EDITORIAL COMMENT

Cardiac Enzyme Elevations After Percutaneous Coronary Intervention: Myonecrosis, the Coronary Microcirculation and Mortality*

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One of the most controversial issues in interventional cardiology concerns the meaningfulness of elevated cardiac enzymes after percutaneous coronary interventions. Both single-center observational studies (1–3) and subset analyses from multicenter clinical trials (4,5) have reported an association between postprocedure creatine kinase myocardial band (CK-MB) elevations and adverse short- and long-term clinical outcomes, including mortality. Other investigators have failed to demonstrate this relationship, maintaining that while cardiac enzymes are frequently elevated after percutaneous coronary procedures, the prognostic implications of this finding are unclear (6).

The controversy has generated a good deal of healthy disagreement leading to debates at national meetings as well as intensive efforts to further study the issue and address some fundamentally important questions in clinical cardiology. Among these questions are: What exactly defines a myocardial infarction (MI) (7)? and, What are the role and importance of the coronary microcirculation during coronary intervention (8)?

Apart from these useful intellectual exchanges, the controversy has produced emotional responses that have served to trivialize the issue, ignoring its potential impact on patients’ outcomes. This is reflected in the phrases used by cardiologists to explain the elevation of CK-MB isoenzymes after coronary intervention (Table 1). The choice of words is meant to suggest a benign laboratory finding that could not possibly represent a meaningful clinical event such as an MI. In fact, some clinicians go to great lengths to avoid calling these events infarctions, instead employing these other terms.

Why do many of us do this? The Hippocratic oath instructs us to “first, do no harm.” When performing interventional procedures, the goal is certainly to alleviate the coronary obstruction without causing or inducing a complication. It is difficult to accept that a procedure that is performed with noble intentions can have adverse clinical consequences, especially when these events are frequently asymptomatic. In addition, coronary intervention is a visually-driven procedure. Decisions regarding revascularization are based upon a subjective visual interpretation of the coronary angiogram, and a procedure is deemed successful when there is a widely patent lumen without angiographic evidence of complications such as abrupt closure, dissection or side branch occlusions. Many, if not most, postprocedure MIs are not visually apparent at the time of the procedure and are, therefore, met with skepticism from the visually oriented interventional cardiologist when the laboratory data the next morning document an infarction.

The article by Saucedo et al. (9) in this issue of the Journal is the latest attempt to examine the long-term implications of CK-MB elevation after percutaneous coronary intervention. This report is especially timely because it focuses on patients receiving a coronary stent, the intervention most commonly performed today (10). This single-center observational study reports on 900 consecutive patients who underwent successful native-vessel stenting. Patients were classified into three groups based on the maximum CK-MB observed after the procedure: normal, elevation of one to five times the local upper limit of normal and elevation of greater than five times the upper limit of normal. The patients were followed for a mean of 14 months for the occurrence of death and other cardiac events. The authors reported higher acute complications in both groups with elevated cardiac enzymes compared with patients without any enzyme elevation and a significantly increased risk of late death for patients with a poststent peak CK-MB greater than five times the upper limit of normal. Multivariate analysis confirmed the significance of the mortality observation (odds ratio 3.25, 95% confidence interval [CI] 1.00 to 10.5, p = 0.04).

The authors should be congratulated for collecting, analyzing and reporting these data, given that many interventional cardiologists have chosen not to check routine cardiac enzymes for patients having a successful procedure. Observational databases like this one provide insight into contemporary practices that complement the findings of randomized clinical trials, which, by their nature, enroll a more selected group of patients. The authors carefully evaluated the patients for a number of acute cardiac complications and then followed them after discharge in a systematic fashion, ascertaining follow-up data on 96% of them. Importantly, the authors used multivariate analysis, which included baseline clinical, as well as lesion and procedural variables, to...
successful stent procedures, defined as those having

values. The authors chose to limit their report to patients having successful stent procedures, defined as those having <50% residual stenosis and the absence of death, Q-wave MI or emergency or urgent coronary bypass surgery. As such, their population differs from those described in the randomized trials where patients are enrolled either just before or during the procedure without regard to its ultimate success. The authors also elected to exclude patients with baseline elevations in CK-MB in order, presumably, to simplify the postprocedure CK-MB analysis. These two decisions, while justifiable, undoubtedly produced a lower-risk population than is typically seen with an “all-comers” analysis. Given this fact, their findings are even more striking, consistent with the notion that myocardial necrosis occurs commonly after even uncomplicated coronary procedures and is associated with significant late-term consequences (11).

More than 8% of patients with a successful stent procedure had a postprocedure peak CK-MB of greater than five times the upper limit of normal and a three-fold increased risk of death compared with patients without any CK-MB elevation. Given the relatively small number of patients in this category, the CIs surrounding the mortality estimate are quite broad. If these findings are borne out, the potential public health and economic implications are enormous because more than 800,000 coronary stents were implanted in the U.S. in 1998 (12).

The authors noted that their group 2 patients (those with enzymes greater than one to five times the normal limit) did not have an increased risk of late mortality, and they seemingly concluded that this group of patients is not at increased risk of major adverse clinical events. Understanding the findings associated with this group is important because most of the controversy involves patients with an intermediate level of enzyme elevations. In the current study, this level of enzyme elevation was very common, being observed in 238 patients (26.4%) after a successful procedure. But in looking at the mean CK-MB levels in the groups, it becomes apparent that the mean CK-MB in group 2 is only approximately two times the upper limit of normal. There is insufficient information to draw adequate conclusions from Group 2 regarding the really controversial subgroup of patients, those with CK-MB elevations three to five times the upper limit of normal. Additionally, despite the low level of peak enzyme elevations in group 2, they had significantly more acute complications than the group without any enzyme elevation, including more recurrent ischemia, repeat cardiac catheterizations and pulmonary edema. The data are, thus, not at all at odds with other reports as concluded by the authors. It would be useful to reexamine these data using CK-MB as a continuous variable because other investigators have suggested that there is an increased risk associated with levels of CK-MB just above the upper limit of normal (4).

The introduction of coronary stenting has revolutionized the practice of interventional cardiology; the predominant effect has been on reducing restenosis and the need for repeat procedures and not on reducing the postprocedure risk of death or MI (13). In the current study, all patients had successful procedures, presumably with wide-open lumens and good coronary blood flow. Why then was there a >30% incidence of elevations in cardiac enzymes? Emerging data suggest that there is distal embolization of atherothrombotic material accompanying the plaque disruption that is essential to the success of the interventional procedure. Data from Neumann et al. (8) support the notion that it is a disorder of microcirculatory flow that leads to a disorder in ventricular function that might be responsible for the adverse clinical consequences. As we are learning in the setting of acute MI and reperfusion therapy, it may well be that flow in the microcirculation is as important as flow in the epicardial vessels (14).

Is all this discussion on postprocedure enzyme elevation an academic controversy, or is the issue of CK-MB elevation important for the clinical community at large? As pointed out by Saucedo et al. (9), this is a common question that is still enmeshed in controversy, has produced an enormous amount of data and has generated many emotional discussions. There are major issues at stake. New devices are being developed that may increase the risk of myonecrosis after interventional procedures. If there is a greater risk of late death associated with these increases in cardiac enzymes, how should the clinical and regulatory communities interpret these data? The platelet glycoprotein IIb/IIIa inhibitors are becoming an increasingly used adjunctive therapy during percutaneous coronary intervention (15). Their predominant effect is to lower the risk of periprocedural MI and not to reduce the risk of death (16). Again, in order for the clinical and regulatory communities to assess the benefit of these new therapies, there must be some agreement as to the meaningfulness of the event.

Along the same line of reasoning, the impact of “scorecards” on clinical practice depends, in part, on there being some consensus that there is clinical benefit in reducing the risk of periprocedural MI. The recently reported one-year mortality data from the Evaluation of Platelet Inhibition in STENTing (EPISTENT) trial (17) suggest that there is a continued accrual of clinical benefit after acute treatment with both abciximab and stenting compared with either

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<td>Infarctlet</td>
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<td>Insignificant enzyme elevations</td>
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CK-MB = creatine kinase-myocardial band; MPEI = minimal postprocedure enzyme increase.
therapy given alone. Wider use of these expensive therapies at the time of coronary intervention requires broader agreement about the meaningfulness of the events being prevented by the therapies.

Data provided by the work of Saucedo et al. (9) add coronary stenting to the list of interventional devices that cause myonecrosis even after a successful procedure and are associated with an increased risk of death in patients having enzyme elevations greater than 5 times the upper limit of normal. More work needs to be done to develop a consensus about what exactly constitutes a postprocedure MI, what should be done to manage patients so affected and what therapies can be developed and used to attenuate that risk.

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REFERENCES