Unstable Angina
Is It Time for a Requiem?
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Historical Origins of Unstable Angina
Stable angina, often referred to as angina of effort, and its principal cause, reduction of the lumen of epicardial coronary arteries, have been recognized for >2 centuries. Acute myocardial infarction (AMI), its clinical picture, and the importance of coronary thrombosis in its origin were described a century ago. These 2 conditions, stable angina and AMI, although manifestations of the same underlying disease process, that is, coronary atherosclerosis, were initially considered to be quite distinct.

However, this distinction began to blur in 1937, when Sampson and Eliaser and Feil described several patients with severe, prolonged anginal pain at rest that differed from stable angina but sometimes preceded AMI. This disorder was variously referred to as preinfarction angina or crescendo angina, and reflecting the belief that it was in a gray zone between stable angina and AMI, it was also called intermediate coronary syndrome. In 1948, Wood proposed that this syndrome was caused by “a coronary circulation insufficient to meet the full demands at rest yet sufficient to prevent MI.” Because coronary thrombosis was believed to be a frequent cause of AMI, Wood thought that this same process also could play a role in coronary insufficiency. He reported that the administration of oral anticoagulants was associated with a reduction in the progression of coronary insufficiency to AMI or death.

At first, like many newly described conditions, unstable angina (UA) was considered to be quite rare, and as late as the 1950s, some authorities even questioned its existence. In 1956, Friedberg, in the leading cardiology textbook of the era, described these patients as “a motley group which are best classified clinically as angina pectoris (more or less severe or prolonged) or as myocardial infarction.”

In 1971, 2 important events in the history of acute coronary syndromes (ACS) occurred. The first was the World Health Organization statement that the diagnosis of AMI requires the presence of at least 2 of the following 3 criteria: typical symptoms; a typical ECG pattern, ie, the development of new Q waves; and an initial increase and subsequent decrease in serum enzymes attributed to myocardial necrosis. The second was the introduction by Fowler and Conti et al of the term UA, the term that we use today for patients falling into the continuum between stable angina and MI.

With the greater attention focused on patients with coronary artery disease as a result of the development of the coronary care unit, coronary arteriography, and advances in both pharmacological and interventional therapy of ischemic heart disease, it appeared that UA was, in fact, quite common. Indeed, the National Center for Health Statistics reported in 1991 that UA was responsible for 570,000 annual hospitalizations in the United States, resulting in >3.1 million hospital days, making UA one of the most common disorders requiring hospital admission.

In the first published guidelines on the diagnosis and management of UA, principal clinical presentations were considered to be typical of this condition: angina at rest; new onset of severe exertional angina (Canadian Cardiovascular Society grade III or higher); and distinct, often sudden, intensification of previously stable angina. In the absence of AMI, any one of these presentations was required for the diagnosis of UA. Patients with this diagnosis were classified according to the severity of the condition, the clinical circumstances in which it occurs, and the presence or absence of ECG ST-segment deviations. In accord with the World Health Organization definition, AMI was excluded in patients with ACS who had no new ECG Q waves or other major changes in the QRS complex and no elevation of serum enzymes on serial testing. Patients with clinical manifestations of myocardial ischemia similar to those of UA but who exhibited a typical pattern of an increase in serum enzymes to abnormally elevated level(s) and a subsequent decrease, suggesting myocardial necrosis, but without the development of new ECG Q waves, were considered to have non–Q-wave MI, a condition subsequently (and here) referred to as non–ST-segment–elevation myocardial infarction (NSTEMI).

By the beginning of the 21st century, 3 subgroups of patients—those with UA, NSTEMI, and STEMI—were included within ACS. Two of these 3 disorders, UA and NSTEMI, are usually considered together because they exhibit indistinguishable clinical and ECG features (ST-segment depressions and T-wave inversion) and constitute the non–ST-segment–elevation ACS (NSTEMI). However, ambiguity has begun to creep into the definition of UA. The World Health Organization revision of the definition of MI in 2008 stated: “Unstable angina is diagnosed when there...
Biomarkers of Myocyte Necrosis

Given the importance of cardiac enzyme elevations in the diagnosis of AMI,8 attention has been directed to the development of progressively more accurate biomarkers of myocardial necrosis. In the 1980s and 1990s, the MB fraction of creatine kinase (CK-MB) was considered to be the most sensitive and specific such biomarker.16 Because serial determinations of CK-MB were not routinely obtained in patients with NSTE-ACS, NSTEMI was not excluded in many patients who were considered to have UA. Therefore, the very high incidence of UA in 199111 appears to have been an overestimate. This was more than a simple matter of terminology because the differentiation between UA and NSTEMI turned out to be of considerable clinical importance. Among patients with NSTE-ACS, those with biomarker evidence of myocardial necrosis, ie, NSTEMI confirmed by a typical temporal pattern of an increase and subsequent decrease in the serum concentrations of CK-MB, exhibited a higher mortality than those with UA, in whom, by definition, CK-MB was not elevated. For example, in the Thrombolysis in Myocardial Infarction (TIMI) 3 trial, carried out in patients with NSTE-ACS,16 we observed that the 42-day mortality in patients with NSTEMI, based on elevation of CK-MB, was more than double that seen in patients with UA.17 In the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial conducted on patients with NSTE-ACS, there was a significant correlation between peak CK-MB level and mortality.18

Cardiac Troponin, the New Player

Although CK-MB was superior to previously available enzymes, it lacked both optimal sensitivity and specificity.19 The introduction by Cummins et al20 of an assay for cardiac-specific troponin I (cTnI) in 1987 and by Katus et al21 for cardiac-specific troponin T shortly thereafter provided 2 closely related biomarkers that were considerably more sensitive and specific than CK-MB and therefore detected myocardial necrosis far more frequently and accurately (Figure).22-25 For example, in the TIMI 3 trial, 25% of the patients classified as having UA on the basis of the absence of detection of CK-MB on serial sampling had cTnI ≥0.4 ng/mL (the cut point of the relatively insensitive assay that was used in the mid-1990s) and could therefore be reclassified as having had NSTEMI rather than UA.17

In the 2000 American College of Cardiology/American Heart Association guidelines for the management of patients with NSTE-ACS, it was estimated that about one third of patients with this condition without CK-MB elevation who were therefore considered to have UA exhibited release of cTnI and should be reclassified as NSTEMI.14 Thus, in retrospect, patients with UA made up a smaller percentage of patients with NSTE-ACS than had previously been believed. Like the earlier reclassification of patients believed to have NSTEMI
on the basis of serial determinations of CK-MB, which identified patients at a higher risk of adverse outcomes, this second reclassification also appeared to be of clinical importance because patients with normal CK-MB but elevated cTn were at higher risk of adverse cardiac events than those without such elevations. Indeed, in the TIMI 11B trial, we observed a 6-fold increase in death or new MI in such patients compared with patients without such an elevation. In a combined analysis of multiple trials of patients with ACS, the risk of death or recurrent MI was almost 4 times as high in the patients with elevated cTn.

Further support for the use of cTn came from 2 findings: A graded increase in mortality with progressively higher levels of cTn was observed in TIMI 3, and the detection of even minor elevations of circulating cTn identified patients with ACS who benefited more from newer therapies than patients in whom this biomarker was not detectable. These include an invasive strategy, the addition of glycoprotein IIb/IIIa inhibitors, and the substitution of low-molecular-weight heparin for the unfractionated form.

The Food and Drug Administration approved an assay for cTn in 1995, and by 2000, both the American College of Cardiology/American Heart Association and the European Society of Cardiology guidelines on NSTE-ACS indicated that cTn had become the preferred markers of myocardial necrosis. However, from the beginning of the troponin era, there has been considerable variability in the analytic characteristics and lack of standardization of the assays for these biomarkers. Initially, this led to some uncertainty as to the definition of abnormal elevations of cTn. A consensus developed among relevant professional societies that a cTn concentration that exceeds the 99th percentile of a reference population, commonly referred to as the upper reference limit (URL), was considered to be abnormally elevated. It was further agreed that for an assay to be acceptable, it must be sensitive, ie, have a very low URL, and its imprecision, ie, its coefficient of variability, must be ≤20% or preferably ≤10% at the 99th percentile.

The analytic sensitivities of the assays for cTn have improved progressively during the past 25 years and continue to do so, driving downward both the limit of detection and the URL. For example, in 1996 in the TIMI 3 trial on NSTE-ACS, the cut point was 0.4 ng/mL, whereas in 2000 in the TIMI 11B trial, conducted on a similar population but using a newer assay with a URL of ≥0.10 ng/mL, we observed that patients with negative serial CK-MB values and cTn values above this URL exhibited adverse cardiac outcomes.

A decade later, in NSTE-ACS patients enrolled in the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST elevation acute coronary syndrome (MERLIN)-TIMI 36 trial, we used a widely used, current-generation, sensitive assay in which the URL had been further reduced to 0.04 ng/mL. Not unexpectedly, cTn had become detectable in an even larger fraction of patients. We examined the subgroup of patients whose cTn was between 0.04 and 0.10 ng/mL in this trial. With the use of the earlier assay, these patients would not have had detectable elevations of cTn and would therefore have been considered to have UA but were now classified as NSTEMI. This reduced further the proportion of NSTEMI-ACS patients with UA, and importantly, this newly identified subgroup of patients with NSTEMI also experienced adverse cardiac event rates that were significantly higher than those in patients below this cut point. This reclassification of patients has been of clinical importance, as evidenced by the report by Mills et al. These investigators noted in patients with ACS that when a more sensitive cTn assay was used, and the decision limit for AMI was reduced from 0.20 to 0.05 ng/mL, the diagnosis of AMI among suspected ACS patients was increased by 27%, the patients newly classified as having MI were treated more aggressively, and their clinical outcomes improved.

High-Sensitivity Troponin

Currently, Food and Drug Administration–approved, commercially available assays in the United States for cTn have detection limits ranging from 0.006 to 0.15 ng/mL and URLs ranging from 0.023 to 0.20 ng/mL. Recently, even more sensitive cTn assays have been developed and are undergoing testing. These so-called high-sensitivity assays have detection limits ranging from 0.00009 to 0.0002 ng/mL (0.09–0.20 mg/L) and URLs ranging from 0.0028 to 0.01 ng/mL. Use of these assays increases further the detection of NSTEMI at the expense of UA. For example, among 50 patients with the clinical features of UA, including typical chest pain at rest and negative serial cTn values with a commercial assay, who were enrolled in the Randomized Trial to Evaluate the Relative PROTECTion against Post-PCI Microvascular Dysfunction (PROTECT)-TIMI 30 trial, with the use of a high-sensitivity cTn assay (Nanosphere) with a detection limit of 0.0002 ng/mL, a URL of 0.003 ng/mL and a coefficient of variability <10% at the URL, 22 patients (44%) were found to have exceeded the URL at presentation; this percentage had risen to 82% by 8 hours. It is now evident that a large majority of patients with clinical manifestations of myocardial ischemia, with rest pain but without elevated cTn by a commercially available assay, and therefore considered to have UA have an elevation of circulating cTn measured by a high-sensitivity assay and could therefore be classified as NSTEMI.

Another high-sensitivity cTn assay, the so-called single-molecule Singulex Erenna assay, has a detection limit of 0.0002 and a URL of 0.009 ng/mL and was evaluated in the TIMI 36 (MERLIN) trial. Among the 1231 patients with a negative contemporary cTn assay (URL <0.04 ng/mL), 99.7% had detectable cTnI by the cTnI assay, and they showed a graded increase of risk of adverse outcomes; 473 patients had a high-sensitivity TnI greater than the URL, and they exhibited a doubling of the risk of cardiovascular death or MI at 1 year compared with those patients who did not exceed this cut point. Recent preliminary observations indicate that concentrations of cTnI even as low as 0.005 ng/mL, below the URL of this assay, may be associated with increased risk of adverse events.

As anticipated, as the sensitivity of cTn assays increases, the specificity of the diagnosis of AMI declines. Abnormal elevations of cTn detected by high-sensitivity assays have...
been observed in a wide variety of conditions other than ACS, including stable coronary artery disease, heart failure, ventricular hypertrophy, other structural heart disease, pulmonary embolism, and sepsis.\textsuperscript{13} Elevations of high-sensitivity troponin have also been observed in the general population, in whom they are associated with an increased risk of future adverse cardiac events.\textsuperscript{42} Although it appears that the myocardium is the origin of these very low serum concentrations of cTn, the pattern of release differs, usually displaying steady concentrations at a low level rather than the temporal rise and fall characteristic of ACS (Figure). Such relatively stable low-level concentrations may exist in patients with stable angina and are associated with an adverse prognosis but are not usually indicative of ACS.\textsuperscript{43}

The sources of detectable cTn by high-sensitivity assays in apparently healthy subjects are not clear, but several possibilities exist.\textsuperscript{44} They include the normal turnover of myocytes, which appears to be accelerated by age, muscular exercise, pharmacological or emotional stress, cardiac hypertrophy, and heart failure. It is also possible that the release of very small quantities of cTn from the cytoplasm, as distinct from its major reservoir in the contractile machinery of the myocardium, can occur as a consequence of transient, ischemia-induced increases in the permeability of the myocyte membrane without cell death.\textsuperscript{38,44}

Because high-sensitivity cTn assays may be approved and are likely to be available commercially soon in the United States (at least 1 cTn assay is already marketed in Europe), the clinical interpretation of the extremely low concentrations of this biomarker that are now detectable represents a new challenge to clinicians. We agree with the recommendation in the third universal definition of MI that patients suspected on clinical grounds of having an ACS should undergo serial sampling for cTn. A typical increase and decrease in cTn, with at least 1 value above the URL for the assay, accompanied by at least 1 other feature of ischemia such as typical symptoms or ECG changes, are necessary for the diagnosis of AMI.\textsuperscript{22} This contemporary approach is reminiscent of the 1971 World Health Organization definition of AMI\textsuperscript{18} but places greater emphasis on the biochemical detection of the biomarker of myonecrosis, using extremely sensitive and specific assays of cTn instead of relatively insensitive, nonspecific enzymes present not only in the myocardium but also in other tissues. The current use of high-sensitivity cTn in Europe and other parts of the world, but not yet in North America, may result in differential ascertainment of AMI, which may complicate the interpretation of clinical trials.

**Therapeutic Implications**

The treatment of patients with spontaneous MI (type I according to the universal definition of MI)\textsuperscript{22} should take into account the risk of subsequent infarcts, the size of the infarct, the underlying function of the left ventricle, and a global assessment of the risk of recurrent cardiovascular complications. Thus, in patients with small NSTEMIs (cTn positive/CK-MB negative) who would have been diagnosed as UA in the pretroponin era, the principal therapeutic goal should be to prevent reinfarction to preserve left ventricular function and should focus on antiplatelet therapy. Invasive evaluation appears appropriate for patients with type I NSTEMI,\textsuperscript{22} even when associated with low-level elevation of cTn.\textsuperscript{28} However, an elevated cTn should not mandate invasive evaluation when the clinical suspicion for type I NSTEMI is low. Noninvasive testing, including echocardiography for assessment of left ventricular function, as well as ECG or echocardiographic stress testing, stress perfusion imaging, and coronary computed tomographic angiography or cardiac magnetic resonance imaging, may be advisable to refine the assessment of risk or when the diagnosis of NSTEMI is uncertain. In patients with STEMI, reperfusion on an emergent basis, with primary percutaneous coronary intervention preferred, as outlined in the current guidelines\textsuperscript{45} should be carried out regardless of the cTn value at presentation.

**Conclusions**

It appears that we have now come full circle in our definition of symptomatic ischemic heart disease. Before the 1930s, 2 manifestations, stable angina and AMI, were recognized. Patients in the gray zone between stable angina and AMI that we now call UA were described 75 years ago and at first appeared to be quite rare. Over the next half-century, they were recognized with increasing frequency, and by 25 years ago, about one half of all patients with NSTE-ACS were considered to have UA. However, use of ever more sensitive biomarkers of myocardial necrosis, especially cTn, has steadily chipped away at the fraction of patients with NSTE-ACS without MI who therefore are still considered to have UA. Indeed, in its 2008–2009 report, the World Health Organization revision of the definition of MI stated: “Many patients who in the past would have been diagnosed as having unstable angina will now be diagnosed as having had an MI.”\textsuperscript{15} In the next few years, there will likely be much wider use of higher-sensitivity assays for cTn and acceptance of the universal definition of MI.\textsuperscript{22} As a consequence, UA is likely to be further marginalized, its definition will become highly dependent on the particular assay for cTn used, and the term will become ever more ambiguous and cause confusion because it will mean different things to different people. Indeed, it is not clear that ACS events can occur without some increase in circulating cTn when measured by a high-sensitivity assay.

As a consequence, we are likely to return to the situation that existed before attention was directed toward patients we now consider to have UA, and patients with ischemic heart disease will again be divided into the original 2 rather than 3 major groups. One group will be patients with angina pectoris, whose angina may be of widely varying severity and classified by the Canadian Cardiovascular Society system.\textsuperscript{13} The second group will comprise patients with AMI as defined by the third universal definition, which includes the type of MI (type I, type II, etc.), the ECG changes (ie, STEMI and NSTEMI), and the extent of myocardial damage that is related to the magnitude of cTn release.

A requiem is a choral musical work that is performed at the funeral of a great personage or at the close of an important era. Has not the time arrived to prepare a requiem for UA?
Disclosures

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