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NON-INVASIVE ASSESSMENT OF CORONARY ARTERY PATENCY AFTER THROMBOLYSIS USING SERUM MYOGLOBIN MEASUREMENTS

Tanasijevic J. M.

Department of Pathology
Brigham and Women's Hospital, Boston, USA

A b s t r a c t: Timely identification of patients with patent infarct-related artery (IRA) may permit rapid triaging to avoid unnecessary repeat thrombolysis or rescue percutaneous coronary intervention (PCI). Various biomarkers have been proposed to assess IRA patency status. Our group found that the ratio of serum myoglobin levels obtainned before and 60-min after initiation of thrombolytic therapy may provide an early indication of the IRA patency status. A 60-min myoglobin ratio of ≥ 4.0 indicated the probability of a patent IRA of 90%, suggesting that follow-up diagnostic modalities such as emergency coronary angiography to determine the IRA status may be unnecessary when these dynamics of myoglobin are observed.

Key words: Acute myocardial infarction, Thrombolysis, Myoglobin, Cardiac Markers.

Abbreviations:
AMI, acute myocardial infarction
CK, Creatine Kinase
CK-MB, creatine-kinase-MB
cTnI, cardiac Troponin-I
ECG, electrocardiogram
IRA, infarct-related artery
PCI, percutaneous coronary intervention
TIMI, Thrombolysis in Myocardial Infarction
TNK-tPA, TNK-tissue plasminogen activator

Introduction

Several studies have shown the benefit of early thrombolysis in patients with acute myocardial infarction (AMI) [1, 2]. Establishment of infarct-related artery (IRA) patency may be achieved with various therapeutic measures, including application of novel thrombolytic agents or percutaneous coronary interventions [3–6]. The unmet clinical need in these clinical settings is the absence of a reliable marker of IRA patency status to allow early identification of patients with patent IRA which may not benefit from repeat thrombolysis or rescue percutaneous coronary intervention (PCI). Historically, coronary angiography has been considered the gold standard [4, 5], but its high cost and limited access constrain its wide application in routine clinical care. Instead, clinicians typically rely on clinical or electrocardiographic (ECG) indices to determine IRA patency status, neither one of which is sufficiently sensitive or specific for an accurate prediction of IRA occlusion [7, 8].

Alternative non-invasive biomarkers have been proposed, including the measurements of creatine kinase-MB (CK-MB) [9–12], total creatine kinase (CK) [10, 13], myoglobin [12, 14–17], cardiac Troponin-T [18–21], CK isoforms [22, 23], cardiac Troponin-I (cTnI) [12, 17, 24], or combinations thereof [12, 17, 19, 25, 26, 27]. In a study conducted by Garabedian and co-workers [9], the ratio of CK-MB levels obtained before and 90-minutes after the initiation of thrombolysis correctly identified 86 % of reperfused patients using ratio cut-points of ≥ 2.5 for the left anterior descending artery and ≥ 2.2 for the right coronary artery after reperfusion. The rapid increase in CK-MB concentration closely correlated with the angiographic documentation of reperfusion. Similar findings were observed by Lewis and co-workers [10], documenting a close correlation between the onset of rapid increase in CK-MB and the angiographic documentation of reperfusion.

Higher CK-MB values within 3 hours of thrombolysis in successfully reperfused patients were corroborated by Ohman and colleagues [11] and others [13] have shown that the time to peak creatine kinase (CK) activity and the reduction in ST-segment elevation were independent predictors of vessel patency. One significant downside of using the time to peak CK concentration is the need to perform serial serum measurements, which could delay considerably the assessment of the IRA patency.

Several groups have examined the utility of serum myoglobin. Ellis and colleagues [15] reported that the myoglobin 60-min ratio cutpoint of 4.6 conferred 100% sensitivity and 85% specificity for the detection of occlusion. Ishii and co-workers [16] assessed serial measurements of multiple markers, including serum CK, CK-MB and myoglobin and reported 100% sensitivity and

100 % specificity for the 60-minute myoglobin ratio. Zabel and co-workers [19] demonstrated that myoglobin measurement was more useful for assessment of reperfusion than CK-MB and cardiac Troponin-T due to its earlier rise conferring a higher area under the receiver-operating characteristic (ROC) curve. Similar findings were observed by Apple and co-workers [24], who found that the myoglobin 90-min cutpoint of 5.0 conferred 100% sensitivity and 76.5% specificity for detection of occlusion. The utility of the time to peak values for myoglobin provided the earliest and best discrimination between reperfusion and continued in a study by Katus and co-workers [25].

There are a number of factors that have prevented a wider adoption of serum myoglobin for non-invasive assessment of reperfusion, including the lack of large-scale studies and concerns related to the lack of cardiac specificity of myoglobin. Our group undertook the TIMI 10B sub-study [17] to confirm its performance in a larger group of patients.

The TIMI 10 B Study Findings

We examined the diagnostic performance of serum myoglobin, CK-MB and cTnI obtained immediately before, and within 60 min of the initiation of thrombolysis using TNK-tissue plasminogen activator (TNK-tPA) in the Thrombolysis in Myocardial Infarction (TIMI) 10B trial. The trial enrolled 442 patients, the largest series to date. We used the TIMI flow grade at 60 minutes as the gold standard, with TIMI flow grade ≥ 2 being considered a patent IRA and a TIMI flow grade ≤ 1 considered an occluded IRA. Baseline (T0) concentrations for all serum markers were significantly higher in the patients with an occluded IRA, suggesting that baseline measurements correlate with the extent of myocardial injury in this patient group. The T60 concentrations of myoglobin and cTnI were significantly higher and CK-MB was only borderline-significantly higher in the patients with a patent IRA. Moreover, these patients had higher ratios of the serum concentration for all three markers measured 60-minutes after the start of the thrombolysis and at baseline (T60/T0 = 60-min ratio). The 60-min myoglobin ratio of < 4.0 yielded a slightly better combination of sensitivity (74%) and specificity (64%) for predicting IRA occlusion than the other two biomarkers. When the 60-min myoglobin ratio was ≥ 4.0, the probability of a patent IRA (i.e. negative predictive value) was 90%, suggesting that emergency coronary angiography to determine their IRA status may be unnecessary in patients showing this pattern of release of myoglobin. The clinical use of the 60-min myoglobin ratio would have allowed determination of IRA patency in a significant number of patients, since 229 (55%) of the total number of patients had myoglobin ratios ≥ 4.0. Only 23 (10%) of patients with values

above these levels showed documented occlusion of the IRA at angiography performed 60 minutes after thrombolysis. However, the probability of an occluded IRA was low (37%), even with absence of elevated 60-min ratios. Moreover, the predictive value for occlusion increased by only 4% when the combination of 60-min ratios of < 4.0 for myoglobin, <2.0 for cTnI and < 3.3 for CK-MB was considered evidence of occlusion. The low positive predictive value for occlusion was probably due to their correlation with the extent of initial myocardial injury. For instance, an extensive AMI may have yielded a high 60-min myoglobin concentration in the absence of IRA patency. Conversely, a small AMI may have resulted in a lower 60-min serum marker value, despite IRA patency.

The performance of the 60-min myoglobin ratio above described should make the 60-minute myoglobin ratio a very important additional diagnostic modality for non-invasive assessment of IRA patency status. Although its usefulness, either alone or in combination with other noninvasive tests, remains limited by false predictions of failed epicardial reperfusion, the 60-min myoglobin ratio may permit rapid triage of patients receiving thrombolytic therapy by ruling out IRA occlusion.

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Р е з и м е

НЕ-ИНВАЗИВНО ОДРЕДУВАЊЕ НА ПРООДНОСТА НА КОРОНАРНИТЕ АРТЕРИИ ПО ДАВАЊЕ НА ТРОМБОЛИТИЦИ КОРИСТЕЈЌИ МЕРЕЊА НА КОНЦЕНТРАЦИЈАТА НА МИОГЛОБИН ВО СЕРУМ

Танасиевиќ Ј. М.

Department of Pathology
Brigham and Women's Hospital, Boston, USA

Навремена идентификација на пациенти со проодна инфактирана коронарна артерија (ИКА) може да овозможи брза тријаза за да се избегне непотребна повторна тромболиза or percutana коронарна интервенција. Brojni

биомаркери се разгледувани за неинвазивно одредување на ИКА статус. Нашата група утврди дека количникот на серум mioglobin концентрации мерени пред и 60 минути по иницијација на тромболитична терапија може да биде рана индикација за проодноста на ИКА. Количникот од 4.0 (≥ 4.0) назначува 90% веројатност на проодната ИКА, и сугерира дека дополнителни дијагностички студии, како ургентна коронарна артериографија, може да се избегнат.

Клучни зборови: акутен миокарден инфаркт, тромболиза, миоглобин, срцеви маркери.

Corresponding Author:

Milenko J. Tanasijevic, M.D., M.B.A.
Clinical Laboratories Division
Department of Pathology
Brigham and Women's Hospital
Amory building, 215 A
75 Francis St.
Boston, MA 02115
Phone: 617-732-6360 Fax 617-713-3056

E-mail: mtanasijev@partners.org