimal condition for cardiac mitochondria is when extreme oxidation, as outlined above, or reduction of the mitochondrial redox state (such as during ischemia) is avoided. The R-ORB concept proposes that under highly reduced conditions, high ROS production at the ETC overwhelms the anti-oxidative capacity. However, considering that the working heart constantly produces ADP, which physiologically accelerates respiration and thereby oxidizes the respiratory chain, increased oxidative stress in heart failure is unlikely due to a pure net increase of ROS production, but rather due to diminished ROS scavenging capacity (Nickel et al. 2015).

Oxidative stress leads to a vicious circle by exacerbating the energy supply and demand mismatch (Kohlhaas and Maack 2011). Mitochondria are in the center of the scene, since they contain typical targets of oxidative damage like iron sulfur clusters, unsaturated fatty acids, and densely packed proteins and mitochondrial DNA (mtDNA) that are all essential to mitochondrial function (Murphy 2009). The proximity of ROS production to the components of the ETC including cardiolipin makes them most vulnerable to oxidative damage (Lesnefsky and Hoppel 2008). Therefore, oxidative stress directly affects enzyme function of ETC complexes and leads to peroxidation of cardiolipin due to the high content of unsaturated fatty acids (Paradies et al. 2010). Peroxidation of cardiolipin impairs cristae formation and disrupts the respirasome and the detachment of cytochrome *c*, a mobile electron carrier in the IMM (Szeto 2014). The net result of these changes is a reduced ATP synthesis and a further increase in electron slippage to oxygen, therefore setting up a feed-forward cycle of ROS-induced ROS production (Zorov et al. 2006). Furthermore, mtDNA is associated with the IMM and vulnerable to oxidative damage by

missing protective histones. Damage of mtDNA further leads to reduced ETC activity and exacerbating the feed-forward cycle of ROS production (Ide et al. 2001; Hebert et al. 2010).

4 Strategies for Mitochondrial Therapies

Initial attempts to improve the outcome of patients with cardiovascular risk and/or disease were performed with the supplementation of vitamins C and E, however, these attempts were not successful (Yusuf et al. 2000). One reason for this failure is that these anti-oxidants do not achieve sufficiently high concentrations within mitochondria (Münzel et al. 2015; Murphy 2016). Furthermore, depending on its concentration, duration, and sources, ROS can also serve physiological signaling roles (Jones and Sies 2015). In this context, the concept of "mitohormesis" promotes ROS-induced health benefits depending on exposure time and concentration (Ristow 2014). For instance, the application of vitamins C and E in healthy young men prevented the health benefits of exercise, in particular on insulin signaling (Ristow et al. 2009). Furthermore, antioxidants prevent myocardial protection provided by "preconditioning" episodes of brief ischemia/reperfusion (Baines et al. 1997; Kaeffer et al. 1997; Vanden Hoek et al. 1998). To some extent, these data conflict with the classical free radical theory of aging (Liochev 2013).

Therefore, other strategies were employed to target anti-oxidants more specifically to those compartments where ROS are thought to produce most damage, i.e., to mitochondria. The principles of such mitochondrial therapies have been reviewed in more detail previously (Smith et al. 2012). Here, we will briefly review the concepts and (if available) clinical results of different mitochondrial therapies – and therapies that affect mitochondria – in the context of heart failure. One approach is to target drugs specifically to mitochondria by coupling a pharmacon to the cation triphenylphosphonium (TPP^+), whose lipophilicity allows the passage across the cell and mitochondrial membranes, and its negative charge facilitates the Nernst's distribution law to accumulate in the negatively charged mitochondrial matrix. The most prominent example of this strategy is MitoQ, where a ubiquinone derivative is coupled to TPP^+ (Kelso et al. 2001).

Ubiquinone is synonymous to coenzyme Q, which is a physiological component of the ETC and functions as an electron carrier. In patients with heart failure, decreased levels of coenzyme Q correlated with the severity of the disease and could be slightly increased by conventional oral coenzyme Q supplementation (Folkers et al. 1985). In fact, a recent clinical trial observed that oral coenzyme Q supplementation was associated with improved morbidity and mortality in patients with heart failure (Mortensen et al. 2014). As an electron acceptor, coenzyme Q can also function as an anti-oxidant, and since it is unclear to what extent non-conjugated coenzyme Q is really taken up by mitochondria, the rationale of the development of MitoQ was therefore the coupling of coenzyme Q (ubiquinone) to TPP^+, forming MitoQ (Smith et al. 2012).

Initially considered a similar class of drugs as MitoQ (Smith et al. 2012), the Szeto-Schiller peptides comprise of alternating aromatic and basic amino acid residues, where the aromatic residues were thought to allow the passage across membranes, and the positive charge attracting the molecule to the mitochondrial matrix and finally, the dimethyltyrosine residue providing anti-oxidative properties (Zhao et al. 2004). However, more recent data suggest that SS-31, the most promising candidate of this family, does not have direct anti-oxidative effects (Brown et al. 2014), but binds to cardiolipin, an essential phospholipid of the IMM (Szeto 2014). This interaction with SS-31 protects cardiolipin from oxidation and dysfunction, preventing disassembly of the ETC supercomplexes and thereby, energetic deficit and mitochondrial ROS production (Szeto et al. 2001; Szeto 2014).

Another important catalytic factor in mitochondria is iron, which participates in numerous iron-sulfur (Fe/S) clusters of the ETC and the Krebs cycle. In patients with heart failure, iron deficiency predicts adverse outcome (Jankowska et al. 2010), and in human failing myocardium, decreased iron levels are associated with decreased respiratory capacity (Melenovsky et al. 2016). Intravenous iron application improves functional status and exercise capacity in heart failure patients (Jankowska et al. 2016), and it may be assumed that this is primarily the result of improved mitochondrial function, although this is not entirely proven and also it is unclear whether this is an effect on cardiac and/or skeletal muscles (Stugiewicz et al. 2016).

Finally, physical exercise improves symptoms and quality of life in patients with heart failure, and this effect may be (at least to some extent) related to an improvement of mitochondrial biogenesis. We discuss these aspects in more detail in the following passages.

5 Coenzyme Q_{10} Supplementation: Myth or Reality?

Coenzyme Q_{10}, also known as ubiquinone, coenzyme Q and ubiquinol (reduced form), is a crucial component of the electron transport chain by transporting electrons from complex I, II and the electron transfer flavoproteins to complex IV (Schwarz et al. 2014). Therefore, Q_{10} undergoes cyclic oxidation-reduction. The molecular structure is related to vitamin k, where "Q" connotates the quinone-, and "10" the 10-isoprene group as the molecular structure found in humans. Ubiquinones are ubiquitous in most mammalian cells, and particularly in organs with the highest energy demand, such as the heart (Crane 2007). The cyclic oxidation-reduction rate is slower than the rate of cytochrome c, but this is compensated by 10 times higher coenzyme Q_{10} concentrations than that of other carriers (Klingenberg 2010). Accordingly, depleting coenzyme Q_{10} concentrations in heart mitochondria can slow mitochondrial respiration, while replenishing Q_{10} accelerates respiration (Redfearn and Burgos 1966). Preclinical data suggest that Q_{10} has a critical role in ATP production, is a potent anti-inflammatory agent, and may improve endothelial function (Sharma et al. 2016). In fact, besides mitochondria, coenzyme Q_{10} is also found in other cellular membranes where it controls

the function of endothelial nitric oxide synthase (eNOS), whose uncoupling upon coenzyme Q_{10} depletion can make it an additional source for ROS and thereby, shifts the nitroso-redox balance towards oxidation (Mugoni et al. 2013).

Under physiological conditions, ~50% of coenzyme Q_{10} is ingested, while the other half is synthesized endogenously through the mevalonate pathway, which is blocked by statins (Bentinger et al. 2007; Crane 2007). Therefore, treatment of patients with cardiovascular risk and/or disease with statins is associated with decreased coenzyme Q_{10} levels (Banach et al. 2015). In patients with heart failure, decreased levels of coenzyme Q_{10} correlated with the severity of disease (Mortensen et al. 1990; Mortensen 2015). As a mechanism of decrease in coenzyme Q_{10} concentrations, lipid oxidation was suggested as a consequence of oxidative stress (Forsmark-Andrée et al. 1997). Coenzyme Q_{10} was initially described as an independent predictor of mortality in 236 patients with heart failure (Molyneux et al. 2008). A pre-specified analysis of the much larger CORONA study, however, could not confirm this (McMurray et al. 2010). In CORONA, rosuvastatin did not reduce the primary endpoint of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in patients with ischemic cardiomyopathy (Kjekshus et al. 2007). In these patients, rosuvastatin reduced coenzyme Q_{10}, but even in patients with a low baseline coenzyme Q_{10}, rosuvastatin treatment was not associated with a worse outcome (McMurray et al. 2010). Accordingly, reduced coenzyme Q_{10} was not an independent prognostic variable in heart failure (McMurray et al. 2010). Together, these data call into question a causal role of the coenzyme Q_{10} deficit in patients with heart failure, with or without statin treatment.

As an established mitochondrial therapy, coenzyme Q_{10} cures a defect in Q_{10} biosynthesis by a permanent dietary Q_{10} supplementation. This is an exception to the mostly (therapeutically) orphaned group of primary mitochondrial diseases (Rötig et al. 2000; Montini et al. 2008). In cardiovascular diseases, however, coenzyme Q_{10} supplementation has been pursued without firm evidence of benefit for several decades. While a meta-analysis of several rather small trials indicated that coenzyme Q_{10} may improve LV ejection fraction, additional well-designed studies were required to assess the effect of coenzyme Q on the outcome of these patients (Fotino et al. 2013). In the recent Q-SYMBIO trial, coenzyme Q_{10} was tested against placebo in 420 patients with systolic heart failure, and indeed, coenzyme Q_{10} improved symptoms and substantially reduced major adverse cardiovascular events (Mortensen et al. 2014). However, since the study was underpowered to prove a benefit in this population, the issue whether coenzyme Q_{10} supplementation really improves outcome and symptoms in heart failure is not fully settled (Ezekowitz 2014), and coenzyme Q10 is not even mentioned in the most recent guidelines on the treatment of heart failure (Ponikowski et al. 2016).

6 MitoQ

Mito Q is a mitochondrial targeted antioxidant, where a ubiquinone moiety is linked by a 10-carbon alkyl chain to the cation triphenylphosphonium (TPP^+), which takes advantage of the electrochemical gradient (150–180 mV) across the IMM. Therefore, compounds coupled to TTP^+ are several hundred-fold higher concentrated in mitochondria (Murphy 2016). The ubiquinol moiety of MitoQ is an antioxidant running through a redox cycle via oxidation by ROS to an ubiquinone and reduction by complex II back to ubiquinol (James et al. 2007).

MitoQ can be administered orally, which is safe in rodents (Rodriguez-Cuenca et al. 2010). Preclinical studies show protection against oxidative damage. Feeding MitoQ to rats reduced cell death and mitochondrial damage and thereby improved cardiac function after ischemia-reperfusion of Langendorff-perfused hearts (Adlam et al. 2005). In a spontaneously hypertensive rat model of heart failure, administration of the mitochondria-targeted antioxidant MitoQ protects against the development of hypertension, improves endothelial function, and reduces cardiac hypertrophy (Graham et al. 2009). The favorable outcome may also be attributed to the reduction in blood pressure and improvement in endothelial function observed in the MitoQ group (Bayeva et al. 2013). Moreover, MitoQ protected against anthracycline- (Chandran et al. 2009), endotoxin- (Supinski et al. 2009), and cocaine-induced cardiotoxicities (Vergeade et al. 2010).

These positive preclinical data led to the assessment of MitoQ in a human phase II trial in Parkinson's disease (PD), the PROTECT trial (NCT00329056) which showed safety, but no difference between MitoQ and placebo on any measure of PD progression (Carlisle et al. 2015). A second small trial with MitoQ was performed on patients with chronic hepatitis C virus (the CLEAR trial; NCT00433108), in which MitoQ significantly decreased liver damage in patients with chronic HCV infection (Gane et al. 2010). Despite these favorable clinical data that also confirmed safety of MitoQ, the drug has not been tested yet in clinical trials on patients with cardiovascular diseases.

7 Szeto-Schiller Peptides (Lead Compound SS-31, Also Known as Elamipretide or Bendavia)

The discovery of the Szeto-Schiller (SS) peptides was serendipity while Hazel Szeto and Peter Schiller were working on a family of dermorphins. SS peptides are a new class of compounds that selectively accumulate 1,000- to 5,000-fold in the inner mitochondrial membrane (IMM) compared to the cytosolic compartment. The mitochondrial uptake does not depend on the mitochondrial membrane potential ($\Delta\Psi_m$), which may be of advantage in conditions in which $\Delta\Psi_m$ is (partly) dissipated, such as ischemia or heart failure.

The central mechanism of action of SS-31 is binding selectively to cardiolipin via electrostatic and hydrophobic interactions. SS-31 protects cardiolipin from damage by oxidative stress (Zhao et al. 2004; Szeto 2014) and thereby maintains

proper function of the respiratory chain, avoiding aberrant slippage of electrons to O_2 to produce superoxide anion radical (O_2^-). Furthermore, SS-31 prevents cardiolipin from converting cytochrome c into a peroxidase while protecting its electron carrying function (Szeto and Schiller 2011; Szeto 2014). Usually, peptides are unsuitable drugs mainly due to rapid degradation through peptidases and their inability to cross cellular membranes. However, SS peptides are water soluble due to their cationic character. After administration, SS-31 is rapidly distributed to highly perfused organs, including the heart, kidney, lung, and brain (Szeto 2008). The enzymatic degradation is low and stable even after 2 h of incubation in whole blood (Szeto et al. 2001).

In mice, a 4-week infusion of angiotensin II induces mitochondrial oxidative stress, myocardial hypertrophy, fibrosis and diastolic heart failure, and SS-31, but not the non-specific antioxidant *N*-acetyl cysteine ameliorated these parameters (Dai et al. 2011a). In mice with trans-aortic constriction, the afterload-induced increase in oxidative stress is caused by the reversal of the mitochondrial transhydrogenase, provoking elevated mitochondrial ROS emission which then causes necrosis, LV dysfunction, and premature death (Nickel et al. 2015). In this model, application of SS-31 prevented the afterload-induced increase in necrosis after 3 days and premature death over 6 weeks (Nickel et al. 2015). In a porcine renovascular hypertension model, SS-31 improved diastolic function and oxygenation and reversed myocardial tissue damage after renal angioplasty and stenting (Eirin et al. 2014b). In a dog model of systolic heart failure, SS-31 not only improved systolic function in the long term (i.e., after 3 months of treatment), but also in the short-term: A 48-h treatment with SS-31 increased LVEF and stroke volume and decreased end-systolic volume, with no changes of heart rate or systemic vascular resistance (Sabbah et al. 2016).

The promising preclinical data and its pharmacokinetic profile warranted further clinical testing in patients with cardiovascular diseases. Since April 2016, the international nonproprietary name of SS-31 is Elamipretide (ELA-, no meaning; MI-, mitochondrial; PR-, protection; TIDE, stem of every peptide and glycopeptide; www.stealthbth.com). Elamipretide entered into clinical development with a for-profit commercial sponsor (Stealth Biotherapeutials Inc., Newton, MA, USA) in 2010. The first clinical phase II trial with Elamipretide to reduce the ischemia-reperfusion injury among subjects with first-time anterior STEMI who underwent successful PCI, intracoronary administration of Elamipretide was safe and well tolerated. However, in this single-dose study, the treatment with Elamipretide was not associated with a decrease in myocardial infarct size as assessed by AUC0 – 72 of CK-MB, but some hypothesis-generating positive signals on LV function were noted (Gibson et al. 2015).

This spurred the launch of a clinical programme comprising three phase II trials on patients with heart failure. The first trial evaluates the effects of 4 weeks' treatment with subcutaneous Elamipretide on LV function in subjects with stable heart failure with preserved ejection fraction (HFpEF) by comparing the delta in E/e' at rest and during submaximal exercise between the Elamipretide and placebo groups (NCT02814097). A second phase II trial evaluates the cardiac and renal effects

of short-term treatment with Elamipretide in patients hospitalized with congestion due to heart failure. The primary outcome measures the change in NT-proBNP between baseline and day 8/early discharge (NCT02914665). A third phase II trial examines the effect of multiple subcutaneous injections of Elamipretide on various measures of heart function in patients with chronic heart failure with a reduced ejection fraction (HFrEF). The primary outcome measures are the change from baseline in left ventricular end systolic volume (LV ESV) assessed by cardiac MRI (NCT02788747). The first results of these heart failure trails are expected for February 2017.

8 Iron Supplementation

Iron is not only required for oxygen transport via hemoglobin and oxygen storage by myoglobin, but is also essential in cellular bioenergetics. Iron is either embedded into a heme molecule or an iron-sulfur (Fe/S) cluster. The biogenesis of Fe/S clusters is a highly complex and coordinated process in living cells (Hentze et al. 2010). Their main purpose is electron transfer by switching between oxidative states as part of the complexes of the mitochondrial ETC (Lill 2009). Furthermore, Fe/S clusters play an important role for the function of various Krebs cycle enzymes, such as aconitase.

Both iron deficiency and iron overload can negatively affect human health (Abbaspour et al. 2014). Due to the importance of iron in tissues with high metabolic demand like the heart, the balance between iron deficiency and overload requires precise regulatory control. As a reactive metal, free iron catalyzes production of highly toxic hydroxyl radicals via the Fenton reaction (Eaton and Qian 2002). In the context of chronic iron overload during hemochromatosis, iron-catalyzed ROS can induce heart failure in addition to liver failure and type II diabetes (Gao et al. 2010; Dixon and Stockwell 2013). Also in patients with β-thalassemia, myocardial iron overload resulting from chronic and excess hemolysis can induce heart failure that is ameliorated by iron chelators (Tanner et al. 2007; Kremastinos et al. 2010). Deficiency of frataxin, a regulator of mitochondrial iron homeostasis, has similar effects in Friedreich's ataxia: Patients develop a mitochondrial iron overload combined with mitochondrial dysfunction and oxidative damage (Whitnall et al. 2008; Payne 2011). Furthermore, doxorubicin induces mitochondrial iron accumulation and thereby contributes to ROS-mediated cardiotoxicity (Ichikawa et al. 2014). Finally, during ischemia/reperfusion injury, upregulation of the mitochondrial iron exporter decreased mitochondrial iron content and protected against ischemia/reperfusion damage in mice (Chang et al. 2016).

On the other hand, in patients with chronic heart failure, serum iron deficiency (ID) is quite prevalent, affecting roughly one third of all heart failure patients, and is associated with decreased exercise capacity and adverse outcome independent of ID-associated anemia (Jankowska et al. 2010; von Haehling et al. 2015). These clinical observations and pathophysiological considerations fostered the development of efficient therapies to refill the depleted iron stores in patients with

heart failure. Ferric carboxymaltose is an intravenous drug in which a ferric hydroxide core is stabilized by a carbohydrate shell, allowing for controlled delivery of high amounts of iron to target tissues (Lyseng-Williamson and Keating 2009). In fact, intravenous iron supplementation over 24 weeks improved the 6-min walk distance, functional status and well-being and reduced hospitalizations of patients with systolic heart failure (Anker et al. 2009; Ponikowski et al. 2015; Jankowska et al. 2016). In contrast, no effects on total or cardiovascular mortality were noticed so far (Jankowska et al. 2016). Therefore, the application of intravenous iron has received a class IIa, A recommendation in the recent ESC Guidelines on the treatment of heart failure (Ponikowski et al. 2015).

It is presently unresolved, however, whether the beneficial effects of iron are mediated by improvement of cardiac or skeletal muscle function, or both (Stugiewicz et al. 2016). In fact, the impact of serum ID on mitochondrial iron content in failing hearts is presently unclear. In a rat model of experimental iron deficiency, the activities of various ETC complexes and mitochondrial respiration were reduced (Blayney et al. 1976). In patients with heart failure, the *total* myocardial iron content is reduced (Maeder et al. 2011; Leszek et al. 2012; Haddad et al. 2016; Melenovsky et al. 2016). However, myocardial iron content did not correlate with serum iron, serum transferrin saturation or the severity of the disease in a cohort of 33 patients with systolic heart failure and a mean of LVEF 22% (Leszek et al. 2012, 2015). In those failing hearts in which myocardial iron content was decreased, the activity of respiratory chain complexes was preserved, while the activity or protein expression of aconitase, citrate synthase, and anti-oxidative enzymes was reduced (Melenovsky et al. 2016). Importantly, in a study that differentiated between *cytosolic* and *mitochondrial* iron contents, mitochondrial iron was actually *increased*, while cytosolic iron was *reduced* (Khechaduri et al. 2013). In mitochondria, iron is integrated in heme molecules which in turn are integrated into the ETC complexes or Krebs cycle enzymes. The mitochondrial heme content was also increased in human failing hearts, and in cell systems, increased heme expression was associated with higher production of ROS (Khechaduri et al. 2013). Together, although most studies show that in human failing hearts, the *total* iron content is reduced, this decrease may not occur in mitochondria (Khechaduri et al. 2013) and appears unrelated to serum iron status (Leszek et al. 2012), severity of the disease (Leszek et al. 2015) or the activity of respiratory chain complexes (Melenovsky et al. 2016).

Cells take up iron bound to transferrin via transferrin receptor 1 (Trf1), which in turn is under the control of iron-regulatory proteins (Irp) 1 and 2 (Hentze et al. 2010). In human failing hearts, Irp activity and Trf1 expression are downregulated (Maeder et al. 2011; Haddad et al. 2016). In mice with cardiomyocyte-specific deletion of both Irp1 and Irp2, myocardial iron stores and Trf1 expression were reduced, and this decreased PCr/ATP ratios and decreased the maximal inotropic response to β-adrenergic stimulation in vivo (Haddad et al. 2016). These energetic defects were related to decreased complex I activities in the LV myocardium and decreased maximal respiration in isolated cardiac myocytes of Irp1/2-deficient mice. Furthermore, after myocardial infarction, the development of LV hypertrophy

and systolic dysfunction was aggravated in mice with cardiomyocyte-specific ID (Haddad et al. 2016). These defects could be restored by systemic application of ferric carboxymaltose, suggesting that in patients with heart failure, iron supplementation may improve cardiac function. However, before translating these experimental results to the human situation, one needs to consider that – as mentioned above – in human heart failure, iron content was not reduced in cardiac mitochondria (Khechaduri et al. 2013), and decreased total myocardial iron content was not associated with serum ID (Leszek et al. 2012) or decreased myocardial ETC activity (Melenovsky et al. 2016). Nevertheless, the study by Haddad et al. (2016) sheds some new light onto cardiac myocyte iron metabolism and supports the notion that therapeutic iron may improve cardiac function of patients with heart failure.

Together, while it is clear that serum ID predicts an adverse outcome and ferric carboxymaltose improves symptoms and quality of life in patients with heart failure, these effects are presumably related to improving skeletal muscle function (Stugiewicz et al. 2016) and potentially also of cardiac function (Haddad et al. 2016). Nevertheless, more research is needed to further elucidate the impact and regulation of iron in cardiac mitochondria.

9 Exercise

Physical exercise appears to be a systemic and genuinely mitochondrial therapeutic strategy. In fact, our growing understanding of the regulation of mitochondrial biogenesis and function also helps to understand how exercise may have positive impacts on health through improving mitochondrial function (Safdar et al. 2011; Picard et al. 2016). In fact, even small improvements in physical fitness are associated with a significantly lowered risk of death (Erikssen et al. 1998). One central molecular hub for several exercise-associated signaling pathways, and in particular, for mitochondrial biogenesis in skeletal and myocardial muscle is the peroxisome proliferator-activated receptor gamma co-activator (PGC-1α) (Handschin and Spiegelman 2008; Safdar et al. 2011). PGC-1α regulates the coordinated expression of key mitochondrial proteins of the respiratory chain and the Krebs cycle (Scarpulla 2008; Ventura-Clapier et al. 2008). Furthermore, the levels of PGC-1α expression correlate with OXPHOS capacity, and in patients with heart failure, myocardial PGC-1α expression is decreased (Garnier et al. 2003; Sebastiani et al. 2007). During physical exercise, ROS activate PGC-1α (and several other signaling pathways) which in turn increases the expression of anti-oxidative enzymes (St-Pierre et al. 2006). In fact, the application of non-selective antioxidants such as vitamins C and E can attenuate endurance training-induced and ROS-mediated enhancements in antioxidant capacity, mitochondrial biogenesis, cellular defence mechanisms, and insulin sensitivity (Ristow et al. 2009). This may further explain the observation that vitamin supplementation (as a *non-targeted* anti-oxidative intervention) did not have any positive impact on the cardiovascular outcome of patients at risk (Yusuf et al. 2000; Münzel et al. 2015).

In the HF Action trial on patients with systolic heart failure, exercise improved quality of life and self-reported health status (Flynn et al. 2009). After adjustment for highly prognostic predictors of the primary end point, exercise training was associated with modest significant reductions for both all-cause mortality or hospitalization and cardiovascular mortality or heart failure hospitalization (O'Connor et al. 2009). Also in patients with heart failure with preserved ejection fraction (HFpEF), exercise training improved exercise capacity (peak oxygen consumption), quality of life and diastolic function (Edelmann et al. 2011; Fukuta et al. 2014; Nolte et al. 2015). The comparison of high intensity interval training versus moderate intensity continuous training showed equal effect in improving quality of life and functional capacity in HF patients (Benda et al. 2015; Ulbrich et al. 2016). Therefore, the current ESC Guidelines recommend exercise training for the treatment of heart failure to improve quality of life and reduce hospitalizations (Ponikowski et al. 2016).

10 Conclusions

A precise understanding of pathophysiological mechanisms affecting mitochondrial function and metabolism in heart failure is key to design efficient drugs that may improve mitochondrial function. While iron therapy and exercise are already recommended in the current ESC Guidelines for the treatment of heart failure, novel drugs such as MitoQ and SS-31 are still under preclinical and clinical investigation and may be promising additions to our current armament of neurohormonal interventions.

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