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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Endogenic erythropoietin secretion in patients undergoing off-pump coronary artery bypass grafting

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Abstract

Background: Erythropoietin (EPO) deficiency or inadequate EPO secretion in response to bleeding may result in profound or prolonged anaemia after cardiac surgery.

Aim: The aim of the study was to evaluate the changes in EPO secretion in patients undergoing off-pump coronary artery bypass grafting (OPCAB).

Methods: Blood samples from 43 patients (mean age 65.1 ± 7.6 years) were obtained before surgery and on the 1st, 2nd, and 6th day post isolated OPCAB. EPO levels ≥ 4.3 mIU/mL were considered normal.

Results: Thirteen (30%) patients had the preoperative EPO level below normal range even though their preoperative haemoglobin was ≥ 13 g/dL. In patients with basal EPO deficiency lower peak EPO levels were observed compared to the group with normal basal EPO levels, even though reduction in haemoglobin concentrations was comparable in both groups. Moreover, lower reticulocytosis was noted on day 1 (8.5 ± 4.0‰ vs. 11.7 ± 4.4‰; p = 0.04) and a tendency toward lower values was seen on day 2 (9.6 ± 4.3‰ vs. 13.0 ± 5.8‰; p = 0.07) among patients with preoperative EPO deficiency.

Conclusions: Erythropoietin deficiency is common in patients scheduled for OPCAB, and it results in diminished increase in EPO secretion in response to bleeding. Consequently, in patients with EPO deficiency, reticulocytosis is lower than it could be predicted based on the observation of patients with normal EPO levels and similar blood loss.

Key words: erythropoietin secretion, erythropoietin deficiency, coronary artery surgery

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INTRODUCTION

Erythropoietin (EPO) is the main endogenic stimulator of red blood cell production. This 30.4-kDa glycoprotein is secreted into the circulation by the peritubular interstitial cells of the kidney. On a molecular level, transcription of EPO is regulated by hypoxia-inducible factor 1, which is sensitive to reduced oxygen tension [1, 2]. In a clinical setting, anaemia is the most obvious factor provoking increased EPO production. In elective procedures, when a significant blood loss is predicted, recombinant human EPO (rH-EPO) may be used. Although the Society of Thoracic Surgeons and the Society of Cardiovascular Anaesthesiologists approved the use of EPO in patients undergoing autologous blood donation before cardiac surgery or in low-risk elective anaemic patients (haemoglobin < 13 g/dL) before cardiac procedures (recommendation class IIA), it is still not a common practice, mostly due to economic reasons. Moreover, it is also suggested that EPO could be given a few days before operation, to increase red cell mass in elective patients who are at risk for postoperative anaemia and depressed endogenous EPO production (recommendation class IIB, level of evidence C) [3]. In fact, the latter recommendation pertains to patients with impaired

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renal function, who often suffer from EPO deficiency [4, 5]. Nephrologists commonly use rH-EPO in anaemic patients with advanced kidney disease. Their experience may be transferred into the field of cardiac surgery. However, there is insufficient evidence supporting this kind of therapy in patients with normal preoperative haemoglobin concentrations and normal or mildly impaired renal function. Moreover, there is also little data regarding endogenic EPO secretion in patients undergoing cardiac surgery. Better understanding of fluctuations in EPO levels in response to perioperative blood loss as well as identification of patients predisposed to absolute or relative EPO deficiency may not only be of scientific value, but also carry practical implications by improving criteria for rH-EPO administration and establishing an optimal model of therapy.

The aim of our study was to evaluate the dynamics of EPO secretion among patients undergoing isolated coronary artery surgery.

METHODS

Patients: clinical data and laboratory test results

Forty-three patients scheduled for isolated first-time off-pump coronary artery bypass grafting (OPCAB) were included in this study. Patients with preoperative estimated glomerular filtration rate (eGFR) lower than 30 mL/min/1.73 m^2 or haemoglobin concentration lower than 11 g/dL were excluded. Further exclusion criteria were: contraindication to potential rH-EPO administration, double anti-platelet therapy within the last few days before the operation (five days for clopidogrel, seven for prasugrel, and three for ticagrelor; the second anti-platelet drug was always aspirin and it was not terminated before surgery), need for chronic anticoagulant treatment, chronic obstructive pulmonary disease requiring treatment, blood donation or haemorrhage within the last month, and thrombocytopaenia.

Blood samples were obtained before OPCAB and on the 1st, 2nd, and 6th postoperative day. Moreover, the lowest haemoglobin concentration during six days post surgery was recorded. EPO levels were measured by commercially available immunoassay with the use of Immulite 2000 Siemens. EPO levels ≥ 4.3 mIU/mL, according to the normal range for this method, were considered normal. GFR was estimated using the MDRD Study equation [6]. Haematological measurements were performed with a Sysmex K-4500 Automated Haematology Analyser and biochemical measurements with a Cobas 6000 Roche analyser.

The clinical characteristics and laboratory test results are presented in Table 1.

Except for one patient, who was operated via lateral thoracotomy, in all other patients a median sternotomy approach was applied. The left internal thoracic artery was always used to graft the left anterior descending branch of the left coronary artery. The remaining grafts were done with right internal thoracic artery (in three patients), radial artery (in one patient), or saphenous vein, if needed.

Table 1. Clinical and laboratory characteristics

Demographic and clinical characteristics	
Sex	6 women, 37 men
Age [years]	65.1 ± 1.2 (45–79)
Hypertension	35
Diabetes mellitus	13
LVEF:	
≥ 50%	38
35–49%	5
Previous myocardial infarction	13
Previous PCI	10
Number of vessels grafted	2.4 ± 0.2 (1–5)
Preoperative laboratory test results	
Haemoglobin [g/dL]:	14.6 ± 0.2 (11.2–16.9)
< 13	2
13–14	12
≥ 14	29
eGFR [mL/min/1.73 m^2]:	76.3 ± 2.3 (42.6–119)
40–50	1
50–60	5
60–90	29
≥ 90	8
MCV [fL]	90.18 ± 0.5 (82.32–99.7)
MCH [pg]	30.70 ± 0.2 (27.9–33.6)
MCHC [g/dL]	34.04 ± 0.2 (32.5–36.2)
Iron concentration [μg/mL]	79.5 ± 3.6 (33.8–143.7)
TIBC [μg/dL]	285.1 ± 5.0 (211.6–351.9)
Ferritin [ng/mL]	214.8 ± 25.3 (32.6–907)
Vitamin B12 [pg/mL]	385.4 ± 24.2 (146.5–830.6)
Folic acid [ng/mL]	9.6 ± 0.7 (4.1–31.6)

Data are presented as mean ± standard error (minimum–maximum). LVEF — left ventricular ejection fraction; PCI — percutaneous coronary intervention; eGFR — estimated glomerular filtration rate; MCV — mean corpuscular volume; MCH — mean corpuscular haemoglobin; MCHC — mean corpuscular haemoglobin concentration; TIBC — total iron binding capacity

The decision about red blood cell transfusion was made by an anaesthesiologist or cardiac surgeon, and in every patient it was made individually based on the patient's clinical status.

EPO levels

The patients were divided into two groups using a cut-off value of 4.3 mIU/mL: the first group with normal (≥ 4.3 mIU/mL) and the second group with decreased preoperative EPO level (< 4.3 mIU/mL). There were 13 (30%) patients with preoperative EPO level below normal range; in all of them preoperative haemoglobin was ≥ 13 g/dL. There were no

correlations between preoperative EPO level and the preoperative value of eGFR, haemoglobin, or age ($p > 0.05$). The prevalence of hypertension and diabetes was similar in both groups. Preoperative levels of folic acid, vitamin B12, ferritin, iron, and total iron binding capacity were comparable in patients with normal and decreased EPO levels. We did not find any statistical difference of high sensitive C-reactive protein concentrations before and after surgery between both groups.

Ethics and statistics

Informed patient consent was obtained in all cases before blood collection. The study was approved by the Local Ethics Committee.

Statistical analysis

Statistical analyses were performed with Statistica 10.0. A p value < 0.05 was considered significant. All continuous variables were expressed as mean ± standard error. Variables with a normal distribution were compared using the Student t-test; those with skewed distribution were compared using the Mann-Whitney U test. The inter-group differences of parametric variables were tested with the χ^2 test. ANOVA test assessed the inter-group differences between repetitive measurements. To estimate interactions between variables, a general linear model was used. Correlations between continuous variables were expressed with correlation coefficients.

RESULTS

Although, according to ANOVA test, the trend of EPO level changes through the whole observation period was comparable in both groups ($F = 1.75$, $p = 0.18$; Fig. 1), on day 6 the EPO level was lower in the group with baseline EPO deficiency. Moreover, peak EPO level was significantly lower in this group, even though blood loss (expressed as haemoglobin concentration drop) as well as the number of red blood cell units transfused were comparable in both groups. Consequently, multivariate analysis showed that the peak EPO value was dependent on the basal EPO level and the number of red blood cell transfusion ($F = 17.4$, $p = 0.0002$ and $F = 6.14$, $p = 0.018$, respectively) but not on age, preoperative eGFR, or minimal postoperative haemoglobin ($p > 0.05$).

Patients with preoperative EPO deficiency had lower reticulocytosis on the 1st and 2nd postoperative day than those with normal preoperative EPO levels.

The detailed data are presented in Table 2.

DISCUSSION

Bleeding is an almost unavoidable consequence of every surgical procedure. As cardiac surgery is related to large tissue injury, it is obvious that blood loss and postoperative anaemia are among the most common complications. Despite reduction in procedural invasiveness by e.g. minimising surgical access or avoiding the use of cardiopulmonary bypass, this problem has not been eliminated. It is estimated that up to 50% of

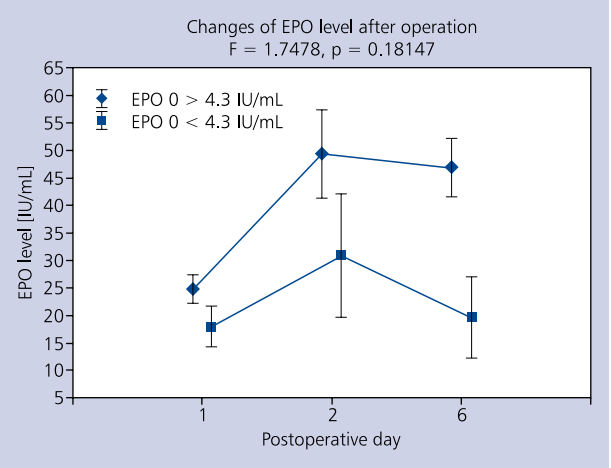

Figure 1. Changes of postoperative erythropoietin (EPO) levels dependent of preoperative value. Data are presented as mean ± standard error

patients undergoing cardiac surgery need a blood transfusion in their postoperative course [3]. What is more, due to the deteriorating profile of patients referred for coronary artery bypass grafting (CABG), there is an observed trend of increasing number of red blood cell transfusions, reaching about three units per patient [7]. High demand for blood products raises economical and organisational issues. Moreover, there is increasing body of evidence that blood transfusions have their negative impact on patients' outcomes [8]. All strategies that might reduce postoperative anaemia and, consequently, the need for blood transfusions are welcome.

In the last two decades there has been growing interest in EPO use in perioperative care in cardiac surgery. Although there have been many studies published, many controversies remain about the optimal protocol. Some authors proved that administration of rH-EPO alone or in addition to autologous blood donation could reduce the number of red blood cells transfused [9–11]. Conversely, some other authors found that postoperative use of lone rh-EPO did not have this effect [12]. Taking into consideration different protocols of rH-EPO administration and their results, it could be concluded that the clue is timing. As the lowest haemoglobin concentration occurs usually during the first postoperative hours, rH-EPO administration should be planned in a way that would result in an increase in reticulocytosis in this period. As our study showed, the increase in endogenous EPO secretion is already seen on the first postoperative day, but followed by the increase in reticulocytosis not earlier than on the third postoperative day and clearly stated on the sixth day. Although it is consistent with the known mechanism of EPO action [13], it is not sufficient to prevent significant anaemia in the early postoperative period. That is why our study supports the hypothesis that exogenous EPO should be supplied at least three to four days before the operation.

Table 2. Haematological characteristics dependent on preoperative erythropoietin (EPO) level

Day		EPO ≥ 4.3 mIU/mL	EPO < 4.3 IU/mL	P
0	EPO [IU/mL]	8.02 ± 0.68	2.78 ± 0.28	< 0.0001
	Haemoglobin [g/dL]	14.47 ± 0.24	14.73 ± 0.25	0.53
	Reticulocytes [‰]	11.03 ± 1.02	8.0 ± 1.06	0.08
1	EPO [IU/mL]	24.82 ± 2.53	17.91 ± 2.91	0.11
	Haemoglobin [g/dL]	11.2 ± 0.21	11.83 ± 0.36	0.12
	Reticulocytes [‰]	11.67 ± 0.84	8.5 ± 1.15	0.04
2	EPO [IU/mL]	46.63 ± 8.08	30.87 ± 7.00	0.15
	Haemoglobin [g/dL]	10.74 ± 0.21	10.97 ± 0.35	0.57
	Reticulocytes [‰]	13.0 ± 1.05	9.61 ± 1.20	0.07
6	EPO [IU/mL]	46.70 ± 6.24	19.63 ± 3.23	0.001
	Haemoglobin [g/dL]	11.2 ± 0.25	11.7 ± 0.26	0.23
	Reticulocytes [‰]	20.89 ± 2.29	19.46 ± 2.79	0.71
	Haemoglobin drop [g/dL]	–4.32 ± 0.21	–4.11 ± 0.35	0.59
	Min haemoglobin [g/dL]	10.15 ± 0.23	10.62 ± 0.30	0.23
	EPO max [IU/mL]	56.52 ± 7.67	33.91 ± 6.75	0.025
	RBC units transfused	0.47 ± 0.17	0.08 ± 0.08	0.12
	RBC transfusion [no. of patients]	8	1	0.32
	Drainage [mL]	809 ± 63	728 ± 76	0.80

Data are presented as mean ± standard error. RBC — red blood cells

In our opinion there is another, even more important, finding in the study; namely, that almost one third of examined patients had preoperative EPO deficiency but did not have anaemia. Conversely, Wenzel et al. [14] observed that EPO levels before coronary artery surgery were within normal ranges. Firstly, we thought about a negative feedback, which has been well described [5] and is a common phenomenon in human physiology. When satisfactory haemoglobin concentration is achieved, there is no need for extensive EPO secretion, and in this case a lower EPO level could be a mechanism preventing polycythaemia. But then we realised that the preoperative lower EPO level was followed by lower peak EPO levels, despite comparable haemoglobin drop after surgery. Furthermore, it seems that patients with preoperative EPO deficiency were not able to maintain increased EPO secretion for a longer period. Whereas all patients with preoperative EPO deficiency were anaemic on day 6 and their haemoglobin concentration was not different than that observed in the group with normal preoperative EPO at that time, their EPO level was not even half as high. Moreover, a lower reticulocytosis increase in the early postoperative period was observed in that group. Although some tendency towards lower reticulocytosis in the group with EPO deficiency was already detected preoperatively, the difference was clearly seen in the first postoperative day and disappeared on the sixth day. Although the preoperative lower reticulocytosis is clinically not relevant, it gains importance in the postoperative period when prompt response of the compensative mechanism is crucial for patients' recovery. We failed to prove that the above-described changes had an influence on the pre-discharge haemoglobin concentration, but even if there were only a few red blood cell transfusions in both groups, this was still a disturbing factor. It is difficult to discuss the results because of very limited data in the literature concerning this issue. A small study by Levine et al. [15] found that patients undergoing CABG had lower EPO increase than patients undergoing cholecystectomy. However, their study could not be directly compared to our results because Levine et al. [15] included only 10 CABG patients who had many more transfusions (3.4 ± 0.7 red blood cell units) than our group. Additionally, all of them were operated with the use of cardio-pulmonary bypass. It should be mentioned here that OPCAB patients (our study group) constituted a better model for the assessment of the changes in EPO secretion: firstly, there were no problems related to extensive haemodilution or haemodynamic changes (which are likely to occur during cardio-pulmonary bypass); and secondly, bleeding and haemoglobin drop were noticeable, but the average unit number of transfused red blood cell was low. All of this significantly simplified the analysis and gave insight into the physiological mechanisms.

Renal failure is the most frequent reason for EPO deficiency. Nowadays, it is obvious that patients with end-stage kidney disease will require rH-EPO administration at some point. However, the prevalence and clinical consequences of

EPO deficiency in patients with normal or only mildly impaired renal function, especially if they are not anaemic, are not widely known. In our study group only six patients had eGFR below 60 mL/min/1.73 m^2, and the lowest eGFR was above 40 mL/min; therefore, most patients were supposed to have normal EPO secretion. Surprisingly, there was no statistical relationship between preoperative EPO level and eGFR or the factors influencing renal function (such as age, presence of diabetes and hypertension). It may suggest that patients undergoing coronary surgery are still at risk of EPO deficiency independently of traditional risk factors. The facts above imply that EPO measurement could be an effective tool in identifying the patients who would benefit from rH-EPO therapy.

Limitations of the study

1. Initially, we planned one-month follow-up, but due to great number of patients lost to follow-up, there was no statistical ground to perform reliable analyses.
2. Response to EPO is also related to EPO-receptor expression. As we did not determine its level, one of the potential disturbing factors was not taken into consideration.
3. Erythropoietin secretion may be dependent on renal hypoperfusion and hypoxaemia not related to anaemia. All patients were monitored intraoperatively and then postoperatively — continuous measurements of arterial blood pressure and serial gasometry were performed. There were no clinically important hypotonia or hypoxaemia observed, but we did not analyse the detailed data. To build a reliable statistical model that would include all parameters (numerous results of blood pressure and gasometry in time-dependent manner) we would have needed to increase the number of patients.

CONCLUSIONS

Erythropoietin deficiency is common in patients scheduled for OPCAB, and it results in diminished increase in EPO secretion in response to bleeding. Consequently, in patients with EPO deficiency, reticulocytosis is lower than it could be predicted based on the observations of patients with normal EPO levels and similar blood loss.

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Wydzielanie endogennej erytropoetyny u chorych poddawanych pomostowaniu naczyń wieńcowych bez użycia krążenia pozaustrojowego

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Streszczenie

Wstęp: Niedobór erytropoetyny (EPO) czy też nieadekwatny wzrost jej wydzielania w odpowiedzi na krwawienie może skutkować nasiloną i/lub dłużej utrzymującą się niedokrwistością po zabiegach kardiochirurgicznych.

Cel: Celem niniejszego badania była ocena zmian w wydzielaniu endogennej EPO u chorych poddawanych operacjom pomostowania naczyń wieńcowych bez użycia krążenia pozaustrojowego (OPCAB).

Metody: Do badania włączono 43 chorych (w średnim wieku 65,1 ± 7,6 roku), u których wykonano izolowany zabieg OPCAB. Przed zabiegiem, a następnie w 1., 2. i 6. dobie po operacji wykonano oznaczenia EPO, hemoglobiny i liczby retikulocytów.

Wyniki: U 13 (30%) chorych poziom EPO przed operacją znajdował się poniżej dolnej granicy normy laboratoryjnej, przy czym u wszystkich tych pacjentów stężenie hemoglobiny było ≥ 13 g/dl. U chorych z wyjściowym niedoborem EPO zaobserwowano w okresie pooperacyjnym niższe szczytowe stężenia niż w grupie z wyjściowo prawidłowymi stężeniami EPO mimo porównywalnego spadku stężenia hemoglobiny. Ponadto, w tej grupie chorych stwierdzono niższą retikulocytozę w 1. dobie po zabiegu (8,5 ± 4,0‰ vs. 11,7 ± 4,4‰; p = 0,04) oraz tendencję do niższych wartości w 2. dobie (9,6 ± 4,3‰ vs. 13,0 ± 5,8‰; p = 0,07).

Wnioski: Niedobór EPO jest częstym zjawiskiem w populacji chorych zakwalifikowanych do pomostowania naczyń wieńcowych i skutkuje mniejszym wzrostem wydzielania endogennej EPO w odpowiedzi na krwawienie. W konsekwencji u osób z niedoborem EPO obserwuje się mniejszy przyrost liczby retikulocytów niż u pacjentów z prawidłowymi stężeniami EPO i podobną utratą krwi.

Słowa kluczowe: erytropoetyna, niedobór erytropoetyny, pomostowanie naczyń wieńcowych

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