Incidence and Clinical Significance of Transient Creatine Kinase Elevations and the Diagnosis of Non-Q Wave Myocardial Infarction Associated With Coronary Angioplasty

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To assess the incidence and clinical significance of elevated total plasma creatine kinase (CK) and MB isoenzyme fraction after apparently successful coronary angioplasty, a prospective study of 272 consecutive elective procedures was undertaken. Total CK (normal <200 IU/liter) and CK MB isoenzyme (normal ≤4%) were measured immediately after successful completion of the procedure and every 6 h for 24 h. All nonelective procedures and results not fulfilling all American Heart Association/American College of Cardiology Task Force guideline criteria for a successful result were excluded from analysis.

Of the 272 elective procedures, 249 (92%) were successful; abnormally elevated CK or CK MB serum levels, or both, were found in 38 (15%) of the successful outcomes. Three patterns of abnormal enzymes were identified: 15 patients with CK ≥200 IU/liter and CK MB ≥5% (group 1), 4 patients with CK ≥200 IU/liter and CK MB ≤4% (group 2) and 19 patients with CK <200 IU/liter and CK MB ≥5% (group 3). The three groups were distinguishable by the nature of the complications causing the enzyme release (in particular, the etiology and clinical manifestations). There were significantly more clinically apparent events in group 1 than in the other groups (13 of 15 versus 11 of 23, P < 0.01) and more events associated with persistent electrocardiographic changes (p = 0.05) and chest pain (p < 0.05). However, no clinically important sequelae were recognizable in any group at hospital discharge.

Thus, abnormal cardiac serum enzyme release after apparently successful coronary angioplasty is 1) relatively common; 2) has many possible causes, including both minor complications and early reversibility of impending major complications; and 3) results in no permanent clinical sequelae.

Methods

Study patients. All patients undergoing elective single or multivessel coronary angioplasty at Northwestern Memorial Hospital between March 1989 and February 1990 were considered candidates for this study. The study group consisted of those patients with successful elective angioplasty of at least one coronary stenosis, as defined by both clinical and angiographic criteria. All patients with major in-hospital complications, including death, resuscitation from cardiac arrest, Q wave myocardial infarction and emergency bypass surgery, were excluded from analysis. Any patient with elevations of cardiac serum enzymes (3). Furthermore, the frequency with which abnormally elevated cardiac serum enzymes are observed after successful angioplasty is unknown. Another clinically relevant issue is the relation between serum creatine kinase (CK) elevations and transient balloon occlusion. Heyndrickx et al. (4) showed conclusively in a baboon model that CK release may occur after short periods of coronary occlusion without myocardial necrosis. Thus, the mere occurrence of elevated serum enzyme levels may not be sufficient to infer the diagnosis of myocardial infarction in this setting.
prolonged hypotension or prolonged ischemia, or both, unresponsive to usual medical measures and necessitating bypass surgery or resulting in Q wave infarction were excluded under these criteria. In addition, patients undergoing cardiac catheterization during acute myocardial infarction or for postinfarction angina within 36 h of symptom onset were excluded on the basis of elevated serum cardiac enzyme levels before angioplasty, as were patients not meeting the definition of a successful angioplasty result. Thus, all patients believed by their physicians to have had a successful elective procedure were entered into the study group on a prospective basis. Patients whose subsequent clinical course necessitated a return to the catheterization laboratory within 72 h for further interventional procedures were excluded.

A successful angioplasty result was that defined by the American Heart Association/American College of Cardiology Task Force on angioplasty (1) and as applied by our group previously (5). The criteria were: 1) no in-hospital complications; 2) improvement in luminal diameter narrowing to <50% of a contiguous normal vessel; and 3) complete resolution of clinical manifestations of ischemia after coronary angioplasty.

Protocol. Electrocardiographic (ECG) monitoring of at least two noncontiguous ECG leads was performed during angioplasty. Acute ST and T wave changes, heart rate and blood pressure were continuously recorded throughout the procedure. Detailed procedural notes of the occurrence, severity and duration of chest pain and ECG changes were recorded by both independent laboratory staff and the catheterization team. In addition to routine follow-up study by the operators, a nurse clinician examined and questioned each patient. The nurse clinician assured that all appropriate follow-up blood specimens and ECGs were obtained for up to 72 h after angioplasty. An ECG was obtained immediately after angioplasty and on the next 2 mornings routinely; other ECGs were performed as deemed clinically necessary. ST segment or T wave changes, or both, that were clearly new compared with preangioplasty baseline data, were (in the absence of subsequent Q wave development) considered clinical events if they persisted for ≥48 h or until hospital discharge.

Angiographic and clinical observations. All coronary angiograms were reviewed by two investigators. Percent luminal narrowing of all dilated stenoses was measured according to the caliper method before and after angioplasty. In addition, a notation was made of any complication, according to the following criteria. Intimal dissection was defined as the angiographic appearance of either a negative intraluminal radiolucency consistent with an intimal flap or subintimal contrast staining that persisted after free flow of contrast medium through the vessel (5). In all cases in which the abnormal enzyme release was ascribed to intimal dissection, there had to be clinical or angiographic evidence, or both, of transient, actual or impending vessel closure necessitating reopening by pharmacologic or mechanical means, or both. Thrombus was defined as an avoid filling defect, with or without contrast staining, that appeared within the lumen. Graft embolism was defined as the visualization of transient or permanent small branch occlusion during angioplasty of a saphenous vein graft ≥6 years old. Spasm was considered present when a subtotal or total occlusion lasting for several minutes occurred in association with a clinical event that completely resolved after sublingual, intravenous or intracoronary nitroglycerin administration. Branch occlusion was defined as transient or permanent occlusion of a minor or major branch of the epicardial vessel observed on the angioplasty angiogram at any time during angioplasty.

Clinical events were defined as either chest pain or the observation of acute ECG changes persisting without significant diminution for ≥3 min after deflation of the balloon and requiring medical therapy. In addition, whether or not these occurrences correlated with angiographic events during the course of the procedure was recorded. The vessel responsible for the enzyme increase was determined prospectively, and for purposes of data analysis, checked retrospectively by correlation with angiographic and ECG changes.

Cardiac enzyme and isoenzyme determinations. Both CK and CK MB isoenzyme fractions were prospectively measured in all study patients. At least one normal determination before angioplasty was required for study entry; in patients with recent (that is, within the preceding 72 h) myocardial infarction, at least two sets with a total CK <120 IU/liter and CK MB isoenzyme fraction <4% in the preceding 24 h were required for study qualification. Blood samples for both CK and CK MB measurements were drawn within 1 h after angioplasty and then every 6 h for four more determinations.

Total CK activity (normal <200 IU/liter). This was analyzed by the Technicon RA-1000 commercial technique. The CK MB isoenzyme values were determined by agarose gel electrophoresis with fluorometric quantification. Results of the isoenzyme measurements were expressed as a percent of total enzyme activity (normal ≤4%) (3).

Patient groups. Patients were candidates for this study if they fulfilled all of the previously noted entry criteria and exhibited at least two abnormal determinations of either total CK or CK MB isoenzyme, or both. Three patterns of abnormal enzyme and isoenzyme levels were detected. Group 1 included patients in whom at least two sets with CK ≥200 IU/liter and CK MB fraction ≥5% were noted. Group 2 comprised patients with elevation of total CK whose CK MB fraction remained within normal limits. Group 3 consisted of those patients with only CK MB fraction elevation without total CK elevation. In all cases, these increases were transient and either completely normalized or showed a definite trend toward normalization after 48 h. For purposes of data analyses, the highest total CK value and the CK MB fraction associated with it were recorded.

Statistical methods. Continuous data were expressed as mean values ± SD. Comparisons among the three groups were performed using analysis of variance techniques (ANOVA). Subgroup comparisons were allowed only if
Table 1. Selected Clinical Manifestations of an Increase in Cardiac Enzyme Levels in 38 Patients

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 15)</th>
<th>Group 2 (n = 4)</th>
<th>Group 3 (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apparent clinical event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(during PTCA)†</td>
<td>13 (87%)</td>
<td>1 (25%)</td>
<td>10 (53%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>14 (93%)</td>
<td>2 (50%)</td>
<td>10 (53%)</td>
</tr>
<tr>
<td>Persistent ECG changes‡</td>
<td>10 (67%)</td>
<td>0 (0%)</td>
<td>8 (42%)</td>
</tr>
</tbody>
</table>

*p < 0.05 (ANOVA); p < 0.05 by chi-square analysis (group 1 versus group 3) and p < 0.01 (group 1 versus groups 2 and 3). tp < 0.08 (ANOVA); p < 0.05 by chi-square analysis (group 1 versus groups 2 and 3). tp < 0.05 (ANOVA); p = 0.05 by chi-square analysis (group 1 versus groups 2 and 3).

See text for other manifestations tested; no others were significantly different between groups. ECG = electrocardiographic; PTCA = percutaneous transluminal coronary angioplasty.

Table 2. Cause of Abnormal Cardiac Serum Enzyme Elevation in 38 Patients

<table>
<thead>
<tr>
<th>Causes</th>
<th>Group 1 (n = 15)</th>
<th>Group 2 (n = 4)</th>
<th>Group 3 (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary branch occlusion</td>
<td>5 (33%)</td>
<td>0 (0%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Intimal dissection</td>
<td>3 (20%)</td>
<td>1 (25%)</td>
<td>7 (37%)</td>
</tr>
<tr>
<td>Coronary spasm</td>
<td>1 (7%)</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>2 (13%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Saphenous vein graft embolism</td>
<td>0 (0%)</td>
<td>1 (25%)</td>
<td>3 (16%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (27%)</td>
<td>2 (50%)</td>
<td>6 (32%)</td>
</tr>
</tbody>
</table>

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p < 0.1 (ANOVA). Comparisons between two groups were made using the chi-square test in the case of discrete data and the two sample t test in the case of continuous data. A p value <0.05 was considered to be statistically significant.

Results

Patient selection. Between the inclusive study dates, 305 consecutive coronary angioplasty procedures were performed. Of these, 33 were performed either during or early after acute myocardial infarction and were excluded (as defined in Methods). Of the remaining elective procedures, there was 1 procedural death (0.4%), 11 acute vessel closures necessitating immediate coronary bypass surgery (4%), 6 additional Q wave myocardial infarctions occurring within 48 h of the procedure (2.2%), 4 unsuccessful results due to an impassable chronic total occlusion (1.5%) and 1 inadequate dilation (0.4%). Thus, 249 (92%) of 272 elective procedures were considered successful by all angiographic and clinical criteria. Total plasma CK and CK MB isoenzyme fraction were determined according to the protocol in all patients.

Distribution of cardiac enzyme elevation. Abnormally elevated total CK or CK MB isoenzyme fraction, or both, was noted in 38 (15%) of the 249 patients and these patients formed the study group. The mean age of this group was 62 ± 11.2 years (range 40 to 87); 25 were men and 13 women. Thirty (79%) of the 38 patients underwent angioplasty of either two or three epicardial vessels or their branches; in contrast, multivessel angioplasty was performed in only 43% of the 211 patients without enzyme elevation (chi-square = 15.1, p < 0.0001).

Coronary angiographic findings revealed that the vessel responsible for the index enzyme increase was the left anterior descending coronary artery in 14 (37%), the right coronary artery in 20 (53%) and the left circumflex coronary artery in 2 (5%); in 2 additional patients, the vessel involved could not be determined. Angioplasty of a saphenous vein graft resulted in an enzyme increase in four patients (two anterior descending, one circumflex, one right coronary artery) and these cases were included for analysis.

The mean total peak CK in the entire 38 patient study group was 221 IU/liter (range 127 to 475). Similarly, the mean CK MB isoenzyme determination accompanying the peak CK was 8.9% (range 0% to 20%).

Clinical and angiographic correlation (Table 1). Nineteen (50%) of the 38 patients had prolonged chest pain during the angioplasty procedure. In addition, seven other patients had distinct episodes of ischemic chest pain at some time in the subsequent 72 h after the angioplasty procedure; altogether, 26 (68%) of the 38 patients had some prolonged chest pain related to the angioplasty procedure. Twenty-one patients (55%) had ECG changes persisting >3 min after balloon deflation. Persistent ST and T wave changes were observed at follow-up study and were present at hospital discharge in 18 patients (47%). Both chest pain and ECG changes during angioplasty occurred in 15 patients (40%). Three (8%) of the 38 patients had hypotension (systolic blood pressure <80 mm Hg) and 5 patients had an arrhythmia associated with the acute clinical event. This included premature ventricular complexes in two patients, atrioventricular block and premature ventricular complexes in one patient, nonsustained ventricular tachycardia in one and intermittent left bundle branch block in one.

Altogether, 24 (63%) of the 38 patients had an apparent clinical event that occurred in the catheterization laboratory. The cause of the abnormal enzyme increase could be determined or inferred angiographically in 26 patients (Table 2). This included coronary branch occlusion in 7 patients, intimal dissection with transient vessel closure in 11, saphenous vein graft embolism in 4 patients, coronary spasm in 2 and thrombosis in 2.

Thirty-seven of the 38 study patients were discharged within 5 days of the angioplasty procedure without further invasive or operative procedures. One patient had a prolonged clinical course due to presumed allergy to a medication.

Analysis by enzyme elevation pattern. The 38 patients with an abnormal increase in cardiac enzyme were further subclassified by the pattern of enzyme elevations, as defined under Methods. Fifteen patients formed group 1, 4 were...
included in group 2 and 19 fulfilled the criteria for group 3. There were no significant differences among these three groups regarding age, gender or artery undergoing angioplasty.

When patients with both total CK and CK MB isoenzyme elevations were compared with those with only a single abnormal determination (Table 1), patients in group 1 had a significantly higher number of apparent clinical events (87% versus 48%) as compared with groups 2 and 3 (p < 0.01). Chest pain was more frequent either during or after angioplasty (p < 0.05) and more persistent ECG changes (p = 0.05) in group 1 than in the other groups.

Importantly, there was a statistically significant difference between groups 1 and 3 in terms of the occurrence of a clinical event in the laboratory. Fifteen (87%) of the 18 group 1 patients had an obvious clinical event, whereas only 10 (53%) of the 19 group 3 patients had an event (p = 0.03). Notably, all three episodes of hypotension and all five episodes of significant arrhythmias occurred in situations marked by both a clinically apparent event and abnormal CK MB isoenzyme elevation (group 3).

In addition, the etiology of the clinical event was clearly different among the three groups. The occurrence of side branch occlusion was more likely in group 1 (5 of 15 versus 2 of 23), whereas the occurrence of intimal dissection was more frequent in group 3 (7 of 19 versus 4 of 19). Of the seven patients with side branch occlusion, all five with both CK and CK MB isoenzyme elevation had involvement of relatively larger branches noted to be closed at some time during the angioplasty procedure, whereas in the two patients with only abnormal CK MB isoenzyme but normal total CK, the occlusion was due to either a small septal or a small marginal branch closure and was only identified when the cine film was reviewed. Similarly, in those intimal dissections with only CK MB isoenzyme elevation, antegrade flow was reestablished more quickly than in group 1.

Discussion

This study was undertaken primarily to describe and characterize the incidence and clinical importance of creatine kinase (CK) and CK MB isoenzyme release after an apparently successful coronary angioplasty procedure. A related but separate objective was to draw a distinction between inconsequential enzyme release, perhaps as a result of multiple or prolonged arterial balloon occlusions, and the occurrence of non-Q wave infarction resulting from minor or transient periprocedural complications. Yet another issue is the possibility of false-positive data supplied by a highly respected clinical laboratory and its potential impact on subsequent patient management. Finally, questions arise concerning the necessity to routinely monitor cardiac serum enzymes after an apparently successful coronary angioplasty procedure and the relevance of abnormal findings to short-term outcome.

Cardiac serum enzyme elevation and clinical events after successful angioplasty. The results of this investigation suggest that modestly elevated total CK and CK-MB fractions occur frequently and unpredictably after a coronary angioplasty procedure fulfilling both clinical and angiographic criteria for success. In the current study, 15% of all successful procedures performed over a 10 month study period were associated with at least one enzymatic criterion suggestive of myocardial necrosis. An apparent clinical event was identified in 63% of these cases, suggesting that events currently judged by interventionists (6,7) as having little permanent clinical sequelae nevertheless are associated with myocardial necrosis and non-Q wave myocardial infarction. The majority of the cases in which enzyme release occurred were associated with an episode of prolonged chest pain or ECG changes, or both. Such events were often due to transient closure of a major vessel as a result of dissection, spasm or thrombosis, but were also associated with side branch occlusion or saphenous vein graft embolization.

Cardiac serum enzyme elevation without a clinical event. Notably, a minority of cases with serum enzyme elevation had no clinically distinguishable event. Whether or not these cases represent merely laboratory error or enzyme release due to repetitive or prolonged vessel occlusion, or both, without necrosis (3), increased enzyme washout or early detection of a minor degree of myocardial necrosis (8,9) is ultimately unanswerable. However, the data do yield several interesting observations in this regard. Creatine kinase MB isoenzyme elevation alone was associated with a significantly lower incidence (53%) of identifiable clinical events than was elevation of both total CK and CK MB fraction (87%) (p < 0.05). This observation suggests that abnormal levels of both enzymes (group 1) may more specifically identify true necrosis. Importantly, all three episodes of symptomatic hypotension and all five episodes of arrhythmias occurred in association with an identifiable event and abnormal CK MB isoenzyme elevation.

Clinical consequences of asymptomatic cardiac serum enzyme elevation. Eighteen (47%) of these patients had persistent ECG changes as a result of an event during coronary angioplasty. Nevertheless, there were no major subsequent cardiac in-hospital complications in any of the 38 patients in the study. Although it is apparent from these observations that no alteration in patient management is warranted on the basis of asymptomatic enzyme elevation alone, subsequent strategies may be appropriately tailored to this group of patients. Clinical decisions may be particularly facilitated when the etiology of the event and the potential for subsequent myocardial jeopardy based on angiographically defined anatomy are known. The major conclusion to be drawn from this study is that, although small enzyme elevations, often associated with a minor clinical event during angioplasty, may result in persistent ECG changes or brief episodes of chest pain, or both, no apparently important clinical consequences are apparent after several days.
Previous studies. The finding that a minority of apparently successful coronary angioplasty procedures are associated with abnormal enzyme elevations but not with increased in-hospital morbidity or mortality is remarkably similar to the results of Oh et al. (10), who retrospectively analyzed the data from 128 patients in the early years of angioplasty (1979 to 1982). Although their data are interesting primarily from a historical perspective, it is noteworthy that the investigators found a 20% incidence of abnormal CK MB isoenzyme elevation. However, the fact that theirs was not a prospective consecutive series limits the study conclusions, as reflected by the timing of cardiac serum enzyme determinations, the absence of precangioplasty enzyme measurements and the exclusion of 15% of otherwise eligible patients because serial enzyme levels were not measured. Additionally, clinical and angiographic observations are far more sophisticated now than they were more than a decade ago, a factor that undoubtedly had an impact on the study results.

The study by Heyndrickx et al. (4), in which 15 min periods of coronary artery occlusion in baboons and their effects on plasma CK MB isoenzyme activity were studied, points out some of the specific difficulties of analyzing increases in enzyme levels in the angioplasty model. In their study, the effect of 15 min of balloon occlusion resulted in significant increases in total CK and CK MB fraction levels. Yet, at autopsy, neither gross pathologic nor histologic evidence of myocardial necrosis was observed. This observation is directly applicable to coronary angioplasty in human patients in whom brief episodes of ischemia are produced and hence it is possible that some cases may be associated with increased serum enzyme activity. There is also indirect evidence to suggest that transient ischemic episodes not accompanied by myocardial necrosis may be associated with enzyme leakage. Chiong et al. (11) reported small but significant CK release in the coronary sinus during pacing-induced ischemia in patients with coronary stenosis. In addition, small amounts of enzymes may leak from myocardial cells during stress, tachycardia and exercise. Fishbein (12), commenting on the study of Heyndrickx et al. (4), stated that it is possible that reversible myocardial injury in the absence of cell death can result in alterations of membrane permeability with resultant release of myocardial enzymes. In the current study, however, no correlation between the number and duration of inflations in the study group as a whole or in subgroups could be discerned. Furthermore, it is recognized that only by repeating angiography in every patient with an abnormal increase in enzyme levels could we exclude the few patients with postangioplasty silent or minor occurrences causing the increase. Such patients would have been incorrectly included in the study group and classified as having no discernible cause of the increased serum level. However, it is unlikely that this sequence provides an explanation in most of these patients.

Arora et al. (13) recently reported on the incidence of enzyme elevations and ECG changes along with the clinical sequelae in patients with side branch occlusion during coronary angioplasty. They found that the maximal CK release was approximately 500 to 700 IU/liter, depending on the particular vessel and branch occluded. In general, ST changes occurred in the minority of cases, as did chest pain. In our study, only relatively small or medium-sized branches were occluded. Thus, our results demonstrate that when side branches do occlude as a part of an angioplasty procedure, there is a price to pay, albeit a small one.

There are no existing studies that deal with the clinical sequelae of acute vessel occlusion during angioplasty that is reversed quickly during the course of the procedure. In our study, this particular event occurred in at least 11 (4%) of 249 ultimately successful elective procedures. Additional cases occurred in our patients in whom no enzyme release was documented. Therefore, this complication appears to be relatively frequent and deserves further study. The incidence of coronary spasm and thrombosis in this patient group is also similar to that previously reported.

Conclusion. Transient CK and CK MB isoenzyme release can occur frequently in patients who meet the most rigorous existing standards for coronary angioplasty success. In those cases where an actual event can be recognized to explain the enzyme release, a non-Q wave myocardial infarction probably occurred; in those cases where even a retrospective consideration fails to identify a cause, the precise meaning often remains uncertain. Although patient management and short-term prognosis are probably not directly altered, knowledge of the etiology of the event and coronary anatomy in conjunction with this information may be important.

References


