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CURRENT OPINION

Interpreting troponin elevations: do we need multiple diagnoses?

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The expanded ability to detect myocardial injury using very sensitive and specific biomarker assays has been a major factor in the evolution of the definition of acute myocardial infarction (MI). This is clearly evident in the 'Universal Definition of Myocardial Infarction' recently developed by a joint task force of experts on behalf of the ESC, ACCF, AHA, and WHF (European Society of Cardiology, American College of Cardiology Foundation, American Heart Association, and World Heart Federation).[1] In a clinical setting consistent with myocardial ischaemia, criteria are presented for defining acute MI that include a rise and/or fall in cardiac biomarkers together with symptoms of ischaemia, and/or appropriate ECG changes, and/or imaging evidence of a new regional wall motion abnormality or loss of myocardium. The task force developed a clinical classification of different types of MI that can be briefly summarized as:

TYPE 1: MI due to a spontaneous coronary atherosclerotic event.
TYPE 2: MI secondary to ischaemia, but not related to coronary atherosclerosis.
TYPE 3: Sudden death with symptoms or signs of ischaemia (not requiring elevated biomarker confirmation).
TYPE 4: MI associated with percutaneous coronary intervention (Subtype 4a), or stent thrombosis (Subtype 4b).
TYPE 5: MI associated with coronary bypass surgery.

This multi-component scheme appears to add complexity in an area that can be quite confounding because of the multiple terms used to describe myocardial ischaemia/infarction in all of its various manifestations. This includes differentiating myocardial damage associated with ST elevation (STEMI) from that occurring without ST elevation (non-STEMI). Patients with a sudden change in cardiac status are often admitted to the hospital with a diagnosis of acute coronary syndrome (ACS), but ACS is not included in the ICD-9-CM codes.[2] Intermediate coronary syndrome (code 411.1), which includes impending infarction, preinfarction angina, or unstable angina, can be used as a substitute for ACS.

How the new definitions of MI become incorporated into future revisions of the ICD codes remains to be determined. Meanwhile, understanding the basis for this classification can help physicians struggling to assess clinical data and develop appropriate diagnoses for cardiac patients. A key concept incorporated into this scheme is that cardiac biomarkers must be interpreted in clinical context. This can be illustrated by considering a case example involving the common problem of interpreting cardiac biomarkers in patients hospitalized for serious non-cardiac diseases.

Our example patient was admitted to the medical intensive care unit with shortness of breath due to acute pneumonia complicating severe chronic obstructive pulmonary disease (COPD). A transient elevation of troponin to a level three times the upper limits of normal occurred following a period of hypotension and hypoxia while he was septic. He had constant diffuse chest pains since he first felt ill, and his ECG showed atrial fibrillation with lateral T wave inversion, unchanged from prior ECGs. His shortness of breath was attributed to his pulmonary disease, and no coronary intervention performed. He recovered to where he could be discharged, and further cardiac evaluation was deferred to the

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discretion of his primary care provider following further recovery from his acute illness. The problem is how best to describe the episode for purposes of documentation and subsequent follow-up.

There is no ICD-9 code to document myocardial injury (as evidenced by transient elevations in cardiac biomarkers) that occurs because of severe extra-cardiac problems such as sepsis, but according to the new Universal Definition of MI, this can be called a TYPE 2 MI. Having this diagnosis available is a definitive improvement compared with the 2000 ESC/ACC consensus on redefinition of MI.[3] The 2000 document stated that 'any amount of myocardial necrosis caused by ischaemia should be labeled as MI'. This statement implied that a typical rise and fall of troponin alone was adequate to make the diagnosis of acute, evolving, or recent MI. In the final (2000) summary, it was stated that the rise and fall in biomarkers should be accompanied by at least one additional finding (symptoms, ECG changes, or imaging findings as noted above). However, this inconsistency left an open question as to when a transient biomarker elevation such as that just described constitutes an MI, and what to label it if it is not an MI.

In this patient, TYPE 2 MI would be a 'working diagnosis', as a coronary lesion was not totally excluded. This lack of certainty is often a source of discomfort when caring for ICU patients with troponin elevation in association with concomitant disease. We are not totally comfortable using symptoms as a major guide in patients who are intubated, or sedated, or under the intra-operative or post-operative effects of anaesthesia. We know that ECG changes can be transient and can be missed when observation is limited to a monitoring lead, or in the presence of significant baseline abnormalities such as a paced ventricular rhythm, left bundle branch block, or pre-existing ST–T abnormalities. We know that severe stress alone can cause biomarker release, but are also concerned about missing a significant coronary event. Moreover, ICU patients with severe non-cardiac problems often have relative contra-indications to anticoagulants, or cardiac catheterization and intervention. Non-invasive evaluation can also be limited in such patients, and even if cardiac catheterization is performed, coronary angiography cannot always differentiate whether or not the episode involved an acute coronary event or represented injury induced in the presence of significant but stable underlying coronary disease.[4] Finally, it is entirely possible that both can be occurring at the same time, with the multiple stresses and pro-coagulants present in a severely ill patient causing acute progression of coronary lesions (TYPE 1) concomitant with cell damage from hypoxia or hypo-perfusion of non-coronary aetiology (TYPE 2).

Despite these problems in clinical decision-making and patient management, this case illustrates the advantages to having the diagnosis of TYPE 2 MI available. In discussing the Universal Definition for MI, the joint commission discussed the importance of also defining the extent or severity of the MI. Based on the relatively small rise in troponin and non-specific abnormalities on ECG, the amount of cardiac damage in this patient was felt to be small, and additional imaging studies to confirm that assessment were deferred. But the term TYPE 2 MI is still applicable, even though we may qualify the diagnosis using appropriate modifiers (such as possible or probable) with the recognition that the diagnosis may be confirmed, excluded, or further refined, depending on further studies.

The Diagnosis of TYPE 2 MI is advantageous not only for documentation purposes, but can also assist in quality review programs. Criteria for optimal care of acute MI often include measures such as time from onset of symptoms to first medical contact, time to first ECG, time from initial diagnosis to cardiac consultation, or time from diagnosis to lytic therapy, arrival in the catheterization lab, or reperfusion. Such measures are meaningless in patients such as the one presented here, and using an alternate diagnosis will prevent misclassification of the event.

An additional advantage of the new terminology should be realized in epidemiological applications. Biomarkers are often used to help predict prognosis, and most prognostic tools to predict long-term outcome post-MI focus on indices of acute myocardial damage, combined with presence/absence of well-established risk factors. In cases of TYPE 2 MI, the prognosis is most likely altered significantly by the nature and severity of the illness precipitating the biomarker elevation. As such, how biomarker data are used in prognostic algorithms will likely differ for TYPE 1 compared with TYPE 2 MI, and a clear distinction is needed.

When making the diagnosis of TYPE 2 MI, the extreme sensitivity of troponin for detecting myocardial injury/infarction makes it imperative to place all results in clinical perspective. It is well recognized that troponin levels can be abnormal in the absence of symptoms, ECG changes, or any gross evidence of myocardial dysfunction or subsequent damage. Indeed, transient troponin elevations into the abnormal range can be detected in approximately one-quarter[5,6] to one-third[7,8] of athletes at the end of a marathon, with no evident functional consequences.[8] However, unlike in the healthy athlete, even when biomarker elevations in seriously ill patients are relatively small, they cannot be ignored. Elevated troponin values can identify critically ill patients with a worse prognosis,[9–13] and this finding extends to vascular surgery patients who have perioperative troponin elevations.[14] Indeed, prognosis may be worse for patients having troponin elevation without other evidence of MI compared with those with TYPE 1 MI.[4,15]

Assessing troponin elevations in sick patients can also be complicated because chronic, low-level elevations in troponin have been documented in stable patients with renal failure, heart failure, left ventricular hypertrophy, and diabetes mellitus,[16] and the list of causes of elevated troponin appears to be growing.[17] These diagnoses are common in intensive care units, and it is clear that a single elevated troponin requires a comparison to baseline, with follow-up to determine its relative stability.

Multiple advantages of using the diagnosis of TYPE 2 MI are evident, but are the diagnostic criteria optimal? TYPE 2 MI fits as a diagnosis for our example patient because the troponin elevation was felt to be due to the episode of hypoxia and hypotension, rather than a new plaque rupture/erosion/dissection/ or fissuring (TYPE 1 MI). Unfortunately, TYPE 2 is not specific to non-coronary myocardial injury, because it also includes MI caused by coronary spasm or embolism. Although not related to atherosclerotic plaque, both spasm and embolism are coronary events and have more in common with a ruptured plaque than with myocardial injury induced by hypoxia, hypotension, myocarditis, etc. It

would appear of primary importance to differentiate a new coronary event from a non-coronary source of myocardial damage, especially when assessing the need for urgent therapy or intervention. In our case, for example, the atrial fibrillation provides a potential source of emboli. If a new coronary occlusion is strongly suspected, it would be quite difficult to know whether it is thrombotic or embolic in origin, even by coronary angiography. The indications for anticoagulation and/or invasive intervention would likely be similar in either case, but not necessarily so if hypotension and hypoxia were the culprit.

The non-descriptive nature of the term TYPE 2 MI is also of concern. Biomarker release from the heart in the absence of a new coronary event has been recognized for some time. The ACC/AHA guidelines for management of unstable angina/non-ST-elevation MI used 'secondary UA' to describe enzyme elevation precipitated by a condition extrinsic to the coronary arterial bed. Since angina may not be present, this appears to be a less desirable alternative. 'Non-specific troponin elevation' and 'non-thrombotic troponin elevation'[15] as well as 'troponin leak' have also been used. The terms 'concomitant myocardial injury' and 'troponin positive non-ACS' are additional possibilities. We would prefer the term 'secondary myocardial injury' because there is usually an obvious illness or acute event related to the cardiac injury.

A descriptive term such as 'secondary MI' would have several advantages over TYPE 2 MI. New, clinically relevant, myocardial dysfunction is often not evident, and the term secondary myocardial injury does not imply significant scarring as does the term MI. Thus, our COPD/pneumonia patient need not be told he had a 'heart attack' as a complication of his pneumonia. Rather, he could be told that his blood tests indicated his heart was under severe stress when he was sick, and (if clinically indicated) follow-up tests may be warranted. In essence, the findings could be treated as a positive cardiac stress test.

Adopting a descriptive approach to the new diagnostic scheme might also help in describing the other proposed categories of MI. As noted by the task force, problems exist when interpreting troponin elevations in other specific clinical settings apart from those patients acutely ill from non-cardiac diseases. Surgical patients undergoing cardiopulmonary bypass, or patients having elective percutaneous coronary intervention (PCI) can have some biomarker elevation even with a very successful procedure. For example, due to micro-emboli in the case of PCI, or direct needle damage to myocardium in the case of coronary artery bypass grafting (CABG). But damage (usually more severe) can also occur due to dissection of a coronary artery (PCI), graft occlusion (CABG), or other coronary event. As such, criteria are needed to differentiate between relative minor injuries that could be expected even with a successful procedure, from damage indicative of what should clearly be considered an undesirable complication of the procedure (MI).

In keeping with this reasoning, interventional cardiologists have opted to use the less sensitive CK-MB to define MI post-PCI. They define an MI as a complication of PCI when CK-MB increases three or more times normal.[18] The task force has recommended (by arbitrary convention) that PCI-related MI (TYPE 4a) be defined by a biomarker elevation greater than three times its 99th URL, assuming a normal baseline value going into the procedure. They do not say which biomarker need be used to meet these criteria.

In either the case of PCI or CABG, the important differentiation is to distinguish an event severe enough to be considered as a complication, from relatively minor (expected) injury related to the procedure. If criteria appropriate for the clinical setting do not qualify for diagnosing MI, small abnormalities in cardiac biomarkers can be ignored. However, if criteria for MI are exceeded it could simply be termed 'PCI complicated by MI, or 'CABG complicated by MI' without the need for using specific subtype letters or numbers. If the problems of diagnosing patients who have suffered sudden death are considered a separate issue, this would greatly simplify incorporation of the new diagnostic scheme into ICD-9 codes.

The preferred terminology may require further debate, but the new scheme for the definition of MI provides an improved framework for assessing and documenting coronary ischaemia/infarct. No matter how the ICD-9 codes evolve, it makes clinical sense to clearly differentiate between troponin elevations that are chronic, vs. transient elevations associated with acute coronary events, vs. transient elevations associated with other myocardial stresses.

Making these distinctions clear may also help in our quest for ever improving therapy. Troponin elevations are quite common in intensive care unit patients such as the one presented above.[10–13,19,20] The in-hospital complication rates for patients hospitalized for ACS are high,[21] and patients who suffer acute MI during hospitalization for other problems differ substantially in their clinical course and outcomes compared with those who present initially with an acute coronary syndrome.[22] The ACC/AHA guidelines for the management of patients with unstable angina/non-ST-elevation MI[23] promote an aggressive approach for treatment of non-ST elevation MI, but no recommendations are made for assessment and treatment of TYPE2 MI. This leaves the optimal treatment strategy for such patients quite uncertain. By providing a specific new diagnosis, it may be possible to encourage further research on how best to manage these patients, and perhaps help determine whether a troponin level should be measured in the first place.[24]

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