Troponin—Past, Present, and Future

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Abstract: Cardiac troponin is the analyte of choice for the diagnosis of cardiac injury. It is highly specific for the heart and much more sensitive than prior biomarkers. Because of this increased sensitivity, clinicians have had to struggle with elevations in novel clinical situations. We have developed new understandings about coronary artery disease but also have begun to appreciate that many other entities as well can result in cardiac injury. As assays have increased in sensitivity over time, this trend has, if anything, accelerated. This review attempts to put the past, the present, and the future into a clinical perspective that will help clinicians. (Curr Probl Cardiol 2012;37:209-228.)

Cardiac troponin has become the marker of choice for the evaluation of patients with possible myocardial injury.1,2 Because our understanding of cardiac troponin (cTn) is still evolving and because old friends like the NB isoenzyme of creatine kinase (CKMB) who have served us well often are hard to give up,3 it has taken a long time for troponin to be used as efficiently as guidelines and experts have suggested.4,5 Indeed, because of its improved sensitivity compared to prior markers, clinicians have been very reluctant to use troponin at the 99th percentile of the upper reference limit (URL) because so many patients had elevated values of troponin even with the first-generation assays.3,5 This level of sensitivity has increased still further with modern day assays.6 Thus, many clinicians and laboratories have used higher cutoffs for cTn to reduce the frequency of elevations of troponin that clinicians have a difficult time explaining.3,5 This of course simply makes the literature and the field far more difficult for clinicians to understand because the heterogeneity of cutoff values leads to tremendous confusion in the literature and mixed messages about how clinicians should use cTn.3,5 The present articulation attempts to resolve some of these issues.
and provides a common sense way of dealing with cTn and cTn elevations. As part of being able to accomplish this important task, certain basic information about troponin is obligatory and a certain limited understanding of the analytical constraints that come with measuring troponin is also of importance. This article does not attempt to review in detail all of these elements but instead identifies those that are critical and provides appropriate references so that those who are interested in more information can augment their understanding about these important issues.

**Cardiac Troponin Basics**

The cTn complex consists of 3 separate proteins encoded by different genes. These include cardiac troponin T (cTnT), cardiac troponin I (cTnI), and cardiac troponin C. Each protein plays an important role in regulating the interaction of actin and myosin filaments and thus on cardiac contraction. Troponin C is encoded by 2 genes, 1 specific for fast twitch skeletal muscle and a second expressed in both slow-twitched skeletal muscle and cardiac muscle. Thus, it might not be expected to have cardiac specificity and, indeed, that is the case. Both cTnT and cTnI come from unique genes. It appears that both cTnI and cTnT have high cardiac specificity. The history in regard to cTnI is fairly clear. As best we can tell, it has never been expressed during neonatal development nor in pathologic circumstances in any tissue outside of the heart. The situation for cTnT is more complex. Fetal isoforms of the protein are expressed during neonatal development and there were isoforms of cTnT that were detected by the initial assay for cTnT many years ago. Part of this was because there was some cross-reactivity between the antibodies used to detect cTn and skeletal muscle troponin. However, it also appeared that there might be re-expressed isoforms of cTnT in diseased skeletal muscle, particularly in renal failure patients. New antibodies were developed that eliminated this problem such that the cross-reacting antibodies that were found were eliminated. Recently, we described that some patients who have skeletal muscle disease express proteins that are detected by the antibodies used in the standard and high-sensitivity cTnT assay. Whether these are re-expressed isoforms is unclear but they do appear capable of causing a signal with the cTnT assay. Because of the high sensitivity of the cTnT, it is impossible to know for sure that there is no concomitant cardiac disease, but, at least in a few cases where extensive evaluations have been done, that has not appeared to be the case. The frequency of this phenomenon is unclear at present and it would be a mistake to think that all elevations that are difficult to explain are false positives caused by
Nonetheless, it does appear that some patients with skeletal muscle disease will have elevated values of cTnT but not cTnI and that, unless clinicians are astute to this possibility, the possibility of confusing such patients with those who have cardiovascular disease could occur (Fig 1). Ongoing research is attempting to define the extent to which this phenomenon occurs.

In addition, it is important to understand the way in which the troponins are released. It appears, in contrast to some proteins, such as CK-MB, which are only localized in the cytosol of myocytes, that troponin has multiple localizations. The initial studies used gentle buffers and defined a pool of troponin, which was called the “cytosolic pool,” which was roughly of the same magnitude as that of CK-MB. In looking back at these studies, it appears, given the way in which they were done, a better term for this pool might be the “early releasable pool” because it is not clear that all the protein is localized in the cytosol of cells. Nonetheless, it is thought that this is the pool that is released early after a cardiac insult and thus leads to early elevations of cTn. However, because this pool is similar in size for both CK-MB and cTn, one could be confused as to why troponin might be more sensitive. In fact, it is more sensitive because the so-called release ratio, ie, the amount of protein

FIG 1. Detection of skeletal muscle proteins by the antibodies used in the cTnT assay. Western blot of SMD from patients with myopathies in lanes 1-4, normal human heart muscle in lane 5, and normal human soleus muscle in lane 6. Note molecular weight designations on the ordinate. The antibodies used in the standard cTnT assay (M7 and M11-7) and those used in the high-sensitivity assay (M7 and 5D8) all tag a protein at a molecular weight of about 39 kDa. This suggests strongly that the 2 antibodies in each of these assays would detect these proteins in blood, indicating that there is a good possibility that elevations in cTnT or the high sensitivity cardiac troponin T assay could occur because of diseased skeletal muscle. (Reproduced with permission.)
released into the circulation over the amount that is depleted from heart, is far greater for the cTn than it is for CK-MB, which is degraded locally.\textsuperscript{16} Thus, greater amounts of protein are elaborated for any given insult via this early releasable pool. This early increase of cTn is followed by a longer period when troponin is released from what is thought to be from a more structurally bound pool that is released as the damaged area is remodeled. This provides an explanation for why troponin elevations persist for many days, perhaps even weeks, despite its short half-life in the blood.\textsuperscript{15} These kinetics have been used to argue that perhaps troponin could be released in the absence of necrosis. Specifically, what has been suggested is that perhaps increases in the early release comes from the early releasable pool and may not represent cell death but rather reversible injury. It is then suggested that the more sustained release, which represents the breakdown of the structural pool, is associated with cell death. Thus, it has been argued that the presence of only early but not late release would indicate reversible injury. Alternatively, it has been argued that all the release is due to cell death. This is an intriguing scientific argument and there is tremendous controversy over this particular issue.\textsuperscript{17} At present, there are inadequate data to adjudicate which of these hypotheses are correct, in part because we have only recently begun to develop sensitive enough assays to be able to probe whether the values we observe are elevated or normal after transient increases.\textsuperscript{17} Even if the values go down totally, there probably will still be controversy about whether the cells need to be irreversibly injured. When this issue first became important in the biomarker field, it did not appear that the heart could regenerate in any substantive way. We now know that that is not the case and that cardiac regeneration can and does occur.\textsuperscript{18} Consequently, perhaps now this is a less important issue. Nonetheless, because this has been described in certain patients with exercise as well as in certain disease entities, it has become an important area of controversy for clinicians. This author would argue, given that most elevations of cTn, perhaps exercise aside, are associated with an adverse prognosis, that from the clinical perspective this distinction is not worth being concerned about\textsuperscript{17} and that troponin should be considered a marker of cardiac damage or injury and that such injury should be taken as a sign of underlying cardiovascular disease in almost all instances\textsuperscript{17} except perhaps exercise.

**Important Preanalytic and Analytical Factors**

No assays are perfect. No antibodies are perfect. Therefore, it should be expected that there will be problems at times with cTn assays. It is important, particularly as we move toward more highly sensitive assays,\textsuperscript{6}
that we take these into account because, absent doing that, we run the risk of being confounded because small changes with these highly sensitive assays would be of importance. Some of these include the following:

1. Preanalytic factors. These include issues like hemolysis, which is known to increase cTn values for some assays and reduce cTnT values with that assay. It is suggested that even small amounts of hemolysis may be important with the modern day highly sensitive assays\(^1\) (Fig 2). There also are other potential problems, the most common of which is fibrin in the sample, which can stick to the well of the plate and cause false-positive results for that reason. Therefore, clinicians should not be uncomfortable about calling and challenging the laboratory in regard to specific results.

2. Analytical factors. In addition, there are other analytical issues that may need to be taken into account in some patients. The most common are what is called cross-reacting or heterophilic antibodies. This designation refers to a group of antibodies either made to the antibodies that are used to make the cTn assay or which cross-react to those antibodies and come from some sort of human disease process that can cause the assay to be falsely elevated. The most well-publicized situation occurred during the early assay days when rheumatoid factor was shown to cross-react with one of the cTnI assays, leading to confusion\(^2\). This is no longer a problem, but heterophilic antibodies still exist, although most companies have done

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**FIG 2.** Hemolysis and cardiac troponin. Influence of hemolysis on the values obtained with 2 different troponin assays, the cTnI assay from Ortho and the high sensitivity cardiac troponin T assay from Roche. With very sensitive assays, these problems become more crucial. (Reproduced with permission\(^1\))
a good job of eliminating them. With very highly sensitive assays, however, even small amounts of these could be problematic.\(^6\) Thus, clinicians must question values that do not appear to fit the clinical picture. The situation where one might suspect such antibody interference is in a patient who has high values that do not change over time. In most situations, elevations of cTn do increase and then decrease over time. There is an occasional renal failure patient who may have high values that do not change but most other marked elevations should either increase or decrease. If one finds a pattern like this, there are several things that good laboratories can do.\(^7\) The first is to add additional blocking antibodies to the sample and see if that resolves the problem. These are widely available in what are called “heterophile blocking tubes” and all good laboratories should have access to them. A second approach is to dilute the sample. Samples that have interferences of any kind will not change until the interfering substance is eliminated. Thus, the failure of a sample to dilute linearly should lead to a suspicion of some sort of interfering substance. Sometimes these interfering substances can be more complex but the vast majority can be diagnosed easily if one remembers the suggestions made above. There are a variety of other relatively less frequent problems, including macrotroponemias (troponin linked to immunoglobulins), which have recently been described.\(^21\)

There are major initiatives going on in an attempt to standardize cTn assays but they thus far have not been highly successful.\(^22,23\) Thus, it should be clear that the numbers generated with any given assay cannot and are not related in any way to the numbers generated with other assays. This in part reflects the different ways of measuring used by various companies but also differences in antibodies as well. All of this information in greater detail can be found in recent reviews.\(^24\)

### Decision Limits and Precision

This is a critical issue of which clinicians often are not aware. The decision limit suggested since 2000 has been the 99th percentile of a normal reference population designated usually as URL.\(^25\) This is roughly 3 SDs from the mean of a normal population and was selected to minimize the frequency of false positives and to take advantage in a good sense of that word of the sensitivity of cTn assays. Although initiated in 2000, because of the reluctance of many clinicians to use these low cutoffs because of the difficulty in explaining more subtle increases, these cutoffs often have not been used and this can cause confusion.\(^4\) Even
more recently, high-level sophisticated studies using cTn have failed to use the recommended cutoff values.\textsuperscript{26} Thus, this remains a problem that clinicians need to be aware of both when seeing patients and when reading the literature. Part of the reluctance in this area occurred with the concern that imprecision at the low end might cause false-positive elevations.\textsuperscript{27} This was a reasonable concern when there was no clue as to where the normal values existed. Thus, some laboratories argued that one should use a cutoff value where there was a high level of precision so that one would not potentially overlap with normal values. This led to the concept that the cutoff value might be the 10\% coefficient of variation (CV) value.\textsuperscript{27} However, over time, it has become clear clinically that normal values are substantially far from anything measured today with the exception of very high sensitivity troponin assays and thus the most predictive clinical cutoff to use is the 99th percentile.\textsuperscript{7} A recent article from the Global Task Force on the redefinition of myocardial infarction was developed in part to clarify this previously confusing issue.\textsuperscript{5} This issue was in part even more confounding for cTnT than for cTnI because with that assay most normal values are undetectable and thus, to define a rising pattern, one often had to go significantly above the 99th percentile and frequently the value used was the 10\% CV value, making it additionally more difficult for clinicians who used that assay to understand the concept of the 99th percentile. Nonetheless, values above the 99th percentile URL should be taken seriously as they imply cardiovascular disease and in almost all instances patient risk.\textsuperscript{7}

A recent article provides a good example of the need to use lower rather than higher cutoff values. In the study, the investigators first evaluated the outcomes of 1038 individuals presenting with chest discomfort evaluated with a contemporary but fairly sensitive cTnI assay using a high cutoff value. They then compared those outcomes to those of 1054 individuals evaluated with the same assay using a lower cutoff value (the 10\% CV cutoff). Each group was stratified into 3 subgroups—clearly normal, clearly abnormal, and a middle group that was initially called normal and subsequently called abnormal. The primary outcome was the combination of recurrent myocardial infarction and death at 1 year. They found that the rates of the use of statins and dual antiplatelet therapy at discharge, were similar in the clearly normal and clearly abnormal groups but improved significantly in the middle group, as might be expected. Importantly, these changes in treatment translated into improved outcomes. In the first cohort, the primary outcome occurred in 39\% of patients in this middle (identified as normal) group compared to 7\% in the clearly normal group and 24\% in the clearly abnormal group. During the second part of the
study, the event rates were similar for those 2 groups but improved significantly in the group newly called abnormal. The outcomes in this group improved from 39% to 21% and were statistically similar to those in the clearly elevated group (Fig 3).

As acknowledged by the authors, these results might have been even better had the 99th percentile URL value been used.28

Interpretation of Troponin Results

It is now clear with more sensitive cTn assays that the development of structural heart disease over time causes values of cTn to rise slowly.29,30 It appears that they do not rise acutely but are chronically elevated. Thus, minor elevations of cTn will be seen more and more frequently as assay sensitivity increases. Therefore, the concept of using a solitary cutoff value for cTn as abnormal and indicative of an acute event is fraught with
danger. If the value is markedly elevated, because most of these structural abnormalities are associated with only minor degrees of elevation (with the possible exception of a rare patient with renal failure), then this may still be a useful concept. However, one cannot and should not believe that a solitary cutoff will work for all assays. For that reason, one of the important issues now that people are attempting to resolve is how to define best a changing pattern of values, which might distinguish those individuals with acute disease from those with more chronic elevations.

This is a highly complex topic, in particular, with high-sensitivity cTn assays. With non-high-sensitivity assays, the best that can be done is to use a metric, asking the question whether the value is different from analytical variability. It is known for any 2 values that they are significantly different analytically if they are roughly 3 SDs of the variance around the values from each other. Thus, by knowing the metrics of a given assay, laboratorians can provide an estimate as to whether these values are above the variation given the imprecision of that assay. This is more complex than it appears because at very low values assay variability goes up substantially. Thus, although this value is probably close to 20% once elevations have occurred, when one is dealing with values near the normal range or perhaps slightly below it, these values could be substantially higher even with some assays as high as 100 or 200%. Therefore, the task of defining that when a significant change occurs that should be taken care of and developed by the laboratory community, who should report these data to help clinicians with this.

For high-sensitivity assays, the issues are more complex. With high-sensitivity assays, one can measure results in normals repetitively and define what is known has biological variation. Unfortunately, biological variation may be higher than what may be clinically significant and this is a tension in the field. However, the theory of biological variation would argue that if one is using a change that is below the level of biological variation, one at least has the risk of including patients who are in that category because of changes related solely to biological and analytical issues. Thus, it should be clear and is the case that the use of any paradigm looking at a changing pattern is very likely to increase specificity for acute change but may reduce sensitivity. At present, many people using high-sensitivity assays are attempting to argue for either percentage changes or absolute changes as the best metrics to define a changing pattern. These data will play out over time. It is this author’s opinion that absolute values as recently reported may turn out to be somewhat better only because, as values increase, the percentage values will cause changes to be mandated that are unlikely to occur except
with very large infarctions, making the use of percentages less efficient. By contrast, as values rise, the use of absolute values will impinge on the biological variation discussed above and likely lead to the exclusion of some patients who have significant disease. This issue is presently very conflicting and needs further investigation.\textsuperscript{33}

Although the distinction between chronic and acute elevations is important, it is also important to understand that, whereas previously assays, because of their relative insensitivity, detected mostly patients with acute ischemic heart disease, cTn, given its improved sensitivity, detects many other pathophysologies. This can include tachycardia or hyper-/hypotension-induced supply-demand abnormalities and therefore “ischemia” as well as a variety of other acute and chronic cardiac stressors diseases. Reviews on these topics can be found elsewhere.\textsuperscript{37} Consequently, an elevated troponin or even a changing pattern should not be taken as indicative of acute myocardial infarction (AMI) but solely of cardiac injury. It is true that very high values of cTn are seen rarely with the exception of an occasional renal failure patient and with either myocarditis or AMI.\textsuperscript{31} Thus, high values (these are assay specific) can be intuited to be due to myocardial infarction or myocarditis. However, modest elevations need to be triaged clinically and cannot be assumed to be due to unstable coronary heart disease. In point of fact, not only could elevations be due to a variety of other acute etiologies (Table 1) but in addition they could be due to coronary artery disease that is stable. Recent data suggest that elevations occur in patients with stable coronary disease but that that group probably is the higher risk subset of those with “stable” coronary disease\textsuperscript{38} and the frequency of these elevations is increasing as assay sensitivity increases.\textsuperscript{39,40} It could turn out eventually that we will find that cTn elevations identify those with chronic stable disease who are at risk and there are some data to suggest that, the worse the disease, the higher the cTn value,\textsuperscript{40} and the worse the prognosis.\textsuperscript{38,39} It is also of interest that women have lower values for any given extent of coronary artery disease than men.\textsuperscript{40} However, chronic stable disease, like hypotension or hypertension without coronary artery disease, does not imply that there was necessarily acute plaque rupture and a myocardial infarction in need of intervention. Thus, what is necessary is a clinical story highly suggestive of ischemic heart disease coupled with a rising pattern of cTn. It should be noted that if one sees patients with elevated cTn (but not a rising pattern) and then relies only on cardiac catheterization, one might presume that many of them have myocardial infarctions because they have coronary artery disease. However, again, a solitary
elevation of cTn does not infer that coronary artery disease is unstable because this could occur with stable coronary artery disease as well.

Another area that is interesting and difficult to deal with in regard to cTn is congestive heart failure. cTn elevations are quite common in this situation, particularly with acute heart failure, and can occur with chronic heart failure as well. These occur with or without the presence of coronary artery disease so they likely represent acute left ventricular dilation, supply-demand imbalance, and endothelial dysfunction. Again, whether these patients should be called AMIs is an issue now being discussed for the new guidelines.

**Michael H. Crawford:** The complexities and difficulties with the troponin assay that Dr Jaffe expertly enumerates have been a source of great frustration for clinicians. Few blood-based laboratory tests are as difficult to interpret as troponin, yet our less knowledgeable colleagues often think that the reported value is as definitive as a serum sodium level. Add to this the...
progressive increase in the sensitivity of the assays and you have a recipe for overutilization of health care resources. The latest insult to clinicians is the point-of-care assay, which can be done by minimally trained individuals at the bedside. Although it is highly variable and uses a markedly different “normal range,” it is being touted as the first arbiter of hospital admission. Fortunately, at my institution, the results were so inaccurate that we were able to discontinue it after a couple of weeks. As Dr Jaffe points out, the newer high-sensitivity troponin assays have not caught on yet in the USA, mainly because of poor reproducibility, but this problem will be overcome. Emergency Department doctors will embrace this assay because it will reduce the false negatives that result in lawsuits. Also, it may permit the earlier detection of myocardial infarction, resulting in a faster turnover in the Emergency Department, which is desirable for patient care as well. However, false positives will abound. The bottom line is that things will worsen before they improve.

**Diagnosis of Acute Myocardial Infarction**

As should be apparent, the diagnosis of AMI is heavily determined by the clinical situation. Thus, the situation must be a circumstance where the clinical situation and/or signs and symptoms of the patient lead to a strong suspicion of AMI before measuring cTn. This could be at times the clinical circumstance that exists because diabetics may have relatively unrecognized AMIs or, in surgery patients who are not doing well, even if they do not complain of chest pain. In the postoperative circumstance, symptoms may not be present and electrocardiography (ECG) changes can be frequent and nonspecific. Thus, one needs to have an open mind and not insist on the classic presentation. By contrast, the idea that simply because a cTn is elevated that acute coronary event has occurred is also not an appropriate stance. Thus, the first issue of importance in the diagnosis of AMI is the clinical circumstances around the presentation of any given patient. The second circumstance is, assuming appropriate of the presentation, is a rising and/or falling pattern of troponin values. AMI, being an acute event, should show an increasing pattern of values and then a decreasing pattern of values. This can be problematic if the time of onset of symptoms is unclear because the persistence of elevations of cTn; one lead is to find relatively slowly changing values of cTn on the “tail end” of the curve. This can be a problem for clinicians to sort out but the only way to deal with this issue is clinically. There are no biochemical determinants that can answer that question.

One also needs to be aware that there are variants of AMI that can occur. For example, there are subsets of patients, more often women, who can have AMI without overt coronary artery disease. Whether this is due to endothelial dysfunction or the fact that an inciting event,
such as a thrombus or a small dissection, may have resolved before angiography is unclear at present but such cases clearly exist. They appear to be associated with a better prognosis than certain other circumstances but that does not mean that AMI should not be diagnosed. Several series have examined this type of presentation and found that magnetic resonance imaging often is often helpful in these individuals. It may well be that identifying these groups, whether it is the females with endothelial dysfunction or the broader group who do not have fixed coronary disease, may be clinically helpful. In fact, it may be that, as the sensitivity of cTn assays increase, the percentage of such patients, because it is thought that their cTn values are somewhat lower, may increase. Therefore, the prior data, developed with less sensitive cTn assays, that an elevated cTn in patients with chest discomfort makes them good candidates for an aggressive therapeutic approach, including aggressive anticoagulation IIB/IIIA agents and an early invasive strategy, may no longer be the case.

Possible Nonacute Myocardial Infarction Etiologies for Elevations of Troponin

One of the most common reasons for marked elevations of cTn that has recently emerged is that of acute myocarditis. Early on, it was clear that
myocarditis could be a mimicker, but a recent article examining patients who present with what appears to be acute infarction but have normal coronary arteries angiographically found a small percentage of individuals who have the pattern associated with AMI but a larger percentage of individuals who had what appears to be acute myocarditis. The therapeutic significance of such a diagnosis is not clear yet but it is now well established that this is a diagnosis that should be considered a possible mimicker of AMI.

Michael H. Crawford: Another cause of AMI mimic with normal coronary arteries is stress cardiomyopathy. In our tertiary care hospital, this diagnosis is more common than myocarditis. Usually, it is characterized by apical ballooning that resolves after several days, but some patients may have persistent heart failure, shock, or death. Rarely, the wall motion abnormality involves mainly the mid-left ventricular wall. In subarachnoid hemorrhage patients, the basal walls are preferentially involved (Zaroff JG, Rordorf GA, Ogilvy CS, et al. Regional patterns of left ventricular systolic dysfunction after subarachnoid hemorrhage: evidence for neurally mediated cardiac injury. J Am Soc Echocardiogr 2000;13:774-9). The common theme is that the walls involved do not follow a single coronary artery distribution. Aside from the unusual wall motion distribution, these patients' presentation is similar to AMI with the major exception that it occurs much more commonly in women. You have to have a high index of suspicion in postsurgical patients who are not doing well hemodynamically and have elevated troponin levels, for stress cardiomyopathy, because these patients are often sedated and do not complain of chest pain. The ECG resembles a typical stent thrombosis elevation MI, which is why the diagnosis is usually made at cardiac catheterization. In the right clinical setting with the characteristic echocardiographic findings, coronary angiography can often be reserved for those who do not do well.

As assay sensitivity increases, there also are likely to be an increased percentage in what are thought to be AMIs related to supply-demand imbalance. These could be due to hypotension or hypertension, or tachycardia with or without hypotension, but more likely than not they reflect some underlying cardiovascular pathology. However, because they may be related more to the supply-demand imbalance than to acute plaque rupture, these individuals may be far less in need of aggressive therapy and an invasive strategy. There is presently ongoing discussion as to whether this group should be culled out separately or should be subsumed under the rubric of AMI. The dilemma of this issue is clear. Should young individuals with Wolf-Parkinson-White syndrome who have severe tachycardia and elevated cTn who often have peculiar chest symptoms and even ECG changes be considered to have AMI? How this evolves in the guidelines remains to be determined.
Patients who are critically ill often have elevated cTn values. Whether they are due to supply-demand imbalance and therefore may meet the definition of AMI or whether such elevations are due to direct toxic effects of catecholamines, sepsis, and other drugs is unclear. The important concept, however, is they are all associated with an adverse prognosis both short and longer term. What to do acutely is unclear other than to treat the underlying disease optimally but these patients continue to be at risk even if they survive to discharge. However, often, the concept of the elevated cTn is out of sight and out of mind at a point when perhaps intervention would be helpful. For that reason, these patients should be at least evaluated clinically and, if they have structural heart disease as is likely, that it be addressed. At present, there are no guidelines for subsequent management and this is an area of need that will likely be helped with time. A similar circumstance occurs in patients with elevated cTn values who are postoperative. It appears that some of the morbidity, perhaps a great deal associated with postsurgical problems, has to do with cardiovascular abnormalities, perhaps mostly a supply-demand imbalance but perhaps some plaque rupture as well. If indeed these events are due to a supply-demand imbalance, careful scrutiny of patients potentially at risk may be necessary to intervene when they this occurs with the idea of reducing the morbidity of cardiovascular disease in this circumstance. There is a large ongoing trial attempting to define the frequency of these acute cardiovascular problems and the preliminary results with a high sensitivity assay suggest that it's quite high.53

Michael H. Crawford: Critically ill or postsurgical patients who are not doing well hemodynamically often have troponin measured to screen for ischemic heart disease. Whether this is an appropriate use of troponin measurement is debatable, but it frequently occurs and cardiology is almost always subsequently involved in the patient’s care. Most such cases have no history or ECG findings consistent with a typical AMI. Thus, most are probably coronary supply-demand mismatch situations with so-called “demand ischemia.” Many have no underlying heart disease, but you do not want to miss those who do have coronary artery disease. Consequently, I usually advise those taking care of the patient to obtain a cardiac stress test with imaging when the patient has recovered enough to tolerate testing. Rarely, we do cardiac catheterization as a first step in such patients unless they are not doing well.

Exercise

There is tremendous controversy about whether exercise acutely damages the heart because of the elevations seen in cTn. This is not a new issue. It has been around for years because elevations of CK-MB were
also observed with exercise and found not to indicate cardiovascular
disease.\textsuperscript{17} Nonetheless, given the high specificity of cTn for the heart, this
has become a major question again. At present it is clear that there does
not appear to be an acute hazard associated with the mild to modest
elevations in cTn seen in patients who have undergone extreme exercise,
such as a marathon.\textsuperscript{17} However, those elevations should resolve promptly
and should not be marked. If they are marked or do not resolve within a
day or so with present-day cTn assays, they should not be considered
because of the extreme exercise. In addition, it is not at all clear whether
in the long run we will find that there may be some detrimental effects
because of exercise.\textsuperscript{55} There are suggestions in several situations that
perhaps there are long-term negative consequences. This remains to be
better defined.

\textbf{The Future}

All of these problems will become much more difficult with high-
sensitivity assays. These assays are starting to be used around the world
with the exception of the USA. They will detect still more patients at
risk.\textsuperscript{33} They will detect more minor elevations and with them new disease
entities to be considered.\textsuperscript{33} However, they also will increase the rapidity
with which AMI is diagnosed,\textsuperscript{56} increase the number of patients identi-
fied,\textsuperscript{57} and in the long run allow us to monitor things, such as drug
toxicity,\textsuperscript{58} that may be subtle and hard to do. It is worth noting that even
with present-day assays there are some preliminary data in this area in
particular developed around Adriamycin cardiotoxicity\textsuperscript{58} and carbon
monoxide poisoning.\textsuperscript{59}

This is an exciting time. We will in the long run have many more
questions and many more answers. For now, following these relatively
straightforward guidelines will help clinicians begin to capture the great
promise of cTn assays.

\textbf{Michael H. Crawford:} Dr Jaffe, one of the world’s experts on myocardial
biomarkers, has contributed an excellent review of the laboratory and clinical
issues surrounding cTn measurements. Despite considerable issues with the
technical aspects of the various assays available, cTn has become the pivotal
diagnostic step in the diagnosis of AMI. Current efforts are improving the
sensitivity of the assays in the hopes that a more sensitive assay will allow for
earlier diagnosis of AMI, which will lead to earlier treatment and better
outcomes. This attractive concept has yet to be proven and the only thing
apparent to clinicians is the increase in false positives. It is clear that cTn
comes from the heart, so these false positives clinically represent conditions
that are not AMI, but release cTn into the blood. It seems that myocardial
ischemia because of an imbalance between myocardial oxygen supply and
demand can under certain circumstances release cTn. This fits with current thinking about ischemia and heightens awareness that many ill hospitalized patients may have underlying coronary artery disease. Thus, it is not surprising that cTn detection indicates a poor prognosis. What is more difficult to understand is why apparently normal individuals can have elevated cTn levels, such as after vigorous exercise. We still have a great deal to learn about cTn, but it has quickly become a key test in our evaluation of suspected myocardial infarction or ischemia. Its detection is necessary to diagnose AMI now and elevated levels in other clinical situations suggest a poor prognosis, probably because of underlying heart disease.

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REFERENCES


32. Jaffe AS. Chasing troponin: how low can you go if you can see the rise? J Am Coll Cardiol 2006;48:1763-4.


