Acute coronary syndromes: changing face
Heart and Metabolism is a journal published three times a year, focusing on the management of cardiovascular diseases. Its aim is to inform cardiologists and other specialists about the newest findings on the role of metabolism in cardiac disease and to explore their potential clinical implications. Each issue includes an editorial, followed by articles on a key topic. Experts in the field explain the metabolic consequences of cardiac disease and the multiple potential targets for pharmacotherapy in ischemic and nonischemic heart disease.

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Since the beginning of this century, an overwhelming body of evidence has prompted a deep revision of our understanding of ischemic heart disease, which was traditionally based on the misconception that myocardial ischemia is closely linked with coronary artery atherosclerotic obstructions. The revision was initially focused on chronic ischemic syndromes or “stable angina” and, with it, the acknowledgment of the multifactorial nature of this condition with a number of possible precipitating mechanisms, including severe stenosis, coronary vasospasm, and microvascular dysfunction. It was also acknowledged that multiple mechanisms might be present at the same time or alternate in time. In addition, the diagnostic and therapeutic implications of this new understanding have yet to be fully implemented in clinical practice.

More recently, the traditional concepts on the pathogenesis of acute ischemic syndrome have also been strongly challenged. The classic model was based on the assumption that acute ischemic syndromes are precipitated by plaque rupture, fissure, or erosion. However, recent reports do not support this concept. In summary, most vulnerable plaques identified in patients with acute ischemic syndrome are located in nonculprit vessels, not all patients with acute ischemic syndrome have vulnerable plaques at coronary angiography, and vulnerable plaques are a common observation, also in stable or asymptomatic patients.

Longitudinal studies with repeat intracoronary imaging have shown that plaques are dynamic structures with rapid changes from a vulnerable pattern to a stable pattern and vice versa, and these changes are not associated with clinical events. The most recent reports on the subject have concluded that, of the more than 82 patients with acute ischemic syndrome analyzed, 31 had no evidence of erosion or rupture at optical coherence tomography, and the latest guidelines from the European Society of Cardiology on non-ST-segment elevation myocardial infarction acute coronary syndrome (NSTEMI-ACS) admit that up to 20% of patients have normal coronary angiography.

This issue of Heart and Metabolism, with its suggestive title, aims to offer the readers some useful hints on being an active participant in this process. Readers will find cases of acute ischemic syndrome in patients with clean coronary arteries, will learn how to interpret the biochemical markers of cardiac damage, will be helped by experts to manage acute ischemic syndromes in patients with no coronary obstruction, will be informed on the role of cardiac energy metabolism as a possible cause of acute ischemic syndrome and, at the same time, a possible therapeutic target, and will also find a critical appraisal of current therapeutic results.

The invited authors have done a spectacular job and I am personally indebted to them for their outstanding contributions.
The changing face of acute coronary syndromes

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Abstract

Acute coronary syndrome is a leading cause of ischemic heart disease mortality and morbidity. Despite the rising prevalence of obesity and diabetes, the epidemiology of acute coronary syndrome appears to be shifting with an observed decreased incidence of ST-segment elevation myocardial infarction (STEMI) and hospital mortality accompanied by an increased incidence of non–STEMI across all age groups and in both women and men. Underlying potential contributors to this change include aging of the population, implementation of primary and secondary prevention strategies, which result in changes in atherosclerotic coronary artery disease, and technological improvements that have increased the sensitivity of cardiac diagnostic tests. Appreciation of sex differences in ischemic heart disease, identification of nonobstructive coronary disease, and the diagnosis of coronary microvascular dysfunction as contributors to ischemia with no obstructive coronary artery disease (INOCA) is increasing. Work is ongoing to fill the gaps in knowledge needed for evidence-based guidelines for the changing face of acute coronary syndrome. — Heart Metab. 2018;75:4-8

Keywords: acute coronary syndrome; non–ST-segment elevation myocardial infarction; stable ischemic heart disease; sex differences; ST-segment elevation myocardial infarction

Introduction

Despite an aging population and an increasing burden of obesity and diabetes, the epidemiology of acute coronary syndromes (ACS) appears to be shifting with an observed decreased incidence of ST-segment elevation myocardial infarction (STEMI) and mortality that is accompanied by an increased incidence of non–STEMI (NSTEMI) across all age groups and in both women and men (Figure 1). In this review, we discuss the evidence and possible contributors to the changing face of ACS.

Evidence

The incidence of acute myocardial infarction (AMI) has been stable with only a modest decline over the past four decades. Recent studies on trends suggested sharper declines in the recent millennial years as compared with the 1980s and 1990s (Figure 2). A shift in ACS presentation was also reported over this period, where the incidence of NSTEMI doubled, which was accompanied by a marked decline in the incidence of STEMI (from 133 to 50 cases per 100 000 person-years). The aging of the population...
likely contributes to the increase in NSTEMI, which is more common in elderly patients. Hospital mortality, on the other hand, has been steadily declining in both groups with a reported decline in overall mortality >50%, mostly for patients with STEMI who are admitted to the intensive or acute coronary care units as shown in multiple studies done in the US and around the world.4,7-10 Of note, patients with NSTEMI complicated by cardiogenic shock had a higher hospital mortality rate than did patients who presented with STEMI and cardiogenic shock. This observation was attributed, at least in part, to delays in revascularization among the NSTEMI group vs the STEMI group.11 An improvement in survival and a reduction in the 6-month mortality rate was significantly associated with the use of invasive coronary strategies among NSTEMI patients.12 Notably, there is an overall significant reduction in the severity of AMI presentation in both groups with decreased complications, specifically that of heart failure.13,14 The decline in mortality was predominantly attributed to technological improvements in cardiac care and shorter times in delivering reperfusion therapy, primarily with percutaneous coronary intervention (PCI). However, recent studies suggest that the secondary prevention and treatment of heart failure have played a more significant role in mortality reduction than reperfusion alone.7

Abbreviations
ACS: acute coronary syndrome; AMI: acute myocardial infarction; CAD: coronary artery disease; CCTA: coronary computed tomography angiography; CK-MB: creatine kinase–myocardial isoenzyme; IHCA: ischemic heart disease; INOCA: ischemia with no obstructive coronary artery disease; IVUS: intravascular ultrasound; NSTEMI: non–ST-segment myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment myocardial infarction

Fig. 1 Acute myocardial infarction hospitalization rate for men and women from 2002 to 2007; not adjusted for age. Rates for men and women are represented by triangles and circles, respectively.
Abbreviations: AMI, acute myocardial infarction.

Fig. 2 Age- and sex-adjusted incidence rates of acute myocardial infarction from 1999 to 2008.
Potential contributors to the change

Potential contributors to the changing face of ACS likely include improved diagnostics and changes in atherosclerotic coronary artery disease (CAD) itself.

Improved diagnostics

Improved diagnostics include the use of high sensitivity cardiac biomarkers, improved noninvasive imaging, and the redefinition of ACS. Many patients who previously met the criteria for unstable angina were reclassified as NSTEMI after the introduction of troponin I (TnI) instead of the creatine kinase–myocardial isoenzyme (CK-MB) in the late 1990s, which led to an increased diagnosis of NSTEMI. In a study of the National Registry of Myocardial Infarction between the years of 1990 and 2006, the proportion of NSTEMI had increased from 14.2% to 59.1%, whereas the proportion of STEMI had decreased.5,16 Further, the increasing use of improved noninvasive imaging techniques (nuclear stress test and stress echocardiogram) has identified patients with evidence of myocardial ischemia after presenting with chest pain, despite not meeting electrical or biochemical criteria for an AMI, and “no obstructive coronary disease” on angiography. This observation is now called ischemia with no obstructive coronary artery disease (INOCA) and it is seen in patients with ACS or stable ischemic heart disease (IHD) populations.17 The exact mechanism for INOCA is unclear, but it is hypothesized that nonatherosclerotic mechanisms may precipitate myocardial ischemia (eg, coronary vasospasm, microvascular dysfunction, and inflammation).

While invasive coronary angiography is considered the gold standard in diagnosing and estimating the severity of coronary stenosis, it is a two-dimensional luminogram, which is insensitive to nonobstructive plaque. Advanced imaging, including intravascular ultrasound (IVUS) and noninvasive coronary computed tomography angiography (CCTA), are sensitive techniques for the measurement of atherosclerosis, which is a contributor to adverse long-term outcomes, coronary remodeling, and STEMI.18,19 Further work with these advanced imaging modalities may characterize and identify the pathophysiology of myocardial ischemia and coronary plaque better to improve prophylactic guideline approaches and reduce the incidence of AMI further.

Changes in atherosclerotic coronary artery disease

Changes in atherosclerotic coronary artery disease include a reduction in overall atherosclerotic plaque burden and high-risk plaque features. This reduction would translate, in theory, to less plaque rupture as well as a lower rate of thrombosis and negative arterial remodeling, which are the major contributors to obstructive CAD, STEMI, and mortality. Secondary prevention is the largest contributor to decreasing ACS mortality in multiple studies, ahead of revascularization or treatment for heart failure.7,20 There has been a significant decrease in the prevalence of selected major cardiovascular risk factors over the years due to the increased public awareness with lower smoking rates, and the widespread implementation of guideline-directed medical therapy, including treatment of hypertension and dyslipidemia.21-24 Conversely, the prevalence of obesity and diabetes is increasing.25

Using the coronary heart disease policy and prevention model, the IMPACT study (IMProving Adherence using Combination Therapy) showed that more than half of the estimated reduction in mortality came from risk factor reduction. Lowering total cholesterol concentrations, systolic blood pressure, and smoking prevalence were all associated with lowered mortality, while decreased physical activity and increased diabetes and obesity prevalence were associated with an estimated increase in mortality.7 A study of the French registries over a 15-year period between 1995 and 2010 concluded that hospital mortality due to STEMI had decreased by more than 60%, which is consistent with other studies worldwide.2,5,26,27 Of interest, the proportion of patients with AMI, particularly STEMI, was increasing at a younger age, more so in women than in men. This trend was hypothesized to be related to the improvement in aggressive medical therapy to patients with recognized obstructive CAD and the increased incidence of smoking among younger women in France over the study period.10 In summary, these data suggest that, rather than a true reduction in ACS and stable IHD, we are observing a change in disease phenotype that is associated with lower mortality.

Sex differences

Men and women can have different ACS and stable IHD presentations and outcomes – there is a greater
proportion of STEMI in younger males, while females have a higher proportion of NSTEMI. Women more often present with more atypical symptoms and suffer worse outcomes. Our understanding of these differences and the complex mechanisms of ACS in women is improving. Women, in comparison to men, generally have a lower burden of coronary atherosclerosis angiographically and by IVUS; however, they tend to have smaller coronary lumens and more coronary microvascular dysfunction and nonobstructing lesions. Also, women tend to have less plaque rupture rates vs men, and, although the presence of thin-cap fibroatheroma (TCFA) was found to be similar in both sexes, it was a stronger marker of plaque vulnerability in women. Sex differences in STEMI and NSTEMI were studied in patients in the SCAAR registry (Swedish Coronary Angiography and Angioplasty Registry), showing that significantly more women in both groups had nonobstructive CAD. STEMI rates are generally lower in women than in men; the rates could potentially be lowered further in men by identifying sex differences in the mechanistic pathways. There is increasing interest in redefining the significance of coronary nonobstructive lesions on angiography in men and women, which may lead to improved therapeutic strategies and contribute to further reductions in ACS.

Conclusions

In recent years, the rates of ACS have been on the decline, with STEMI and mortality sharply declining, largely due to the widespread implementation of primary and secondary prevention strategies with aggressive risk factor modification. Modern technological advancements, as well as improvements in reperfusion therapy and treatments for heart failure also play a role. Developing sensitive diagnostic tests and identifying INOCA and nonobstructive CAD appear to be important. Contemporary data suggest that, rather than a true reduction in ACS and stable IHD, we are observing a change in disease phenotype, which is associated with lower mortality. This fact may be particularly relevant to women, due to the higher prevalence of nonobstructive CAD and coronary microvascular dysfunction. Work is ongoing to fill knowledge gaps needed for evidence-based guidelines for the changing face of ACS.

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The changing face of acute coronary syndromes


Acute coronary syndrome without coronary obstructions: diagnosis and treatment

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Abstract
Myocardial infarction with no obstructive coronary atherosclerosis (MINOCA) is a syndrome with different causes. Its prevalence ranges between 5% and 25% of all myocardial infarctions. The prognosis is extremely variable, as it strictly depends on the cause of MINOCA. Clinical history, electrocardiography, cardiac enzymes, echocardiography, coronary angiography, and left ventricular angiography represent first-level diagnostic investigations to identify the causes of MINOCA. This preliminary step helps divide patients presenting with epicardial or microvascular patterns and to perform specific additional tests for an adequate management workflow. This article will focus on the diagnosis and treatment of MINOCA.

Keywords: acute myocardial infarction; microcirculation; no obstructive coronary atherosclerosis

Introduction
Myocardial infarction (MI) with no obstructive coronary atherosclerosis (MINOCA) is characterized by clinical evidence of MI with normal or near-normal coronary arteries on angiography (stenosis severity <50%). The prevalence ranges between 5% and 25%,1,2 with a prevalence up to 25% among women and up to 10% among men who present with non–ST-segment elevation MI (NSTEMI).3

The first-level diagnostic investigations for MINOCA include clinical history, electrocardiography (ECG), cardiac enzymes, echocardiography, coronary angiography, and left ventricular (LV) angiography (Figure 1 and Table I).4 Regional wall motion abnormalities at LV angiography that are limited to a single epicardial coronary artery territory identify an “epicardial pattern,” whereas regional wall motion abnormalities that extend beyond a single epicardial coronary artery territory identify a “microvascular pattern.” Epicardial causes of MINOCA include coronary artery spasm and positive remodeling of unstable plaque, but no obstructive atherosclerosis. Takotsubo syndrome, coronary microvascular spasm, myocarditis mimicking MI, and coronary embolism can be considered microvascular causes of MINOCA (Figure 1).4

The rate of all-cause mortality during admission ranged from 0.1% to 2.2% and the 1-year post–MINOCA ranged from 2.2% and 4.7%.3,5 This article will focus on the diagnosis and treatment of MINOCA (Table I).
Epicardial causes of MINOCA

Coronary artery spasm

Coronary artery spasm occurs in 3% to 95% of patients with MINOCA; the extreme variability depends on the stimuli used to trigger the spasm (ergonovine vs acetylcholine), the definition of spasm, and ethnic reasons. Patients with coronary artery spasm typically have angina at rest, during the night, or early in the morning, which is associated with a transient ST-segment elevation at ECG. In the absence of ECG documentation, the diagnosis is based on an intracoronary provocative test and defined as a reduction of at least 75% of the vessel caliber together with symptoms/signs of myocardial ischemia. While the intracoronary ergonovine test is a standardized procedure, the dosage of intracoronary acetylcholine can vary from 2 to 200 µm for the left coronary artery and from 2 to 80 µm for the right coronary artery. The prevalence of coronary artery spasm is higher in the Japanese population compared with the Caucasian population, and it results in a poor outcome. Standard treatment includes nonspecific vasodilators, such as nitrates and calcium channel blockers. In cases that are refractory to standard treatment (10% to 20%), high doses of calcium channel blockers can be used. Fasudil, a Rho-kinase inhibitor, is effective in Japanese patients. Other potential treatments include β1-adrenergic receptor agonists and antioxidant therapy with vitamin E and C, and, in selected cases, stent implantation or partial sympathetic denervation can be considered. In patients at a high risk of spasm-related cardiac death, the use of an implantable cardiac defibrillator is required.

No obstructive coronary atherosclerosis with positive remodeling

The presence of eccentric plaques with positive remodeling resulting in a lack of obstructive coronary
artery disease represents another epicardial cause of MINOCA. These lesions frequently show characteristics of vulnerability, ie, a large lipid pool and thin fibrous cap. Of note, hypercoagulability might enhance the detrimental consequences of these lesions. The instability of a nonobstructive unstable plaque can be caused by rupture of a thin fibrous cap (73%) or by plaque erosion (23%).

Coronary angiography can underestimate eccentric plaque with positive remodeling, thus justifying the use of intravascular imaging modalities, eg, intravascular ultrasound and optical coherence tomography. In particular, optical coherence tomography is more sensitive than intravascular ultrasound for identifying plaques with a large lipid pool and thin fibrous cap. These lesions are associated with a risk of cardiovascular events at follow-up that is comparable to that of patients with acute coronary syndrome and obstructive atherosclerosis. An observational study in the SWЕDEHEART registry (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) that included 9466 consecutive, unique patients with MINOCA, showed long-term beneficial effects of treatment with statins and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, a trend toward a positive effect with β-blocker treatment, and a neutral effect with dual antiplatelet therapy.

### Microvascular causes of MINOCA

#### Takotsubo syndrome

One of the microvascular causes of MINOCA is takotsubo syndrome. Its prevalence ranges between 1.2% and 2.2% of all cases of acute coronary syndrome. Although several etiopathogenetic mechanisms have been proposed, reversible coronary microvascular dysfunction seems to represent a common pathophysiological determinant of takotsubo syndrome.

Takotsubo syndrome is characterized by a high prevalence of postmenopausal females reporting a recent physical or emotional stress. The most common ECG abnormalities (eg, ST-segment elevation and T wave inversion) are usually observed during the acute and subacute phases. Typically, all patients exhibit marked LV dysfunction on admission, with a sizeable proportion showing a dramatic functional improvement over a period of days to weeks. Left ventriculography, after documentation of MINOCA, allows takotsubo syndrome to be diagnosed. These patients typically have hypokinesia or akinesia in the mid and apical segments, with preserved or hyperkinetic functions in the basal regions. However, other variants of takotsubo syndrome have been described. Myocardial contrast echocardiography with adenosine may confirm the diagnosis by showing reversible coronary microvascular constriction.

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Table I Diagnostic tests, prognostic characteristics, and therapeutic treatments stratified for specific causes of MINOCA. Abbreviations: CM, contrast medium; CMR, cardiac magnetic resonance; EMB, endomyocardial biopsy; IVUS, intravascular ultrasound; OCT, optical coherence tomography. Adapted from reference 4: Niccoli et al. Eur Heart J. 2015;36(8):475-481. © 2015, Crown copyright.
nance with contrast medium shows a typical LV dysfunction without detectable myocardial necrosis after gadolinium administration.\textsuperscript{21} Intra-hospital mortality varies from 0\% to 8\% and 1-year mortality is about 5.6\% per patient-year.\textsuperscript{22}

LV dysfunction may require the prescription of β-blockers, angiotensin-converting enzyme inhibitors, and diuretics, sometimes together with anticoagulant therapy in patients who are at risk of a ventricular mural thrombus.\textsuperscript{23} Antiarrhythmic drugs play a crucial role in the acute and subacute phases of takotsubo syndrome.\textsuperscript{23} In patients with cardiogenic shock, intravascular treatment with inotropic agents, intra-aortic balloon pumping, and utilization of LV assist devices are mandatory.\textsuperscript{23}

**Coronary microvascular spasm**

Coronary microvascular spasm is characterized by transient transmural myocardial ischemia, as indicated by ST-segment changes during spontaneous or provoked angina and in the presence of normal epicardial coronary arteries.\textsuperscript{24} It accounts for approximately 25\% of cases of acute coronary syndrome with MINOCA.\textsuperscript{25} Microvascular angina can be diagnosed when an intracoronary acetylcholine test reproduces the symptoms usually experienced by the patients and triggers ischemic ECG changes (ie, ST-segment depression or ST-segment elevation that is ≥0.1 mV or T-wave peaking in at least 2 contiguous leads), in the absence of epicardial spasm (≥75\% diameter reduction).\textsuperscript{24} The long-term prognosis of these patients needs to be explored in adequate studies. The standard first-line treatment is the use of calcium channel blockers; however, in the case of refractory angina (25\%), fasudil may be considered a possible alternative treatment.

**Myocarditis mimicking a myocardial infarction**

Acute myocarditis mimicking an MI represents a microvascular cause of MINOCA in about one-third of patients. The clinical presentation seems to be related to the type of virus.\textsuperscript{26} In particular, parvovirus B19 (PVB19) may cause myocarditis-mimicking MINOCA, probably because it targets endothelial cells through the blood group P antigen.\textsuperscript{27} Patients with myocarditis are usually young and with a recent history of fever or respiratory infection.

The ECG findings vary from nonspecific T wave and ST-segment changes to ST-segment elevation. An endomyocardial biopsy is the gold-standard method for the in vivo diagnosis of myocarditis, which also provides prognostic information.\textsuperscript{28} It should be performed in patients with suspected myocarditis mimicking an MI and in the setting of unexplained new-onset heart failure (<2 weeks), with hemodynamic compromise and an uncertain etiology.\textsuperscript{28} Cardiac magnetic resonance is emerging as a useful method to detect global and regional wall motion abnormalities and to provide a differential diagnosis from takotsubo syndrome.\textsuperscript{29} Of note, late gadolinium enhancement reveals two common patterns of myocardial damage—an intramural, rim-like pattern in the septal wall or a subepicardial patchy distribution in the free left ventricle lateral wall.\textsuperscript{29}

The prognosis of patients with myocarditis strictly depends on clinical presentation. Treatment of a myocarditis-mimicking MI that is characterized by LV dysfunction is based on the use of β-blockers and angiotensin-converting enzyme inhibitors. Of note, Frustraci et al\textsuperscript{30} demonstrated that, in patients with active lymphocytic myocarditis with circulating cardiac autoantibodies and no viral genome in the myocardium, treatment with prednisone and azathioprine for 6 months caused a prompt improvement in LV ejection fraction.

**Coronary embolism**

Coronary embolism is included as a microvascular cause of MINOCA because it usually involves the microcirculation, although an angiographically visible embolization of the epicardial coronary artery branches may occur.

A paradoxical embolism can be related to a patent foramen ovale (PFO), a large atrial septal defect, or a coronary arteriovenous fistula.\textsuperscript{21} It should be suspected in patients presenting with MINOCA and one of the conditions associated with a high risk of systemic embolism. Of note, a hypercoagulable state might predispose the patient to thrombus formation. The criteria for the diagnosis of a paradoxical embolism include evidence of arterial embolism in the absence of a source in the left heart, source of embolism in the venous system, and the communication between venous and arterial circulation.\textsuperscript{32} Transthoracic, transesophageal, and contrast-enhanced echocardiogra-
phy are the cornerstone methods for detecting the cardiac sources of embolism as a cause of MINOCA. Importantly, the coronary angiography needs to be analyzed carefully for the identification of an amputation or percutaneous closure, as the efficacy and safety of triple anticoagulation therapy (warfarin + dual antiplatelet therapy) in the treatment and prevention of coronary thrombi. The efficacy and safety of triple anticoagulation therapy (warfarin + dual antiplatelet therapy) in the treatment and prevention of coronary embolisms remains unclear at this point. Regarding an atrial septal defect, paradoxical thromboembolism requires transcatheter device closure or surgical repair. If the cause of paradoxical embolization is a patent foramen ovale, the options for the secondary prevention of cryptogenic embolism consist of administering antithrombotic medications or percutaneous closure, although there is contrasting evidence for these methods.

Conclusions

MINOCA is frequently detected in patients admitted to the hospital with a diagnosis of MI. Our article shows that identifying the causes of MINOCA is the first step in guiding risk stratification and adequate management of these patients.

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Does unstable angina still exist?

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Abstract
The term unstable angina was popularized in the 1970s to describe angina-type symptoms and signs that did not fit into the category of either stable angina or acute myocardial infarction (AMI) and evolved from the term pre-infarction angina. Unstable angina was generally used for the sudden onset of severe chest pain (or change), which was longer in duration than stable angina, occurred without precipitating events, and was not associated with persistent electrocardiogram changes or cardiac biomarker elevation indicative of AMI. The incidence of unstable angina reached a peak in the 1990s, after which use of the term decreased progressively. Some of the factors that contributed to its decreasing incidence include more sensitive cardiac biomarkers, an increasing emphasis on preventative medicine, and the advent of early invasive therapy in high-risk patients. This article reviews the evolution of the term unstable angina, describes some reasons for the decrease in the prevalence of this condition in recent years, and forecasts for discontinuing its use. It appears that patients with ischemic heart disease are now best served by simply dividing them into only two groups, either stable angina or AMI. ■ Heart Metab. 2018;75:15-18

Keywords: myocardial infarction; troponin; unstable angina

Introduction
Although apparent for many decades, the seeming clear distinction between stable angina and myocardial infarction (MI) began to blur in the 1930s, when Sampson et al described the presence of “pre-infarction angina” or “crescendo angina.”¹ ² These terms were used to categorize patients with spontaneous attacks of prolonged angina-type chest discomfort occurring at rest that was associated with coronary artery thrombus formation. ³ At that time, this symptom was thought to result from coronary blood flow that was not sufficient to supply the resting metabolic demands of the cardiomyocytes, but sufficient enough to prevent the development of an acute MI (AMI).⁴ In the 1970s, a definition of the syndrome was formulated to describe patients who fell between stable angina and AMI. This syndrome was termed unstable angina.⁴ ⁵ Unstable angina has been defined as the relatively sudden onset (or change) of one or more angina attacks per day from a previous background of reasonably good health; in other words, a dramatic change in the symptom pattern of a patient with previously identified coronary artery disease (CAD).⁴ These angina attacks could be longer in duration than the patient’s prior stable angina, may occur at rest or at a much lower level of activity or even without a precipitating activity, and they are not associated with persistent electrocardiogram changes or cardiac biomarker
Does unstable angina still exist?

Abbreviations
AMI: acute myocardial infarction; CAD: coronary artery disease; CK-MB: creatinine kinase–myoglobin isoenzyme; cTnT: cardiac troponin T; cTnI: cardiac troponin I; IHD: ischemic heart disease; MI: myocardial infarction; NSTEMI: non–ST-segment elevation myocardial infarction

Elevation indicative of AMI.

In the decades following the popularization of the term “unstable angina,” there was an exponential increase in the diagnosis of this syndrome. However, with this increasing incidence, our understanding of the syndrome advanced. In a prospective study of patients with pre-infarction angina who were followed for 10 years, only about 1 in 5 actually developed an AMI within 8 months of the diagnosis. In another retrospective study of patients with an AMI, only a little more than a third described a pattern of unstable angina in the month prior to the AMI. Thus, it became clear that most patients with unstable angina did not develop an AMI later on, as has been the prevailing notion. Unstable angina may precede an AMI, may follow an AMI, or may neither precede nor follow an AMI and be the sole manifestation of ischemic heart disease (IHD).

Cardiac biomarker elevations, or lack thereof, played an essential role in the evaluation of the diagnosis of unstable angina. In the 1980s, the transition in practice to the use of the creatinine kinase–myoglobin isoenzyme (CK-MB), a more sensitive and specific cardiac biomarker when compared with lactate dehydrogenase and aspartate transaminase, led to an increase in the recognition of AMI. Similarly, in the 1990s, the development of cardiac-specific troponin T (cTnT) and I (cTnI) immunoassays for the detection of AMI showed improved sensitivity and specificity vs CK-MB, which, again, contributed to an increase in the diagnosis of AMI. Since then, high-sensitivity cTnT or cTnI assays have been developed that measure troponin values 10- to 100-fold lower than previous assays. The remarkable development of cardiac biomarker assays for the detection of myocardial injury over the past 40 years has allowed for a more accurate diagnosis of non–ST-segment elevation myocardial infarction (NSTEMI), which would otherwise have been labeled as unstable angina. This diagnosis capability is another important factor that has contributed to an apparent decrease in the incidence of unstable angina.

However, while high-sensitivity troponin remains an appropriate test for individuals with suspected acute ischemic myocardial injury, the higher sensitivity of this test has resulted in decreased specificity in some situations, such as postprocedural AMI. The Third Universal definition of myocardial infarction emphasizes the routine monitoring of cardiac biomarkers in high-risk patients both prior to and after major noncardiac surgery. However, it is worth noting that up to 45% of patients in this setting have elevated high-sensitivity troponin levels and up to 22% of patients have an elevated level with a rising pattern. In these patients, close clinical monitoring and judgment is warranted. It is also important to understand that, as with all markers of cardiomyocyte injury, cTnT and cTnI elevations do not necessarily indicate an ischemic mechanism. Other disorders may be associated with these elevations (eg, contusion, ablation, pacing, severe hypertension, heart failure, pulmonary embolism, myocarditis, renal failure, etc).

In addition to the improvement in cardiac biomarkers, there has been an increasing emphasis on preventative medicine over the past 40 years. This emphasis has resulted in progressive reductions in blood pressure, tobacco use, and cholesterol levels, which have contributed to the reduced incidence of IHD-related adverse outcomes via risk factor modification. Considerable emphasis has been placed on the improved management of hypertension, diabetes, cholesterol, and smoking. For example, in the 4S trial (Scandinavian Simvastatin Survival Study), patients with angina pectoris or a previous myocardial infarction and elevated cholesterol levels were randomized to either simvastatin or placebo. At 5.4 years, patients who were assigned to simvastatin had a 30% lower relative risk of death (P<0.0003), a 34% lower relative risk of major coronary events (P=0.00001), and a 37% reduction in the risk of myocardial revascularization (P=0.0001). Likewise, in the ASCOT-LLA trial (Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm), in hypertensive patients, atorvastatin 10 mg daily resulted in a 36% reduction in the risk of fatal and nonfatal MI at a median of only 3.3 years. Similarly, additional studies have confirmed the reduction in AMI and mortality associated with smoking cessation. One mechanism by which these preventative measures have been pro-
posed to lead to decreased ischemic events is via the transformation of vulnerable atherosclerotic plaques to more stable plaques. Major plaque ruptures appear to have been replaced by only minor erosions. This mechanism has been proposed, at least in part, for the reduction in STEMI, with an increase in NSTEMI. Parallel to these changes, there has also been a reduction in the incidence of unstable angina.

Furthermore, many, if not most, patients with unstable angina and high-risk features are now likely to undergo early invasive therapy, which has the potential to reduce the incidence of ischemia-related adverse outcomes, such as death or MI. In an updated meta-analysis of 12 trials with almost 10,000 patients treated with stents and adenosine diphosphate antagonists, a routine invasive strategy was associated with a reduction in the risk of death or MI (predominantly due to a reduction in the risk of MI) at 39 months. This benefit has been noted even in the subgroups in which an early invasive strategy has been previously thought to be harmful, such as in women. Additionally, with the development of improved noninvasive methods for detecting high-risk CAD, such as pharmacological stress tests, computed tomography of coronary arteries, and cardiac magnetic resonance angiography, there has been a rise in the earlier diagnosis and management of CAD with the potential to reduce ischemia-related outcomes.

Given the expected continued decrease in unstable angina over the next several years, and its lack of significant association with AMI, its inclusion as an "event" in trials as a 4-item outcome (death, AMI, stroke, or hospitalization for unstable angina) has recently been questioned. Inclusion of unstable angina in such a composite outcome could lower the prognostic relevance and potentially favor a shift in the hazard ratio toward the null.

Conclusions

In summary, the diagnosis of unstable angina reached its peak in the 1990s. Advances in the detection of previously subclinical AMI with more sensitive cardiac biomarkers, an increased emphasis on preventative medicine, and perhaps the adoption of an early invasive strategy for the management of patients with acute IHD at a high risk of adverse outcomes have contributed to this marked reduction in the prevalence of unstable angina. Over the next several years, some might argue that this syndrome might need to be renamed as an intermediate syndrome between stable angina and AMI. Our group and others have opined that the taxonomy for IHD needs a major revision (Figure 1).

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![Fig. 1 Evolution of unstable angina.](image)

**Abbreviations:** LDH, lactate dehydrogenase; AST, aspartate aminotransferase; CK-MB, creatinine kinase–myoglobin isoenzyme; UA, unstable angina.
Acute coronary syndrome: the illusion of treatment!

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Abstract
Acute coronary syndrome is a critical area for the “illusion of treatment,” which is a phenomenon where there is an unjustified enthusiasm for a treatment by both patients and doctors. Therapeutic illusion is not the only factor driving overtreatment, as treatment decisions are also influenced by reimbursement pressures, quality measures, fear of litigation, and patients’ expectations. Despite the other factors involved in overtreatment, therapeutic illusion is the one contributor that all cardiologists can begin to address immediately by evaluating their own practice, verifying adherence to the guidelines, and applying simple conscious heuristics to more rational evidence-based care. ■ Heart Metab. 2018;75:19-21

Keywords: acute coronary syndrome; percutaneous coronary intervention; therapeutic illusion

Introduction
In recent years, increasing efforts are recommended to reduce inappropriate tests and treatments in medicine, the most visible one being the Choosing Wisely Campaign in the United States. To be successful, these efforts must overcome the tendency of human beings to overestimate the effects of their actions, a phenomenon well known to psychologists who call it the “illusion of control.” In medicine, it can be called the “illusion of treatment,” which is an unjustified enthusiasm for treatment on the part of both patients and doctors.1,2 Acute coronary syndrome is a critical area for the “illusion of treatment,” both for the pathophysiologic approach, which may be too simplistic, and for the therapeutic approach, which may be too optimistic.

The “simplistic” approach to the pathogenesis of acute coronary syndrome
Acute coronary syndrome is commonly attributed to acute coronary thrombosis superimposed to atherosclerotic plaques. Several features have been identified as predictive of plaque instability. These features of vulnerability vary according to the diagnostic tool. At intravascular ultrasound, plaques presenting with a large lipid core and a thin superficial layer (thin-cap fibroatheroma) are supposed to be the most prone to sudden rupture, erosion, or fissuring. However, these features are not consistently found in patients with acute coronary syndrome. Actually, up to 30% of patients with acute coronary syndrome do not have any visible plaque at invasive angiography.3,4 Moreover, in patients with acute coronary syndrome, only 37.5%
had plaque rupture at the presumed culprit lesions, while 79% presented with ruptured plaques in non-culprit lesions.5

When searching for ruptured plaques in patients with an acute myocardial infarction and in patients with stable angina, it was observed that up to 30% of patients with an acute myocardial infarction had no ruptured plaque and that 30% of patients with stable angina did have ruptured plaques.6 Finally, it is interesting to note that longitudinal intravascular ultrasound studies have shown that plaques undergo dynamic changes with most of the lesions that initially present with the features of a "vulnerable" profile, progressing to a stable profile at follow-up and vice versa and that these dynamic changes had no clinical counterpart.7 Therefore, the common assumption of a close link between “vulnerable” plaques and acute coronary syndromes is not supported by conclusive evidence, and acute ischemic syndromes in patients with no visible atherosclerotic obstruction are increasingly recognized and diagnosed, such as acute myocardial infarction with normal angiogram (eg, takotsubo syndrome, etc).

It is interesting to note that, in patients with known coronary and/or systemic atherosclerosis that do suffer an incident myocardial infarction, 79% of these infarctions were not classified as a type 1 myocardial infarction (the classic thrombosis-on-plaque infarction), but as a type 2 myocardial infarction, that, according to the universal definition of myocardial infarction, identifies the infarctions due to conditions other than coronary atherosclerosis.8

The “optimistic” approach to treatment

Two recent trials in acute coronary syndrome—PROSPECT and Compare-Acute—clearly show how biased the reading of clinical reports may be today.

PROSPECT trial

In the PROSPECT trial (Providing Regional Observations to Study Predictors of Events in the Coronary Tree), which was conducted in 37 sites in the United States and Europe, 697 patients presenting with an acute coronary syndrome (ie, unstable angina, non–ST-segment elevation myocardial infarction [NSTEMI], or ST-segment elevation myocardial infarction [STEMI]) were included and followed for 3.4 years.9 Each patient underwent a detailed investigation of all major coronary vessels by invasive angiography and intravascular ultrasound. Study inclusion required a successful and uncomplicated percutaneous coronary intervention (PCI) of all culprit lesions; 697 culprit lesions were identified and treated by PCI and stenting. Angiography post–PCI identified 1814 untreated lesions, whereas intravascular ultrasound post–PCI identified 3160 untreated lesions that were located in the proximal- to middle-third of the three major epicardial coronary arteries, including 596 lesions that presented with the ultrasonic markers of highly unstable plaques, ie, thin-cap fibroatheromas.

Despite the incredibly high number of plaques identified in patients deemed to be at an elevated cardiovascular risk, the number of hard events at follow-up (death and myocardial infarction) was as low as 1.4% per year. Moreover, the number of events occurring at the site of a stented lesion (n=118) was similar to the number of events occurring at the site of an untreated lesion (n=104). Taking into consideration that untreated lesions were in much greater number than the stented lesions, the hard event rate at the untreated sites was 3.3%, while the hard event rate at the stented sites was 16.9%.

An unbiased reading of these data can only conclude that PCI and stenting do not exert a preventive action against future ischemic events and that the ultrasonic markers of instability are much poorer predictors of hard clinical events at follow-up than commonly thought.

Compare-Acute study

The Compare-Acute study (Comparison between fractional flow reserve–guided revascularization versus conventional strategy in Acute STEMI patients with multivessel disease) randomized 885 patients...
with STEMI and multivessel disease who had undergone primary PCI on an infarct-related coronary artery in a 1:2 ratio to undergo complete revascularization of noninfarcted coronary arteries guided by fractional flow reserve (295 patients) or no revascularization of noninfarct-related coronary arteries (590 patients). At the 12-month follow-up, the mortality rates were 1.4% in the “complete” vs 1.7% in the “noncomplete” revascularization group, the myocardial infarction rates were 2.4% vs 4.7%, respectively, and the cerebrovascular event rates were 0% vs 0.7%, respectively. None of these differences was statistically significant. Therefore, the additional procedures to achieve a “complete” revascularization did not result in a significant reduction in the risk of death, reinfarction, or stroke in patients with an acute myocardial infarction. Despite this evidence, the authors concluded by recommending the strategy of complete revascularization.

Actually, in both trials, the only difference at follow-up was the number of revascularization procedures. Both trials compared two strategies that resulted in a similar number of hard adverse events (death, acute myocardial infarction, and stroke), but differed in the number of PCIs. In both cases, the authors recommended adopting the strategy that increased the number of procedures. To reach this surprising conclusion, the same event, namely coronary revascularization, is considered a treatment or a major adverse coronary event simply based on the timing of its performance and despite the observation that, admittedly, in most cases, there was no compelling clinical indication.

Conclusions

Clearly, the therapeutic illusion is not the only factor driving overtreatment. Decisions about performing PCI and stenting are influenced by reimbursement pressures, quality measures, fear of litigation, and patients’ expectations. Overuse of medical services that are more likely to cause harm than good is a per-

vasive problem and cardiovascular procedures are listed among those with direct and indirect evidence of inappropriate care. Research is needed to determine whether and how management of the therapeutic illusion could reduce overtreatment. However, this is unlikely to occur in the near future. In the meantime, the therapeutic illusion is one contributor to overtreatment (and rising health care costs) that all cardiologists can begin to address immediately, by evaluating their own practice, verifying adherence to the guidelines, and applying simple conscious heuristics to more rational evidence-based care.

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Focus on trimetazidine in acute coronary syndrome

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Abstract
Trimetazidine is an anti-ischemic agent that acts at the cellular level by shifting the cardiac energy metabolism from β-oxidation of free fatty acids to the more efficient glucose oxidation. In patients with an acute myocardial infarction (AMI) who are treated with thrombolysis and/or a percutaneous coronary intervention (PCI), ischemia-reperfusion injury may occur after reestablishing myocardial blood supply to an ischemic region. In animal models of ischemia-reperfusion injury, trimetazidine markedly reduced casein kinase and lactate dehydrogenase activities and decreased the infarct size. In patients with an AMI, trimetazidine reduced the rate of any form of reperfusion arrhythmias, more so with potentially life-threatening arrhythmias. In the EMPI-FR study (European Myocardial Infarction Project – Free Radicals), in the subset of patients not receiving thrombolyis assessed as per-protocol analysis, there was an 11.9% and 13.8% risk reduction in 35-day mortality and in-hospital mortality, respectively, in patients receiving trimetazidine. More recently, it was shown that trimetazidine, as an adjunctive therapy to PCI, reduced myocardial damage and preserved left ventricular function more than PCI alone. In a large registry of patients with AMI, the use of trimetazidine was associated with significant reductions in all-cause mortality and combined major adverse cardiac events (MACE), a finding that was confirmed in the first meta-analysis to report these benefits in patients with AMI treated with trimetazidine, showing a 67% risk reduction for MACE, which was defined as the composite of death, recurrent nonfatal MI, target vessel revascularization, coronary artery bypass graft, recurrence of angina, and/or hospitalization for heart failure.  ■ Heart Metab. 2018;75:22-27

Keywords: arrhythmia; myocardial infarction; prognosis; treatment; trimetazidine

Introduction
Until the early 1960s, in-hospital mortality due to acute myocardial infarction (AMI) was approximately 30%, not counting those dying before being admitted to a hospital.1 Advances in both adjuvant pharmacological therapy (modern antithrombotic therapy and secondary prevention) along with early reperfusion (thrombolysis or percutaneous coronary intervention [PCI]) in patients with ST-segment elevation MI (STEMI) are responsible for a significant decrease in acute and long-term mortality following an acute coronary syndrome (ACS). Still, in the national registries of the European Society of Cardiology countries, mortality of unselected patients with STEMI varies between 4% and 12%.2 Therefore, it is fair to say that there is an ongoing challenge to achieve a greater reduction in morbidity and mortality in patients with ACS.
Trimetazidine in acute coronary syndrome

The potential role for cardioprotection at the cellular level during acute ischemia

Trimetazidine is an anti-ischemic agent that acts at the cellular level by shifting the cardiac energy metabolism from β-oxidation of free fatty acids to the more efficient glucose oxidation. The use of trimetazidine in patients with stable angina has been extensively documented to significantly reduce angina attacks, increase exercise tolerance, and improve quality of life. In patients with left ventricular dysfunction, trimetazidine in addition to optimal medical therapy improves cardiac function and decreases cardiovascular events, including hospitalizations and all-cause death.

In patients with AMI who are treated with thrombolysis and/or PCI, ischemia-reperfusion injury may occur after reestablishing myocardial blood supply to an ischemic region. Several studies have shown that ischemia-reperfusion injury may not only precipitate arrhythmias and suppress or delay the recovery of contractile function, but may also cause cell death in potentially salvageable ischemic tissue. In an animal model of ischemia-reperfusion injury, trimetazidine markedly reduced casein kinase and lactate dehydrogenase activities (Figure 1) and decreased the infarct size (Figure 2) compared with the control group.

The activation of AMP-activated protein kinase (AMPK), an energy sensor that controls ATP supply from substrate metabolism and protects the heart from energy stress, exerts a protective effect against ischemia-reperfusion injury. In a mouse model of in vivo regional ischemia and reperfusion, ie, by ligation of the left anterior descending coronary artery, trimetazidine significantly stimulated cardiac AMPK and extracellular signal-regulated kinase (ERK) signaling pathways, thereby reducing myocardial infarct size.

Due to the aforementioned actions of trimetazidine at the cellular level during acute ischemia, its role in patients with ACS has long been explored.

Effects of trimetazidine on patients with AMI in the thrombolytic era

One of the first clinical demonstrations of the effects of trimetazidine on reperfusion arrhythmias in patients with an AMI came from the work of Papodopoulos et al in the mid–1990s. In this controlled, randomized trial, 169 patients with a first AMI were included and

**Abbreviations**

ACS: acute coronary syndrome; AMI: acute myocardial infarction; CK-MB: creatinine kinase–myoglobin isoenzyme; cTnl: cardiac troponin I; EMPI-FR: European Myocardial Infarction Project – Free Radicals; KAMIR: Korean Acute Myocardial Infarction Registry; LIST: Limitation of Infarct Size by trimetazidine Trial; MACE: major adverse cardiovascular events; METRO: ManagEment of angina: a reTRospective cOhort [study]; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction

**Fig. 1** Trimetazidine exerts protective effects against CK (A) and LDH (B) activities in rats following cardiac I/R injury. **Fig. 2** Trimetazidine reduces infarct size.

underwent thrombolytic treatment with intravenous administration of recombinant tissue plasminogen activator. Trimetazidine was given at an initial single oral dose of 60 mg on admission, followed by 20 mg twice a day for the next 5 days. There was a significant reduction in the rate of any form of reperfusion arrhythmias in the trimetazidine-treated group vs controls (30.1% vs 56.3%; P<0.01). The beneficial effects of trimetazidine were more evident in patients with more severe and potentially life-threatening arrhythmias (sustained ventricular tachycardia, ventricular fibrillation); in this group of patients, arrhythmias were almost totally suppressed by trimetazidine vs controls (1.2% vs 7.0%; P<0.05), an effect that is possibly related to trimetazidine’s ability to reduce late potentials after an AMI. Similar findings were found in another small trial on 81 patients with an anterior MI in which trimetazidine was given before thrombolysis, which led to a decrease in the occurrence of ventricular arrhythmias, a reduction in infarct size, and less left ventricular remodeling after 6 months.

Due to the clinical benefits observed with trimetazidine in small trials in patients with an AMI, a large, randomized, double-blind, placebo-controlled trial was performed. The EMPIR-PCI trial (European Myocardial Infarction Project – Free Radicals) was a prospective European multicenter trial in which 19,725 patients presenting with symptoms of an AMI within the previous 24 hours were randomized. An intravenous bolus injection of trimetazidine (40 mg) was given just before or simultaneously with thrombolysis, followed by continuous infusion (60 mg/day) for 48 hours. Overall, there was no difference between trimetazidine and placebo for short-term mortality (35 days) in an intention-to-treat analysis. However, in the subset of nonthrombolysed patients (corresponding to 44% of all patients included in the trial), a nonsignificant reduction in mortality was observed for patients receiving trimetazidine in the intention-to-treat analysis, which became significant in the per-protocol population analysis for 35-day mortality (13.3% vs 15.1%; P=0.027) and in-hospital mortality (11.9% vs 13.8%; P=0.013).

More recently, the cardioprotective effect of trimetazidine was tested in 100 diabetic patients with an anterior MI who were treated with thrombolysis. Confirming previous study results, the use of trimetazidine in this high-risk population was associated with a 2-fold increase in the proportion of patients achieving resolution of their ST-segment elevation (70% vs 36%; P<0.05). Total serum creatinine kinase and creatinine kinase–myoglobin isoenzyme (CK-MB) levels were significantly lower in the trimetazidine group at different sampling times. Taken together, trimetazidine-treated patients had significantly lower myocardial damage and faster reperfusion times at the 6-month follow-up, with fewer cardiac events.

Effects of trimetazidine on patients with AMI in the PCI era

According to the most recent international guidelines, primary PCI is the preferred reperfusion strategy in patients with STEMI within 12 hours of symptom onset, provided it can be performed <120 minutes from the time of diagnosis. The first clinical trial exploring the benefits of trimetazidine in 94 patients undergoing primary PCI for an AMI was the LIST trial (Limitation of Infarct Size by trimetazidine Trial). Trimetazidine was given intravenously before angioplasty and continued for 48 hours, and, compared with placebo, it yielded a significantly more important and faster reduction in ST-segment elevation with a trend to lower ST-segment exacerbation.

Due to its mode of action at the cellular level, trimetazidine may protect cardiomyocytes in patients with an ACS who are undergoing a PCI, thus minimizing myocardial damage and improving left ventricular function. This hypothesis was tested in a study involving 52 patients hospitalized for a recent ACS (17 STEMI, 11 non–STEMI [NSTEMI], and 24 unstable angina patients), in whom a primary PCI had not been performed. Trimetazidine was given 15 days prior to PCI and serum troponin I and CK-MB levels were measured before PCI and up to 48 hours after the procedure. Figure 3 shows that fewer patients treated with trimetazidine vs placebo had higher levels of CK-MB at 24 and 48 hours after a PCI. Due to the lower amount of myocardial damage, left ventricular function, as assessed by echocardiography in the first 3 months after the PCI, improved in trimetazidine-treated patients compared with placebo-treated patients. While left ventricular ejection fraction (%) increased significantly from 51.7±7.9 (baseline) to 58.6±5.5 in trimetazidine-treated patients, it remained unchanged in the placebo group (53.5±7.5 vs 54.7±6.0).

To further test the capability of trimetazidine in protecting the cardiac cells during PCI, a single, oral
loading dose (60 mg) of trimetazidine was given to 136 patients 30 minutes before recanalization, whereas the 130 patients in the control group did not receive trimetazidine. Cardiac troponin I (cTnI) levels were significantly reduced in the trimetazidine group at each time point (Figure 4)\(^{23}\); moreover, the total amount of cTnI released after PCI was significantly reduced in the trimetazidine group \(P<0.05\). Although this trial was performed in patients with stable angina, the cardioprotection demonstrated during the study may be extrapolated to patients undergoing PCI for ACS.

In a similar study, but which is now enrolling 45 patients with NSTEMI undergoing PCI,\(^{24}\) trimetazidine, given prior to the intervention, was associated with a greater improvement in the myocardial performance index as well as a decrease in both left ventricular end-diastolic volume and brain natriuretic peptide levels compared with standard care.

**Clinical benefits of trimetazidine in patients with ACS**

The comparative effect of antianginal drugs in patients with stable angina on the predicted mortality risk after surviving an MI was the main objective of the METRO study (ManagEment of angina: a reTRospective cOhort).\(^{25}\) In 353 consecutive patients with stable angina who were selected if they were discharged following an AMI, the effect of the prior use of any antianginal drug (nitrates, \(\beta\)-adrenoceptor antagonists, calcium channel antagonists, trimetazidine, or nicorandil) on mortality was assessed. In a multivariate logistic regression model, the prior use of trimetazidine was the only factor independently associated with a significant reduction in mortality compared with other antiangular drugs. A recent study demonstrated that pretreatment with trimetazidine can significantly inhibit coronary microembolization–induced myocardial apoptosis, improving cardiac function in a swine model of coronary microembolization,\(^{26}\) a well-described complication in patients undergoing PCI and which is usually associated with an acute elevation in cardiac troponins and adverse long-term outcomes.\(^{27}\)

The KAMIR registry (Korean Acute Myocardial Infarction Registry) was a large registry comprising 13 733 patients with AMI, where the effect of adding trimetazidine to standard treatment was assessed on clinical outcomes.\(^{28}\) Patients were divided into two groups: those treated with trimetazidine during their in-hospital management period and those who were not. During the first year after a PCI, trimetazidine lowered the relative risk of all-cause mortality by 59% and major adverse cardiovascular events (MACE) by 76%. The positive findings in this registry prompted investigators from China to run a controlled, randomized trial in 173 diabetic patients with AMI who were undergoing a PCI to compare the effects of trimetazidine on the release of cardiac markers and improvement in cardiac function. All patients received 300 mg of aspirin and 180 mg of ticagrelor upon admission, followed by 100 mg of aspirin once a day and 90 mg of ticagrelor twice a day. Trimetazidine-treated pa-

![Histogram of CK-MB levels in patients at 24 and 48 hours post–PCI who were treated with trimetazidine or placebo.](image)

**Fig. 3** Histogram of CK-MB levels in patients at 24 and 48 hours post–PCI who were treated with trimetazidine or placebo.

**Abbreviations:** *P*<0.05 vs group B; CK-MB, creatinine kinase–myoglobin isoenzyme; PCI, percutaneous coronary intervention.

**Based on data from reference 22:** Labrou et al. Am J Cardiovasc Drugs. 2007;7(2):143-150.
Patients received a loading dose of 60 mg trimetazidine at admission, followed by 20 mg twice a day. There were no significant between-group differences at baseline; on the second day post–PCI, trimetazidine significantly reduced total creatinine kinase and CK-MB levels by as much as 27% and 24%, respectively, compared with the control group; in addition, after days 1 and 6, trimetazidine significantly reduced cTnI levels by 32% and 31%, respectively. At 14 days post–MI, the left ventricular ejection fraction was greater in trimetazidine-treated patients (58.4%±8.6%) compared with controls (54.9%±8.4%).

**Conclusions**

Due to its unique mode of action at the cellular level, there was a strong physiopathological rationale for trimetazidine to be effective in patients with ACS. ACS is a condition in which the myocardial cells are at great risk due to the low blood supply before recanalization ensues. Moreover, even after blood supply has been restored, the cells must deal with the ischemia-reperfusion phenomena. In fact, experimental and clinical data obtained in the past 30 years confirmed that trimetazidine might protect the cells during ischemia and after reperfusion to consistently prevent myocardial damage, preserve left ventricular function, and improve outcomes. The first meta-analysis to report these benefits in patients with AMI who were treated with trimetazidine (Figure 5) showed no effect on ear-

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**Fig. 4** Time course of cTnI release. cTnI levels were measured in blood samples collected from patients before (T0) and 6, 12, 18 and 24 hours after PCI. Values are the mean ± SD obtained for 130 (control, open symbols) and 136 (TMZ, filled symbols) patients. The arrow indicates the time of PCI. ***P<0.001.

Abbreviations: **P<0.05 vs group B. cTnI, cardiac troponin I; PCI, percutaneous coronary intervention; TMZ, trimetazidine.


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**Fig. 5** Forest plot and funnel plot of early/short-term all-cause mortality (A) and total major adverse cardiovascular events (B).

Abbreviations: M-H, Mantel-Haenszel; OR, odds ratio.

ly/short-term all-cause mortality, but a 67% risk reduction for MACE, which was defined as the composite of death, recurrent nonfatal MI, target vessel revascularization, coronary artery bypass graft, recurrence of angina, and/or hospitalization for heart failure.

Despite clear signs of benefit and due to the lack of a large, properly designed clinical trial that is powered to assess hard end points, with the use of primary PCI and contemporary adjuvant therapy, trimetazidine in patients with ACS has not made it into the guidelines. Until then, it is up to the clinician’s discretion to consider adding trimetazidine in the management of this high-risk population of patients with ACS.

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From atropine eye drops to takotsubo syndrome in an 89-year-old lady

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Abstract
A few hours after receiving atropine drops for an eye examination, an 89-year-old lady complained of compressive chest pain that was associated with an ST-segment elevation in the anterolateral and inferior leads. Emergency coronary angiography showed normal coronary arteries; however, contrast ventriculography showed an “apical ballooning” pattern (octopus trap) in end systole that is typical of takotsubo syndrome. The left ventricular function, monitored by a 2D echocardiogram, fully recovered at follow-up. Atropine eye drops can have systemic effects, especially in the elderly, inducing, through a sympathetic imbalance, an acute coronary microvascular dysfunction that may trigger takotsubo syndrome in the absence of classic emotional stress. This case report provides support for the hypothesis that takotsubo syndrome is a manifestation of acute microvascular dysfunction. ■ Heart Metab. 2018;75:29-32

Keywords: acute microvascular dysfunction; atropine; takotsubo syndrome

Introduction
Takotsubo syndrome was initially recognized in Japan1 and later in the US, where the first report dates back to 1998. It is a condition where the signs and symptoms of acute myocardial ischemia occur in patients with no evidence of obstructive coronary atherosclerosis at angiography.2 Given the established assumption that acute myocardial infarction is consistently associated with coronary atherothrombosis, the real nature of this syndrome has been strongly debated, with most cardiologists denying its ischemic nature and preferring to call it stress cardiomyopathy.3 This case report of a female patient who was recently admitted to our coronary care unit offers the opportunity to review our understanding of this syndrome.

Clinical presentation
AT is a charming 89-year-old lady who has been followed in our outpatient clinic due to her history of hypertension, hypercholesterolemia, and chronic kidney disease. At the last echocardiographic examination, her left ventricular function was normal (ejection fraction, 62%), with normal chamber dimensions and wall thickness. On June 20th at 9 AM, she started complaining about chest pain shortly after receiving atropine drops for an eye examination. She presented to the emergency department at 10 AM. The physical ex-
amination was unremarkable, the blood tests showed elevated high-sensitivity troponin T at 169 ng/L (normal value <14). The electrocardiogram showed a marked ST-segment elevation in the anterolateral and inferior leads (Figure 1). Based on these data, the patient was given antithrombotic agents (aspirin + clopidogrel) at the recommended doses and referred to the catheterization lab for a primary percutaneous coronary intervention.

When the patient reached the catheterization table at 10:30 AM, she was still symptomatic and the ST segment was still elevated. Coronary angiography showed a normal left and right coronary artery (Figures 2 and 3). Left ventricular angiography in the right anterior oblique view showed a normal diastolic profile of the ventricular cavity (Figure 4) that assumed the “apical ballooning” pattern (octopus trap) in end systole (Figure 5) that is typical of takotsubo syndrome.

A diagnosis of takotsubo syndrome was confirmed and the patient was transferred to the coronary care unit. At arrival, she was still complaining of chest pain; the physical examination showed bilateral rales with fine crackles on the entire lungs, a further increase in cardiac biomarkers (high-sensitivity troponin, 754 ng/L; creatine kinase-myocardial isoenzyme [CK-MB], 23.75 ng/mL [normal value <6.3]), elevated white blood cell count, and elevated blood glucose levels. Chest x-rays confirmed augmented extravascular lung water and a dilated heart. The echocardiogram showed akinesis of the apex, mid, and api-
cal segments in all left ventricular segments, severe systolic dysfunction with an ejection fraction of 15%, mild mitral regurgitation, and pulmonary hypertension (pulmonary artery pressure, 65 mm Hg).

The patient was treated with IV diuretics and morphine. The next day, June 21st, the patient had tachycardia, chest pain, dyspnea, and a further increase in cardiac markers. Ivabradine and ramipril were added to the treatment regimen. The patient’s symptoms, physical examination, and CK-MB normalized on June 25th. Atrial fibrillation appeared on the echocardiography monitor, but it spontaneously reverted to sinus rhythm on June 27th. The echocardiogram showed hypoakinesis of the apex and mid-distal segments in all ventricular walls, with hyperkinesis of the proximal segments, severe global systolic dysfunction with an ejection fraction of 25%, and pulmonary hypertension (pulmonary artery pressure, 46 mm Hg). The patient was discharged on June 28th. She was prescribed ramipril, aspirin, dabigatran, and trimetazidine.

The patient came back for a programmed follow-up visit on July 18th. She was asymptomatic, the lungs were clear, the electrocardiogram had reverted to normal, and the left ventricular function had markedly improved with an ejection fraction of 50%.

Discussion

In spite of extensive research in recent years, takotsubo syndrome remains a challenging entity with elusive and heterogeneous epidemiological, pathophysiological, and clinical features. Initially described in Japan, it is now increasingly recognized in the Western world, including Italy and the US, and accounts for 5% of all admissions with acute coronary syndromes. Described as a benign and self-limiting disease, it is now associated with a 5% intrahospital mortality and an approximate 10% chance of recurrences in the mid- to long-term follow-up. Even more surprising, it was initially described as a stress cardiomyopathy, and therefore, a primary disease of the muscle, but it is now considered a transient, severe abnormality of the coronary microcirculation, which mirrors in an atypical distribution of the wall motion abnormalities, shifting the focus from the myocardium as the culprit to the myocardium as a victim of the abnormal microcirculation.4 This change in thinking has important potential therapeutic implications, since we have several drugs that target the coronary microcirculation, which could potentially be useful in patients with takotsubo syndrome.

In the new pathophysiological perspective, takotsubo syndrome is just another point in the spectrum of coronary microvascular disease,5 with a trigger that is linked to a neurohormonal storm, particularly to an excess of circulating catecholamines, produced by structures mediating the stress response in both the central and autonomic nervous system.6 The same storm (and the same effect on myocardial wall motion) can be iatrogenically induced during exogenous catecholamine infusion, during dobutamine stress, or in patients with brain hemorrhages who suffer from a catecholamine surge that provokes takotsubo syndrome–like abnormalities (also called takotsubo syndrome phenocopy). The trigger event is usually an emotional or psychological stress, which is missing in the described case. In this perspective, it is interesting that the triggering event in our 89-year-old patient was the administration of the parasympatholytic agent atropine. Eye drops can have systemic effects, and systemic adverse events have been described after commonly used ophthalmic preparations, especially in the elderly who are more likely to have elevated systemic drug concentrations due to impaired drug metabolism and renal excretion. In particular, mydriatic agents, such as atropine, can cause hypertension and tachycardia due to a sympathetic imbalance, which is especially likely in the presence of renal insufficiency, as with our patient.7
The responsibility of the microcirculation in takotsubo syndrome has also been witnessed in clinical studies showing a transient, profound, reversible impairment in coronary flow velocity reserve that slowly and spontaneously improves over days or weeks, paralleling the recovery in left ventricular function. Coronary microvascular dysfunction may be effectively targeted by cardiometabolic agents. Ivabradine has been shown to increase the coronary flow reserve in angina patients, with and without diabetes, in the poststenotic territory as well as areas remote from the epicardial coronary stenosis. It remains to be clarified with prospective randomized studies whether an improvement, anecdotally described in this case and possibly achieved with drugs, such as ivabradine (and/or trimetazidine, which is also effective with a different cardiometabolic effect in patients who are still symptomatic on standard therapy), modifies the long-term prognosis of patients with takotsubo syndrome. In particular, the role of trimetazidine has a strong pathophysiological rationale, since takotsubo syndrome also affects the microcirculation, which cannot be treated with revascularization, and is the preferential target of trimetazidine treatment.

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The heart must continuously produce large amounts of adenosine triphosphate (ATP) to maintain contractile function. The majority of this cardiac ATP is derived from mitochondrial oxidative phosphorylation, a process that consumes large amounts of oxygen. Ischemia results in a mismatch between oxygen demand and oxygen supply to the heart, which, in turn, results from a decrease in mitochondrial oxidative phosphorylation and an energy deficient state in the heart muscle. The magnitude of the decrease in mitochondrial oxidative phosphorylation during ischemia depends on the severity of ischemia and the degree to which oxygen supply is impaired. Glycolysis (which does not require oxygen) accelerates during ischemia in an attempt to increase ATP production. During ischemia, there are also changes in the source of energy substrate used to support residual mitochondrial oxidative phosphorylation, which includes an increase in the contribution of fatty acid oxidation, a decrease in glucose oxidation, and residual mitochondrial oxidative metabolism. Increased glycolysis accompanied by a decrease in glucose oxidation during ischemia results in an accumulation of H+ and lactate. Accumulation of these glycolytic byproducts decreases cardiac efficiency and adds to the severity of the oxygen supply-demand mismatch seen during ischemia. Therapeutic strategies that inhibit the contribution of fatty acid oxidation to residual mitochondrial oxidative metabolism will result in an increase in glucose oxidation, an improved coupling between glycolysis and glucose oxidation, a decrease in glycolytic byproduct accumulation, an increase in cardiac efficiency, and a decrease in the severity of ischemic injury. 

**Keywords:** fatty acid oxidation; glucose oxidation; glycolysis
artery) and/or an increased demand of oxygen to the heart (i.e., increased workload) that is not met by an increased oxygen supply to the heart (such as seen with angina pectoris). Myocardial ischemia disrupts normal oxygen delivery to the heart, resulting in impaired mitochondrial oxidative phosphorylation, which decreases mitochondrial ATP production, resulting in an energy deficiency in the heart. This decreased energy production compromises cardiac contractile function, and, in the presence of severe ischemia, can lead to myocyte cell death. This “Refresher Corner” article reviews the cardiac energy metabolic changes that occur in the heart during both mild and severe ischemia.

### Cardiac energy metabolic changes during mild ischemia

Oxygen is consumed by the mitochondria primarily at the level of the electron transport chain, which is coupled to the phosphorylation of adenosine diphosphate to form ATP (hence the term oxidative phosphorylation). In the presence of mild ischemia, a decreased oxygen supply decreases mitochondrial oxidative phosphorylation, resulting in a decrease in ATP synthesis. The entry of NADH and FADH₂ into the electron transport chain is decreased, resulting in a build-up of these nucleotides.
in the mitochondria, which feedback and inhibit the pathways involved in their synthesis; i.e., the tricarboxylic acid cycle and the metabolic pathways of oxidative metabolism. As a result, the oxidation of the two main carbon substrates, fatty acids and glucose, decreases during mild ischemia (Figure 1B).

The decrease in mitochondrial ATP production during mild ischemia is accompanied by an increase in glycolysis, which can generate ATP in the absence of O\textsubscript{2} (Figure 1B). The glucose for glycolysis during mild ischemia originates from both extracellular glucose and from an increased mobilization of glucose from intracellular glycogen stores.\textsuperscript{2} While the glycolytically derived ATP provides an additional source of energy during ischemia, it cannot completely compensate for the loss of mitochondrial ATP production, since glycolysis only produces 2 ATP molecules per molecule of glucose passing through glycolysis (compared with the 30 ATP molecules produced per molecule of glucose oxidized).

While glycolysis increases during mild ischemia, mitochondrial glucose oxidation is impaired.\textsuperscript{1} The consequence of the increased glycolytically derived ATP uncoupled from subsequent glucose oxidation is an increased generation of H\textsuperscript{+} and lactate, which can result in a decrease in intracellular pH within the ischemic myocardium.\textsuperscript{4} The accumulation of H\textsuperscript{+} results in disturbances in ionic homeostasis during ischemia (e.g., by increasing Na\textsuperscript{+} influx into the cardiomyocytes during ischemia), which can lead to a decrease in cardiac efficiency (i.e., cardiac work/O\textsubscript{2} consumed), since ATP is consumed in order to reestablish this ionic imbalance.

During a mild ischemic episode, mitochondrial ATP production decreases in proportion to the decrease in oxygen supply to the heart. However, the proportion of fatty acid and glucose used for residual mitochondrial oxidative metabolism changes. During ischemia, blood levels of fatty acids increase and there are alterations in the control of mitochondrial fatty acid uptake.\textsuperscript{5} As a result, fatty acid oxidation dominates as the main residual source of ATP production, which occurs at the expense of a greater decrease in glucose oxidation.\textsuperscript{5} This decrease in glucose oxidation contributes to an uncoupling of glycolysis from glucose oxidation, which increases the production of both H\textsuperscript{+} and lactate.\textsuperscript{6,7} This increase contributes to a decrease in cardiac efficiency, as ATP is directed away from contractile processes to deal with the intracellular H\textsuperscript{+} accumulation.\textsuperscript{7} As a result, myocardial ischemia not only compromises cardiac ATP production, it also decreases the efficiency of using ATP for muscle contraction.

**Cardiac energy metabolism during severe ischemia**

During a severe decrease in coronary flow, both oxygen supply and energy substrate supply to the myocardium are decreased, which dramatically decreases mitochondrial oxidative phosphorylation and ATP production. A decrease in glucose supply to the heart also results in a dramatic mobilization of glucose from endogenous glycogen stores in an attempt to maintain the myocardial glucose supply for glycolysis (Figure 1C). Increased glycolysis and a marked impairment in mitochondrial glucose oxidation result in an increased production of H\textsuperscript{+} and lactate in the heart. Since coronary flow is markedly reduced, these glycolytic by-products accumulate in the myocardium, resulting in a drop in cellular pH, which can lead to cell death. The accumulation of H\textsuperscript{+} in severely ischemic heart muscle eventually feedbacks and inhibits glycolysis in an attempt to prevent the further accumulation of H\textsuperscript{+}.

If previously reversibly injured ischemic myocardium is reperfused (e.g., by mechanical revascularization or using thrombolytic agents after a myocardial infarction), mitochondrial oxidative phosphorylation recovers as oxygen is reintroduced. However, mitochondrial fatty acid oxidation recovers to a greater extent than the rates of glucose oxidation (Figure 1D),\textsuperscript{7,8} which occurs due to hearts being exposed to increased fatty acids in the coronary circulation and to the alterations in the subcellular control of fatty acid oxidation.\textsuperscript{1} The high levels of fatty acid oxidation decrease the rate of recovery of glucose oxidation (Figure 1D).\textsuperscript{9} Glycolysis rates remain high in the early period of reperfusion postischemia, resulting in a continued uncoupling of glycolysis and glucose oxidation,\textsuperscript{7} which results in a continued production of both H\textsuperscript{+} and lactate in the reperfusion period, contributing to continued alterations in ionic homeostasis and decreased cardiac efficiency following ischemia.\textsuperscript{6,7,10,11} This decrease in cardiac efficiency contributes to a decreased contractile function into the reperfusion period.
Inhibition of fatty acid oxidation and stimulation of glucose oxidation as an approach to treat myocardial ischemia

In mild ischemia, one therapeutic strategy is to increase glucose oxidation to improve coupling of glycolysis to glucose oxidation; this can be achieved by inhibiting residual fatty acid oxidation or directly stimulating with glucose. Inhibition of fatty acid oxidation during mild ischemia switches any residual oxidative metabolism from fatty acid oxidation to glucose oxidation, while inhibition of fatty acid oxidation during reperfusion following severe ischemia decreases the high rates of fatty acid oxidation seen postischemia.2,7,12 During both ischemia and reperfusion following severe ischemia, inhibiting fatty acid oxidation will increase glucose oxidation, which can improve the coupling between glycolysis and glucose oxidation,7 which decreases both $\text{H}^+$ and lactate production, leading to an increase in cardiac efficiency, a decrease in tissue injury, and an increase in contractile function. An example of a clinically available drug that inhibits fatty acid oxidation and stimulates glucose oxidation in the heart is trimetazidine.13-15 Inhibition of fatty acid oxidation by trimetazidine increases glucose oxidation both during and following ischemia,13,14 which decreases the severity of pH changes during ischemia16 and improves contractile function. This metabolic action may explain the beneficial effects of trimetazidine in the clinical setting of ischemia.17-19

Conclusions

Dramatic alterations in energy metabolism occur in mildly and severely ischemic hearts. High glycolysis rates accompanied by low mitochondrial glucose oxidation rates result in a decrease in cardiac efficiency and a depressed contractile function. Stimulating glucose oxidation by inhibiting fatty acid oxidation can improve both cardiac efficiency and function, and therefore, protect the ischemic heart.

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False positive troponins

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Abstract
The measurement of the troponins T and I has revolutionized the diagnosis of acute myocardial infarction. However, as the assays have become more sensitive, they inevitably have become less specific for acute myocardial infarction; the consequence is an increased prevalence of “false positive troponins.” This article explains how this has come about and describes the strategies that can be used to improve specificity. ■ Heart Metab. 2018;75:37-39

Keywords: acute coronary syndrome; biomarker; necrosis; troponin

What is “false positive”?
Cardiologists have a love-hate relationship with troponin! The use of troponin has revolutionized the management of patients with suspected non–ST-segment elevation acute coronary syndrome (NSTE-ACS) and the identification of patients with non–ST-segment elevation myocardial infarction (NSTEMI). This revolution has been led by the increasing analytic sensitivity of the troponin assays. However, when sensitivity increases, specificity always declines. Thus, an increased prevalence of “false positive” troponins is an inevitable consequence of our desire for extreme sensitivity. To dissect how to deal with false positive troponin, we first need to define what we mean by “false positive.” This is the crux of the problem; the threshold at which troponin becomes abnormally elevated (positive) is set at the 99th percentile,1 while, as cardiologists, we view “positivity” as the identification of a culprit atherosclerotic plaque. Below, I will attempt to set out why this gap between definition and expectation can never be bridged. The best we can do is to understand the problem. Through a better understanding, we can adopt strategies and apply a framework to maximize the identification of type 1 NSTEMI (acute plaque events) and other forms of acute myocardial injury.

Concept of the 99th percentile
For most assays, we define the normal range as that encompassing 95% of the healthy population. Troponin has evolved differently since the early assays lacked the analytic sensitivity needed to accurately measure low concentrations of troponin in the blood (Figure 1). Therefore, it was impossible to define the lowest 2.5% of the presumed normal distribution of troponin. There were also concerns of “false positives” and, for this reason, the threshold at which troponin was deemed to become positive was defined as above the 99th percentile of the “healthy” reference population.1 The adoption of this criterion was fairly arbitrary, but it became immortalized in the first and subsequent universal definitions of acute myocardial infarction (AMI). The 99th percentile threshold for positivity did not upset the cardiology
community when the troponin assays were imprecise, which is difficult to understand without doing the thought experiment depicted in Figure 1. In essence, the imprecision of the early assays meant that the 99th percentile was high since the concentrations returned by the assays encompassed the biological variance of the population together with the analytic variance of the assays, and the noise of the latter drowned the former. Thus, the 99th percentile threshold only identified patients with substantial myocardial injury and a high prevalence of AMI (type 1). As the troponin assays became analytically more sensitive, they began to return the true distribution of troponin in the general population, which is when the frustration of “false positive” troponins surfaced. Robert Jesse encapsulated this by saying “when troponin was a lousy assay it was a great test, but now that it’s becoming a great assay, it’s getting to be a lousy test.” With improved analytic sensitivity, we also realized that troponin was not distributed normally, since all studies have shown a positive skew (Figure 1), which has further diminished the statistical validity of the 99th percentile.

Differentiating acute from chronic myocardial injury

Having set the upper limit of normal at the 99th percentile of the healthy reference population, we have an immediate and predictable consequence. The distribution of troponin in the population at risk for type 1 AMI is not the same as that of the healthy reference population! Consequently, approximately 15% to 20% of patients presenting to emergency departments without an AMI have troponin concentrations above the 99th percentile of the reference population. This percentage increases the more rigorous selection of the healthy reference population (eg, excluding patients with high blood pressure, raised cholesterol, abnormal electrocardiograms, etc), and it increases as the risk of the population presenting with suspected NSTE-ACS increases, since advancing age, male sex, structural heart disease, and renal dysfunction each significantly increase the median troponin concentration. So, the “false positive” rate is always likely to be at least 20% if we use the 99th percentile as a cut point (Figure 1). Patients with troponins that are elevated chronically and stably above the 99th percentile are defined as having chronic myocardial injury. The latest European Society of Cardiology rapid rule-in / rule-out guidelines attempt to minimize the impact of chronic myocardial injury in two ways. First, the 99th percentile is replaced by a much higher rule-out threshold (Figure 1). Second, for patients in the grey zone (between immediate rule-in and immediate rule-out thresholds), the troponin concentration on a second blood draw is subtracted from that of the first blood draw to calculate the absolute delta change value, the magnitude of this change in concentration can then be used to determine if the troponin is constant or acutely changing.
Causes of “false positive troponin” other than chronic myocardial injury

The adoption of a rule-in threshold above the 99th percentile and the use of delta change values increases the specificity of troponin for the diagnosis of NSTEMI to about 75%. These NSTEMI diagnoses include type 2 AMI, which is when there is no identifiable culprit plaque. Despite including type 2 AMI, which some cardiologists would view as a false positive diagnosis by itself, at least 25% of the patients above the immediate rule-in threshold do not have an AMI. The causes for these remaining “false positive” troponins are heterogeneous. Troponin release is not restricted to ischemic myocyte necrosis and it occurs with any form of injury, including viral myocarditis and cancer chemotherapy. Thus, troponin release almost always reflects true myocardial injury. The only exceptions are so called analytic false positive troponins from assays that misread the concentration for a variety of reasons, all of which are rare with contemporary assays and the appropriate quality controls that exclude hemolysed, clotted, and lipemic samples.

Conclusions

Various conditions, other than an acute atherosclerotic plaque rupture event, cause troponins to be released from the heart and to enter the circulation. These conditions cause frustration and create the impression that the assays are at fault and prone to false positive reads, which is not the case! Rather, we are at fault for assuming the assays are able to determine a binary assignment into AMI and no AMI. The solution is a better understanding of how troponin can be used in a clinical framework that still requires an assessment of the pretest probability of disease and of individual risk. Troponin aids, but does not replace, clinical assessment.

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Atropine

Atropine is a parasympatholytic agent that exerts its effects via competitive antagonism of the muscarinic acetylcholine receptors. Atropine decreases vagal tone to the heart and causes tachycardia by blocking cardiac muscarinic receptors. Atropine is clinically utilized via intravenous administration to treat sinus bradycardia.

Biomarker

A biomarker is a functional, physiological, biochemical, cellular, or metabolic characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathological processes, or pharmacological responses to therapeutic intervention. In the setting of clinical trials, where appropriate, biomarkers can be utilized as surrogate end points that substitute for clinically meaningful end points.

Troponins

Troponin(s) are a complex of three regulatory proteins (troponin C, I, and T) essential for muscle contraction in skeletal and cardiac muscle. Troponin(s) (troponin-1 and troponin-2) are heterotrimeric complexes present in striated muscle (skeletal and cardiac muscle) that are comprised of a Ca^{2+} binding subunit (troponin-C), an inhibitory subunit (troponin-1), and an elongated troponin molecule (troponin-2), which binds both troponin-C and troponin-1. In conjunction with tropomyosin, the troponin heterotrimer forms a regulatory complex that controls the interaction of actin and myosin. The binding of Ca^{2+} to troponin permits muscle contraction. Cardiac troponins (troponins 1 and 2) are released from cardiac myocytes following myocardial damage and loss of membrane integrity, and serve as highly sensitive and specific biomarkers for establishing the diagnosis of myocardial infarction.

Late gadolinium enhancement

Late gadolinium enhancement is a cardiac magnetic resonance imaging methodology that utilizes gadolinium bound to extracellular contrast agents that do not gain entry into the intracellular space. Under pathological conditions, where the extracellular space is increased, the volume of gadolinium distribution is increased, consequently leading to gadolinium enhancement. As late gadolinium enhancement is dependent on differences in extracellular space in different areas of the myocardium, it is useful for detecting regional disease, including acute myocardial infarction, myocardial scar, and cardiomyopathies (eg, cardiac sarcoidosis).

Taxonomy

Taxonomy refers to the science of defining/naming groups of biological organisms based on shared characteristics, and its development was primarily advanced by Carl Linnaeus. Taxonomy involves organisms being grouped into taxa that are given a taxonomic rank that includes domain, kingdom, phylum, class, order, family, genus, and species.

AMP-activated protein kinase (AMPK)

AMPK is a key kinase that controls many cellular processes, particularly pathways involved in cellular energy status. AMPK is activated during metabolic stress, where it then can either activate energy-producing pathways or inhibit energy-consuming pathways. For these reasons, it has been termed a “fuel gauge” of the cell.

Myocardial apoptosis

Myocardial apoptosis refers to programmed cell death of cardiac myocytes within the myocardium. Apoptosis involves a series of events resulting in cellular morphological changes and subsequent death, including cell shrinkage, blebbing, nuclear fragmentation, and chromatin condensation. One of its key features is that, unlike cell death via necrosis, the cellular contents do not spill out due to phagocytic cells engulfing the apoptotic cell, which is a primary reason why apoptotic cell death does not result in inflammation.