Measurement and Clinical Interpretation of Whole Blood Lactate Concentration.

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Measurement of blood lactate is useful in management of patients in critical care, such as for monitoring tissue oxygenation, assessing the degree of hypoxia during surgery and other procedures, and as a guide to the effectiveness of therapeutic intervention for patients in critical care. Because lactate increases rapidly in stored blood after collection, whole blood samples for lactate measurements must either be analyzed very rapidly, centrifuged to remove cells, or stabilized with a preservative. Rapid measurement of lactate is also essential for timely management of patients in a variety of critical care settings. Currently, the most widely used methods for lactate in critical care are based on electrochemical sensors that utilize a membrane-bound enzyme and amperometric detection of the reaction product.

Production and Removal of Lactate
Lactate is produced from pyruvate as a by-product of glucose metabolism. During typical glucose metabolism, the supply of oxygen is adequate (aerobic conditions), and plenty of NAD$^+$ is generated. This condition favors conversion of pyruvate to acetyl CoA in the mitochondria. Subsequent oxidation of acetyl CoA in the Krebs cycle and by electron transport in the mitochondria produce a large amount of ATP. However, if oxygen is in short supply, a decrease in NAD$^+$ favors the conversion of pyruvate to lactate. While this process generates some NADH, it is far less than by aerobic metabolism (Krebs cycle and electron transport), and only a small amount of ATP is generated. Ultimately, a high ratio of NAD$^+$ to NADH leads to production of large amounts of ATP (1).

Lactate is produced in virtually all tissues, with production greatly increased when an oxygen deficit exists. Even with adequate oxygen, many organs produce lactate: resting skeletal muscle, brain, and erythrocytes produce about 5 to 10 mmol lactate per hour. Smaller amounts are produced by the intestine, kidney, skin, and other cells in blood. In a human at rest, the liver removes most lactate, with the kidney, heart, and skeletal muscle also contributing to removal of lactate (2).

Because erythrocytes have no mitochondria, lactate is the normal product of glucose metabolism in red cells, and lactate increases rapidly in whole blood after collection. With no glycolytic inhibitors present in whole blood at room temperature, lactate increases by 0.3-0.5 mmol/L (a 30-50% increase) in only 30 min (3,4). Ice storage slows this increase to about 0.05 mmol/L in 30 min, while fluoride/oxalate slows the increase to about 0.1 mmol/L in 30 min at room temperature (4).

Patient Preparation and Specimen Collection
If a blood lactate test is necessary for diagnostic purposes, proper blood collection is highly important. The patient should be fasting and at complete rest for at least 2 hours to allow the blood lactate concentration to stabilize. Patients should avoid exercise of the hand or arm before and during the collection of blood. Ideally, venous specimens should be obtained without the use of a tourniquet. If a tourniquet must be used, the blood should be drawn immediately after the tourniquet is applied (5).

Stability of Lactate in Samples
At room temperature storage, lactate increases in whole blood by 0.3-0.5 mmol/L after 30 min (3,4,6). Ice slows this rate to about 0.1 mmol/L after 60 min (3,4). Lactate in plasma is quite stable, with no detectable change after 120 min on ice, and changing by 0.1 mmol/L after 120 min at room temperature (3).
For lactate methods that are not interfered by fluoride or oxalate, these preservatives (especially fluoride) minimize increases in lactate to very low rates. In whole blood samples containing F/Ox at room temperature, the mean increase was 0.15 mmol/L over 24 hours. In samples with high white cell counts, lactate increased by 0.3 mmol/L over 8 hours. This suggests that samples collected in F/Ox will be stable for at least 8 hours at room temperature (4).

Because fluoride interferes with most lactate-sensing electrodes, heparin is nearly always the anticoagulant used for critical care situations where whole blood must be analyzed rapidly. Because heparin provides no inhibition to lactate production, rapid analysis is necessary, not only for a rapid result, but to minimize changes in lactate concentrations.

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To avoid in vitro metabolic effects in either venous or arterial whole blood, lactate should be measured within 15 min after collection. While storage on ice minimizes lactate generation in vitro, ice storage affects other analytes, such as increasing potassium (7) and PO₂ (8).

**Clinical Use of Blood Lactate Measurements**

Lactate results have their greatest importance in guiding therapeutic needs during critical care situations, especially to treat hypoxia due to myocardial infarction, cardiac insufficiency or inappropriate blood flow. Consequently, rapid response is necessary and diagnostic test results are helpful if provided in 5 min or less. As mentioned, we have observed dramatic increases in lactate requests when these results are provided within 5 min.

**Pediatric Open-Heart Surgery**

The usefulness of serial blood lactate measurements is well established in monitoring the post-op course of pediatric open-heart surgery. In a normal recovery after surgery, the blood lactate is expected to be only modestly elevated, then decline to near normal levels within 24 hours. If the blood lactate results immediately after and within 24 hours after surgery do not conform to this expected pattern, therapeutic interventions with volume support, cardiac stimulants, vasodilators, and ventilatory support may be initiated (9).

**Extracorporeal Membrane Oxygenation (ECMO)**

Because of the intensive nature and high cost of ECMO, the decision to place a patient on ECMO should only be made when the patient’s condition is serious enough to warrant this procedure. Blood lactate measurements are used both to determine the need for placing a patient on ECMO and for assessing the effectiveness of ECMO in supplying oxygen to tissues (9).

**Evaluation of Shock States**

Elevated blood lactate is a common finding in patients with circulatory shock. Circulatory shock (severe hypotension) may be caused by decreased blood volume (blood loss or dehydration), decreased cardiac output, or disturbances to flow patterns caused by sepsis (septic shock). Although the mechanisms differ among these conditions, the causes of elevated lactate in shock states appear related to a tissue deficit of oxygen or oxygen utilization. Blood lactate monitoring is also useful in guiding the effectiveness of therapy. Therapy is most effective in these shock states if detected early, and lactate results can be an important indicator of both the presence and severity of shock (10).
Coronary Bypass Surgery
As a routine part of cardiopulmonary bypass (CPB) surgery, cardiac arrest is induced, which normally results in increased production of lactate. If the peak blood lactate level measured during CPB surgery reaches 4.0 mmol/L or higher, that patient is at a higher risk of postoperative mortality (11).

Following surgery, the heart is reperfused with blood and lactate normally declines. If lactate continues to be produced following reperfusion, as indicated by an elevated or non-decreasing blood lactate concentration, there may be a delayed return to normal oxygen utilization (aerobic metabolism) in the heart. This correlates with depressed myocardial function which may require additional support with cardiac stimulants or intraaortic balloon pumping (12).

Intra-aortic Balloon Pumping After Cardiac Surgery
As mentioned in the above section, intra-aortic balloon pumping (IABP) is a therapeutic support sometimes used following difficult cardiac surgical procedures. Even with this procedure, mortality rates are high. If a marker were available to give an early indication that IABP was not successful, other mechanical cardiovascular support options could be considered. A recent study suggests that an elevated blood lactate is an early indicator that the patient is not responding favorably to IABP (13).

Use in ED to Evaluate and Triage Patients With Chest Pain
An elevated blood lactate on arrival in the ED is useful in identifying patients with chest pain related to a critical cardiac illness such as acute myocardial infarction (AMI), serious congestive heart failure, or severe arrhythmia. The level of lactate clearly correlates with an increased mortality and a need for urgent medical intervention. A normal blood lactate on admission strongly suggests the patient does not have an AMI (14).

Evaluation of Trauma in ED Setting
Elevated venous blood lactate measurements >2.0 mmol/L at admission to the ED were a better triage tool than Standard Triage Criteria for correctly assessing the severity of trauma patients admitted to ED of a major trauma center (15).

Diagnosis of Acute Abdominal Disease
In patients with acute abdominal symptoms, an elevated blood lactate concentration was an excellent marker for an acute life-threatening abdominal condition such as mesenteric ischemia, bacterial peritonitis, intestinal obstruction, and acute pancreatitis (16).

Use in Fluid Resuscitation of Patients With Burn Injuries
Burn patients are typically given fluids to maintain adequate blood volume and renal function. Both blood pressure >70 mmHg and urine output of >30 mL/h have been used to indicate the adequacy of fluid resuscitation. Blood lactate levels appear to indicate adequate fluid resuscitation in trauma patients. However, in burn patients, the blood lactate and base deficit remained elevated despite both blood pressure and urine output being maintained above the recommended thresholds.

Historical Developments in Rapid Lactate Measurements

Pre-packaged individual test devices
One of the first lactate methods in wide use that provided lactate results rapidly at all hours was the duPont aca, which used self-contained reaction packets to measure lactate in plasma by an enzymatic colorimetric method. Lactate dehydrogenase oxidized lactate to pyruvate with simultaneous reduction of NAD+ to NADH, which was monitored at two wavelengths: 340 nm (NADH absorbance) and 383 nm (background absorbance) (1).

In the method for the J&J Vitros (former Ektachem), lactate is measured by a dry, multi-layered slide coated on a polyester support. After centrifugation, plasma is deposited on the slide. As the sample penetrates into the chemical layers, lactate in the sample is oxidized by lactate oxidase to pyruvate and hydrogen peroxide (H2O2). The H2O2 then oxidizes dye precursors which are measured by reflectance spectrophotometry. These methods cannot analyze whole blood, but require plasma from blood collected in a tube containing either sodium fluoride/potassium oxalate or heparin (1).

Electrochemical sensors
For over ten years, electrochemical methods have been used to measure blood lactate. While early methods measured lactate on diluted whole blood (such as the YSI), more recent analyzers measure lactate in undiluted whole blood, which has been a major factor in these analyzers achieving wide use in the critical care setting. Because it can be analyzed soon after collection, heparinized whole blood can be used. Typically, lactate is included with blood gases,
electrolytes, and glucose, to provide a very useful panel of tests in critical care.

The principle of measurement is based on diffusion of lactate from the whole-blood sample through a membrane that both screens out interfering substances and oxidizes lactate to pyruvate. A platinum electrode then oxidizes the H$_2$O$_2$ generated in this reaction. The current generated is proportional to the lactate concentration. The typical reaction sequence is:

Lactate + O$_2$ $\xrightarrow{\text{lactate oxidase}}$ Pyruvate + H$_2$O$_2$

H$_2$O$_2$ $\xrightarrow{675 \text{ mV}}$ 2H$^+$ + O$_2$ + 2 e$^-$ \hspace{1cm} (6)

Glucose and lactate are often combined in a sensor consisting of special membranes containing either lactate or glucose oxidase covering platinum electrodes. The lactate or glucose sensor is constructed of a three-layer composite membrane: an inner layer for screening interferences, a bound-enzyme layer for the oxidation reactions, and an outer layer for controlling the diffusion of lactate or glucose into the enzyme layer. Glucose or lactate are determined by enzymatic reaction with glucose or lactate oxidase to produce H$_2$O$_2$, which is detected amperometrically by the platinum electrode under the specific membrane containing either lactate or glucose oxidase (17).

References

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