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Cardiac Lipid Metabolism, Mitochondrial Function, and Heart Failure: A Review Article

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ABSTRACT

The heart is a highly energy-demanding organ that depends mainly on fatty acid oxidation to maintain continuous contractile activity and ATP production. Under normal physiological conditions, cardiac lipid metabolism is tightly regulated through a balance between fatty acid uptake, storage, and mitochondrial oxidation. In heart failure, this metabolic balance becomes disrupted, resulting in altered substrate utilization, impaired mitochondrial function, and abnormal lipid accumulation. Excessive accumulation of lipid species, including triglycerides, diacylglycerols, ceramides, and cholesterol, can promote lipotoxicity, oxidative stress, mitochondrial dysfunction, and cardiomyocyte injury. These metabolic disturbances may contribute to impaired energy production, cardiac remodeling, and progressive deterioration of cardiac function. This review summarizes the major pathways of cardiac lipid metabolism and examines the role of mitochondrial regulation and lipid-induced toxicity in heart failure. Understanding these mechanisms may help clarify the contribution of metabolic dysfunction to heart failure progression and identify potential targets for metabolic-based therapeutic strategies

INTRODUCTION

Heart failure is a complex clinical condition in which the heart is unable to pump sufficient blood to meet the metabolic and functional demands of the body. Although heart failure is commonly described in terms of impaired cardiac contraction, relaxation, and structural remodeling, it is also associated with major changes in cellular metabolism. Cardiomyocytes require a continuous and highly efficient supply of energy because the heart contracts throughout life without significant interruption. To maintain this activity, cardiac cells must constantly produce ATP to support contraction, relaxation, ion transport, calcium handling, maintenance of membrane potential, and other essential cellular processes. Therefore, disturbances in cardiac energy metabolism can

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have a major impact on cardiac function and may contribute to the progression of heart failure.

Under normal physiological conditions, the heart has a high capacity to generate energy from different metabolic substrates. Fatty acids are an important source of energy and normally contribute a major proportion of ATP production through mitochondrial β-oxidation and oxidative phosphorylation. However, the heart is not completely dependent on fatty acids. Glucose, lactate, ketone bodies, and other substrates can also contribute to energy production depending on their availability and the physiological state of the heart. This ability to switch between different energy substrates is known as metabolic flexibility. It allows cardiomyocytes to adjust their metabolism according to changes in workload, hormonal signals, nutrient availability, and oxygen supply. Maintaining this flexibility is important for ensuring that ATP production remains matched to the continuously changing energy requirements of the heart.

In heart failure, this metabolic flexibility becomes disturbed. The normal balance between substrate uptake, storage, oxidation, and energy production may be altered. Changes in fatty acid uptake and oxidation can occur along with changes in glucose metabolism and mitochondrial activity. In some forms and stages of heart failure, fatty acid oxidation is reduced and glucose utilization becomes relatively more prominent. However, this metabolic shift does not necessarily improve energy production because the failing heart may also have impaired mitochondrial function and reduced oxidative capacity. As a result, the heart may become less efficient at converting available substrates into ATP despite having a very high energy demand.

Lipid metabolism is particularly important in this process because the heart continuously receives fatty acids from the circulation. Fatty acids can enter cardiomyocytes as free fatty acids or can be released from circulating lipoproteins through the action of lipoprotein lipase. After entering the cell, fatty acids may be transported into mitochondria for β-oxidation, incorporated into triglycerides for storage in lipid droplets, or used for other cellular functions. Under normal conditions, these pathways remain closely coordinated. The amount of lipid entering the cardiomyocyte is generally balanced by the amount being oxidized, stored, or otherwise metabolized. This balance prevents excessive accumulation of fatty acids and helps maintain a stable intracellular lipid environment.

During heart failure, however, this balance may become disrupted. Increased lipid delivery or uptake, together with impaired fatty acid oxidation, can result in a situation in which the amount of lipid entering the cardiomyocyte exceeds its capacity for utilization. Excess fatty acids may then be converted into triglycerides and stored within lipid droplets. Although triglyceride storage can initially serve as a protective mechanism by reducing exposure to free fatty acids, persistent lipid accumulation may indicate an underlying metabolic imbalance. When the capacity for safe storage is exceeded or lipid metabolism becomes abnormal, potentially harmful lipid intermediates such as diacylglycerols and ceramides may accumulate.

These abnormal lipid species can contribute to cardiac lipotoxicity, a process in which excessive lipid exposure causes cellular injury. Lipotoxicity can affect several important cellular pathways, including mitochondrial function, oxidative balance, intracellular signaling, and endoplasmic reticulum function. Excess saturated fatty acids may increase the production of reactive oxygen species (ROS), leading to oxidative stress. At the same time, lipid-induced mitochondrial dysfunction can reduce oxidative phosphorylation and ATP production. This creates an unfavorable cycle in which impaired mitochondrial function reduces the ability of cardiomyocytes to utilize

fatty acids efficiently, while continued lipid accumulation places additional stress on already dysfunctional mitochondria.

Mitochondria therefore represent an important connection between abnormal lipid metabolism and energy deficiency in heart failure. Healthy mitochondria are responsible for converting metabolic substrates into large amounts of ATP through oxidative phosphorylation. When mitochondrial function is impaired, ATP production may decrease and ROS production may increase. Mitochondrial dysfunction may also involve abnormal mitochondrial fission and fusion, reduced mitochondrial biogenesis, and impaired removal of damaged mitochondria. These changes further reduce the ability of cardiomyocytes to maintain an adequate and healthy mitochondrial population. As mitochondrial damage progresses, the energy deficit and oxidative stress can become increasingly severe.

Persistent lipid accumulation can also interfere with normal cellular signaling and calcium handling. Cardiomyocytes depend on precisely regulated calcium movements for contraction and relaxation, and these processes require considerable amounts of ATP. Changes in membrane lipid composition or accumulation of toxic lipid intermediates can interfere with ion channels, receptors, and intracellular signaling pathways. In addition, lipid overload may induce endoplasmic reticulum stress and activate cellular stress responses. If these responses persist for a prolonged period, they can contribute to inflammation, mitochondrial injury, and activation of pathways leading to cardiomyocyte death.

The loss of cardiomyocytes and persistent metabolic dysfunction can eventually contribute to structural and functional remodeling of the heart. Damaged or dying cardiomyocytes may reduce the contractile capacity of the myocardium, while chronic cellular stress can promote fibrosis, changes in ventricular structure, and further impairment of cardiac performance. This creates a reciprocal relationship between metabolic dysfunction and mechanical dysfunction: impaired cardiac function can worsen metabolic abnormalities, while metabolic abnormalities can further weaken cardiac function.

Thus, abnormal cardiac metabolism should not be considered merely a secondary consequence of heart failure. Changes in lipid uptake, fatty acid oxidation, lipid storage, mitochondrial function, and cellular stress pathways can actively contribute to the progression of cardiac dysfunction. The interaction between impaired energy production, lipid accumulation, lipotoxicity, oxidative stress, and mitochondrial injury creates a metabolic environment that can progressively damage cardiomyocytes. Understanding these interconnected mechanisms is therefore important for explaining how metabolic disturbances contribute to the development and progression of heart failure and may also help identify potential targets for metabolic and mitochondria-directed therapeutic strategies.

2. Cardiac Energy Metabolism

The heart requires a large amount of ATP because it contracts continuously throughout life. Most cardiac ATP, about 95%, is produced in the mitochondria through oxidative phosphorylation, while glycolysis provides a smaller amount of energy. Under normal conditions, the healthy heart is metabolically flexible and can use different energy sources according to their availability. Fatty acids are the main energy source, but glucose and other substrates can also be used when needed. In heart failure, this metabolic flexibility is reduced. The heart may increase its use of glucose while fatty acid oxidation decreases, although the exact changes depend on the type and stage of heart failure. These changes can reduce the

efficiency of energy production and contribute to an energy shortage in cardiomyocytes. At the same time, mitochondrial dysfunction can impair ATP production and disturb normal cellular metabolism.

Metabolic disturbances in the failing heart can also affect calcium handling and increase the production of reactive oxygen species (ROS). Excess ROS can cause oxidative stress and damage cellular proteins, membranes, and mitochondria. Together, reduced energy production, mitochondrial dysfunction, abnormal calcium handling, and oxidative stress contribute to cardiomyocyte injury and progressive deterioration of cardiac function.

3. Lipid Uptake in the Heart

The heart obtains most of its lipids from the blood through two major pathways. The first is the uptake of free fatty acids (FFAs), also called non-esterified fatty acids (NEFAs), which circulate in the blood mainly bound to albumin. The second pathway involves fatty acids released from circulating lipoproteins, particularly chylomicrons and very-low-density lipoproteins (VLDL). Low-density lipoproteins (LDL) also contribute to cardiac lipid supply, mainly through receptor-mediated uptake of lipoprotein particles and their lipid components. These circulating lipids provide cardiomyocytes with an important source of fatty acids that can be used for energy production.

Fatty acid entry into cardiomyocytes is mainly facilitated by transport proteins, with CD36 being one of the major fatty acid transporters in the heart. CD36 helps move long-chain fatty acids from the blood into cardiac cells, where they can either be transported to mitochondria for β-oxidation or stored as triglycerides in lipid droplets. Another important component is lipoprotein lipase (LPL), an enzyme located on the surface of cardiac capillary endothelial cells. LPL breaks down triglycerides contained in circulating chylomicrons and VLDL, releasing free fatty acids that can then be taken up by nearby cardiomyocytes. In this way, LPL helps control the delivery of fatty acids from circulating lipoproteins to the heart.

Under normal physiological conditions, these pathways work together to provide a continuous supply of fatty acids according to the energy requirements of the heart. After entering cardiomyocytes, fatty acids can be activated to fatty acyl-CoA and transported into mitochondria, where they undergo β-oxidation to produce acetyl-CoA and reducing equivalents for ATP generation. When fatty acid supply is greater than the immediate energy requirement, some fatty acids can be converted into triglycerides and safely stored within lipid droplets. This storage mechanism helps protect cardiomyocytes from excessive exposure to free fatty acids and provides an energy reserve that can be used when required.

The problem arises when lipid uptake and delivery become greater than the heart's ability to oxidize or safely store these lipids. Increased CD36-mediated fatty acid uptake, enhanced lipoprotein-derived fatty acid delivery, or excessive circulating lipid levels can increase the lipid burden of cardiomyocytes. When mitochondrial fatty acid oxidation cannot match this increased supply, fatty acids may accumulate inside the cells and may also be converted into potentially harmful lipid intermediates such as diacylglycerols and ceramides. This condition is referred to as intracellular lipid overload or cardiac lipotoxicity.

Excess lipid accumulation can interfere with normal mitochondrial function, increase reactive oxygen species production, disturb cellular signaling, and promote oxidative and endoplasmic reticulum stress. These changes can impair ATP production and contractile function and may eventually contribute to cardiomyocyte injury or death. Therefore, cardiac lipid uptake is essential for normal energy production, but it must remain

balanced with lipid oxidation and storage. Disruption of this balance can lead to metabolic dysfunction and may contribute to the development and progression of heart failure.

4. Fatty Acid Oxidation and Mitochondrial Function

Fatty acid oxidation (FAO) is one of the major pathways through which the heart produces energy. Because the heart contracts continuously throughout life, it requires a constant supply of ATP, and fatty acids normally provide a large proportion of this energy. The regulation of cardiac fatty acid metabolism is strongly influenced by the transcription factor peroxisome proliferator-activated receptor alpha (PPARα). PPARα regulates the expression of several genes involved in fatty acid uptake, transport, and oxidation, thereby helping the heart match fatty acid utilization with its energy requirements.

After fatty acids enter cardiomyocytes, they are transported to the mitochondria, where they undergo β-oxidation. This process breaks fatty acids down into acetyl-CoA, which enters the citric acid cycle. The resulting reducing equivalents, mainly NADH and $FADH_2$, then supply electrons to the mitochondrial electron transport chain. Through oxidative phosphorylation, this process generates large amounts of ATP needed for continuous cardiac contraction. Therefore, efficient fatty acid oxidation depends heavily on the presence of healthy and functional mitochondria.

In heart failure, this metabolic system becomes disturbed. Fatty acid oxidation may decrease or become less efficient because mitochondrial function is impaired. The mitochondria may produce less ATP, while their ability to maintain normal energy metabolism becomes progressively compromised. In addition, mitochondrial biogenesis, the process by which cells produce and maintain healthy mitochondria, may be reduced. This can decrease the overall mitochondrial capacity of cardiomyocytes to generate energy.

Heart failure can also disturb the normal balance between mitochondrial fission and fusion. Fission divides mitochondria into smaller units, whereas fusion allows mitochondria to join together and exchange their contents. A proper balance between these processes is important for maintaining mitochondrial quality and function. When this balance is disrupted, damaged mitochondria may accumulate and become less efficient at producing ATP.

Another important consequence of mitochondrial dysfunction is increased production of reactive oxygen species (ROS). Small amounts of ROS are normally produced during mitochondrial respiration and can participate in cellular signaling. However, excessive ROS can cause oxidative stress and damage mitochondrial proteins, lipids, membranes, and DNA. This further reduces mitochondrial efficiency and can create a cycle in which mitochondrial dysfunction increases oxidative stress, while oxidative stress causes additional mitochondrial damage.

As a result of these changes, the failing heart may produce less ATP despite having a very high energy demand. This creates an energy deficit in cardiomyocytes, making it more difficult for the heart to maintain normal contraction, ion transport, calcium handling, and other energy-dependent processes. Over time, mitochondrial dysfunction, impaired fatty acid oxidation, reduced ATP production, and oxidative stress can contribute to cardiomyocyte injury and progressive deterioration of cardiac function. Thus, abnormalities in fatty acid metabolism and mitochondrial function are closely interconnected and represent important metabolic features of heart failure.

5. Lipid Droplet Formation and Storage

When the amount of fatty acids available to the heart becomes greater than its suitable energy requirements, cardiomyocytes need a safe way to handle the excess fatty acids. One important mechanism is their conversion into triglycerides (TGs) and storage inside specialized structures called lipid droplets (LDs). Lipid droplets are small intracellular organelles that contain a core of neutral lipids, mainly triglycerides and cholesterol esters, surrounded by a layer of phospholipids and associated proteins. In this way, lipid droplets act as temporary storage sites for excess fatty acids and help prevent large amounts of free fatty acids from remaining in the cytoplasm.

This storage mechanism is important because excessive free fatty acids can be harmful to cardiomyocytes. Free fatty acids can interfere with cellular membranes, mitochondria, and intracellular signaling when present in high concentrations. By converting excess fatty acids into relatively neutral triglycerides and storing them in lipid droplets, the cell reduces exposure to potentially toxic lipid molecules. Therefore, lipid droplets should not be considered simply as sites of abnormal fat accumulation; under normal conditions, they are an important part of cardiac lipid metabolism and can provide a readily available energy reserve.

The amount of lipid stored within lipid droplets is continuously regulated by a balance between triglyceride synthesis and triglyceride breakdown. One important enzyme involved in triglyceride breakdown is adipose triglyceride lipase (ATGL). ATGL initiates the hydrolysis of triglycerides stored in lipid droplets, releasing fatty acids that can subsequently be transported to mitochondria and used for β-oxidation. This allows stored lipid to contribute to ATP production when the energy requirements of the heart increase. Therefore, ATGL helps connect intracellular lipid storage with fatty acid oxidation.

The lipid droplet surface also contains proteins known as perilipins (PLINs), which help regulate lipid storage and mobilization. Among them, PLIN2 and PLIN5 are particularly important in cardiomyocytes. These proteins help control access to the triglycerides stored within lipid droplets and influence whether fatty acids remain stored or are released for oxidation. PLIN5 is especially associated with the coordination between lipid droplets and mitochondria, helping direct fatty acids toward mitochondrial oxidation when required.

On the other hand, diacylglycerol acyltransferase (DGAT) enzymes are involved in triglyceride formation. DGAT catalyzes the final step of triglyceride synthesis by adding a fatty acyl group to diacylglycerol, producing triglyceride. This allows excess fatty acids to be incorporated into a safer storage form within lipid droplets. Therefore, DGAT activity and ATGL activity work in opposite directions: DGAT promotes triglyceride storage, whereas ATGL promotes triglyceride breakdown and fatty acid release.

Under normal conditions, this system maintains a dynamic balance between lipid storage and lipid utilization. When fatty acid supply increases, more fatty acids can be converted into triglycerides and stored in lipid droplets. When the heart requires additional energy, stored triglycerides can be broken down, releasing fatty acids for mitochondrial β-oxidation. This flexibility allows cardiomyocytes to manage fluctuations in fatty acid availability while protecting the cell from excessive exposure to free fatty acids.

However, when lipid supply remains chronically elevated or mitochondrial fatty acid oxidation becomes impaired, this balance can be disrupted. Lipid droplets may become enlarged and excessive amounts of triglycerides and other lipid species may accumulate within cardiomyocytes. Although

triglyceride storage itself can initially be protective, persistent lipid accumulation may indicate that lipid uptake and storage are exceeding the heart's capacity for lipid utilization. Over time, this metabolic imbalance can be associated with mitochondrial dysfunction, oxidative stress, abnormal lipid intermediates, and cardiomyocyte injury.

Thus, lipid droplets have a dual role in cardiac metabolism. In the normal heart, they provide a protective storage system and an energy reserve by safely packaging excess fatty acids as triglycerides. However, chronic expansion of lipid storage may reflect an underlying metabolic imbalance and can be associated with cardiac lipotoxicity and disease progression. Understanding the regulation of lipid droplets through proteins such as ATGL, PLIN2, PLIN5, and DGAT is therefore important for understanding how abnormal lipid metabolism contributes to heart failure and other metabolic diseases.

6. Lipid-Induced Lipotoxicity

When lipid accumulation in cardiomyocytes becomes excessive, the protective role of lipid storage can be overwhelmed, leading to a condition known as lipotoxicity. Cardiac lipotoxicity occurs when the amount of fatty acids and lipid-derived molecules inside cardiomyocytes exceeds the cell's ability to safely store, metabolize, or oxidize them. Instead of being converted into harmless storage forms or efficiently used for ATP production, excess fatty acids can give rise to several potentially harmful lipid intermediates. These metabolic changes can interfere with normal cellular function and contribute to progressive cardiomyocyte injury.

Among the most important harmful lipid intermediates are ceramides and diacylglycerols (DAGs). These molecules can act as signaling lipids and, when present in excessive amounts, activate pathways associated with inflammation, impaired insulin signaling, and cell death. Increased DAG levels can interfere with insulin signaling and reduce the ability of cardiomyocytes to respond normally to insulin. Ceramides can also promote cellular stress and activate pathways involved in apoptosis. Therefore, the accumulation of these lipid intermediates can have effects beyond simple fat storage and can directly alter cardiomyocyte function.

Excessive exposure to saturated fatty acids, particularly palmitate, is another important contributor to lipotoxicity. High levels of palmitate can increase the production of reactive oxygen species (ROS), resulting in oxidative stress. When ROS production exceeds the cell's antioxidant capacity, cellular proteins, lipids, membranes, and DNA can become damaged. Palmitate and other excess fatty acids can also interfere with mitochondrial function, reducing the efficiency of oxidative phosphorylation and further impairing ATP production. This creates a harmful cycle in which lipid overload damages mitochondria, while impaired mitochondria become less capable of handling the increased lipid supply.

Lipid overload can also change the normal composition and physical properties of cellular membranes. Cell membranes contain a carefully regulated mixture of phospholipids, cholesterol, and other lipids that determines their fluidity and function. Excessive incorporation or accumulation of certain lipid species can make membranes less flexible or alter their organization. This can interfere with membrane proteins, receptors, ion channels, and intracellular signaling pathways. Because cardiomyocytes depend heavily on coordinated membrane signaling and ion movement, these changes can disturb important processes such as calcium handling, which is essential for normal cardiac contraction and relaxation.

Another important consequence of lipid overload is endoplasmic reticulum (ER) stress. The endoplasmic reticulum is responsible for protein synthesis, folding, and several aspects of cellular lipid metabolism. Excess lipid accumulation and metabolic disturbances can interfere with normal ER function, causing an accumulation of improperly folded or misfolded proteins. In response, the cell activates the unfolded protein response (UPR) to restore normal ER function. Initially, this response is protective; however, if the stress is severe or persists for a long period, these pathways can promote inflammation, mitochondrial dysfunction, and activation of apoptotic signaling.

The combined effects of toxic lipid intermediates, oxidative stress, mitochondrial dysfunction, membrane alterations, abnormal calcium handling, and ER stress can eventually lead to cardiomyocyte apoptosis or other forms of cell injury. Loss of cardiomyocytes reduces the functional contractile capacity of the heart and may stimulate pathological remodeling. Over time, these changes can contribute to impaired ventricular function and worsening heart failure.

Therefore, cardiac lipotoxicity is not simply the accumulation of excess fat within cardiomyocytes. It represents a complex metabolic process in which excessive lipid supply and abnormal lipid metabolism generate harmful intermediates and cellular stress. The interaction between lipid accumulation, mitochondrial dysfunction, oxidative stress, ER stress, and impaired calcium handling creates a cycle of cellular injury that can contribute significantly to the development and progression of heart failure.

7. Cholesterol and Oxysterols in Cardiac Dysfunction

Cholesterol is an essential lipid that plays an important role in maintaining the structure and function of cell membranes. It helps regulate membrane stability, fluidity, and the activity of several membrane proteins. Cardiomyocytes require cholesterol for normal cellular function, but its amount must be carefully controlled. Unlike fatty acids, which are extensively used by the heart for energy production, cholesterol is not a major fuel for ATP generation. Instead, it is mainly involved in membrane structure, cellular signaling, and lipid metabolism.

Cardiomyocytes obtain cholesterol from the circulation, mainly through lipoproteins such as low-density lipoprotein (LDL) and high-density lipoprotein (HDL), with cellular uptake and cholesterol handling being tightly regulated. Under normal conditions, cholesterol is distributed between cellular membranes, stored in esterified form, or transported out of the cell. However, when cholesterol delivery exceeds the cell's ability to utilize, store, or remove it, intracellular cholesterol accumulation can occur.

Excess cholesterol can be incorporated into lipid droplets, where it may be stored in a relatively less harmful form, or it can undergo chemical modification to form oxidized cholesterol derivatives known as oxysterols. Oxysterols are biologically active molecules that can influence lipid metabolism, inflammation, and cellular signaling. However, excessive accumulation of certain oxysterols can become harmful to cardiomyocytes. One important example is 7-ketocholesterol, which has been associated with oxidative stress, mitochondrial injury, and activation of cell-death pathways.

Mitochondria are particularly vulnerable to abnormal cholesterol accumulation. Excess cholesterol within mitochondrial membranes can alter their normal lipid composition and interfere with membrane properties. Because the mitochondrial membrane must maintain a carefully controlled structure for efficient electron transport and oxidative phosphorylation, abnormal cholesterol accumulation can disturb the function

of the electron transport chain. This may reduce mitochondrial respiration and impair ATP production.

Excess cholesterol can also weaken the cell's ability to protect itself against oxidative stress. When mitochondrial function becomes impaired, electron transfer through the respiratory chain may become less efficient, increasing the generation of reactive oxygen species (ROS). At the same time, cholesterol-related changes can reduce the effectiveness of antioxidant defenses. The resulting increase in oxidative stress can damage mitochondrial proteins, membrane lipids, and mitochondrial DNA, further reducing mitochondrial function.

Persistent cholesterol and oxysterol accumulation may also activate pathways involved in apoptosis, leading to cardiomyocyte loss. Since adult cardiomyocytes have limited regenerative capacity, prolonged loss of these cells can contribute to reduced contractile function and structural remodeling of the heart. In this way, abnormal cholesterol metabolism can interact with mitochondrial dysfunction and oxidative stress to promote progressive cardiac injury.

Therefore, cholesterol is essential for normal cardiomyocyte function, but its accumulation can become harmful when cellular cholesterol homeostasis is disturbed. Excess cholesterol and its oxidized derivatives can affect mitochondrial membranes, increase ROS production, impair antioxidant defenses, reduce mitochondrial respiration, and promote cardiomyocyte apoptosis. These effects can worsen the metabolic and structural abnormalities already present in heart failure and may contribute to its progression.

8. Mitochondrial Dysfunction in Heart Failure

Mitochondria are often described as the powerhouses of the cell, but this role is particularly important in cardiomyocytes because the heart requires a continuous supply of ATP to maintain contraction throughout life. Cardiac contraction, relaxation, calcium cycling, ion transport, and maintenance of membrane potential all require large amounts of energy. Most of this energy is generated within mitochondria through oxidative phosphorylation. Therefore, maintaining a sufficient number of healthy and functional mitochondria is essential for normal cardiac performance.

In heart failure, mitochondrial function becomes progressively impaired. One of the major consequences is a reduction in oxidative phosphorylation, which decreases the ability of mitochondria to convert nutrients into ATP efficiently. Although the failing heart may still have access to fatty acids, glucose, and other metabolic substrates, impaired mitochondrial function limits their effective utilization for energy production. As a result, cardiomyocytes may experience an energy deficit, making it increasingly difficult to maintain normal contraction and other energy-dependent cellular processes.

Mitochondrial dysfunction is also associated with increased production of reactive oxygen species (ROS). Under normal conditions, small amounts of ROS are produced during electron transport and are controlled by antioxidant systems. However, when the electron transport chain becomes dysfunctional, electrons may escape and react with oxygen, resulting in excessive ROS production. High levels of ROS cause oxidative stress, which can damage mitochondrial proteins, membrane lipids, and mitochondrial DNA. This further reduces mitochondrial efficiency and creates additional cellular stress.

Another important abnormality involves mitochondrial dynamics, which refers to the continuous processes of mitochondrial fission and fusion. Fission divides mitochondria into smaller units, while fusion allows mitochondria to join together. These processes are important for

maintaining mitochondrial quality, distributing mitochondrial components, and removing damaged mitochondria. In heart failure, this balance may shift toward excessive fission and reduced fusion. Excessive fragmentation can produce dysfunctional mitochondria that are less efficient at generating ATP and may be more likely to produce ROS.

Mitochondrial dysfunction is also associated with reduced mitochondrial biogenesis, the process through which cells produce new mitochondria and maintain their mitochondrial population. An important regulator of mitochondrial biogenesis is peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α). PGC-1α stimulates the expression of genes involved in mitochondrial formation, oxidative metabolism, and energy production. In heart failure, reduced PGC-1α activity can decrease mitochondrial biogenesis and limit the heart's ability to replace or maintain functional mitochondria.

These abnormalities are closely interconnected. Reduced mitochondrial biogenesis decreases the availability of healthy mitochondria, while abnormal fission and fusion can promote the accumulation of damaged mitochondrial fragments. At the same time, impaired oxidative phosphorylation reduces ATP production and increases ROS generation. Excess ROS can then cause further mitochondrial damage, creating a self-reinforcing cycle of mitochondrial dysfunction and oxidative stress.

As mitochondrial dysfunction progresses, cardiomyocytes become increasingly unable to meet the high energy demands of the continuously beating heart. Reduced ATP availability can impair contraction, calcium handling, ion transport, and other essential cellular functions. Persistent oxidative damage and mitochondrial injury may also activate pathways leading to cardiomyocyte death. Loss of functional cardiomyocytes further weakens cardiac performance and contributes to pathological remodeling.

Thus, mitochondrial dysfunction is not simply a consequence of heart failure but can also actively contribute to its progression. The combination of reduced oxidative phosphorylation, increased ROS production, abnormal mitochondrial fission and fusion, and reduced PGC-1α-dependent mitochondrial biogenesis creates a vicious cycle of energy deficiency and cellular injury. Breaking this cycle and restoring mitochondrial quality and energy production may therefore represent an important strategy for limiting cardiac dysfunction and slowing the progression of heart failure.

CONCLUSION

Cardiac lipid metabolism is a highly coordinated process that plays a central role in maintaining the continuous energy requirements of the heart. Because cardiomyocytes contract throughout life, they require a constant and efficient supply of ATP. Fatty acids are an important energy substrate for the healthy heart, and their uptake, transport, storage, and mitochondrial oxidation are carefully regulated to match cardiac energy demands. Lipid droplets also provide an important mechanism for safely storing excess fatty acids as triglycerides, while proteins such as ATGL, PLIN2, PLIN5, and DGAT help maintain the balance between lipid storage and mobilization. Under normal physiological conditions, these pathways work together to maintain metabolic flexibility and protect cardiomyocytes from excessive lipid exposure.

In heart failure, however, this tightly regulated metabolic system becomes progressively disturbed. Changes in fatty acid uptake, fatty acid oxidation, lipid storage, and mitochondrial function can create an imbalance between lipid availability and lipid utilization. When lipid delivery exceeds the capacity of the heart to oxidize or safely store fatty acids, excess lipids

accumulate within cardiomyocytes. Although triglyceride storage within lipid droplets can initially serve a protective function, persistent lipid accumulation may lead to the formation of harmful lipid intermediates such as ceramides and diacylglycerols. These molecules can interfere with cellular signaling, promote inflammation and insulin resistance, and activate pathways leading to cardiomyocyte injury and apoptosis.

Mitochondria represent a major link between abnormal lipid metabolism and cardiac dysfunction. Impaired fatty acid oxidation, reduced oxidative phosphorylation, abnormal mitochondrial fission and fusion, and decreased mitochondrial biogenesis can reduce the ability of cardiomyocytes to produce ATP. Reduced PGC-1α activity may further limit mitochondrial biogenesis and the maintenance of healthy mitochondria. At the same time, mitochondrial dysfunction increases the production of reactive oxygen species, resulting in oxidative stress and additional damage to mitochondrial proteins, membranes, and DNA. This creates a vicious cycle in which lipid overload damages mitochondria, while damaged mitochondria become less capable of efficiently metabolizing lipids and producing energy.

Excessive lipid accumulation can also affect other important cellular systems. Saturated fatty acids such as palmitate can promote oxidative stress and mitochondrial injury, while abnormal cholesterol accumulation and oxysterol formation may further impair mitochondrial respiration and promote apoptosis. Lipid overload can alter membrane composition, disturb membrane signaling and calcium handling, and induce endoplasmic reticulum stress. The combined effects of these processes can impair cardiomyocyte contraction, reduce cellular energy availability, and eventually promote cardiomyocyte death and pathological cardiac remodeling.

Importantly, cardiac lipid metabolism should not be viewed as an isolated metabolic pathway. Lipid uptake, fatty acid oxidation, triglyceride storage, cholesterol metabolism, mitochondrial function, oxidative stress, and cell survival are closely interconnected. A disturbance in one component can influence several others and amplify the overall metabolic dysfunction. For example, increased lipid delivery can overload mitochondria, while mitochondrial dysfunction can reduce fatty acid oxidation and further increase intracellular lipid accumulation. This interaction helps explain why metabolic abnormalities can persist and progressively worsen during heart failure.

Understanding these relationships provides important opportunities for therapeutic intervention. Strategies aimed at restoring a healthier balance between lipid uptake and utilization, improving mitochondrial function, reducing oxidative stress, regulating lipid droplet metabolism, and preventing the accumulation of toxic lipid intermediates may help protect cardiomyocytes from metabolic injury. However, because fatty acids and cholesterol are also essential for normal cardiac function, the goal should not simply be to eliminate cardiac lipids, but rather to restore appropriate lipid homeostasis and metabolic flexibility.

Overall, abnormal cardiac lipid metabolism is an important component of heart failure progression rather than merely a secondary consequence of cardiac dysfunction. The interaction between lipid accumulation, lipotoxicity, mitochondrial dysfunction, oxidative stress, and impaired energy production can contribute to progressive cardiomyocyte injury and loss of cardiac function. A better understanding of these interconnected mechanisms may help identify new metabolic targets and support the development of therapies designed to preserve mitochondrial health, maintain efficient energy production, and

ultimately slow or prevent the progression of heart failure.

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