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Narrative Review

Contributions of Pathobiological and Translational Science to Understanding and Managing Ischemic Heart Disease: Progress, Impediments, and Future Directions

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Abstract

Key pathobiological components of ischemic heart disease have been identified as follows: (1) In 1970 to 1973, myocardial infarct size was found to be the primary determinant of prognosis after acute myocardial infarction (AMI); (2) in 1973 to 1989, vulnerable coronary artery plaques were found to predispose individuals to coronary plaque disruption and thrombosis, causing major AMI; (3) in 1972, timely coronary reperfusion was demonstrated to limit the size of evolving AMI but with risk of reperfusion injury; and (4) in 1986, myocardial conditioning was found to be a clinically significant modulator capable of delaying AMI progression. Promising cardioprotective strategies combining timely reperfusion with conditioning in experimental animal and proof-of-concept human studies have not been shown to optimize cardioprotection, and this area of research has stalled. Nevertheless, opportunities for further progress against ischemic heart disease have come from new perspectives and approaches, including (1) recognition that functionally significant ischemic heart disease can result from microvascular dysfunction or epicardial coronary atherosclerosis; (2) rapid diagnosis of AMI subtypes through application of the Universal Definition of Myocardial Infarction based on high-sensitivity cardiac troponin measurements; (3) the Canadian Cardiovascular Society classification of AMI based on stages of tissue injury severity, as detected by advanced imaging; (4) implementation of the occlusion vs nonocclusion MI paradigm to prompt aggressive management of all ST-segment elevation MI and the one-third of non–ST-segment elevation MI with total occlusion; and (5) implementation of the Early Heart Attack Care program, which emphasizes prodromal symptom recognition to prevent AMI progression.

Keywords: Ischemic heart diseases; myocardial infarction; death, sudden, cardiac; myocardial reperfusion injury

Introduction

In the mid-20th century, ischemic heart disease due to coronary atherosclerosis, also known as coronary heart disease or coronary artery disease (CAD), was identified as a clinically significant cause of morbidity and mortality that was increasing at an alarming rate.[1] Recognition of the CAD epidemic led to accelerated research involving epidemiology, experimental pathobiology, and clinical investigation to determine its causes and consequences and to develop approach to prevention.[2-5]

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Experimental and Clinical Investigation Aimed at the Basic Pathobiology of Myocardial Ischemic Injury and Cardioprotection

Beginning with the seminal work of Jennings and associates, extensive experimental studies provided insights into the pathobiology of cardiomyocyte injury and acute myocardial infarction (AMI).[6-8] This field of experimental research led to recognition of the importance of the modulatory effects of reperfusion (in 1972) and conditioning (in 1986) on the evolution of AMI and cardiomyocyte injury (Table I).[6-10] Pathologic studies were also instrumental in establishing the concept of vulnerable plaques (in 1973-1989) as plaques with features predisposing individuals to coronary plaque erosion, fissuring, rupture, hemorrhage, and thrombosis leading to major AMI.[11]

In 1970 to 1973, autopsy studies showed that MI size was the primary determinant of morbidity and mortality after AMI.[5] This insight gave rise to an imperative to develop interventions to limit MI size.[12] Cardioprotection studies were conducted based on the hypothesis that pharmacologic agents could reduce AMI size by reducing myocardial oxygen demand. Promising experimental findings with various drugs did not translate into clinical effectiveness, however.[13,14] Contrary to the underlying hypothesis, reducing the contractile determinants of myocardial consumption had little impact on ischemic, noncontractile myocardium. The only consistently successful strategy to reducing AMI size was reperfusion after reversal of a coronary occlusion. Timely reperfusion proved to be the breakthrough of the modern era and the basis for all clinical infarct therapy.[6-10]

Timely coronary reperfusion was the latest of several initiatives aimed at improving the management of AMI. Short-term mortality after AMI was reduced from 30%

Key Points

- Progress in cardioprotection against ischemic myocardial injury beyond timely reperfusion has stalled.
- Ischemic heart disease results from coronary microvascular dysfunction and epicardial coronary atherosclerosis.
- Opportunities for further progress against ischemic heart disease have come from new perspectives and approaches, including an Early Heart Attack Care program that emphasizes prodromal symptom recognition to prevent the progression of AMI.

Abbreviations

ACS, acute coronary syndrome
AMI, acute myocardial infarction
CAD, coronary artery disease
hs-cTn, high-sensitivity cardiac troponin
NSTEMI, non–ST-segment elevation myocardial infarction
PCI, percutaneous coronary intervention
STEMI, ST-segment elevation myocardial infarction
UDMI, Universal Definition of Myocardial Infarction

TABLE I. Major Modulators of Myocardial Ischemic Injury[10]

Reperfusion therapy
Thrombolytic agents (streptokinase, tissue plasminogen activating factor)
PCIs: percutaneous transluminal coronary angioplasty, coronary artery stenting
Myocardial conditioning
Physical interventions, pharmacologic interventions
Ischemic preconditioning: conditioning protocol before PCI
Ischemic preconditioning: conditioning protocol during PCI
Ischemic postconditioning: conditioning protocol immediately after PCI
Second wave of preconditioning: return of conditioning effect after a 24-h refractory period
Remote ischemic conditioning: conditioning produced by intermittent leg or arm ischemia

PCI, percutaneous coronary intervention.
Reference: Hausenloy DJ, Yellon DM. Ischaemic conditioning and reperfusion injury. *Nat Rev Cardiol*. 2016;13(4):193-209. doi:10.1038/nrcardio.2016.5

in the pre–coronary care unit era (before 1962) to 15% in the coronary care unit era (from 1962 to 1984), with the introduction of electrophysiologic and hemodynamic monitoring and cardioversion of ventricular fibrillation; a further reduction to 6% was achieved at the start of the reperfusion era (beginning in 1984).[15] This era featured the introduction of thrombolytic therapy and percutaneous coronary interventions (PCIs), including percutaneous transluminal coronary angioplasty and coronary stenting, along with pharmacologic interventions, including β-adrenergic blockers and aspirin.[16,17] Pathologic studies identified complications of coronary artery bypass grafting and interventional cardiology procedures and also contributed to progressive improvements in these therapies.[18-20]

Guidelines for Experimental Research

A lack of rigor in many experimental studies was identified as a significant reason for the largely unsuccessful clinical translation of positive experimental results to the clinical arena.[5,14] This finding led to several initiatives aimed at developing consensus guidelines for the conduct of rigorous preclinical animal work: the National Heart, Lung, and Blood Institute Cooperative Study in 1985; the National Heart, Lung, and Blood Institute–sponsored Consortium for Preclinical Assessment of Cardioprotective Therapies in 2015; and the European Improving Preclinical Assessment of Cardioprotective Therapies initiative in 2021 to 2024.[7,21-24]

Myocardial Conditioning

Myocardial conditioning was discovered in 1986 (Table I). Ischemic conditioning produced by brief episodes of coronary occlusion and reperfusion was found to delay the onset and temporarily limit the extent of myocardial injury after sustained coronary occlusion.[6] Ischemic conditioning involves activating a complex molecular self-defense program by autocoids and cytokines, which act as triggers, and transduction pathways acting as mediators on effectors, including mitochondrial adenosine triphosphate–sensitive potassium channels and the mitochondrial permeability transition pore.[7-10] The result is protection against the sustained opening of the mitochondrial membrane permeability transition pore. Preservation of mitochondrial integrity is critical for cardiomyocyte survival, and loss of mitochondrial integrity leads to irreversible cardiomyocyte injury.[25] Several forms of conditioning have been found to induce the molecular self-defense mechanism in at-risk cardiomyocytes (Table I).[6-10]

Rationale for Combining Coronary Reperfusion With Myocardial Conditioning

The variables affecting MI size are (1) the site of the occluded coronary artery and the extent of preexisting collateral vessels and their actual perfusion, which together modulate the size of the area at risk; (2) the duration of flow deprivation and timing of recanalization; and (3) the efficacy of recanalization in terms of both reestablishment of the original arterial lumen and maintenance of the opened lumen.[26-28]

In patients presenting with acute coronary syndrome (ACS), timely reperfusion with thrombolytics or PCI reduces the extent of AMI, mainly when introduced within 90 to 120 minutes of onset of the acute event.[28] Patients were found to be at risk of developing clinically significant reperfusion injury, however, as occurred in experimental animal models.[9,10] Reperfusion injury manifests as arrhythmias and death of injured cardiomyocytes at the leading edge of the evolving infarct as well as microvascular damage, hemorrhage, and a "no-reflow" phenomenon. Lethal reperfusion injury contributes up to 50% of the resultant subendocardial infarct (Fig. 1).[8,9] No-reflow is a serious complication of reperfused MI and carries, independent of infarct size, an unfavorable prognosis.[5-10,29] Because of this complexity, reperfusion is considered a double-edged sword.[30]

The Second Wave of Cardioprotection Studies

A second wave of experimental cardioprotection studies was undertaken to combine timely PCI with various forms of conditioning to decrease reperfusion injury and increase myocardial salvage. Again, promising experimental results did not translate into consistently successful improvements.[13] This finding was confirmed in an umbrella review of 228 systematic reviews and meta-analyses comparing results of pharmacologic treatments and conditioning protocols in animal experiments with results in human patients with unstable angina pectoris, AMI, or cardiovascular surgery.[14] As this umbrella review documented, further progress in cardioprotection has stalled.

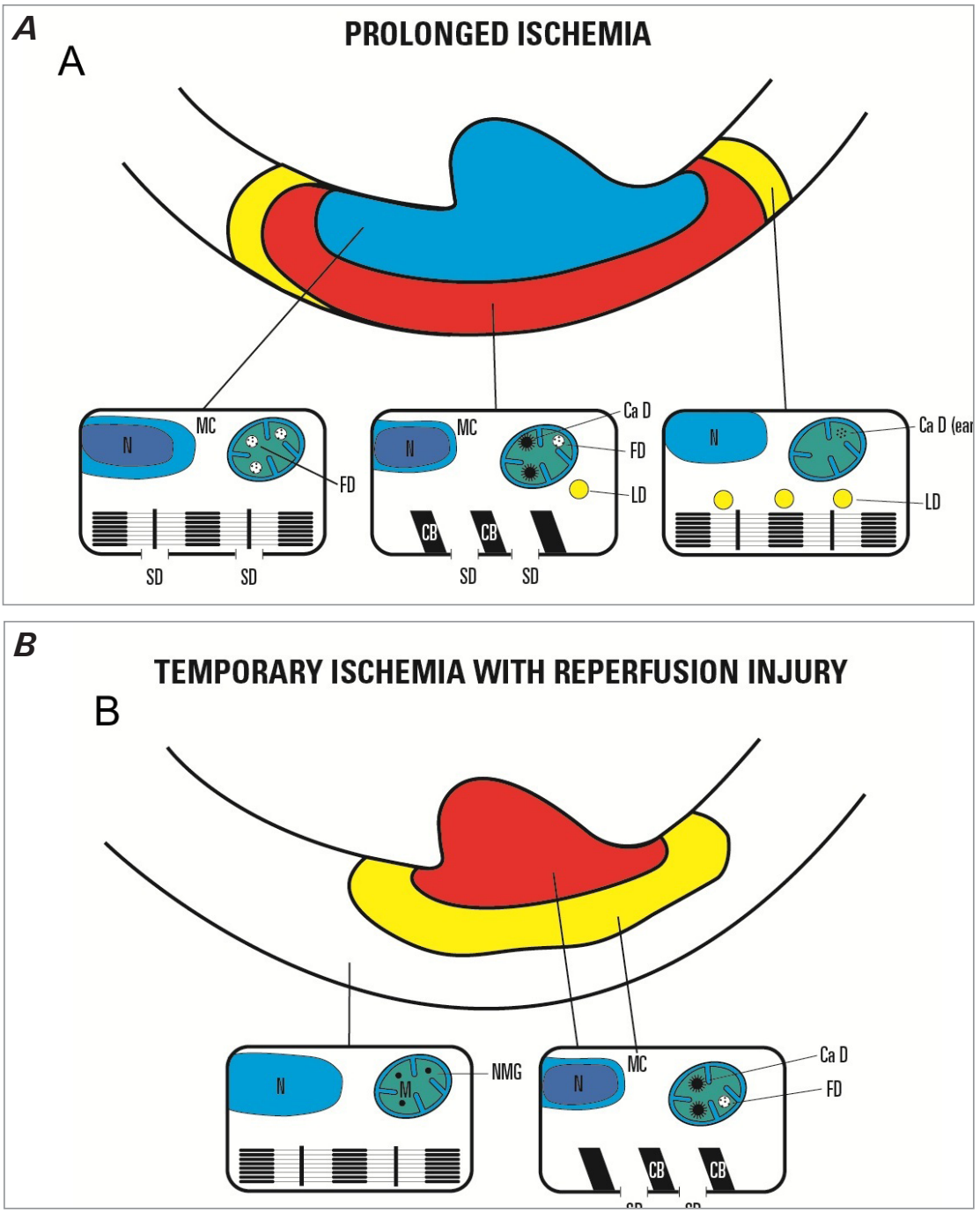

Fig. 1 Illustrations of transmural infarct following persistent myocardial ischemia caused by coronary artery occlusion and subendocardial infarct resulting from temporary myocardial ischemia followed by reperfusion caused by opening of the occluded coronary artery. (**A**) Permanent coronary occlusion results in the formation of a transmural AMI with central (blue), peripheral (red), and border (yellow) zones. (**B**) Subendocardial MI following temporary coronary artery occlusion for 90 minutes and reperfusion. Early reperfusion after coronary occlusion limits AMI to the subendocardium. The infarct consists of myocardium that developed irreversible injury during coronary occlusion (red) and myocardium at the edge of the evolving AMI that developed irreversible injury during reperfusion (lethal reperfusion injury) (yellow). Lethal reperfusion injury can account for 50% of the resultant subendocardial MI. The ultrastructure of the cardiomyocytes in the different regions is illustrated.
AMI, acute myocardial infarction; CaD, calcium deposits, mitochondria; CB, contraction bands, myofibrils; FD, flocculent (amorphous matrix) densities, mitochondria; LD, lipid (triglyceride) droplets; M, mitochondria; MC, myocardium; MI, myocardial infarction; N, nucleus; NMG, normal matrix granules, mitochondria; SD, sarcolemmal defect.
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Critical Analysis of Stalled Cardioprotection Research

Even with improved preclinical screening through the rigorous Consortium for Preclinical Assessment of Cardioprotective Therapies and Improving Preclinical Assessment of Cardioprotective Therapies guidelines, complexities in the design and conduct of clinical trials present ongoing challenges for demonstrating effective cardioprotection strategies.[13,14] The failure to translate cardioprotection from successful preclinical and smaller proof-of-concept studies to patient benefit can be attributed to many confounding conditions related to patient selection, end points, and conduct of clinical cardioprotection trials.[13] In addition to the well-recognized confounders, it is possible that a given cardioprotective intervention may not be effective in humans. In some patients, primordial nonresponsiveness of the myocardium to cardioprotective interventions may also be caused by genetic factors beyond the recognized confounding factors. Primordial nonresponsiveness was demonstrated in a study comparing results of ischemic conditioning in 2 pig strains.[31] Primordial genetic factors will be challenging to overcome.

Current Clinical Profile of Ischemic Heart Disease

Because of the sustained application of primary, secondary, and tertiary protective measures, the death rate from CAD has been reduced from more than 400 per 100,000 in 1950 to fewer than 100 per 100,000 today.[1,32] At present, however, emergency medical services and emergency departments see an estimated 8 million patients with signs or symptoms of an acute cardiac ischemic event every year in the United States (Fig. 2).[33] Of these patients, 2.6 million have confirmed evidence of acute cardiac ischemia, and the remaining 5.4 million are diagnosed as having low probability of an AMI and are triaged for further evaluation for chronic, stable ischemic heart disease.[33]

Among the 2.6 million patients with acute cardiac ischemia, the events manifest as AMI in 1.3 million patients, unstable angina pectoris in 810,000, and cardiac arrest in 490,000. Among these 2.6 million patients, 600,000 (23%) deaths occur (Fig. 3).[33] Most deaths occur shortly after the cardiac ischemia begins with the onset of ventricular fibrillation, occur outside the hospital, and are classified as *sudden cardiac death*. Individuals who do not die suddenly will progress to AMI. Most of the heart muscle damage in this group occurs within 2 hours of the onset of chest pain.[33]

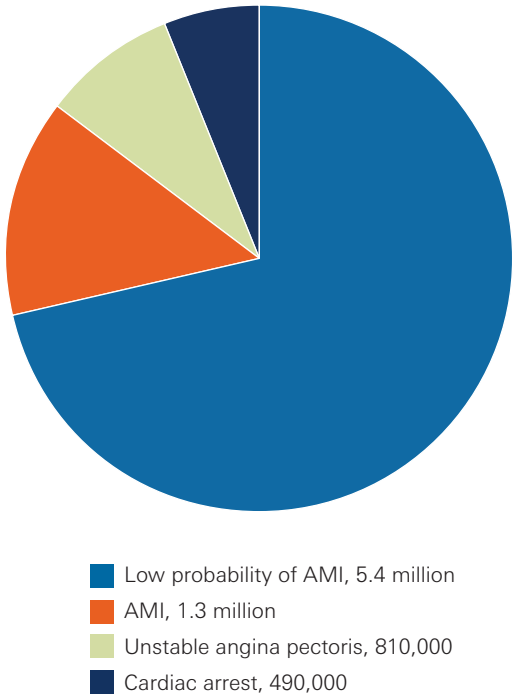

Fig. 2 Emergency medical services and emergency department encounters for suspected acute cardiac ischemia episodes in the United States (8 million per year).
AMI, acute myocardial infarction.
Adapted from Bahr RD. *Herz.* 49:167-174. Used with permission from *Herz* (©2024). Springer Nature. All Rights Reserved.

Although advances in cardioprotection have stalled for the past 20 years, progress has been made in diagnosing and managing unstable angina pectoris and AMI. Major randomized clinical trials of patients with transmural AMI have shown progressive reductions in early mortality rates: from 13% to 10.7% in 1986, to 8% in 1988, and to 6.3% in 1993 and from 3.9% to 3.8% in 2006 and 2.5% in 2008.[16] Despite the progress in reducing short-term mortality from AMI in hospitalized patients, 1-year mortality after hospital discharge remains substantial. It has been recorded as 15% to 21% in European registry databases.[5,8] Hospitalization for heart failure in survivors of AMI is also high, at 20% to 30% at 1 year after discharge, as recorded in the same registries. Advanced heart failure caused by ischemic heart disease has not responded to stem cell therapy and necessitates major circulatory support with ventricular assist devices and cardiac transplantation for survival.[34-36]

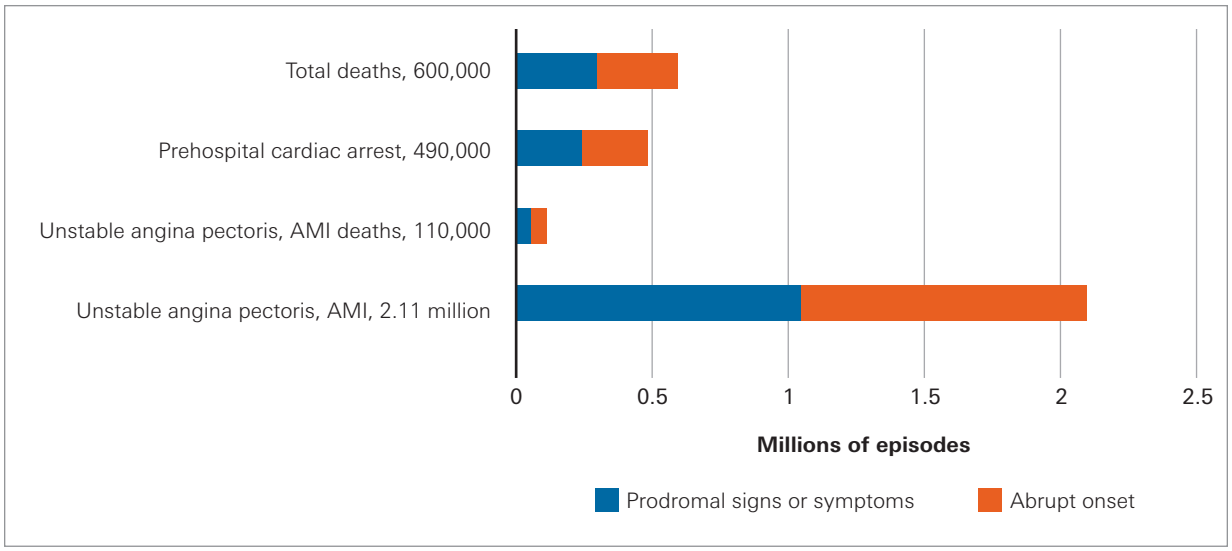

Fig. 3 Acute cardiac ischemic episodes, United States (2.6 million per year)
AMI, acute myocardial infarction.
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Opportunities for Further Progress in Ischemic Heart Disease Patient Diagnosis, Selection, and Management

New perspectives and approaches to diagnosing ACS and matching patients with specific manifestations of ischemic heart disease to the appropriate treatments have created opportunities for further progress. Functionally significant CAD is now recognized to involve the entire coronary vascular system, not just the angiographically identifiable epicardial coronary arteries.[37-39] Clinically, the conditions are referred to as *ischemia with nonobstructive coronary arteries* and *MI with nonobstructive coronary arteries*.[37-39]

Universal Definition of Myocardial Infarction

Clinicians recognize the challenges in rapidly differentiating various types of ACS and other causes of chest pain. The echocardiogram has been used to characterize AMI as Q wave or non–Q wave and subsequently as ST-segment elevation MI (STEMI) or non–STEMI (NSTEMI). Cardiac enzyme measurements have been used to confirm the diagnosis of AMI, and they have been particularly helpful when electrocardiogram changes are equivocal.[40]

The Universal Definition of Myocardial Infarction (UDMI) has been validated as an approach to diagnosing and differentiating types of AMI and distinguishing AMI from other conditions presenting with acute chest pain.[41,42] The UDMI is based on coupling measurements of high-sensitivity cardiac troponin (hs-cTn) with clinical evidence of myocardial ischemia (Table II). Applying hs-cTn assays has led to substantial changes in the clinical approach to evaluating AMI. The UDMI is designed to distinguish a type 1 AMI caused by coronary atherothrombosis from other types of AMI. Although the UDMI has gained widespread acceptance as a clinical standard of practice, its application has proven particularly challenging in acute cardiac illness outside the hospital or in the absence of evidence of atherothrombotic CAD.[43] Further insights are being gleaned from clinicopathologic studies.[43,44]

Paradigm Shift in AMI: From STEMI to Occlusion MI

With more frequent use of UDMI diagnosis based on hs-cTn assays in patients presenting with acute chest pain, a worldwide increase in the reported incidence of NSTEMI has emerged.[45-47] Registries in the United States and Europe now show that approximately two-thirds of patients with AMI are classified as having NSTEMI. ST-segment elevation MI results from acute total or near total coronary artery occlusion, associated with the characteristic transient ST-segment elevation on electrocardiogram.[45-47] Acute total occlusion has also been observed, however, on coronary angiography in

TABLE II. Universal Definition of Myocardial Infarction[41,42]

Diagnostic criteria				
Myocardial injury	Elevated high-sensitivity cardiac troponin in blood			
Myocardial ischemia	Symptoms	New ischemic electrocardiogram changes or pathological Q waves	Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality	Identification of coronary thrombus by angiography or autopsy
Type	**Characteristic**	**Pathophysiology**		
Type 1 MI	Spontaneous MI related to ischemia caused by primary coronary event	Coronary arterial plaque erosion or rupture, fissuring, or dissection		
Type 2 MI	MI secondary to ischemia caused by either increased oxygen demand or decreased supply	Coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension		
Type 3 MI	Sudden unexpected cardiac death	Cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumed ST-segment elevation, new left bundle branch block, or fresh thrombus in a coronary artery by angiography or autopsy		
Type 4A MI	MI associated with PCI	PCI-induced reduced coronary blood flow		
Type 4B MI	MI associated with stent thrombosis as documented by angiography or at autopsy	Thrombosis-induced reduced coronary blood flow		
Type 5 MI	MI associated with coronary artery bypass grafting	Hypotension, thrombosis during coronary artery bypass grafting		

MI, myocardial infarction; PCI, percutaneous coronary intervention.

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approximately 25% to 30% of patients with NSTEMI. Pathology studies also have documented recent coronary occlusive lesions in one-third of patients with fatal subendocardial AMI.[5] Based on current guidelines, patients with NSTEMI are assigned to delayed revascularization procedures and therefore do not receive the benefit of early percutaneous transluminal coronary angioplasty. This deficiency has led to a proposed a new classification and approach to ACS based on replacing the STEMI vs NSTEMI paradigm with the occlusion vs nonocclusion MI paradigm, with the implementation of multimodal diagnostic methods and algorithms providing for rapid identification of all patients with total coronary artery occlusion and implementation of rapid invasive intervention (Table III).[45-47]

TABLE III. Sequential Paradigms for ACS[45]

I. Before 2000: Q-wave vs non–Q-wave MI
Rationale: Electrocardiogram provides information about the natural history of ACS: Q-wave MI is associated with acute total occlusion and transmural AMI, and non–Q-wave MI is associated with subendocardial AMI of diverse pathophysiology.

II. After 2000: STEMI vs NSTEMI
Rationale: With the advent of thrombolytic therapy, acute changes on electrocardiograms allow rapid distinction of patients with STEMI and NSTEMI AMIs. STEMI is equated with acute total occlusion necessitating thrombolytic therapy or PCI.

III. 2020 and beyond: Occlusion vs nonocclusion MI
Rationale: With the application of the Universal Definition of Myocardial Infarction, NSTEMI is now recognized to constitute two-thirds of all MIs. As seen on coronary angiogram, AMIs are classified as occlusion MI or nonocclusion MI. All patients with occlusion MI should receive aggressive PCI.

ACS, acute coronary syndrome; AMI, acute myocardial infarction; MI, myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.
Reference: Avdikos G, Michas G, Smith SW. From Q/non-Q myocardial infarction to STEMI/NSTEMI: why it's time to consider another simplified dichotomy; a narrative literature review. *Arch Acad Emerg Med*. 2022;10(1):e78. doi:10.22037/aaem.v10i1.1783

Canadian Cardiovascular Society Classification of Acute Atherothrombotic Reperfused MI

A new classification of acute atherothrombotic MI (type 1 MI) with reperfusion has recently been described by the Canadian Cardiovascular Society.[48] This classification is based on experimental pathology studies that provided documentation and quantitation of microvascular dysfunction and myocardial edema in early myocardial ischemic injury, which is increased with reperfusion.[5] Recent advances in imaging procedures have allowed these tissue changes to be studied in vivo, leading to an understanding that not all MIs are the same at the tissue level. According to this construct, evolving atherothrombotic AMI after early reperfusion develops tissue changes in 4 sequential, progressive stages (Table IV). Each stage reflects progression of tissue pathology of myocardial ischemia and reperfusion injury from the previous stage. This classification has the potential to stratify risk in patients with AMI and lay the groundwork for the development of new, stage-specific injury and tissue pathology–based therapies for MI.[48] This scheme and therapeutic approach also fit well with the clinical recognition of the stuttering nature of many AMIs.[33]

New Perspective on the Spectrum of Ischemic Heart Disease

The Society of Chest Pain Centers and Providers has championed early identification of prodromal symptoms as the "Rosetta stone" in addressing the heart attack problem. Of the 2.6 million patients presenting with ACS, approximately 50% have prodromal symptoms of intermittent or progressive chest pain before the onset of sustained severe chest pain—that is, unstable angina pectoris before AMI (Fig. 3).[33] Thus, there are 2 kinds of heart attacks: those with an abrupt onset and those in which the AMI is preceded by symptoms for hours to days.[33]

Thus, the collective observations indicate that 50% of patients can be considered to have stuttering MI, whereas 50% of patients sustain the onset of irreversible myocardial injury caused by coronary occlusion at a fixed point in time. If the deaths are distributed evenly, 300,000 of the 600,000 would be considered to have prodromal AMI with stuttering AMI. This scheme and therapeutic approach also fit well the Canadian Cardiovascular Society classification of stages in the evolution of acute atherothrombotic reperfused AMI.[33]

Results of pathologic studies support this concept. These studies have documented multifocal areas of ischemic necrosis in patients with episodes of unstable angina pectoris and organizing coronary thrombi retrieved at PCI.[5] In clinicopathologic studies, prodromal symptoms and evidence of myocardial fibrosis indicative of previous episodes of myocardial ischemia have been documented in substantial numbers of patients with sudden cardiac death (Table V).[49-53]

The Society of Chest Pain Centers and Providers is championing the stuttering infarct concept as providing

TABLE IV. Canadian Cardiovascular Society Classification of Acute Atherothrombotic MI Based on Stages of Tissue Injury Severity[48]

Canadian Cardiovascular Society stage	Designation	Pathologic changes	Typical incidence
Stage 1 MI	Aborted MI	Cardiomyocyte dysfunction, reversible loss of contractility, viability preserved, intracellular cardiomyocyte edema, no microvascular involvement	5%-15%
Stage 2 MI	MI with cardiomyocyte necrosis and no microvascular injury	Cardiomyocyte necrosis, interstitial edema, cardiomyocyte viability lost, irreversible injury, no microvascular involvement	30%-50%
Stage 3 MI	MI with cardiomyocyte necrosis and microvascular obstruction	Cardiomyocyte necrosis, interstitial edema, microvascular injury with microvascular obstruction	40%-50%
Stage 4 MI	MI with significant cardiomyocyte necrosis and intramyocardial hemorrhage	Cardiomyocyte necrosis, interstitial edema, severe microvascular injury with microvascular necrosis, myocardial hemorrhage	25%-40%

MI, myocardial infarction.
Reference: Kumar A, Connelly K, Vora K, et al. The Canadian Cardiovascular Society Classification of Acute Atherothrombotic Myocardial Infarction Based on Stages of Tissue Injury Severity: an expert consensus statement. *Can J Cardiol*. 2024;40(1):1-14. doi:10.1016/j.cjca.2023.09.020

TABLE V. Clinicopathologic Findings in Sudden Cardiac Death Caused by Ischemic Heart Disease (5 Studies)[49-53]

Cases, No.	653
Prodromal pain before cardiac arrest, %	40-57
Coronary atherosclerosis, %	
Severe coronary atherosclerosis (>75% stenosis) in ≥1 coronary artery	87-100
Old subtotal or complete occlusion	34-59
Acute coronary lesion (plaque fissure, rupture, mural thrombus, occlusive thrombus), %	10-81
Intramural platelet aggregates, %	30
Myocardial lesions, %	
Healing or old MI or fibrosis	57-85
Recent MI	17-39
Multifocal myocyte injury with contraction bands	86-88

MI, myocardial infarction.
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a public health opportunity to develop heightened public awareness, leading patients with prodromal symptoms to access the health care system for life-saving diagnosis and interventions.[33] The Society of Chest Pain Centers and Providers has launched the Early Heart Attack Care program as a public health initiative to increase public awareness, leading patients with prodromal symptoms to promptly access the health care system for life-saving diagnosis and interventions.

Conclusions

The current state of ischemic heart disease warrants a 2-pronged approach to reduce morbidity and mortality from ischemic heart disease. One approach is support for continued basic pathologic and translational research to identify new approaches to cardioprotection. The second approach is to advance clinical diagnosis and management of ischemic heart disease based on evidence-based effective approaches, including (1) rapid diagnosis of subtype of ACS, unstable angina pectoris, and AMI through application of the UDMI via hs-cTn assays and the Canadian Cardiovascular Society classification through advanced imaging; (2) implementation of the occlusion vs nonocclusion MI paradigm to prompt aggressive management of all STEMI and the one-third of NSTEMI with total occlusions; (3) rapid identification of prodromal AMI, stuttering MI, and implementation of aggressive therapy in patients who present to medical attention before onset of MI; and (4) public health campaigns to get patients with prodromal symptoms to medical attention before the occurrence of ventricular fibrillation–induced sudden cardiac death.

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