Creatine Kinase-MB Enzyme Elevation Following Successful Saphenous Vein Graft Intervention Is Associated With Late Mortality

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Background—Although the risk for development of creatine kinase (CK-MB) elevation after saphenous vein graft (SVG) intervention is high, its prognostic significance remains unknown. This study evaluated the impact of periprocedural CK-MB elevation on late clinical events following successful SVG angioplasty.

Methods and Results—We studied 1056 consecutive patients with successful (defined by angiographic success and absence of major complications) intervention of 1693 SVG lesions. These patients were grouped as normal CK-MB (n=556), minor CK-MB rise (CK-MB 1 to 5 times normal, n=339), and major CK-MB rise (CK-MB >5 times normal, n=161). There were no differences in major clinical events at 30-day follow-up among the 3 groups. However, 1-year mortality was 4.8%, 6.5%, and 11.7%, respectively, P<0.05 (ANOVA). Even within a population without any intraprocedure or in-hospital complications (n=727, 69% of the overall cohort), 1-year mortality remained significantly higher with CK-MB elevation: 2.4%, 5.5%, and 10.7%, respectively, P<0.05 (ANOVA). Multivariate analysis revealed major CK-MB elevation as the strongest independent predictor of late mortality (odds ratio 3.3, with 95% CI 1.7 to 6.2), followed by diabetes mellitus (odds ratio 2.6, with 95% CI 1.5 to 4.5).

Conclusions—Major CK-MB elevation occurs after 15% of otherwise successful SVG interventions and is associated with increased late mortality. (Circulation. 1999;100:2400-2405.)

Key Words: angioplasty ■ stents ■ myocardial infarction ■ creatine kinase

In native coronary arteries, there are conflicting reports regarding the prognostic significance of creatine kinase-MB fraction (CK-MB) elevation following a successful angioplasty procedure. Although initial studies confined to balloon angioplasty showed no correlation between the CK-MB elevation and subsequent in-hospital or late adverse events,1,2 more recent studies in the era of new device angioplasty3 suggest that major or even minor CK-MB elevation is associated with late adverse events.4–8 The risk of developing CK-MB elevation is higher during saphenous vein graft (SVG) than native coronary intervention,7 mainly due to more friable atherosclerotic or thrombotic components of the SVG lesions. However, the impact of periprocedural CK-MB elevations on late clinical events following successful SVG angioplasty is unknown.

The present study evaluated the long-term clinical significance of CK-MB elevation following an elective, successful SVG intervention (angiographically successful and free of major in-hospital complications). Furthermore, to exclude the possibility that CK-MB elevation merely reflects a complicated interventional procedure, we also determined the prognostic significance of isolated CK-MB elevations in the absence of any procedural or in-hospital ischemic complications.

Methods

The overall patient population (Overall) included 1056 consecutive patients, with 1693 SVG lesions, who underwent successful elective SVG intervention between 1991 and 1996 at the Washington Hospital Center. Procedural success was defined as final diameter stenosis of <50% in the absence of in-hospital death, Q-wave myocardial infarction, or emergency coronary artery bypass surgery. Thus, patients were excluded from this study (<5% of the SVG intervention population) if they had acute myocardial infarction within 72 hours or abnormal CK-MB value before intervention, cardiogenic shock, unsuccessful procedure, in-hospital death, Q-wave myocardial infarction, or emergency coronary artery bypass surgery.

From the Overall patient population, we identified a subset of 727 patients (68.8% of Overall) with 1082 lesions (63.9% of Overall) who had no intraprocedural angiographic complications (defined as any evidence of distal embolization, postprocedural intragraft thrombus, final Thrombolysis In Myocardial Infarction [TIMI] flow-grade <3, or no reflow) or in-hospital nonmajor clinical complications (defined as any electrocardiographic evidence of recurrent ischemia, abrupt closure, emergency intra-aortic balloon pump insertion, or...
repeat intervention of the treatment site). This patient subset comprised the no-complication (Nocomp) population and was used to determine the clinical significance of isolated CK-MB elevation following an otherwise truly uncomplicated SVG intervention.

Baseline demographic and procedural variables were recorded and entered prospectively in a prespecified database by a dedicated data coordinating center. All patients were serially interviewed by experienced research nurses at 1, 3, 6, and 12 months after their procedure, and yearly thereafter. The patients were questioned regarding the occurrence of cardiac events or the need for repeat coronary revascularization. The cause of death and any cardiac event were source-documented and adjudicated.

**CK-MB Determinations and Classification**

CK-MB values were measured by radioimmunoassay (mass determination method) and measured before angioplasty at 6 and 24 hours after intervention. If any values were elevated, repeat measurements were made every 8 hours until the peak value was reached and the values decreased to normal (defined as <4 mg/dL by our laboratory). For this study, only the peak CK-MB values were used.

Patients were divided into 3 groups according to the level of peak CK-MB elevation: normal CK-MB (peak CK-MB <4 ng/mL), minor CK-MB rise (peak CK-MB >1 and <5 times the upper normal limit), and major CK-MB rise (peak CK-MB >5 times the upper normal limit).

**Quantitative and Qualitative Angiographic Analysis**

All cineangiograms at baseline and following angioplasty were analyzed in blinded manner with regard to the CK-MB levels or late outcome using the previously published definitions of the qualitative assessment of the lesions. The quantitative analysis was performed using an automated edge-detection algorithm (CMS, MEDIS) in the projection showing the most severe stenosis in unforeshortened view, using the contrast-filled guiding catheter as the reference standard.

**Statistics**

Statistical analyses were performed using the SAS statistical software (SAS Institute). Continuous variables are presented as mean±1 SD and categorical variables as percentages. One-way ANOVA was used to determine differences among the 3 groups; separate analyses were conducted within the Overall and within the Nocomp populations. Clinical, morphological, and procedural variables that had demonstrated statistically significant difference among the 3 groups were included in the multivariate logistic regression model to identify the independent predictors of major CK-MB elevation and late mortality. P<0.05 was considered significant.

**Results**

In the Overall population, there were 556 patients with normal CK-MB levels (52.7%), 339 patients with minor CK-MB rise (32.1%), and 161 patients with major CK-MB rise (15.2%). There were no differences among the groups at baseline except for significantly older patients, greater SVG age, and less diabetes in the CK-MB elevation groups (Table 1).

In the Nocomp population (ie, without any procedural or in-hospital nonmajor complications), normal CK-MB was present in 447 patients (61.5%), minor CK-MB rise in 224 patients (30.8%), and major CK-MB rise in 56 patients (7.7%). Among these 3 groups, there were no significant differences in baseline characteristics, except for significantly greater SVG age in the CK-MB elevation groups (Table 1).

**Angiographic Findings**

In the Overall population, we found significantly more eccentric lesions, more degenerated SVGs, and less ostial lesions in patients with CK-MB elevation (Table 2). The CK-MB elevation groups also tended to have greater prevalence of intragraft thrombus before intervention. Intragraft thrombus, distal embolization, intraprocedure transient abrupt closure, and final TIMI flow <3 were also associated with CK-MB elevation. Approximately 55% of the patients had been treated with stents.

Within the Nocomp population, the CK-MB elevation groups had significantly more degenerated SVGs than patients with normal CK-MB. Otherwise, the baseline lesion characteristics were not significantly different among the groups. By definition (see Methods), these patients did not have evidence of any angiographic complications during the intervention.

**In-Hospital Outcome**

By definition, all patients included in this study had a successful SVG intervention and no major in-hospital ischemic complications (ie, death, Q-wave myocardial infarction or emergent revascularization). However, in the Overall population there were significantly greater in-hospital complications in the CK-MB elevation groups, including significantly higher incidence of repeat intervention, emergency intra-aortic balloon pump insertion, and abrupt closure after...
the intervention (Table 3). All patients with any of these nonmajor in-hospital complications were excluded from the Nocomp study population (see Methods).

Late Clinical Outcome
At 30 days after the procedure, the overall event rates were very low (0.3% to 0.6%) and did not differ among the groups (Table 4). At 1 year, the mortality rate was significantly higher in the CK-MB elevation groups, with incremental rise in late mortality associated with higher CK-MB elevation. This significantly higher mortality with CK-MB elevation was documented even in Nocomp population. On the other hand, the overall cardiac event rates were similar among the 3 groups, including Q-wave myocardial infarction and repeat bypass surgery.

Target lesion revascularization was low (5% to 11%) in all groups in the Overall population. In the Overall population, repeat percutaneous intervention at the target lesion occurred significantly less frequently with CK-MB elevation, in contrast to late mortality. In the Nocomp group, there was no significant difference in the target lesion revascularization rate.

Multivariate Analysis
In the Overall population, independent predictors of late mortality included major CK-MB elevation (the strongest predictor: odds ratio of 3.3, 95% CI 1.7 to 6.2), and diabetes mellitus (Table 5). The reference vessel diameter was the only variable inversely associated with late mortality (the greater the reference vessel diameter, the lower the late mortality rate). Similarly, major CK-MB elevation was also a significant independent predictor of late mortality in the Nocomp population. None of the other baseline demographic or lesion characteristics were predictive of late mortality.

Independent predictors of major CK-MB elevation in the Overall patients included procedural distal embolization and lesion eccentricity (Table 5).

Cause of Late Death
The majority of late deaths (63% to 74%) was due to cardiac etiology, ranging from sudden out-of-hospital death to uncompensated congestive heart failure; this pattern did not differ among the 3 groups. The distribution of the various causes of noncardiac deaths was also similar among the groups (Table 6).

Discussion
This study demonstrates that following an otherwise successful SVG intervention, major CK-MB elevation (defined as >5 times the normal range) occurred in 15% of cases and was associated with significantly increased late cardiac mortality.
Even after excluding patients with any procedural or inhospital complications, CK-MB elevation was still an independent predictor of late mortality.

**Previous CK-MB Studies**

Previous studies evaluating the prognostic significance of CK-MB elevation following angioplasty have been mainly in the native coronary arteries.1–8 These studies have reported no late adverse sequelae from CK-MB elevation in smaller series confined to balloon angioplasty,1–2 but larger series, especially those including new device angioplasty, have shown unfavorable long-term outcome in those patients experiencing CK-MB elevations.3–8 Previous studies also suggest that the prognostic significance of minor CK-MB elevation may depend on the particular device used, with atheroablative devices resulting in unfavorable long-term outcome.5,6

There has been no large series evaluating this important issue in SVG intervention. Most studies included mainly patients undergoing native coronary interventions and only a small fraction of patients undergoing SVG angioplasty, ranging from <2% to 30%.2,3,5–8 Because of the small percentage of SVG intervention patients in these studies, it is difficult to separate the contribution of CK-MB elevation following SVG intervention on in-hospital or long-term outcome. One study with <10% SVG patients showed that angioplasty of SVG lesions is associated with greater incidence of CK-MB elevation compared with those undergoing native coronary angioplasty.7

The only study consisting exclusively of SVG angioplasty patients is a subgroup analysis of the EPIC trial,10 comprising only 101 patients with SVG (29 placebo, 34 abciximab bolus only, 38 abciximab bolus plus infusion). The results showed that abciximab bolus plus infusion significantly reduced distal embolization (2% versus 18%, P<0.05) and also tended to reduce non-Q–wave myocardial infarctions (2% versus 12%, P=0.165) compared with placebo. The lack of significant differences in the composite cardiac endpoints at 30 days and 6 months was attributed to fact that this subgroup analysis was underpowered for clinical outcome analysis because of the small sample size.

**TABLE 5. Independent Predictors of Late Mortality and Major CK-MB Elevation (Multivariate Analysis)**

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall population</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK-MB &gt;5×normal</td>
<td>3.3</td>
<td>1.7–6.2</td>
<td>0.0003</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.6</td>
<td>1.5–4.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Reference diameter</td>
<td>0.7</td>
<td>0.4–0.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Nocomp population</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK-MB &gt;5×normal</td>
<td>4.2</td>
<td>1.2–14.3</td>
<td>0.02</td>
</tr>
<tr>
<td>History of MI</td>
<td>5.7</td>
<td>1.3–26.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Major CK-MB elevation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal embolization</td>
<td>4.4</td>
<td>1.9–10.1</td>
<td>0.0006</td>
</tr>
<tr>
<td>Eccentric lesion</td>
<td>1.7</td>
<td>1.1–2.7</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**TABLE 6. Cause of Late Death in the Overall Population**

<table>
<thead>
<tr>
<th></th>
<th>Normal CK-MB (n=31)</th>
<th>Minor CK-MB Rise (n=24)</th>
<th>Major CK-MB Rise (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac, %</td>
<td>74</td>
<td>63</td>
<td>70</td>
</tr>
<tr>
<td>Pulmonary, %</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Renal, %</td>
<td>6</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Cancer, %</td>
<td>6</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Other noncardiac, %</td>
<td>8</td>
<td>16</td>
<td>20</td>
</tr>
</tbody>
</table>

No comparison was statistically significant.
A recent review by Adgey et al. addressed the fact that postprocedural elevation of cardiac injury markers portended unfavorable late prognosis. The study by Kugelmass et al., which included ≈30% SVG procedures, showed that only major CK-MB elevation (≥5 times normal) was associated with a trend toward decreased late survival. This result is consistent with our finding. Another interesting finding from this study was that SVG angioplasty and multivessel disease, but not the major CK-MB elevation, were independent predictors of late mortality. The number of patients with SVG angioplasty was not large enough to allow separate evaluation of the prognostic significance of CK-MB elevations in this specific group.

Potential Explanations of Increased Late Mortality Associated With CK-MB Elevation

It is important to emphasize that there has been no confirmation of the cause and effect relationship between CK-MB elevation and late mortality. Despite many hypotheses and likely explanations, the mechanism(s) of this association remains unknown, and it is possible that a “common ancestor” may exist, ie, the reason for CK-MB elevation may also cause late mortality.

First, it is possible that the patients with CK-MB elevation have more procedural and in-hospital complications and the poor prognosis is due to the latter. Indeed, in the Overall population in the present study, distal embolization during SVG intervention was a predictor of CK-MB elevation. However, in the analysis of the subset without any procedural or in-hospital complications (Nocomp group), major CK-MB elevation was still an independent predictor of late mortality, ie, regardless of procedural risk and the target lesion-related complications.

Another theoretical possibility might be that the late mortality is mostly noncardiac, unrelated to the coronary artery disease. However, majority of the mortalities (≈70%) was cardiac in origin and did not differ among the groups, similar to previous studies.5,11

It is conceivable that CK-MB elevation may be associated with micro-infarctions, predisposing to foci of malignant ventricular arrhythmias. Although these patients as a group did not experience any sustained arrhythmia in the hospital and 30-day event rate was markedly low, many of the late deaths occurred suddenly out of the hospital. These late follow-up findings support the possibility that malignant arrhythmias from the microinfarctions and reentrant circuits may be responsible for late mortality.

An intriguing finding of the present study, different from previous studies, is that although the late mortality was significantly higher in the CK-MB elevation groups, this was accompanied by significantly lower target lesion revascularization, especially with respect to the need for repeat percutaneous intervention. An explanation might be that late mortality might have precluded repeat revascularization; ie, had the patients survived, they might have declared the need for target lesion revascularization. It is also possible that recurrent regional myocardial ischemia may be more frequently clinically overt in patients with decreased regional myocardial necrosis (ie, with minor or no CK-MB elevation).

Alternatively, there may be a relationship between pathogenesis of CK-MB elevation-related late mortality and accelerated atherothrombosis (possibly total occlusion) in the treated SVG. It is tempting to hypothesize that the CK-MB elevation may be due to distal embolization, which may also cause microcirculation abnormality and relative outflow obstruction.10 Because outflow obstruction may predispose to SVG thrombosis, patients with CK-MB elevation may have more frequent sudden thrombotic SVG occlusion (manifesting a sudden death). In contrast, patients without CK-MB elevation may experience accelerated angina due to progressively worsening stenosis as the recurrent presentation rather than SVG thrombosis.

Finally, there may be no causal relationship between CK-MB rise and late mortality, as they may both be markers of more severe underlying atherosclerotic disease.

Clinical Implications and Future Directions

The results of the present study suggest that avoidance of major CK-MB elevation during SVG angioplasty is desirable. There have been many attempts to reduce procedural complications during SVG interventions, including ablative and thrombectomy devices, and potent antiplatelet agents,10 thus far with debatable efficacy. Novel catheter-based systems may more effectively achieve distal emboli containment, whereas the beneficial effect of platelet glycoprotein IIb/IIIa inhibitors needs to be confirmed in a larger study.10 Furthermore, as arrhythmia appears to be a reasonable explanation for the mechanism of late mortality, β-blocker therapy in patients with documented periprocedural CK-MB elevation is worthy of further investigation.12

Limitations

The main limitation of this study is the retrospective methodology. However, chart review, data entry, and event adjudication were independently performed according to prespecified criteria of the data coordinating center. The definition of major CK-MB rise as >5 times normal was a prespecified definition of the data coordinating center. We did not include patients who had unsuccessful procedures or major in-hospital complications because both these events are associated with both CK-MB elevation and poor late outcome. Despite our effort, it was impossible to eliminate all potential confounding factors, and we cannot, therefore, reach the conclusion that the association of CK-MB with mortality is causal.

Conclusions

We documented major CK-MB elevation in 15% of otherwise successful SVG interventions and showed an independent association of CK-MB elevation with distal embolization during the intervention and with significantly increased late mortality.

Acknowledgment

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References


*JAMA.* 1997;277:461–466.


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