Myoglobin as a cardiac marker

Yuweree Vanavanitkun*


Determination of Myoglobin, a low molecular weight heme protein, present in both cardiac and skeletal muscle, is an old test with new perspectives. Recently, rapid and accurate methods for the assay of this protein have greatly enhanced interest in the clinical utilization of the test. Since myoglobin is present in both skeletal and cardiac muscle, any damage to these muscle types results in its release into blood. New strategies for myoglobin measurement may resolve this limitation. These strategies include both the combined measurement of myoglobin and a skeletal muscle specific marker (carbonic anhydrase III) or a cardiac specific marker (troponin I or T), as well as the evaluation of myoglobin in serial samples. Combined measurement of myoglobin and troponins significantly improve diagnostic efficiency in laboratory assessment of suspected AMI patients. Further efforts are necessary to improved the standardization of present methods for myoglobin measurement.

Key words: Myoglobin, Acute myocardial infarction.

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Received for publication. July 15, 2000.
Myoglobin เป็นโปรตีนที่มีมีผลลักษณะเฉพาะพื้นที่ในกล้ามเนื้อเลือดและกล้ามเนื้อหัวใจ วิธีการตรวจวัดค่า Myoglobin เป็นวิธีการตรวจวิเคราะห์ที่มีมาตรฐานและในช่วงระยะเวลา 2 – 3 ปี ที่ผ่านมา วิธีการตรวจวิเคราะห์ได้รับการพัฒนา ให้ตรวจได้อย่างรวดเร็ว และถูกต้องยิ่งขึ้น ทำให้การตรวจวิเคราะห์ Myoglobin ได้รับความสนใจมากขึ้น ในแหล่งการเข้ามาใช้ประโยชน์ทางด้านคลินิก และเนื้อจากว่า Myoglobin มีชื่อจำากัด ในเรื่องของความจำท่าทางการตรวจ (specificity) การเบาปะจับของกล้ามเนื้อเลือด และกล้ามเนื้อหัวใจจะตรวจพบ Myoglobin ในกระแสเลือดได้ทั้งสิ้น เพื่อสอดคล้องกับหลักการ ซึ่งมีการรวมแนวทิศทางการใช้ Myoglobin ต่าง ๆ ดังนี้ที่พิจารณาสามารถในการวิจัย ได้แก่ การตรวจวิเคราะห์ Myoglobin รวมไปถึง specific skeletal muscle marker (carbonic anhydrase III) หรือรวมกับ cardiac specific marker (Troponin T, I) หรือตรวจวิเคราะห์ Myoglobin เป็นระยะ พบว่าการตรวจวิเคราะห์ Myoglobin รวมไปถึง Troponin จะเพิ่มความสามารถในการวิจัยโดยหลักกล้ามเนื้อหัวใจตามที่สูง แต่ยังไม่ที่จะต้องพัฒนาวิธีการตรวจวัดซึ่งมีหลายวิธีให้ได้มาตรฐานเดียวกันก่อน ซึ่งจะสามารถนำมาใช้ได้อย่างเต็มที่.
Improvement in the accuracy and rapidity of diagnosis and management of patients with chest discomfort has led to the investigation of new biochemical diagnostic methods and strategies for acute myocardial infarction (AMI) and related diseases. Among other serum biochemical markers under investigation, myoglobin and troponins seem to be the most promising alternative to enzymatic markers, providing a range of assays that are an early non-specific indicator of infarction and an absolute cardiac specific marker.

Recently, the National Academy of Clinical Biochemistry committee, has recommended utilization of two biochemical markers for routine AMI diagnosis: an early marker (reliably increased in blood within 6 h after onset of symptoms) and a definitive marker (increased in blood within 6-9 h, but with a high sensitivity and specificity for myocardial injury, remaining abnormal for several days after onset). Currently, cardiac troponins have been recognized as the best markers for definitive AMI diagnosis. More controversial is the choice of the early indicator, but at present myoglobin is the marker that most effectively fits this role.

**Biochemical properties**

Determination of myoglobin, a low molecular weight heme protein (17.8 kDa) present in both cardiac and skeletal muscle, is an old test with new perspectives. The advantages and disadvantages of myoglobin determination are well known.

Myoglobin is the earliest known, commercially available biochemical marker of myocardial infarction; it has rapid kinetics and it is an early, good marker of reperfusion.

A rise in myoglobin is detectable in blood as early as 1-2 h after the infarction, reaching peak concentrations in 6-9 h. (Figure 1) Serum myoglobin level is generally acknowledged to be significantly increased earlier than those of other biochemical markers. At presentation and within the first few hours after chest pain, its sensitivity is greater than that of creatine kinase (CK), creatinine kinase isoenzyme MB (CK-MB) and cardiac troponin T and I. (Table 1) Although there have been some reports that myoglobin is not detectable any earlier than CK-MB mass assays, currently the NACB committee believes that myoglobin is an earlier marker than CK-MB mass and more conveniently measured on automated immunoassay analyzers than CK-MB isoforms.

**Table 1.** Sensitivity and specificity values of biochemical markers performed as single test.

<table>
<thead>
<tr>
<th>Test</th>
<th>Upper reference Value</th>
<th>Sensitivity (%) (95 % CI)</th>
<th>Specificity (%) (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>To</td>
<td>T1</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>70 μg / L</td>
<td>69</td>
<td>100</td>
</tr>
<tr>
<td>TnI</td>
<td>0.4 μg /</td>
<td>54</td>
<td>81</td>
</tr>
<tr>
<td>TnT</td>
<td>0.1 mg /</td>
<td>51</td>
<td>78</td>
</tr>
<tr>
<td>CK</td>
<td>90 U / L (male)</td>
<td>31</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>160 U / L (female)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK-MB</td>
<td>5 μg / L</td>
<td>46</td>
<td>88</td>
</tr>
</tbody>
</table>
Figure 1. Plot of the appearance of cardiac markers in blood vs time after onset of Symptoms.

(Peak A, early release of myoglobin or CK-MB isoforms after AMI; peak B, cardiac troponin after AMI; peak C, CK-MB after AMI; peak D, cardiac troponin after unstable angina. Data are plotted on a relative scale, where 1.0 is set at the AMI cutoff concentration.)

Therefore, myoglobin is a sensitive but non-specific marker of AMI. Because it is present in both skeletal and cardiac muscle, any injuries of these muscle types causes myoglobin release into blood. Serum myoglobin level is consequently elevated in conditions unrelated to AMI, such as skeletal muscle and neuromuscular disorders, trauma, intramuscular injection, strenuous exercise and exposure to several toxins and drugs. Furthermore, because myoglobin is rapidly cleared by the kidney, decreased renal function can result in elevated serum level. (10) (Table 2)

Methods of Measurement

In the past, various different immunological methods for determination of myoglobin were used, that were often time-consuming and required special equipment. The time needed for determination ranged from three to four hours and was one of the factors

<table>
<thead>
<tr>
<th>Causes of myoglobin elevation&lt;sup&gt;10&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>Angina without infarction</td>
</tr>
<tr>
<td>Rhabdo myolysis</td>
</tr>
<tr>
<td>Multiple fracture, muscle trauma</td>
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<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>Myopathies</td>
</tr>
<tr>
<td>Vigorous exercise</td>
</tr>
<tr>
<td>Open heart surgery</td>
</tr>
<tr>
<td>Tonic-clonic seizure</td>
</tr>
<tr>
<td>Electric shock</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
</tr>
<tr>
<td>Certain toxin</td>
</tr>
</tbody>
</table>
that limit the use of myoglobin measurement in clinical practice, particularly in emergencies.\(^{(11-13)}\) Now reliable, rapid and automated methods are available for there's measurement, with a turnaround time of less than 20 min.\(^{(14-18)}\) (Table 3) However, advancements in the development of myoglobin assays have led to some analytical and interpretative problems, that need inter-methods standardization.\(^{(20)}\)

At present, for myoglobin, the goals for analytical precision can be directly derived from biologival variability studies : \(\leq 5.6\%\) CV\(^{(21)}\). This should provide an objective target for manufacturers of instruments and kits in the construction of new assays. In an Italian multicenter study\(^{(22)}\) that evaluated the clinical performance of several assays for myoglobin measurement, they have found that some commercial assays for myoglobin determination do not meet this target of quality. Thus an improvement in the precision of measurement is required if these assays are to be used on a routine basis.

Moreover, the inter-methods comparison study demonstrated a significant disagreement between some assays leading to different reference values, the upper level ranging from 69 \(\mu\)g/L (Hitachi 747, Boehringer Mannheim) to 92 \(\mu\)g/L (Opus magnum, Dade Behring). This should be carefully considered in clinical practice.\(^{(4)}\)

The IFCC established a committee on "standardization of markers of cardiac damage" (C-SMCD). For the development of standardization C-SMCD decided to concentrate its attention on immunoassays for determination of CK-MB mass, myoglobin, and cTnI. The objective of the programme of standardization of myoglobin measurement is selection and characterization of an appropriated reference material that can be used for the harmonization of myoglobin assays.\(^{(23)}\)

**Diagnostic strategies**

1. **Diagnosis of acute myocardial infarction**

These strategies include the simultaneous measurement of a skeletal specific marker, such as carbonic anhydrase III or that of a cardiac specific marker (cardiac Troponin T, cardiac Troponin I) as well as myoglobin evaluation on serial samples.

<table>
<thead>
<tr>
<th>Method</th>
<th>Analytical TAT</th>
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<tbody>
<tr>
<td>Radioimmunoassay</td>
<td>2 h</td>
</tr>
<tr>
<td>Chemiluminescent immunoassay</td>
<td>4 h</td>
</tr>
<tr>
<td>Enzyme immunoassay</td>
<td>3 h</td>
</tr>
<tr>
<td>Latex agglutination</td>
<td>5 min</td>
</tr>
<tr>
<td>Nephelemetric</td>
<td>12 min</td>
</tr>
<tr>
<td>Turbidimetric immunoassay</td>
<td>2 min</td>
</tr>
<tr>
<td>Fluorimetric enzyme immunoassay</td>
<td>10 min</td>
</tr>
<tr>
<td>Indirect chemiluminescence immunoassay</td>
<td>15 min</td>
</tr>
<tr>
<td>Fluorimetric radial partition enzyme immunoassay</td>
<td>8 min</td>
</tr>
</tbody>
</table>

Table 3. Methods for serum myoglobin measurement.\(^{(4)}\)
Firstly, carbonic anhydrase III (CAIII) is mainly present in skeletal muscle, with only trace amount being found in cardiac tissue. The simultaneous measurement of serum myoglobin and CA III ratio can be used to differentiate between myocardial and skeletal muscle damage. Vuori et al. found that during the first 2 hr. after the onset of symptoms, only myoglobin and myoglobin / CA-III ratio showed an appreciable sensitivity (0.40, 0.60) when compared with CK and CK-MB (1 %). In 2 to 6 hr after the onset of chest pain, the sensitivities were still greater than those for CK-MB alone (93 %, 100 % and 43 %) while in late phase of AMI, the clinical sensitivities of all tests were comparable.

Van Nieuwenhoven FA, et al. evaluated the diagnostic use of the ratio of myoglobin to fatty acid-binding protein (FABP), another cytoplasmic protein present not only in the heart but also in skeletal muscle. The ratio of plasma concentration of myoglobin and FABP reflects the injured tissue, being about 4.5 for the heart and 20 - 70 for skeletal muscle.

These strategies have been proposed to improve the specificity of the myoglobin assay in AMI diagnosis, the limitations in their routine applications are the overlong analytical turnaround time for CA-III and FABP measurements, and the increased costs for the measurement of two parameters.

The second strategy is based on serial measurement of myoglobin. Detection of increasing myoglobin release rate over 1-2 h. increases the specificity of the marker by up to 98 %. The use of the initial rate of myoglobin release with a cut-off value of 20 µg/L/hour could be use for the diagnosis of AMI in the emergency department, suggesting that a myoglobin assay may be an early marker for ruling out a diagnosis of AMI in patients without any complication known to cause an increase in myoglobin. The amount of change in serum myoglobin, rather than the absolute value, is a good index of AMI as well as early indicator of coronary reperfusion.

Finally, the third strategy is based on the use of a serum myoglobin assay in combination with cardiac specific markers such as troponins. In particular, the use of myoglobin and troponin I as single parameters and combined in parallelly and serially. Bhayana V, et al, found that the highest efficacy was obtained when two parameters (myoglobin, troponin I) were used serially. (Table 4)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single</td>
<td>Myoglobin</td>
<td>0.92</td>
<td>0.55</td>
</tr>
<tr>
<td>Single</td>
<td>CK-MB mass</td>
<td>0.846</td>
<td>0.770</td>
</tr>
<tr>
<td>Single</td>
<td>Troponin I</td>
<td>0.710</td>
<td>1.00</td>
</tr>
<tr>
<td>Series</td>
<td>Myoglobin and CK-MB mass</td>
<td>0.85</td>
<td>0.77</td>
</tr>
<tr>
<td>Series</td>
<td>Myoglobin and troponin I</td>
<td>0.85</td>
<td>1.0</td>
</tr>
<tr>
<td>Parallel</td>
<td>Myoglobin or CK-MB mass</td>
<td>0.92</td>
<td>0.55</td>
</tr>
<tr>
<td>parallel</td>
<td>Myoglobin or troponin I</td>
<td>0.92</td>
<td>0.55</td>
</tr>
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Table 4. Biochemical markers of myocardial damage.
The combination of myoglobin and troponin I or T measurement appears the most efficient strategy for diagnosis and monitoring of AMI patients.\textsuperscript{(29)}

2. Monitoring of reperfusion after thrombolytic therapy

The rapid release of myoglobin into the circulation due to damage of the heart muscle cells following myocardial infarction and the quick decrease in its blood concentration because of its short half-life, make this protein the most suitable marker for assessing the effect of thrombolytic treatment. The usefulness of myoglobin for non-invasive prediction of coronary reperfusion in patients undergoing thrombolysis or percutaneous transluminal coronary angioplasty (PTCA) has been well demonstrated.\textsuperscript{(30)}

In the analysis of the initial rate of increase in blood myoglobin, three well-defined criteria may be used to ascertain reperfusion: the first is the rate of increase within the first two hours, a value higher than 150 μg/L/hr. considers the sign of a reopened artery.\textsuperscript{(31)} The second criterion, proposed by Ellis, is the ratio between the first myoglobin value at the starting time of lysis and the second value obtained 2 h later, the value should be a 4.6 fold increased.\textsuperscript{(32)} The third criterion is the time to peak concentration of myoglobin, perfusion of the infarct-related artery is indicated if this is less than 5 h.

Conclusion

Currently, myoglobin is the marker that most effectively fits, the role as an early biochemical tool for diagnosis of AMI. The limitation of the measurement can be circumvented by combining with the assay of cardiospecific markers such as troponins. The benefit is that AMI can be effectively ruled out within 6 - 9 h after the onset of chest pain.

References


กิจกรรมการศึกษาต่อเนื่องสำหรับแพทย์

ท่านสามารถได้รับการรับรองกิจกรรมการศึกษาต่อเนื่องสำหรับแพทย์ประจำปี 3 (ศึกษาด้วยตนเอง) ได้ จากการช่วยทำความเรื่อง "บทบาทของ Myoglobin ในฐานะ Cardiac Marker" โดยตอบคำถาม ข้างล่างนี้ พร้อมกับส่งคำตอบที่ท่านคิดว่าถูกต้องโดยใช้แบบฟอร์มคำตอบท้ายคําถามแล้วใส่ของพร้อมของไปสิ่งเดียวกันที่จ่าหน้าขอลงด้วยท่าน ลงถึง

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เขตปทุมวัน กทม. 10330

ท่านจะได้รับละเอียดคำตอบพร้อมหนังสือรับรองกิจกรรมการศึกษาต่อเนื่อง

คำถาม - คำตอบ

1. How many biochemical markers for routine AMI diagnosis that National Academy of Clinical Biochemistry committee has recommended ?.
   a. 1
   b. 2
   c. 3
   d. 4
   e. 5

2. What is the best marker for definitive AMI diagnosis ?.
   a. CK-MB isoenzyme
   b. Myoglobin
   c. Cardiac troponin
   d. Carbonic anhydrase III
   e. LDH-1 isoenzyme

สําหรับบทความเรื่อง "บทบาทของ Myoglobin ในฐานะ Cardiac Marker" จุฬาลงกรณ์มหาวิทยาลัย ปีที่ 45 ฉบับที่ 2 เดือนกุมภาพันธ์ พ.ศ. 2544

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2. [ ] [ ] [ ] [ ] [ ]
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5. [ ] [ ] [ ] [ ] [ ]
3. What is the most efficient strategy for diagnosis of AMI?
   a. Measurement of myoglobin combined with carbonic anhydrase III
   b. Measurement of myoglobin combined with CK-MB
   c. Serial measurement of myoglobin
   d. Measurement of myoglobin combined with cardiac troponin
   e. Measurement of myoglobin combined with fatty acid-binding protein

4. What is true about Myoglobin?
   a. early marker for diagnosis of AMI
   b. need intermethod standardization
   c. good marker of reperfusion
   d. can rule out AMI within 6-9 hrs. after onset of symptoms
   e. all of the above

5. For myoglobin, What is the goal for analytical imprecision?
   a. ≤ 4.5% CV
   b. ≤ 5.6% CV
   c. ≥ 2% CV
   d. > 3.5% CV
   e. ≥ 5% CV

ท่านที่ประสงค์จะได้รับเครดิตการศึกษาต่อเนื่อง (CME credit) กรุณาส่งคำตอบ