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Review Article

Mitochondrial dysfunction in refractory angina: therapeutic rationale for cardiolipin stabilization with elamipretide

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ABSTRACT

Refractory angina remains a significant clinical challenge despite advances in pharmacological therapy and coronary revascularization. Conventional anti-anginal agents primarily target myocardial oxygen demand or coronary blood flow; however, a substantial proportion of patients continue to experience persistent symptoms, particularly those with coronary microvascular dysfunction or ischemia in the absence of obstructive coronary artery disease. Increasing evidence suggests that impaired myocardial energetics and mitochondrial dysfunction play a central role in ischemic symptom generation. Cardiolipin, a key phospholipid of the inner mitochondrial membrane, is essential for maintaining electron transport chain integrity and efficient oxidative phosphorylation. Disruption of cardiolipin structure during ischemia contributes to mitochondrial dysfunction, reduced adenosine triphosphate (ATP) production, and increased susceptibility to ischemia. Elamipretide is a novel mitochondria-targeted peptide designed to stabilize cardiolipin and improve mitochondrial function under ischemic conditions without significant hemodynamic effects. This review examines the pathophysiological basis of refractory angina with a focus on mitochondrial dysfunction, outlines the pharmacological rationale for targeting cardiolipin, and critically appraises the preclinical and emerging clinical evidence supporting elamipretide as a potential therapeutic strategy. Targeting myocardial bioenergetics represents a mechanistically distinct and promising approach for selected patients with refractory angina.

Keywords: Refractory angina, Mitochondrial dysfunction, Cardiolipin, Elamipretide, Myocardial energetics, Coronary microvascular dysfunction

INTRODUCTION

Angina pectoris remains one of the most common clinical manifestations of ischemic heart disease and continues to impose a substantial burden on patients and healthcare systems worldwide. Despite major advances in pharmacological therapy and coronary revascularization, a significant subset of patients experiences persistent anginal symptoms. Chronic refractory angina is defined as angina lasting for more than three months despite optimal medical therapy and revascularization, and it affects approximately 5-10% of patients with chronic coronary syndromes.[1] These patients often have severely impaired quality of life, frequent hospital visits, and limited therapeutic options.

Conventional anti-anginal therapies, including β-adrenergic blockers, nitrates, calcium channel blockers, and late sodium current inhibitors, primarily reduce myocardial oxygen demand or improve coronary blood flow.

While effective in patients with obstructive epicardial coronary artery disease, these therapies frequently fail to provide adequate symptom relief in patients with diffuse coronary disease, coronary microvascular dysfunction, or ischemia with non-obstructive coronary arteries (INOCA).[2,3] Recognition of INOCA has challenged the traditional epicardial-centric paradigm of angina and highlighted the need for alternative mechanistic approaches.

Coronary microvascular dysfunction and endothelial abnormalities contribute significantly to ischemic symptoms in refractory angina. Impaired coronary flow reserve, abnormal vasomotor responses, and endothelial dysfunction may result in inadequate myocardial perfusion during periods of increased demand, even in the absence of significant epicardial coronary stenosis.[2,3] Importantly, symptom severity often correlates poorly with angiographic findings, suggesting that downstream myocardial mechanisms play a critical role in angina pathogenesis.

The myocardium is an energetically demanding organ that relies predominantly on mitochondrial oxidative phosphorylation for ATP production. More than 90% of myocardial ATP is generated within mitochondria.[4] During ischemia, reduced oxygen availability disrupts mitochondrial respiration, leading to impaired ATP synthesis, accumulation of metabolic intermediates, and increased oxidative stress. These changes impair myocardial relaxation and contraction and may persist even in the absence of irreversible myocardial injury, thereby lowering the ischemic threshold and promoting recurrent anginal symptoms.[5]

Growing evidence indicates that mitochondrial dysfunction is not merely a consequence of ischemia but an active contributor to myocardial ischemic susceptibility. Structural and functional mitochondrial abnormalities have been demonstrated in ischemic heart disease and heart failure, conditions frequently associated with refractory angina.[6,7] These observations have led to increasing interest in therapeutic strategies that target myocardial energetics rather than exclusively focusing on coronary vasomotion or hemodynamic modulation.

Elamipretide is a novel mitochondria-targeted peptide designed to stabilize cardiolipin, a key phospholipid of the inner mitochondrial membrane. By preserving mitochondrial structure and improving oxidative phosphorylation efficiency, elamipretide represents a mechanistically distinct approach to ischemic heart disease.

This review focuses on the role of mitochondrial dysfunction in refractory angina and evaluates the pharmacological rationale and available evidence supporting the elamipretide as a potential therapeutic option.

PATHOPHYSIOLOGY OF REFRACTORY ANGINA: FOCUS ON MITOCHONDRIAL DYSFUNCTION

Refractory angina is increasingly recognized as a heterogeneous clinical syndrome rather than a uniform consequence of obstructive epicardial coronary artery disease. Although fixed coronary stenosis remains an important contributor to myocardial ischemia, a substantial proportion of patients with persistent anginal symptoms demonstrate either non-obstructive coronary arteries or diffuse disease that is not amenable to further revascularization. This shift in clinical understanding has directed attention toward alternative mechanisms, particularly coronary microvascular dysfunction as well as the abnormalities in myocardial energy metabolism.[2,3]

Coronary microvascular dysfunction plays a pivotal role in refractory angina, especially in patients with ischemia with non-obstructive coronary arteries. Structural remodeling of small coronary arterioles, endothelial dysfunction, impaired nitric oxide signaling, and abnormal vasomotor responses contribute to reduced coronary flow reserve and inadequate myocardial perfusion during periods of increased metabolic demand.[2] I

mportantly, the severity of anginal symptoms in these patients often correlates poorly with the angiographic findings, indicating that ischemia may arise downstream of the epicardial coronary anatomy.[3]

At the cellular level, mitochondrial dysfunction has emerged as a critical determinant of ischemic vulnerability in cardiomyocytes. The myocardium is highly dependent on mitochondrial oxidative phosphorylation to sustain continuous contractile activity. During ischemia, impaired oxygen delivery disrupts electron transport chain activity, leading to reduced ATP synthesis, altered calcium handling, and increased generation of reactive oxygen species. These changes impair both systolic contraction and diastolic relaxation, thereby lowering the ischemic threshold and facilitating anginal symptoms even during minimal exertion.[4,5]

Importantly, mitochondrial dysfunction is not confined to acute ischemia-reperfusion injury but is also evident in chronic ischemic heart disease and heart failure states commonly associated with refractory angina. Persistent abnormalities in mitochondrial respiration, substrate utilization, and high-energy phosphate metabolism have been demonstrated in chronically ischemic myocardium, even in the absence of ongoing myocyte necrosis.[4,6] These findings support the concept that chronic energetic inefficiency contributes to sustained ischemic symptoms and exercise intolerance.

Oxidative stress further amplifies mitochondrial injury in refractory angina. Recurrent ischemic episodes promote excessive production of reactive oxygen species, which damage mitochondrial DNA, proteins, and membrane lipids.

This oxidative milieu perpetuates a vicious cycle in which mitochondrial dysfunction leads to further oxidative stress, progressive impairment of oxidative phosphorylation, and increasing susceptibility to ischemia.[5,7] Over time, this cycle reduces myocardial energetic reserve and heightens anginal sensitivity (Figure 1).

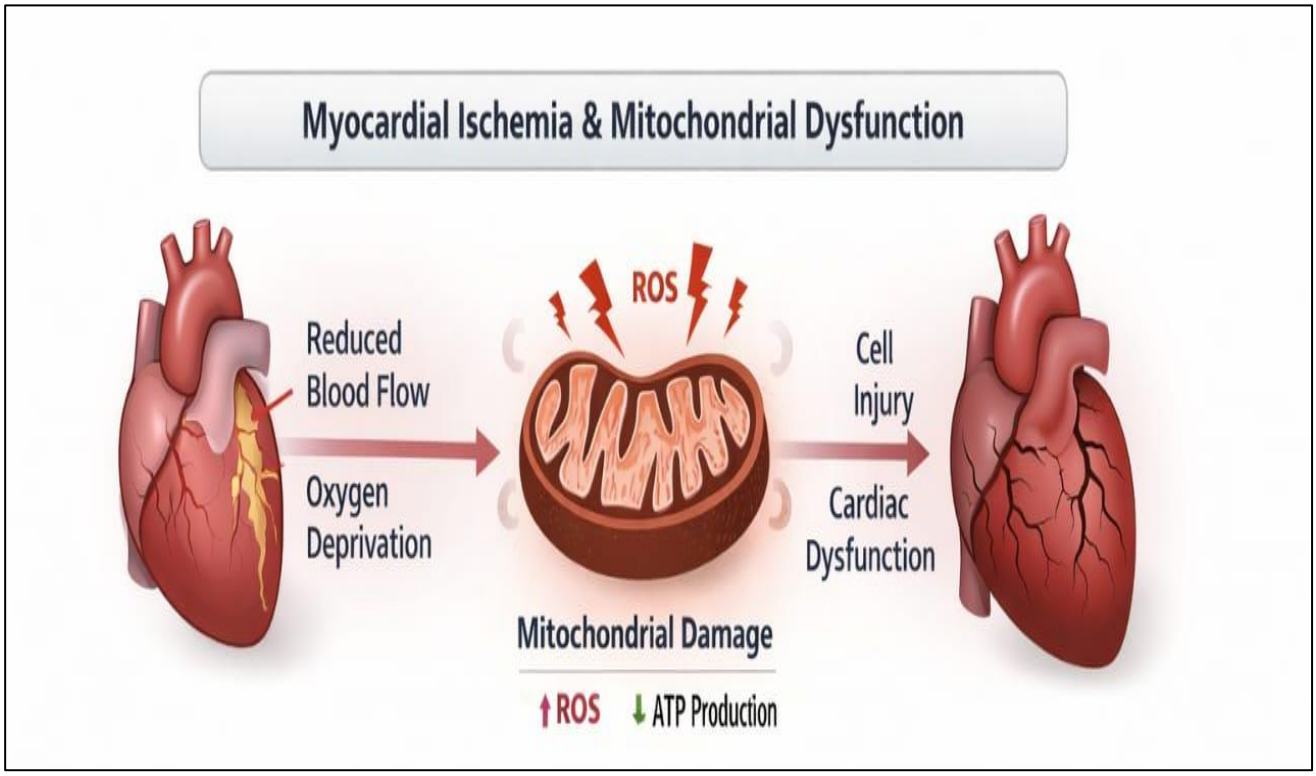

Figure 1: Myocardial ischemia and mitochondrial dysfunction.

*Collectively, these observations indicate that refractory angina is, at least in part, a disorder of myocardial bioenergetics rather than solely a consequence of impaired coronary blood flow. Therapeutic strategies that focus exclusively on coronary vasodilation or hemodynamic modulation may therefore be insufficient in a significant subset of patients. Targeting mitochondrial dysfunction and restoring efficient myocardial energy metabolism represents a mechanistically grounded approach to addressing persistent anginal symptoms.

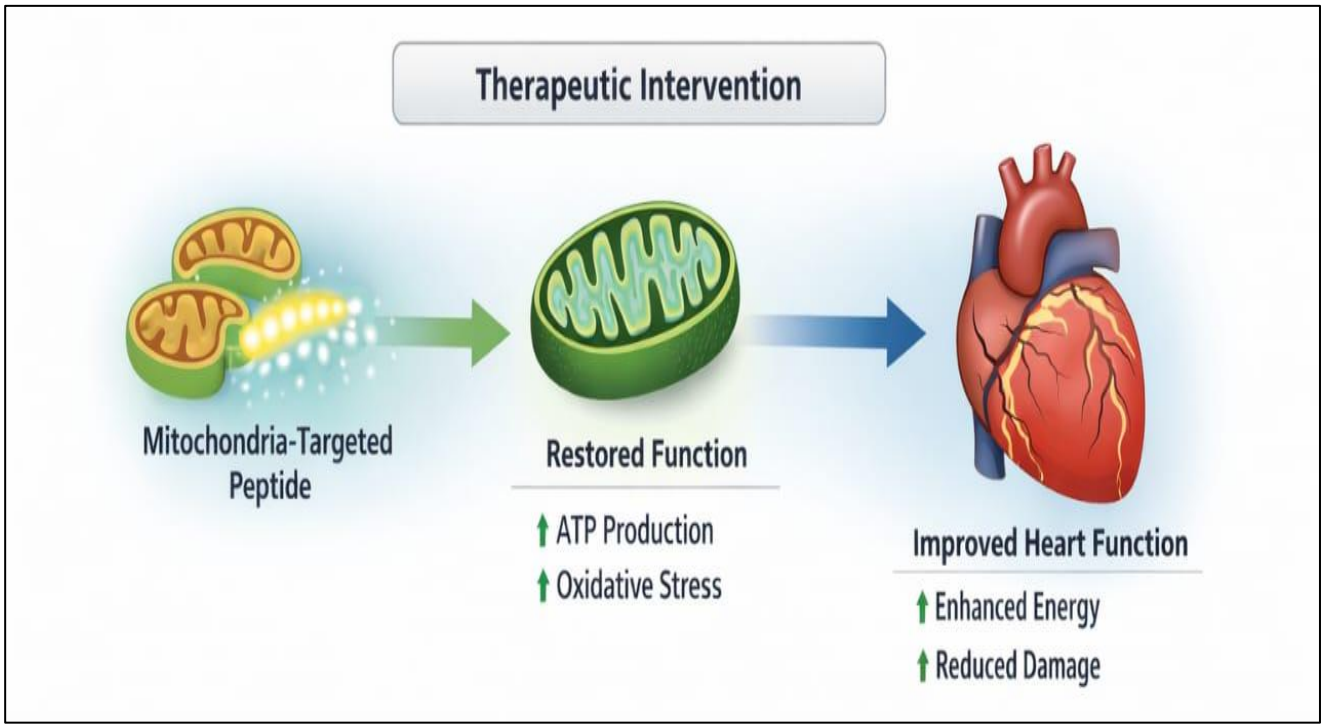

Figure 2: Therapeutic targeting of mitochondrial dysfunction with elamipretide.

*Conceptual illustration depicting the therapeutic intervention using a mitochondria-targeted peptide. Binding of elamipretide to mitochondrial membranes restores mitochondrial function, enhances ATP production, reduces oxidative stress, and improves myocardial energetic efficiency without major hemodynamic effects.

PHARMACOLOGICAL RATIONALE FOR TARGETING CARDIOLIPIN IN REFRACTORY ANGINA

Mitochondrial dysfunction in ischemic heart disease is closely linked to structural and functional abnormalities of the inner mitochondrial membrane, where oxidative phosphorylation takes place. A key determinant of inner mitochondrial membrane integrity is cardiolipin, a unique dimeric phospholipid that is almost exclusively localized to this membrane. Cardiolipin plays a central role in maintaining mitochondrial architecture, stabilizing electron transport chain complexes, and facilitating the formation of respiratory supercomplexes required for efficient ATP generation.[8,9]

Unlike other membrane phospholipids, cardiolipin contains four acyl chains, a structural feature that enables tight interaction with multiple mitochondrial proteins. These interactions are essential for optimal function of respiratory chain complexes I, III, and IV, as well as ATP synthase. Disruption of cardiolipin structure or composition therefore has profound consequences for mitochondrial bioenergetics and cellular energy homeostasis.[8,9]

During myocardial ischemia, cardiolipin is particularly vulnerable to oxidative damage. Its high content of polyunsaturated fatty acids and close proximity to sites of reactive oxygen species generation render it a preferential target for lipid peroxidation. Oxidative modification of cardiolipin disrupts its interaction with key mitochondrial proteins, leading to impaired electron transport chain activity, increased electron leak, and further amplification of oxidative stress.[10,11] These alterations result in reduced ATP synthesis and impaired myocardial energetic efficiency, even before irreversible myocyte injury occurs.

Experimental studies have demonstrated that cardiolipin peroxidation is not merely a downstream consequence of ischemia but a critical driver of mitochondrial dysfunction. Oxidative damage to cardiolipin destabilizes respiratory chain complexes, reduces mitochondrial membrane potential, and impairs coupling between electron transport and ATP synthesis. As a result, cardiomyocytes become energetically inefficient and increasingly susceptible to ischemia during periods of increased metabolic demand, a hallmark feature of refractory angina.[12]

Importantly, cardiolipin abnormalities are not restricted to acute ischemia-reperfusion injury. Alterations in cardiolipin content and acyl chain composition have been consistently observed in chronic ischemic heart disease and heart failure-conditions frequently associated with refractory angina. Studies of human and experimental failing myocardium have demonstrated a selective loss of tetralinoleoyl cardiolipin, the predominant cardiolipin species in healthy cardiac tissue, which correlates with impaired mitochondrial respiration and reduced myocardial energetic reserve.[13]

Given the central role of cardiolipin in mitochondrial structure and function, pharmacological strategies aimed at preserving cardiolipin integrity represent a rational therapeutic approach in refractory angina. Unlike conventional anti-anginal therapies that primarily modulate myocardial oxygen supply or demand, cardiolipin-targeted interventions directly address downstream energetic failure at the cellular level. Such an approach has the potential to improve myocardial efficiency without inducing significant hemodynamic effects, which is particularly relevant in patients with refractory angina who often have limited tolerance to further reductions in heart rate or blood pressure.[14]

These mechanistic insights provide the foundation for the development of cardiolipin-targeted therapies such as elamipretide, which are designed to stabilize mitochondrial membranes, preserve oxidative phosphorylation efficiency, and restore myocardial energy balance under ischemic conditions.

PHARMACOLOGY OF ELAMIPRETIDE

Chemical structure and mitochondrial targeting

Elamipretide (also known as SS-31 or Bendavia) is a synthetic aromatic–cationic tetrapeptide composed of alternating aromatic and basic amino acids. This unique molecular structure confers both lipophilicity and a positive charge, enabling elamipretide to readily cross cellular membranes and selectively accumulate within mitochondria. Unlike conventional mitochondrial-targeted compounds that rely on mitochondrial membrane potential for uptake, elamipretide localizes to mitochondria through high-affinity binding to cardiolipin in the inner mitochondrial membrane.[15,16]

This cardiolipin-directed targeting allows elamipretide to accumulate preferentially in mitochondria-rich tissues such as the myocardium, skeletal muscle, and kidneys. Importantly, mitochondrial localization of elamipretide is preserved under ischemic conditions, when mitochondrial membrane potential may be partially dissipated. This characteristic represents a pharmacological advantage over other mitochondrial-targeted agents whose uptake may be compromised during ischemia.[16]

Mechanism of action

Stabilization of mitochondrial structure and electron transport

Elamipretide exerts its primary pharmacological effect by selectively binding cardiolipin and stabilizing cardiolipin–protein interactions within the inner mitochondrial membrane. By preserving cardiolipin integrity, elamipretide maintains the structural organization of electron transport chain complexes and respiratory supercomplexes, thereby enhancing electron flux and

improving coupling between electron transport and oxidative phosphorylation.[17]

In ischemic myocardium, destabilization of cardiolipin leads to impaired electron transport chain activity and increased electron leak, which is a major source of mitochondrial reactive oxygen species. By stabilizing cardiolipin, elamipretide reduces electron leak and indirectly attenuates mitochondrial oxidative stress without acting as a conventional free-radical scavenger.[17,18]

Elamipretide

↓

Binds cardiolipin in inner mitochondrial membrane

↓

Stabilizes mitochondrial structure

↓

Improved electron transport chain efficiency

↓

↑ ATP production ↓ Oxidative stress

↓

Improved myocardial energetic efficiency

(No major hemodynamic effect)

Improvement of myocardial energetics

Through stabilization of mitochondrial structure and enhancement of electron transport chain efficiency, elamipretide improves ATP production without increasing myocardial oxygen consumption. This mechanism distinguishes elamipretide from inotropic agents, which enhance contractility at the expense of increased energetic demand. Experimental studies have demonstrated that elamipretide improves myocardial energetic efficiency and preserves mitochondrial respiration under ischemic conditions.[18,19]

Improved energetic efficiency is particularly relevant in refractory angina, where ischemic symptoms often arise from an imbalance between myocardial energy demand and impaired energy production rather than from absolute reductions in coronary blood flow.

Modulation of cytochrome c and cytoprotective effects

Oxidative modification of cardiolipin during ischemia promotes dissociation of cytochrome c from the inner mitochondrial membrane, facilitating apoptotic signaling and further mitochondrial dysfunction. By stabilizing cardiolipin–cytochrome c interactions, elamipretide limits cytochrome c release and attenuates activation of downstream apoptotic pathways. This cytoprotective effect contributes to preservation of viable myocardium and improved myocardial function following ischemic stress.[11,17]

Pharmacokinetic and pharmacodynamic considerations

Pharmacokinetic studies have demonstrated that elamipretide exhibits rapid systemic distribution following intravenous or subcutaneous administration, with minimal plasma protein binding and limited hepatic metabolism. Elamipretide is primarily eliminated via renal excretion, largely as unchanged drug. Despite a relatively short plasma half-life, sustained binding to cardiolipin results in prolonged pharmacodynamic effects at the mitochondrial level.[15,19]

From a pharmacodynamic perspective, elamipretide does not significantly influence heart rate, systemic blood pressure, or coronary vasomotor tone. Its therapeutic effects are mediated through improvement of mitochondrial bioenergetics rather than hemodynamic modulation. This profile is particularly advantageous in patients with refractory angina, who often have limited tolerance to further reductions in heart rate or blood pressure and remain symptomatic despite maximal conventional therapy.[14]

CLINICAL EVIDENCE FOR ELAMIPRETIDE IN ISCHEMIC HEART DISEASE AND ANGINA

Preclinical and translational evidence relevant to myocardial ischemia

The rationale for clinical evaluation of elamipretide in ischemic heart disease is supported by extensive preclinical and translational evidence demonstrating its ability to preserve mitochondrial function during ischemic stress. Experimental studies of myocardial ischemia and ischemia–reperfusion injury have shown that mitochondrial dysfunction plays a central role in cardiomyocyte injury and post-ischemic contractile dysfunction.[5,6] Stabilization of mitochondrial structure and preservation of oxidative phosphorylation have therefore emerged as key therapeutic targets in ischemic myocardium.

In animal models of myocardial ischemia, mitochondrial-targeted peptides such as elamipretide have been shown to reduce mitochondrial swelling, preserve respiratory chain activity, and improve post-ischemic myocardial function. These effects are mediated through stabilization of cardiolipin and improved electron transport chain efficiency, resulting in enhanced adenosine triphosphate production under ischemic conditions.[15,17] Importantly, these benefits occur independently of changes in coronary

blood flow, supporting a primary energetic mechanism rather than a vascular effect.

Evidence from human studies in ischemic and failing myocardium

Direct clinical evidence for elamipretide in refractory angina remains limited; however, insights can be drawn from studies conducted in related cardiovascular conditions characterized by impaired myocardial energetics. In patients with heart failure, a condition frequently coexisting with chronic ischemic heart disease, mitochondrial dysfunction and impaired oxidative phosphorylation are well-established contributors to disease progression.[6,7]

Clinical studies in heart failure populations have demonstrated that elamipretide improves mitochondrial energetics and myocardial efficiency without exerting significant hemodynamic effects. Improvements in indices of mitochondrial function and myocardial performance have been observed, although changes in global systolic function have been modest.[19] These findings suggest that elamipretide primarily enhances myocardial energy utilization rather than acting as a conventional inotropic or vasodilator agent.

The relevance of these findings to refractory angina lies in the shared pathophysiological substrate of impaired myocardial energetics. In both conditions, ischemic symptoms and functional limitation may arise from an inability of cardiomyocytes to meet energy demands rather than from fixed reductions in coronary perfusion.[4,6]

Functional evidence from disorders of mitochondrial dysfunction

Additional insight into the clinical effects of elamipretide can be derived from studies conducted in disorders characterized by primary mitochondrial dysfunction. Although these studies were not designed to assess anginal symptoms, they provide important evidence regarding the functional consequences of improving mitochondrial bioenergetics. Elamipretide has been shown to enhance exercise tolerance and functional capacity in conditions associated with impaired oxidative phosphorylation.[19]

Exercise intolerance and early fatigue are hallmark features of refractory angina, reflecting an imbalance between myocardial energy demand and energy production. The observation that elamipretide improves functional capacity without altering heart rate or blood pressure supports the biological plausibility that similar energetic benefits could translate into symptom improvement in patients with refractory angina.

Current status of evidence in refractory angina

At present, large randomized controlled trials specifically evaluating elamipretide in patients with refractory angina are lacking. Consequently, available clinical data should be regarded as hypothesis-generating rather than confirmatory. Nonetheless, the consistency of mechanistic and functional benefits observed across preclinical models, heart failure studies, and disorders of mitochondrial dysfunction provides a coherent translational framework supporting further investigation of elamipretide in angina populations.

Importantly, contemporary understanding of refractory angina emphasizes that symptom burden often correlates poorly with epicardial coronary anatomy and hemodynamic parameters.[1,2] In this context, therapies targeting myocardial energetics rather than coronary vasomotion may represent a complementary approach, particularly in patients with microvascular dysfunction or ischemia with non-obstructive coronary arteries.[3]

Safety considerations

Across available studies, elamipretide has demonstrated a favorable safety and tolerability profile. Its lack of significant effects on systemic blood pressure, heart rate, and coronary vasomotor tone reduces the risk of hemodynamic intolerance, a common limitation of conventional anti-anginal therapies.[14] This pharmacological profile is particularly relevant in patients with refractory angina, who often have multiple comorbidities and limited tolerance to additional cardiovascular medications.

CLINICAL IMPLICATIONS, LIMITATIONS, AND FUTURE DIRECTIONS

Clinical implications

Refractory angina represents a substantial unmet clinical need, particularly in patients who are not suitable candidates for further revascularization and who remain symptomatic despite optimal medical therapy. Conventional anti-anginal drugs primarily target myocardial oxygen supply or demand and may be poorly tolerated due to hemodynamic effects such as hypotension or bradycardia. In contrast, therapies that target myocardial energy metabolism offer a mechanistically distinct approach by addressing ischemia at the cellular level rather than through modulation of coronary blood flow or heart rate.[1,2]

The emerging understanding of refractory angina as a disorder of myocardial bioenergetics has important clinical implications. Patients with coronary microvascular dysfunction or ischemia with non-obstructive coronary arteries frequently exhibit persistent symptoms despite angiographically normal epicardial vessels. In such patients, impaired mitochondrial function and reduced energetic reserve may lower the ischemic threshold and contribute to symptom persistence.[2,3] Elamipretide, by stabilizing cardiolipin and improving mitochondrial

efficiency, may therefore serve as a complementary therapy to conventional anti-anginal agents.

An important clinical advantage of elamipretide is its lack of significant effects on heart rate, systemic blood pressure, or coronary vasomotor tone. This pharmacodynamic profile makes it particularly attractive for patients with refractory angina who are intolerant to further hemodynamic modulation or who remain symptomatic despite maximal doses of conventional therapies.[14] By improving myocardial energetic efficiency rather than altering hemodynamics, elamipretide may enhance exercise tolerance and symptom control without increasing myocardial oxygen demand.

Limitations of current evidence

Despite a strong mechanistic rationale and encouraging translational data, several limitations must be acknowledged. First, direct clinical evidence supporting the use of elamipretide in refractory angina remains limited. Most available human data are derived from studies in heart failure or other conditions characterized by impaired mitochondrial function rather than from angina-specific clinical trials.[19] As such, extrapolation of these findings to refractory angina should be approached with caution.

Second, existing studies have generally involved small sample sizes and short-term administration. The long-term efficacy of elamipretide in reducing angina frequency, improving quality of life, and enhancing exercise capacity has not yet been established. Additionally, the durability of mitochondrial benefits with chronic therapy and their translation into sustained clinical improvement remain uncertain.

Third, refractory angina encompasses a heterogeneous patient population with diverse underlying mechanisms, including microvascular dysfunction, diffuse atherosclerosis, and metabolic abnormalities. It is likely that only a subset of patients-particularly those with predominant energetic impairment-will derive meaningful benefit from mitochondrial-targeted therapy. At present, reliable clinical or imaging biomarkers to identify such patients are not well defined.[4,6]

Future directions

Future research should focus on well-designed, randomized controlled trials specifically evaluating elamipretide in patients with refractory angina. Such studies should incorporate patient-centered endpoints, including angina frequency, exercise tolerance, and quality of life, alongside mechanistic assessments of myocardial energetics. Given the limitations of traditional angiographic and hemodynamic measures in this population, functional and metabolic endpoints may provide more meaningful insights into therapeutic efficacy.[1,2]

Further investigation is also needed to identify patient subgroups most likely to benefit from mitochondrial-targeted therapy. Integration of advanced imaging techniques, metabolic profiling, and functional assessments may help refine patient selection and optimize therapeutic outcomes. Beyond elamipretide, continued exploration of mitochondrial biology may lead to the development of additional agents targeting myocardial energetics, potentially expanding the therapeutic armamentarium for refractory angina.

CONCLUSION

Refractory angina remains a challenging clinical condition with limited therapeutic options. Growing evidence implicates mitochondrial dysfunction and impaired myocardial energetics as key contributors to persistent ischemic symptoms. Elamipretide represents a novel, mechanistically distinct therapeutic approach that targets mitochondrial dysfunction by stabilizing cardiolipin and improving oxidative phosphorylation efficiency. While definitive angina-specific clinical trial data are still needed, mitochondrial-targeted therapy offers a promising adjunctive strategy for selected patients with refractory angina and highlights the importance of addressing ischemic heart disease at the level of cellular energy metabolism.

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