Erythropoietin Reduces Post-PCI Arrhythmias in Patients With ST-elevation Myocardial Infarction

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Background: Arrhythmia is the foremost cause of sudden death after myocardial infarction (MI). Animal models have recently shown that erythropoietin (EPO) can reduce the incidence of arrhythmia after MI.

Methods: We investigated the effects of administrating 33,000 IU EPO on the occurrence of post-MI arrhythmia in 40 patients with ST-elevation MI who were randomly assigned in either EPO or placebo groups. Arrhythmias were blindly documented using full 12-lead configuration during 24 hours after percutaneous coronary intervention (PCI) by a cardiologist. Afterward, CK-MB, hematologic, and hemodynamic data were examined within 2 weeks after MI.

Results: A comparison made between the 2 groups showed significant differences in the incidence of arrhythmias (20% in EPO group and 35% in placebo group, $P = 0.043$). However, no significant differences in type of arrhythmias were observed between the groups. There was no significant difference between levels of CK-MB in the 2 groups during 24 hours ($P = 0.186$). Hematologic and hemodynamic data showed no significant changes 2 weeks after PCI.

Conclusion: High-dose administration of EPO in patients with ST-elevation MI who have been treated by primary PCI and standard antiplatelet therapy reduces the occurrence of arrhythmias. For clinical interpretation of the results, further well-designed trials are required.

Key Words: arrhythmia, erythropoietin, myocardial infarction

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INTRODUCTION

Being the prime cause of sudden cardiac death, arrhythmia is defined as irregularity in electrical activity and rhythmic beating of the heart. Arrhythmia occurs in approximately 70% of patients after myocardial infarction (MI).[1] Life-threatening ventricular tachyarrhythmias occur during first 24–48 hours of MI.[2] Additionally, preventing arrhythmias has been shown to decrease mortality and cardiac death.[3,4]

Numerous studies have been designed to verify the efficacy of device-based therapies, catheter- and surgery-based interventions, or electrophysiological testing.[1,5,6] Therefore, an investigation into the proper medication for reducing arrhythmias after MI is required.

There is promising evidence that erythropoietin (EPO) may prevent arrhythmias in the ischemic heart.[7,8] EPO is a renal hormone secreted in response to hypoxia with an essential role in regulating plasma hemoglobin concentrations.[9] In addition to hematopoiesis effect, a considerable body of data supports pleiotropic effects of EPO including cardioprotection due to reduction in size of the infarct and improvement in left ventricular (LV) function.[10–12] Such effects are mainly mediated by inhibiting apoptosis, mobilizing endothelial progenitor cells, inhibiting migration of inflammatory cells, and promoting angiogenesis.[9] Although cardioprotective effects of high doses of recombinant human EPO (rh-EPO) have been investigated in ischemia/reperfusion injury in human, studies about its effects on lethal arrhythmias are limited to a few animal models.[13–16] These research have shown that administration of EPO immediately before reperfusion can significantly reduce the incidence of ventricular fibrillation (VF) in animal models.[7,8]

As mentioned above, the effects of rh-EPO on arrhythmias in human remain unidentified. This study is the first research evaluating the effects of administration of high-dose rh-EPO on the incidence of arrhythmias in patients with ST-elevation MI (STEMI) after successful primary percutaneous coronary intervention (PCI).

MATERIALS AND METHODS

Study Population

The study was conducted in the Cardiology Department of Ghaem Educational, Research and Treatment Center, Mashhad, Iran, from October 2013 to March 2014. One hundred patients with ST-elevation acute MI (AMI) were screened for inclusion in the study (Table 1), and finally 40

TABLE 1. The Inclusion and Exclusion Criteria for AMI Patients Entering the Study

Inclusion criteria
Age between 18 and 76 yrs
Indication for primary PCI
Risk of cardiogenic shock
Killip class ≥3
Contraindication of fibrinolytic therapy
Primary PCI has been performed within the first 6 h of the onset of ischemic symptoms
Exclusion criteria
Hemoglobin levels >16.0 g/dL
AMI, pretreated with thrombolysis
Previous MI
Systolic blood pressure ≥160 mm Hg
Diastolic blood pressure ≥100 mm Hg
Bundle branch block
Serum creatinine >1.40 mg/dL
Previous treatment with rh-EPO
Blood transfusion <12 wk before entering the study
Indication for blood transfusion
Polycythemia vera
Concomitant inflammatory or malignant diseases
Recent trauma or major surgery
Previous thromboembolic complication

patients were randomized by www.randomizer.org to receive either placebo (n = 20) or EPO (n = 20) and entered this double-blind, placebo-controlled randomized trial (Fig. 1). This study was approved by the Ethics Review Boards of Mashhad University of Medical Science. All patients participated in the study after signing a written informed consent.

AMI was defined as experiencing severe chest pain for >30 minutes, ST elevations in electrocardiogram (≥2 mm in precordial leads and ≥1 mm in limb leads), and elevated serum levels of cardiac enzymes (creatine kinase-MB and troponin I).

Study Design

Subsequent to primary PCI, patients were randomized into EPO and placebo groups. The EPO group received 33,000 units of rh-EPO (PDpoetin; Pooyesh Daru Co) immediately after PCI that had been infused with 50 mL isotonic solution of sodium chloride for 30 minutes. A volume of 50 mL sodium chloride was administered to the placebo group.

Creatine kinase-MB (CK-MB) levels and ST-elevation resolution were evaluated as ischemic parameters. The resolution for the sum of ST-segment elevation [sum STR (ST resolution)] following 60 minutes of primary PCI in addition to biochemical markers was considered to verify the prognostic value of these indices in patients with STEMI.

The sum STR is depicted as percentage from the baseline.

$$\text{STR percentage} = \frac{\text{Sum of STR before PCI} - \text{Sum of STR after PCI}}{\text{Sum of STR before PCI}} \times 100.$$

CK-MB was assessed 3, 12, and 24 hours after PCI.[17,18]

Arrhythmias were blindly documented by full 12-lead configuration 24 hours after PCI by a cardiologist who judged arrhythmia development, and diagnosis was unaware of the patient's clinical information. Significant arrhythmias after STEMI were categorized as follows: nonsustained ventricular tachycardia (VT), sustained VT, and VF (Table 2). All arrhythmias were filed in Nihon Kohden Cardiofax C Model-1150, and afterward, the type, duration, and the frequency in which they occurred were analyzed.

To assess the hemodynamic effects of EPO, blood pressure and heart rate were continuously recorded once before PCI and subsequently 3, 6, 12, 24, and 48 hours and then 7 and 14 days after PCI. Patients with systolic blood pressure below 80 mm Hg and heart rate above 100/min had hemodynamic disturbances. Patients with systolic blood pressure ≥160 had significant hypertension. Blood samples were collected before PCI and then 24 and 48 hours and 14 days after PCI to quantify blood cell count, hemoglobin, and hematocrit levels. Levels of potassium, sodium, and serum creatinine were adjusted before PCI in the 2 groups.

Coronary Angiography, Primary PCI, and Medical Treatments

A standard coronary angiography was performed in all patients followed by stenting ± ballooning primary PCI, and reperfusion was achieved in all patients with Thrombolysis in MI score 3 within the first hour after AMI. Throughout the PCI, 100 U/kg bolus of heparin was administrated to each patient. After angioplasty, 600 mg of clopidogrel and 300 mg of aspirin were administered to patients as a loading dose followed by 75 and 80 mg/d of clopidogrel and aspirin, respectively. Beta-blockers, statins, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors were prescribed according to referrals' orders.

Statistical Analysis

Descriptive statistics are presented as mean ± SD for continuous variables, whereas absolute frequencies are shown for categorical data. Baseline characteristics of patients between the 2 groups were compared using independent *t* test (continuous variables), and χ^2 was applied for evaluating categorical data. One-way and 2-way repeated measure tests were used to estimate the treatment effects and calculate the intragroup and intergroup differences (2 sides and $P < 0.05$). SPSS 16 (SPSS, Inc, Chicago, IL) was used to perform all statistical analyses.

RESULTS

Baseline Characteristics of Patients

Forty patients were randomly divided into EPO and placebo groups (20 patients in EPO group and 20 patients in placebo group). In the each group, 14 patients had anterior MI and 6 patients had inferior posterior right ventricular MI. A comparison was made between demographic characterizations (age, body mass index, and sex) and cardiovascular risk factors (smoking, hypertension, hyperlipidemia, and diabetes mellitus). No significant differences were observed between

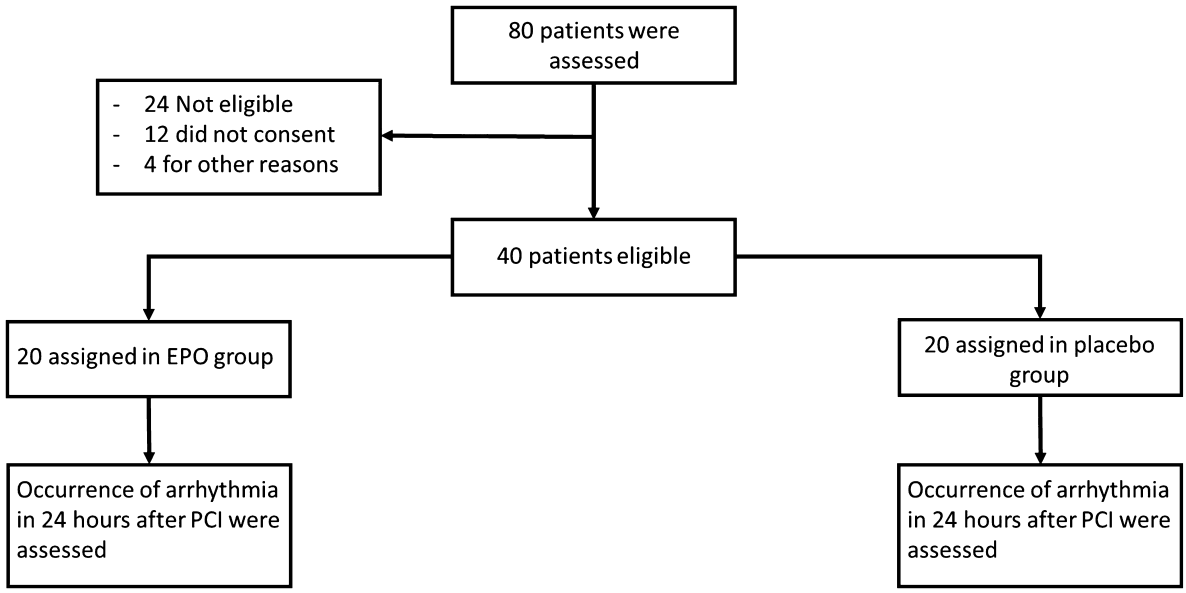

FIGURE 1. Flowchart.

the groups. Moreover, there were no significant differences between the baseline level of sodium, potassium, and blood urea nitrogen between the 2 groups (Table 3).

Evaluation of Anti-ischemic Effects

A comparison made between percentage of STR in the 2 groups did not show any significant differences (EPO group = 82.72% ± 12.84%, placebo group = 78.68% ± 35.78%, $P = 0.650$).

There were no significant differences between levels of CK-MB in the 2 groups during 24 hours ($P = 0.186$) (Fig. 2).

Comparing the Incidence of Arrhythmias Between the 2 Groups

Figure 3 shows all arrhythmias that occurred in our patients; 75% of patients had normal sinus rhythm during the first 24 hours following PCI. The most frequent arrhythmia was nonsustained VT (20% of all arrhythmias), and VT and VF had minor incident (5%) (Fig. 3).

Comparison of the occurrence of arrhythmias between the 2 groups showed significant differences (20% in EPO group and 35% in placebo group, $P = 0.043$). When the occurrence of nonsustained VT (EPO = 20% and placebo = 25%, $P = 0.112$), sustained VT (there was no VT in EPO group and placebo = 5%, $P = 0.499$), and VF (there was no VF in EPO group and placebo = 5%, $P = 0.499$) was compared, no significant differences between the groups were observed.

Hematologic and Hemodynamic Evaluations

RBC, WBC, and platelet counts did not show any significant differences between the 2 groups before PCI. The differences remained nonsignificant 24 and 48 hours after PCI. Hematocrit and hemoglobin levels were within normal

TABLE 2. Arrhythmia Characteristics[19]

Arrhythmia	Define
VT	P-wave maybe seen, rate 60–100/min, regular rhythm
	QRS complex: rate 110–250/min, regular or irregular rhythm abnormal contour (>0.12 s)
	Nonsustained VT: VT lasting shorter than 30 s
	Sustained VT: VT lasting longer than 30 s or with hemodynamic collapse
VF	P-wave: difficult to see
	QRS complex: rate 400–600/min, grossly irregular, baseline undulation no QRS complex

TABLE 3. Basic Characteristics of Patients

	EPO Group	Placebo	*P*
No. patients	20	20	
Sex			0.365*
Male	15	14	
Female	5	6	
Age (yr)	50.35 ± 6.39	54.60 ± 9.2	0.122†
BMI (kg/m^2)	27.13 ± 2.58	26.22 ± 3.18	0.320†
Risk factors			
Diabetes mellitus (%)	15	26	0.430*
Hyperlipidemia (%)	30	26	1.000*
Hypertension (%)	30	20	1.000*
Smoking (%)	40	46	0.741*
Infarct-related coronary artery			0.309*
LAD	12	10	
LCX	1	3	
RCA	7	7	

LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery.
*Chi-square test.
†Independent *t* test.
BMI, body mass index.

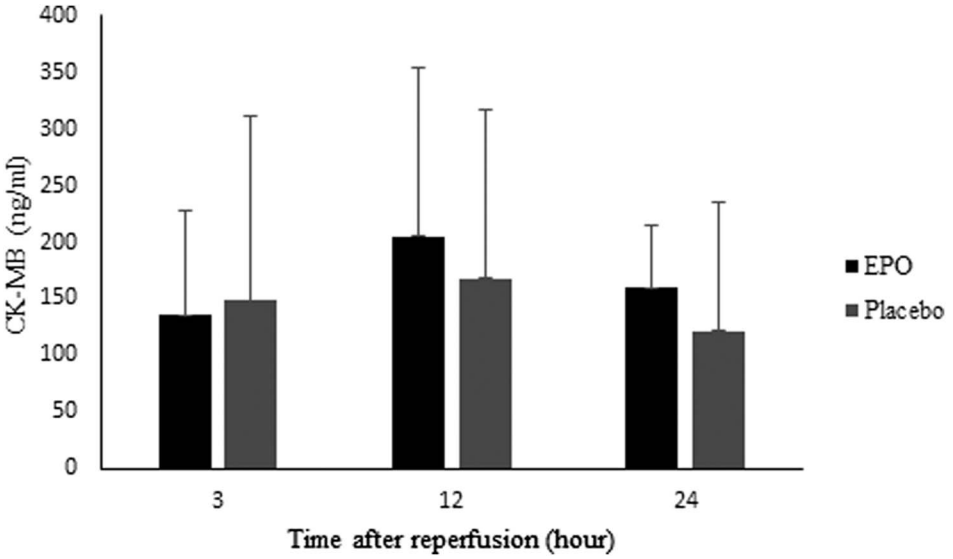

FIGURE 2. Serum levels of CK-MB after PCI (2-way repeated measure, $P < 0.05$).

ranges, and there were no significant differences between the 2 groups after 14 days (Table 4).

Evaluation of systolic and diastolic blood pressures and heart rate among the 2 groups did not show any significant differences before PCI and a week after PCI (Table 5). Moreover, there were no significant hypertension (SBP ≥ 160 mm Hg) and hemodynamic disturbances (systolic blood pressure [SBP] <80 mm Hg and heart rate [HR] >100/min) in the EPO group before and after PCI.

DISCUSSION

This is the first study to demonstrate that the administration of rh-EPO after PCI significantly reduces the occurrence of arrhythmias in patients with STEMI. Investigations have shown that 90% of VT and VF events occur within the first 48 hours after PCI. Not being benign, such arrhythmias result in a considerable increase in morbidity and mortality rate of patients undergoing primary PCI.[20]

In previous studies, using both EPO and darbepoetin revealed that erythropoietin-stimulating agents with a higher first dose (>20,000 IU) or total dose (≥30,000 IU) improved LV ejection fraction more significantly when compared with that of lower doses (<20,000 IU).[21] High-dose EPO was superior to placebo, statistically improving LV ejection fraction by 1.02% and LV end systolic volume by −4.61 mL in patients with acute STEMI, and it was generally well tolerated. The adverse effects reported in patients receiving high-dose EPO were essentially consistent with those in the placebo group. Therefore, in this study, we administered the dose of 33,000 IU of EPO.[22]

In the clinical setting for patients, episodes of ventricular arrhythmias arose and continued for 12–48 hours after the onset of MI.[23] In this study, occurrence of arrhythmias was monitored for 24 hours after PCI, and results showed significant differences in this regard. Burger et al[8] suggested beneficial effects of pretreatment with EPO on high-risk patients; although, treatment in the sufferers of coronary artery occlusions usually starts after the onset of symptoms.

The role of EPO in the protection of the heart from injury has been studied extensively in animal models, and it is increasingly becoming obvious that EPO provides significant protection against cell death and cardiac dysfunction.[10–12,24,25] In rodent models, EPO has been reported to decrease mortality.[26] Nevertheless, the controversy about administration of EPO continues in human studies. Nakamura et al[14] demonstrated that short-term therapy with low-dose rh-EPO could improve LV function and decrease the size of infarct with no noticeable effects on neointimal hyperplasia in PCI-treated coronary arteries. Ferrario et al[27] showed that administration of

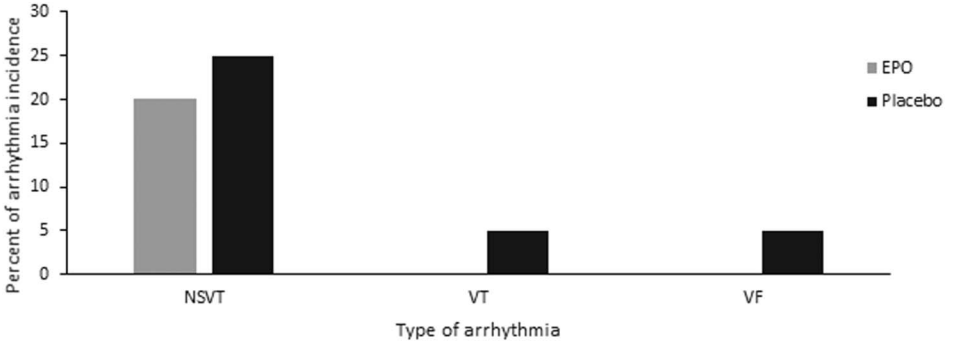

FIGURE 3. Comparison of the incidence of arrhythmias in patients with STEMI within 24 hours of PCI. Chi-squared, $P < 0.05$. NSVT, nonsustained VT.

TABLE 4. Comparison of Patient's Blood Cell Count Before PCI and After 1, 2, and 14 Days (Independent *t* test)

	Before PCI	1 d	2 d	14 d
WBCs, 10^3/mL				
EPO	10.01 ± 3.52	8.84 ± 2.23	7.24 ± 1.71	6.28 ± 15.33
Placebo	10.01 ± 2.78	9.61 ± 2.63	7.77 ± 2.19	7.11 ± 1.49
P	0.977	0.354	0.424	0.130
RBCs, million/μL				
EPO	4.63 ± 0.0.67	4.24 ± 0.69	4.62 ± 0.75	4.54 ± 0.52
Placebo	4.51 ± 0.70	4.40 ± 0.41	4.38 ± 1.00	4.52 ± 0.49
P	0.604	0.440	0.427	0.910
Platelets, $\times 10^3$/mL				
EPO	231.80 ± 62.62	207.80 ± 66.72	240.10 ± 86.12	221.60 ± 62.75
Placebo	198.20 ± 60.50	176.47 ± 68.51	206.73 ± 47.366	200.93 ± 61.42
P	0.121	0.183	0.186	0.347
Hemoglobin, g/dL				
EPO	12.99 ± 1.37	12.10 ± 1.33	13.12 ± 1.80	13.12 ± 1.40
Placebo	13.54 ± 1.12	13.06 ± 1.74	15.08 ± 6.30	13.67 ± 1.32
P	0.215	0.066	0.194	0.255
Hematocrit, %				
EPO	39.58 ± 3.34	36.75 ± 3.73	37.51 ± 4.14	39.58 ± 4.58
Placebo	41.31 ± 3.91	39.11 ± 4.43	38.50 ± 3.07	40.80 ± 3.56
P	0.074	0.097	0.445	0.579

short-term high-dose EPO in the early phase of PCI-treated AMI could ameliorate LV function and diminish the size of infarct, while hemoglobin and hematocrit values remained normal. However, In REVEAL administration of 60,000 IU rh-EPO after PCI in patients with STEMI was successful neither in the reduction of the size of MI nor in attenuation of cardiac remodeling.[28] Similarly, a study on patients with non–ST-elevation acute coronary syndromes receiving a single bolus of rh-α-EPO did not show any positive clinical effects or changes in cardiac enzymes levels. Despite numerous research, the effects of EPO on the human cardiac electrophysiology have remained unidentified thus far.[29]

This study demonstrated that administration of high-dose rh-EPO after PCI can significantly reduce arrhythmias in patients with STEMI, and when types of arrhythmias were analyzed, the incidence of significant arrhythmias in the placebo group was more than 2-fold in comparison with the EPO group. Such finding is in agreement with the initial observations of Hirata et al,[7] who detected PI3-kinase–dependent reductions in VF after myocardial ischemic/reperfusion in dogs, and that of Burger et al[8] who demonstrated EPO-mediated reductions in ventricular arrhythmia through increased expression of neuronal nitric oxide synthase (nNOS) in cardiomyocytes during myocardial ischemic/reperfusion in mice. Another research on rats showed that a single bolus dose of 5000 U/kg EPO at the time of resuscitation from VF could maintain the hemodynamic efficacy of chest compression and enable the return of spontaneous circulation with greater aortic pressure.[30]

As shown in animal models, antiarrhythmic effects of rh-EPO are applied through PI3-kinase–dependent pathways and through several plausible mechanisms. First, on reperfusion conditions, activation of phospholipase C (PLC) through membrane α-adrenoreceptors of the myocardial cells augments the production of inositol-1,4,5-trisphospate (IP3), which in turn triggers IP3 receptors on sarcoplasmic reticulum and releases Ca^{2+}. An elevation of the intracellular Ca^{2+} levels initiates slow Ca^{2+} oscillations that lead to a delayed afterdepolarization, generating many arrhythmias such as VF. Moreover, PLC hydrolyzes phosphatidylinositol-4,5-bisphospate (PIP2) to form IP3. Given that PIP2 is a similar substrate for PI3-kinase and PLC, rh-EPO may prevent lethal arrhythmias through activation of PI3-kinase pathways that decreases PIP2 levels and results in the inhibition of Ca^{2+} overload by IP3.

Second, oxygen-derived free radicals participate in the creation of reperfusion arrhythmias; therefore, rh-EPO may decrease reperfusion arrhythmias through averting the release of free radicals from neutrophils or act as a radical scavenger.[7] The third mechanism for antiarrhythmic effects of EPO is possible augmentation in nNOS. Burger et al[8] declared that the EPO-mediated declines in arrhythmias were probably in part mediated by nNOS, as there were not any noticeable antiarrhythmic effects subsequent to treating nNOS (−/−) mice with EPO.

Finally, pervious researchers have found evidence for antiarrhythmic effects of EPO that is possibly attributable to decrease in the size of myocardial infarct. Our findings were in accordance with that of Burger et al and showed that antiarrhythmic effects of EPO were not related to its anti-ischemic effects; because, in our study, the ischemic factors (CK-MB and STR percentage) had no significant changes, whereas the occurrence of arrhythmias was significantly decreased in the EPO group.

There are some concerns about the safety of administration when high doses of EPO are used. Some of the reported adverse effects for EPO are as follows: hypertension, seizure, elevated hematocrit and hemoglobin levels, and potential thrombogenic and carcinogenic effects.[31,22] Moreover, EPO can enhance the formation and reactivity of the

TABLE 5. Comparison of Hemodynamic Data of Patients (Independent *t* test)

	3 h	6 h	12 h	24 h	48 h	7 d	14 d
Systolic blood pressure, mm Hg							
EPO	115.35 ± 20.47	115.0 ± 17.78	113.21 ± 18.86	113.90 ± 16.54	109.32 ± 16.20	111.81 ± 16.63	119.31 ± 16.75
Placebo	124.38 ± 22.44	119.23 ± 13.61	113.75 ± 14.12	113.75 ± 14.12	108.36 ± 13.40	115.71 ± 6.64	115.91 ± 12.78
P	0.101	0.472	0.243	0.980	0.870	0.447	0.575
Diastolic blood pressure, mm Hg							
EPO	77.00 ± 13.30	75.35 ± 11.72	73.63 ± 11.78	72.74 ± 12.12	72.21 ± 12.30	72.50 ± 7.56	73.88 ± 10.24
Placebo	80.92 ± 20.60	80.46 ± 10.60	80.85 ± 10.80	74.92 ± 12.41	71.36 ± 10.36	76.73 ± 7.54	71.73 ± 12.03
P	0.517	0.214	0.089	0.633	0.849	0.165	0.622
Heart rate, /min							
EPO	83.55 ± 15.55	85.95 ± 15.66	80.37 ± 12.96	75.26 ± 17.60	76.80 ± 9.41	74.00 ± 7.90	73.63 ± 9.10
Placebo	89.75 ± 18.10	90.92 ± 12.29	85.58 ± 12.66	82.08 ± 13.16	78.09 ± 10.75	77.00 ± 6.78	76.36 ± 9.25
P	0.312	0.356	0.280	0.259	0.731	0.315	0.452

platelets and red blood cells.[32,33] In this study, levels of hematocrit and hemoglobin remained within normal ranges after 2 weeks of administration. There were no significant differences in systolic and diastolic blood pressures and heart rate between the 2 groups within 2 weeks. Therefore, it seems that administration of EPO with this dose can be considered safe in patients with STEMI. In other studies, however, EPO has been administered with a dose of nearly twice more than 33,000 IU, and no adverse effects have reported.[34,35]

As a limitation, this investigation was a pilot study examining a small population of patient; therefore, the authors suggest the aforementioned results be considered cautiously.

This study demonstrated that treatment with EPO could reduce the incidence of significant arrhythmias after PCI in patients with STEMI. Although, our findings require a comprehensive investigation in order to be translated into clinical practice, they may support the use of rh-EPO as a cardioprotective agent in the treatment of patients with MI.

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REFERENCES

1. Yesil M. Management of arrhythmias during transportation in patients with acute myocardial infarction. *Anadolu Kardiyol Derg.* 2007;7 (suppl 1):85–87.
2. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for practice guidelines (writing committee to develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006;114:e385–e484.
3. Gillis DB, Hamilton DR. Estimating outcomes of astronauts with myocardial infarction in exploration class space missions. *Aviat Space Environ Med.* 2012;83:79–91.
4. Holler CP, Wichmann S, Nielsen SL, Moller AM. Large discrepancy between prehospital visitation to mobile emergency care unit and discharge diagnosis. *Dan Med J.* 2012;59:A4415.
5. Feltes TF, Bacha E, Beekman RH III, et al. Indications for cardiac catheterization and intervention in pediatric cardiac disease: a scientific statement from the American Heart Association. *Circulation*. 2011;123:2607–2652.
6. Recommendations of a task force of the European Society of Cardiology and the European Resuscitation Council on the pre-hospital management of acute heart Attacks. *Resuscitation*. 1998;38:73–98.
7. Hirata A, Minamino T, Asanuma H, et al. Erythropoietin just before reperfusion reduces both lethal arrhythmias and infarct size via the phosphatidylinositol-3 kinase-dependent pathway in canine hearts. *Cardiovasc Drugs Ther.* 2005;19:33–40.
8. Burger DE, Xiang FL, Hammoud L, et al. Erythropoietin protects the heart from ventricular arrhythmia during ischemia and reperfusion via neuronal nitric-oxide synthase. *J Pharmacol Exp Ther.* 2009;329:900–907.
9. Burger D, Xenocostas A, Feng QP. Molecular basis of cardioprotection by erythropoietin. *Curr Mol Pharmacol.* 2009;2:56–69.
10. Lipsic E, Schoemaker RG, van der Meer P, et al. Protective effects of erythropoietin in cardiac ischemia: from bench to bedside. *J Am Coll Cardiol.* 2006;48:2161–2167.
11. Lipsic E, van der Meer P, Henning RH, et al. Timing of erythropoietin treatment for cardioprotection in ischemia/reperfusion. *J Cardiovasc Pharmacol.* 2004;44:473–479.

12. Westenbrink BD, Lipsic E, van der Meer P, et al. Erythropoietin improves cardiac function through endothelial progenitor cell and vascular endothelial growth factor mediated neovascularization. *Eur Heart J.* 2007;28:2018–2027.
13. Lipsic E, van der Meer P, Voors AA, et al. A single bolus of a long-acting erythropoietin analogue darbepoetin alfa in patients with acute myocardial infarction: a randomized feasibility and safety study. *Cardiovasc Drugs Ther.* 2006;20:135–141.
14. Nakamura R, Takahashi A, Yamada T, et al. Erythropoietin in patients with acute coronary syndrome and its cardioprotective action after percutaneous coronary intervention. *Circ J.* 2009;73:1920–1926.
15. Voors AA, Belonje AM, Zijlstra F, et al. A single dose of erythropoietin in ST-elevation myocardial infarction. *Eur Heart J.* 2010;31:2593–2600.
16. Belonje AM, Voors AA, van Gilst WH, et al. Effects of erythropoietin after an acute myocardial infarction: rationale and study design of a prospective, randomized, clinical trial (HEBE III). *Am Heart J.* 2008;155: 817–822.
17. Woo JS, Cho JM, Kim SJ, et al. Combined assessments of biochemical markers and ST-segment resolution provide additional prognostic information for patients with ST-segment elevation myocardial infarction. *Korean Circ J.* 2011;41:372–378.
18. Schroder R. Prognostic impact of early ST-segment resolution in acute ST-elevation myocardial infarction. *Circulation*. 2004;110:e506–e510.
19. Braunwald E. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. Vol 1. 9th ed. Philadelphia: Elsevier Saunders; 2011: 2136.
20. Mehta RH, Starr AZ, Lopes RD, et al; APEX AMI Investigators. Incidence of and outcomes associated with ventricular tachycardia or fibrillation in patients undergoing primary percutaneous coronary intervention. *JAMA*. 2009;301:1779–1789.
21. Li J, Xu H, Gao Q, Wen Y. Effect of erythropoiesis-stimulating agents in acute ST-segment elevation myocardial infarction: a systematic review. *Eur J Clin Pharmacol.* 2012;68:469–477.
22. Wen Y, Xu J, Ma X, Gao Q. High-dose erythropoietin in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized controlled trials. *Am J Cardiovasc Drugs.* 2013;13:435–442.
23. Winkler C, Funk M, Schindler DM, et al. Arrhythmias in patients with acute coronary syndrome in the first 24 hours of hospitalization. *Heart Lung.* 2013;42:422–427.
24. 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.
25. Talan MI, Ahmet I, Lakatta EG. Did clinical trials in which erythropoietin failed to reduce acute myocardial infarct size miss a narrow therapeutic window? *PLoS One*. 2012;7:e34819.
26. Hamed S, Barshack I, Luboshits G, et al. Erythropoietin improves myocardial performance in doxorubicin-induced cardiomyopathy. *Eur Heart J.* 2006;27:1876–1883.
27. Ferrario M, Arbustini E, Massa M, et al. High-dose erythropoietin in patients with acute myocardial infarction: a pilot, randomised, placebo-controlled study. *Int J Cardiol.* 2011;147:124–131.
28. Melloni C, Rao SV, Povsic TJ, et al. Design and rationale of the reduction of infarct Expansion and ventricular remodeling with erythropoietin after large myocardial infarction (REVEAL) trial. *Am Heart J.* 2010;160: 795–803 e2.
29. Liem A, van de Woestijne AP, Bruijns E, et al. Effect of EPO administration on myocardial infarct size in patients with non-STE acute coronary syndromes; results from a pilot study. *Int J Cardiol.* 2009; 131:285–287.
30. Radhakrishnan J, Upadhyaya MP, Ng M, et al. Erythropoietin facilitates resuscitation from ventricular fibrillation by signaling protection of mitochondrial bioenergetic function in rats. *Am J Transl Res.* 2013;5: 316–326.
31. Singbartl G. Adverse events of erythropoietin in long-term and in acute/short-term treatment. *Clin Investig.* 1994;72:S36–S43.
32. Heinisch BB, Vcelar B, Kapiotis S, et al. The effect of erythropoietin on platelet and endothelial activation markers: a prospective trial in healthy volunteers. *Platelets*. 2012;23:352–358.
33. Stohlawetz PJ, Dzirlo L, Hergovich N, et al. Effects of erythropoietin on platelet reactivity and thrombopoiesis in humans. *Blood*. 2000;95: 2983–2989.
34. Ferrario M, Massa M, Rosti V, et al. Early haemoglobin-independent increase of plasma erythropoietin levels in patients with acute myocardial infarction. *Eur Heart J.* 2007;28:1805–1813.
35. Ott I, Schulz S, Mehilli J, et al. Erythropoietin in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: a randomized, double-blind trial. *Circ Cardiovasc Interv.* 2010;3:408–413.