

CALIFORNIA ASSOCIATION FOR MEDICAL LABORATORY TECHNOLOGY

DISTANCE LEARNING COURSE

ISCHEMIA-MODIFIED ALBUMIN (Newest Cardiac Marker)

by

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**Course Number: DL-962
1.0 CE/Contact Hour
Level of Difficulty: Basic**

CAMLT is approved by the California Department of Health Services as a
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This is a reminder that all the continuing education units required to renew your license must be earned no later than the expiration date printed on your license. If some of your units are made up of Distance Learning courses, please allow yourself enough time to retake the test in the event you do not pass on the first attempt. CAMLT urges you to earn your CE units early!

ISCHEMIA-MODIFIED ALBUMIN

Course Objectives:

After completing the course, the participant will be able to

1. Define ischemia
2. Outline the history of Ischemia-Modified Albumin (IMA) testing
3. State the advantages and disadvantages of the use of IMA testing
4. Discuss Ischemia-Modified Albumin as a diagnostic tool

Introduction:

Ischemia (literally, hold back blood) occurs when there is restricted blood flow to a tissue so that oxygen demands are not met. Cardiac ischemia results when an artery becomes narrowed or blocked or when cardiac oxygen demand is increased in the presence of a narrowed artery. In most cases, temporary blood shortage to the heart causes angina (chest pain, especially with exertion). If ischemia is severe and lasts too long, it can cause a heart attack (myocardial infarction). Myocardial infarct is the actual death of muscle or part of the muscle. Most cases of ischemia cause reduction of oxygen to the cells but do not cause cell death.

Albumin is modified in the presence of ischemia. This modification does not rely on cell death. Most of the previous cardiac markers do not become positive until cell death occurs. However, the test for Ischemia-Modified Albumin (IMA) becomes positive when ischemia occurs with or without cell death.

The American Heart Association estimates that three to four million Americans have episodes of cardiac ischemia per year. People who have had previous heart attacks or those who have diabetes are especially at risk for developing ischemia. Heart muscle disease caused by ischemia is among the more common causes of heart failure in the United States.

Initial diagnosis of acute coronary syndrome (ACS) is based almost entirely on history, risk factors and electrocardiogram (ECG). With the introduction of Ischemia-Modified Albumin testing, physicians now have an early predictor of oncoming cell damage.

History of ischemia-modified albumin:

- 1990: A practicing emergency room physician made the original discovery that albumin had decreased metal binding properties following exposure to ischemia (ischemia-modified albumin). A test called *Albumin Cobalt Binding (ACB)* was developed.
- 1992: Pilot clinical study showed IMA to be elevated in acute myocardial infarction (AMI) and unstable angina
- 1994: First patent on IMA core technology
- 1997: Ischemia Technologies was formed to commercialize IMA marker
- 1998: Pilot clinical study which showed that elevated IMA occurring during angioplasty was due to ischemia.
- 1999: *ACB (Albumin Cobalt Binding)* test to measure IMA was developed and put on clinical chemistry instruments.
- 2000: First multicentered clinical trial showed IMA improves diagnostic sensitivity of Troponin I.
- 2001: First test sales in Europe.
- 2003: Test approved by FDA for use in the United States.

2003: FDA approved *Albumin Cobalt Binding (ACB)* for diagnostic use in the United States by a company called Ischemia Technologies, Inc., which was formed strictly to work on this issue. The test is now called the IMA test instead of the ACB test.

Ischemia-Modified Albumin Chemistry:

Human serum albumin is a circulating protein with a metal binding site at the N-terminus. Although albumin is a fairly large complex protein, it is one of the most often measured compounds. Since physicians frequently look at the serum albumin to help assess what is going on in the patient, this has become a relatively straight forward test.

Free radicals seem to be produced during ischemia. These are strongly oxidative compounds which affect the N-terminal portion of albumin. Acetylation or depletion of one or more amino acids at the N-terminus results in a modified albumin protein that loses the ability to bind cobalt (or other metals). Cobalt happens to be used as the indicator in this assay.

In the test free cobalt atoms are incubated with the patient's serum. When there is increased ischemia, the modified albumin is not able to bind with cobalt. The amount of free cobalt is measured and is increased above normal proportional to the amount of ischemia-modified albumin present.

IMA is produced continuously during an ischemic event and rises rapidly; it is not episodic. When a cell dies (necrosis) it releases compounds which are measured in cardiac marker tests such as troponin, myoglobin, CK-MB. This is something that happens more dynamically.

Cardiac angioplasty-balloon catheter studies helped demonstrate the dynamics of the production of ischemia modified albumin. In balloon catheter procedures the coronary arteries are temporarily occluded during a carefully controlled time period. It was found that ischemia-modified albumin rises so rapidly that it is present in the peripheral blood within 6-10 minutes after the episode. It occurs more rapidly than any other indicator. It also clears fairly rapidly, in about 6 hours from the blood.

Diagnostic Value of IMA:

Dr. Alan Wu (1) states, "Ideally the test would be used in the hospital emergency department on the millions of patients who present early with chest pain. These patients would probably have a negative troponin and other cardiac markers of cell death which don't become positive until 4-6 hours after the episode. A negative IMA would place the patient at low risk for a cardiac ischemic event and consideration could be made to discharge the patient. A positive IMA would put the individual at much higher risk for cardiac ischemia and consideration could be made to more aggressively treat this individual. In either case, management decisions could be made sooner than having to wait 6 hours for a troponin rise or to reliably determine a negative troponin result."

The advantages of IMA include:

- The IMA test becomes positive right after the ischemic episode occurs. A negative test indicates that an ischemic episode did not occur. The test returns to baseline within 6-12 hours after an ischemic event.
- When using traditional cardiac markers such as troponin, there is a substantial delay before the factor is expressed after cardiac damage, and many ischemic episodes do not lead to increased troponin levels.

- IMA detects the majority of patients (82%) with unstable angina or so called acute coronary syndrome (ACS). Troponin actually has a very poor record detecting ACS; it is only 14% sensitive.
- Negative values are especially useful; if there is a negative IMA, negative troponin, and a nondiagnostic ECG, the patient is 99% negative (predictive value) for acute coronary syndrome.
- IMA, troponin and electrocardiogram (ECG) comprise an excellent combination for non-invasive tests (except for the blood draw). When the physician is trying to decide whether to send the patient home or keep him in the hospital, the information from these tests is very useful.

The disadvantage of IMA is that it is non-specific for cardiac ischemia; other kinds of ischemia, especially gastrointestinal or cerebral, will cause a positive result. It is also elevated in other conditions such as cancer, acute infections, end stage renal disease, and liver cirrhosis. A positive result does not indicate where the ischemia has occurred. So this test, if positive, has to be used in conjunction with other tests. Therefore a negative result is fairly reliable and a positive result is not so valuable, due to the nonspecific nature of the marker (similar to myoglobin). In patients with low pre-test odds of disease, a negative test may allow reduction of workup and additional precautionary testing.

The workup of chest pain patients often depends upon the patient’s situation. If the patient is a 35 year old female who is seen because of a short duration of pain, is a nonsmoker, and has no other risk factors like hyperlipidemia and the IMA test is negative, the physician is more likely to conclude that this patient has non-cardiac pain and is sent home.

On the other hand, if the patient is a 65 year old male smoker, the physician is probably going to work him up anyway because his chest pain is more likely to be significant rather than elusive. So, as always, these tests are used in the context of the clinical setting. Again, a positive test is not so useful because there are other causes for positive IMA.

Table 1

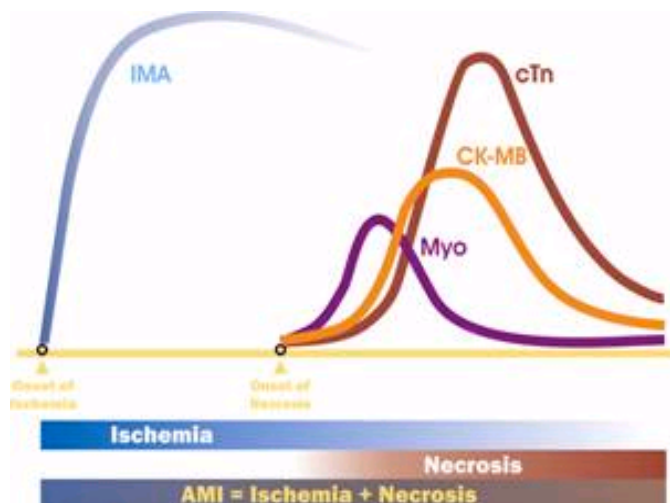


Table 1 shows the response curve of various cardiac markers used now--troponin, CK-MB and myoglobin, which all increase with necrosis, not with ischemia alone. They all basically start

increasing at the same time. This table shows that ischemia generally happens earlier than necrosis-how much earlier is hard to say. It all depends on why the patient has ischemia. For instance, if a plaque breaks open and closes up the artery, ischemia is followed by necrosis fairly quickly.

Advantages of IMA:

- Rapid presence after ischemia.
- Negative IMA predicts negative troponin.
- It can be done on a chemistry analyzer (non-immuno assay).
- The method is simple and rapid (it is just an absorbance-type of test that is compatible with high volume automation).

Disadvantages of IMA:

- Non-specific for cardiac ischemia.
- Potential false positive results (there could be brain ischemia, gastrointestinal ischemia, or something else).
- Must be used in conjunction with other cardiac markers (e.g., troponin).
- Possible unnecessary cardiac catheterization if done because the test is positive without considering results of other cardiac tests.
- Although it is not altered by albumin concentrations, some effect may be seen in extreme levels.

Summary:

IMA is a good test because it is positive within 6-10 minutes of an ischemic event and doesn't depend on cell death markers. There is a return back to baseline within about 6 hours after the event. Negative IMA and troponin with non-diagnostic ECG gives 99% negative predictive value for acute coronary syndrome. In addition, Ischemia-Modified Albumin used in combination with stress ECG, might allow reduction in the number of other cardiac marker tests as well as expensive and invasive nuclear scans for cardiac ischemia.

References for Ischemia Course by Michael Weilert M.D.

1. AACC - Expert Access: Wu AHB. Ischemia-Modified Albumin and Other Biochemical Markers and Diagnostic Methods for Risk Stratification of Chest Pain Patients. December 2, 2003. Available at: <http://www.aacc.org> Click on “Jump to”; choose “Expert Access”; click on “Search Previous Discussions”.
2. Evaluation of Technologies for Identifying Acute Cardiac Ischemia in Emergency Departments. Summary, Evidence Report/Technology Assessment: Number 26. AHRQ Publication No. 00-E031. September 2000.
3. Texas Heart Institute Heart Information Center.
4. Christenson RL, Duh SH, Sanhai WR, et al. Characteristics of an Albumin Cobalt Binding Test for Assessment of Acute Coronary Syndrome Patients: A Multicenter Study. *Clinical Chemistry*. 2001;47-3, 464-470.
5. Pollack CV, Sieck S, Summers RW, et al. Use of Ischemia – Modified Albumin in Emergency Department Risk Stratification of Chest Pain is Both Clinically Effective and Cost Effective. *Annals of Emergency Medicine, Supp.* 2003;42:4-S37.
6. Bhagavan NV, Lai EM, Rios PA, et al. Evaluation of Human Serum Albumin in Cobalt Binding Assay for the Assessment of Myocardial Ischemia and Myocardial Infarction. *Clinical Chemistry*. 2003;49-4, 591-585.

Review Questions
Course #046-962

Choose the **one** best answer

1. Ischemia is a condition where:
 - a. platelet levels are low
 - b. cell death occurs
 - c. the ECG is abnormal
 - d. oxygen-rich blood flow is restricted

2. The American Heart Association estimates there are how many episodes of cardiac ischemia in America per year?
 - a. 3-4 million
 - b. 7-10 million
 - c. 1-2 million
 - d. 10-15 million

3. FDA approval for IMA testing was received in the United States:
 - a. 1990
 - b. 2003
 - c. 1997
 - d. Still pending

4. IMA Test measures:
 - a. Free cobalt
 - b. Free troponin
 - c. Free myoglobin
 - d. CPK

5. How soon is IMA present in the blood after an ischemia episode?
 - a. 3-4 hours
 - b. 50-60 minutes
 - c. 6-10 minutes
 - d. 6-10 hours

6. Test results of a negative IMA, negative Troponin and a non-diagnostic ECG indicate that the patient is:
 - a. at risk of acute coronary syndrome
 - b. positive for acute coronary syndrome
 - c. negative for acute coronary syndrome
 - d. at risk for diabetes

7. A positive IMA test result alone
 - a. indicates the patient is at risk for diabetes
 - b. tells the physician that the patient has acute coronary syndrome
 - c. indicates the patient is at risk of acute coronary syndrome
 - d. does not tell the physician anything

8. Advantages of the IMA test include a method that is:
 - a. simple and IMA stays in the system 24 hours
 - b. simple and there is a rapid presence of IMA
 - c. complex and there is a rapid presence of IMA
 - d. complex and IMA stays in the system 24 hours

9. Disadvantages of the IMA test include which of the following?
 - a. IMA is non-specific for cardiac ischemia, has potential of false positive, must be used with other cardiac markers
 - b. IMA is specific for cardiac ischemia, has potential of false positive and must be used with other cardiac markers
 - c. IMA is non specific for cardiac ischemia, has potential of false negative, must be used with other cardiac markers
 - d. IMA is non specific for cardiac ischemia, has potential of false positive, cannot be used with other cardiac markers

10. IMA levels return back to baseline within:
 - a. 48 hours after ischemia event
 - b. 24 hours after ischemia event
 - c. 6 hours after ischemia event
 - d. 72 hours after ischemia event

Course #962 ISCHEMIA-MODIFIED ALBUMIN
Registration/Answersheet
1.0 CE Credit

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Signature (Required) _____

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Please circle the one best answer for each question.

- | | | | | | | | | | |
|----|---|---|---|---|----|---|---|---|---|
| 1. | a | b | c | d | 6 | a | b | c | d |
| 2. | a | b | c | d | 7 | a | b | c | d |
| 3. | a | b | c | d | 8 | a | b | c | d |
| 4. | a | b | c | d | 9 | a | b | c | d |
| 5. | a | b | c | d | 10 | a | b | c | d |

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