

Serum Level Of Erythropoietin In Patients With Slow Coronary Flow Syndrome

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Abstract

Introduction:

Cardiovascular disease constitute a major cause of death worldwide .inflammatory and anti inflammatory cytokines plays an important role in atherosclerosis formation and function of endothelial cells ; one the presentation of athrosclerosis and endothelial dysfunction is Slow coronary flow(SCF) syndrome and treatment of SCF patients has always been challenging , erythropoietin as a cytoprotective cytokine and also thorombotic factor can play a role in the prevention or progression of coronary events by effect on endothelial cells, due to dual physiological function of this hormone ,we will compare the blood level of erythropoietin in three different groups of patients who underwent angiography to find out its effect.

Materials and methods:

This cross-sectional study was performed on 173 candidats patients for angiography at Shafa Hospital in Kerman. the patient's serum erythropoietin measured by SANDWICH method and STATFOX ELISA device. Coronary angiography of patients was performed by Seldinger technique ,patients were classified into three groups: normal coronary artery (n = 50), SCF patients (n = 55) and coronary artery obstructive patients (n = 68). Data were analyzed using SPSS / 18 software.

Results:

In the SCF group, 50.9% (n=28) were female, in the coronary artery occlusion group, 63.2% (n=43) were male and , and in the normal group, 62% (n=31) were female (P = 0.024). The coronary artery occlusion and SCF patients show higher history of diabetes than normal coronary artery subjects (P = 0.027). Mean and standard deviation of erythropoietin were 53.3 ± 61.6 pg / ml, 72.8 ± 134.4 pg / ml and 61.6 ± 109.5 pg / ml (P = 0.646) in normal coronary arteries, SCF patients and coronary artery disease patients, respectively. The coefficient of determination of erythropoietin in the regression model was 34.5%.

Keywords: Erythropoietin, atherosclerosis risk factors, Slow Coronary Flow

Introduction

Slow coronary flow syndrome (SCF) was introduced as a new angiographic phenomenon about 50 years ago. SCF is associated with normal or near-normal coronary angiography, which is characterized by the slow flow of contrast agent injected into the coronary arteries without obstruction in the coronary epicardial arteries. SCF can occur in one or all of the coronary arteries of the heart (1-3). SCF is seen in 1-5% of patients undergoing angiography and 4% of patients with unstable chest pain (4, 5). The prevalence of SCF is higher in young men, smokers, obese and those with metabolic syndrome risk factors (3). These patients suffer from recurrent chest pain, frequent hospitalizations, and recurrent cardiac catheterization. Unstable angina is the most common clinical manifestation in SCF patients, who often need readmission and reassessment with recurrent periods of resting chest pain with electrocardiographic changes. Although this phenomenon is generally benign, patients with SCF are highly symptomatic and are associated with recurrent symptoms of chest pain and poor quality of life. This disorder is life-threatening in severe cases, usually with ventricular tachyarrhythmias, conduction abnormalities, or cardiogenic shock (3).

The SCF etiology is unknown but endothelial dysfunction is one of the main causes of SCF syndrome (6). Histological studies show hypertrophy of myofibers, thickening of elastic muscle fibers of small vessels with inflammation and endothelial cell breakdown, and narrowing of the vascular lumen in these patients (7). Microvascular disorders, extensive atherosclerosis, endothelial dysfunction, and increased platelet aggregation are seen in these patients (8-10). In the pathogenesis of SCF, several hypotheses have been proposed, including some of the early stages of atherosclerosis, dysfunction of the small vessels, the Hagen-Poiseuille equation model, an imbalance between vasoconstrictors, and platelet dysfunction. (11) Endothelium plays an important role in regulating vascular tone, platelet activity, leukocyte adhesion, proliferation of vascular smooth muscle, and is strongly involved in the development of atherosclerosis. On the other hand, endothelial dysfunction is involved in the occurrence of SCF. Recently, there has been increasing evidence of the role of inflammation in the onset, development, and progression of atherosclerosis, and the results suggest that atherosclerosis is an inflammatory disease and that inflammation, in turn, may be involved in the development of SCF (11). Studies over the past decade have shown that erythropoietin is expressed in a number of cell types, including the cardiovascular and nervous systems, and despite its important role in stimulating hematopoiesis, it affects the heart and vascular tissues. Erythropoietin is expressed in cardiomyocytes, vascular endothelial cells, and smooth muscle cells (12, 13) and can protect vascular tissue as a cytokine with its non-erythropoietic effects on the vascular endothelium (14, 15). In fact, erythropoietin can reduce tissue damage by inhibiting apoptosis and inhibiting inflammatory cytokines (16, 17). Given the small number of studies on the effects of erythropoietin in cardiovascular patients, the present study was performed to evaluate the serum level of erythropoietin in slow coronary flow patients compared with coronary artery occlusion patients and individuals with normal coronary blood flow.

Method :

The current cross-sectional study was performed on patients who were admitted to the cardiac ward of Shafa Hospital in Kerman with a diagnosis of coronary artery problems and the possibility of coronary artery disease. Inclusion criteria were having signs and symptoms of ischemic heart disease and coronary angiography indications and exclusion criteria included history of acute myocardial infarction, valvular heart disease, myocarditis, liver disease, use of lipid-lowering drugs and history of acute infection two weeks before hospitalization. Given the following sample size formula the sample of 173 people was calculated, taking into account the minimum value of the clinically significant difference is 4.12, the significance level is 0.05, the standard deviation is 5.7 (17), the test power is 80%, $z_{\alpha/2} = 1.96$ and $z_{\beta} = 0.84$ and the correction coefficient of the population for the three groups calculations.

$$n = \frac{2(Z_{\alpha/2} + Z_{\beta})^2 \sigma^2}{(\mu_1 - \mu_2)^2}$$

First demographic and background characteristics for each patient were recorded, including age, sex, height, weight, BMI, systolic and diastolic blood pressure, history of hypertension, diabetes, smoking, addiction, family

history of heart disease, ejection fraction, hemoglobin, hematocrit and erythropoietin. Ejection fraction (EF) of patients was measured by echocardiography. To measure the serum level of erythropoietin, 5 cc of venous blood sample was taken in the morning. Blood samples were sent to the laboratory immediately and after serum isolation, they were stored at minus 20 ° C. Erythropoietin level (mU / mL) was measured by erythropoietin kits (Elisa Erythropoietin kit, IB196) by SANDWICH method and using STATFOX ELISA reader. The patients underwent coronary angiography by Seldingers method and the angiographic film was examined by a cardiologist. According to the diagnostic results by the specialist, patients were classified into one of three groups: normal coronary artery (50 patients), SCF patients (55 patients) and obstructive coronary artery patients (68 patients). Primary SCF diagnostic criteria (Beltrame criteria) include coronary artery occlusion less than 40% on angiography, delayed distal vascular contrast (TIMI 2 flow) or corrected TIMI frame count > 27 frames, delayed distal filling of at least one epicardial vessel, and elimination of SCF secondary causes (including: no-reflow phenomenon, coronary embolism, coronary ectasia and vasoconstrictor administration from outside the body)(18). Data were analyzed using SPSS / 18 software and One-way ANOVA, chi-square test and Linear Regression model.

Results: The mean age of patients was 55.2 ± 9.7 years. In the SCF group, 49.1% (n=27) were male and 50.9% (n=28) were female, in the coronary artery occlusion group, 63.2% (n=43) were male and 36.8% (n=25) were female, and in the normal group, 38% (n=19) were male and 62% (n=31) were female (P = 0.024). Table 1 shows the results of determining and comparing the frequency distribution of demographic and contextual variables in the three study groups. Diabetes was higher in coronary artery occlusion and SCF patients than in those with normal coronary blood flow (P = 0.027). In terms of family history of heart disease, coronary artery occlusion patients and individuals with normal coronary blood flow had a higher frequency than SCF patients (P = 0.027).

Table 1: demographic and contextual variables in the three studied groups

Group Variable	People with normal coronary blood flow	SCF patients	Patients with coronary artery disease	P-Value [¥]
Age* (Year)	55.1 ± 10.3	53.5 ± 11.1	56.7 ± 7.6	0.198
Height* (centimeter)	164.1 ± 12.3	166.4 ± 11.5	168.5 ± 8.9	0.095
Weight* (Kg)	68.6 ± 13.5	72.4 ± 14.0	71.4 ± 13.6	0.342
BMI* (kg / m ²)	25.6 ± 5.1	26.3 ± 5.1	25.2 ± 4.8	0.486
Systolic blood pressure* (mmHg)	126.9 ± 18.8	126.3 ± 18.7	122.7 ± 22.3	0.492
Diastolic blood pressure* (mmHg)	80.1 ± 11.8	79.3 ± 11.8	77.3 ± 9.4	0.383
Hypertension**	17(34)	20 (36.4)	21(30.9)	0.812
Diabetes**	5(10)	13(23.6)	21(30.9)	0.027
Smoking**	6(12)	7(12.7)	6 (8.8)	0.760
History of addiction**	11 (22)	21(38.2)	29 (42.6)	0.058
Family history of heart disease**	25(50)	16 (29.1)	35 (51.5)	0.027

*: Data are expressed as mean ± standard deviation

**: Data are expressed as number (percent)

¥: One-way ANOVA test and significance level 0.05.

The levels of erythropoietin in the two groups of patients with obstructive coronary artery disease and SCF patients had higher values and higher distribution. Minimum and maximum erythropoietin levels in individuals with normal coronary blood flow were 1.2 to 321 pg / ml, SCF patients 0.5 to 740.7 pg / ml and coronary artery occluded patients 0.4 to 655.2 pg / ml Respectively.

Comparison of standard deviation values ± mean of cardiac output fraction variables, hemoglobin, hematocrit and erythropoietin in Table 2 by the three groups shows that the difference between the mean of the variables in the three groups was not statistically significant in any of the cases (P > 0.05). SCF patients with a mean of 72.8 pg / ml had the highest value and in the next order the erythropoietin level in the group of patients with coronary

artery occlusion with a mean of 61.1 pg / ml. In individuals with normal blood flow, erythropoietin had the lowest mean of 41 pg / ml, but the differences were not statistically significant (P = 0.646)

Table 2: Ejection fraction, hemoglobin, hematocrit and erythropoietin in the three groups

Group Variable	People with normal coronary blood flow	SCF patients	Patients with coronary artery disease	P-Value [‡]
Cardiac output* (%)	50.5 ± 8.6	51.8 ± 7.6	47.7 ± 12.2	0.098
Hemoglobin* (g / dL)	13.4 ± 1.7	13.9 ± 1.9	13.5 ± 2.1	0.312
Hematocrit* (%)	41.0 ± 4.2	42.8 ± 5.1	40.4 ± 6.6	0.069
Erythropoietin* (pg / ml)	53.3 ± 61.6	72.8 ± 134.4	61.1 ± 109.5	0.646

*: Data are expressed as mean ± standard deviation

‡: One-way ANOVA test and significance level 0.05.

Table 3 shows the results of linear regression model with Enter method of factors affecting the erythropoietin level in patients. Using the variables entered in the regression model, 34.5% of erythropoietin values can be predicted ($R^2 = 0.345$). Thus, only the relationship between smoking and erythropoietin was significantly different, so that the amount in smokers is higher than non-smokers (P = 0.012). No significant relationship was observed for other variables entered in the model.

Table 3: Regression analysis of factors associated with the erythropoietin level in patients

Variables	β (95%CI)	Standardized β	t	P*
Age	-2.694 (-3.44,113,507.003)	-.180	0.386	0.702
Gender (female)	15.058 (-63.083,93.199)	38.733	0.388	0.700
BMI	-1.807 (-8.756,5.142)	-0.075	-0.524	0.603
History of high blood pressure (yes)	-5.558 (-75.015,63.839)	-0.022	-0.162	0.872
History of diabetes (yes)	-45.023 (-177.078,27.033)	-0.181	-1.259	0.215
Smoking (yes)	136.241 (32.096,240.386)	0.357	2.636	0.012
History of addiction (yes)	-12.681 (-82.293,56.930)	-0.054	-0.367	0.715
Family history of heart disease (yes)	-54.955 (-120.522,10.612)	-0.234	-1.689	0.098
Number of vessels involved	25.606 (-14.470,65.681)	0.180	1.288	0.205
Cardiac output	2.275 (-0.390,4.939)	0.238	1.720	0.092
Hemoglobin	-1.410 (-35.6.5,32.785)	-0.024	-0.038	0.934
Hematocrit	1.546 (-8.856,11.948)	0.087	0.299	0.766

*: Leane regression test and significant level 0.05.

Discussion

The results of this study showed that SCF patients show higher levels of erythropoietin compared to the two groups of coronary artery occluded patients and normal coronary flow group, but this difference was not statistically significant. The erythropoietin level in patients with coronary artery occlusion was also higher than the group with normal coronary blood flow, but this difference was not significant. Erythropoietin is a glycoprotein hormone produced by endothelial cells of capillaries around the tubule and is involved in hematopoiesis, hemoglobin concentration, hematocrit, and reticulocyte count by stimulating the bone marrow (19). Recent studies have shown that erythropoietin, in addition to these effects, by non-hematopoietic mechanisms, such as anti-apoptotic, anti-inflammatory, and angiogenesis stimuli, reduces renal damage by

ischemia (20-23). The role of erythropoietin in reducing ischemia and reperfusion injury in animal models (24, 25) as well as in patients undergoing coronary artery bypass grafting has been investigated (26). Protective effects of erythropoietin on myocardial cells to prevent ischemia, through various mechanisms including stimulation of neovascularization by activation of phosphatidylinositol trichinase, ERK1 / 2 and phosphorylation of Jak2-ERK, reduced cell damage and death (26, 27). A study in a rat model showed that erythropoietin administration was associated with a reduction in myocyte damage (28). Erythropoietin has also been reported to have a protective effect on apoptosis due to ischemic damage by restored blood flow and has improved left ventricular deformity in animal models. Plasma endogenous erythropoietin has been increased in patients with acute myocardial infarction or acute coronary syndrome undergoing primary coronary intervention, leading to a reduction in the size of the infarct lesion (29).

Despite the effectiveness of erythropoietin administration in these studies, there are conflicting reports on the ineffectiveness of erythropoietin. The results of Tabari et al showed that erythropoietin administration did not play a role in reducing tissue damage by ischemia and reperfusion (30). The results of Mocini et al. showed that erythropoietin administration had no effect on reducing myocyte cell damage (31). Studies have also reported common side effects of erythropoietin, including hypertension and thrombotic events. These complications are mainly due to increased platelets, hematocrit and blood viscosity, which may be seen in long-term use of erythropoietin (32, 33). Increased platelet-endothelial binding has been reported to increase the chance of thrombosis due to increased VWF antigen, increased factor 8 antigen, and decreased C and S protein levels after treatment with erythropoietin (34). Therefore, given the results of the this paper, an increase in erythropoietin was observed in patients with SCF and coronary artery occlusion. Therefore, as the results of the present study showed, an increase in erythropoietin level was observed in patients with SCF and obstructive CAD, although this finding will bring beneficial effects such as reducing inflammation and protecting vascular tissues, on the other hand an increase in erythropoietin level can be more likely the occurrence of subsequent adverse outcomes such as thrombotic events, it should be noted that although higher amount of erythropoietin were observed in SCF and coronary artery occlusion patients this increase was not associated with hemoglobin and hematocrit rising, wich we can be considered a positive point in reducing the possibility of subsequent adverse outcomes.

Another finding of this study showed that up to 34.5% of erythropoietin values can be predicted with the input variables to the regression model, which is a low level. This finding indicates that there are other effective variables on the erythropoietin level overlooked by this paper. It was also found that erythropoietin levels were higher in smokers and no significant relationship was observed for other variables included in the model. Studies show that smoking can cause erythrocytosis, which is thought to be caused by elevated serum erythropoietin levels. Polycythemia occurs in smokers due to constant exposure to tobacco smoke containing carbon monoxide and eventually hypoxia. Tissue hypoxia caused by smoking stimulates the secretion of erythropoietin and ultimately increases blood concentration (35). The results of other studies indicate different results of erythropoietin levels in smokers and non-smokers. The results of Eisenga et al. showed that although hematocrit levels were higher in smokers than in non-smokers, erythropoietin levels were lower in smokers than in non-smokers (36). Tanabe et al. showed that the level of erythropoietin in smokers was lower than non-smokers (35). Miler et al. also did not observe a difference between erythropoietin concentrations in smokers and non-smokers (37). Contradictory findings about the relationship between smoking and erythropoietin can change due to differences in smoking duration, amount of cigarettes smoked, and other confounders that need to be further investigated in future studies.

Conclusion:

Higher erythropoietin levels in SCF and coronary artery disease patients than healthy coronary arteries and also low predictive power of the studied variables compared to erythropoietin indicate the role of other influential factors and variables other than those addressed by this paper on erythropoietin levels in cardiovascular disease patients. the higher serum level of erythropoietin in SCF patients and its inconsistency with the hematocrit of this patients can contribute to the protective function of erythropoietin in this patients so is better to compare SCF syndrome between patients with normal GFR and CKD ; Also, higher erythropoietin levels in smokers candidates of angiography, although consistent with physiological findings, the results of studies are still contradictory. Prospective studies and measurement of this erythropoietin levels during long-term follow-up in SCF patients,

patients with coronary artery disease and healthy coronary artery are necessary to understand the main protective or destructive effects of erythropoietin on coronary artery disease.

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