Impact of Ultrasensitive Cardiac Troponin I Dynamic Changes in the New Universal Definition of Myocardial Infarction

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Abstract

We evaluated the impact of using the new universal definition of myocardial infarction (MI) criteria implemented with a 20% increment between 2 cardiac troponin I (cTnI) measurements. The study included 284 consecutive episodes of patients admitted to the emergency department with suspected acute coronary syndrome (ACS) and an initial cTnI measurement of 0.10 ng/mL (0.10 µg/L) or less followed by 1 or more measurements within 24 hours. Episodes with a maximum cTnI above the 99th percentile (0.04 ng/mL [0.04 µg/L]) and a dynamic increase between 2 measurements of 20% or more were considered to meet MI criteria. Of the 284 episodes, 109 (38.4%) had a maximum cTnI higher than 0.04 ng/mL (0.04 µg/L). However, only 66 episodes (23.2%) also had an increase of 20% or more in the cTnI concentration and met MI criteria. These 66 episodes included 37 patients diagnosed with an MI and 29 patients not diagnosed with an MI. The 29 patients who also met MI criteria were more frequently readmitted for ACS within 6 months.

Increased cardiac biomarker levels was one of the World Health Organization (WHO) criteria for definition of myocardial infarction (MI).1,2 Specifically, the WHO definition based an MI diagnosis on the presence of at least 2 of 3 criteria: symptoms, electrocardiogram abnormalities, and increased cardiac enzyme levels. Progressive availability of more accurate biomarkers of cardiac necrosis has been reflected in an increasingly significant role of laboratory biomarkers in definition of MI. Thus, whereas an acute MI could be diagnosed without biochemical evidence of myocardial necrosis according to the WHO definition, the current consensus definition3,4 demands an elevation in cardiac biomarker level, preferably cardiac troponin (cTn) because of its higher sensitivity and cardiac specificity.5 Specifically, the European Society of Cardiology and American College of Cardiology (ESC/ACC) redefinition of MI3 and the recent universal definition of MI4 are based on the consideration that any elevation of the cTn level should be considered to be diagnostic of acute MI in the clinical setting of myocardial ischemia. Elevation of the cTn level is defined as a value exceeding the 99th percentile of a reference control group, and an analytic coefficient of variation of 10% or less at the 99th percentile is recommended. Furthermore, to distinguish MI from other causes of elevation in the cTn level, a rise and/or fall of the cTn level is necessary.

Despite the time elapsed since redefinition of MI,3 the clinical acceptance of the new criteria is incomplete,6,7 particularly regarding the difficulty of cTn assays to reach the recommended analytic precision at low levels.8 At present, progressive incorporation of highly sensitive analytic assays for cTnI determination9-11 significantly overcomes this inconvenience, thus constituting a significant opportunity to fully adopt new diagnostic criteria. With this in mind, the aim of
our study was to evaluate the clinical implications of cTnI determination by using an ultrasensitive assay.9,12 The study also assessed the impact on the number of episodes that met the universal definition of MI when an objectively defined change (20%) in cTnI concentration was implemented as a true change in a population with chest pain suspected of having acute coronary syndrome (ACS).

Materials and Methods

We included in the study 284 consecutive episodes of 261 patients admitted to the emergency department with acute chest pain and an initial cTnI measurement of 0.10 ng/mL (0.10 μg/L) or less, followed by 1 or more cTnI measurements within 24 hours. Table 1 gives the final discharge diagnosis and population characteristics of each diagnostic group. Patients who were admitted to the emergency department on separate occasions were considered as independent episodes. Ten patients were admitted twice, 5 were admitted 3 times, and 1 patient was admitted 4 times. The mean age of the patient population was 66.1 years (range, 19-92 years). Of the 261 patients, 164 (62.8%) were men.

A discharge diagnosis of MI was based on an increase in the cTnI level (>0.1 ng/mL [0.1 μg/L]) with cardiac chest pain and/or electrocardiogram alterations indicative of ischemia. For comparison and to evaluate the impact of implementing the new consensus definition of MI with a quantitatively defined increment between 2 cTnI measurements, all patients with a cTnI level of more than 0.04 ng/mL (0.04 μg/L; 99th percentile reference limit) and a dynamic change of 20% or more within 24 hours were considered to have met the criteria for the new universal definition of MI. Episodes of ACS documented in a period of 6 months after admission in our hospital were also evaluated.

Results

Table 2 shows the percentage of episodes, classified according to the final diagnosis, with maximum cTnI values of more than 0.04 ng/mL (0.04 μg/L). Also shown in Table 2 is the percentage of episodes with maximum cTnI values of more than 0.04 ng/mL (0.04 μg/L) and a dynamic change of 20% or more. Of the 284 episodes evaluated, 109 (38.4%) had a maximum cTnI level of more than 0.04 ng/mL (0.04 μg/L). However, only 66 episodes (23.2%) also had an increase in the cTnI concentration of 20% or more and met the new universal definition of MI if this change is considered a true change. Figure 1 reflects how the frequency of episodes that met the new universal definition of MI criteria varied as a function of the percentage of the change considered significant.

Table 1
Study Population Classified According to Final Diagnosis

<table>
<thead>
<tr>
<th>Final Diagnosis</th>
<th>No. of Cases</th>
<th>Male/Female</th>
<th>Mean ± SD Age (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>37</td>
<td>29/8</td>
<td>70.1 ± 13.8</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>33</td>
<td>26/7</td>
<td>70.8 ± 10.1</td>
</tr>
<tr>
<td>Typical angina</td>
<td>8</td>
<td>4/4</td>
<td>71.2 ± 10.7</td>
</tr>
<tr>
<td>Secondary angina</td>
<td>11</td>
<td>5/6</td>
<td>72.2 ± 5.4</td>
</tr>
<tr>
<td>Heart failure</td>
<td>28</td>
<td>10/18</td>
<td>75.5 ± 10.0</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>5</td>
<td>2/3</td>
<td>45.3 ± 24.7</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>9</td>
<td>7/2</td>
<td>66.2 ± 17.1</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>1</td>
<td>0/1</td>
<td>68.9</td>
</tr>
<tr>
<td>Nonanginal chest pain</td>
<td>90</td>
<td>48/42</td>
<td>63.7 ± 13.0</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>8</td>
<td>8/0</td>
<td>75.5 ± 10.0</td>
</tr>
<tr>
<td>Ictus</td>
<td>6</td>
<td>2/4</td>
<td>55.1 ± 20.8</td>
</tr>
<tr>
<td>Syncope</td>
<td>10</td>
<td>10/0</td>
<td>67.2 ± 15.2</td>
</tr>
<tr>
<td>Atypical angina</td>
<td>18</td>
<td>13/5</td>
<td>59.3 ± 13.3</td>
</tr>
<tr>
<td>Other</td>
<td>20</td>
<td>16/4</td>
<td>59.1 ± 20.2</td>
</tr>
<tr>
<td>Total</td>
<td>284</td>
<td>180/104</td>
<td>66.1 ± 14.7</td>
</tr>
</tbody>
</table>

The cTnI level was measured by the TnI-Ultra assay method on an ADVIA Centaur CP instrument (Siemens Healthcare Diagnostics, Tarrytown, NY). This method is a 3-site sandwich immunoassay using direct chemiluminometric technology. It includes a polyclonal goat anti–troponin I antibody labeled with acridinium ester and 2 biotinylated mouse monoclonal anti–troponin I antibodies. The detection limit provided by the manufacturer is 0.006 ng/mL (0.006 μg/L), and the assay range is 0.006 to 50 ng/mL (0.006-50 μg/L). The 99th percentile reference limit and 10% total imprecision reported by the manufacturer are 0.04 and 0.03 ng/mL (0.04 and 0.03 μg/L), respectively.
Of the 284 episodes, 37 (13.0%) were diagnosed as acute MI. All 37 MI cases had a maximum cTnI level of more than 0.04 ng/mL (0.04 µg/L), and the median amount of change between 2 cTnI measurements was 4,328% and ranged from 30% to 342,271%. Of the 37 diagnosed MIs, 22 patients (59%) had an initial cTnI level between 0.04 and 0.1 ng/mL (0.04 and 0.1 µg/L). In the whole study population, an initial cTnI level between 0.04 and 0.1 ng/mL (0.04 and 0.1 µg/L) was present in 76 patients (26.8%).

Table 3 shows additional episodes that met MI criteria when the new universal definition was applied with a 20% elevation considered significant. Table 3 shows the initial cTnI level, the second cTnI level (a follow-up determination within 24 hours), the amount of the dynamic change of the cTnI level, and the final discharge diagnosis. Overall, 29 additional episodes met the new diagnostic criteria when a 20% change was implemented, corresponding to 18 cases of cardiac diseases associated with high cTnI levels and 11 cases of noncardiac diseases (Table 3). The median change between cTnI measurements in these cases was 75% (range, 20%-900%).

Of the 29 additional patients who met the MI definition, 3 (10%) were readmitted for ACS within 6 months (2 for MI and 1 for unstable angina). In comparison, only 4 (2.3%) of 176 patients with a maximum cTnI level of less than 0.04 ng/mL (0.04 µg/L) were readmitted for ACS within 6 months (0 for MI and 4 for angina). Of the 42 patients with a maximum cTnI level of more than 0.04 ng/mL (0.04 µg/L) but a change between measurements of less than 20%, 3 (7%) were readmitted for ACS within 6 months (0 for MI and 3 for unstable angina).

Discussion

Universal adoption of new diagnostic criteria is incomplete particularly because of the difficulty of cTn assays in reaching the recommended analytic precision at low levels. Therefore, clinical application of higher cut points than the recommended 99th percentile has been frequent to avoid false-positive results. At present, progressive incorporation of highly sensitive analytic assays for cTn determination significantly overcomes this inconvenience, thus constituting a significant opportunity to fully adopt new diagnostic criteria. Specifically, a new ADVIA Centaur cTnI assay (TnI Ultra), which has high agreement with the old ADVIA Centaur cTnI assay, shows improved analytic sensitivity. The TnI-Ultra assay has acceptable analytic variation, which is greatly improved in relation to the 99th percentile of the old ADVIA Centaur Assay (0.1 ng/mL [0.1 µg/L]). This prompted us to evaluate the clinical implications of using the TnI-Ultra assay at the 99th percentile cut point (0.04 ng/mL [0.04 µg/L]) provided by the manufacturer.
In the year 2000, the ESC/ACC defined acute MI as rising and falling concentrations of cTn higher than the 99th percentile of a reference population in the presence of symptoms of ischemia. However, incomplete adoption of the new ESC/ACC definition of MI is documented in various studies. Hasdai et al13 analyzed data collected in the prospective Euro-Heart Survey of Acute Coronary Syndromes, which included 10,484 patients admitted owing to ACS in 103 hospitals in 25 countries in Europe and the Mediterranean basin between September 2000 and May 2001. Of the 4,398 patients with a discharge diagnosis of unstable angina, 28.1% had documented increases in cTn levels that suggested an MI diagnosis. Furthermore, about a quarter of the 6,086 patients with a discharge diagnosis of MI had normal cTn and/or creatine kinase levels. Afterward, Polanczyk et al14 reported that in 363 patients with chest pain admitted to the emergency department, when new criteria were applied with a cTnT level of 0.035 ng/mL (0.035 µg/L) or more, there would be 75 additional cases (21%) diagnosed as MI, which represented an increase of 127% in the incidence of MI. More recently, Roger et al8 reported that fewer than half of the cases identified with the new criteria were documented as MI in the medical record.

At present, serial testing is considered necessary to determine the clinical significance of low levels of cTn with use of high-sensitivity assays.15 However, although the new ESC/ACC consensus definition of MI3 and the universal definition of MI4 require a dynamic change in cTn concentration between specimens, there are no specific criteria in terms of the amount of cTn or the interval that determines a change as significant. In 2003, the American Heart Association (AHA) operationalized the ESC/ACC criteria and specified how to use cardiac biomarkers.16 Specifically, the AHA Scientific Statement defined an adequate set of biomarkers as at least 2 measurements of the same marker taken at least 6 hours apart. Definite MI was defined with at least 1 measurement exceeding the 99th percentile of a healthy population and with a rising or falling pattern in the setting of clinical cardiac ischemia and the absence of noncardiac causes of the elevation in the biomarker level.

The authors of the AHA Scientific Statement called for comparison studies to evaluate these definitions. Kavsak et al17 observed a substantial increase in the frequency of MI using the 2003 AHA case definition in comparison with diagnoses made using the 1994 WHO MONICA definition. In their study, AHA case definition for MI was based on the criterion for change of 20% or more between specimens, and the Beckman Coulter Accu cTn assay (Beckman Coulter, Chaska, MN) was used. Macrae et al18 also used a change of 20% or more and the same assay for studying acute MI prevalence in 258 patients admitted to the emergency department with symptoms of cardiac ischemia. It is interesting that their study shows that prevalence was not significantly diminished when the interval of 6 hours between specimens was reduced to only 3 hours. More recently, the National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines recommended using changes in cTnI values of 20% or more to define acute MI in patients with baseline elevations of cTnI.19 The 20% change represents twice the requisite precision performance for a highly sensitive assay and is, therefore, thought unlikely to be caused by analytic imprecision.

In our study, we performed a comparison between results obtained from clinical diagnoses and those obtained using the new consensus criteria for MI in a population with suspected ACS. New consensus criteria were implemented with a change of 20% between 2 cTn measurements within 24 hours as a significant, true change produced by ischemia. The results show that adoption of new criteria resulted in an important increase in the number of MI episodes. Specifically, in contrast with the 66 episodes classified as MI by criteria based on the 99th percentile and a 20% change, only 37 episodes were classified as MI by discharge diagnosis. The 29 additional episodes classified as MI when a 20% change was considered significant represented an increase of 78% in the number of episodes classified as MI. These episodes include 18 cardiac diseases related to high baseline cTnI levels20 and 11 other diseases (Table 3), which also included 3 patients with a diagnosis of atypical angina. It is important to note that the 29 patients who additionally met the MI criteria were more frequently readmitted for ACS within 6 months, and they had all the episodes of MI (n = 2) observed in the follow-up after admission. It is well documented that elevated cTn levels predict the risk of adverse outcome in patients with ACS.21,22 However, more studies are necessary to evaluate prognostic implications of minor cTnI changes with highly sensitive assays.

The absence of specific criteria in terms of the amount of cTn that determines a significant cTnI change implies that, despite the introduction of highly sensitive analytic methods for cTnI quantification, consideration that a true cTnI change exists in a patient with suspected ACS relies on subjective criteria. At present, as stated, a 20% change between 2 cTnI measurements seems to be an appropriate criterion. However, there are no data concerning biologic variation of cTnI, and it is also not known whether diseases such as acute heart failure can produce high variations of cTnI levels in the absence of ACS. Therefore, clinical decisions determining that a true dynamic change produced by ischemia exists may be based on considerably greater changes. In our study, the prevalence of episodes that met the criteria for MI was 23% when a 20% change was defined as significant. When other amounts of cTnI changes were considered (Figure 1), the prevalence of MI ranged from 14% (for a 200% change) to 26% (for a 10% change). Therefore, the amount of change considered significant is important and may be a source of variation in the prevalence of the diagnosis of MI.
Another important clinical aspect related to improving the analytic sensitivity of cTnI assay is the possibility of early detection of MI. In our study, all patients had an initial cTnI level of 0.1 ng/mL (0.1 µg/L) or less, but more than half of the diagnosed MI cases had an initial cTnI level of more than 0.04 ng/mL (0.04 µg/L), thus showing an important impact of the TnI-Ultra assay in the early detection of MI.

Adoption of the new universal consensus definition of MI in a suspected ACS population with an initial cTnI level of 0.1 ng/mL (0.1 µg/L) or less, operationalized with a 20% change between 2 cTnI measurements and using a highly sensitive assay, showed an important increase in the number of episodes (78% in our study) that met the criteria for MI. In addition, more readmissions for ACS within 6 months were observed in the group of patients not diagnosed as having an MI but who met the MI criteria. More studies with more patients are necessary to evaluate if, as our results suggest, patients with maximum cTnI levels higher than the 99th percentile (0.04 ng/mL [0.04 µg/L]) and a dynamic change of 20% or more have a worse prognosis. On the other hand, an elevated proportion (59%) of the 37 diagnosed MI cases had an initial cTnI level above the 99th percentile (0.04 ng/mL [0.04 µg/L]), which implies that ultrasensitive assays for cTnI offer a high rate of early detection of MI.

References


