CHAPTER **52**

ERYTHROCYTE SEDIMENTATION RATE

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Erythrocyte sedimentation rate, or "sed rate", as many of us have come to know it, is a commonly ordered test in the clinical setting. What is a sed rate? What does it tell you? Is it sensitive or specific for anything? How much weight should be given to a normal or abnormal value? The erythrocyte sedimentation rate (ESR) is a simple, inexpensive laboratory test that clinicians have used for over 50 years. Despite its long-term use, many criticize the test because of its lack of specificity, and claim that using the ESR as a "sickness index" is scientifically unsound.

HISTORICAL BACKGROUND

Historically, the sedimentation of drawn blood was one of the principles on which ancient Greek medicine was based. For the Greeks, the rate of sedimentation of red cells was a way to detect the presence of certain bad bodily "humors." They were able to determine that with certain diseases, the blood sedimented quickly.

In 1918, German scholar Robin Fåhraeus introduced the erythrocyte sedimentation rate to modern medicine. He published a paper describing his observations on the ESR in pregnancy. His original research dealt with the erythrocyte sedimentation changes that occur with pregnancy, and he at first proposed it as a test for pregnancy. Three years later, in 1921, he wrote a more detailed report in which the erythrocyte sedimentation rate was related to many factors other than pregnancy. Even as early as this, he was able to determine that the rate of sedimentation depends on the ability of plasma to lower the electrostatic charge on the surface of the red blood cells so that agglutination can occur. Fåhraeus was able to quantify the agglutination potential of some plasma proteins and showed that fibrinogen is a more powerful agglutinator than globulin, and globulin more active than albumin. He also examined the effect of environmental and technical factors on the sedimentation rate, as well as the rate of sedimentation of red cells in various pathologic and physiologic conditions.

MECHANISM AND FACTORS THAT AFFECT ESR

Investigation into the mechanism of the sedimentation of erythrocytes has revealed several intrinsic and extrinsic factors. Erythrocyte sedimentation depends on the aggregation of red blood cells and the formation of rouleaux. Both rouleaux formation and aggregation are determined by the characteristics of the erythrocytes, the properties of the plasma, and by mechanical or technical factors.

Erythrocytes settle in vitro because the density of the cell is greater than the density of the plasma. As the red blood cells fall, there is an upward displacement of plasma, which produces an upward current and acts as a retarding force. Normally, these downward and upward forces are approximately equal and little settling occurs. However, when red cells aggregate along a single axis to form rouleaux, the weight of the particles increases relative to their surface area, and the rate of fall through the plasma increases.

Erythrocytes are negatively charged and normally repel each other, thus preventing aggregation or rouleaux formation. This negative charge is known as the *zeta potential*, and is a result of the negatively charged sialic acid groups on the erythrocyte membrane. In order to overcome the negative charge between erythrocytes, there has to be something that absorbs this force (decreases the *zeta potential*). This absorption is performed by protein molecules and other macromolecules in the plasma. The greatest decrease in the *zeta potential* is exhibited by asymmetric molecules such as fibrinogen and immunoglobulins. Therefore, when the plasma concentration of fibrinogen and immunoglobulin is increased, the *zeta potential* of the erythrocytes is decreased, and rouleaux formation and aggregation is increased. One can assume that the sedimentation rate should be increased in those diseases or conditions characterized by hyperfibrinogenemia (tissue necrosis, infection, pregnancy) or elevated immunoglobulins (multiple myeloma and other immunoglobulinopathies).

ELEVATED ERYTHROCYTE SEDIMENTATION RATE

When faced with an elevated sedimentation rate, it is first important to consider the patient's age, gender, medications, and past medical history. Gender has an important influence on the erythrocyte sedimentation rate, as women tend to have a higher baseline sedimentation rate than men. Androgens are believed to be responsible for this difference. In vitro studies show that androgens do lower the sedimentation rate. In normal men, castration leads to an increase in the sedimentation rate, while eunuchs given testosterone exhibit a lowering in the sedimentation rate.

Age also influences the erythrocyte sedimentation rate. The sedimentation rate rises steadily with age. Overall, the erythrocyte sedimentation rate will increase by 0.85 mm an hour for each five-year increase in age. After menopause, at around age 50, the erythrocyte sedimentation rate rises faster for women than for men. The cause of the increase in erythrocyte sedimentation rate with age is unclear, but it is postulated that it reflects increased levels of fibrinogen. A simple formula for estimating a patient's ESR, based on age and gender is presented:

Formula for normal range Westergren ESR
Men: ESR = age/ 2
Women: ESR = [age + 10] / 2

A variety of medications, such as heparin and oral contraceptives, increase the erythrocyte sedimentation rate. Any disease that causes an increase in fibrinogen or immunoglobulins will cause the ESR to increase. Most any disease or illness will do so. There are a limited number of diseases that do not increase the ESR, but have similar presenting symptomatology to those that do. Therefore, the ESR can be used to help differentiate and rule-out certain diseases. Malignancy, infection, and collagen vascular diseases are diseases that are associated with an increased ESR. Certain entities within these groups have erythrocyte sedimentation rates which fall within certain "ranges" of an elevated ESR (Table 1).

Table 1

CLINICAL CORRELATION OF SEDIMENTATION RATE

I. MARKEDLY INCREASED SEDIMENTATION RATE (>100mm)

- Waldenström's macroglobulinemia
- Acute severe bacterial infections
- Active portal or biliary cirrhosis
- Viral pneumonitis (early)
- Multiple myeloma
- Malignant lymphoma
- Leukemia
- Carcinoma
- Severe anemia
- Sarcoma
- Ulcerative colitis
- Severe renal disease
- Collagen diseases

II. MODERATELY INCREASED SEDIMENTATION RATE

- Acute and chronic infectious diseases
- Acute localized infections
- Reactivation of a chronic infection
- Malignant tumors with necrosis
- Lead and arsenic intoxication
- Normal pregnancy after third month
- Ingestion of oral contraceptives
- Rheumatic fever
- Rheumatic arthritis
- Myocardial infarction
- Menstruation
- Hyperthyroidism
- Hypothyroidism
- Internal hemorrhage
- Nephrosis
- Acute hepatitis (viral)
- Tuberculosis
- Hyperlipidemia
- Advanced age

III. USUALLY NORMAL SEDIMENTATION RATE

- Early acute appendicitis (first 24 hours)
- Early unruptured ectopic pregnancies
- Infectious mononucleosis (uncomplicated)
- Uncomplicated viral diseases
- Rheumatic carditis with cardiac failure
- Cirrhosis of liver
- Acute allergies
- Degenerative arthritis
- Peptic ulcer
- Typhoid fever
- Undulant fever
- Pertussis
- Rickettsial ds.
- Toxoplasmosis
- Malaria

IV. LOW OR "ZERO" SEDIMENTATION RATE

- Polycythemia vera
- Hb C disease
- Sickle cell anemia
- Spherocytosis

LOW ERYTHROCYTE SEDIMENTATION RATE

A low sedimentation rate results from either a change in the erythrocyte itself, or from an abnormality in plasma proteins. Polycythemia tends to decrease the compactness of the rouleaux network and artificially lower the sedimentation rate. Abnormally shaped cells, as in Sickle Cell Anemia, also lower the erythrocyte sedimentation rate. As a result of this characteristically low ESR, any increase in the ESR of a patient with sickle cell disease should raise an index of suspicion for possible occult disease, the most common of which is osteomyelitis. Hemolytic anemia, hemoglobinopathy, hereditary spherocytosis, and pyruvate kinase deficiency will lead to an abnormally low sedimentation rate. Hypofibrinogenemia is the most common abnormality of plasma proteins that results in a low erythrocyte sedimentation rate. This can be attributed to either hereditary factors or may occur secondarily in diseases such as DIC (disseminated intravascular coagulation) where fibrinogen is consumed. Waldenström's macroglobulinemia will cause an increase in the viscosity of the plasma and a predictable decrease in the rate of sedimentation.

Drugs such as anti-inflammatory agents, high dose salicylate, cortisone, and asparaginase have been reported to lower the sedimentation rate. This is particularly important because the erythrocyte sedimentation rate is often used to assess the activity of collagen vascular diseases. These are common illnesses for which patients are treated with anti-inflammatory medications. Among the other conditions that may lower the erythrocyte sedimentation rate are trichinosis, bile salt excess, or extreme elevation in the white blood cell count, as in chronic lymphocytic leukemia.

Although the diseases and physiological conditions that are associated with a low erythrocyte sedimentation rate have been discussed, it is paramount that one realize the diagnostic significance of a low ESR. In a study in which 358 patients with a low sedimentation rate were reviewed (less than or equal to 1mm per hour), it was found that only 6% had a disease associated with a low sedimentation rate. Thirty-eight percent had no demonstrable abnormality. On the basis of this data and other information, it appears that a low erythrocyte sedimentation rate is of no diagnostic value. It is important, however, to check the hematocrit and protein level of these patients, as polycythemia and hyperproteinemia are conditions associated with a low ESR. Any elevated ESR in a patient with Sickle Cell Anemia, with its classically low ESR, should be monitored closely and should raise a high index of suspicion for infection.

METHODS USED TO MEASURE THE ERYTHROCYTE SEDIMENTATION RATE

Approximately seven methods are used to measure the erythrocyte sedimentation rate. Each measures the rate of fall of red blood cells in a tube. The two most common techniques used today are the Westergren method and the Wintrobe method.

The Westergren method was one of the earliest methods used, and is still considered the gold standard for measuring the erythrocyte sedimentation rate. This method mixes 4 volumes of blood with 1 volume of 3.8% sodium citrate. A standard 200 mm Westergren glass tube is filled to the zero mark at the top, set in a vertical position, and left for one hour. The result is expressed as the Westergren erythrocyte sedimentation rate "X" mm per hour. For men, the normal values are less than 16mm/hr, and for women, less than 25mm/hr.

The second most commonly used method to measure the erythrocyte sedimentation rate is the Wintrobe method. This test is performed with a 100 mm tube containing oxalate as the anticoagulant. For men, the normal values for the Wintrobe method are less than 6.5mm/hr, and for women, less than 16mm/hr. The Westergren method is more accurate, while the Wintrobe method is more convenient. Other methods include Linzenmeier, Cutler, Lindow Adam, Smith, and Rourke Ernstene.

TECHNICAL FACTORS THAT EFFECT THE ESR

Whatever the method used to measure the erythrocyte sedimentation rate, there is the potential that mechanical, environmental, or technical factors can influence the rate and provide potentially misleading results. First and foremost, the test should be run within two hours after the blood sample is drawn, or it will be susceptible to artificial lowering of the sedimentation rate. Adequate anticoagulation is necessary, or clotting will consume fibrinogen and artificially lower the erythrocyte sedimentation rate. The blood must be adequately mixed before it is put into the tube because any preformed rouleaux will lead to an increase in the sedimentation rate. The dimension of the tube will also affect the rate of fall. As the bore diameter increases, sedimentation rate increases, and vice-versa. Both the size of the tube and the anticoagulant used will be determined by the method or technique employed. The temperature must be controlled (maximal rouleaux formation will occur at 37°C). And finally, the surface on which the test will be performed must be level and free from any vibration. A tilt in the table will increase the rate, while vibration, as from a centrifuge, will inhibit it.

Because of the multitude of factors that must be considered for accurate execution of this test, it is important to establish the reliability of the test within a given institution. Without proof of the test's reliability, the results should be interpreted with skepticism.

C-REACTIVE PROTEIN

C-reactive protein exists at trace amounts in the serum of individuals while they are healthy. After tissue injury or destruction, C-reactive protein is one of several heterogeneous serum proteins whose production is increased. After insult, C-reactive protein may be found in the serum within a matter of hours. This rapid response to injury classifies C-reactive protein as an acute phase reactant.

The various functions of C-reactive protein are not fully understood, but it is known to activate the complement system, enhance phagocytosis, block the receptors of T-lymphocytes, and inhibit platelet aggregation. To date, it is speculated that C-reactive protein's primary purpose is to recognize and bind to toxic materials which are present in or released from injured cells, and render them harmless to host tissues. It is synthesized by hepatocytes and is probably under the influence of humoral mediators such as endogenous pyrogens and prostaglandins. After production in the liver, C-reactive protein localizes at the site of tissue injury or inflammation.

CRP VERSUS ESR

An elevated ESR is often found in patients with infectious disease. Serious bacterial infections usually result in high ESR and CRP values, however, in viral infections, CRP values do not elevate to the same degree as the ESR. The sedimentation rate increases relatively slowly and may remain elevated for weeks after the infection has subsided. ESR increases during pregnancy, making it less suitable as a disease-monitoring parameter during this period.

The C-reactive protein concentration usually increases more than a hundred times within 24 hours after the onset of serious infection. The half-life of C-reactive protein is short and the level falls rather quickly after effective therapy or spontaneous improvement of disease. Pregnancy does not cause significant changes in C-reactive protein levels.

In hospitals, quantitative C-reactive protein measurement has become increasingly important as an emergency test for rapid diagnosis of serious infectious diseases, such as sepsis, meningitis, and pneumonia. It is also used to monitor the effect of antibacterial treatment. C-reactive protein has largely replaced the use of the erythrocyte sedimentation rate in many clinical settings, especially in departments of pediatrics.

CONCLUSION

Erythrocyte sedimentation rate is one of the most commonly used laboratory tests in general practice, and physicians have extensive experience in interpreting the results. Erythrocyte sedimentation rate indicates the presence and intensity of an inflammatory process but is never diagnostic of a specific disease. It may be useful in detecting occult disease, assisting in differential diagnosis, or confirming or excluding a diagnosis. A normal ESR, however, does not exclude malignancy or other serious diseases. A patient found to have a markedly elevated erythrocyte sedimentation rate has a 95% likelihood of an infectious, inflammatory, or neoplastic process. However, the range of specific diseases that may cause the elevation is so diverse that the erythrocyte sedimentation rate is not useful as a diagnostic test, but rather as a "sickness index."

Our understanding of the erythrocyte sedimentation rate has not changed over the last 50 years. Because the sensitivity is low or unknown for most infectious, inflammatory, and malignant conditions, many claim that judicious clinicians would not use the erythrocyte sedimentation rate to rule-out a disorder.

In podiatric medicine and surgery, our most common nemesis or complication is infection. Both the erythrocyte sedimentation rate and C-reactive protein are indices for such. C-reactive protein levels appear to be a more sensitive test when dealing with any acute inflammatory change. C-reactive protein shows an earlier and more intense increase than ESR. With recovery, disappearance of C-reactive protein precedes the ESR's return to normal.

BIBLIOGRAPHY

Bedell S, Bush B: Erythrocyte sedimentation rate, from folklore to facts. *Am J Med* 78:1001-1009, 1985.

Cohen A: *Rheumatology and Immunology* New York, Grune and Stratton, 1979, pp 65-81.

Crosby L, Powell D: The potential value of the sedimentation rate in monitoring treatment outcome in puncture-wound-related Pseudomonas osteomyelitis. *Clin Orthop Rel Res* 188:168-171, 1984.

de Man P, Jodal U, Svanborg C: Dependence among host response parameters used to diagnose urinary tract infection. *J Infect Dis* 163:331-335, 1991.

Hellgren U, Julander I: Are white blood cell count, platelet count, erythrocyte sedimentation rate and C-reactive protein useful in the diagnosis of septicaemia and endocarditis. *Scand J Infect Dis.* 18:487-488, 1986.

Hjortdahl P, Landaas S, et al. C-Reactive protein: A new rapid assay for managing infectious disease in primary health care. *Scand J Prim Health Care.* 9:3-10, 1991.

Jönsson B, Söderholm R, Strömqvist Björn: Erythrocyte sedimentation rate after lumbar spine surgery. *Spine.* 16:1049-1050, 1991.

Katz P, Gutman S, et al: Erythrocyte Sedimentation Rate and C-Reactive Protein Compared in the Elderly. *Clin Chem.* 35:466-468, 1989.

Kirkeby O, Risøe, Vikland R: Significance of a high Erythrocyte Sedimentation rate in general practice. *Br J Clin Pract.*43:252-254, 1989.

Lascari A: The erythrocyte sedimentation rate. *Ped Clin North Am.* 19:1113-1121, 1972.

Miale JB: *Laboratory Medicine: Hematology* St. Louis,CV Mosby, 1984, pp 350-357.

Singer J, Buchino J, Chalbali R: Selected laboratory in pediatric emergency care. *Emerg Med Clin North Am.* 4:377-396, 1896.

Wallach, J: *Interpretation of Diagnostic Tests.* Boston, Little, Brown and Company, 1992, pp 74-77.

Zacharski LR, Kyle RA: Low erythrocyte sedimentation rate: clinical significance in 358 cases. *Am J Med Science.* 250:208-211, 1965.