The Erythrocyte Sedimentation Rate (ESR)

Introduction

The erythrocyte sedimentation rate (ESR) is one of the most commonly ordered yet least well understood laboratory tests. In the United Kingdom, one ESR is done for every three to four blood counts. The Hematology Laboratory at the San Francisco General Hospital currently performs an average of 40 to 50 ESRs per day. Despite these large numbers of tests ordered, there is virtually no quality control or enthusiasm towards automation of the ESR. This procedure is used as a nonspecific indicator of disease and a monitor of response to therapy of certain disorders; however, recent literature reflects a resurgence of interest in the ESR and its clinical utility.

Principle

Sedimentation occurs because the density of erythrocytes (RBCs) is greater than that of plasma. Sedimentation is increased when RBCs aggregate, a process that is inhibited by the negative charge (zeta potential) of the cell membrane. Plasma proteins, especially fibrinogen and immunoglobulins, increase the cell-cell attractive forces and thus facilitate stacking and rouleaux formation. In addition, acute-phase reactants (alpha\(_1\) antitrypsin and alpha\(_1\) glycoprotein) which are elevated in inflammatory states increase the ESR. Thus, conditions associated with hyperfibrinogenemia (infection, necrosis, pregnancy), elevated immunoglobulins, or acute-phase reactants usually show an increased ESR.

Methodology

The measurement of the ESR is basically unchanged from the early 1920's when the test was reported by Fahraeus and technically refined by Westergren. The modified Westergren method measures the settling of EDTA anti-coagulated blood diluted with saline for one hour in a 300 mm calibrated column. This method is simple and conveniently handled by technologists. The modified Westergren method has been recommended by the International Committee for Standardization in Hematology as the international reference method. Other methods have been introduced, such as that of Wintrobe, employing undiluted blood and different column lengths and diameters with or without correction factors for anemia. However, the results between the various methods are not directly comparable.

Reference Ranges

Reference ranges for the ESR vary from 0 to 10 mm/hr (for children), to 0 to 15 mm/hr (for men), and up to 0 to 30 mm/hr (for women). Currently there is much controversy regarding the appropriate upper limit of the ESR in the elderly since the
ESR increases with age. Sharland (1980) examined 258 normal (non-hospitalized) subjects whose ages ranged from 70 to 89 years, who were followed from one to eleven years. The ESR ranged from 3 to 65 mm/hr (mean 13 mm/hr) and the authors concluded that this test was of limited diagnostic value in the elderly. Milne and Williamson (1972) examined 487 patients older than 62 years of age, and the ESR ranged from 1 to 80 mm/hr. Twenty-eight % of these subjects had an ESR greater than 20 mm/hr, and only 25% of these had associated factors known to elevate the ESR. An elevated ESR is not of itself associated with decreased longevity in persons older than 65 years of age (Sparrow et al, 1980).

Spurious Results

False elevations of the ESR may occur in anemia, pregnancy, and hypercholesterolemia. Falsely low values are reported with polycythemia, markedly elevated white cell counts, and RBC abnormalities (sickle cell disease, anisocytosis, and spherocytosis). Although the red cell count influences the ESR, correction for anemia after the test is completed cannot recapture sensitivity lost by analysis at a low or high hematocrit. The modified Westergren method induces an artificial "anemia" by dilution of the specimens, and additional changes in hematocrit have a minimal effect on ESR.

Conditions Associated with an Elevated ESR

Diseases classically associated with an elevated ESR include:

1) infectious (bacteria, fungus, hepatitis, cat scratch disease),
2) neoplastic (leukemia, lymphoma, myeloma, carcinoma, sarcoma),
3) gastrointestinal (ulcerative colitis, regional ileitis, pancreatitis),
4) collagen-vascular (rheumatoid arthritis, SLE, scleroderma, temporal arteritis),
5) renal (acute and chronic glomerulosclerosis, nephrosis, pyelonephritis).

Zacharski and Kyle (1967) reported that 263/37,450 (0.7%) patients at their referral center had an ESR greater than 100 mm/hr. Diagnostic groups included 152 (58%) patients with malignancies, 66 (25%) patients with infectious or inflammatory disorders, 22 (8%) patients with renal diseases, and 17 (6%) patients with unknown etiologies.

In contrast, Wyler (1977) found approximately 3% of a general clinic population had an elevated ESR greater than 100 mm/hr. Data from 200 such patients revealed that 35% had infectious diseases, 26% had miscellaneous disorders including renal disease and post operative fevers, 22% had inflammatory diseases, only 15% had malignancies, and 7% had no apparent illnesses. This study and others emphasized that a markedly elevated ESR was not usually caused by a malignancy and that an extensive work-up for cancer was not warranted.

Of 300 patients with malignancy, only 13 (4%) had an ESR greater than 100 mm/hr, and there was no correlation with metastatic disease. Forty-eight % of these patients had an ESR less than 20 mm/hr and patients with high ESR's had either secondary infections or skeletal metastasis. In contrast, 11 of 25 myeloma patients
had an ESR greater than 80 mm/hr and only 2 of these 25 patients had an ESR less than 20 mm/hr (Peyman, 1962).

**Conditions Associated with a Normal or Low ESR**

Inflammatory or infectious disorders associated with a normal ESR include: appendicitis, malaria, degenerative arthritis, uncomplicated viral diseases, pertussis, toxoplasmosis, in addition to other entities (Miale, 1982). A study of 358 patients with an ESR of 1 mm/hr or less revealed only 6% of the patients had conditions thought to retard sedimentation. Several patients actually had conditions that are associated with elevated ESRs; thus an isolated low ESR is of no significance (Zacharski and Kyle, 1965).

**Clinical Applications of the ESR**

1) To follow the course and results of therapy in certain diseases such as tuberculosis, rheumatoid arthritis, and collagen vascular diseases which cannot be monitored by other, more specific means.

2) To distinguish organic from functional diseases (lower back pain), to certain forms of organic disease when the differential diagnosis is unclear, e.g., rheumatoid arthritis versus osteo-arthritis.

3) As a practical, nonspecific indicator of active disease. This last application is the main category in which more study is needed to evaluate the usefulness of the ESR.

**Inappropriate utilization of the ESR**

1) ESR will not distinguish malignant from non-malignant states (Beresford, 1951).

2) ESR will not indicate the presence of metastatic disease (Harrold and Slade, 1961).

3) "There is little benefit in measuring the ESR, if a definitive diagnosis, such as malignancy, pneumonia, or rheumatoid arthritis, has already been made." (Zacharski, 1976)

**Conclusion**

The ESR is one of the most widely utilized laboratory tests, but its low sensitivity and specificity make it ill-suited for mass screening. The ESR is of some clinical value in certain conditions as outlined above; however, other factors that elevate or retard sedimentation may render the ESR uninterpretable. A definitive cost-effectiveness study is required in order to determine the real value, if any, of this test in current medical practice.
References


