

Relationship of creatine kinase-myocardial band release to Thrombolysis in Myocardial Infarction perfusion grade after intracoronary stent placement: An ESPRIT substudy

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Background The etiology of creatine kinase-myocardial band (CK-MB) release after percutaneous coronary intervention (PCI) remains unclear. The goal of this study was to evaluate the relationship of both epicardial and tissue level perfusion at the completion of stent placement to CK-MB release after the procedure. Given the high rates of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow after PCI, we hypothesized that abnormalities in tissue level perfusion would instead explain CK-MB release.

Methods Data were drawn from the angiographic substudy of the Enhanced Suppression of the Platelet IIb/IIIa Receptor With Integrilin Therapy (ESPRIT) trial of eptifibatid versus placebo in patients undergoing planned coronary stent implantation. In the substudy, cinefilms of 65 patients were analyzed by an angiographic core laboratory blinded to enzymatic and clinical outcomes.

Results The release of CK-MB was not associated with TIMI grade 3 flow or the corrected TIMI frame count; 100% of patients had TIMI grade 3 flow at the completion of PCI. In contrast, tissue level perfusion using the TIMI myocardial perfusion grade (TMPG) was related to postintervention CK-MB release: patients with a closed myocardium (TMPG 0/1) or delayed myocardial perfusion (TMPG 2) had an average CK-MB release 2.2 ± 2.7 times the upper limit of normal ($n = 34$), whereas those patients with normal myocardial perfusion (TMPG 3, $n = 24$) had CK-MB 0.8 ± 0.6 times the upper limit of normal ($P = .01$). Although no patients with TMPG 3 sustained death/myocardial infarction/urgent target vessel revascularization or thrombotic bailout, 17.7% of patients with TMPG 0/1/2 did by 48 hours ($P = .037$).

Conclusions Impaired tissue level perfusion as assessed by the TMPG and not epicardial coronary blood flow is associated with CK-MB elevation after PCI. These data provide a pathophysiologic link between impaired tissue level perfusion, post-PCI infarction, and adverse clinical outcomes. (*Am Heart J* 2002;143:106-10.)

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Although there is evidence that periprocedural myocardial infarction after percutaneous coronary intervention (PCI) is associated with a worse long-term prognosis,^{1,2} the etiology of creatine kinase-myocardial band (CK-MB) elevations after PCI remains unclear. Although stenting improves epicardial large-vessel lumen diameters, this procedure may be detrimental to the microcirculation as a result of downstream embolization, release of vasospastic agents,³ or neural-mediated vasospasm.⁴ The goal of this study was to evaluate the relationship of both epicardial and tissue level perfusion at the completion of PCI to CK-MB release after the procedure. Given the high rates of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow after PCI, we hypothesized that

Table I. Baseline characteristics by maximum CK-MB elevation >1 times the upper limit of normal

	CK-MB >1 × ULN	CK-MB ≤1 × ULN	P value
No. of patients	27	38	
Age (y)	62.0 ± 11.4	58.8 ± 11.0	NS
Sex (% male)	77.8	76.3	NS
Weight (kg)	83.6 ± 16.8	90.8 ± 15.3	.077
History of myocardial infarction (%)	48.1	34.2	NS
Previous PCI (%)	11.1	15.8	NS
History of diabetes (%)	25.9	23.7	NS
History of hypertension (%)	63.0	63.2	NS
History of smoking (%)	77.8	60.5	.143
Baseline CK-MB/ULN ratio	0.79 ± 1.59	0.33 ± 0.25	.087
Primary diseased vessel left anterior descending artery (%)	48.2	31.6	.176
Pre-PCI CTFC (frames)	43.3 ± 31.7	38.1 ± 33.1	NS
Pre-PCI TMPG 3 (%)	33.3	42.9	NS

ULN, Upper limit of normal; NS, not significant.

abnormalities in tissue level perfusion rather than epicardial perfusion might explain CK-MB release in patients in the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial.⁵

Methods

The ESPRIT trial was a double-blind, multicenter, randomized, parallel-group, placebo-controlled trial of planned, nonurgent stenting of native coronary arteries in 2064 patients. The details of the trial have been described elsewhere.⁵ In brief, patients were allocated in a 1:1 ratio to either eptifibatid or placebo immediately before planned percutaneous coronary stent implantation. Eptifibatid was administered as a 180 mg/kg bolus followed by a 2.0 mg/kg/min infusion for 18 to 24 hours, with a second 180 mg/kg bolus given 10 minutes after the first. Follow-up was obtained at 48 hours, 7 days, 30 days, and 1 year. An angiographic substudy was conducted at 3 sites that enrolled 65 patients to assess angiographic results at the completion of the intervention and to serve as the subject of this report. CK-MB was sampled every 6 hours for the first 24 hours, and the blood specimens were analyzed by a central core laboratory (Covance). The upper limit of normal was defined by the central core laboratory as 4.9 ng/mL. A periprocedural enzymatic myocardial infarction was defined as 2 values of CK-MB >3 times the upper limit of normal.

An angiographic core laboratory blinded to study assignment and outcomes analyzed the films of the 65 patients. The TIMI flow grade was assessed as described previously.⁶ The corrected TIMI frame count (CTFC), the number of cine-frames required for contrast to first reach standardized distal coronary landmarks in the culprit artery, was measured with use of a frame counter on a cineviewer.^{7,8} Tissue level perfusion on the angiogram, also known as the myocardial blush, was assessed visually by use of the TIMI myocardial perfusion grade (TMPG) as previously defined.⁹ In brief, in TIMI myocardial perfusion grade 0, there is minimal or no myocardial blush; in TIMI myocardial perfusion grade 1, dye stains the

myocardium and this stain persists on the next injection; in TIMI myocardial perfusion grade 2 dye enters the myocardium but washed out slowly so that dye is strongly persistent at the end of the injection; and in TIMI myocardial perfusion grade 3 there is normal entrance and exit of dye in the myocardium so that dye is mildly persistent at the end of the injection.

Analyses were performed with use of Stata statistical software version 6.0.¹⁰ Variables were compared with use of the Fisher exact test or the χ^2 test for categorical data and the Student *t* test or Wilcoxon rank-sum test for continuous variables. Data are summarized as mean ± SD.

Results

Baseline characteristics

There were no significant differences in baseline characteristics between patients with a post-PCI CK-MB greater than the upper limit of normal and those with a post-PCI CK-MB less than or equal to the upper limit of normal (Table I). Weight trended lower (*P* = .077) and baseline CK-MB (before PCI) trended higher (*P* = .087) in patients whose peak CK-MB became greater than the upper limit of normal after PCI.

There were also no significant differences in baseline characteristics among patients with TMPG 3 compared with those with TMPG 0/1/2 (Table II). Patients with TMPG 3 trended to be younger (*P* = .15), to more frequently have a history of hypertension (*P* = .066), and to less frequently smoke (*P* = .066).

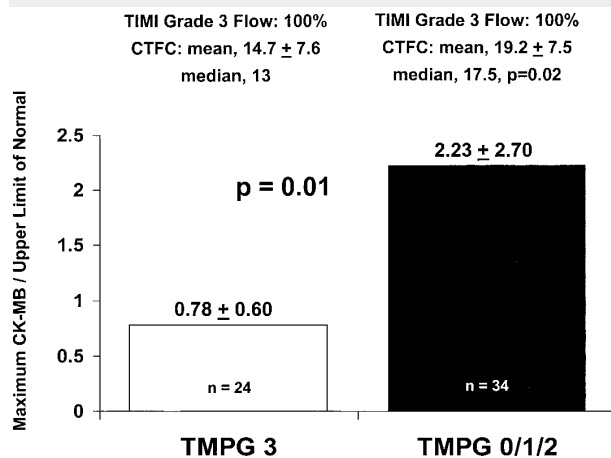
Maximum post-PCI CK-MB and TMPG

The release of CK-MB was not explained by TIMI grade 3 flow because 100% of patients had TIMI grade 3 flow at the completion of PCI. In contrast, tissue level perfusion with use of the TMPG was related to postintervention CK-MB release: patients with a closed myocardium (TMPG 0/1) or delayed myocardial perfusion (TMPG 2) had an average CK-MB release 2.2 ± 2.7

Table II. Baseline characteristics by TMPG

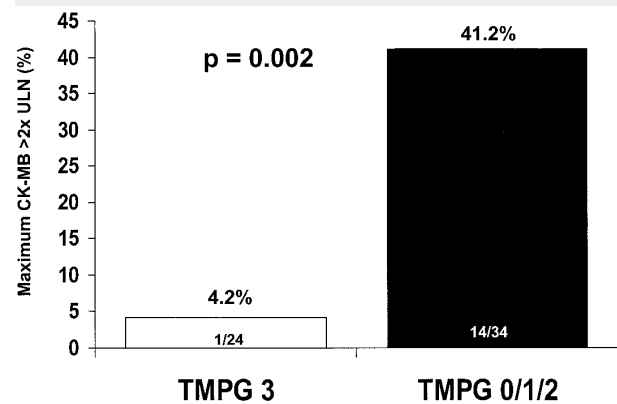
	TMPG 3	TMPG 0-2	P value
No. of patients	24	34	
Age (y)	57.6 ± 12.6	62.1 ± 10.3	.15
Sex (% male)	70.8	82.4	NS
Weight (kg)	88.4 ± 16.1	88.4 ± 16.8	NS
History of myocardial infarction (%)	33.3	47.1	NS
Previous PCI (%)	16.7	8.8	NS
History of diabetes (%)	29.2	26.5	NS
History of hypertension (%)	79.2	55.9	.066
History of smoking (%)	50.0	73.5	.066
Primary diseased vessel left anterior descending artery (%)	41.7	38.2	NS

NS, Not significant.

Figure 1

TMPG and maximum CK-MB 24 hours after stenting. The release of CK-MB was not explained by TIMI grade 3 flow because 100% of patients had TIMI grade 3 flow at the completion of PCI. In contrast, tissue level perfusion with use of the TMPG was related to postintervention CK-MB release: patients with a closed myocardium (TMPG 0/1) or delayed myocardial perfusion (TMPG 2) had an average CK-MB release 2.2 ± 2.7 times the upper limit of normal (ULN) (n = 34), whereas those patients with normal myocardial perfusion (TMPG 3, n = 24) had a CK-MB 0.8 ± 0.6 times the upper limit of normal (P = .01).

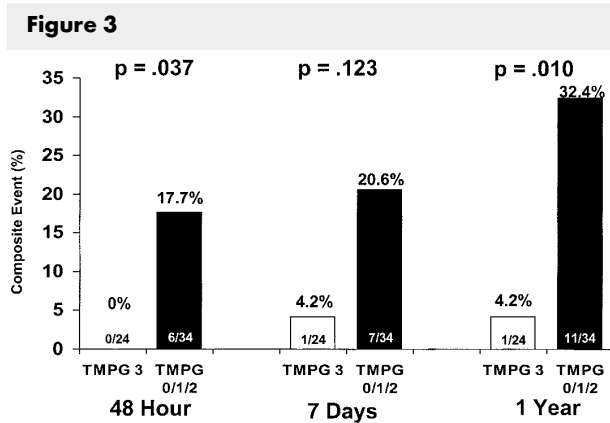
times the upper limit of normal (n = 34), whereas those patients with normal myocardial perfusion (TMPG 3, n = 24) had a CK-MB only 0.8 ± 0.6 times the upper limit of normal (P = .01) (Figure 1). Only 4.2% of patients with post-PCI TMPG 3 had a CK-MB leak >2 times the upper limit of normal compared with 41.2% of patients with TMPG 0/1/2 (P = .002) (Figure 2). In a multivariable regression model adjusting for treatment group and baseline CK-MB, normal myocardial perfusion (TMPG 3) was related to lower peak CK-MB

Figure 2

TMPG and maximum CK-MB 24 hours after stent placement. Among patients with post-PCI TMPG 3, only 4.2% had CK-MB leak >2 times the upper limit of normal (ULN) compared with 41.2% of patients with TMPG 0/1/2 (P = .002).

release (P = .016). Likewise, the rise in CK-MB from baseline to post-PCI was reduced among patients with TMPG 3 at the completion of PCI (0.37 ± 0.67, n = 24 vs TMPG 0-2 = 1.63 ± 2.77, n = 33, P = .034). Although there was no direct correlation between the CTFC after stent placement and CK-MB release, it is notable that the poststent CTFC was lower (ie, flow was faster) among patients with TMPG 3 after stent placement (13 vs 17.5, P = .02, Figure 1). In a multivariable regression model, TMPG 3 remained independently associated with poststent CK-MB release after correcting for the TIMI frame count.

A total of 3 of 64 (4.7%) patients sustained loss of a sidebranch after stent placement, and the peak CK-MB was higher among those patients with loss of a sidebranch (4.97 ± 6.93, n = 3, vs 1.36 ± 1.60, n = 61, P = .003). Even when patients with sidebranch occlusion



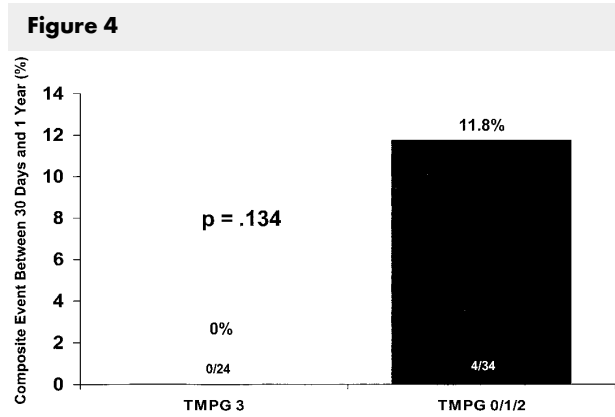
TMPG after stent placement and composite event by 48 hours, 7 days, and 1 year. Although no patients with TMPG 3 sustained death, myocardial infarction, urgent target vessel revascularization, or thrombotic bailout, 17.7% of patients with TMPG 0/1/2 did by 48 hours ($P = .037$). Similarly, there was only 1 event by 7 days and 30 days (4.2% vs 20.6%, $P = .123$). At 1 year follow-up, the event rate in the TMPG 3 group was 4.2% vs 32.4% in the TMPG 0/1/2 group ($P = .010$).

were excluded from the analysis, TMPG 3 was associated with a lower release of CK-MB (0.76 ± 0.57 , $n = 22$, vs 1.91 ± 1.96 , $n = 33$, $P = .01$).

Although no patients with TMPG 3 sustained death, MI, urgent target vessel revascularization, or thrombotic bailout, 17.7% of patients with TMPG 0/1/2 had a composite event by 48 hours ($P = .037$). The majority of these events were myocardial infarctions (0% vs 14.7%, $P = .07$). Similarly, there was only 1 subsequent event by 7 days and 30 days in the TMPG 3 group (4.2% vs 20.6% at 7 and 30 days, $P = .123$) (Figure 3). At 1-year follow-up, there were no additional events in the TMPG 3 group (new events from 30 days to 1 year 0% vs 11.8%, $P = .134$; total events by 1 year 4.2% vs 32.4%, $P = .010$, Figures 3 and 4).

Discussion

Previously we have demonstrated that in the acute myocardial infarction setting not all TIMI grade 3 flow is created equally: the achievement of TIMI grade 3 flow with a persistently closed microvasculature is associated with a 5.4% mortality, whereas there is a >7-fold reduction in mortality to 0.7% if the microvasculature is also open (ie, TMPG 3 flow is present).⁹ Although the sample size for patients with angiographic data in the ESPRIT trial was small, several important observations were seen between CK-MB and TMPG. In this study, although all patients had epicardial TIMI grade 3 flow at the completion of the intervention, a closed or delayed



TMPG after stent placement and late composite events (30 days to 1 year). There were no additional events between 30-day follow-up and 1 year among patients with TMPG 3; however, 11.8% of patients with TMPG 0/1/2 had an event between 30 days and 1 year ($P = .134$).

microvasculature was associated with a mean CK release over 2 times the upper limit of normal, whereas normal tissue level perfusion was associated with the absence of a significant CK-MB release. This finding was true even after adjustments were made for any imbalances in the baseline CK-MB levels and epicardial flow. Although all patients had TIMI grade 3 flow, it is notable that the poststent CTFC was lower (ie, flow was faster) among patients with TMPG 3 after stent placement, and, as such, the CTFC may provide an indirect assessment of microvascular perfusion. Thus abnormalities in tissue level perfusion rather than epicardial artery perfusion appear to explain the release of CK-MB after PCI.

Although intracoronary stenting may improve the angiographic appearance and diameter of the lumen and may restore epicardial flow to normal in many cases, there is concern that intracoronary stenting may displace both microembolic and macroembolic atherothrombotic debris. Stenting may also increase serotonin release as a result of deep tissue injury and platelet activation, which may then result in vasospasm in the microvasculature.³ Finally, stretching vessels after stent placement may trigger α -adrenergic activity in the microvasculature and a reduction in left ventricular function that is relieved by α -blockers.⁴ It is notable that, although stenting reduced the incidence of restenosis in the Primary Angioplasty in Myocardial Infarction (PAMI) stent trial,¹¹ it did so at the risk of higher mortality, particularly among patients who had an occluded vessel before the intervention.¹² It has been speculated that this may be the result of downstream embolization or vasospasm.

Depending on the definition and the vigilance of surveillance used, 5% to 30% of patients sustain a myocardial infarction (release of CK-MB) after PCI.^{1,2} Recently we reported that the use of eptifibatid during planned stent placement is associated with a reduced incidence of adverse events such as CK-MB release.⁵ We have also recently reported that eptifibatid use is associated with improved tissue level perfusion as assessed by coronary flow reserve and digital subtraction angiography.¹³ Filling of the myocardium was more rapid, larger, and brighter among patients treated with eptifibatid compared with placebo control subjects.¹³ Taken together, these data suggest that impaired tissue level perfusion and not only impaired epicardial coronary blood flow is associated with the release of CK-MB after PCI. These data thus provide a pathophysiologic link among impaired tissue level perfusion, post-PCI infarction, and adverse clinical outcomes and may explain in part the growing body of literature relating the release of CK-MB to the worsened clinical outcomes observed in large-scale trials of acute coronary syndromes and PCI. Finally, these observations may also explain in part the long-term benefit of eptifibatid in particular and the platelet glycoprotein IIb/IIIa inhibitors as a class in improving clinical outcomes.^{1,2,5,13}

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