

Can Preoperative Erythrocyte Sedimentation Rate Serve as an Indicator for Midterm Adverse Events after Coronary Bypass Grafting?

Turhan Togan, MD,¹ Murat Günday, MD,² Özgür Çiftçi, MD,³ Hakan Bingöl, MD²

Departments of ¹Infectious Diseases and Clinical Microbiology, ²Cardiac and Vascular Surgery, and ³Cardiology, Başkent University, Ankara, Turkey

ABSTRACT

Objective: Erythrocyte sedimentation rate (ESR) may serve as a reasonably good indicator for coronary heart disease as usually ESR is elevated in these patients. The measurement of ESR is a very simple and cheap laboratory test that can be performed in routine blood examinations. In this study, we investigated the association between preoperative erythrocyte sedimentation rate and postoperative midterm adverse events after coronary artery bypass grafting (CABG).

Methods: In the study, only male patients were included. The patients were divided into two groups: group 1 (preoperative sedimentation rate [<20 mm/h] normal [$n = 232$, 63.9%]) and group 2 (preoperative sedimentation rate [>20 mm/h] above normal [$n = 131$, 36.1%]). The hemogram and biochemistry panel values were measured one day before operation, on the postoperative first day, on the postoperative seventh day, and on the postoperative third month.

Results: Among the laboratory values, there was a statistically significant difference between the two groups with respect to postoperative first-day ESR and postoperative third-month high-sensitivity C-reactive protein ($P < .05$). In terms of postoperative morbidity, there was also a statistically significant difference ($P < .05$) between the two groups with regard to pleural effusion, infection of the soft tissue over the sternum, pulmonary infection, return to the intensive care unit, rehospitalization, and mortality.

Conclusion: Elevated preoperative sedimentation rate is associated with postoperative adverse events in patients who undergo CABG. For this purpose, we suggest that patients with higher sedimentation rates undergo detailed examination to prevent mortality and morbidity.

INTRODUCTION

Today arteriosclerosis is regarded as a chronic low-grade inflammatory disease. It has been found that a number of systemic markers of inflammation, like erythrocyte sedimentation rate (ESR), may serve as predictors of coronary

heart disease [Gillum 1995; Andresdottir 2003; Danesh 2004]. Coronary artery bypass grafting (CABG) is an effective revascularization method that provides improvement in terms of cardiac mortality and morbidity. The chief gain of CABG is the patency of the grafts in the short and long term [Demirkan 2010].

Inflammatory markers come into increasing use today as independent predictors of adverse cardiovascular events. In their study, Özlü et al found that elevated ESR levels on admission to the hospital were associated with impaired coronary flow in those patients who had undergone primary percutaneous coronary interventions that had led to poor short- and long-term prognosis. For this reason, an assessment of ESR on admission may help identify patients with poor prognosis [Ozlu 2012]. It was reported before by Erikssen et al that ESR may serve as a good indicator of mortality, coronary heart disease, and the risk of death from it [Erikssen 2000]. However, we did not encounter any studies about the relationship between elevated ESR values and midterm adverse events after CABG.

In this study, we investigated the association of preoperative mildly or moderately elevated ESR values with postoperative midterm adverse events that occur after CABG. Our aim was to see whether elevated preoperative ESR was associated with a midterm adverse prognosis in those patients who had undergone CABG.

MATERIALS AND METHODS

In the present study, we analyzed data from 476 consecutive patients who had undergone CABG during the period 2011-2013. This prospective study included 363 patients under follow-up about whom we were able to access sound data. In the study, only male patients were included. The patients were divided into two groups: group 1 (preoperative sedimentation rate [>20 mm/h] above normal, [$n = 131$, 36.1%]) and group 2 (preoperative sedimentation rate [<20 mm/h] normal [$n = 232$, 63.9%]).

In terms of sex, sedimentation rates of females are higher than males. The main reason is androgen, as is well known [Shearn 1986]. Therefore, our study did not include females.

A total of 113 patients fulfilling the criteria for exclusion was determined as follows: 8 patients with signs and/or symptoms of infection; 4 patients on antibiotic treatment or with antibiotic allergy; 15 patients with a sedimentation rate of over 60 mm/hour; 5 patients with malignancy; 8 patients with

Received January 12, 2015; received in revised form February 25, 2015; accepted April 9, 2015.

Correspondence: Turhan Togan, MD, Baskent University, Konya Uygulama ve Araştırma Merkezi, Hocaciban Mab, Saray Cad. No: 1, Selçuklu / Konya, Turkey; +90 332 257 06 06; fax: +90 332 257 06 37 (e-mail: dr.togan@gmail.com).

hypo- and hyperthyroidism, 13 patients with chronic renal or hepatic failure; and 16 patients with abnormal hemogram, leukocyte, or high-sensitivity C-reactive protein (hs-CRP). Also excluded from this study were 8 cases with anti-streptolysin O or thrombocyte count in the preoperative blood; 10 emergencies; 4 patients in cardiogenic shock (because of the preoperative use of high-dose inotropes or of intraaortic balloon); 7 patients with an ejection fraction of 30 or below, as revealed by preoperative echocardiography, cases with repeated cardiac surgery; 6 patients with valvular heart disease; and 4 patients who had undergone combined operation involving heart valve surgery and CABG. Five patients were excluded from the study because of a change of address with postoperative follow-up period.

The hemogram and biochemistry panel values were measured one day before the operation, on the postoperative first day, on the postoperative seventh day, and on the postoperative third month. In order to measure the blood counts, an Abbott Cell-Dyn 3700 Hematology Analyzer (Abbott Diagnostics, Santa Clara, CA, USA) was used.

Westergren's method was used to determine the ESR. In this method, 0.4 cc of 3.8% sodium citrate solution is drawn into a 2-cc injector. Then, 1.6 cc of blood from the patient to undergo ESR measurement is drawn to the same injector, bringing the volume of its contents up to 2 cc. The injector is slightly shaken a few times. Then this blood sample is drawn up to the mark "0" of the Westergren pipette (a special tube 200 mm in height and 2.5 mm in diameter) and placed in a special location. The sinking rate of the erythrocytes is then read from the marks on the tube after half an hour, 1 hour, and 2 hours. The sedimentation rate values for a healthy person turned out to be between 0-20 mm/hour in our laboratory.

The primary outcome, which was the combination of adverse events, covered the following factors: the length of stay in the intensive care unit (ICU), the length of hospitalization, atrial fibrillation, pleural effusion, infection of the soft tissue over the sternum, pulmonary infection, rehospitalization, return to the ICU, and mortality within six months.

The study was performed according to the dictates of the Declaration of Helsinki and carried out as a single-center study in Baškent University, Cardiology Department. The informed consent of all the participants was received, and the study protocol was approved by the institutional ethics committee (KA07/193).

Surgical Technique

All of our patients were operated on by the same surgical team. Under general anesthesia, median sternotomy was performed on each patient. Standard aorta-caval cannulation was applied using a membrane oxygenator and a roller pump. After systemic heparinization, the activated clotting time was maintained in the range of 480-600 seconds. Routinely, the patients were cooled off to around 28-30°C. The venous and arterial grafts were harvested. A cold crystalloid cardioplegic solution (St. Thomas II) was used for the protection of the myocardium, administered every 20 minutes. The anastomoses were applied first to the right coronary artery or its posterior descending branch, after that to the circumflex coronary

artery branches, then to the diagonal artery, and finally to the left anterior descending (LAD) coronary artery. Routinely, the left internal mammary artery (LIMA) was taken out to be used for the LAD artery anastomosis. Under a side clamp, the proximal anastomoses were applied to the aorta. Routinely, the patients were weaned from cardiopulmonary bypass as the rectal temperature reached 37°C.

Patient Follow-Up

Following the operation, all patients were followed in the ICU for two days. Their hemodynamic parameters and urine output were observed. Prophylactic cefazolin was administered intravenously to all patients (1 g, 3 times daily). In cases of infection of the soft tissue over the sternum and pulmonary infection, antibiotherapy was applied according to the cultural antibiogram (β -lactam, cinolon, and glycopeptide antibiotics). After the operation, the patients were administered equivalent amounts of cardiovascular medication, among them aspirin (300 mg/day), lipid-lowering drug (atorvastatin/according to the blood cholesterol level), angiotensin-converting enzyme inhibitors (ramipril/according to the arterial blood pressure), and β blocker (metoprolol/according to the arterial blood pressure).

Statistical Analysis

The statistical analyses were performed using SPSS software (SPSS 10.0; SPSS Inc, Chicago IL, USA). The numeric values were expressed as mean $\pm$ SD. For continuous variables the independent-samples t test was used and for categorical variables Mann-Whitney U test was used. The Kolmogorov-Smirnov test was used to test the continuous variables for

Table 1. Preoperative Demographic Data*

	Group 1	Group 2	P
Age, y	63.69 $\pm$ 8.33	64.73 $\pm$ 11.16	.085
DM (present/absent)	118/110	55/79	.493
HT (present/absent)	57/171	44/83	.06
HL (present/absent)	125/103	67/64	.187
Smoking (present/absent)	109/114	59/72	.339
Peripheral arterial disease (present/absent)	219/9	123/8	.354
Preoperative ESR	43.24 $\pm$ 20.94	10.45 $\pm$ 4.56	<.001**
Preoperative hs-CRP, mg/L	6.89 $\pm$ 4.25	6.85 $\pm$ 4.51	.952
Preoperative leukocyte	8.02 $\pm$ 2.1	8.00 $\pm$ 2.38	.944
Preoperative lymphocyte	30.73 $\pm$ 9.73	32.02 $\pm$ 9.27	.250
BMI	1.89 $\pm$ 0.16	1.92 $\pm$ 0.18	.148

*Data are presented as the mean $\pm$ SD where indicated. BMI indicates body mass index; DM, diabetes mellitus; hs-CRP, high-sensitivity C-reactive protein; Hg, hemoglobin; HL, hyperlipidemia; HT, hypertension.

**Statistically significant.

Table 2. Comparison of the Two Groups with Respect to Laboratory Values, Details of Surgery, and Length of Stay in the Hospital and ICU*

	Group 1	Group 2	P
Postop. 1st day hs-CRP, mg/L	89.52 ± 49.96	81.45 ± 38.81	.114
Postoperative 3rd day hs-CRP	21.76 ± 37.66	8.49 ± 11.06	<.001**
Postoperative 1st day ESR	61.03 ± 18.18	28.96 ± 14.52	<.001**
Postoperative 3rd month ESR, mm/h	49.91 ± 23.70	17.33 ± 28.54	<.001**
Number of anastomoses	3.64 ± 1.15	3.61 ± 0.86	.795
X clamp, min	54.51 ± 14.29	52.48 ± 11.00	.175
Length of CPB, min	106.31 ± 27.90	103.43 ± 20.21	.309
Length of stay in the ICU, d	2.76 ± 2.33	2.39 ± 0.60	.025**
Length of hospitalization, d	10.07 ± 7.32	7.18 ± 2.76	<.001**

*Data are presented as the mean ± SD where indicated hs-CRP indicates high-sensitivity C-reactive protein; ICU, intensive care unit; X clamp, cross clamp; CPB, cardiopulmonary bypass.

**Statistically significant.

normal distribution. Pearson's correlation test was used to look for correlations. The values of $P < .05$ were considered statistically significant.

RESULTS

The mean age was 63.69 ± 8.33 in group 1 and 64.73 ± 11.16 in group 2 ($P = .085$). In terms of the preoperative demographic data, there was no difference between the two groups in regard to age, diabetes mellitus, hypertension, hyperlipidemia, peripheral arterial disease, smoking, and BMI. In terms of the laboratory values, there was no difference between the two groups with respect to preoperative leukocyte, lymphocyte, and hs-CRP values (Table 1). Again, there was no difference between them in regard to first-day hs-CRP, postoperative third-month ESR, the number of anastomoses, X clamp, and cardiopulmonary bypass duration. However, there was a difference between the two groups with respect to their length of stay in the ICU and length of hospitalization (Table 2). In terms of the laboratory values, there was a difference with regard to first-day ESR and postoperative third-month hs-CRP ($P < .05$) (Table 2). In terms of postoperative morbidity, moreover, a statistically significant difference was detected between pleural effusion, infection of the soft tissue over the sternum, pulmonary infection, return to the ICU, rehospitalization, and mortality ($P < .05$) (Table 3). In the correlation analysis, elevated sedimentation rate was found to be correlated with hemoglobin ($r = -0.440$; $P < .001$), MPV ($r = 0.267$; $P < .001$), acute renal failure ($r = 0.116$; $P < .029$), infection of the soft tissue over the

Table 3. Comparison of the Two Groups with Respect to Postoperative Morbidity and Mortality

	Group 1	Group 2	P
AF (absent/present)	108/117	68/63	.832
Pleural effusion (absent/present)	183/41	115/16	<.001*
Infection of the soft tissue over the sternum (absent/present)	211/13	131/0	<.001*
Pulmonary infection (absent/present)	181/43	103/28	<.001*
Return to the ICU (absent/present)	208/16	127/4	<.001*
Rehospitalization (absent/present)	204/16	131/0	<.001*
Exitus (absent/present)	208/24	127/4	<.001*

AF indicates atrial fibrillation; ICU, intensive care unit.

sternum ($r = 0.149$; $P < .005$), the length of hospitalization ($r = 0.260$; $P < .001$), rehospitalization ($r = 0.169$; $P < .002$), the ratio of exitus ($r = 0.131$; $P < .012$), and heart failure ($r = -0.112$; $P < .033$) (Table 4).

In the mid-term follow-up of the patients (6 months after the operation), in group 1, there was stroke in 1 patient, preoperative undetectable diabetes mellitus in 2 patients, and 2 patients developed renal failure not requiring dialysis.

In group 2, lung cancer was detected in 1 patient, SLE in 1 patient, rheumatoid arthritis in 2 patients, stroke in 2 patients, prostate cancer in 1 patient, developed renal failure requiring dialysis in 1 patient, preoperative undetectable diabetes mellitus in 3 patients, and tuberculosis in 2 patients, who were administered treatment. The values of $P < .05$ were considered not statistically significant.

DISCUSSION

For the adequate preoperative selection of patients, it is of utmost importance to identify the factors associated with an increased risk of developing complications following surgery. This implies that either the patient's condition should be optimized before surgery, or the operation should be cancelled if the operative risk is too high. Although there are various studies on the association between hs-CRP and other inflammatory markers on the one hand and adverse events in the early postoperative period after CABG [Biancari 2003] on the other, we did not encounter any studies on the association of ESR with such events. In the literature, our study was the first to show that elevated ESR is a predictor for midterm adverse events after CABG (pleural effusion, infection of the soft tissue over the sternum, pulmonary infection, return to the ICU, rehospitalization, and exitus).

With the sedimentation test, the sinking rate of the erythrocytes is measured. The normal range of values for the sedimentation test differs between male and female. Sex plays an important role as well, since females have a higher baseline ESR than males [Miller 1983; Sax 1986]. This is most likely

Table 4. Correlation Table

	Group	Hg	hs-CRP	Pleural Effusion	IST over the Sternum	Pulmonary Infection	Length of Hospitalization	Length of Stay in the ICU	Rehospitalization	Postop. Heart Failure	Exitus
Group											
R	1.000	-0.440**	0.020	0.080	0.149**	-0.026	0.260**	0.054	0.169**	-0.011	0.131*
P		<.001	.728	.132	.005	.622	<.001	.310	.002	.829	.012
Hg											
R		1.000	-0.127*	-0.200**	-.137(*)	0.067	-0.179**	-.171**	-0.268**	-0.106	-0.096
P			.028	<.001	.017	.250	.002	.003	<.001	.067	.093
hs-CRP											
R			1.000	0.023	0.020	0.056	-0.048	0.054	0.150**	0.097	-0.118*
P				.697	.729	.335	.405	.355	.010	.096	.039
Pleural Effusion											
R				1.000	0.282**	0.107*	0.287**	0.238**	0.237**	0.138**	0.100
P					<0.001	0.043	<0.001	<0.001	<0.001	0.009	0.060
IST over the sternum											
r					1.000	-0.060	0.174**	0.038	0.319**	0.106*	-0.057
P						0.260	0.001	0.475	<0.001	0.047	0.284
Pulmonary infection											
r						1.000	0.338**	0.066	0.137*	0.173**	0.167**
P							<.001	.213	.010	.001	.002
Length of hospitalization											
r							1.000	0.386**	0.118*	0.106*	0.034
P								<.001	.027	.045	.523
Length of stay in the ICU											
r								1.000	0.082	0.091	0.124*
P									.125	.087	.020
Rehospitalization											
r									1.000	0.450**	-0.059
P										<.001	.269
Postop. heart failure										1.000	0.192**
P											<.001
Exitus											
r											1.000
P											

Hg indicates hemoglobin; hs-CRP, high-sensitivity C-reactive protein; ICU, intensive care unit; IST, infection of the soft tissue.

*Correlation is significant at the 0.05 level (2-tailed).

**Correlation is significant at the 0.01 level (2-tailed).

linked to both the level of androgens and to the sex-related differences in packed cell volume. For males and females under the age of 50, the upper limit of the normal range is 15 mm/h and 20 mm/h, respectively. For those over 50, these

limits are 20 mm/h and 30 mm/h, respectively [Olshaker 1997]. Since chronic inflammatory diseases could cause problems in clarifying the association between ESR and CABG, we excluded from the study patients with this disease.

In order to eliminate the influence of sex on the results of the research, the study included only male patients. The cause of accelerated erythrocyte aggregation is the existence of large, asymmetrical plasma proteins that hinder the negative electrical forces that keep the erythrocytes away from each other. A number of laboratory methods are available for assessing the acute phase reaction of the body to inflammation and infection. The measurement of ESR has come into frequent use in this context in most fields of medicine. It continues to play an important role in the diagnosis and follow-up of many inflammatory and non-inflammatory conditions such as rheumatoid and temporal arthritis, sickle cell disease, osteomyelitis, stroke, and prostate cancer [Saadeh 1998].

Faced with an elevated ESR, the clinician should first consider such factors as age, sex, received medications, and known medical conditions. Usually, patients with collagen vascular disease tend to have an elevated ESR.

To our knowledge, only three other prospective studies have previously reported an association between ESR and cardiovascular disease, even though these were less comprehensive than ours or had a shorter follow-up period [Erikssen 2000]. Two of these studies had roughly comparable ranges of erythrocyte sedimentation rate at the baseline, but shorter follow-up periods, while the third [Gillum 1995] only reported the associations in males who had an ESR >21 mm/h. As of yet there are no established reference values for ESR among healthy males, and these tend to vary slightly from one part of the world to another. Values of ESR <10 mm/h are recommended for males below 50 years of age, and ESR >14 for male above 60 years of age [Erikssen 2000]. In all the studies cited above, except for a single one, the mean ESR at the baseline was low (between 6-9 mm/h), and in all studies the subjects were “apparently healthy” at the baseline [Gillum 1995; Erikssen 2000].

Since ESR is elevated in many diseases, it is not generally deemed important in the clinic, and elevated ESR values are usually overlooked. In the literature, it is possible to encounter many different studies examining the association between coronary diseases and the sedimentation rate. For example, a study performed by Natali et al on 1726 patients revealed that ESR is independently correlated with the coronary extension of coronary atherosclerosis, while it is a predictor of cardiac death in male patients with probable ischemic heart disease [Natali 2003]. Another study by Ingelsson et al, based on three decades of follow-up in a population-based sample of middle-aged men, showed that ESR may serve as a significant predictor of heart failure, one that is independent of the established risk factors as well as of interim myocardial infarction [Ingelsson 2005]. Erikssen et al have also reported that ESR may serve as a good indicator for mortality, coronary heart disease, and the risk of death from it [Erikssen 2000]. The association between ESR and the risk of coronary heart disease was also evaluated in a cohort study performed by Andresdottir et al [Andresdottir 2003]. The conclusion of the authors was that ESR, on the basis of an inflammatory process of atherosclerosis, may serve as an independent prognostic factor for coronary heart disease in both males and females.

ESR has often been found to be high in patients with coronary heart disease. Elevation in ESR yields information concerning the inflammatory etiology of coronary heart disease. Therefore ESR may well be another helpful diagnostic tool for coronary heart disease [Yayan 2012]. In this study as well, we determined in corroboration of the existing literature that after CABG there is an increased risk of complications in patients with elevated ESR. We found that elevated ESR was associated with prolonged length of stay in the hospital and the ICU, was associated with a higher frequency of rehospitalization, return to the ICU, pleural effusion, infection of the soft tissue over the sternum, pulmonary infection, and exitus. In the correlation analysis, preoperative elevated ESR was found to be correlated with infection of the soft tissue over the sternum ($r = 0.149$; $P < .005$), the period of hospitalization ($r = 0.260$; $P < .001$), rehospitalization ($r = 0.169$; $P < .002$), and the ratio of exitus ($r = 0.131$; $P < .012$).

It can be stated in conclusion that preoperative serum concentration of ESR in patients who undergo CABG constitutes an important determinant of adverse outcomes in the early postoperative period. In other words, we found that in the group with elevated ESR, in comparison with the group with normal ESR, the period of hospitalization was significantly longer and the frequency of postoperative atrial fibrillation, sternal infection, and mortality was significantly higher ($P < .05$). Surgeons often overlook patients with elevated preoperative ESR. Although the measurement of ESR is considered a simple test, it should be considered a warning marker for postoperative pathologies and diseases that could cause a serious rate of morbidity and mortality in the midterm in particular.

For this purpose, we suggest that patients with higher sedimentation rates should undergo detailed examination to prevent mortality and morbidity.

REFERENCES

- Andresdottir MB, Sigfusson N, Sigvaldason H, Gudnason V. 2003. Erythrocyte sedimentation rate, an independent predictor of coronary heart disease in human: the Reykjavik Study. *Am J Epidemiol* 158:844-51.
- Biancari F, Lahtinen J, Lepojärvi S, et al. 2003. Preoperative C-reactive protein and outcome after coronary artery bypass surgery. *Ann Thorac Surg* 76:2007-12.
- Danesh J, Wheeler JG, Hirschfield GM, et al. 2004. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 350:1387-97.
- Demirkan B, Güray Y, Güray Ü, Turak O, Hajro E, Korkmaz S. 2010. The relationship between saphenous coronary bypass graft occlusion and serum gamma-glutamyl transferase activity. *Türk Kardiyol Dern Ars* 38:321-6.
- Erikssen G, Liestol K, Bjornholt JV, Stormorken H, Thaulow E, Erikssen J. 2000. Erythrocyte sedimentation rate: a possible marker of atherosclerosis and a strong predictor of coronary heart disease mortality. *Eur Heart J* 21:1614-20.
- Gillum RF, Mussolino ME, Makuc DM. 1995. Erythrocyte sedimentation rate and coronary heart disease: the NHANES I Epidemiologic Follow-up Study. *J Clin Epidemiol* 48:353-61.
- Ingelsson E, Arnlov J, Sundström J, Lind L. 2005. Inflammation, as

- measured by the erythrocyte sedimentation rate, is an independent predictor for the development of heart failure. *J Am Coll Cardiol* 45:1802-6.
- Miller A, Green M, Robinson D. 1983. Simple rule for calculating normal erythrocyte sedimentation rate. *Br Med J* 266-86.
- Natali A, L'Abbate A, Ferrannini E. 2003. Erythrocyte sedimentation rate, coronary atherosclerosis, and cardiac mortality. *Eur Heart J* 24:639-48.
- Olshaker JS, Jerrard DA. 1997. The erythrocyte sedimentation rate. *J Emergency Med* 15:869-74.
- Ozlu FM, Sen N, Karakas FM, et al. 2012. Erythrocyte sedimentation rate in acute myocardial infarction as a predictor of poor prognosis and impaired reperfusion. *Med Glas (Zenica)* 9:189-97.
- Saadeh C. 1998. The erythrocyte sedimentation rate: old and new clinical application. *South Med J* 91:220-5.
- Sax HC, Liang MH. 1986. The erythrocyte sedimentation rate. Guidelines for rational use. *Ann Intern Med* 104:515-23.
- Shearn MA, Kang IY. 1986. Effect of age and sex on erythrocyte sedimentation rate. *J Rheumatol* 13:297-8.
- Yayan J. 2012. Erythrocyte sedimentation rate as a marker for coronary heart disease. *Vasc Health and Risk Management* 8:219-23.