Original Studies

Incidence and Mechanism of Creatine Kinase-MB Enzyme Elevation After Coronary Intervention With Different Devices

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The present study was conducted to evaluate the incidence of CK-MB elevation and to identify the possible mechanisms of CK-MB release after various coronary interventional devices. We prospectively studied 1,675 consecutive patients following various coronary interventions for CK-MB elevation, from January 1997 to February 1998 and followed them for in-hospital events. CK-MB elevation was detected in 313 patients (18.7%); with 1–3 × normal in 12.8%, 3–5 × normal in 3.5%, and >5 × normal in 2.4%. CK-MB elevation was more common after nonballoon devices (19.5% vs. 11.5% after balloon angioplasty; P < 0.01). Among the newer nonballoon devices, rotational atherectomy alone had a lower CK-MB elevation compared to stent-alone group (16.0% vs. 20.5%; P = 0.07). On univariate analysis, due to selective use of abciximab in high-risk coronary interventions, there was higher incidence of CK-MB elevation with abciximab (24.5% vs. 15.0% without abciximab; P < 0.01). Some kind of procedural complication was observed in 49% of the CK-MB elevation group, with side-branch closure being the most frequent (22.7%). In conclusion, CK-MB elevation is common after successful coronary interventions and is higher after nonballoon devices. Cathet. Cardiovasc. Intervent. 48:123–129, 1999.

Key words: CK-MB isoenzyme; angioplasty; new devices; coronary intervention; abciximab

INTRODUCTION

Elevation of CK-MB isoenzymes can occur in 6%–30% of otherwise successful percutaneous coronary interventions [1–7]. Recent trials involving newer devices such as rotational atherectomy (PRCA), directional coronary atherectomy (DCA), and stents have shown a higher incidence of CK-MB release postprocedure compared to balloon angioplasty (PTCA) despite lower long-term cardiac events and target lesion revascularization (TLR) [8–10]. A stable and larger lumen attained after newer devices results in a lower TLR, which possibly is responsible for a lower late cardiac event despite higher CK-MB release during the intervention. Factors that have been postulated for CK-MB elevation postprocedure include transient vessel closure, slow flow, distal thromboembolism, side-branch closure, coronary spasm, hypotension, and prolonged ischemia caused by longer balloon inflations [11,12]. It is also not clear whether CK-MB release represents true myocardial necrosis or profound ischemic injury with retention of cell viability [4,13]. Several randomized trials have shown that platelet glycoprotein IIb/IIIa inhibitors by reducing platelet aggregation have led to a reduction in incidence of periprocedural myocardial infarction (MI) and other major ischemic complications of acute closure, emergency bypass surgery, or death [14]. The present prospective study was presented in part at the 9th annual symposium of Transcatheter Cardiovascular Therapeutics in Washington, October 1997, and the 47th annual scientific session of the American College of Cardiology in Atlanta, Georgia, March 1998.

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conducted with the following objectives: to evaluate the incidence of CK-MB elevation after various coronary interventional devices; to identify the possible mechanisms of CK-MB elevation after various devices; and to assess CK-MB elevation after selective use of abciximab in high-risk coronary lesions.

**MATERIALS AND METHODS**

**Patients**

All patients who underwent percutaneous coronary interventions at Mount Sinai Hospital, New York, between January 1997 and February 1998 were included in the study. Patients who had coronary intervention within 24 hr of an acute myocardial infarction (n = 82), urokinase infusion (n = 8), elevated preprocedure CK-MB (n = 16), incomplete CK-MB values (n = 32), and major complications (emergency bypass surgery, refractory acute closure, and death) occurring in the catheterization laboratory (n = 8) were excluded from the analysis. We studied 1,675 consecutive patients who had procedure, 6–8 hr and 16–24 hr postprocedure CK-MB values available for analysis.

**Protocol**

All patients had a baseline 12-lead electrocardiogram (EKG) within 24 hr prior to the procedure and blood sample was drawn from the arterial sheath for baseline total CPK and CK-MB values prior to intervention. During the interventional procedure, two noncontiguous EKG leads were continuously monitored for heart rate and ST-T wave changes. All procedures were carried out in a standard fashion and procedural complications such as coronary spasm, arterial dissection, thromboembolism, transient vessel closure, abrupt closure, slow flow, side-branch closure, prolonged hypotension (systolic blood pressure <80 mm Hg lasting for >5 min), prolonged balloon inflation (>5 min), and persistent chest pain (>30 min postprocedural) were recorded. Subsequently, blood samples were drawn at 6–8 hr and 16–24 hr postprocedural for cardiac enzymes, routine chemistry, and complete blood cell counts. A routine 12-lead EKG was performed after the procedure and on the following morning (for inpatients). In case of an adverse clinical event such as recurrent postprocedural chest pain requiring prolonged hospitalization, repeat blood tests and EKGs were performed on clinical grounds. Stable patients were discharged the following day.

CK-MB measurement was done using the Mass technique. Total CK was measured by a Hitachi 747 analyzer and CK-MB was measured by immunoinhibition using Johnson and Johnson Vitros 950 analyzer. If CK-MB was abnormal (absolute total ≥ 16 units or ≥ 10% of total CK), then it was further confirmed using enzyme mass immunoassay by Baxter Stratus-2 analyzer. Final CK-MB values of mass immunoassay were used for the analysis.

**Intervention**

Most of the coronary interventional procedures were done using the femoral route (98%). All patients received aspirin 325mg orally and a 70–100 U/kg intravenous bolus of heparin at the beginning of the procedure, followed by periodic intravenous boluses to keep the activated clotting time between 200–300 sec throughout the procedure with a trend toward lower values if abciximab was used. The devices for coronary interventions were as follows: PTCA in 10.4%, PRCA in 25.1%, stent in 28.5%, PRCA + stent in 31.9%, DCA ± stent 2.3%, transluminal extraction catheter (TEC) ± stent in 1.8%. All interventions were performed using conventional technique and the selection of a device was left to the operator’s discretion, with some consistency based on the lesion morphology: PRCA for calcified, ostial, long, diffuse, and in-stent restenotic lesions; DCA for noncalcified, ostial, and bifurcation lesions in vessels > 3.0 mm; TEC for thrombotic lesions. Stents were used in most coronary lesions (~65%) as primary device (28%) or after debulking (36%) and were rarely used as bailout device (<2%). PTCA only was used for treatment of in-stent restenosis and lesions in small vessels (<2.5 mm). Abciximab was used in 38.8% of cases, particularly in high-risk coronary interventions such as rest angina, postmyocardial infarction, multivessel intervention, staged procedure, thrombus containing lesions, saphenous vein graft lesion, ACC/AHA type C lesion, ostial lesions, heavily calcified and bifurcation lesions. In some cases, abciximab was used only after procedural complications were noted. The sheath was removed 3–6 hr after the intervention except in cases of recurrent chest pain or if staged procedure was planned for next day. Coronary interventions were classified as single vessel if the intervention was done in one coronary vessel distribution (including branches) or multivessel if the intervention was done in two or more coronary vessel distribution. Single-vessel intervention was done in 89% and multivessel interventions in 11% of the cases and of these, 9% were performed in saphenous vein grafts (SVG). Lesion length was measured visually or by on-line digital caliper.

**In-Hospital Course**

Clinically stable patients with normal CK-MB were discharged on the next day; on aspirin only following nonstent device use and on aspirin plus ticlopidine 250 mg twice daily for 4 weeks, if a stent was implanted. Patients with 1–5 × normal CK-MB elevation were discharged once levels started declining and were stable
clinically despite elevated CK-MB values. Patients with >5 × normal CK-MB elevation were kept in hospital and monitored for a longer period until CK-MB declined to baseline and clinical condition stabilized.

Definitions

CK-MB elevations are defined as: CK-MB < 16 units/liter = no elevation; CK-MB ≥ 16 U/L = any elevation; 16–48 U/L = 1–3 × normal; 49–80 U/L = 3–5 × normal; > 80 U/L = 5 × normal. Angiographic success is < 50% diameter obstruction postprocedure with ≥ TIMI II flow at end of procedure. Major complications are Q-wave myocardial infarction, emergent bypass surgery, or in-hospital death. Clinical success is angiographic success of at least one lesion and no major complications. Transient abrupt closure is reversible complete occlusion of the treated vessel anytime during the intervention. Acute closure is postprocedure out of the catheterization laboratory symptomatic occlusion of the treated vessel. Stent thrombosis is acute or subacute closure in the stented vessel within 4 weeks after stent deployment. Slow flow is delayed distal clearance of the dye in the absence of proximal dissection or spasm. Coronary dissection is coronary dissection graded from A to F according to the NHLBI classification and dissection grades A–C were considered minor and grades D–F were considered major. Distal thromboembolism is visible translucent filling defect or abrupt cutoff in the distal vessel. Coronary spasm is focal or diffuse narrowing of vessel without any evident coronary dissection. Side-branch closure is < TIMI III flow in a side branch of >1.0-mm diameter with normal flow preprocedure. Prolonged hypotension is systolic blood pressure < 80 mm Hg lasting for > 5 min. Prolonged balloon inflation is continuous balloon inflation of > 5 min. Persistent chest pain is chest pain lasting for > 30 min postprocedure.

Statistics

The data were entered in a Microsoft Excel database and transferred to the statistical program Stat View 4.1 for analysis. Results are presented as mean ± SD or n (%). Comparison between groups was done using Chi-square analysis and between continuous variables by using two tail Student’s t-test. Statistical significance was defined at the level of P < 0.05. In the multiple logistic regression analysis contribution of individual variables was achieved in a stepwise fashion and results were reported as odds ratio (OR) and 95% confidence interval (CI) with statistical significance at P < 0.05.

RESULTS

Of the 1,675 patients and 4,068 lesions, angiographic success was attained in 94.5% of lesions and clinical success in 96.3% cases with a very low incidence of major complications (0.72%). Any CK-MB elevation was noted in 313 of 1,675 patients (18.7%); with 1–3 × normal in 12.6%, 3–5 × normal in 3.7%, and >5× normal in 2.4%. Peak CK-MB elevation was observed at 6–8 hr in 69%, at 16–24 hr in 23%, and after 24 hr in 8% of the patients.

Clinical Characteristics

Mean age for the entire group was 65 ± 13 years with 31.6% being females. Two or more risk factors for coronary artery disease were present in 75.8% of cases. Other clinical characteristics were as follows: diabetes mellitus (24.9%), prior myocardial infarction (34.7%), CCS angina class III–IV (36.5%), prior interventions (23.1%), prior bypass surgery (15.3%), congestive heart failure (10.9%), multivessel disease (32.9%), abciximab use (38.8%).

Vessel Characteristics

The incidence of CK-MB elevation was 17.7% after single-vessel intervention (19% after LAD, 16.7% after LCX, 16.4% after RCA; P = NS), 20.2% after multivessel intervention, and 25.8% after SVG intervention (Fig. 1). The CK-MB release was not different between single-vessel intervention and multivessel intervention (17.7% vs. 20.2%; P = 0.2), but was higher after SVG interventions vs. native vessel interventions (25.8% vs. 17.9%; P = 0.01). There was no significant difference in the magnitude of CK-MB release in native vessel intervention vs. SVG intervention (Fig. 2).

Device Type

Incidence of CK-MB release and its magnitude after various interventional devices is shown in Figure 3. The
incidence was 11.5% after PTCA, 16% after PRCA,
20.5% after stent, 21% after PRCA + stent, 23% after
DCA ± stent, and 22.5% after TEC ± stent. PTCA had a
significantly lower incidence of CK-MB release com-
pared to non-balloon devices (11.5% vs. 19.5%; P <
0.01). On univariate analysis, PRCA alone had a slightly
lower incidence of CK-MB elevation compared to stent
alone (16% vs. 20.5%; P = 0.07), but on multivariate
analysis PRCA use was not associated with lower CK-MB
release (OR 1.04, 95% CI 0.92–1.26; P = NS). There
was no statistically significant difference in CK-MB
elevation after PTCA vs. PRCA (11.5% vs. 16%; P =
0.16). Stenting following PRCA was not associated with
higher CK-MB release compared to stenting alone (21%
vs. 20.5%; P = NS). On multivariate analysis stent use
remained a predictor of higher CK-MB release (OR 1.26,
95% CI 0.98–1.84; P = 0.04).

**CK-MB Elevation and Abciximab Use**

As shown in Figure 4, CK-MB release was higher in
patients with abciximab vs. without abciximab (24.5% vs.
15%; P < 0.001). This pattern of higher CK-MB
elevation after abciximab was observed after all different
devices and was highest after stent use and lowest after
PTCA. On multivariate analysis, abciximab use was not
associated with higher CK-MB release (OR 1.07, 95% CI
0.86–1.11; P = 0.1).

**Mechanism of CK-MB Elevation After Various
Devices**

Various minor and major procedural complications
following different devices were observed in 49% of the
CK-MB elevation cases, while in the remaining 51%,
CK-MB elevation occurred despite no evident procedural
event. In 32% of the cases, more than one procedural
complication was noted. As shown in Figure 5, CK-MB
elevation was usually minor (1–3 × normal) in patients
with no discernable procedural complications. Side-
branch closure was the most common (22.7%) procedural
complication responsible for CK-MB release, followed
by persistent/recurrent chest pain (10.2%), but both had a
relatively lower predictive value for CK-MB elevation;
43% and 28.6%, respectively. Some type of EKG changes
postprocedure were observed in 47.9% of patients with
CK-MB elevation with a predictive value of 63.6%.

The distribution of individual procedural events after
different devices is shown in Table 1. Following were the
frequently noted procedural events after different de-
vices: PTCA–side-branch closure, dissection, and pro-
longed balloon inflation; PRCA–slow flow, prolonged
hypotension; stent–side-branch closure, slow flow, persis-
tent chest pain; PRCA + stent–slow flow, transient abrupt
closure; DCA ± stent–spasm, side-branch closure, slow
### Discussion

Numerous studies have shown CK-MB isoenzyme to be more specific and sensitive for myocardial damage than total CK, both after myocardial infarction and coronary intervention [11,12,14]. In some cases, CK-MB elevation may occur due to balloon inflation, side-branch closure, prolonged ischemia, or termination of myocardial ischemia or cell viability [4,13]. The mechanism of CK-MB release after coronary intervention is multifactorial, such as transient abrupt vessel closure, dissection, spasm, slow flow, distal thromboembolization, side-branch closure, prolonged ischemia, or prolonged hypotension due to balloon inflation, or prolonged hypotension [2,11,12,15]. In some cases, CK-MB elevation may occur despite no discernible procedural events, the cause of CK-MB elevation could not be isolated, although elevation was mostly minor (1–3 × normal) in this group of patients.

#### Hospital Course

In-hospital cardiac events were clustered mostly in >5% normal CK-MB elevation group, requiring prolonged telemetry monitoring and longer hospital stay in other subgroups. The incidence of major complications was 0.72%.

#### Table I: Mechanism of CK-MB Elevation After Various Devices

<table>
<thead>
<tr>
<th>Procedural events</th>
<th>PTCA n = 174</th>
<th>PRCA n = 420</th>
<th>Stent n = 477</th>
<th>PRCA + stent n = 534</th>
<th>DCA n = 39</th>
<th>TEC n = 31</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[CKMB n = 20, NL CKMB n = 154]</td>
<td>[CKMB n = 67, NL CKMB n = 353]</td>
<td>[CKMB n = 98, NL CKMB n = 379]</td>
<td>[CKMB n = 112, NL CKMB n = 422]</td>
<td>[CKMB n = 9, NL CKMB n = 30]</td>
<td>[CKMB n = 7, NL CKMB n = 24]</td>
</tr>
<tr>
<td>Side-branch closure (%)</td>
<td>30</td>
<td>6.5</td>
<td>13.4</td>
<td>12.2</td>
<td>16</td>
<td>14.2</td>
</tr>
<tr>
<td>Persistent/recurrent chest pain (%)</td>
<td>25</td>
<td>1.9</td>
<td>6</td>
<td>2</td>
<td>11.6</td>
<td>33.3</td>
</tr>
<tr>
<td>Prolonged balloon inflation (%)</td>
<td>20</td>
<td>1</td>
<td>6.2</td>
<td>0.3</td>
<td>9.7</td>
<td>49</td>
</tr>
<tr>
<td>Dissection grades C-F (%)</td>
<td>15</td>
<td>3.2</td>
<td>1</td>
<td>0.8</td>
<td>4.5</td>
<td>14.2</td>
</tr>
<tr>
<td>Slow flow/no reflow (%)</td>
<td>5</td>
<td>0</td>
<td>7.6</td>
<td>5.1</td>
<td>5.3</td>
<td>28.5</td>
</tr>
<tr>
<td>Coronary spasm (%)</td>
<td>0</td>
<td>0.6</td>
<td>1</td>
<td>0.5</td>
<td>1.8</td>
<td>14.2</td>
</tr>
<tr>
<td>Transient abrupt closure (%)</td>
<td>5</td>
<td>0.6</td>
<td>3</td>
<td>0.6</td>
<td>4.5</td>
<td>28.5</td>
</tr>
<tr>
<td>Distal thromboembolism (%)</td>
<td>5</td>
<td>0</td>
<td>0.3</td>
<td>2</td>
<td>0.2</td>
<td>28.5</td>
</tr>
<tr>
<td>Delayed closure (%)</td>
<td>5</td>
<td>0.6</td>
<td>3</td>
<td>0.3</td>
<td>1.8</td>
<td>28.5</td>
</tr>
<tr>
<td>Prolonged hypotension (%)</td>
<td>0</td>
<td>0.6</td>
<td>4.5</td>
<td>0.6</td>
<td>1.8</td>
<td>28.5</td>
</tr>
<tr>
<td>Stent thrombosis (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.9</td>
<td>14.2</td>
</tr>
</tbody>
</table>

[CKMB = elevated CK-MB; NL CKMB = normal CK-MB.]
CK-MB Elevation After Various Devices

In our study, CK-MB elevation was seen in 18.7% of the cases, which is similar to the published data. Like other studies, CK-MB elevation was higher after nonballoon devices [16–19]. Cutlip et al. [9] from three randomized multicenter trials (BOAT, STARS, STRATAS) of new devices involving 3,387 patients, reported higher CK-MB release after nonballoon devices, but observed the lack of association of CK-MB elevation and mortality at a mean follow-up of 15 ± 5 months. The lack of correlation of CK-MB elevation with mortality after new device intervention despite its higher incidence may be explained on the basis of a stable large lumen achieved, resulting in lower in-hospital events and possible lower repeat revascularization. This is also in accordance with studies reporting that a large postprocedure lumen independently correlates with better prognosis [16,18]. Traditionally PRCA has been implicated with higher CK-MB elevation postprocedure [16,17]. Technical advances like slow burr advancement, short ablation runs, multiple burr approach, and avoidance of hypotension during ablation have been attributed to lower CK-MB release, which was observed in our study [20]. Our center performs PRCA in a high percentage of interventions (~50%) and CK-MB elevation after PRCA (by univariate analysis only) was slightly higher than PTCA but lower than stent alone [19].

CK-MB and Abciximab Use

In the randomized trials [14], use of glycoprotein IIb/IIIa inhibitors during coronary intervention have been shown to reduce CK-MB elevation. In the present study, this beneficial effect of abciximab was not observed perhaps due to the selective use of abciximab in complex coronary lesions and high-risk clinical states like rest angina and postmyocardial infarction. However, on multivariate analysis in the present study, abciximab use was not associated with higher CK-MB release [19].

Mechanism of CK-MB Elevation After Different Devices

Individual interventional devices can cause CK-MB elevation from one or more specific procedural complications [8,10,12,21–24]. Side-branch closure and persistent/recurrent chest pain were the two most frequent procedural complications noted in patients with CK-MB elevation, but with a relatively lower predictive value. Side-branch closure was higher after PTCA and stent placement, coronary dissection was higher after PTCA, and slow flow was higher after PRCA, DCA, and TEC. Distal thromboembolism was the most frequent mechanism responsible for CK-MB elevation after DCA and TEC. To our knowledge, the present study has reported for the first time the occurrence of various procedural events after different interventional devices in a large cohort of patients.

Study Limitations

The present study needs to be interpreted with the following limitations. Only two CK-MB values were routinely measured postprocedure and it is possible that in some cases CK-MB might be elevated after 24 hr of interventions. Any perfusion or physiological flow studies were not performed to rule out microembolization during intervention. Patients were grouped according to the final interventional device used but it may be possible that adjunct balloon dilatation (pre- or post-) might be responsible for CK-MB release rather than the nonballoon device, but individual contribution cannot be measured. Operator’s skill and technical expertise was not taken into account in the present study, but one operator (SS) performed ~58% of the interventions. Troponin, a more sensitive marker of myocardial necrosis, was not measured in the present study because of its unavailability at our center until July 1998 [24].

The present study reveals that CK-MB elevation occurs commonly after otherwise successful coronary interventions and is higher after nonballoon devices compared to PTCA. Procedural events were encountered in only half of the cases with CK-MB elevation and side-branch closure was the most frequent procedural complication. In a nonrandomized setting, like the present study, where abciximab was used only in complex or high-risk cases, on univariate analysis abciximab use was not associated with lower CK-MB release. The impact of higher CK-MB elevation after nonballoon devices on long-term mortality needs to be determined by continued follow-up, which is ongoing.

REFERENCES