A Call for Universal Definitions in Cardiovascular Disease

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Defining concept or object enables humans to communicate effectively with each other concerning that defined entity. Medicine has struggled through its long history to define accurately the various diseases that are a daily component of the human condition. Accurate, clear, and easily interpreted definitions of a disease entity allow physicians to communicate among themselves and ultimately to explain to patients the implications of the specific conditions from which they suffer. The clinical scientist also requires an accurate definition of a specific disease. Often, a checklist is used to assist the investigator in identifying patients with the specific illness that is being studied. If the clinical scientist’s diagnostic criteria are accurate and reproducible, then similar patients with that disease entity can be entered into the clinical trial, the results of which may be generalized for the management of other patients who satisfy the same disease criteria. Furthermore, under favorable circumstances, results from one clinical trial can be compared and even combined with the results of other trials, as long as the same disease definition and criteria were used in the comparative investigations.

Unfortunately, the ideal world of a universally understood and applied definition does not exist in the domain of acute myocardial infarction (MI). Over the many years that clinical research has been performed on patients with acute MI, different definitions using contemporary diagnostic tools have been used, and consequently it is often a challenge to compare the “apples” in 1 study to the “oranges” in another. Similar problems arise in the arena of public health statistics because physicians use different algorithms to define MI in the clinical setting, leading to inaccuracies when public health data are collated from discharge summaries. Thus, studies involving large databases that use hospital discharge diagnoses can contain significant inaccuracies because different physicians have used different definitions of MI.

In an attempt to improve the accuracy of the diagnosis of MI by physicians and to make it simpler to compare results in future MI clinical trials, a multinational task force met in 1999 under the auspices of the European Society of Cardiology and the American College of Cardiology. The goal of this task force was to develop a simple, clinically oriented, universal definition for MI that could be used both in daily clinical practice and in clinical investigation and that could be used to correct the gap between therapeutic achievements and diagnostic advances. The task force was successful in creating such a document, which was published simultaneously in the European Heart Journal and the Journal of the American College of Cardiology. Since the publication of this report, which emphasized the use of newer, highly sensitive and specific biomarkers of myocardial cell necrosis in the diagnosis of MI, many investigators have explored the implications of the revised definition of MI compared with older, more traditional (and less specific) diagnostic criteria. Most of these studies have demonstrated that the new biomarker-based definition of MI resulted in an increased number of patients identified as having had an MI. This is, of course, not surprising, because the new biomarker used, troponin, is considerably more sensitive and more specific than biomarkers such as total creatine kinase (CK) and its isof orm, CK-MB, that had been used routinely before the advent of troponin assays. Because the new troponin assay identified smaller infarcts than did CK-MB, it was predicted early on that the short-term prognosis for patients with such troponin-positive, CK-MB-negative infarcts would be better than that for patients with both positive troponin and positive CK-MB measurements.

This increase in the number of patients labeled with the disease entity “myocardial infarction” presents clinical and investigative cardiologists with a number of conundrums. For example, a patient who formerly would have been discharged from the hospital with a diagnosis of angina or even unstable angina now falls under the diagnostic rubric of MI. The latter diagnosis has important psychological and social implications for the patient. Depending on the patient’s employment, certain careers may be interdicted by a diagnosis of MI. Thus, commercial or military jet pilots may be precluded from returning to work. Driving or flying licenses may be temporarily suspended. The specter of disability may be raised by the patient, his or her family members, or an employer. All of these factors can also bring about major psychological distress for the patient. Indeed, post-MI depression and sexual dysfunction have been reported commonly in patients after a recent MI. Further controversy has been generated by the observation that a sizable number of patients develop elevated blood troponin values after successful percutaneous coronary intervention (PCI). Given the widespread use of PCI, evidence of postprocedural myocardial cell necrosis is of great concern to cardiologists, patients, and, of course, in our society, civil liability attorneys. The first task force assembled to draft a universal definition of MI was cognizant of this potentially controversial outcome, ie, a sizeable number of patients undergoing PCI would be labeled as having had a postprocedural MI. The challenge of this aspect of the new definition for MI remains a conundrum to this day.

To seek a resolution to the post-PCI difficulty just elucidated, as well as to strengthen and clarify a number of the points made in the original redefinition-of-MI document, a second task force was convened in 2004 to rework, clarify, and expand on the
original redefinition. The final report of this second task force for an expanded redefinition of MI is anticipated during 2007. The new report will expand the criteria for defining an MI by adding new material on ECG criteria, imaging modalities, the patient who presents with sudden death as the initial manifestation of his or her infarct, and finally, implications of the redefinition for developing countries. The question of how to label small elevations in blood troponin values that occur after PCI remains controversial. Most of the delegates on the second task force favored calling these tiny, procedure-related episodes of myocardial injury true infarcts because they occurred in the setting of recognizable coronary arterial ischemic interventions. However, it was believed that these PCI-related events should be classified as infarcts distinct from the spontaneous or “wild-type” MI that usually presents with the traditional clinical scenario of substandard chest discomfort accompanied by ischemic ECG alterations.

Given the continuing interest, discussion, and debate surrounding the redefinition of MI, the prospective investigation by Roger and colleagues from the Minnesota Mayo Clinic, published in this issue of Circulation, is of considerable scientific and clinical importance. These investigators used several meticulously standardized definitions of MI, including that suggested by the first task force for the revision of the definition. Their carefully done comparison involved 1851 patients with the after-discharge diagnoses of acute and old MI, unstable angina, coronary heart disease, angina pectoris, and other forms of ischemic heart disease. After informed consent was obtained, each patient had at least 1 and often serial determinations of blood troponin, CK, and CK-MB. The biochemical data were correlated with clinical information and with short-term (30-day) follow-up.

As expected, the new (troponin) definition of MI identified substantially more patients with ischemic myocardial necrosis than did CK alone or CK combined with CK-MB. Depending on the level of troponin selected as the cutoff point beyond which MI was diagnosed, as well as on the number of samples taken and the comparator used, the percentage increase in the number of infarcts diagnosed by troponin alone ranged from 35% to 112%. In all subsets, the number of infarcts identified by the troponin definition was substantially larger than the number of infarcts that would have been identified by CK or CK-MB determinations. Equally interesting was a much smaller but noticeable group of patients who were diagnosed as having had an MI by elevated CK-MB measurements in the face of normal troponin values. Clearly, this small but clinically important group of patients was falsely diagnosed as having had an infarct by the CK-MB criterion. This observation underscores the fact that troponin analysis increases both sensitivity and specificity of infarct diagnosis.

Patients with troponin-positive infarcts were older, more likely to be women, and less likely to have clinically evident left ventricular failure than the CK-positive or CK-MB–positive patients. In addition, troponin-positive patients were less likely to experience chest discomfort suggestive of ischemia. The overwhelming majority (94%) of troponin-positive infarct patients had non–ST-elevation MI. Many of the patients with troponin-positive but CK-negative or CK-MB–negative infarcts were discharged with the diagnosis of unstable angina. Indeed, fewer than half of the patients with infarcts diagnosed solely on the basis of an abnormal troponin measurement received a discharge diagnosis of MI. Finally, the prognosis of patients with infarcts diagnosed solely by abnormal troponin values was better at 30 days (5% mortality) than patients with positive CK-determined or CK-MB–determined MI (11% mortality).

There are a number of important implications of this carefully done prospective, observational trial. First, the new troponin-based definition of MI has yet to be accepted and applied by many clinicians. Second, there are a substantial number of patients with quite small infarcts who can only be identified by highly sensitive and specific troponin measurements. These latter patients tend to be older women with less reported chest discomfort and with a better short-term prognosis than individuals who are found to have elevated CK-MB values. Presumably, the better short-term prognosis is the result of the smaller size of the troponin-diagnosed infarcts. It is the fervent hope of the authors of this editorial that, after the publication during 2007 of the new and more thoroughly revised definition of MI that will result from the current deliberations of the second task force, the suggested redefinition of MI will be universally used.

Disclosures

Dr Alpert serves as a consultant for Sanofi-Aventis, Novartis, and Exeter Communications. Dr Thygesen serves as a consultant for Sanofi Aventis, Servier, Pfizer, and Medtronic. Neither author consults or receives any remuneration from companies involved in the manufacture or sale of equipment, chemicals, etc. in diagnostic testing for patients with possible myocardial infarction, the topic of the editorial.

References


Key Words: Editorials ■ myocardial infarction ■ coronary disease ■ diagnosis
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*Circulation*. 2006;114:757-758
doi: 10.1161/CIRCULATIONAHA.106.648030
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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