Original Paper

Saphenous Vein Graft Disease Is Associated with a Low Serum Erythropoietin Level

İbrahim Kocaoğlu[a] Uğur Arslan[b] Yavuzer Koza[c] Mustafa Mücahit Balcı[c]
Gizem Çelik[c] Sinan Aydoğdu[b]

Departments of Cardiology at [a]Aydın State Hospital, Aydın, [b]Samsun Education and Research Hospital, Samsun, and [c]Turkiye Yuksek Ihtisas Education and Research Hospital, Ankara, Turkey

Abstract

Objective: To measure the serum erythropoietin (EPO) level in patients with saphenous vein grafts (SVGs) and to compare the EPO level in those with and without SVG disease. ***Subjects and Methods:*** The study included 85 consecutive patients with a history of coronary artery bypass graft surgery that underwent elective coronary angiography. Patients with >30% stenosis (diseased grafts) in at least one saphenous graft were included in group 1 (diseased group: n = 40), and group 2 (nondiseased group: n = 45) consisted of patients without diseased SVGs. The EPO level was measured using enzyme-linked immunosorbent assay (ELISA) using a commercially available ELISA kit; χ^2 test and independent samples t test were used where appropriate. Logistic regression was used for multivariate analysis. ***Results:*** There were not any significant differences in age, gender, or cardiovascular risk factors between the two groups except for increased triglyceride and low high-density lipoprotein levels in group 2. The EPO level was significantly higher in the nondiseased SVG group than in the diseased SVG group (25.5 ± 9.6 vs. 17.8 ± 6.8 mU ml^{-1}, p = 0.002). Multivariate logistic regression analysis showed that the serum EPO level was an independent predictor of SVG disease (OR 1.14, 95% CI 1.06–1.24, p = 0.001). ***Conclusion:*** In this study, SVG disease was associated with a low serum EPO level, suggesting that a low EPO level could be predictive of and contributes to the pathophysiology of SVG disease.

© 2015 S. Karger AG, Basel

Introduction

Coronary artery bypass graft surgery remains an important procedure despite improvements in percutaneous transluminal coronary interventions, especially for three-vessel and left main coronary artery disease [1]. The saphenous vein is the most widely used conduit [1]; however, only 50% of all vein grafts are patent without significant restenosis after 10 years and most failures occur 1–18 months after implantation [2–4]. Intermediate to late vein graft failure is caused by intimal hyperplasia with superimposed atherosclerosis [5]. Despite surgical and medical advances, saphenous vein graft (SVG) disease remains a significant problem that is associated with high morbidity and mortality rates [3]. Apart from statins, no drug has yet been proven to be clinically effective in pre-

Uğur Arslan, MD, Associate Professor
Department of Cardiology
Samsun Education and Research Hospital
Baris Avenue, No. 199, TR–55090 Ilkadım, Samsun (Turkey)
E-Mail ugurarslan5@yahoo.com

venting late vein graft failure [5]. Hence, an understanding of the pathophysiological mechanism of SVG disease is essential for preventing its formation and progression.

Erythropoietin (EPO) is a glycosylated protein hormone produced by renal peritubular fibroblasts in response to tissue hypoxia [6, 7]. EPO was once thought to act only on erythroid progenitor cells and was used to treat anemia in patients with renal disease; however, EPO messenger ribonucleic acid expression and EPO receptor have been observed in various types of tissues, including the brain, bone marrow, reproductive system, and heart [8, 9]. The EPO had been shown to act as a direct antioxidant by scavenging oxyradicals and is thought to have an antiatherogenic effect by down-regulating production of proinflammatory cytokine-induced endothelin-1 [10, 11]. The role of EPO in the atherosclerotic process remains to be fully elucidated.

To date, no study has investigated the relationship between the serum EPO level and SVG disease. Therefore, the aim of the present study was to determine the level of EPO in patients with and without SVGs in order to decipher the role of EPO in SVG disease.

Subjects and Methods

The study population included 85 consecutive patients that had undergone coronary artery bypass graft surgery ≥12 months ago and then underwent elective coronary angiography for stable angina pectoris despite optimal medical treatment and had signs of ischemia based on noninvasive cardiac imaging tests. Exclusion criteria were any malignancy, renal failure (estimated glomerular filtration rate <40 ml min^{-1}) and hepatic failure, anemia, rheumatoid arthritis, sickle cell anemia, acquired immune deficiency syndrome, pulmonary hypertension, chronic obstructive lung disease, acute coronary syndrome during the previous month, severe valvular heart disease, and living at high altitudes. Written informed consent was obtained from each patient and the Institutional Ethics Committee approved the study protocol.

Coronary angiography was performed using standard angiographic techniques. All cineangiograms were reviewed by 2 interventional cardiologists who were blinded to the study protocol. Bypass grafts were examined in multiple projections and the degree of stenosis was determined based on the projection that showed the most severe narrowing. The stumps of occluded (100% stenosis) grafts were selectively injected or visualized via aortography in the appropriate projection. Any degree of stenosis of an SVG >30% (moderate stenosis) was accepted as diseased. Patients with >30% stenosis (diseased grafts) in at least one saphenous graft were included in group 1 (diseased group, n = 40), and group 2 (nondiseased group, n = 45) consisted of patients without diseased saphenous grafts.

Venous blood samples were drawn into a tube without anticoagulant following fasting of ≥8 h on the same day as coronary angiography; all the patients rested in the supine position for ≤1 h at

Table 1. Baseline characteristics of the patients with SVGs

	Diseased (n = 40)	Nondiseased (n = 45)	p value
Age, years	63±9.2 (42–82)	64±9.3 (46–83)	NS
SVG age, years	7.7±4.9 (1–18)	6.7±4.2 (1–18)	NS
Hypertension	29 (64.5)	27 (67.5)	NS
Diabetes mellitus	25 (62.5)	29 (64.5)	NS
Acetylsalicylic acid	36 (90.0)	45 (100)	NS
Statin	27 (67.5)	28 (62.2)	NS
Chronic lung disease	6 (15.0)	6 (13.3)	NS

Values are means ± SD (range) or n (%). NS = Nonsignificant (p > 0.10).

the same time of day (13.00–14.00 h) to avoid diurnal variation. The EPO level was measured using enzyme-linked immunosorbent assay (ELISA) using a commercial ELISA kit (Biomerica, USA).

Statistical Analysis
Data were analyzed using SPSS v.15.0 for Windows (SPSS Inc., Chicago, Ill., USA). Continuous variables are presented as mean ± SD, and categorical variables as frequency and percentage. Student's t test was used to compare normally distributed continuous variables and the Mann-Whitney U test was used for variables not normally distributed. Categorical variables were compared using the χ^2 test. A two-tailed p value <0.05 was considered statistically significant. Multivariate logistic regression analysis was performed to evaluate the independent associations with SVG disease. Parameters with a p value <0.10 based on univariate analysis were included in the model. The odds ratio (OR) and 95% confidence interval (CI) were calculated.

Results

The demographic and clinical characteristics of both groups are presented in table 1. There were not any significant differences in age, gender, body mass index, and baseline medications between the groups. Laboratory parameters of both groups are summarized in table 2. There were not any significant differences between the two groups, except for the lower serum high-density lipoprotein (HDL) cholesterol level (38.1 ± 8.2 vs. 43.8 ± 10.2 mg dl^{-1}, p = 0.015) and higher triglyceride level (173.8 ± 88.5 vs. 131 ± 63.4 mg dl^{-1}, p = 0.016) in groups 1 and 2, respectively. The mean EPO level in group 2 (25.5 ± 9.6 mU ml^{-1}) was significantly higher than in group 1 (17.8 ± 6.8 mU ml^{-1}, p = 0.002; fig. 1).

The multivariate logistic regression analysis showed that low serum EPO level was an independent predictor

Table 2. Echocardiographic and blood test results in patients with SVGs

|	Diseased (n = 40)	Nondiseased (n = 45)	p value
Creatinine, mg dl^{-1}	0.98±0.16 (0.7–1.5)	0.93±0.23 (0.58–1.62)	NS
Urate, mg dl^{-1}	5.4±1.67 (2.4–9.9)	5.2±1.32 (3.1–9.4)	NS
Total cholesterol, mg dl^{-1}	168.8±38.1 (97–258)	165.9±47.2 (85–320)	NS
HDL cholesterol, mg dl^{-1}	38.1±8.2 (12–54)	43.8±10.2 (26–70)	0.015
LDL cholesterol, mg dl^{-1}	95.8±30.3 (47–176)	96.1±39.5 (29–232)	NS
Triglyceride, mg dl^{-1}	173.8±88.5 (68–490)	131±63.4 (51–320)	0.016
Hemoglobin, g dl^{-1}	14.6±1.14 (36.2–50)	14.3±1.11 (12.0–16.9)	NS
Hematocrit, %	43.4±3.57 (26.4–35.1)	42.6±3.42 (35.4–50.9)	NS
Sedimentation rate, mm h^{-1}	12.2±6.6 (3–32)	10.7±4.7 (2–21)	NS
Fibrinogen, g l^{-1}	3.03±0.51 (2.0–4.3)	3.12±0.61 (2.1–4.4)	NS
EPO, mU ml^{-1}	17.8±6.8 (5.2–32.3)	25.5 (10.4–52.2)	0.002
Ejection fraction, %	58.4±2.8 (42–65)	57.5 (40–67)	NS

Values are mean ± SD (range). LDL = Low-density lipoprotein; NS = nonsignificant (p > 0.10).

of SVG disease (OR 1.14, 95% CI 1.06–1.24, p = 0.001), also low HDL level was an independent predictor of SVG disease (OR 1.08, 95% CI 1.01–1.15, p = 0.017), but TG levels did not differ significantly between groups (OR 0.99, 95% CI 0.99–1.01, p = 0.42).

Discussion

In the present study, the serum EPO levels were significantly lower in patients with than without diseased SVGs. This association remained significant after multivariate analysis, thereby indicating decreased serum EPO levels as an independent predictor of SVG disease. Hence, there were two independent predictors of SVG disease: low plasma EPO and low HDL levels. Failure to find a significant association between the classical risk factors of atherosclerosis, hypertension, diabetes mellitus, dyslipidemia and smoking except low HDL and SVG disease confirmed the finding of a previous study [12]. Additionally, the association between the serum EPO level and SVG disease persisted following logistic regression analysis.

A probable explanation of the role of serum EPO in SVG disease could be that it had been shown to have tissue-protecting effects, including suppression of atherosclerosis [13]. Earlier studies reported that administration of EPO decreased the cholesterol ester content in the aorta in animal models [14]. EPO was also shown to decrease intima-media thickness in hemodialyzed patients [15] and to suppress foam cell formation in murine mac-
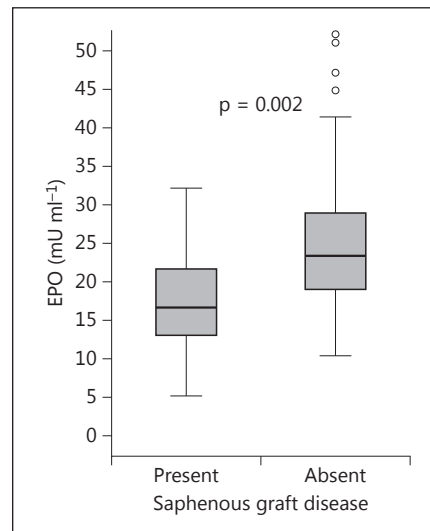
Fig. 1. Decreased serum EPO levels in patients with diseased SVGs.

rophages [16]. Development of vascular endothelial injury while harvesting SVGs was shown to affect SVG patency [17]. EPO promotes reendothelialization and inhibits neointimal formation following vascular injury [18]. The antioxidant effect of EPO was also demonstrated in animal studies [19]. The present findings show that SVG disease was associated with a low serum EPO level, indicating that a low EPO level might be predictive of atherosclerosis and might contribute to atherosclerosis in patients with SVG disease.

Kocaoğlu/Arslan/Koza/Balcı/Çelik/
Aydoğdu

Studies on recombinant human EPO showed that it had beneficial effects in heart failure models via stimulating angiogenesis and neovascularization [20–22]. Animal studies also suggested that there is a potential therapeutic role for recombinant human EPO in the treatment of myocardial ischemia and infarction, as it prevents apoptosis and reduces left ventricular functional decline. Based on the present study's findings, additional research on the role of EPO in SVG disease and its treatment is warranted.

The present study had some limitations. The direct role of EPO in SVG disease was not examined because of the study's observational and cross-sectional design. In addition, the study sample was small, which limits the value of the findings.

Conclusion

A low EPO level was associated with SVG disease, suggesting that a low EPO level might play a pathophysiological role in the development of atherosclerotic lesions in SVGs. Hence, the use of EPO analogues might constitute a novel therapeutic strategy for suppressing atherosclerotic progression in SVGs.

Disclosure Statement

None.

References

1 Osgood MJ, Hocking KM, Voskresensky IV, et al: Surgical vein graft preparation promotes cellular dysfunction, oxidative stress, and intimal hyperplasia in human saphenous vein. J Vasc Surg 2014;60:202–211.

2 Favaloro RG, Effler DB, Cheanvechai C, et al: Acute coronary insufficiency (impending myocardial infarction and myocardial infarction): surgical treatment by the saphenous vein graft technique. Am J Cardiol 1971;28:598–607.

3 Motwani JG, Topol EJ: Aortocoronary saphenous vein graft disease: pathogenesis, predisposition, and prevention. Circulation 1998;97:916–931.

4 Owens CD: Adaptive changes in autogenous vein grafts for arterial reconstruction: clinical implications. J Vasc Surg 2010;51:736–746.

5 Campeau L: Lipid lowering and coronary bypass graft surgery. Curr Opin Cardiol 2000;15:395–399.

6 Kido M, Du L, Sullivan CC, et al: Hypoxia-inducible factor 1α reduces infarction and attenuates progression of cardiac dysfunction after myocardial infarction in the mouse. J Am Coll Cardiol 2005;46:2116–2224.

7 Le Jemtel TH, Arain S: Mediators of anemia in chronic heart failure. Heart Fail Clin 2010;6:289–293.

8 Dame C, Fahnenstich H, Freitag P, et al: Erythropoietin mRNA expression in human fetal and neonatal tissue. Blood 1998;92:3218–3225.

9 Sytkowski AJ: The neurobiology of erythropoietin. Cell Mol Neurobiol 2011;31:931–937.

10 Yang WS, Chang JW, Han NJ, et al: Darbepoetin alfa suppresses tumor necrosis factor-α-induced endothelin-1 production through antioxidant action in human aortic endothelial cells: role of sialic acid residues. Free Radic Biol Med 2011;50:1242–1251.

11 Chattopadhyay A, Choudhury TD, Bandyopadhyay D, et al: Protective effect of erythropoietin on the oxidative damage of erythrocyte membrane by hydroxyl radical. Biochem Pharmacol 2000;59:419–425.

12 Campeau L, Enjalbert M, Lespérance J, et al: The relation of risk factors to the development of atherosclerosis in saphenous-vein bypass grafts and the progression of disease in the native circulation. A study 10 years after aortocoronary bypass surgery. N Engl J Med 1984;311:1329–1332.

13 Ueba H, Shiomi M, Brines M, et al: Suppression of coronary atherosclerosis by helix B surface peptide, a nonerythropoietic, tissue-protective compound derived from erythropoietin. Mol Med 2013;19:195–202.

14 Buemi M, Allegra A, Corica F, et al: Does erythropoietin administration affect progression of atherosclerosis in Watanabe heritable hyperlipaemic rabbits? Nephrol Dial Transplant 1998;13:2706–2708.

15 Pawlak K, Pawlak D, Mysliwiec M: Long-term erythropoietin therapy decreases CC-chemokine levels and intima-media thickness in hemodialyzed patients. Am J Nephrol 2006;26:497–502.

16 Lu KY, Ching LC, Su KH, et al: Erythropoietin suppresses the formation of macrophage foam cells: role of liver X receptor alpha. Circulation 2010;121:1828–1837.

17 Kim FY, Marhefka G, Ruggiero NJ, et al: Saphenous vein graft disease: review of pathophysiology, prevention, and treatment. Cardiol Rev 2013;21:101–109.

18 Urao N, Okigaki M, Yamada H, et al: Erythropoietin-mobilized endothelial progenitors enhance reendothelialization via Akt-endothelial nitric oxide synthase activation and prevent neointimal hyperplasia. Circ Res 2006;98:1405–1413.

19 Ardalan MR, Estakhri R, Hajipour B, et al: Erythropoietin ameliorates oxidative stress and tissue injury following renal ischemia/reperfusion in rat kidney and lung. Med Princ Pract 2013;22:70–74.

20 van der Meer P, Lipsic E, Henning RH, et al: Erythropoietin induces neovascularization and improves cardiac function in rats with heart failure after myocardial infarction. J Am Coll Cardiol 2005;46:125–133.

21 Nishiya D, Omura T, Shimada K, et al: Effects of erythropoietin on cardiac remodeling after myocardial infarction. J Pharmacol Sci 2006;101:31–39.

22 Westenbrink BD, Visser FW, Voors AA, et al: Anaemia in chronic heart failure is not only related to impaired renal perfusion and blunted erythropoietin production, but to fluid retention as well. Eur Heart J 2007;28:166–171.