

Hibernating Myocardium: Pathophysiology, Diagnostic Challenges, and Therapeutic Strategies



Rishita Dave^{1*}, Alberto Ayala², Chinyere Pamugo³, Arnold Ocoro⁴, Krish Telang⁵, Vianka Vanessa Yanez Montalvo⁶, Melanie Dayana Yanez Montalvo⁷, Mary Joe Esquivel Romero⁸ and Maria Isabel Gomez-Coral⁹

¹University of Medicine and Health Sciences, Saint Kitts

²Universidad del Noreste, México, MD Anderson Cancer Center, Houston, Texas

³UTHealth Science of Houston, USA

⁴Mount Sinai Medical Center, Miami Beach, Florida, USA

⁵The University of Georgia, School of Health Sciences, Tbilisi

⁶Universidad de Guayaquil, Ecuador

⁷Universidad de Guayaquil, Ecuador

⁸Universidad Autónoma de Centroamérica, Costa Rica

⁹Universidad del Valle, México

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***Corresponding author:** Rishita Dave, Alberto Ayala, University of Medicine and Health Sciences, Saint Kitts

Abstract

Background: Hibernating Myocardium (HM) is a state of chronic but reversible left ventricular dysfunction due to sustained myocardial hypoperfusion. Proper identification and management of HM are critical for optimizing patient outcomes in ischemic heart disease and heart failure.

Objectives: This review explores the pathophysiology, diagnostic modalities, clinical implications, and therapeutic strategies for hibernating myocardium.

Methods: A comprehensive literature review focused on the mechanisms underlying HM, advancements in imaging techniques, prognostic implications, and treatment approaches, including revascularization and emerging regenerative therapies.

Results: HM is an adaptive myocardial response characterized by metabolic downregulation, mitochondrial dysfunction, and impaired calcium homeostasis. Diagnostic modalities such as PET, SPECT, and CMR facilitate differentiation between viable and non-viable myocardium, guiding revascularization decisions. CABG and PCI effectively restore perfusion and improve left ventricular function, while pharmacologic interventions complement myocardial recovery. Emerging therapies, including stem cell transplantation and gene therapy, show promise in myocardial regeneration.

Abbreviations: HM: Hibernating Myocardium; PET: Positron Emission Tomography; SPECT: Single-Photon Emission Computed Tomography; CMR: Cardiac Magnetic Resonance Imaging; CABG: Coronary Artery Bypass Grafting; PCI: Percutaneous Coronary Intervention; ACE: Angiotensin-Converting Enzyme; ARB: Angiotensin Receptor Blocker; LGE: Late Gadolinium Enhancement; CT: Computed Tomography; FFR: Fractional Flow Reserve; IMR: Index of Microcirculatory Resistance; DM: Diabetes Mellitus; COPD: Chronic Obstructive Pulmonary Disease; ATP: Adenosine Triphosphate

Keywords: Hibernating myocardium; Ischemic heart disease; Revascularization; Myocardial viability; Cardiac imaging

Introduction

Hibernating Myocardium (HM) is a condition characterized by chronic yet reversible left ventricular dysfunction resulting from persistently reduced coronary blood flow. In this state, myocardial contractile function diminishes to match the decreased blood

supply, thereby preventing myocardial necrosis [1]. This adaptive response allows the myocardium to survive under conditions of limited perfusion, with the potential for functional recovery upon restoration of adequate blood flow through revascularization

procedures [2]. Clinically, HM is significant in ischemic heart disease and heart failure. In patients with coronary artery disease, regions of the myocardium may enter a hibernating state, leading to impaired left ventricular function and contributing to heart failure symptoms [3]. Identifying hibernating myocardium is crucial, as these regions remain viable and can regain normal function following revascularization procedures such as coronary artery bypass grafting or percutaneous coronary intervention [4]. Accurate detection of HM can guide therapeutic decisions, potentially improving patient outcomes by targeting reversible myocardial dysfunction. Advanced imaging techniques, including Positron Emission Tomography (PET), Single-Photon Emission Computed Tomography (SPECT), and cardiac Magnetic Resonance Imaging (MRI), are employed to detect hibernating myocardium. These modalities assess myocardial perfusion and viability, aiding the differentiation between hibernating tissue and irreversibly damaged myocardium [5]. Timely and precise identification of HM enables clinicians to tailor revascularization strategies, thereby enhancing left ventricular function and alleviating heart failure symptoms in affected patients.

Pathophysiology

Hibernating myocardium is a condition of chronic yet reversible myocardial dysfunction that arises from prolonged but incomplete coronary ischemia. The pathogenesis involves an adaptive downregulation of myocardial metabolism and contractile function in response to sustained hypoperfusion, allowing the heart muscle to survive despite reduced oxygen and nutrient supply [6]. There are two primary hypotheses regarding the development of hibernating myocardium. One theory suggests that the myocardium reduces energy and oxygen consumption due to limited coronary perfusion by suppressing metabolic activity and contractile force, a phenomenon termed the “smart heart” hypothesis. This metabolic shift maintains a balance between supply and demand, preserving cellular viability at the expense of function. Another hypothesis proposes that in the presence of reduced coronary flow reserve, intermittent surges in metabolic demand lead to recurrent episodes of ischemia and myocardial stunning, ultimately resulting in chronic dysfunction [7-9]. At the cellular level, cardiomyocytes in hibernating myocardium experience a shift from oxidative phosphorylation (which primarily uses fatty acids) to anaerobic glycolysis. This metabolic adaptation increases glucose uptake and accumulates lactate, causing intracellular acidosis and energy inefficiency.

Concurrently, mitochondrial dysfunction exacerbates ATP depletion, generating oxidative stress that further compromises myocardial viability. Impaired calcium homeostasis also plays a crucial role, as dysregulation of calcium-handling proteins contributes to contractile dysfunction. These combined factors create an energy-starved yet viable myocardium that remains in a state of chronic hypercontractility [8,9]. A critical distinction exists between hibernating myocardium and stunned

myocardium. While stunned myocardium results from a transient ischemic event followed by delayed functional recovery despite restored perfusion, hibernating myocardium represents a chronic adaptive response to persistent hypoperfusion. Unlike infarcted myocardium, which undergoes irreversible necrosis due to prolonged ischemia, hibernating myocardium retains the potential for functional recovery if adequate blood flow is restored through revascularization strategies such as Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Grafting (CABG) [6-10]. Understanding the hibernating myocardium’s molecular and metabolic adaptations is essential for refining diagnostic techniques and optimizing therapeutic interventions to restore myocardial function.

Diagnostic Approaches

The diagnostic evaluation of hibernating myocardium relies on a multimodal imaging approach to assess myocardial viability, perfusion, and contractile reserve. Dobutamine Stress Echocardiography (DSE) is a widely used, cost-effective technique that evaluates contractile reserve by identifying improvements in wall motion during low-dose dobutamine infusion, which strongly predicts recovery of function after revascularization [11]. Nuclear imaging, particularly Positron Emission Tomography (PET) with 18F-fluorodeoxyglucose (FDG), is considered the gold standard for detecting viable myocardium, as it identifies a perfusion-metabolism mismatch—a hallmark of hibernating myocardium [12]. Single-Photon Emission Computed Tomography (SPECT) also provides valuable insights into myocardial perfusion and viability, though it is less sensitive than PET. Cardiac Magnetic Resonance imaging (CMR) offers unparalleled spatial resolution. It combines Late Gadolinium Enhancement (LGE), which identifies scarred myocardium, with stress perfusion imaging and low-dose dobutamine CMR to assess ischemia and contractile reserve. LGE-CMR is particularly effective in distinguishing viable from non-viable myocardium based on the extent of fibrosis. Coronary angiography remains essential for delineating coronary anatomy and guiding revascularization strategies, while coronary CT angiography provides a non-invasive alternative to assess coronary artery disease and myocardial perfusion. Integrating these modalities—such as hybrid PET/CT or PET/MRI—enhances diagnostic accuracy by simultaneously evaluating perfusion, metabolism, and structural integrity, offering a comprehensive assessment of hibernating myocardium to guide clinical decision-making [3].

Clinical Implications & Prognostic Relevance

In patients with coronary artery disease, Hibernating Myocardium (HM) contributes to heart failure by reducing myocardial contractility and dysfunctional heart muscle [13]. Revascularization procedures, such as Coronary Artery Bypass Grafting (CABG), can restore blood flow to these regions (heart muscles), leading to improved cardiac function and symptoms

[14]. Studies have demonstrated that patients with hibernating myocardium who undergo successful revascularization experience enhanced left ventricular prognosis and positive health outcomes. Discussed that diagnostic modalities such as dobutamine stress echocardiography, cardiac MRI, and Positron Emission Tomography (PET) are instrumental in detecting hibernating myocardium, which can contribute to chronic left ventricular dysfunction [2]. Also, these tools help differentiate between viable and non-viable myocardial tissue, guiding therapeutic decisions and improving left ventricular ejection fraction [2].

Studies have demonstrated that revascularization procedures, including Coronary Artery Bypass Grafting (CABG) and Percutaneous Coronary Interventions (PCI), can lead to significant improvements in heart function and survival rates for patients with hibernating myocardium.

For instance, a study by Duan, L., & Zhang, X. revealed that revascularization was associated with better long-term survival than medical therapy alone in patients with hibernating myocardium [15]. The authors opined that HM may be more prevalent in IHF patients with DM compared with non-DM. Hence, the prognostic value of hibernating myocardium and cardiac remodeling using gated 99mTc-MIBI SPECT and 18F-FDG PET in patients with ischemic heart failure and diabetes requires further studies and process improvement [16]. A balance between recovery and progression is determined by factors such as the duration and severity of ischemia, collateral circulation, comorbid conditions such as diabetes, COPD, and autoimmune diseases, and the patient's overall health status [8,17]. As Duan, L., & Zhang, X. highlighted, "Advanced imaging techniques, such as gated 99mTc-MIBI SPECT and gated 18F-FDG PET, play a crucial role in assessing HM and guiding treatment decisions" [15]. Meanwhile, if the ischemia persists without timely management, HM can progress to irreversible damage, leading to myocardial fibrosis, heart failure, and death [15-17]. In effect, timely recognition and intervention are sacrosanct to the hibernating myocardium in restoring myocardial function, symptom control, and enhanced prognosis in heart failure patients.

Therapeutic Strategies

Managing hibernating myocardium primarily involves restoring blood flow to viable but dysfunctional myocardial tissue. Revascularization remains the cornerstone of treatment, with two primary modalities: Coronary Artery Bypass Grafting (CABG) and Percutaneous Coronary Intervention (PCI). CABG has been historically favored in patients with extensive Coronary Artery Disease (CAD) and impaired left ventricular function, particularly when multiple vessels are affected. Studies have demonstrated that CABG provides superior long-term survival benefits and improved left ventricular function in patients with viable myocardium compared to medical therapy alone [18]. However, PCI offers a less invasive alternative, particularly in patients with focal lesions or high surgical risk. While PCI effectively restores

perfusion, its long-term benefits in patients with hibernating myocardium remain a subject of ongoing research, with some studies suggesting that its impact on left ventricular recovery may be less robust than CABG [19]. The choice between CABG and PCI should be individualized, taking into account the extent of coronary disease, patient comorbidities, and myocardial viability assessments. Beyond revascularization, optimal medical therapy plays a crucial role in managing hibernating myocardium. Beta-blockers are fundamental in reducing myocardial oxygen demand and improving ventricular function over time, particularly in patients with underlying heart failure [20].

Angiotensin-Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs) have demonstrated benefits in reducing left ventricular remodeling and improving survival in ischemic cardiomyopathy. Additionally, metabolic modulators such as trimetazidine have shown promise in shifting myocardial metabolism from fatty acid oxidation to glucose utilization, thereby enhancing myocardial efficiency under ischemic conditions [21]. These pharmacological interventions serve to optimize myocardial function and mitigate the progression of ischemic heart disease, particularly in patients not eligible for revascularization. Emerging therapies in regenerative medicine offer novel potential in the management of hibernating myocardium. Stem cell therapy has been explored to promote myocardial repair by enhancing angiogenesis and cardiomyocyte regeneration. Early clinical trials have suggested that mesenchymal stem cells and induced pluripotent stem cells may improve left ventricular function and perfusion in patients with chronic ischemic heart disease [22]. However, these approaches' long-term efficacy and safety remain under investigation, and further research is needed to establish their role in clinical practice. Advances in gene therapy and tissue engineering may also provide future avenues for myocardial recovery beyond conventional revascularization strategies.

Future Directions & Research Gaps

Despite recent advancements in understanding chronic but reversible ischemic dysfunction pathophysiology, many uncertainties remain. Definite evidence that the initial stages of dysfunction are caused by chronic stunning is still lacking, and further research is needed to identify biochemical markers, such as troponin I cleavage and activation of calcium-dependent proteases, to differentiate stunning from hibernation. Future research on hibernating myocardium (HM) should focus on personalized approaches to selecting patients for revascularization and advancements in imaging and biomarkers for better detection [22,3]. While studies like the STICH trial have questioned the role of viability testing in guiding revascularization, the ongoing REVIVED-BCIS2 trial aims to clarify its clinical utility [3]. A more tailored approach integrating myocardial viability, coronary flow reserve, and metabolic markers could improve patient selection and outcomes. Advancements in imaging technologies, such as hybrid PET/MRI and stress/LGE-CMR, allow for a more

comprehensive assessment of myocardial viability by combining metabolic, perfusion, and structural data. Invasive coronary physiology techniques, including Fractional Flow Reserve (FFR) and Microcirculatory Resistance (IMR) index, may further refine ischemia and HM evaluation. 2 Additionally, biomarkers like high-sensitivity troponin have shown promise in identifying ongoing myocardial stress, while emerging molecular markers linked to oxidative stress and metabolism warrant further investigation [22]. Research should address gaps in predicting post-revascularization recovery, as functional improvement is often delayed despite complete revascularization. Proteomic remodeling is incomplete, with persistent reductions in contractile and metabolic proteins, which may explain why some patients fail to regain full myocardial function [23]. The variability in myocardial recovery time suggests that a one-size-fits-all approach to revascularization may be insufficient, emphasizing the need for adjunctive strategies such as metabolic modulation, regenerative medicine, and pharmacologic support to accelerate myocardial recovery. Furthermore, the integration of Artificial Intelligence (AI) and machine learning in imaging interpretation could enhance diagnostic accuracy and predictive modeling for personalized treatment decisions. Standardizing imaging protocols, refining novel biomarker assessments, and conducting long-term follow-up studies will be essential in defining the optimal management of hibernating myocardium [3,23].

Conclusion

Hibernating myocardium represents a critical yet reversible form of chronic myocardial dysfunction resulting from sustained hypoperfusion. Its identification and management hold significant implications for patients with ischemic heart disease and heart failure. Advances in diagnostic imaging, including PET, SPECT, and CMR, have refined the ability to differentiate viable myocardium from irreversibly damaged tissue, allowing for precise therapeutic decision-making. Revascularization strategies, particularly CABG and PCI, remain the cornerstone of treatment, with compelling evidence supporting their role in restoring myocardial function and improving prognosis. Pharmacologic interventions, including beta-blockers, ACE inhibitors, and metabolic modulators, provide adjunctive benefits in optimizing myocardial efficiency. Emerging regenerative therapies, such as stem cell transplantation and gene therapy, offer promising avenues for future treatment but require further investigation. Addressing research gaps, particularly in predicting post-revascularization recovery and refining patient selection criteria, will enhance clinical outcomes. Continued advancements in imaging technologies, biomarker development, and artificial intelligence integration will further refine the management of hibernating myocardium, ultimately improving patient survival and quality of life.

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