REVIEW

Metabolic Flexibility and Mitochondrial Bioenergetics in the Failing Heart. Therapeutic Approaches

Mariana G. ROSCA[1]

ABSTRACT

Objectives. We will review current concepts regarding bioenergetic decline in heart failure (HF). In the heart, the high energy demand must be met by continuous ATP generation. Cardiac energetic machinery orchestrates the ATP production by using oxidation of multiple energetic substrates including fatty acids (FA), glucose, amino acids and ketone bodies. The normal heart is metabolically flexible and able to use different energetic fuels during physiologic or pathologic circumstances to better match the energy demand. Mitochondria have critical role in maintaining cardiac metabolic flexibility.

Methods. We analyzed the scientific literature pertinent to HF and mitochondrial dysfunction.

Results. The general consent is that metabolic flexibility is lost in HF with either preserved or reduced ejection fraction (HFpEF and HFrEF, respectively). The prototype of HFpEF is the metabolic heart disease that is characterized by increased reliance on FA oxidation for ATP production and decreased glucose oxidation, while HFrEF presents a decreased FA oxidation. Both types of HF are associated with a decline in mitochondrial function leading to increased oxidative stress, abnormalities in the redox status and energy deficit.

Conclusion. Current research is committed to find novel metabolically targeted therapeutic approaches to improve energetic metabolism and alleviate HF progression.

Keywords: mitochondria, heart failure, energy.

REZUMAT

Objective. Lucrarea reprezintă o revizuire a conceptelor curente referitoare la declinul bioenergetic în insuficiența cardiacă (IC). În cord, consumul mare de energie trebuie compensat prin generare continuă de ATP. Sistemul energetic cardiac orchestrează producția de ATP prin folosirea de substraturi energetice multiple incluzând acizi grași (AG), glucoză, aminoacizi și corpi cetonici. Inima sănătoasă este metabolic flexibilă și capabilă să utilizeze substraturi energetice variate în diferite circumstanțe fiziologice și patologice pentru a răspunde cerinței energetice. Mitocondriile au un rol critic în menținerea flexibilității metabolice cardiace. Metode. Am analizat literatura științifică referitoare la IC și disfuncția mitocondrială.

Rezultate. Consensul general este că flexibilitatea metabolică este pierdută în ambele forme de IC, IC cu fracția de ejecție prezervată sau redusă (ICpFE și ICrFE, respectiv). Prototipul de ICpFE este boala cardiacă metabolică care este caracterizată prin creșterea oxidării AG pentru producerea de ATP și scăderea oxidării glucozei, în timp ce ICrFE prezintă scăderea oxidării AG. Ambele tipuri de IC sunt asociate cu declinul funcției mitocondriale care determină creșterea stresului oxidativ, anomalii în statusul redox, și deficit energetic.

Concluzie. Cercetarea curentă este determinată să găsească noi abordări terapeutice orientate spre metabolism cu intenția de a îmbunătăți metabolismul energetic și atenua evoluția în IC.

Cuvinte cheie: mitocondrii, insuficiență cardiacă, energie.

INTRODUCTION

Heart Failure (HF) is a growing public health concern, and a leading cause of morbidity and mortality in industrialized countries worldwide. HHF is a frequent disease with a prevalence of approximately 37.7 million globally[1] and accounting for 2-3% of total healthcare worldwide[2]. There are two major types of HF, HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF), which share similar prevalence and poor prognosis with mortality rates of 50% 5 years after diagnosis[3]. HFrEF is defined by the presence of systolic dysfunction with an ejection

[1] Department of Foundational Sciences, Central Michigan University College of Medicine, Mount Pleasant Michigan, USA

Contact address:
Mariana G. ROSCA, Central Michigan University College of Medicine, 2630 Denison Drive, Research Building Room 105, Mount Pleasant MI 48858, USA.

fraction lower than 45% disregarding the diastolic dysfunction. HFpEF is characterized by an increased left ventricle (LV) filling pressure without LV dilation, and with ejection fraction higher than 50%[4]. Disregarding the type, effective therapeutic strategies to preserve the remaining functional myocardium and delay the progression of HF are yet to be determined. In addition, although both types of HF have different features, they are treated with similar traditional drugs[5] with little success.

As a complex clinical syndrome induced by impaired contractile and/or relaxation performances of the myocardium, HF leads to inability of the heart to supply adequate amounts of blood to meet the peripheral tissues metabolic needs. Cardiac ischemia, increased preload and afterload, neurohormonal dysregulation, and intrinsic abnormalities of the myocardium are common etiologic factors of HF[2]. Major pathogenic mechanisms responsible for HF progression are abnormalities of calcium homeostasis and bioenergetics, alterations of the cardiac contractile apparatus with impaired mechanics, and increased oxidative stress 2 (Figure 1).

The impairment of bioenergetics is considered a key pathogenic mechanism in HF. The heart needs energy in the form of ATP in both systolic and diastolic periods to sustain the excitation contraction coupling and myosin-actin cross-bridge cycles, as well as termination of contraction supported by energy dependent processes including calcium sequestration in the sarcoplasmic reticulum and its extrusion from cardiomyocytes. During maximal exercise cardiac muscle uses 90% of its oxidative capacity indicating that the heart lacks an excess capacity for energy production over energy utilization. There is no significant energy deposit, and the coupling between energy supply and consumption follows a "pay as you go" basis. This means that the energy demand dictates the intensity of energy production.

Ninety percent of cardiac energy requirement is provided by mitochondrial oxidative phosphorylation, which is finely tuned to the energy demand. An optimal energy balance is achieved when energy production matches the energy consumption. HF is associated with altered mitochondrial bioenergetics[2], which may induce a state of energy starvation and is correlated

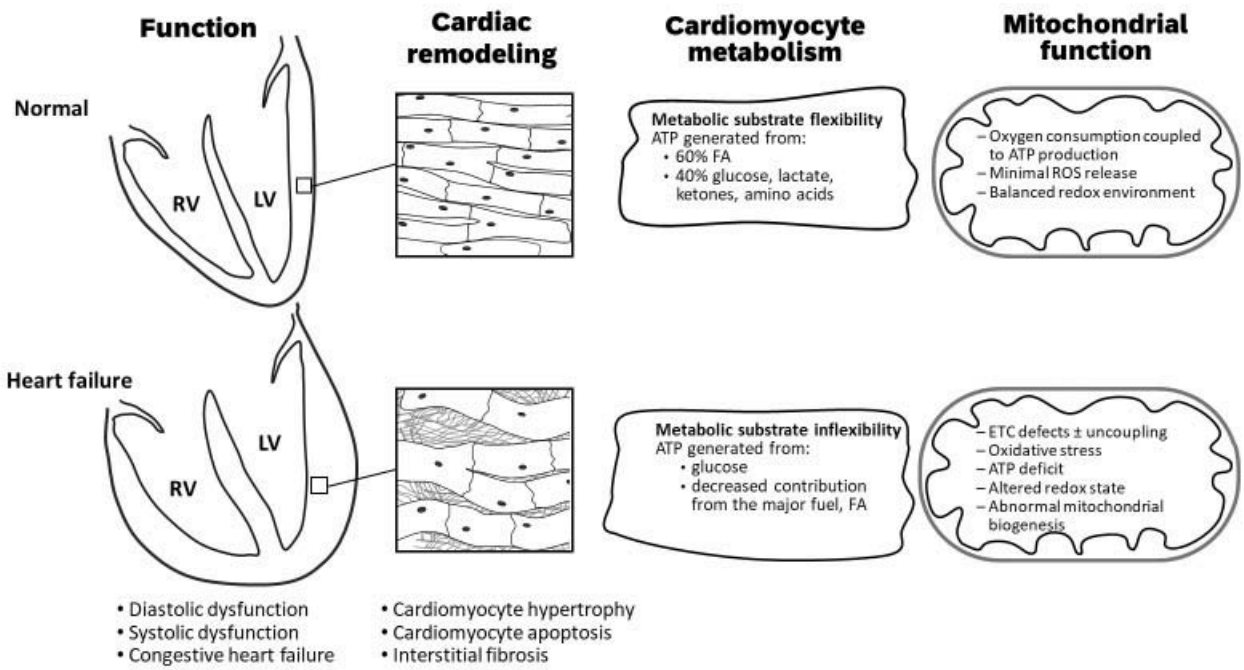

Figure 1. Major structural, functional, metabolic and bioenergetic features of the failing heart. Heart failure (HF) with preserved ejection fraction and HF with reduced ejection fraction may both evolve to congestive HF. These functional abnormalities are progressively induced by either primary stiffness of the ventricular wall (defect in cardiomyocyte relaxation, interstitial fibrosis and cardiomyocyte hypertrophy) or contractile dysfunction, cardiomyocyte death and eventually chamber dilation. The heart relies on constant ATP supplied by oxidative metabolism. Heart failure is considered a disease of the myocardial energetic metabolism induced by mitochondrial dysfunction leading to energy deficit, increased oxidative stress and altered redox status.

with hemodynamic markers of severity in human subjects with HF[6,7].

Current therapies are mostly focused on decreasing myocardial oxygen consumption and energy demand, and aimed to decrease heart rate and afterload. These therapies are limited by their own effects that include hypotension and bradycardia. The results of the majority of phase III clinical trials with cardioprotective agents performed in the last decade have been largely negative[8]. Current inotropic therapy is also limited by its disadvantage of increasing oxygen consumption by the less efficient failing heart. Therefore, there is a need for therapies to act on activating signals to increase energy production. Mitochondria is central for cardiac bioenergetics, and the major site of ATP production. This review focuses on alterations in mitochondrial bioenergetics in HF, and novel therapeutic strategies aimed to correct mitochondrial dysfunction in order to balance the bioenergetics and improve the HF outcome.

MITOCHONDRIAL ENERGY METABOLISM IN THE NORMAL HEART

The heart weights only approximately 0.5% of the human body and consumes 8% of the 65 Kg of ATP produced by the whole body per day. Therefore, the heart is the highest metabolically active tissue in the human body. Approximately 95% of cardiac ATP results from mitochondrial oxidative metabolism with the rest deriving from glycolysis[6]. Cardiomyocytes are rich in mitochondria that are located both beneath the plasma membrane (subsarcolemmal) and within the interfibrillar regions of cardiomyocytes (Figure 2).

In order to accomplish their energetic mission, cardiac mitochondria transform the chemical energy stored in fuel substrates into ATP through oxidative phosphorylation. The normal adult heart obtains 60% of ATP from fatty acids (FA) oxidation with the remaining 40% originating from the oxidation of other fuel substrates including glucose, lactate, amino acids and ketones (mainly β-hydroxybutyrate, βHB) (Figure 3).

While glucose uptake into cardiomyocytes is dependent on insulin activity, the uptake of FA and βHB is not hormonally regulated[9,10]. Glucose enters cardiomyocytes mostly via the insulin-dependent glucose transporter[4] (GLUT4)[11] and is directed through multiple metabolic pathways such as glycolysis, glycogen synthesis, polyol, hexosamine biosynthetic or pentose phosphate pathways. The end product of glycolysis,

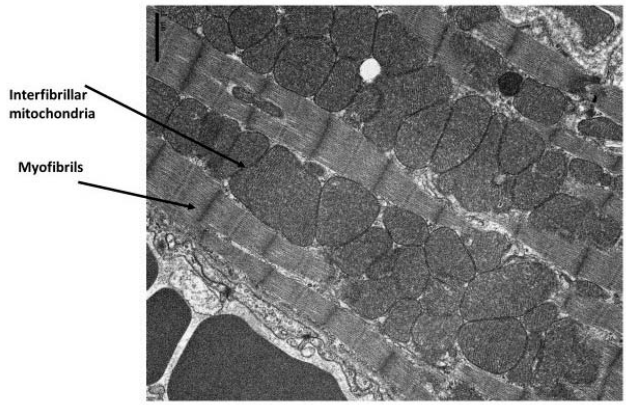

Figure 2. Electron microscopy image of the mouse heart.

pyruvate, is either converted to lactate or transported into mitochondria via the mitochondrial pyruvate carrier, and converted by pyruvate dehydrogenase (PDH) to acetyl-CoA for the tricarboxylic acid (TCA) cycle, also known as Krebs cycle (Figure 3).

After entry into cardiomyocytes, long chain FAs (i.e., palmitate) are activated to FA-CoA that is either esterified as triacylglycerol or enter the mitochondria via carnitine palmitoyltransferases (CPT1 and 2) to be oxidized via FA β-oxidation. The end products of each FA β-oxidation cycle are NADH, FADH2 and acetyl-CoA, which are further oxidized by electron transport chain (ETC) complexes or Krebs cycle, respectively, ultimately leading to ATP synthesis via mitochondrial oxidative phosphorylation. FA β-oxidation is controlled at different steps including the inhibitory effect of malonylCoA (formed from AcCoA via AcCoA carboxylase, ACC), $FADH2/FAD^+$ and $NADH/NAD^+$ redox ratios, and acetyl-CoA/CoA ratio, all unfavorable to FA oxidation[12]. MalonylCoA is degraded by malonyl-CoA decarboxylase (MCD) thus releasing its inhibitory effect on CPT1 (Figure 3).

βHB is produced by the liver at rates proportional to FA oxidation and $NADH/NAD^+$ ratio, and represents the main ketone body utilized by the heart as an energy fuel. Within mitochondria, βHB is sequentially converted to acetoacetate, acetoacetyl-CoA and acetyl-CoA for the Krebs cycle[10] (Figure 3). Cardiac mitochondria can also fully metabolize branched chain amino acids (leucine, isoleucine and valine) providing acetyl-CoA for the Krebs cycle and succinyl-CoA for anaplerosis. Krebs cycle is a source of reducing equivalents in the form of NADH and NADPH.

While electrons are transferred from the reducing equivalents, NADH and FADH2, to oxygen by the ETC

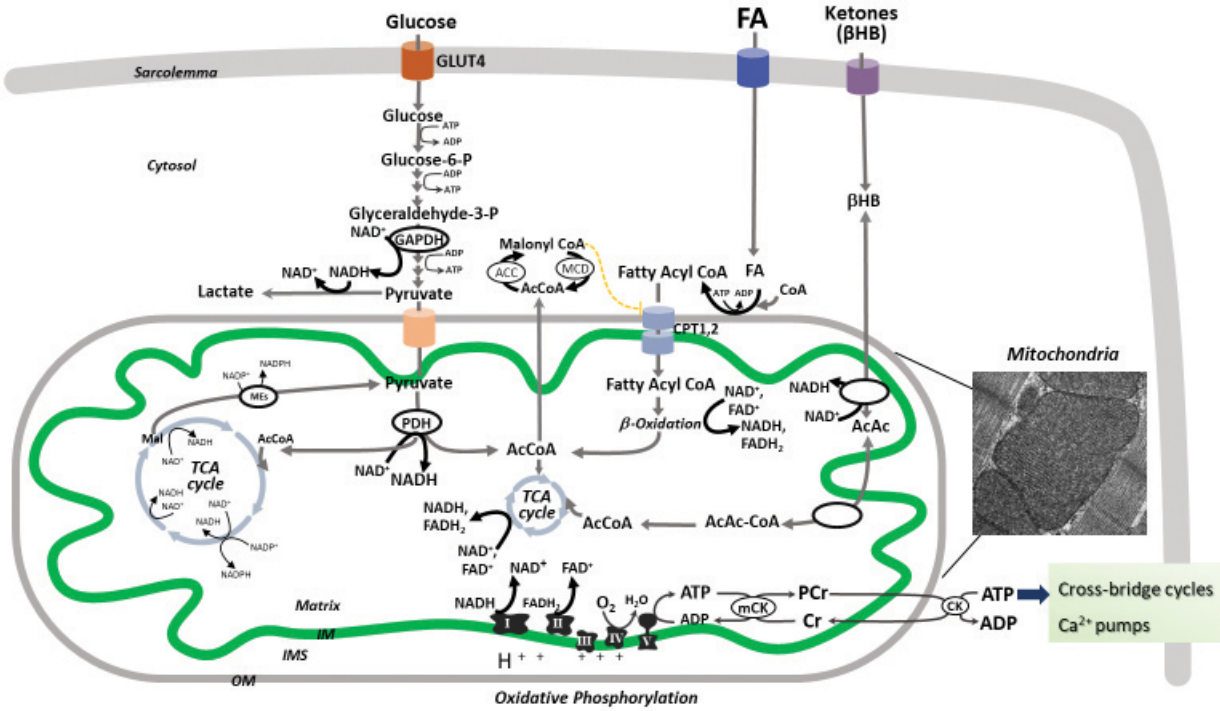

Figure 3. Cardiac oxidative metabolism. Normal adult heart obtains ATP mostly from fatty acid (FA) oxidation with the remaining delivered from glucose, amino acids and ketones (mainly β-hydroxybutyrate, βHB)[5]. Glucose uptake is mediated by the glucose transporter[4] (GLUT4), and follows multiple metabolic pathways including glycolysis and mitochondrial glucose oxidation. For simplicity, other metabolic pathways are not depicted in this figure. The end product of extramitochondrial glycolysis, pyruvate, is converted by mitochondrial pyruvate dehydrogenase (PDH) to acetyl-CoA (AcCoA) that enters the tricarboxylic acid (TCA) cycle (Krebs cycle). Long chain FAs are activated to FA-CoAs that enter the mitochondria via carnitine palmitoyltransferases (CPT1 and 2) and are oxidized via FA β-oxidation. The end products of pyruvate and FA β-oxidation spiral are NADH, $FADH_2$ and acetyl-CoA, which are further oxidized by electron transport chain (ETC) complexes or Krebs cycle, respectively, ultimately leading to ATP synthesis via mitochondrial oxidative phosphorylation. FA β-oxidation is inhibited by malonylCoA (formed from AcCoA via AcCoA carboxylase, ACC), $FADH_2/FAD^+$ and $NADH/NAD^+$ redox ratios, and acetyl-CoA/CoA ratio. MalonylCoA is degraded by malonylCoA decarboxylase (MCD) thus releasing its inhibitory effect on CPT1. βHB is oxidized within cardiac mitochondria to acetoacetate (AcAc) that is converted to acetyl-CoA for Krebs cycle. Mitochondrial oxidative phosphorylation provides more than 95% of the cardiac ATP, with the remainder derived from glycolysis. While electrons are transferred from the reducing equivalents, NADH and $FADH_2$, to oxygen by the ETC complexes, an electrochemical gradient is developed across the mitochondrial inner membrane (IM), which is used by the ATP synthase (complex V) to form ATP. Mitochondrial generated ATP is transferred to the cytosol by the mitochondrial and cytosolic creatine kinases (CK) for contractile apparatus, sarcoplasmic reticulum Ca^{2+}-ATPase and other ion pumps. The inset represents an electron micrograph of mouse cardiac muscle showing interfibrillar mitochondria.

complexes, an electrochemical gradient is developed across the mitochondrial inner membrane (IM), which is used by the ATP synthase (complex V) to phosphorylate ADP and form ATP. Mitochondrial ATP is transferred to the cytosol by phosphate exchange networks including mitochondrial and cytosolic creatine kinases (CK) for contractile apparatus, sarcoplasmic reticulum Ca^{2+}-ATPase and other ion pumps.

CARDIAC METABOLIC FLEXIBILITY

Although the heart is enzymatically equipped to simultaneously utilize multiple fuels to produce energy, it is also able to change the relative contribution of these substrates to cardiac ATP in an effort to better adjust to different physiological and pathological conditions[5]. This characteristic is vital for the ability of the normal heart to respond properly to the energy demand. Energetic substrates have different energy efficiency, which is defined by the amount of ATP produced for the oxygen consumed and expressed as P/O ratio. While FA oxidation gives the greatest ATP yield, it also uses the highest amount of oxygen with a P/O ~2.3. Glucose is the most efficient energy substrate with a P/O ratio of 2.58. 5. βHB oxidation has an intermediate efficiency with a P/O~2.5.

βHB is oxidized by the normal heart in proportion to its availability at the expense of FA and glucose[10]. It is reported that HFpEF associated with diabetes acquires the ability to shift the acetyl-CoA towards ketone body synthesis, a characteristic of the fetal heart[13]. A decrease in glucose oxidation induces HFpEF indicating that maintaining proper glucose metabolism is re-

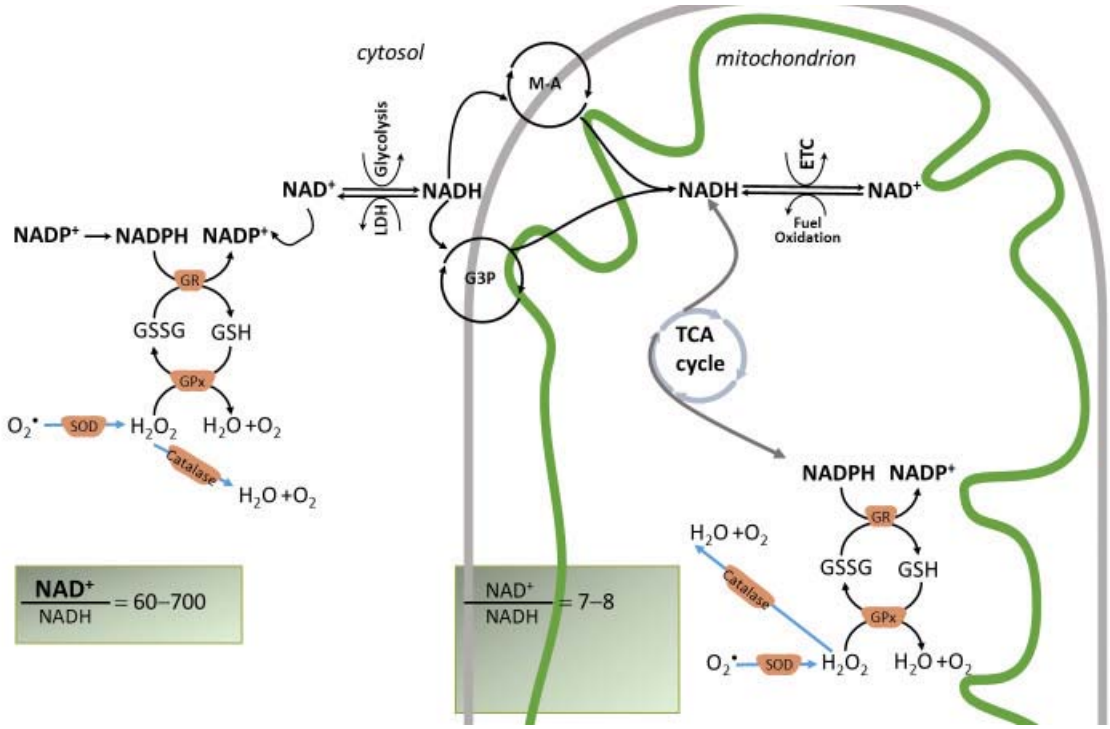

Figure 4. The main redox couples governing the redox balance in cardiac mitochondria (NAD^+/NADH, $NADP^+$/NADPH, and GSH/GSSG). Normal cardiomyocytes maintain a constant NAD pool. Both oxidized forms, NAD^+ and $NADP^+$, are hybrid acceptors, and are converted to the reduced forms, NADH and NADPH. NADH is oxidized by complex I, and therefore, the NADH/NAD^+ couple is important for ATP generation. The NADPH/$NADP^+$ redox couple is central to the antioxidant defense by donating electrons to glutathione (GSH/GSSG) that scavenges the hydrogen peroxide (H_2O_2, a Reactive Oxygen Species, ROS) via the enzymes glutathione reductase (GR), glutathione peroxidase (GPx). H_2O_2 is generated from superoxide, $O•_2$, by dismutation via the enzyme, superoxide dismutase (SOD). For simplicity, the thioredoxin antioxidant system is not shown. Mitochondrial antioxidant system is mirrored by a similar scavenging mechanism in the cytosol. In these reactions, the reduced and oxidized members of the redox couples interconvert but are not consumed. Catalase also scavenges H_2O_2.
Mitochondrial NADH/NAD^+ and NADPH/$NADP^+$ redox couples are linked by the enzyme nicotinamide nucleotide transhydrogenase (NNT) that reduces $NADP^+$ at the expense of NADH oxidation and utilizing the mitochondrial inner membrane proton motive force to drive this process. NNT is a physiologically relevant source of NADPH to drive the enzymatic degradation of H_2O_2. The figure shows that the mitochondrial redox state of the NADH/NAD^+ and NADPH/$NADP^+$ redox couples are maintained different as these nucleotides have different metabolic roles. The NADH/NAD^+ pool supports the divergent transfer of electrons from fuel substrates to both the ETC and antioxidant system via NNT, and thus is only partially reduced in comparison to NADPH/$NADP^+$. The cytosolic NADH is imported in mitochondria by redox shuttles, most commonly the malate-aspartate (M-A) and glycerol 3 phosphate shuttles (G3P).

quired for cardiac metabolic health[14,15]. An excessive dependence on FA oxidation occurs in the heart exposed to an excess in energy fuels (overfeeding-induced obesity, metabolic syndrome and diabetes).

In contrast, a reversal back to a fetal metabolic state with overreliance on glucose oxidation and decreased FA oxidation occurs in the failing heart, and is associated with a state of "energy starvation" as glucose, although a low oxygen consuming substrate, is also a low ATP-yield when calculated per mole[5]. Most clinical[16,17] and experimental[18] studies confirm this type of cardiac metabolic inflexibility, and show that the decrease in mitochondrial FA oxidation predicts the onset of contractile dysfunction in pressure overload-challenged rats[19]. In overt HF, disregarding the etiology, the severe decrease in FA oxidation may be due to the collapse of mitochondrial function. In terms of ATP production, one molecule of palmitate yields far more ATP than does glucose. Therefore, to maintain a constant ATP content, a pronounced increase in glucose oxidation must accompany a relatively modest decrease in FA oxidation. Most studies report that the decrease in FA oxidation is not compensated for by an increase in glucose oxidation[20,21].

The decrease in mitochondrial oxidative metabolism is associated with an increase in cytosolic glycolytic rates[5]. Although glycolysis is an alternate source of energy, producing 2 ATP molecules from one glucose molecule, this is insufficient to compensate for energy deficit because the complete glucose oxidation would produce 31 ATP molecules. The general conclusion is that there is no true metabolic switch characterized

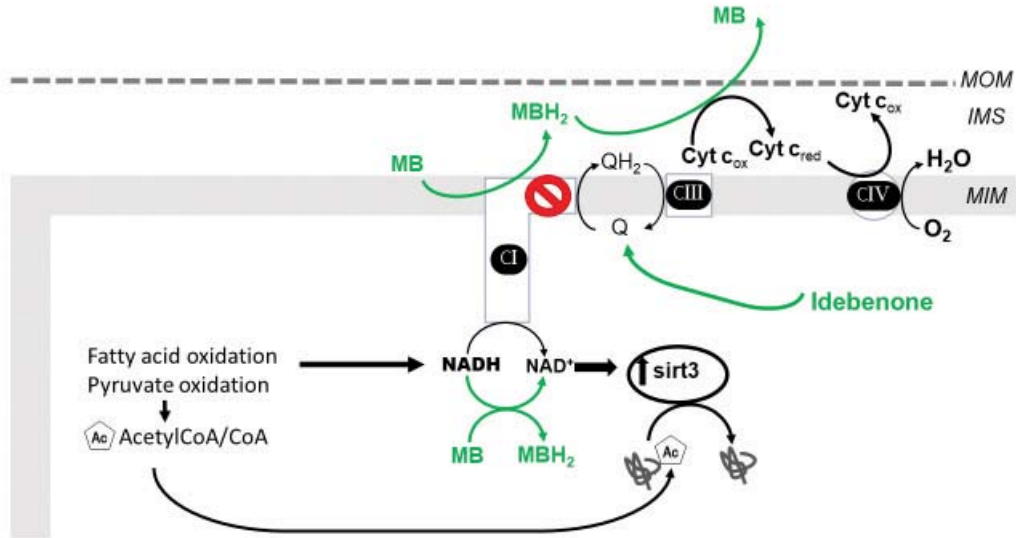

Figure 5. Mitochondrial redox modulators. Increasing the efficiency of the electron transport chain. The figure shows a proposed mechanism for the NAD^+ enhancing and lysine deacetylating effect of methylene blue (MB). A complex I defect causes a decrease in NADH oxidation. In experimental models of complex I defect MB accepts electrons from catalytic subunits of complex I and become reduced (MBH2) whereas cytochrome c reoxidizes MBH2 to MB. Therefore, MB provides an alternative electron route within complex I-deficient cardiac mitochondria and favors NADH oxidation thus increasing NAD^+ and SIRT3 activity. The administration of exogenous NAD or precursors (+) improved the mitochondrial NAD pool and cardiac function (discussed in the main text). Idebenone increases the coenzyme Q pool.

by a decrease in FA oxidation and a corresponding increase in glucose oxidation, and that the failing heart is an energy-compromised (starved) organ[20].

CARDIAC MITOCHONDRIA IN HF

The ATP amount in the failing heart is reported decreased compared with the normal heart, suggesting a decrease in mitochondrial oxidative phosphorylation. The decrease in mitochondrial oxidative capacity is multifactorial and may be induced by 1) decreased mitochondrial biogenesis pathway; 2) specific defects in the ETC complexes.

Mitochondrial biogenesis

The formation of new mitochondria (mitochondrial biogenesis) is supported by synthesis of mitochondrial proteins and replication of mitochondrial DNA, both processes under the control of the transcription factor peroxisome proliferator-activated receptor γ (PPAR γ) and its co-activator α (PGC1α). PGC1α is considered the master regulator of mitochondrial biogenesis due to the activation of nuclear respiratory factors 1 and 2, (NRF1 and 2) as well as mitochondrial transcription factor A (TFAM), all targeting genes encoding for mitochondrial proteins and mtDNA[22,23]. PGC1α is downregulated in humans with HF leading to decreased mitochondrial density[24,25]. PPARα is an isoform predominantly regulating FA oxidation enzymes, and is downregulated in both animal models and humans with HFrEF[26] but is increased in HFpEF associated with metabolic syndrome, which is associated with an increase in FA oxidation[19].

ETC abnormalities

There is plethora of evidence that specific activities of individual ETC complexes are decreased in HF[20]. ETC complexes aggregate into functional supercomplexes[27], and this form of organization provides a more efficient electron transport and is protective against excessive mitochondrial reactive oxygen species (ROS) generation[27]. A decrease in mitochondrial supercomplexes has been reported in HF[28].

Cardiolipin (CL) is an anionic phospholipid with four acyl chains that are enriched in linoleic acid ((C18:2)4-CL), which resides in the inner mitochondrial membrane. CL provides structural and functional support to ETC components[29], and its depletion results in reduced activities of ETC complexes. CL is also proposed to maintain the structural integrity of ETC supercomplexes, as it may act as a molecular 'glue' to hold the complex protein subunits together in a supramolecular organization[30,31]. In humans, reduced (C18:2)4-CL, due to defective CL remodeling (Barth syndrome), causes dilated cardiomyopathy associated with destabilization of all supercomplexes containing complex IV, loss of complex I from the supermolecu-

lar assembly and decrease in the individual enzymatic activities of complexes I, III and IV[31], indicating that CL is essential for the function of cardiac mitochondria. Myocardial ischemia[32] and HF[33-35] are associated with mitochondrial dysfunction and CL peroxidation, loss of total CL content and decrease in (C18:2)4-CL. Approaches that target cardiolipin are likely to improve electron transport across the ETC and, by correcting mitochondrial function, might be beneficial in treating HF.

CONSEQUENCES OF ALTERATIONS IN MITOCHONDRIAL BIOENERGETICS IN HF

Oxidative stress is defined by an increase in reactive oxygen species (ROS) related to the antioxidant mechanisms. The ROS-generating sources in the heart are both extramitochondrial and mitochondrial. Defects in the ETC complexes lead to an impaired electron flow with accumulation of electrons at ETC sites that, according to their redox potential, can donate electrons and univalently reduce the molecular oxygen to form superoxide, a strong ROS. Similarly, an increase in mitochondrial proton gradient (mitochondrial hyperpolarization) also slows down the electron transport and increases ROS generation[36].

A mild generation of reactive oxygen species has beneficial effects on the heart by facilitating physiological adaptive responses such as adaptation to physical exercise[37]. In addition, exercise training causes beneficial adaptation in the heart such as an increase in endogenous ROS-scavenging mechanisms[37], restores bioenergetics in porcine models of HFpEF[38], and alleviates symptomology in patients with HFrEF[39,40] and HFpEF[41].

Uncoupling proteins dissipate the electrochemical gradient by allowing proton translocation back into the mitochondrial membrane, thus uncoupling the oxidation and phosphorylation processes. The observed increased expression of mitochondrial uncoupling proteins in HF[42] might be a compensatory mechanism to reduce ROS by inducing a mild decrease in the mitochondrial inner membrane electrochemical gradient, a process called "mild uncoupling"[43]. However, the decrease in ROS production by uncoupling may be an efficient ROS decreasing mechanism in absence of ADP, a state that is unlikely to occur in the heart *in vivo*.

Alterations in the redox state. Classic examples of redox reactions are the transfer of electrons between reduced and oxidized subunits within the mitochondrial ETC according to their redox potential. Mitochondria have multiple redox couples (redox players)[44] including NAD^+ (oxidized)/NADH (reduced), $NADP^+$/NADPH, GSSG (glutathione disulfide)/GSH (glutathione) (Figure 3). Energized mitochondria have a high NADH concentration to provide electrons for oxidative phosphorylation[45]. In contrast, in the extramitochondrial space, the NADPH/$NADP^+$ ratio is maintained in a reduced state (the reduced NADPH > the oxidized NADP) via several enzymatic reactions in order to drive reductive biosynthesis and maintain antioxidant defense. The cytosolic GSH/GSSG couple is also maintained in a reduced state that is needed for ROS detoxification. These redox couples are interconnected (Figure 4). In mitochondria, the inner membrane nicotinamide nucleotide transhydrogenase (NNT) reduces $NADP^+$ at the expense of NADH oxidation, utilizing the mitochondrial inner membrane protonmotive force to drive this process. NNT is a physiologically relevant source of mitochondrial NADPH[46]. The NADPH/$NADP^+$ couple supplies electrons to keep mitochondrial GSH pool in order to scavenge H_2O_2, a strong ROS[47]. In conclusion, redox signaling regulates metabolism while metabolic state influences redox signaling. The NAD^+/NADH redox couple is a critical node integrating metabolic and signaling events.

The redox signaling network linked to the NAD^+/NADH couple depends on the total mitochondrial NAD pools. NAD is a substrate for enzymes including the SIRT family, which continuously converts NAD^+ to nicotinamide. As NAD is degraded, cardiomyocytes must maintain a constant pool by de novo synthesis or recycle nicotinamide to replenish NAD. In cardiomyocytes, mitochondrial NAD pool is relatively high matching its critical role in mitochondrial Krebs cycle and ETC[48]. Pathological cardiac hypertrophy, the prerequisite of HF, is associated with a decrease in the cardiomyocyte NAD pool[49]. Similar observation was reported in diabetic cardiomyopathy, a model of HFpEF[50].

The oxidized form, NAD^+, is an electron acceptor in the redox reactions. Therefore, NAD^+ and NADH interconvert but are not irreversibly consumed. NAD^+ participates in all major energetic pathways including glycolysis, Krebs cycle, FA oxidation, ketone body metabolism, and ETC (Figure 2). NAD^+ is a potent activator of the Krebs cycle enzymes whereas NADH is a Krebs cycle allosteric inhibitor, and increases in ETC defects[45,51,52]. For example, Complex I[45] and IV[53] defects lead to increased mitochondrial NADH content. The

deficiency of frataxin, a mitochondrial protein integral to the assembly and function of iron-sulfur proteins in ETC complexes I, II and III and aconitase (Krebs cycle), is associated with an 85-fold decrease in cardiomyocyte NAD^+/NADH ratio and pathologic cardiac hypertrophy[52]. Approaches to correct mitochondrial ETC defects increased NAD^+ content[51]. In conclusion, the disruption of the electron flow to oxygen by ETC defects increases NADH causing a highly-reduced redox environment within mitochondria. The cardiac amount of the oxidized form, NAD^+, is reported reduced in HFrEF[54], and either unchanged[55] or altered[56] in HFpEF.

While NADH/NAD^+ redox ratio determines the production of mitochondrial ROS, the NADPH/NADP ratio is key to antioxidant defense. They are linked by the NNT enzyme that transfers electrons from NADH to $NADP^+$ (Figure 3).

Sirtuins (SIRTs) remove an acetyl group from lysine residues in an NAD^+-dependent manner by cleaving NAD^+ to nicotinamide[57], and are reported to prolong lifespan in mammals[58]. There are seven mammalian SIRTs that differ in their cellular localization. Although all SIRTs are NAD+-dependent, the extramitochondrial SIRT 1 and mitochondrial SIRT3 are well-known players in the heart. SIRT 1 protects against pathologic cardiac hypertrophy, and SIRT 1 knockout mice exhibit developmental cardiac defects[59]. Sustained SIRT 1 overexpression causes cardiomyopathy whereas moderate SIRT 1 expression ameliorates age-induced cardiac hypertrophy and dysfunction[60], suggesting its effect is dose-dependent. SIRT 1 also protects mitochondrial function by activating PGC-1a[61] to increase mitochondrial FA oxidation[62]. Overall, NAD^+, via SIRT 1, regulates pathological hypertrophy and mitochondrial metabolism.

SIRT3 is the major mitochondrial NAD^+-dependent deacetylase[63]. SIRT3 knockout causes cardiac hypertrophy and failure under stress[64] while overexpression protects against pathological hypertrophy via activating antioxidant mechanisms[65].

SIRT 1 and SIRT3 regulate bioenergetic metabolism during energetic crises. SIRT3-mediated deacetylation activates enzymes involved in glycolysis[66,67], FA oxidation[68-70], Krebs cycle cycle[71], and the ETC[72]. By upregulating metabolic machinery during states of decreased fuel availability, SIRT3 appears to be a critical metabolic regulator of coupling substrate oxidation with the formation of reducing equivalents to ATP production thus maximizing efficiency.

Energy deficit. There is a large variability regarding the reported mitochondrial ETC defects in HF. The causal relationship between these defects and the decrease in ATP has not been defined. For example, a severe murine complex I defect did not cause energy deficit[45] suggesting that in the murine heart ATP production is not directly related to complex I activity. In contrast, most studies report bioenergetic impairment in human subjects diagnosed with HF, which manifest as decrease in cardiac ATP, phosphocreatine (PCr)[73,74], or, most common, a decline in the pCr/ATP ratio[73,75,76].

THERAPEUTIC APPROACHES

Change the metabolic substrate preference

Metabolic inflexibility with an excessive increase in FA oxidation seems detrimental in HFpEF[77]. In this regard, the β-adrenergic receptor antagonist, carvedilol, used in HF to reduce cardiac workload and decrease oxygen consumption, also inhibited mitochondrial FA uptake, increased glucose oxidation and limited the infarct size after ischemia[78] indicating that balancing the metabolic health is beneficial for the heart.

Malonyl-CoA inhibits carnitine palmitoyltransferase (CPT)[1], the rate-limiting enzyme in mitochondrial FA uptake (Figure 2), and its amount is dependent on the balance between the synthesis via acetyl-CoA carboxylase and degradation via malonyl-CoA decarboxylase. Inhibiting malonyl-CoA decarboxylase in animal models improved ischemic-induced cardiac dysfunction, reduced cardiac FA oxidation, and increased the glycolytic flux[79]. Studies of malonyl-CoA decarboxylase inhibitors are yet to be performed in human patients with HF.

Due to the observed and possibly incomplete metabolic switch towards increased glucose use in both animal models and humans with HF, it is proposed that stimulating glucose oxidation may be an attractive therapeutic strategy to compensate for the energetically 'starved' failing heart[80]. Ketone body metabolism is altered in HF. There is an increased ketone utilization in the severely failing heart in humans[81,82]. Further research is needed to understand the role of ketone oxidation in the failing heart, and to determine whether targeting ketone metabolism is an efficient approach to improve energetics in HF.

Normalize the increased oxidative stress

Although the increased oxidative stress is an accepted pathogenic mechanism in HF, clinical trials yielded

negative results to support the long term role of ROS scavengers to alleviate HF[83,84]. The lack of long-term benefits may be related to the inability to reach effective therapeutic doses to stoichiometrically scavenge the ROS due to poor absorption, decreased cellular uptake or lack of strategy to match the ROS generation which is a continuous process. Mitochondrial targeted antioxidants have been tested on experimental models of cardiac disease and HF. For example, XJB-5-131, a mitochondria-targeted ROS scavenger is reported to decrease ROS generation and maintain mitochondrial and cardiac functions in rats subjected to ischemia-reperfusion injury[85]. Similar effects were obtained with another mitochondrial antioxidant, MitoTEMPO[86]. The compound EUK-8, a mimetic of two major mitochondrial antioxidant enzymes (superoxide dismutase and catalase, Figure 4), suppressed the progression of cardiac dysfunction and diminished ROS production and oxidative damage in dilated cardiomyopathy in mice[87]. These compounds are yet to be tested in human subjects with HF.

Mitochondrial redox therapy

As cardiac[54] and circulating[88] NAD pool are reported decreased in HF, NAD-boosting strategies are expected to be beneficial to the cardiac metabolic health. For example, the food supplementation with nicotinamide riboside, the most energy efficient NAD precursor was found beneficial in a murine model of dilated cardiomyopathy and transverse aorta constriction by stabilizing myocardial NAD^+ levels in the failing heart[89]. The oral supplementation with nicotinamide riboside in patients with advanced HF decreased systemic inflammation by normalizing mitochondrial function in peripheral blood mononuclear cells[90]. Elevating the NAD level suppressed mitochondrial protein hyperacetylation and cardiac hypertrophy, and improved cardiac function in responses to stresses[91].

NAD^+-dependent SIRTs have been investigated as therapeutic targets in HFpEF induced by diabetes. For example, resveratrol, a polyphenol and well-known SIRT 1 activator, alleviated diabetic cardiomyopathy via activating SIRT 1, 2, 3 and 5[92,93], improved glucose metabolism in human subjects[94,95] and decreased oxidative stress in cultured cardiomyocytes[96]. In a rodent model of genetic obesity, resveratrol decreased cardiac fibrosis and improved FA metabolism[97].

In the mitochondrial ETC, electrons are passed from donors to acceptors according to their redox potential. As ETC defects delay or reverse the electron transport, providing alternative paths for electron transport, which bypass the ETC defect, rescued mitochondrial function in ETC defects. For example, methylene blue (MB), an FDA approved pharmacological drug used to treat various ailments in human subjects[98-109] and rodents[110-114], may provide such an electron route. MB has a low redox potential that allows the compound to receive electrons from complex I[114-116] and become reduced (MBH2) while being able to be re-oxidized by cytochrome c back to MB[114,117]. Therefore, MB is protective because it helps the electrons to bypass the complex I and III defects and still maintain oxidative phosphorylation (Figure 5). We recently reported that MB protected retinal photoreceptors in a murine model of mitochondrial complex I defect[118], and improved cardiac function by shifting electron away from NADH in diabetic cardiomyopathy, a model of HFpEF[119].

Increase the efficiency of the electron transport within the mitochondrial ETC

Coenzyme Q (CoQ) pool is composed by two redox coenzymes, the reduced uniquinol and the oxidized ubiquinone. CoQ is endogenously synthesized, converted to ubiquinol by two-electron reduction from energetic substrates fed into complexes I and II (i.e., pyrucate, acetylCoA), which is then oxidized back to ubiquinone by donating electrons to complex III (Figure 2). Incomplete, one-electron reduction of CoQ produces semiquinone, which is a highly reactive radical. An increase in the reduced CoQ pool (ubiquinol) causes a reverse electrons flow back to complex I resulting in ROS generation[120]. Circulating CoQ is decreased in patients with HF[121], which correlated with poor clinical outcome and increased mortality[122]. Q-SYMBIO clinical trial[123] revealed a reduction in mortality after 2 years of treatment with CoQ. Recently, CoQ analogues with more efficient penetrability into the mitochondria have been developed. The delivery to mitochondria was improved by novel quinone conjugates that are tethered to lipophilic, cationic triphenyl-phosphonium moieties, such as MitoQ and SkQ[124], which have proved efficient in experimental models of HF[125]. The administration of idebenone, a short-chain synthetic CoQ analogue[126], has had promising benefits in small clinical trial of genetic mitochondrial defects[127] and HF in experimental models[128] and human subjects[129].

Protection of cardiolipin

Cardiolipin is decreased of oxidized in HF. Maintaining the amount and integrity of cardiolipin may be an efficient therapeutic approach to improve mitochondrial

bioenergetics in HF. The cell-permeable tetrapeptide MTP-131 (Bendavia or Elamipretide) localizes to the mitochondrial inner membrane[130], protects against cardiolipin oxidation and improves mitochondrial function[131,132]. MTP-131 reduced pathologic hypertrophy and cardiac remodeling, and improved mitochondrial and cardiac function in murine[133-135], porcine[136] and canine[137] models of HF. In human subjects with HFrEF, elamipretide is safe and well tolerated, and improved left ventricular function[138].

Calcium homeostasis

Altered Ca^{2+} homeostasis leading to impaired excitation–contraction coupling occurs in many types of HF[139]. Mitochondria are critical in regulating cardiomyocyte calcium dynamics because all membrane-bound Ca^{2+} pumps are ATP- dependent. In the myocardium, Ca^{2+} necessary for the cross-bridge actin-myosin cycles derives mostly from the extracellular space via the voltage-dependent Ca^{2+} channels with a lower contribution from the sarcoplasmic reticulum (SR) via the SR Ca^{2+} release channels, also called ryanodine receptors. Diastolic relaxation depends upon the Ca^{2+} sequestration within the SR via the SR Ca^{2+} ATPase (SERCA2a) and expulsion out of cardiomyocyte versus a Ca^{2+} pump and Na-Ca exchanger.

HFpEF is defined by impaired diastolic relaxation. Increasing the duration of the diastole by decreasing heart rate led to modest benefits in patients with HFpEF[140] potentially by providing more time for Ca^{2+} to move to the SR via SERCA2a. However, SERCA2a is reported downregulated in HF[141], and SERCA2a overexpression improved cardiac function in experimental models of HF[142,143]. Gene therapy through infusion of adeno-associated virus 1/SERCA2a in patients with HFrEF did not improved the clinical course[144] suggesting that it is the SERCA2a ATP-dependent activity rather than amount that is impaired in human HF.

CONCLUSION

Heart failure is the unfortunate outcome of many cardiac diseases. Disregarding the etiology, bioenergetic collapse is reported by most studies in human HF. Before the heart becomes an energy starved organ, cardiac tissue suffers multiple consequences induced by mitochondrial defects including increased oxidative stress and changes in the redox status, both detrimental to the contractile apparatus and leading to poor mechanics. Research conducted on experimental models of HF have contributed to our understanding of multiple aspects of bioenergetic impairment, and are used to discover novel therapeutic targets and mitochondrial modulator to mitigate HF.

Compliance with ethics requirements:

The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

Financial support: This research has been funded by Central Michigan University College of Medicine and American Heart Association Institutional Research Enhancement Award.

References

1. Ziaeian B and Fonarow GC. Epidemiology and aetiology of heart failure. Nat Rev Cardiol. 2016;13:368-78.
2. Brown DA, Perry JB, Allen ME, Sabbah HN, Stauffer BL, Shaikh SR, Cleland JG, Colucci WS, Butler J, Voors AA, Anker SD, Pitt B, Pieske B, Filippatos G, Greene SJ and Gheorghiade M. Expert consensus document: Mitochondrial function as a therapeutic target in heart failure. Nat Rev Cardiol. 2017;14:238-250.
3. Writing Group M, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jimenez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER, 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB, American Heart Association Statistics C and Stroke Statistics S. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation. 2016;133:e38-360.
4. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Alexandru Popescu B, Waggoner AD, Houston T, Oslo N, Phoenix A, Nashville T, Hamilton OC, Uppsala S, Ghent, Liege B, Cleveland O, Novara I, Rochester M, Bucharest R and St. Louis M. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016;17:1321-1360.
5. De Jong KA and Lopaschuk GD. Complex Energy Metabolic Changes in Heart Failure With Preserved Ejection Fraction and Heart Failure With Reduced Ejection Fraction. Can J Cardiol. 2017;33:860-871.
6. Stanley WC, Recchia FA and Lopaschuk GD. Myocardial substrate metabolism in the normal and failing heart. Physiol Rev. 2005;85:1093-129.
7. Barth AS, Kumordzie A, Frangakis C, Margulies KB, Cappola TP and Tomaselli GF. Reciprocal transcriptional regulation of metabolic and signaling pathways correlates with disease severity in heart failure. Circ Cardiovasc Genet. 2011;4:475-83.
8. Senni M, Gavazzi A, Gheorghiade M and Butler J. Heart failure at the crossroads: moving beyond blaming stakeholders to targeting the heart. Eur J Heart Fail. 2015;17:760-3.
9. Bayeva M, Sawicki KT and Ardehali H. Taking diabetes to heart—deregulation of myocardial lipid metabolism in diabetic cardiomyopathy. Journal of the American Heart Association. 2013;2:e000433.
10. Puchalska P and Crawford PA. Multi-dimensional Roles of Ketone Bodies in Fuel Metabolism, Signaling, and Therapeutics. Cell metabolism. 2017;25:262-284.

11. Abel ED. Glucose transport in the heart. Front Biosci. 2004;9:201-15.
12. Kerner J and Hoppel C. Fatty acid import into mitochondria. Biochim Biophys Acta. 2000;1486:1-17.
13. Cook GA, Lavrentyev EN, Pham K and Park EA. Streptozotocin diabetes increases mRNA expression of ketogenic enzymes in the rat heart. Biochimica et biophysica acta. 2017;1861:307-312.
14. Sun W, Quan N, Wang L, Yang H, Chu D, Liu Q, Zhao X, Leng J and Li J. Cardiac-Specific Deletion of the Pdha1 Gene Sensitizes Heart to Toxicological Actions of Ischemic Stress. Toxicol Sci. 2016;153:411.
15. Abel ED, Kaulbach HC, Tian R, Hopkins JC, Duffy J, Doetschman T, Minnemann T, Boers ME, Hadro E, Oberste-Berghaus C, Quist W, Lowell BB, Ingwall JS and Kahn BB. Cardiac hypertrophy with preserved contractile function after selective deletion of GLUT4 from the heart. The Journal of clinical investigation. 1999;104:1703-14.
16. Anderson EJ, Kypson AP, Rodriguez E, Anderson CA, Lehr EJ and Neufer PD. Substrate-specific derangements in mitochondrial metabolism and redox balance in the atrium of the type 2 diabetic human heart. J Am Coll Cardiol. 2009;54:1891-8.
17. Anderson EJ, Lustig ME, Boyle KE, Woodlief TL, Kane DA, Lin CT, Price JW, 3rd, Kang L, Rabinovitch PS, Szeto HH, Houmard JA, Cortright RN, Wasserman DH and Neufer PD. Mitochondrial H2O2 emission and cellular redox state link excess fat intake to insulin resistance in both rodents and humans. J Clin Invest. 2009;119:573-81.
18. Aon MA, Tocchetti CG, Bhatt N, Paolocci N and Cortassa S. Protective mechanisms of mitochondria and heart function in diabetes. Antioxid Redox Signal. 2015;22:1563-86.
19. Bayeva M, Sawicki KT and Ardehali H. Taking diabetes to heart--deregulation of myocardial lipid metabolism in diabetic cardiomyopathy. J Am Heart Assoc. 2013;2:e000433.
20. Rosca MG, Tandler B and Hoppel CL. Mitochondria in cardiac hypertrophy and heart failure. J Mol Cell Cardiol. 2013;55:31-41.
21. Rosca MG and Hoppel CL. Mitochondrial dysfunction in heart failure. Heart Fail Rev. 2013;18:607-22.
22. Lai L, Leone TC, Zechner C, Schaeffer PJ, Kelly SM, Flanagan DP, Medeiros DM, Kovacs A and Kelly DP. Transcriptional coactivators PGC-1alpha and PGC-lbeta control overlapping programs required for perinatal maturation of the heart. Genes Dev. 2008;22:1948-61.
23. Lehman JJ, Barger PM, Kovacs A, Saffitz JE, Medeiros DM and Kelly DP. Peroxisome proliferator-activated receptor gamma coactivator-1 promotes cardiac mitochondrial biogenesis. J Clin Invest. 2000;106:847-56.
24. Sack MN, Rader TA, Park S, Bastin J, McCune SA and Kelly DP. Fatty acid oxidation enzyme gene expression is downregulated in the failing heart. Circulation. 1996;94:2837-42.
25. Sihag S, Cresci S, Li AY, Sucharov CC and Lehman JJ. PGC-1alpha and ERRalpha target gene downregulation is a signature of the failing human heart. J Mol Cell Cardiol. 2009;46:201-12.
26. Goikoetxea MJ, Beaumont J, Gonzalez A, Lopez B, Querejeta R, Larman M and Diez J. Altered cardiac expression of peroxisome proliferator-activated receptor-isoforms in patients with hypertensive heart disease. Cardiovasc Res. 2006;69:899-907.
27. Lapuente-Brun E, Moreno-Loshuertos R, Acin-Perez R, Latorre-Pellicer A, Colas C, Balsa E, Perales-Clemente E, Quiros PM, Calvo E, Rodriguez-Hernandez MA, Navas P, Cruz R, Carracedo A, Lopez-Otin C, Perez-Martos A, Fernandez-Silva P, Fernandez-Vizarra E and Enriquez JA. Supercomplex assembly determines electron flux in the mitochondrial electron transport chain. Science. 2013;340:1567-70.
28. Rosca MG, Vazquez EJ, Kerner J, Parland W, Chandler MP, Stanley W, Sabbah HN and Hoppel CL. Cardiac mitochondria in heart failure: decrease in respirasomes and oxidative phosphorylation. Cardiovasc Res. 2008;80:30-9.
29. Rosca M, Minkler P and Hoppel CL. Cardiac mitochondria in heart failure: normal cardiolipin profile and increased threonine phosphorylation of complex IV. Biochim Biophys Acta. 2011;1807:1373-82.
30. Pfeiffer K, Gohil V, Stuart RA, Hunte C, Brandt U, Greenberg ML and Schagger H. Cardiolipin stabilizes respiratory chain supercomplexes. J Biol Chem. 2003;278:52873-80.
31. McKenzie M, Lazarou M, Thorburn DR and Ryan MT. Mitochondrial respiratory chain supercomplexes are destabilized in Barth Syndrome patients. J Mol Biol. 2006;361:462-9.
32. Lesnefsky EJ, Chen Q, Slabe TJ, Stoll MS, Minkler PE, Hassan MO, Tandler B and Hoppel CL. Ischemia, rather than reperfusion, inhibits respiration through cytochrome oxidase in the isolated, perfused rabbit heart: role of cardiolipin. Am J Physiol Heart Circ Physiol. 2004;287:H258-67.
33. Sparagna GC, Chicco AJ, Murphy RC, Bristow MR, Johnson CA, Rees ML, Maxey ML, McCune SA and Moore RL. Loss of cardiac tetralinoleoyl cardiolipin in human and experimental heart failure. J Lipid Res. 2007;48:1559-70.
34. Chatfield KC, Sparagna GC, Sucharov CC, Miyamoto SD, Grudis JE, Sobus RD, Hijmans J and Stauffer BL. Dysregulation of cardiolipin biosynthesis in pediatric heart failure. J Mol Cell Cardiol. 2014;74:251-9.
35. Saini-Chohan HK, Holmes MG, Chicco AJ, Taylor WA, Moore RL, McCune SA, Hickson-Bick DL, Hatch GM and Sparagna GC. Cardiolipin biosynthesis and remodeling enzymes are altered during development of heart failure. J Lipid Res. 2009;50:1600-8.
36. Korshunov SS, Skulachev VP and Starkov AA. High protonic potential actuates a mechanism of production of reactive oxygen species in mitochondria. FEBS Lett. 1997;416:15-8.
37. Frasier CR, Moore RL and Brown DA. Exercise-induced cardiac preconditioning: how exercise protects your achy-breaky heart. J Appl Physiol (1985). 2011;111:905-15.
38. Marshall KD, Muller BN, Krenz M, Hanft LM, McDonald KS, Dellsperger KC and Emter CA. Heart failure with preserved ejection fraction: chronic low-intensity interval exercise training preserves myocardial O2 balance and diastolic function. J Appl Physiol (1985). 2013;114:131-47.
39. Flynn KE, Pina IL, Whellan DJ, Lin L, Blumenthal JA, Ellis SJ, Fine LJ, Howlett JG, Keteyian SJ, Kitzman DW, Kraus WE, Miller NH, Schulman KA, Spertus JA, O'Connor CM, Weinfurt KP and Investigators H-A. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA. 2009;301:1451-9.
40. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Pina IL and Investigators H-A. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA. 2009;301:1439-50.
41. Edelmann F, Gelbrich G, Dungen HD, Frohling S, Wachter R, Stahrenberg R, Binder L, Topper A, Lashki DJ, Schwarz S, Herrmann-Lingen C, Loffler M, Hasenfuss G, Halle M and Pieske B. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. J Am Coll Cardiol. 2011;58:1780-91.
42. Akhmedov AT, Rybin V and Marin-Garcia J. Mitochondrial oxidative metabolism and uncoupling proteins in the failing heart. Heart Fail Rev. 2015;20:227-49.
43. Brand MD. Uncoupling to survive? The role of mitochondrial inefficiency in ageing. Exp Gerontol. 2000;35:811-20.
44. Jones DP and Sies H. The Redox Code. Antioxidants & redox signaling. 2015;23:734-46.
45. Karamanlidis G, Lee CF, Garcia-Menendez L, Kolwicz SC, Jr., Suthammarak W, Gong G, Sedensky MM, Morgan PG, Wang W and Tian R. Mitochondrial complex I deficiency increases protein acetylation and accelerates heart failure. Cell Metab. 2013;18:239-50.
46. Ronchi JA, Francisco A, Passos LA, Figueira TR and Castilho RF. The Contribution of Nicotinamide Nucleotide Transhydrogenase to Peroxide Detoxification Is Dependent on the Respiratory State and Counterbalanced by Other Sources of NADPH in Liver Mitochondria. The Journal of biological chemistry. 2016;291:20173-87.
47. Rydstrom J. Mitochondrial NADPH, transhydrogenase and disease. Biochimica et biophysica acta. 2006;1757:721-6.
48. Alano CC, Tran A, Tao R, Ying W, Karliner JS and Swanson RA. Differences among cell types in NAD(+) compartmentalization: a comparison of neurons, astrocytes, and cardiac myocytes. Journal of neuroscience research. 2007;85:3378-85.

49. Pillai VB, Sundaresan NR, Kim G, Gupta M, Rajamohan SB, Pillai JB, Samant S, Ravindra PV, Isbatan A and Gupta MP. Exogenous NAD blocks cardiac hypertrophic response via activation of the SIRT3-LKB1-AMP-activated kinase pathway. The Journal of biological chemistry. 2010;285:3133-44.
50. Khanra R, Dewanjee S, T KD, Sahu R, Gangopadhyay M, De Feo V and Zia-Ul-Haq M. Abroma augusta L. (Malvaceae) leaf extract attenuates diabetes induced nephropathy and cardiomyopathy via inhibition of oxidative stress and inflammatory response. Journal of translational medicine. 2015;13:6.
51. Akie TE, Liu L, Nam M, Lei S and Cooper MP. OXPHOS-Mediated Induction of NAD+ Promotes Complete Oxidation of Fatty Acids and Interdicts Non-Alcoholic Fatty Liver Disease. PloS one. 2015;10:e0125617.
52. Wagner GR, Pride PM, Babbey CM and Payne RM. Friedreich's ataxia reveals a mechanism for coordinate regulation of oxidative metabolism via feedback inhibition of the SIRT3 deacetylase. Human molecular genetics. 2012;21:2688-97.
53. Sung HJ, Ma W, Wang PY, Hynes J, O'Riordan TC, Combs CA, McCoy JP, Jr., Bunz F, Kang JG and Hwang PM. Mitochondrial respiration protects against oxygen-associated DNA damage. Nature communications. 2010;1:5.
54. Horton JL, Martin OJ, Lai L, Riley NM, Richards AL, Vega RB, Leone TC, Pagliarini DJ, Muoio DM, Bedi KC, Jr., Margulies KB, Coon JJ and Kelly DP. Mitochondrial protein hyperacetylation in the failing heart. JCI insight. 2016;2.
55. Kouzu H, Miki T, Tanno M, Kuno A, Yano T, Itoh T, Sato T, Sunaga D, Murase H, Tobisawa T, Ogasawara M, Ishikawa S and Miura T. Excessive degradation of adenine nucleotides by up-regulated AMP deaminase underlies afterload-induced diastolic dysfunction in the type 2 diabetic heart. Journal of molecular and cellular cardiology. 2015;80:136-45.
56. Bhatt NM, Aon MA, Tocchetti CG, Shen X, Dey S, Ramirez-Correa G, O'Rourke B, Gao WD and Cortassa S. Restoring redox balance enhances contractility in heart trabeculae from type 2 diabetic rats exposed to high glucose. American journal of physiology Heart and circulatory physiology. 2015;308:H291-302.
57. Imai S, Armstrong CM, Kaeberlein M and Guarente L. Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase. Nature. 2000;403:795-800.
58. Satoh A, Brace CS, Rensing N, Cliften P, Wozniak DF, Herzog ED, Yamada KA and Imai S. SIRT 1 extends life span and delays aging in mice through the regulation of Nk2 homeobox 1 in the DMH and LH. Cell metabolism. 2013;18:416-30.
59. Cheng HL, Mostoslavsky R, Saito S, Manis JP, Gu Y, Patel P, Bronson R, Appella E, Alt FW and Chua KF. Developmental defects and p53 hyperacetylation in Sir2 homolog (SIRT 1)-deficient mice. Proceedings of the National Academy of Sciences of the United States of America. 2003;100:10794-9.
60. Alcendor RR, Gao S, Zhai P, Zablocki D, Holle E, Yu X, Tian B, Wagner T, Vatner SF and Sadoshima J. SIRT 1 regulates aging and resistance to oxidative stress in the heart. Circulation research. 2007;100:1512-21.
61. Nemoto S, Fergusson MM and Finkel T. SIRT 1 functionally interacts with the metabolic regulator and transcriptional coactivator PGC-1{alpha}. The Journal of biological chemistry. 2005;280:16456-60.
62. Gerhart-Hines Z, Rodgers JT, Bare O, Lerin C, Kim SH, Mostoslavsky R, Alt FW, Wu Z and Puigserver P. Metabolic control of muscle mitochondrial function and fatty acid oxidation through SIRT 1/PGC-1alpha. The EMBO journal. 2007;26:1913-23.
63. Lombard DB, Alt FW, Cheng HL, Bunkenborg J, Streeper RS, Mostoslavsky R, Kim J, Yancopoulos G, Valenzuela D, Murphy A, Yang Y, Chen Y, Hirschey MD, Bronson RT, Haigis M, Guarente LP, Farese RV, Jr., Weissman S, Verdin E and Schwer B. Mammalian Sir2 homolog SIRT3 regulates global mitochondrial lysine acetylation. Molecular and cellular biology. 2007;27:8807-14.
64. Koentges C, Pfeil K, Schnick T, Wiese S, Dahlbock R, Cimolai MC, Meyer-Steenbuck M, Cenkerova K, Hoffmann MM, Jaeger C, Odening KE, Kammerer B, Hein L, Bode C and Bugger H. SIRT3 deficiency impairs mitochondrial and contractile function in the heart. Basic research in cardiology. 2015;110:36.
65. Sundaresan NR, Gupta M, Kim G, Rajamohan SB, Isbatan A and Gupta MP. Sirt3 blocks the cardiac hypertrophic response by augmenting Foxo3a-dependent antioxidant defense mechanisms in mice. The Journal of clinical investigation. 2009;119:2758-71.
66. Jing E, O'Neill BT, Rardin MJ, Kleinridders A, Ilkeyeva OR, Ussar S, Bain JR, Lee KY, Verdin EM, Newgard CB, Gibson BW and Kahn CR. Sirt3 regulates metabolic flexibility of skeletal muscle through reversible enzymatic deacetylation. Diabetes. 2013;62:3404-17.
67. Ozden O, Park SH, Wagner BA, Yong Song H, Zhu Y, Vassilopoulos A, Jung B, Buettner GR and Gius D. SIRT3 deacetylates and increases pyruvate dehydrogenase activity in cancer cells. Free radical biology & medicine. 2014;76:163-72.
68. Hirschey MD, Shimazu T, Goetzman E, Jing E, Schwer B, Lombard DB, Grueter CA, Harris C, Biddinger S, Ilkayeva OR, Stevens RD, Li Y, Saha AK, Ruderman NB, Bain JR, Newgard CB, Farese RV, Jr., Alt FW, Kahn CR and Verdin E. SIRT3 regulates mitochondrial fatty-acid oxidation by reversible enzyme deacetylation. Nature. 2010;464:121-5.
69. Hirschey MD, Shimazu T, Jing E, Grueter CA, Collins AM, Aouizerat B, Stancakova A, Goetzman E, Lam MM, Schwer B, Stevens RD, Muehlbauer MJ, Kakar S, Bass NM, Kuusisto J, Laakso M, Alt FW, Newgard CB, Farese RV, Jr., Kahn CR and Verdin E. SIRT3 deficiency and mitochondrial protein hyperacetylation accelerate the development of the metabolic syndrome. Molecular cell. 2011;44:177-90.
70. Bharathi SS, Zhang Y, Mohsen AW, Uppala R, Balasubramani M, Schreiber E, Uechi G, Beck ME, Rardin MJ, Vockley J, Verdin E, Gibson BW, Hirschey MD and Goetzman ES. Sirtuin 3 (SIRT3) protein regulates long-chain acyl-CoA dehydrogenase by deacetylating conserved lysines near the active site. The Journal of biological chemistry. 2013;288:33837-47.
71. Someya S, Yu W, Hallows WC, Xu J, Vann JM, Leeuwenburgh C, Tanokura M, Denu JM and Prolla TA. Sirt3 mediates reduction of oxidative damage and prevention of age-related hearing loss under caloric restriction. Cell. 2010;143:802-12.
72. Ahn BH, Kim HS, Song S, Lee IH, Liu J, Vassilopoulos A, Deng CX and Finkel T. A role for the mitochondrial deacetylase Sirt3 in regulating energy homeostasis. Proceedings of the National Academy of Sciences of the United States of America. 2008;105:14447-52.
73. Smith CS, Bottomley PA, Schulman SP, Gerstenblith G and Weiss RG. Altered creatine kinase adenosine triphosphate kinetics in failing hypertrophied human myocardium. Circulation. 2006;114:1151-8.
74. Weiss RG, Gerstenblith G and Bottomley PA. ATP flux through creatine kinase in the normal, stressed, and failing human heart. Proc Natl Acad Sci U S A. 2005;102:808-13.
75. Phan TT, Abozguia K, Nallur Shivu G, Mahadevan G, Ahmed I, Williams L, Dwivedi G, Patel K, Steendijk P, Ashrafian H, Henning A and Frenneaux M. Heart failure with preserved ejection fraction is characterized by dynamic impairment of active relaxation and contraction of the left ventricle on exercise and associated with myocardial energy deficiency. J Am Coll Cardiol. 2009;54:402-9.
76. Esposito A, De Cobelli F, Perseghin G, Pieroni M, Belloni E, Mellone R, Canu T, Gentinetta F, Scifo P, Chimenti C, Frustaci A, Luzi L, Maseri A and Maschio AD. Impaired left ventricular energy metabolism in patients with hypertrophic cardiomyopathy is related to the extension of fibrosis at delayed gadolinium-enhanced magnetic resonance imaging. Heart. 2009;95:228-33.
77. Berthiaume JM, Kurdys JG, Muntean DM and Rosca MG. Mitochondrial NAD(+)/NADH Redox State and Diabetic Cardiomyopathy. Antioxid Redox Signal. 2019;30:375-398.
78. Igarashi N, Nozawa T, Fujii N, Suzuki T, Matsuki A, Nakadate T, Igawa A and Inoue H. Influence of beta-adrenoceptor blockade on the myocardial accumulation of fatty acid tracer and its intracellular metabolism in the heart after ischemia-reperfusion injury. Circ J. 2006;70:1509-14.
79. Stanley WC, Morgan EE, Huang H, McElfresh TA, Sterk JP, Okere IC, Chandler MP, Cheng J, Dyck JR and Lopaschuk GD. Malonyl-CoA decarboxylase inhibition suppresses fatty acid oxidation and reduces

lactate production during demand-induced ischemia. Am J Physiol Heart Circ Physiol. 2005;289:H2304-9.
80. Fukushima A, Milner K, Gupta A and Lopaschuk GD. Myocardial Energy Substrate Metabolism in Heart Failure : from Pathways to Therapeutic Targets. Curr Pharm Des. 2015;21:3654-64.
81. Kolwicz SC, Jr., Airhart S and Tian R. Ketones Step to the Plate: A Game Changer for Metabolic Remodeling in Heart Failure? Circulation. 2016;133:689-91.
82. Bedi KC, Jr., Snyder NW, Brandimarto J, Aziz M, Mesaros C, Worth AJ, Wang LL, Javaheri A, Blair IA, Margulies KB and Rame JE. Evidence for Intramyocardial Disruption of Lipid Metabolism and Increased Myocardial Ketone Utilization in Advanced Human Heart Failure. Circulation. 2016;133:706-16.
83. Heart Outcomes Prevention Evaluation Study I, Yusuf S, Dagenais G, Pogue J, Bosch J and Sleight P. Vitamin E supplementation and cardiovascular events in high-risk patients. N Engl J Med. 2000;342:154-60.
84. Downey JM and Cohen MV. Why do we still not have cardioprotective drugs? Circ J. 2009;73:1171-7.
85. Escobales N, Nunez RE, Jang S, Parodi-Rullan R, Ayala-Pena S, Sacher JR, Skoda EM, Wipf P, Frontera W and Javadov S. Mitochondria-targeted ROS scavenger improves post-ischemic recovery of cardiac function and attenuates mitochondrial abnormalities in aged rats. J Mol Cell Cardiol. 2014;77:136-46.
86. Liang HL, Sedlic F, Bosnjak Z and Nilakantan V. SOD1 and Mito-TEMPO partially prevent mitochondrial permeability transition pore opening, necrosis, and mitochondrial apoptosis after ATP depletion recovery. Free Radic Biol Med. 2010;49:1550-60.
87. Kawakami S, Matsuda A, Sunagawa T, Noda Y, Kaneko T, Tahara S, Hiraumi Y, Adachi S, Matsui H, Ando K, Fujita T, Maruyama N, Shirasawa T and Shimizu T. Antioxidant, EUK-8, prevents murine dilated cardiomyopathy. Circ J. 2009;73:2125-34.
88. Breton M, Costemale-Lacoste JF, Li Z, Lafuente-Lafuente C, Belmin J and Mericskay M. Blood NAD levels are reduced in very old patients hospitalized for heart failure. Exp Gerontol. 2020;139:111051.
89. Diguet N, Trammell SAJ, Tannous C, Deloux R, Piquereau J, Mougenot N, Gouge A, Gressette M, Manoury B, Blanc J, Breton M, Decaux JF, Lavery GG, Baczko I, Zoll J, Garnier A, Li Z, Brenner C and Mericskay M. Nicotinamide Riboside Preserves Cardiac Function in a Mouse Model of Dilated Cardiomyopathy. Circulation. 2018;137:2256-2273.
90. Zhou B, Wang DD, Qiu Y, Airhart S, Liu Y, Stempien-Otero A, O'Brien KD and Tian R. Boosting NAD level suppresses inflammatory activation of PBMCs in heart failure. J Clin Invest. 2020;130:6054-6063.
91. Lee CF, Chavez JD, Garcia-Menendez L, Choi Y, Roe ND, Chiao YA, Edgar JS, Goo YA, Goodlett DR, Bruce JE and Tian R. Normalization of NAD+ Redox Balance as a Therapy for Heart Failure. Circulation. 2016;134:883-94.
92. Bagul PK, Dinda AK and Banerjee SK. Effect of resveratrol on sirtuins expression and cardiac complications in diabetes. Biochemical and biophysical research communications. 2015;468:221-7.
93. Bagul PK, Deepthi N, Sultana R and Banerjee SK. Resveratrol ameliorates cardiac oxidative stress in diabetes through deacetylation of NFkB-p65 and histone 3. The Journal of nutritional biochemistry. 2015;26:1298-307.
94. Bhatt JK, Thomas S and Nanjan MJ. Resveratrol supplementation improves glycemic control in type 2 diabetes mellitus. Nutrition research. 2012;32:537-41.
95. Liu K, Zhou R, Wang B and Mi MT. Effect of resveratrol on glucose control and insulin sensitivity: a meta-analysis of 11 randomized controlled trials. The American journal of clinical nutrition. 2014;99:1510-9.
96. Tanno M, Kuno A, Yano T, Miura T, Hisahara S, Ishikawa S, Shimamoto K and Horio Y. Induction of manganese superoxide dismutase by nuclear translocation and activation of SIRT 1 promotes cell survival in chronic heart failure. The Journal of biological chemistry. 2010;285:8375-82.
97. Beaudoin MS, Perry CG, Arkell AM, Chabowski A, Simpson JA, Wright DC and Holloway GP. Impairments in mitochondrial palmitoyl-CoA respiratory kinetics that precede development of diabetic cardiomyopathy are prevented by resveratrol in ZDF rats. The Journal of physiology. 2014;592:2519-33.
98. Visarius TM, Stucki JW and Lauterburg BH. Inhibition and stimulation of long-chain fatty acid oxidation by chloroacetaldehyde and methylene blue in rats. The Journal of pharmacology and experimental therapeutics. 1999;289:820-4.
99. Callaway NL, Riha PD, Bruchey AK, Munshi Z and Gonzalez-Lima F. Methylene blue improves brain oxidative metabolism and memory retention in rats. Pharmacology, biochemistry, and behavior. 2004;77:175-81.
100. Callaway NL, Riha PD, Wrubel KM, McCollum D and Gonzalez-Lima F. Methylene blue restores spatial memory retention impaired by an inhibitor of cytochrome oxidase in rats. Neuroscience letters. 2002;332:83-6.
101. Furian AF, Fighera MR, Oliveira MS, Ferreira AP, Fiorenza NG, de Carvalho Myskiw J, Petry JC, Coelho RC, Mello CF and Royes LF. Methylene blue prevents methylmalonate-induced seizures and oxidative damage in rat striatum. Neurochemistry international. 2007;50:164-71.
102. Kwok ES and Howes D. Use of methylene blue in sepsis: a systematic review. Journal of intensive care medicine. 2006;21:359-63.
103. Clifton J, 2nd and Leikin JB. Methylene blue. American journal of therapeutics. 2003;10:289-91.
104. Demirbilek S, Sizanli E, Karadag N, Karaman A, Bayraktar N, Turkmen E and Ersoy MO. The effects of methylene blue on lung injury in septic rats. European surgical research Europaische chirurgische Forschung. 2006;38:35-41.
105. Riedel W, Lang U, Oetjen U, Schlapp U and Shibata M. Inhibition of oxygen radical formation by methylene blue, aspirin, or alpha-lipoic acid, prevents bacterial-lipopolysaccharide-induced fever. Molecular and cellular biochemistry. 2003;247:83-94.
106. Rezzani R, Rodella L, Corsetti G and Bianchi R. Does methylene blue protect the kidney tissues from damage induced by ciclosporin A treatment? Nephron. 2001;89:329-36.
107. Hrushesky WJ, Olshefski R, Wood P, Meshnick S and Eaton JW. Modifying intracellular redox balance: an approach to improving therapeutic index. Lancet. 1985;1:565-7.
108. Haluzik M, Nedvidkova J and Skrha J. Treatment with the NO-synthase inhibitor, methylene blue, moderates the decrease in serum leptin concentration in streptozotocin-induced diabetes. Endocrine research. 1999;25:163-71.
109. Salaris SC, Babbs CF and Voorhees WD, 3rd. Methylene blue as an inhibitor of superoxide generation by xanthine oxidase. A potential new drug for the attenuation of ischemia/reperfusion injury. Biochemical pharmacology. 1991;42:499-506.
110. Rojas JC, John JM, Lee J and Gonzalez-Lima F. Methylene blue provides behavioral and metabolic neuroprotection against optic neuropathy. Neurotoxicity research. 2009;15:260-73.
111. Miclescu A, Basu S and Wiklund L. Methylene blue added to a hypertonic-hyperoncotic solution increases short-term survival in experimental cardiac arrest. Critical care medicine. 2006;34:2806-13.
112. Medina DX, Caccamo A and Oddo S. Methylene blue reduces abeta levels and rescues early cognitive deficit by increasing proteasome activity. Brain pathology (Zurich, Switzerland). 21:140-9.
113. O'Leary JC, 3rd, Li Q, Marinec P, Blair LJ, Congdon EE, Johnson AG, Jinwal UK, Koren J, 3rd, Jones JR, Kraft C, Peters M, Abisambra JF, Duff KE, Weeber EJ, Gestwicki JE and Dickey CA. Phenothiazine-mediated rescue of cognition in tau transgenic mice requires neuroprotection and reduced soluble tau burden. Molecular neurodegeneration. 5:45.
114. Wen Y, Li W, Poteet EC, Xie L, Tan C, Yan LJ, Ju X, Liu R, Qian H, Marvin MA, Goldberg MS, She H, Mao Z, Simpkins JW and Yang SH. Alternative mitochondrial electron transfer as a novel strategy for neuroprotection. The Journal of biological chemistry. 286:16504-15.
115. Gabrielli D, Belisle E, Severino D, Kowaltowski AJ and Baptista MS. Binding, aggregation and photochemical properties of methylene blue in mitochondrial suspensions. Photochemistry and photobiology. 2004;79:227-32.

116. Mellish KJ, Cox RD, Vernon DI, Griffiths J and Brown SB. In vitro photodynamic activity of a series of methylene blue analogues. Photochemistry and photobiology. 2002;75:392-7.
117. Tretter L, Horvath G, Holgyesi A, Essek F and Adam-Vizi V. Enhanced hydrogen peroxide generation accompanies the beneficial bioenergetic effects of methylene blue in isolated brain mitochondria. Free radical biology & medicine. 2014;77:317-30.
118. Mekala NK, Kurdys J, Depuydt MM, Vazquez EJ and Rosca MG. Apoptosis inducing factor deficiency causes retinal photoreceptor degeneration. The protective role of the redox compound methylene blue. Redox Biol. 2019;20:107-117.
119. Berthiaume JM, Hsiung CH, Austin AB, McBrayer SP, Depuydt MM, Chandler MP, Miyagi M and Rosca MG. Methylene blue decreases mitochondrial lysine acetylation in the diabetic heart. Mol Cell Biochem. 2017;432:7-24.
120. Chouchani ET, Pell VR, Gaude E, Aksentijevic D, Sundier SY, Robb EL, Logan A, Nadtochiy SM, Ord ENJ, Smith AC, Eyassu F, Shirley R, Hu CH, Dare AJ, James AM, Rogatti S, Hartley RC, Eaton S, Costa ASH, Brookes PS, Davidson SM, Duchen MR, Saeb-Parsy K, Shattock MJ, Robinson AJ, Work LM, Frezza C, Krieg T and Murphy MP. Ischaemic accumulation of succinate controls reperfusion injury through mitochondrial ROS. Nature. 2014;515:431-435.
121. Molyneux SL, Florkowski CM, George PM, Pilbrow AP, Frampton CM, Lever M and Richards AM. Coenzyme Q10: an independent predictor of mortality in chronic heart failure. J Am Coll Cardiol. 2008;52:1435-41.
122. McMurray JJ, Dunselman P, Wedel H, Cleland JG, Lindberg M, Hjalmarson A, Kjekshus J, Waagstein F, Apetrei E, Barrios V, Bohm M, Kamensky G, Komajda M, Mareev V, Wikstrand J and Group CS. Coenzyme Q10, rosuvastatin, and clinical outcomes in heart failure: a pre-specified substudy of CORONA (controlled rosuvastatin multinational study in heart failure). J Am Coll Cardiol. 2010;56:1196-204.
123. Mortensen SA, Rosenfeldt F, Kumar A, Dolliner P, Filipiak KJ, Pella D, Alehagen U, Steurer G, Littarru GP and Investigators QSS. The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. JACC Heart Fail. 2014;2:641-9.
124. Murphy MP. Targeting lipophilic cations to mitochondria. Biochim Biophys Acta. 2008;1777:1028-31.
125. Graham D, Huynh NN, Hamilton CA, Beattie E, Smith RA, Cocheme HM, Murphy MP and Dominiczak AF. Mitochondria-targeted antioxidant MitoQ10 improves endothelial function and attenuates cardiac hypertrophy. Hypertension. 2009;54:322-8.
126. Jaber S and Polster BM. Idebenone and neuroprotection: antioxidant, pro-oxidant, or electron carrier? J Bioenerg Biomembr. 2015;47:111-8.
127. El-Hattab AW, Zarante AM, Almannai M and Scaglia F. Therapies for mitochondrial diseases and current clinical trials. Mol Genet Metab. 2017;122:1-9.
128. Buyse GM, Van der Mieren G, Erb M, D'Hooge J, Herijgers P, Verbeken E, Jara A, Van Den Bergh A, Mertens L, Courdier-Fruh I, Barzaghi P and Meier T. Long-term blinded placebo-controlled study of SNT-MC17/idebenone in the dystrophin deficient mdx mouse: cardiac protection and improved exercise performance. Eur Heart J. 2009;30:116-24.
129. Lerman-Sagie T, Rustin P, Lev D, Yanoov M, Leshinsky-Silver E, Sagie A, Ben-Gal T and Munnich A. Dramatic improvement in mitochondrial cardiomyopathy following treatment with idebenone. J Inherit Metab Dis. 2001;24:28-34.
130. Szeto HH. Mitochondria-targeted cytoprotective peptides for ischemia-reperfusion injury. Antioxid Redox Signal. 2008;10:601-19.
131. Szeto HH, Liu S, Soong Y, Wu D, Darrah SF, Cheng FY, Zhao Z, Ganger M, Tow CY and Seshan SV. Mitochondria-targeted peptide accelerates ATP recovery and reduces ischemic kidney injury. J Am Soc Nephrol. 2011;22:1041-52.
132. Birk AV, Liu S, Soong Y, Mills W, Singh P, Warren JD, Seshan SV, Pardee JD and Szeto HH. The mitochondrial-targeted compound SS-31 re-energizes ischemic mitochondria by interacting with cardiolipin. J Am Soc Nephrol. 2013;24:1250-61.
133. Dai DF, Chen T, Szeto H, Nieves-Cintron M, Kutyavin V, Santana LF and Rabinovitch PS. Mitochondrial targeted antioxidant Peptide ameliorates hypertensive cardiomyopathy. J Am Coll Cardiol. 2011;58:73-82.
134. Dai DF, Hsieh EJ, Chen T, Menendez LG, Basisty NB, Tsai L, Beyer RP, Crispin DA, Shulman NJ, Szeto HH, Tian R, MacCoss MJ and Rabinovitch PS. Global proteomics and pathway analysis of pressure-overload-induced heart failure and its attenuation by mitochondrial-targeted peptides. Circ Heart Fail. 2013;6:1067-76.
135. Shi J, Dai W, Hale SL, Brown DA, Wang M, Han X and Kloner RA. Bendavia restores mitochondrial energy metabolism gene expression and suppresses cardiac fibrosis in the border zone of the infarcted heart. Life Sci. 2015;141:170-8.
136. Eirin A, Williams BJ, Ebrahimi B, Zhang X, Crane JA, Lerman A, Textor SC and Lerman LO. Mitochondrial targeted peptides attenuate residual myocardial damage after reversal of experimental renovascular hypertension. J Hypertens. 2014;32:154-65.
137. Sabbah HN, Gupta RC, Kohli S, Wang M, Hachem S and Zhang K. Chronic Therapy With Elamipretide (MTP-131), a Novel Mitochondria-Targeting Peptide, Improves Left Ventricular and Mitochondrial Function in Dogs With Advanced Heart Failure. Circ Heart Fail. 2016;9:e002206.
138. Daubert MA, Yow E, Dunn G, Marchev S, Barnhart H, Douglas PS, O'Connor C, Goldstein S, Udelson JE and Sabbah HN. Novel Mitochondria-Targeting Peptide in Heart Failure Treatment: A Randomized, Placebo-Controlled Trial of Elamipretide. Circ Heart Fail. 2017;10.
139. Brown DA and O'Rourke B. Cardiac mitochondria and arrhythmias. Cardiovasc Res. 2010;88:241-9.
140. Kosmala W, Holland DJ, Rojek A, Wright L, Przewlocka-Kosmala M and Marwick TH. Effect of If-channel inhibition on hemodynamic status and exercise tolerance in heart failure with preserved ejection fraction: a randomized trial. J Am Coll Cardiol. 2013;62:1330-8.
141. Gorski PA, Ceholski DK and Hajjar RJ. Altered myocardial calcium cycling and energetics in heart failure--a rational approach for disease treatment. Cell Metab. 2015;21:183-194.
142. Gong HB, Wang L, Lv Q and Wang J. Improved systolic function of rat cardiocytes during heart failure by overexpression of SERCA2a. Eur Rev Med Pharmacol Sci. 2016;20:1590-6.
143. Mattila M, Koskenvuo J, Soderstrom M, Eerola K and Savontaus M. Intramyocardial injection of SERCA2a-expressing lentivirus improves myocardial function in doxorubicin-induced heart failure. J Gene Med. 2016;18:124-33.
144. Greenberg B, Butler J, Felker GM, Ponikowski P, Voors AA, Desai AS, Barnard D, Bouchard A, Jaski B, Lyon AR, Pogoda JM, Rudy JJ and Zsebo KM. Calcium upregulation by percutaneous administration of gene therapy in patients with cardiac disease (CUPID 2): a randomised, multinational, double-blind, placebo-controlled, phase 2b trial. Lancet. 2016;387:1178-86.