PHYSIOLOGICAL BASIS AND CLINICAL UTILITY OF ERYTHROCYTE SEDIMENTATION RATE

M Amjad Hameed[1], Sobia Waqas[2]

ABSTRACT

The erythrocyte sedimentation rate (ESR) determination is a commonly performed laboratory test with a time-honored role. However, the usefulness of this test has decreased as new methods of evaluating disease have been developed. The test remains helpful in the specific diagnosis of a few conditions, including temporal arteritis, polymyalgia rheumatica and, possibly, rheumatoid arthritis. It is useful in monitoring these conditions and may predict relapse in patients with Hodgkin's disease. Use of the ESR as a screening test to identify patients who have serious disease is not supported by the literature. Some studies suggest that the test may be useful as a "sickness index" in the elderly or as a screening tool for a few specific infections in certain settings. An extreme elevation of the ESR is strongly associated with serious underlying disease, most often infection, collagen vascular disease or metastatic malignancy. When an increased rate is encountered with no obvious clinical explanation, the physician should repeat the test after an appropriate interval rather than pursue an exhaustive search for occult disease

KEY WORDS: ESR, Acute phase reactant, Rouleaux, Sickness Index.

Pak J Med Sci April - June 2006 Vol. 22 No. 2 214 - 218

HISTORY

Edmund Biernacki (1866-1912), a Polish physician, first noted the increased sedimentation rate of blood from ill individuals and realized that it was due to the presence of fibrinogen.[1] In 1918, Robin Fahraeus (1888-1968) furthered Biernacki's work.[2] His initial motivation to study the ESR was as a pregnancy test but his interest expanded to the study of the ESR in disease states. Alf Westergren (1981-1968) refined the technique of performing the ESR and reported its usefulness in determining the prognosis of patients with tuberculosis.[3] A variation of the methodology of the ESR was published by Wintrobe in 1935 and was at one time in wide use. In 1977, the International Committee for Standardization in Hematology recommended the adoption of the Westergren method worldwide.[3,4]

1. Brig(R) Prof. M Amjad Hameed
Professor of Physiology
2. Dr. Sobia Waqas
Demonstrator in Physiology
1-2: Islamic International Medical College, Rawalpindi, Pakistan.

Correspondence:

Brig(R) Prof. M Amjad Hameed
E-Mail: amjadh39@hotmail.com

* Received for Publication: February 26, 2005
Revision Received: May 26, 2005
Accepted: October 17, 2005

METHODOLOGY

The Westergren method employs a 200 mm, 2.5 mm diameter tube vertically aligned column. The column is filled with blood anticoagulated with K3EDTA. The distance that the column of blood falls in one hour is recorded and reported in mm/ at the end of 1st hour. The Wintrobe method employs a shorter tube (100mm) and an different anticoagulant (ammonium oxide and potassium oxalate). It also corrects for anemia. It is generally accepted that the Wintrobe method is more sensitive for mild elevations but also has a higher false positive rate while the Westergren method is more sensitive for changes at elevated levels and may be more useful where the ESR is being used to evaluate the response to

therapy, i.e., in diseases such as temporal arteritis.[5]

MECHANISM

Sedimentation of red cells in this system is affected by forces both for and against sedimentation. The forces resisting sedimentation are the negative charge on the red cell surface (causing red cells to repel each other (zeta potential)), the up flow of plasma displaced by falling red cells, and the rigidity of red cells. The forces accelerating sedimentation are anemia and plasma proteins. Plasma proteins bind to red cell membranes thereby reducing the zeta potential thus allowing rouleaux formation to occur. The degree to which proteins reduce the zeta potential can be rated on a scale of 1-10: fibrinogen 10, beta-globulin 5, alpha globulin 2, gamma globulin 2, and albumin 1.

There are a number of artifactual causes of an elevated ESR. These include vibration of the ESR tube; the tube being non-vertical, inadequate anticoagulation with clotting of blood sample will consume fibrinogen and may artifactually lower the ESR and the age of the sample (increasing age decreases the ESR).[6]

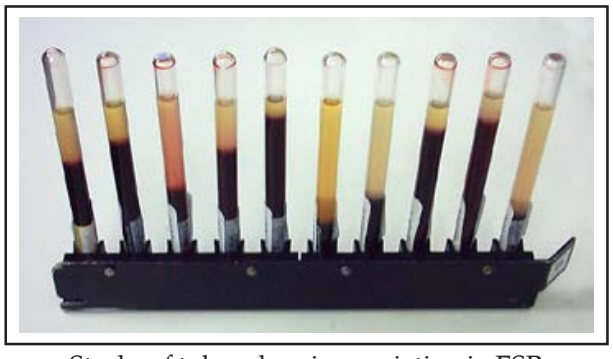
ESR is called an acute-phase reactant test, meaning that it reacts to acute conditions in the body, such as infection or trauma. The rate increase follows a rise in temperature and white blood cells count, peaks after several days, and usually lasts longer than the elevated temperature or white blood cells count.[7]

TERMS:[8]

Acute phase reactant: A substance in the blood that increases as a response to an acute conditions such as infection, injury, tissue destruction, some cancers, burns, surgery, or trauma.

Erythrocyte sedimentation rate (ESR): The distance that red blood cells settle in a tube of blood in one hour. Rise more than normal indicates some infection or inflammation. Helpful in prognosis of disease.

Rouleaux: The stacking up of red blood cells, caused by extra or abnormal proteins in the blood that decrease the normal distance red cells maintain between each other.



Stacks of tubes showing variation in ESR

PHYSIOLOGIC BASIS FOR THE TEST

As with other laboratory tests, the actual reference range used for the ESR should be established by the laboratory performing the test. Women tend to have higher ESR values, as do the elderly.[9] For unknown reasons, obese people have also been noted to have slightly elevated ESRs, although this is not thought to have clinical significance.[10]

Reference Interval:[11]

Child:			2-15 mm in 1 hour
Adult:	*Male:*	17-50 years:	1-10 mm in 1 hour
		>50 years:	2-14 mm in 1 hour
	Female:	17-50 years:	3-12 mm in 1 hour
		>50 years:	5-20 mm in 1 hour

Any condition that elevates fibrinogen (e.g., pregnancy, diabetes mellitus, end-stage renal failure, heart disease, collagen vascular diseases, malignancy) may also elevate the ESR.[3] Anemia and macrocytosis increase the ESR. In anemia, with the hematocrit reduced, the velocity of the upward flow of plasma is altered so that red blood cell aggregates fall faster. Macrocytic red cells with a smaller surface-to-volume ratio also settle more rapidly.A decreased ESR is associated with a number of blood diseases in which red blood cells have an irregular or smaller shape that causes slower settling.[12]

In patients with polycythemia, too many red blood cells decrease the compactness of the rouleaux network and artifactually lower the ESR. An extreme elevation of the white blood cell count as observed in chronic lymphocytic leukemia has also been reported to lower the

ESR.[13] Hypofibrinogenemia, hypergammaglobulinemia associated with dysproteinemia, and hyperviscosity may each cause a marked decrease in the ESR. Although it has been reported that drug therapy with aspirin or other nonsteroidal anti-inflammatory agents may decrease the ESR, this has been disputed.[6,7,14]

Interpretation: The ESR is a non-specific test and so can be difficult to interpret. Recent trials of the ESR have demonstrated no value in screening asymptomatic individuals, because not only is the number of abnormal is low but also in most cases the abnormal test returns to normal over several months without any significant diagnosis being made.[15]

USEFULNESS AS A SICKNESS INDEX IN THE ELDERLY

Some authors have proposed that the ESR be used as an inexpensive "sickness index" in the elderly.[15,16] There is also little evidence of value in screening symptomatic patients because a complete history and physical examination is a much better tool for detecting abnormalities. An extensive search should be made for the cause of an elevated ESR but provide little evidence of the benefits of such a search. Recent cost-benefit analysis has suggested that tests in addition to a complete history and physical examination are not cost effective.

However, there are several groups of patients where the ESR is important, patients suspected of having temporal arteritis or polymyalgia rheumatica. In these cases treatment is often initiated after an elevated ESR result is known and prior to a definitive biopsy. In these patients the diagnosis is difficult to sustain, but not excluded, if the ESR is normal.[18]

The ESR can also be useful in monitoring certain groups of patient's rheumatoid arthritis, temporal arteritis, polymyalgia rheumatica, and Hodgkin's disease life (H.D.), where disease activity is mirrored by changes in the ESR.[19,20]

There is debate as to whether this test is useful in distinguishing between organic and psychosomatic disease.[21] There is no evidence of any diagnostic value to the ESR when attempting to evaluate acutely ill patients already known to have acute or chronic infections, or cancer (except H.D.). Even in screening patients with possible myeloma the ESR has been replaced by measurement of

Factors That May Influence ESR[14]

Factors that increase ESR	*Factors that decrease ESR*	*Factors with no clinically significant effect or questionable effect*
Old age	Extreme leukocytosis	Obesity
Female	Polycythemia	Body temperature
Pregnancy	Red blood cell abnormalities	Recent meal
Anemia	Spherocytosis	Aspirin
Red blood cell abnormalities	Acanthocytosis	NSAIDs
Macrycytosis	Microcytosis	
Technical factors	Technical factors	
Dilution problem	Dilution problem	
Increased temperature of specimen	Inadequate mixing	
Tilted ESR tube	Clotting of blood sample	
Elevated fibrinogen level	Short ESR tube	
Infection	Vibration during testing	
Inflammation	Protein abnormalities	
Malignancy	Hypofibrinogenemia	
	Hypogammaglobulinemia	
	Dysproteinemia with hyperviscosity state	

NSAIDs = nonsteroidal anti-inflammatory drugs; ESR = erythrocyte sedimentation rate.

total protein and globulin fraction.[22]

Extreme Elevation of the ESR: An extreme elevation of the ESR (defined as greater than 100 mm per hour) is associated with a low false-positive rate for a serious underlying disease.[22,23] The conditions found in this situation have varied in individual populations, depending on patient age and inpatient versus outpatient status. In most series, infection has been the leading cause of an extremely elevated value, followed by collagen vascular disease and metastatic malignant tumors.[22,24] Renal disease has also been a notable etiologic factor.[2]

UTILITY OF THE ESR KEY CONSIDERATIONS

- The ESR is an inexpensive, simple test of chronic inflammatory activity.
- Indications for the ESR have decreased as the sophistication of laboratory testing has increased.
- The ESR rises with age, but this increase may simply reflect a higher disease prevalence in the elderly.
- The use of the ESR as a screening test in asymptomatic persons is limited by its low sensitivity and specificity.
- An elevated ESR is a key diagnostic criterion for polymyalgia rheumatica and temporal arteritis, but normal values do not preclude these conditions.
- When there is a moderate suspicion of disease, the ESR may have some value as a "sickness index."
- An extremely elevated ESR (>100 mm/hr) will usually have an apparent cause—most commonly infection, malignancy or temporal arteritis.
- A mild to moderately elevated ESR without obvious etiology should prompt repeat testing after several months rather than an expensive search for occult disease.

RECOMMENDATIONS

* The ESR may be used to evaluate patients with unexplained symptoms or a deterioration of health status when[25] an inflammatory, neoplastic, or infectious disease is suspected;
* The ESR may be used to monitor the activity of giant cell arteritis,polymyalgia rheumatica, inflammatory arthritis and some infections.[5,17,26] A specific diagnosis is not made effectively by other means.
* There is no evidence to support the use of the ESR in asymptomatic individuals and this test should not be appended to routine investigations.
* The ESR will only be performed if a written indication is provided on the requisition.

Rationale: The erythrocyte sedimentation rate (ESR) is a relatively nonspecific test that is frequently ordered during the diagnosis and monitoring of disease. A variety of factors influence the sedimentation rate. Disease-related factors that may affect the ESR include the plasma immunoglobulin and fibrinogen concentrations, and the presence and degree of anemia.[27,28] Factors unrelated to disease. That process may affect ESR values include age, sex, and drug therapy.[29,30]

REFERENCES

1. Biernacki E. Increased sedimentation rate of blood from ill individuals. Historical background: 1866-1912. uwcme.org/site/courses/legacy/rheumlab/esr.php - 19k - 3 May 2005.
2. Fahraeus R. Historical Article MeSH Terms Blood Sedimentation* Hematology /history: 1888-1968. www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd
3. Alf Westergren) refined the technique of performing the ESR and reported its usefulness in determining the prognosis of patients with tuberculosis:1981-1968 www.proz.com/?sp=h&id=484222 - 35k
4. Wintrobe WW, Landsberg JW. A standardized technique for blood sedimentation test. Am J med Sci 1935; 189: 102-15.
5. Fauchald P, Rygvold O, Oystese B. Temporal arteritis and polymyalgia rheumatica: Clinical and biopsy findings. Ann Intern Med 1972; 77: 845-52.
6. Brigden M. The erythrocyte sedimentation rate: still a helpful test when used judiciously. Postgrad Med 1998; 103: 57-74.
7. Sox HC Jr, Liang MH. The erythrocyte sedimentation rate: guidelines for rational use. Ann Intern Med 1986; 104: 515-23.
8. Stuart J, Whicher JT. Tests for detecting and monitoring the acute phase response. Arch Dis Child 1988; 63: 115-7.

9. Katz PR, Karuza J, Gutman SI, Bartholomew W, Richman G. A comparison between erythrocyte sedimentation rate (ESR) and selected acute-phase proteins in the elderly. Am J Clin Pathol 1990; 94: 637-40.
10. Smith EM, Samadian S. Use of the erythrocyte sedimentation rate in the elderly. Br J Hosp Med 1994; 51: 394-7.
11. Bottiger LE, Svedberg CA. Normal erythrocyte sedimentation rate and age. Br Med J 1967; 2: 85-7.
12. Saadeh C. The erythrocyte sedimentation rate: old and new clinical applications. South Med J 1998; 3: 220-5.
13. Wolfe F, Michaud K. The clinical and research significance of the erythrocyte sedimentation rate. J Rheumatol 1994; 21: 1227-37.
14. Thomas EA, Bennett JC, Carpenter CJ, Charles Plum F. Cecil essential Med. 4th edit. W.B. Saunders Company 1997; 592-600.
15. Wolfe F, Michaud K. The clinical and research significance of the erythrocyte sedimentation rate. J Rheumatol 1994; 21: 1227-37.
16. Tinetti ME, Schmidt A, Baum J. Use of the erythrocyte sedimentation rate in chronically ill, elderly patients with a decline in health status. Am J Med 1986; 80: 844-8.
17. T Brigden ML. Iron deficiency anemia: every case is instructive. Postgrad Med 1993; 93: 181-92.
18. Goodman BW Jr. Temporal arteritis. Am J Med 1979; 67: 839-52.
19. Henry-Amar M, Friedman S, Hayat M, Somers R, Meerwaldt JH, Carde P. Erythrocyte sedimentation rate predicts early relapse and survival in early-stage Hodgkin's disease. Ann Intern Med 1991; 114: 361-5.
20. Wise CM, Agudelo CA, Chmelewski WL, McKnight KM. Temporal arteritis with low erythrocyte sedimentation rate: a review of five cases. Arthritis Rheum 1991; 34: 1571-4.
21. Fincher RM, Page MI. Clinical significance of extreme elevation of the erythrocyte sedimentation rate. Arch Intern Med 1986; 146: 1581-3.
22. Johansson JE, Sigurdsson T, Holmberg L, Bergstrom R. Erythrocyte sedimentation rate as a tumor marker in human prostatic cancer: an analysis of prognostic factors in 300 population-based consecutive cases. Cancer 1992; 70: 1556-63.
23. Lluberas-Acosta G, Schumacher HR Jr. Markedly elevated erythrocyte sedimentation rates: consideration of clinical implications in a hospital population. Br J Clin Pract 1996; 50: 138-4.
24. Ljungberg B, Grankvist K, Rasmuson T. Serum acute phase reactants and prognosis in renal cell carcinoma. Cancer 1995; 76: 1435-9.
25. Zlonis M: The mystique of the erythrocyte sedimentation rate. Clin Laboratory Med 1993; 13: 787-800.
26. Witte DL, Angstadt DS, Davis SH, Schrantz RD. Predicting bone marrow iron stores in anemic patients in a community hospital using ferritin and erythrocyte sedimentation rate. Am J Clin Pathol 1988; 90: 85-7.
27. Sox HC Jr, Liang MH. The erythrocyte sedimentation rate: guidelines for rational use. Ann Intern Med 1986; 104: 515-23.
28. Thoren B, Wigren A. Erythrocyte sedimentation rate in infection of total hip replacements. Orthopedics 1991; 14: 495-7.
29. Barland P, Lipstein E: Selection and use of laboratory tests in the rheumatic diseases. Am J Med 1996; 100(suppl 2A): 16S-23S.
30. Sox HC, Liang MH: The erythrocyte sedimentation rate: guidelines for rational use. Ann Intern Med 1986; 104: 515-23.