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# Partial Fatty Acid Oxidation (pFOX) Inhibitors: A Metabolic Modulation Strategy in Cardiovascular Disease

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## Abstract:

Myocardial energy metabolism plays a critical role in the pathophysiology of ischemic heart disease and chronic heart failure, where impaired substrate utilization and mitochondrial dysfunction lead to reduced adenosine triphosphate (ATP) production and diminished cardiac efficiency. Under pathological conditions, persistent reliance on oxygen-intensive fatty acid oxidation suppresses glucose oxidation, resulting in metabolic uncoupling, intracellular acidosis, and contractile dysfunction. Partial fatty acid oxidation (pFOX) inhibitors have emerged as a novel class of metabolic modulators that improve myocardial energetics by shifting substrate utilization toward more oxygen-efficient glucose oxidation. This review discusses the biochemical basis of myocardial metabolism, mechanisms of metabolic remodelling, and the therapeutic rationale for pFOX inhibition. Key agents including ranolazine, trimetazidine, etomoxir, perhexiline, meldonium, and oxfenicine are evaluated for their mechanisms of action and pharmacological profiles. Available evidence indicates that these agents improve exercise tolerance, reduce anginal symptoms, and enhance ventricular function without significant hemodynamic effects. Additionally, pFOX inhibitors demonstrate potential benefits in heart failure and other metabolic conditions. Despite promising outcomes, limitations related to safety and long-term efficacy warrant further investigation. Overall, pFOX inhibitors represent a promising strategy for improving myocardial efficiency through targeted metabolic modulation.

***Keywords***: Partial fatty acid oxidation inhibitors; Myocardial energy metabolism; Metabolic modulation; Chronic heart failure; Fatty acid oxidation; Glucose oxidation; Mitochondrial dysfunction

## 1. INTRODUCTION

Cardiovascular diseases remain a leading cause of morbidity and mortality worldwide, with ischemic heart disease and heart failure accounting for a substantial proportion of the global disease burden. Despite advances in pharmacological and interventional therapies, many patients continue to experience persistent symptoms and progressive myocardial dysfunction. Conventional cardiovascular drugs predominantly target hemodynamic parameters such as heart rate, blood pressure, and vascular tone; however, these approaches do not directly address the underlying metabolic inefficiency that characterizes the diseased myocardium. The heart is a highly energy-dependent organ, generating adenosine triphosphate (ATP) primarily through mitochondrial oxidative metabolism. Under normal physiological conditions, fatty acid oxidation serves as the dominant energy source, contributing approximately 60–70% of myocardial ATP production, with the remainder derived from glucose, lactate, and ketone bodies. Although fatty acid oxidation yields a high quantity of ATP, it is an oxygen-intensive process. In pathological states such as myocardial ischemia and heart failure, oxygen availability becomes limited, rendering fatty acid oxidation metabolically inefficient and energetically costly.

During ischemia, continued reliance on fatty acid oxidation suppresses glucose oxidation through inhibitory effects on pyruvate dehydrogenase, resulting in a mismatch between glycolysis and glucose oxidation. This metabolic uncoupling leads to increased lactate production, intracellular acidosis, impaired calcium handling, and reduced mechanical efficiency of the myocardium. Similar metabolic disturbances are

  

observed in chronic heart failure, where persistent fatty acid utilization contributes to progressive contractile dysfunction and adverse ventricular remodelling. In recent years, modulation of myocardial substrate utilization has emerged as a promising therapeutic strategy aimed at improving cardiac efficiency rather than altering hemodynamic load. Partial fatty acid oxidation (pFOX) inhibitors constitute a unique class of metabolic agents that selectively reduce mitochondrial fatty acid oxidation without completely suppressing energy production. By partially inhibiting fatty acid oxidation, these agents promote a metabolic shift toward glucose oxidation, which generates more ATP per unit of oxygen consumed. This shift enhances myocardial oxygen efficiency, reduces proton accumulation, and improves overall cardiac performance under conditions of limited oxygen supply. [1-2]

Several pharmacological agents with pFOX inhibitory properties have demonstrated beneficial effects in both experimental and clinical settings. These agents have been shown to improve exercise tolerance, reduce anginal symptoms, enhance ventricular function, and decrease myocardial oxygen consumption without significantly affecting heart rate or blood pressure. Such characteristics make pFOX inhibitors particularly attractive as adjunctive therapies in patients who remain symptomatic despite optimal conventional treatment. This review aims to provide a comprehensive overview of partial fatty acid oxidation inhibitors, focusing on their biochemical basis, mechanisms of action, and pharmacological characteristics. Preclinical and clinical evidence supporting their therapeutic role in ischemic heart disease and heart failure is critically examined, along with safety considerations and current limitations. Finally, emerging research directions and future therapeutic potential of pFOX inhibitors in cardiovascular medicine are discussed.

## 2. NORMAL MYOCARDIAL ENERGY METABOLISM

The heart is a highly energy-dependent organ that requires a continuous and substantial supply of adenosine triphosphate to maintain rhythmic contraction, electrical stability, and cellular homeostasis. To meet these demands, cardiomyocytes exhibit remarkable metabolic flexibility and are capable of utilizing a wide range of substrates, including glucose, fatty acids, amino acids, and ketone bodies. The relative contribution of each substrate to myocardial energy production is not static but dynamically regulated by developmental stage, physiological status, pathological conditions, and environmental influences.

During foetal life, the myocardium develops in a relatively hypoxic environment characterized by low circulating fatty acid concentrations. Under these conditions, the foetal heart relies predominantly on glucose and lactate metabolism to sustain ATP production. Glycolysis and lactate oxidation provide sufficient energy for cardiac development while minimizing oxygen consumption, which is advantageous in the intrauterine environment. Following birth, the heart undergoes a profound metabolic transition driven by increased oxygen availability, elevated cardiac workload, and hormonal changes. This transition is accompanied by a rapid expansion of mitochondrial content and a marked enhancement of oxidative capacity within cardiomyocytes. As a result, reliance on glycolytic metabolism gradually diminishes, circulating lactate levels decline, and oxidative phosphorylation becomes the dominant pathway for ATP generation. Concurrently, increased availability of circulating fatty acids and rising intracellular triacylglycerol content promote a shift toward fatty acid oxidation. As cardiomyocytes mature from the neonatal period into adulthood, oxidative metabolism becomes increasingly efficient, and fatty acids emerge as the primary energy substrate. In the adult heart, fatty acids contribute the majority of ATP production, while glucose, amino acids, lactate, pyruvate, and ketone bodies serve as complementary or conditionally important fuel sources.

**2.1. Fatty Acid Energy Metabolism:** Fatty acids constitute the principal energy substrate for the adult myocardium and play a central role in sustaining high-energy phosphate production. In addition to serving as an abundant fuel source, fatty acids provide reducing equivalents necessary for mitochondrial oxidative phosphorylation. Long-chain fatty acids are transported across the cardiomyocyte plasma membrane through

  

specialized transport systems, including fatty acid translocase and fatty acid-binding proteins. Once inside the cytoplasm, fatty acids are activated to form long-chain fatty acyl-CoA molecules, a prerequisite for mitochondrial oxidation. Because long-chain fatty acyl-CoA molecules cannot freely cross the mitochondrial inner membrane, their transport depends on the carnitine shuttle system. This system facilitates the conversion of fatty acyl-CoA to acylcarnitine at the outer mitochondrial membrane, followed by translocation into the mitochondrial matrix and reconversion to fatty acyl-CoA. Within the matrix, fatty acids undergo β-oxidation, a cyclic process that progressively shortens the fatty acyl chain. β-Oxidation generates acetyl-CoA, reduced nicotinamide adenine dinucleotide (NADH), and reduced flavin adenine dinucleotide ($FADH_2$). Acetyl-CoA enters the tricarboxylic acid cycle, while NADH and $FADH_2$ donate electrons to the electron transport chain. This coordinated process results in the generation of large quantities of ATP, enabling the myocardium to sustain prolonged mechanical work. Despite its high ATP yield, fatty acid oxidation requires substantial oxygen consumption, making it a relatively oxygen-intensive metabolic pathway.

**2.2. Glucose Energy Metabolism:** Glucose represents an important and highly regulated energy substrate for the heart. It is derived either from circulating glucose or from intracellular glycogen stores, although myocardial glycogen reserves are limited compared with skeletal muscle and liver.

Glucose enters cardiomyocytes through specific glucose transporters embedded in the plasma membrane. Once inside the cell, glucose is rapidly phosphorylated to glucose-6-phosphate, effectively trapping it within the cytoplasm and committing it to metabolic pathways. Through glycolysis, glucose-6-phosphate is converted into pyruvate, generating a modest amount of ATP and reducing equivalents. Under aerobic conditions, pyruvate is transported into mitochondria and oxidized to acetyl-CoA by the pyruvate dehydrogenase complex. Acetyl-CoA subsequently enters the tricarboxylic acid cycle, where it is fully oxidized, leading to efficient ATP generation via oxidative phosphorylation. Glucose oxidation is particularly advantageous because it produces more ATP per unit of oxygen consumed compared with fatty acid oxidation, making it a more oxygen-efficient energy source. In contrast, under hypoxic or ischemic conditions, mitochondrial oxidative capacity is impaired, and pyruvate is preferentially converted to lactate in the cytosol. This anaerobic pathway yields limited ATP and leads to lactate and proton accumulation, which can adversely affect intracellular pH, calcium handling, and contractile function. In addition to glycolysis, pyruvate can serve as an anaplerotic substrate, replenishing intermediates of the tricarboxylic acid cycle and supporting ongoing oxidative metabolism.

**2.3. Ketone Body Energy Metabolism:** Ketone bodies, including acetoacetate and β-hydroxybutyrate, are water-soluble metabolites produced primarily in the liver during periods of increased fatty acid oxidation. Although traditionally viewed as alternative fuels during fasting or starvation, ketone bodies are increasingly recognized as important myocardial energy substrates under both physiological and pathological conditions. Ketone body utilization is particularly prominent during the neonatal period, prolonged fasting, endurance exercise, and metabolic stress. In these states, ketone bodies provide an efficient source of acetyl-CoA for oxidative metabolism. In the failing heart, ketone body oxidation may be upregulated and may partially compensate for impaired glucose and fatty acid metabolism. Within cardiomyocytes, β-hydroxybutyrate is first converted to acetoacetate, which is subsequently activated to acetoacetyl-CoA through a key mitochondrial transfer reaction. Acetoacetyl-CoA is then cleaved to form acetyl-CoA, which enters the tricarboxylic acid cycle and contributes to ATP generation. Continuous utilization of ketone bodies is required to maintain favourable reaction kinetics and support sustained energy production. [3]

## 3. MYOCARDIAL METABOLIC MODULATION

Heart failure is a progressive syndrome driven by complex interactions among neurohormonal activation, ventricular remodelling, and metabolic dysfunction. While

  

traditional concepts of Heart failure pathophysiology have focused primarily on hemodynamic impairment and neurohormonal dysregulation, increasing evidence indicates that myocardial energy deficiency plays a central role in disease progression. Myocardial metabolic modulation has therefore emerged as a therapeutic strategy aimed at improving cardiac performance by optimizing energy production rather than directly altering loading conditions. [4-6]

**3.1. Neurohormonal Activation and Ventricular Remodelling as Drivers of Metabolic Stress:** The classical pathophysiological mechanisms of Heart failure include sustained activation of neurohormonal systems and progressive ventricular remodelling. Neurohormonal activation involves stimulation of the sympathetic adrenergic nervous system, the renin–angiotensin–aldosterone system, and inflammatory signalling pathways. Initially, these mechanisms act as compensatory responses to maintain cardiac output by increasing heart rate, myocardial contractility, peripheral vasoconstriction, and renal retention of sodium and water. However, chronic overactivation becomes maladaptive and exerts deleterious effects on both the myocardium and the peripheral circulation. Ventricular remodelling is a hallmark of Heart failure and occurs at multiple structural levels. At the organ level, remodelling is characterized by changes in left ventricular mass, chamber volume, geometry, and myocardial composition, leading to ventricular dilation and impaired systolic and diastolic function. At the cellular level, cardiomyocyte hypertrophy, altered contractile properties, and progressive myocyte loss through necrosis, apoptosis, and autophagic cell death reduce the heart's contractile reserve. At the subcellular level, remodelling involves extensive alterations in intracellular organelles and structural components, including the sarcolemma, sarcoplasmic reticulum, myofibrils, extracellular matrix, and particularly mitochondria. These neurohormonal and structural changes substantially increase myocardial workload and oxygen demand while simultaneously impairing the cellular machinery responsible for energy production. As a result, the failing heart enters a state of chronic metabolic stress that contributes directly to contractile dysfunction and disease progression.

**3.2. Metabolic Remodelling and the Concept of Energy Starvation:** Metabolic remodelling represents a fundamental component of Heart failure pathophysiology and is characterized by impaired substrate utilization, mitochondrial dysfunction, and reduced availability of high-energy phosphates. The concept of myocardial "energy starvation" describes a state in which the production of adenosine triphosphate (ATP) becomes insufficient to meet the energetic demands of the myocardium. Depletion of ATP and phosphocreatine reserves compromises the energy buffer system essential for normal excitation–contraction coupling. In the early stages of heart failure, the myocardium often continues to rely predominantly on fatty acid oxidation despite declining mitochondrial efficiency and reduced oxygen utilization. This persistent reliance on an oxygen-intensive substrate leads to inefficient ATP generation. As heart failure progresses, metabolic flexibility is lost, mitochondrial oxidative capacity declines further, and total energy reserves become progressively depleted. Metabolic remodelling is also characterized by changes in substrate availability and reduced metabolic capability. Although glycolysis may be upregulated as a compensatory response, it is frequently uncoupled from glucose oxidation, resulting in lactate accumulation, intracellular acidosis, and impaired mechanical efficiency. These metabolic abnormalities amplify ventricular dysfunction and contribute to adverse remodelling.

**3.3. Concept and Principles of Myocardial Metabolic Modulation:** Myocardial metabolic modulation refers to therapeutic interventions designed to optimize cardiac energy metabolism by altering substrate utilization and improving the efficiency of ATP generation. Unlike conventional cardiovascular therapies that primarily target heart rate, preload, afterload, or neurohormonal signalling, metabolic modulation aims to restore the balance between myocardial energy supply and demand at the cellular and mitochondrial levels. Under physiological conditions, the heart maintains energy homeostasis through dynamic

  

selection of metabolic substrates based on availability and energetic requirements. Fatty acids are the predominant energy source in the adult heart; however, fatty acid oxidation consumes more oxygen per unit of ATP generated than glucose oxidation. In contrast, glucose oxidation is more oxygen-efficient and particularly advantageous during ischemia or hypoxia. The central principle of metabolic modulation is therefore to shift myocardial substrate utilization away from excessive fatty acid oxidation toward more efficient glucose oxidation. This shift enhances the coupling between glycolysis and oxidative metabolism, reduces proton accumulation, and improves myocardial mechanical efficiency without increasing oxygen demand.

**3.4. Substrate Switching and Restoration of Metabolic Flexibility:** A key objective of myocardial metabolic modulation is the restoration of metabolic flexibility, defined as the heart's ability to adaptively switch between substrates in response to physiological and pathological stimuli. In Heart failure, metabolic inflexibility develops as fatty acid oxidation remains disproportionately elevated despite impaired mitochondrial function. This maladaptive substrate preference suppresses glucose oxidation and exacerbates energetic inefficiency. By promoting substrate switching toward glucose oxidation, metabolic modulators improve ATP production efficiency and reduce metabolic stress. Enhanced glucose oxidation supports improved calcium handling, reduces intracellular acidosis, and preserves myofilament sensitivity, thereby improving both systolic and diastolic function. Restoration of metabolic flexibility may also contribute to attenuation of adverse ventricular remodelling.

**3.5. Mitochondrial Function and Energetic Efficiency:** Mitochondria play a central role in myocardial metabolic modulation, as they integrate substrate oxidation with ATP synthesis. In heart failure, mitochondrial abnormalities include impaired oxidative phosphorylation, reduced electron transport chain efficiency, increased generation of reactive oxygen species, and diminished ATP output. These changes not only limit energy availability but also promote oxidative stress and cellular injury. Metabolic modulation strategies seek to improve mitochondrial efficiency by optimizing substrate flux through oxidative pathways. Enhancing glucose oxidation relative to fatty acid oxidation reduces oxygen consumption per ATP generated and improves coupling within the electron transport chain. By alleviating mitochondrial overload and reducing oxidative stress, metabolic modulation may preserve mitochondrial integrity and slow the progression of myocardial dysfunction.

**3.6. Hemodynamically Neutral Nature of Metabolic Modulation:** An important advantage of myocardial metabolic modulation is its relative independence from systemic hemodynamic effects. Many conventional cardiovascular therapies lower blood pressure or heart rate, which can limit their tolerability in patients with advanced heart failure. In contrast, metabolic modulators exert their effects primarily at the myocardial cellular level, improving energy efficiency without significantly altering heart rate, blood pressure, or coronary perfusion. This hemodynamically neutral profile makes metabolic modulation an attractive adjunctive strategy in patients who remain symptomatic despite optimal standard therapy. By directly targeting myocardial energetics, metabolic modulation complements neurohormonal blockade and addresses a critical pathophysiological component of Heart failure that is not adequately corrected by hemodynamic interventions alone.

**3.7. Partial Fatty Acid Oxidation Inhibition as a Central Metabolic Strategy:** Among available metabolic modulation approaches, partial inhibition of fatty acid oxidation represents a core and well-established strategy. Partial fatty acid oxidation inhibitors reduce excessive reliance on fatty acid metabolism while preserving overall mitochondrial function. By decreasing fatty acid oxidation flux, these agents relieve inhibition of glucose oxidation, enhance pyruvate utilization, and improve ATP production efficiency. The rationale for partial fatty acid oxidation inhibition aligns closely with the metabolic abnormalities observed in ischemic and failing hearts. By

  

improving the balance between oxygen consumption and energy generation, pFOX inhibitors directly address myocardial energetic inefficiency. Their ability to enhance metabolic efficiency without increasing myocardial workload supports their potential role as disease-modifying therapies rather than purely symptomatic agents.

## 4. METABOLIC REMODELLING AS A THERAPEUTIC RATIONALE FOR PARTIAL FATTY ACID OXIDATION INHIBITION

The recognition that chronic heart failure is not solely a disorder of impaired hemodynamic but also a disease of maladaptive myocardial energy metabolism has reshaped therapeutic strategies. Neurohormonal activation and ventricular remodelling increase myocardial workload and oxygen demand, while progressive metabolic remodelling limits the heart's ability to generate sufficient energy. This imbalance between energy demand and energy supply creates a state of chronic energetic stress that directly contributes to contractile dysfunction and disease progression. One of the hallmark features of metabolic remodelling in heart failure is the persistent reliance on fatty acid oxidation despite declining mitochondrial efficiency and reduced oxygen availability. Fatty acid oxidation is energetically costly in terms of oxygen consumption and suppresses glucose oxidation through substrate competition at the level of mitochondrial metabolism. In the failing heart, this metabolic preference becomes maladaptive, as it exacerbates oxygen inefficiency, promotes uncoupling of glycolysis from glucose oxidation, and contributes to intracellular acidosis and impaired mechanical performance.

Partial fatty acid oxidation (pFOX) inhibitors have emerged as a targeted metabolic approach designed to address this fundamental inefficiency. Rather than completely suppressing fatty acid metabolism, pFOX inhibitors selectively reduce fatty acid oxidation flux, thereby relieving inhibition of glucose oxidation. This metabolic shift enhances the coupling between glycolysis and glucose oxidation, increases ATP production per unit of oxygen consumed, and improves myocardial energy efficiency under conditions of limited oxygen supply. Importantly, pFOX inhibition directly targets the metabolic consequences of neurohormonal and ventricular remodelling without interfering with systemic hemodynamic. Unlike conventional therapies that primarily reduce preload, afterload, or heart rate, pFOX inhibitors act at the level of myocardial substrate utilization. By improving mitochondrial efficiency and restoring metabolic flexibility, these agents may interrupt the vicious cycle linking neurohormonal activation, structural remodelling, and energetic failure. Furthermore, metabolic modulation through pFOX inhibition may have secondary benefits on ventricular remodelling and cellular survival. Improved energy availability supports calcium handling, reduces oxidative stress, and may limit progressive myocyte loss. By enhancing energetic efficiency rather than increasing myocardial workload, pFOX inhibitors represent a complementary strategy to established neurohormonal therapies in heart failure management. [7-8]

## 5. MECHANISMS OF ACTION OF PARTIAL FATTY ACID OXIDATION (PFOX) INHIBITORS

Partial fatty acid oxidation (pFOX) inhibitors exert their therapeutic effects by modulating myocardial substrate utilization and improving the efficiency of energy production in cardiomyocytes. Unlike agents that completely suppress fatty acid metabolism, pFOX inhibitors selectively reduce fatty acid oxidation flux, thereby preserving mitochondrial energy generation while correcting metabolic inefficiencies characteristic of ischemic and failing myocardium. Their mechanisms of action span multiple interconnected levels, including enzymatic regulation, mitochondrial metabolism, substrate competition, and cellular energetic balance. [9-10]

**5.1. Partial Inhibition of Mitochondrial Fatty Acid β-Oxidation:** The primary mechanism of pFOX inhibitors involves selective attenuation of mitochondrial fatty acid β-oxidation. In the adult heart, fatty acid oxidation dominates ATP production but consumes more oxygen per unit of ATP generated than glucose oxidation. In pathological states such as ischemia and heart failure, continued reliance on fatty acid oxidation

  

becomes maladaptive due to impaired oxygen availability and mitochondrial dysfunction. pFOX inhibitors partially reduce fatty acid entry into mitochondria or inhibit key enzymatic steps within the β-oxidation pathway. This controlled reduction limits excessive generation of acetyl-CoA, NADH, and $FADH_2$ from fatty acids without completely abolishing lipid metabolism. As a result, mitochondrial oxidative metabolism is preserved while excessive oxygen consumption is curtailed.

**4.2. Relief of Fatty Acid–Mediated Suppression of Glucose Oxidation:** Fatty acid and glucose metabolism are tightly linked through substrate competition at the mitochondrial level. Elevated fatty acid oxidation increases intramitochondrial acetyl-CoA and reducing equivalents, which suppress the activity of the pyruvate dehydrogenase complex and inhibit glucose oxidation. This inhibition leads to uncoupling of glycolysis from glucose oxidation, promoting lactate accumulation and intracellular acidosis. By partially inhibiting fatty acid oxidation, pFOX inhibitors reduce this inhibitory pressure on glucose oxidation. This effect enhances pyruvate entry into mitochondria and promotes its oxidation to acetyl-CoA. Consequently, glucose oxidation increases, restoring metabolic coupling and improving the efficiency of ATP generation. This shift toward glucose utilization is particularly advantageous under ischemic or hypoxic conditions, where oxygen efficiency is critical.

**4.3. Improvement in Oxygen Efficiency and Energetic Yield:** A central benefit of pFOX inhibition is improved myocardial oxygen efficiency. Glucose oxidation yields more ATP per molecule of oxygen consumed compared with fatty acid oxidation. By promoting glucose oxidation relative to fatty acid oxidation, pFOX inhibitors enhance ATP production without increasing myocardial oxygen demand. This improved energetic efficiency is especially relevant in ischemic myocardium, where oxygen delivery is limited. By optimizing the balance between oxygen consumption and ATP generation, pFOX inhibitors support sustained contractile function and reduce ischemia-induced metabolic stress.

**4.4. Reduction of Proton Accumulation and Intracellular Acidosis:** In failing and ischemic hearts, increased glycolysis without corresponding glucose oxidation leads to excessive proton and lactate production. Intracellular acidosis impairs calcium handling, reduces myofilament sensitivity, and compromises both systolic and diastolic function. By restoring coupling between glycolysis and glucose oxidation, pFOX inhibitors reduce proton accumulation and limit lactate production. This normalization of intracellular pH improves excitation–contraction coupling, enhances calcium homeostasis, and contributes to improved myocardial mechanical efficiency.

**4.5. Modulation of Mitochondrial Function and Oxidative Stress:** Mitochondrial dysfunction is a hallmark of heart failure and contributes to impaired ATP synthesis and increased reactive oxygen species generation. Excessive fatty acid oxidation places a high metabolic burden on mitochondria and may exacerbate oxidative stress. pFOX inhibitors reduce mitochondrial substrate overload by limiting fatty acid flux, thereby improving the efficiency of oxidative phosphorylation. Enhanced glucose oxidation produces a more favourable redox balance within mitochondria, which may reduce electron leakage from the electron transport chain and attenuate oxidative stress. Preservation of mitochondrial function supports sustained ATP production and may slow progressive myocardial injury.

**4.6. Hemodynamically Neutral Mechanism of Action:** An important distinguishing feature of pFOX inhibitors is their hemodynamically neutral mode of action. Unlike conventional anti-anginal or heart failure therapies that reduce heart rate, blood pressure, or preload, pFOX inhibitors primarily act at the metabolic level within cardiomyocytes. They do not significantly alter systemic hemodynamics, coronary blood flow, or myocardial oxygen supply. This property allows pFOX inhibitors to improve myocardial efficiency without increasing workload or compromising perfusion. As a result, they are well suited for use as adjunctive therapies in patients who cannot tolerate further hemodynamic manipulation.

  

**4.7. Integrated Effects on Myocardial Function and Remodelling:** Through combined effects on substrate utilization, mitochondrial efficiency, intracellular pH regulation, and oxidative stress, pFOX inhibitors exert integrated benefits on myocardial function. Improved energy availability supports better contractile performance, enhances diastolic relaxation, and stabilizes electrophysiological properties of the myocardium. Over time, these metabolic improvements may also influence structural remodelling by reducing energetic stress, limiting myocyte loss, and supporting cellular survival pathways. Thus, pFOX inhibitors have the potential to act not only as symptomatic agents but also as modifiers of disease progression in ischemic heart disease and chronic heart failure.

## 6. PHARMACOLOGICAL AGENTS ACTING AS PARTIAL FATTY ACID OXIDATION (PFOX) INHIBITORS

Several pharmacological agents exert beneficial cardiovascular effects through partial inhibition of myocardial fatty acid oxidation. Although these agents differ in chemical structure and primary molecular targets, they share a common therapeutic principle: improving myocardial energy efficiency by reducing excessive fatty acid oxidation and promoting glucose utilization. These agents can be broadly categorized into clinically established pFOX inhibitors and experimental or investigational compounds.

**6.1. Ranolazine:** Ranolazine is one of the most extensively studied pharmacological agents with partial fatty acid oxidation (pFOX) inhibitory properties and represents a key example of myocardial metabolic modulation in clinical practice. Initially developed as an anti-anginal agent, ranolazine improves myocardial efficiency without exerting significant effects on heart rate or systemic blood pressure, distinguishing it from conventional hemodynamic therapies. The primary metabolic action of ranolazine involves partial inhibition of fatty acid oxidation, which promotes a shift in myocardial substrate utilization toward glucose oxidation. Since glucose oxidation requires less oxygen per unit of ATP generated compared to fatty acid oxidation, this metabolic shift enhances myocardial oxygen efficiency, particularly under ischemic conditions. As a result, ranolazine improves the coupling between glycolysis and glucose oxidation, reduces lactate accumulation, and enhances overall energetic efficiency of the myocardium. In addition to its metabolic effects, ranolazine exerts important electrophysiological actions by inhibiting the late inward sodium current in cardiomyocytes. This inhibition reduces intracellular sodium accumulation, which in turn decreases calcium overload via the sodium–calcium exchanger. The reduction in intracellular calcium improves diastolic relaxation, decreases myocardial wall tension, and lowers oxygen consumption. These combined metabolic and ionic effects contribute to improved myocardial mechanical performance without increasing cardiac workload. Ranolazine has also been associated with secondary cellular benefits, including a reduction in oxidative stress through decreased generation of reactive oxygen species and improved myocardial function during reperfusion. These effects further support its role in protecting the myocardium under conditions of ischemia and metabolic stress. An important pharmacological characteristic of ranolazine is its hemodynamically neutral profile. It does not significantly alter heart rate, blood pressure, or coronary blood flow, making it particularly useful in patients who cannot tolerate additional hemodynamic changes. However, ranolazine is known to prolong the corrected QT interval, although this effect has not been strongly associated with an increased incidence of clinically significant ventricular arrhythmias in most studies. Clinically, ranolazine has been approved for the treatment of chronic stable angina, particularly in patients who remain symptomatic despite treatment with conventional anti-anginal therapies such as beta-blockers, calcium channel blockers, or nitrates. It is commonly administered as an extended-release oral formulation and is often used as an adjunctive therapy. [11]

**6.2. Trimetazidine:** Trimetazidine (2,3,4-trimethoxybenzyl piperazine dihydrochloride) is a metabolic anti-ischemic agent that exerts its therapeutic effects independently of changes in myocardial oxygen supply–demand balance. Unlike conventional anti-anginal drugs, it does not

  

significantly affect heart rate, blood pressure, or rate–pressure product, either at rest or during exercise. The primary mechanism of trimetazidine involves partial inhibition of mitochondrial fatty acid β-oxidation, leading to a reduction in fatty acid utilization and a compensatory increase in glucose oxidation. This metabolic shift enhances ATP production efficiency by improving oxygen utilization. In addition, trimetazidine exerts several cytoprotective effects, including limitation of intracellular acidosis, correction of transmembrane ion imbalances that contribute to calcium overload, reduction of oxidative stress through decreased free radical generation, and modulation of inflammatory responses. These actions collectively promote preservation of cellular integrity and enhance the resynthesis of high-energy phosphates following ischemic episodes. Clinically, trimetazidine is widely used in the management of stable angina, particularly as an adjunct therapy in patients who remain symptomatic despite conventional treatment or who are intolerant to further hemodynamic interventions. Its hemodynamically neutral profile allows improvement in myocardial performance without increasing cardiac workload. Additionally, trimetazidine has shown potential benefits in heart failure, where it may improve left ventricular function and reduce symptoms by optimizing myocardial energy metabolism. [12]

**6.3. Etomoxir:** Etomoxir is a potent inhibitor of carnitine palmitoyltransferase-1 (CPT-1), the rate-limiting enzyme responsible for the transport of long-chain fatty acids into mitochondria. By inhibiting CPT-1, etomoxir prevents the formation of acyl-carnitine intermediates required for mitochondrial uptake of fatty acyl chains, thereby significantly reducing fatty acid β-oxidation. This inhibition promotes a compensatory shift toward glucose oxidation, enhancing the efficiency of adenosine triphosphate (ATP) production under conditions of limited oxygen availability. In addition to its primary metabolic action, etomoxir has been reported to exhibit secondary effects, including activation of peroxisome proliferator-activated receptor alpha (PPARα) and modulation of cellular metabolism. However, at higher concentrations, off-target effects have been observed, including disturbances in coenzyme A metabolism and inhibition of mitochondrial electron transport chain complex I, which may impair overall mitochondrial function. Although etomoxir has demonstrated promising metabolic and functional benefits in experimental models of heart failure, its clinical application has been limited due to safety concerns associated with excessive inhibition of fatty acid metabolism. These findings highlight the importance of partial, rather than complete, inhibition of fatty acid oxidation and emphasize the therapeutic advantage of selective pFOX inhibitors that maintain metabolic balance while improving myocardial efficiency. [13]

**6.4. Perhexiline:** Perhexiline maleate is a metabolic anti-anginal agent that exerts its therapeutic effects by modulating myocardial substrate utilization. It acts primarily through inhibition of mitochondrial carnitine palmitoyltransferase-1 and -2 (CPT-1 and CPT-2), enzymes responsible for the transport of long-chain fatty acids into mitochondria. By limiting mitochondrial fatty acid uptake, perhexiline reduces fatty acid oxidation and promotes a metabolic shift toward glucose utilization. This shift enhances myocardial efficiency, as glucose oxidation generates more adenosine triphosphate per unit of oxygen consumed compared with fatty acid oxidation. The resulting oxygen-sparing effect improves the balance between myocardial energy demand and supply, thereby contributing to its anti-anginal efficacy, particularly in patients with refractory angina. Despite its effectiveness, the clinical use of perhexiline is limited by safety concerns, including hepatotoxicity and peripheral neuropathy, largely due to variability in drug metabolism. With therapeutic drug monitoring, its use has re-emerged in selected patients. In addition to angina, perhexiline shows potential benefits in heart failure and other cardiac conditions by improving myocardial energetics. [14]

**6.5. Meldonium:** Meldonium (also known as Mildronate) is a metabolic modulator that exerts its cardioprotective effects by inhibiting fatty acid oxidation and promoting glucose utilization. Its primary mechanism involves inhibition of γ-butyrobetaine hydroxylase, a key enzyme in the biosynthesis of L-carnitine. By reducing carnitine

  

availability, meldonium limits the transport of long-chain fatty acids into mitochondria via the carnitine shuttle, thereby decreasing fatty acid β-oxidation. Additionally, meldonium has been shown to interfere with fatty acid transport by inhibiting components of the carnitine transport system, further reducing mitochondrial fatty acid uptake. This results in a metabolic shift from fatty acid oxidation toward glucose metabolism, which is more oxygen-efficient, particularly under ischemic conditions. Another important effect of meldonium is the prevention of accumulation of cytotoxic intermediates, such as acylcarnitines, which are associated with mitochondrial dysfunction and metabolic stress. By reducing fatty acid flux into mitochondria, meldonium helps protect against ischemia-induced cellular injury and improves overall myocardial energy efficiency. Clinically, meldonium is used in the management of cardiovascular conditions such as angina pectoris, heart failure, and coronary artery disease, particularly in certain regions. Its benefits are attributed to improved myocardial energetics, reduced oxidative stress, and enhanced tolerance to ischemia. Additionally, meldonium has demonstrated potential metabolic benefits, including improved insulin sensitivity. Overall, meldonium represents a distinct approach to metabolic modulation by targeting carnitine biosynthesis and fatty acid transport, thereby complementing other strategies aimed at optimizing myocardial energy metabolism. [15]

**6.6. Oxfenicine and Related Compounds:** Oxfenicine is an orally active inhibitor of carnitine palmitoyltransferase-1 (CPT-1) that reduces mitochondrial fatty acid uptake and oxidation, thereby promoting a metabolic shift toward glucose utilization. This shift improves myocardial energy efficiency, particularly under conditions of ischemia and metabolic stress. Primarily investigated in experimental settings, oxfenicine has contributed significantly to understanding cardiac substrate competition and metabolic modulation. It has demonstrated protective effects against ischemia-induced myocardial injury and has also shown potential in improving metabolic parameters such as insulin sensitivity. However, similar to other CPT-1 inhibitors, its clinical application remains limited due to concerns regarding long-term safety and systemic metabolic effects. These limitations highlight the importance of selective and partial inhibition of fatty acid oxidation, as achieved by pFOX inhibitors, to maintain metabolic balance while improving myocardial efficiency. [16]

## 7. THERAPEUTIC IMPLICATIONS

Pharmacological agents acting as partial fatty acid oxidation (pFOX) inhibitors highlight the clinical feasibility of myocardial metabolic modulation as a therapeutic strategy. By targeting substrate utilization at the mitochondrial level, these agents address a fundamental component of myocardial dysfunction—energetic inefficiency—which is not adequately corrected by conventional hemodynamic therapies. Their ability to enhance energy production without increasing myocardial workload positions pFOX inhibitors as valuable adjuncts in the management of cardiovascular diseases. pFOX inhibitors, including trimetazidine and ranolazine, improve cardiac metabolic efficiency by shifting myocardial energy production from fatty acid oxidation to glucose oxidation, a more oxygen-efficient process. This metabolic shift results in improved adenosine triphosphate (ATP) generation, reduced oxygen consumption, and enhanced mechanical performance of the heart, particularly under ischemic conditions. Importantly, these benefits are achieved without significant effects on heart rate, blood pressure, or coronary blood flow. Key Therapeutic Implications include

- Management of Angina Pectoris: pFOX inhibitors are widely used in the treatment of chronic stable angina, either as monotherapy or in combination with conventional anti-anginal agents. They reduce the frequency and severity of anginal episodes, improve exercise tolerance, and are particularly beneficial in patients who remain symptomatic despite standard therapy.
- Myocardial Protection During Ischemia and Reperfusion: By limiting fatty acid oxidation, these agents reduce the generation of reactive oxygen species and lipid peroxidation, thereby protecting cardiomyocytes from ischemia-induced

  

injury and minimizing reperfusion damage.

- Heart Failure Management: Both experimental and clinical evidence suggest that pFOX inhibitors can improve left ventricular function and overall cardiac performance in chronic heart failure. These benefits are attributed to enhanced myocardial efficiency, reduced oxygen demand, and improved ATP utilization.
- Improvement in Metabolic Efficiency: Inhibition of fatty acid oxidation pathways, particularly at the level of mitochondrial transport and enzymatic regulation, promotes increased glucose and pyruvate oxidation. This reduces lactate accumulation, improves intracellular pH, and enhances coupling between glycolysis and oxidative metabolism.
- Emerging Applications Beyond Cardiology: Modulation of fatty acid oxidation has also attracted interest in oncology and metabolic diseases. Inhibition of fatty acid oxidation pathways may interfere with tumour growth, metastasis, and metabolic adaptability, suggesting potential therapeutic roles when combined with other metabolic interventions.

## CONCLUSION:

pFOX inhibitors represent a paradigm shift in cardiovascular therapy by targeting myocardial energetic inefficiency rather than hemodynamic parameters, thereby enhancing ATP production and oxygen utilization. Their ability to improve cardiac performance without increasing workload positions them as promising adjunctive and potentially disease-modifying agents in ischemic heart disease and heart failure, warranting further clinical investigation.

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