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REVIEW ARTICLE

Navigating the complex landscape of cardiac metabolism in health and disease states

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Abstract

The intricate interplay between cardiovascular health and metabolic regulation forms a critical junction in understanding the complexities of heart-related conditions. Cardiometabolic regulation orchestrates a sophisticated network of factors governing energy utilization, substrate metabolism, and cellular processes within the cardiovascular system. Balancing these mechanisms is pivotal for optimal heart function, considering the substantial energy demands for both contractile and non-contractile activities. In a healthy heart, fatty acids (FAs) derived from FA β-oxidation contribute to approximately 70% of total energy production. However, emerging evidence sheds light on pathological changes in the heart that lead to profound metabolic alterations. These alterations involve a shift from predominant FA utilization to alternative substrates such as glucose and ketone bodies, accompanied by an increased reliance on FAs. This metabolic remodeling extends beyond substrate metabolism, encompassing changes in transporter expression, the activity of metabolic-related proteins, hormonal functions, and cardiac mitochondrial energetics. This comprehensive review article delves into the intricate web of cardiometabolic regulation, elucidating the multifaceted factors influencing cardiac metabolism across diverse states encompassing health, metabolic disorders, and heart diseases. Unraveling the molecular intricacies and interconnected pathways shaping cardiac metabolism in various physiological and pathological conditions provides critical insights into the adaptive mechanisms and dysregulations associated with heart-related conditions. Furthermore, the exploration of these regulatory mechanisms offers promising avenues for targeted therapeutic interventions and diagnostic strategies in cardiovascular medicine. Integrating multidisciplinary approaches and leveraging advanced technologies will facilitate a deeper understanding of cardiac metabolism, paving the way for innovative interventions to mitigate metabolic dysregulation and optimize cardiac health.

Keywords: Cardiac metabolism; Obesity; Metabolic syndrome; Diabetes mellitus; Myocardial ischemia; Cardiac hypertrophy; Heart failure

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1. Introduction

Mitochondrial fatty acid (FA) utilization, glycolysis, and glucose oxidation are pivotal processes responsible for generating almost all of the total adenosine triphosphate

(ATP) in healthy adult human hearts.[1,2] Typically, around 70% of the heart's total ATP is derived from FA β-oxidation (FAO) under normal physiological conditions.[3,4] Studies have indicated that heart diseases trigger changes in cellular mechanisms and metabolic regulations, leading to alterations in cellular morphology and damage to cellular structures. Considering the heart's high-energy demanding function, especially during contractions, metabolic control within the heart is of utmost importance for sustaining its high energy requirements.[3,4] However, under pathological conditions, the primary energy source in the cardiac metabolic pathway can undergo alterations, resulting in varied major energy sources among different types of heart diseases.

Currently, several concepts attempt to elucidate these metabolic changes in heart diseases. First, there is the observed shift from utilizing mitochondrial FAO to glycolysis and/or ketone bodies, documented in cardiac hypertrophy and heart failure.[5-7] Second, there is an elevated utilization of mitochondrial FAO, beyond normal physiological levels, noted in conditions such as obesity, diabetes, diabetic cardiomyopathy (DCM), and cardiac ischemia/reperfusion injury.[8-12] Various conditions, such as obesity, diabetes, and heart diseases, disrupt this equilibrium, leading to alterations in energy utilization, substrate preferences, and cellular metabolism within cardiac tissues.[3,4] These disruptions often manifest as changes in the utilization of primary energy sources, such as FA, glucose, and ketone bodies. In healthy states, the heart predominantly relies on FAO to meet its energy demands. However, under pathological conditions, such as heart failure or DCM, this preference may shift, leading to an increased reliance on glucose or alternative substrates.[8-12]

Moreover, hormonal imbalances, mitochondrial dysfunction, and alterations in enzyme activity further compound these pathological changes, impacting the heart's ability to generate sufficient energy for its functions. This dysregulation not only affects energy production but also influences cardiac contractility, efficiency, and overall performance.[13-15]

Understanding these intricate regulatory pathways and the factors influencing cardiac metabolism in health and disease is pivotal for developing targeted therapies. By elucidating the underlying molecular mechanisms, identifying genetic predispositions, and uncovering the complex network of metabolic alterations, researchers strive to refine therapeutic strategies. Ultimately, the goal is to mitigate the impact of metabolic disorders on heart health and improve the efficacy of treatments for various cardiac conditions.

This review focuses on elucidating metabolic regulation in healthy hearts and adaptive mechanisms in metabolic disorders and heart diseases. In addition, it examines influential factors affecting cardiac metabolisms, such as oxygen demand, myocardial substrate metabolism, cardiac mitochondrial performance, and energetics in health, metabolic disorders, and heart diseases.

2. Cardiac metabolism in health

The heart, with its high energy demands but limited energy reserves, heavily relies on specific substrates for myocardial energy metabolism. In a normal, healthy human heart, approximately 70% of ATP is derived from FAs, with glucose contributing about 25% and the remaining 5% originating from alternate substrates such as ketone bodies and pyruvate.[3,4,8,16-19] Transport mechanisms for FAs into the heart vary; short-chain and medium-chain FAs utilize passive diffusion, while long-chain FAs rely on plasma membrane-bound FA binding proteins (FABP) and FA transport proteins.[8,20-22] Subsequently, the acyl-coenzyme A (CoA) group is added to FAs before their entry into mitochondria through specific transporters. Carnitine palmitoyltransferase-1 (CPT-1), a crucial enzyme located on the outer mitochondrial membrane (OMM), acts as a rate-limiting step in this process, converting long-chain fatty acyl CoA to carnitine forms for mitochondrial entry, where they are reconverted back to fatty acyl CoA for FAO.[8,20] Key regulators of FA transporters include factors such as acetyl CoA carboxylase, malonyl CoA, malonyl CoA decarboxylase, and other enzymes, exerting direct and indirect effects on CPT-1 activity.[23-25]

In contrast, glucose, which contributes approximately 25% of total ATP in the basal state, cannot pass through the cell membrane by simple diffusion due to its hydrophilic nature. The human heart employs two classes of glucose transporters, namely glucose transporters (GLUTs) and sodium-glucose co-transporters (SGLTs).[26] GLUT1, GLUT2, and GLUT4 are three identified isoforms, with GLUT4 taking precedence in adult hearts, responsible for approximately 70% of glucose transport after birth.[27,28] GLUT1 serves as a basal cardiac glucose transporter primarily responsible for embryonic cardiac glucose transport. However, after birth, there is a rapid transition to utilizing GLUT4 for transporting glucose, which contributes to approximately 70% of glucose transport in the adult heart.[29] Insulin mediates GLUT4 translocation in cardiomyocytes, while SGLT1, abundantly expressed in the heart, is regulated by insulin and leptin, though its exact role remains unclear.[19] A previous study demonstrated that SGLT1 is an abundantly expressed isoform in the human heart, with expression levels approximately 10-fold higher than those in the kidney.[30] Surprisingly, another study demonstrated that cardiac SGLT1 expression and activity are regulated by insulin and leptin.[31] However, the crucial

mechanisms through which this regulation occurs, as well as the role of SGLT1 in the heart, are still unknown and were not examined in this study.[31]

Regarding ketone bodies, primarily generated within hepatocyte mitochondria during ketogenesis, they serve as an alternative fuel source, particularly in states such as fasting, exercise, pregnancy, and when following low-carbohydrate diets.[32,33] Acetoacetate and beta-hydroxybutyrate serve as energy sources, particularly beneficial for the brain and heart. While efficient, their contribution to total cardiac energy production under normal physiological conditions is relatively minimal, typically <5%. Despite their efficiency, their role in cardiac energy provision remains modest within the broader context of the heart's energy metabolism.[16,34] However, during specific physiological states such as fasting, post-exercise recovery, and pregnancy, ketone bodies play a more significant role in cardiac energy metabolism. They augment ATP synthesis by maintaining oxidized ubiquinone and widening the redox span in the electron transport chain (ETC).[16,34,35]

3. Cardiometabolic alteration in heart diseases

The shift in cardiac substrate utilization for ATP production to sustain cardiac contractile function signifies a notable change in the heart's biological activity, often linked to various heart diseases.[8,19-21] Recent evidence supports two distinct concepts indicating that metabolic changes occurring in heart diseases result from alterations in the primary substrates utilized for ATP generation within diseased cardiomyocytes.

The first concept involves a shift from mitochondrial FA utilization (via FAO) to alternative energy sources such as glucose and potentially other substrates such as ketone bodies, notably observed in cardiac hypertrophy and heart failure.[5-7] This transition also includes an observed increase in ketone body utilization.[36] While ketone bodies enhance cardiac metabolism by facilitating ATP synthesis through the maintenance of oxidized ubiquinone and extending the redox span in the ETC,[16,34,35] their oxidation concurrently elevates reactive oxygen species production, contributing to oxidative stress.[35] Despite increased hepatic ketogenesis in pathological heart conditions or metabolic disorders such as hormone resistance and diabetes mellitus (DM),[32,33] ketone body metabolism remains a contributor to heightened ATP production.[16,34,35] However, this process is also associated with acidosis and increased oxidative stress, potentially resulting in a redox imbalance,[35,37] subsequently elevating the morbidity and mortality risk among patients.[37]

The second concept revolves around the heightened utilization of mitochondrial FAs in pathological states such as obesity, diabetes, DCM, and cardiac ischemia/reperfusion, exceeding the normal physiological levels.[8-12] In these conditions, cardiomyocyte metabolism shifts to derive over 70% of cardiac energy from mitochondrial FAs, which, despite being a less efficient energy source (having a higher oxygen consumption-to-ATP production ratio compared to glucose and ketone bodies),[8,16-18,20] leads to compromised cardiac function.[38,39] Conversely, in other cardiac pathological states such as cardiac hypertrophy and heart failure, the metabolic profile of cardiomyocytes reverses to predominantly derive ATP from glucose rather than FAs, offering a more efficient energy source (with a lower oxygen consumption-to-ATP production ratio compared to FA),[8,16-18,20] potentially leading to improved cardiac function.[5] These observations underscore the difference between mitochondrial FAO and glycolysis in their respective oxygen consumption per ATP produced (differences in oxygen demands).[8,16-18,20] For instance, complete glucose oxidation consumes six oxygen molecules to yield 31 ATP molecules (Glucose oxidation: O_2:ATP = 1:5.167), while one palmitate molecule, in full mitochondrial FAO, requires 23 oxygen molecules to generate 105 ATP molecules (Palmitate: O_2:ATP = 1:4.565).[8,20] The comparatively lower ATP production per oxygen molecule consumed in the mitochondrial FAO system elucidates why heightened mitochondrial FAO diminishes cardiac efficiency.[8,20]

4. The reciprocal alteration of metabolism under the "Randle cycle" concept

Randle *et al.* demonstrated that elevated mitochondrial FAO disrupts mitochondrial glucose oxidation, establishing a reciprocal relationship between the two metabolic pathways.[11] This reciprocal interaction is articulated in the widely recognized "Randle cycle" or "glucose-FA cycle".[11] According to the "Randle cycle," heightened mitochondrial FAO can impede both glycolysis and mitochondrial glucose oxidation through several mechanisms: (i) increased mitochondrial FAO enhances nicotinamide adenine dinucleotide and acetyl CoA production, thereby inhibiting pyruvate dehydrogenase (PDH) activity;[38,39] (ii) elevated citrate levels resulting from increased FAO can inhibit phosphofructokinase 1 (PFK1) activity; and (iii) elevated glucose-6-phosphate levels can inhibit hexokinase enzymes in glycolysis oxidation.[10,20] These mechanisms collectively contribute to the suppression of glycolysis and glucose oxidation.[23] Conversely, reducing mitochondrial FAO levels can lead to an upsurge in glycolysis and glucose oxidation.[23]

5. Cardiac metabolism in obesity and diabetes

In obesity and DM, elevated levels of circulating FAs and/or glucose, alongside hormonal resistance, including

resistance to insulin, fibroblast growth factor 21 (FGF21), and leptin, have been observed.[12,40-49] These conditions correlate with heightened myocardial FAO and a predominant reliance on FAO as the primary myocardial metabolism. Moreover, the proportion of FAO is increased in these pathological states. The impairment of hormonal signaling pathways in the heart especially disturbs cardiac insulin signaling pathways and can also contribute to decreased GLUT4 vesicle trafficking to the plasma membrane, leading to decreased glucose uptake into cells,[48,49] since GLUT4 is the dominant glucose transporter in the human heart.[29] Therefore, in DM, increased plasma FA levels are attributed to elevated glucagon levels activating lipolysis and cholesterol synthesis.[23]

Cardiac insulin resistance in DM involves the overexpression of FA transporters such as CD36 and FABP on cardiomyocyte membranes, augmenting FA uptake.[50,51] In addition, high expression levels of peroxisome proliferator-activated receptor alpha and peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α) in insulin resistance and DM contribute to elevated mitochondrial FAO levels by regulating genes involved in FAO, thereby reducing cardiac glycolysis and mitochondrial glucose oxidation (via the "Randle cycle").[52-54] Insulin resistance leads to impaired cardiac mitochondrial function, diminishing cardiac efficiency due to increased mitochondrial FAO, which elevates the cardiac mitochondrial workload and oxygen demands for substrate metabolism.[55,56]

In terms of SGLT1 activity and expression in DM, studies have revealed type-dependent effects: SGLT1 expression significantly increased in end-stage DCM in type 2 DM (T2DM) patients and animal models (db/db mice), while it decreased in type 1 DM (T1DM) animal models (streptozotocin-diabetic mice).[31] The elevated SGLT1 expression in T2DM might be influenced by chronic hyperinsulinemia, as SGLT1 activity is regulated by insulin. However, the contradictory findings regarding the effects of DM on SGLT1 expression necessitate further investigation, particularly considering the severe insulin resistance observed in end-stage cardiomyopathy.

6. Cardiac metabolism in myocardial ischemia and/or reperfusion

During myocardial ischemia, the myocardium experiences a decrease in oxygen supply, leading to reduced circulating FAs available for FAO. Conversely, there is an increase in glucose derived from glycogen breakdown, facilitated by enhanced glucose transport through GLUT1 and GLUT4 translocation to the plasma membrane, resulting in a metabolic shift toward glycolysis. This metabolic shift aligns with the concept described earlier, involving a shift from mitochondrial FAO to glycolysis or other substrates. In addition, during myocardial ischemia, SGLT1 expression increases approximately two to threefold, promoting increased glucose uptake into cardiomyocytes. These alterations are beneficial, protecting cardiomyocytes from irreversible injury, necrosis, and apoptosis.[57-59]

In clinical settings, a randomized controlled trial conducted with acute myocardial infarction (MI) patients using glucose–insulin–potassium (GIK) as a supplementary treatment alongside myocardial reperfusion showed no efficacy in cardioprotection. This lack of effectiveness in this trial might be attributed to delays in initiating therapy, which was administered only during reperfusion. However, findings from the IMMEDIATE study revealed that early intravenous GIK for acute coronary syndrome (ACS) in out-of-hospital emergency medical service settings demonstrated an 80% reduction in infarct size at 30 days. Although there was no significant reduction in serious endpoints at 1 year among patients with suspected ACS compared to placebo controls, individuals with ST-elevation MI treated with GIK exhibited reduced rates of cardiac arrest, 1-year mortality, or heart failure hospitalization within the year.[60-62]

During myocardial reperfusion following ischemia, reperfusion therapy elevates FA levels and reduces malonyl CoA, a potent inhibitor of CPT-1, leading to increased cardiac FAO. ATP production during this phase primarily arises from mitochondrial FAO. Moreover, there is a decrease in glycolysis, increasing cellular oxygen demand for ATP production, as described by the "Randle cycle," which outlines reciprocal changes between mitochondrial FAO and glycolysis. This aligns with the second concept mentioned earlier, which involves a shift toward a higher degree of FAO.[8,9]

In the context of myocardial reperfusion injury, reperfusion therapy contributes to this type of injury. Mitochondrial dysfunction triggers cellular apoptosis and ATP depletion. Despite hyperoxygenation at the onset of reperfusion, impaired cardiac mitochondrial function induces oxidative stress and mediates myocardial injury.[63,64] This impairment intensifies the cardiac mitochondrial workload due to a shift from glucose oxidation to FAO, increasing oxygen demands and potentially accelerating apoptosis, thereby decreasing cardiac efficiency and function.

7. Cardiac metabolism in cardiac hypertrophy and heart failure

Cardiac hypertrophy is an adaptive response of the myocardium to pressure or volume stress in the heart

chambers.[65,66] This response serves to decrease wall stress and oxygen consumption.[67-69] However, while it provides compensation, cardiac hypertrophy also significantly increases the risk of heart failure and malignant arrhythmias.[70,71] Previous studies have divided hypertrophic transformation of the heart into three stages: (i) hypertrophy with excessive load surpassing output, (ii) compensatory hypertrophy maintaining workload and cardiac output, and (iii) heart failure with ventricular dilation and a progressive decline in cardiac output.[66]

A previous study has demonstrated that in cardiac hypertrophy, there is a suppression of the mitochondrial FAO gene PGC-1α, resulting in a metabolic shift from mitochondrial FAO to glucose oxidation.[72] This compensatory shift decreases oxygen demand compared to mitochondrial FAO, enhancing cardiac efficiency.[20] However, in hypertrophic conditions, cardiac mitochondrial function is impaired, prompting a reduction in cardiac mitochondrial workload through a shift to anaerobic glycolysis.[19,73]

In heart failure, altered energy metabolism and reduced ATP production are well-documented, with levels dropping by approximately 30% compared to a normal adult myocardium.[74,75] Concurrently, cardiac mitochondrial function decreases, further contributing to a total ATP production drop to 30%–40% of normal physiological levels.[76,77] A majority of studies reveal reduced cardiac FAO during heart failure, prompting the myocardium to shift its energy metabolism from substrates that demand high oxygen consumption (FAO) to primary energy sources with lower oxygen demands (glucose and ketone bodies) to maintain cardiac function,[20,78,79] aligning with concepts described earlier.

While glycolysis increases in models of cardiac hypertrophy induced by abdominal aortic constriction, glucose oxidation remains unchanged.[79,80] Impaired glucose oxidation in heart failure is associated with mitochondrial dysfunction, reduced expression of glycolysis and glucose oxidation-related genes, and decreased abundance of pyruvate dehydrogenase complex, potentially contributing to cardiac dysfunction.[78,81] Intriguingly, elevated glycolysis coexists with diminished mitochondrial function and energetics in heart failure,[20] culminating in ATP depletion and apoptosis, consequently reducing cardiac efficiency and function.[20]

Controversial data suggest that high-plasma FA levels elevate cardiac mitochondrial FAO, potentially improving cardiac function under MI and heart failure conditions.[82,83] However, conflicting findings propose that decreased mitochondrial FAO levels could be detrimental, further reducing total ATP production, which is already diminished in heart failure.

8. Cardiac calcium homeostasis and signaling in health and diseases

Calcium signaling plays a crucial role in cardiac cellular function, particularly within mitochondria, influencing energy metabolism, redox balance, and cell fate determination. Disruptions in mitochondrial calcium handling significantly impact the progression of cardiac disease. In conditions such as ischemic heart disease, disturbed calcium homeostasis leads to mitochondrial dysfunction, reducing ATP production and triggering cell death pathways, thereby exacerbating tissue damage during ischemia–reperfusion injury.[83,84] Similarly, in heart failure, aberrant calcium handling contributes to pathological remodeling, affecting excitation-contraction coupling and prompting metabolic shifts. This dysfunctional signaling alters reliance on oxidative phosphorylation, favoring glycolysis, and affects mitochondrial dynamics, exacerbating cardiac dysfunction. While initially adaptive, mitochondrial changes can fuel chronic dysfunction, perpetuating cardiac pathology.[80]

A comprehensive understanding of the relationship between mitochondrial calcium dynamics and cardiac disease necessitates a detailed exploration of the molecular mechanisms governing calcium transport, buffering, and signaling within mitochondria. Identifying calcium-dependent effectors such as the mitochondrial calcium uniporter complex, mitochondrial permeability transition pore, and calcium-sensitive enzymes holds promise for developing therapeutic interventions aimed at restoring mitochondrial calcium balance and preserving bioenergetics in cardiac diseases.[84]

Mitochondrial calcium homeostasis serves not only as a secondary messenger but also as a feedback and feed-forward mechanism in the development of cardiac myopathy, particularly associated with ETC dysfunction.[85] Moreover, calcium plays an intricate role in cardiomyocyte function, particularly in excitation–contraction coupling, influencing various electrophysiological processes that impact cardiac metabolism and arrhythmias. While computational modeling has advanced our understanding, critical questions regarding macromolecular regulation, calcium-dependent pathways, and the interplay between electrophysiology and cardiac metabolism remain unanswered.[85] Addressing these uncertainties through *in vitro* and *in silico* studies could pave the way for improved therapeutic strategies.

9. Discussion

The investigation into cardiac metabolism unveils a multifaceted landscape, delineating intricate patterns of energy utilization in both physiological and pathological

Table 1. Substrate utilization for ATP production in cardiac metabolism across health and disease states

Conditions	Substrates			References
	Fatty acid	Glucose	Alternative substrates	
Normal heart	70% of total ATP production	25% of total ATP production	5% of total ATP production	1,2
Obesity	Increase	Decrease	Decrease	8-12
Diabetes mellitus	Increase	Decrease	Decrease	8-12
Ischemic heart	Decrease	Increase	Increase	8-12
Reperfusion heart	Increase	Decrease	Decrease	8-12
Cardiac hypertrophy	Decrease	Increase	Increase	5-7
Heart failure	Decrease	Increase	Increase	5-7

Notes: "Increase" signifies an increase exceeding a certain percentage from the normal condition; "Decrease" signifies a decrease exceeding a certain percentage from the normal condition.
Abbreviation: ATP: Adenosine triphosphate.

states. Central to this paradigm are the intersecting pathways of mitochondrial FAO, glycolysis, and glucose utilization, which establish the energetic framework of a healthy heart.[3,4] However, in pathological conditions, a noticeable divergence emerges: while cardiac hypertrophy and heart failure exhibit adaptations favoring more oxygen-efficient substrates such as glycolysis or ketone bodies, conditions such as obesity, diabetes, and DCM showcase heightened mitochondrial FAO. This juxtaposition underscores the complex interplay between substrate preferences and energy pathways, epitomizing the nuanced metabolic shifts characterizing cardiac pathology.

Hormonal imbalances, mitochondrial irregularities, and enzymatic disruptions add layers of complexity to cardiac metabolism in disease states. Diverse research perspectives propose varying degrees of reliance on glycolysis, alternative substrates, or increased mitochondrial FAO, presenting a mosaic of hypotheses. The exploration of these intricate pathways offers a multitude of potential therapeutic targets for understanding and intervening in metabolic dysregulation in various cardiac diseases.[13-15]

The "Randle cycle" concept, elucidating the reciprocal relationship between mitochondrial FAO and glycolysis, governs substrate utilization within the cardiac milieu. The adaptability of the heart during myocardial ischemia and reperfusion, adjusting substrate preferences based on oxygen availability, emphasizes the dynamic nature of cardiac metabolism under stress.[11]

The divergence between adaptive responses favoring glucose oxidation and heightened mitochondrial FAO in cardiac hypertrophy and heart failure necessitates further investigation to comprehend its impact on compromised cardiac energetics. Addressing this discrepancy is pivotal for understanding and mitigating metabolic dysregulation in diseased hearts.

Future strides in understanding cardiac metabolism entail elucidating regulatory mechanisms governing substrate preferences, exploring the "Randle cycle," and probing the molecular intricacies in disease states. Integrating diverse disciplines encompassing metabolomics, genetics, and systems biology with clinical data can facilitate tailored interventions and innovative diagnostic tools, revolutionizing cardiovascular medicine. Collaborative efforts leveraging advanced technologies promise to reshape the landscape of cardiac disease management by providing deeper insights into metabolic regulation in the heart.

10. Conclusion

Understanding the profound impact of metabolic disorders and heart diseases on myocardial metabolism is crucial, as these conditions influence various facets such as energy demand, substrate utilization, and cardiac mitochondrial function. These factors intricately regulate cardiac energy metabolism and efficiency. Unraveling the molecular mechanisms behind these metabolic alterations during such conditions holds promise in refining therapeutic strategies and pinpointing targets to treat heart diseases while bolstering cardiac efficiency. A schematic representation of substrate utilization for ATP production in cardiac metabolism across both healthy and diseased conditions is depicted in Table 1. Despite the potential benefits of modulating cardiac metabolism to enhance heart function, the intricate links between metabolic alterations and pathological conditions remain poorly elucidated. Clinical efforts to intervene and modulate cardiac metabolism have not provided comprehensive insights into this domain. Therefore, future investigations should aim at deeper exploration, unraveling the intricate molecular changes, genetic mutations, and complex networks involved in altering cardiac energy metabolism. Advancements in understanding these mechanisms hold the key to

enhancing the effectiveness of metabolic therapies for heart diseases.

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