MEDICAL CHANNEL

Original Article

# THE ACUTE TREND OF ERYTHROPOIETIN ON PLATELET COUNT DURING HYPOXIA-REOXYGENATION INJURY IN RATS

** C. Tsompos, ** C. Panoulis, *** K Toutouzas, **** A. Triantafyllou, ***** G. Zografos, ****** A. Papalois*

* Constantinos Tsompos: Consultant A, Department of Obstetrics & Gynecology, Mesologi County Hospital, Etoloakarnania, Greece ** Constantinos Panoulis: Assistant Professor, Department of Obstetrics & Gynecology, Aretaieion Hospital, Athens University, Attiki, Greece *** Konstantinos Toutouzas: Assistant Professor, Department of Surgery, Ippokrateion General Hospital, Athens University, Attiki, Greece **** Aggeliki Triantafyllou: Associate Professor, Department of Biologic Chemistry, Athens University, Attiki, Greece ***** George Zografos: Professor, Department of Surgery, Ippokrateion General Hospital, Athens University, Attiki, Greece ****** Apostolos Papalois: Director, Experimental Research Centre ELPEN Pharmaceuticals, S.A. Inc., Co., Attiki, Greece

Received on 07-12-2015
Accepted on 31-12-2015

***Correspondence Author:*:**
**TSOMPOS CONSTANTINOS**
Department of Obstetrics & Gynecology
Mesologi County Hospital
Nafpaktou street
Mesologi 30200
Etoloakarnania
Greece
Tel: 00302631360237 & 00306946674264
Fax: 00302106811215
E-mail:
Tsomposconstantinos@gmail.com

## ABSTRACT

**Objective:** This experimental study examined the effect of erythropoietin (Epo) on rat model and particularly in a hypoxia-reoxygenation (HR) protocol. The effect of epo was studied hematologically using blood mean platelets (plt) count.
**Materials and methods:** 40 rats of mean weight 247.7 g were used in the study. Platelets count were measured at 60 min (groups A and C) and at 120 min (groups B and D) of reoxygenation. Erythropoietin was administered only in groups C and D. **Results:** Epo administration non-significantly decreased the plt count by 2.14%+8.04% (p=0.7581). Reoxygenation time non-significantly increased the plt count by 0.31%+7.89% (p=0.9653). However, epo administration and reoxygenation time together produced a non significant combined effect in decreasing the plt count by 0.16+4.76% (p=0.9725). Particularly, a reduction of 7.32%+13.11% was noted in groups of 1h reoxygenation (p-value=0.5219); whereas an increase of 3.04%+10.78% was noted in groups of 2h reoxygenation (p-value=0.7204).
**Conclusions:** Erythropoietin administration whether it interacted or not with reoxygenation time, had a no significant short-term decrease on plt count. Perhaps, a longer study time than 2 hours or a higher Epo dose may reveal more significant effects.

**Key words:** hypoxia, erythropoietin, reoxygenation, platelets
**MC Karachi 2016; 22 (1 ): 7-13**

## INTRODUCTION

Erythropoietin (Epo) is generally one of the more well studied growth factors. Epo implicates over 28,527 known biomedical studies at present. 8.69% at least of these studies concern tissue hypoxia and reoxygenation (HR) experiments.

Certainly, important progress has been made concerning the Epo usage in reversing the HR kind of transient or permanent injuries including adjacent organs and certainly patients' health. Nevertheless, satisfactory answers

have not been provided yet to basic questions, as, its action velocity, the administration timing and the dosage. The concept is to forward the knowledge away from the original action of Epo in stem blood cells recovery. However, just few related reports were found, not covering completely more specific matters. A numeric evaluation of the Epo efficacy was yielded by a meta-analysis of 23 published seric variables, based on the same experimental setting, at the same endpoints (Table 1).

The special aim of this experimental work was to study the effect of Epo on a rat model and mainly in an HR protocol. The effect of Epo molecule was tested by measuring the blood mean platelets (plt) count.

## MATERIALS AND METHODS

### Animal preparation

Prefectural veterinary Address of East Attiki licensed the experiment "Investigation of Epo capacities apart from red blood cells recovery" under 3693/12-11-2010 & 14/10-1-2012 decisions. All substances, equipment and consumable needed for the study was a courtesy of ELPEN Pharmaceuticals Co Inc. S.A. at Pikermi, Attiki. Formal humane animal care was adopted for female albino Wistar rats. Normal 7 days pre-experimental housing in laboratory included *ad libitum* diet. Prenarcosis preceded of continuous pre-experimental general anesthesiologic techniques [1-4], electrocardiogram, acidometry and oxygen supply. Post-experimental preservation of the rodents was not permitted even if euthanasia was required.

The rodents were randomly delivered to four experimental groups, each one consisted by 10 animals. The 4 groups had common the stage of preceded hypoxia of 45 min induced by laparotomic forceps clamping inferior aorta over renal arteries. Afterwards, reoxygenation was restored by removing the clamp and reestablishment of inferior aorta patency. Reoxygenation of 60 min was followed for group A. Reoxygenation of 120 min was followed for group B. Immediate Epo intravenous (IV) administration and reoxygenation of 60 min was followed for group C. Immediate Epo IV administration and reoxygenation of 120 min was followed for group D. The dosage for molecule Epo was 10 mg/kg body mass per animal. Epo administration was performed at the time of reoxygenation, through catheterized inferior vena cava.

The platelet count evaluations were performed at 60 min of reoxygenation for A and C groups and at 120 min of reoxygenation for B and D groups. The mean mass of the forty (40) female Wistar albino rats used was 247.

7 g [Standard Deviation (SD): 34.99172 g], min weight 165 g and max weight 320 g. Rats' mass could be probably a confusing factor, e.g. the more obese rats to have higher platelets count. This assumption was also investigated.

### Model of hypoxia-reoxygenation injury

### Control groups

20 control rats of mean weight 252.5 g [SD: 39.31988 g] experienced hypoxia for 45 min followed by reoxygenation.

**Group A**

Reoxygenation which lasted 60 min concerned 10 control rats of mean weight 243 g [SD: 45.77724 g] and mean plt count 1003.2 $10^3$/μL [SD: 143.9852 $10^3$/μL] (Table 2).

**Group B**

Reoxygenation which lasted 120 min concerned 10 control rats of mean weight 262 g [SD: 31.10913 g] and mean plt count 956 $10^3$/μL [SD: 196.8389 $10^3$/μL] (Table 2).

**Erythropoietin group**

20 Epo rats of mean weight 242.9 g [SD: 30.3105 g] experienced hypoxia for 45 min followed by reoxygenation in the beginning of which 10 mg Epo /kg body weight were IV administered.

**Group C**

Reoxygenation which lasted 60 min concerned 10 Epo rats of mean weight 242.8 g [SD: 29.33636 g] and mean plt count 932.3 $10^3$/μL [SD: 345.6543 $10^3$/μL] (Table 2).

**Group D**

Reoxygenation which lasted 120 min concerned 10 Epo rats of mean weight 243 g [SD: 32.84644 g] and mean plt count 985.6 $10^3$/μL [SD: 238.1079 $10^3$/μL] (Table 2).

### Statistical analysis

Every weight and platelet count group was compared with each other from 3 remained groups applying respective statistical standard t-tests (Table 3). If any probable significant difference among platelet count was raised, it would be investigated whether owed in any respective probable significant mass one (Table 3). Then, the application of generalized linear models (glm) was followed. It included as dependant variable the platelet

**TABLE 1.**
**The erythropoietin (Epo) trends (+SD) on the levels of some seric1 variables concerning reperfusion (rep) time**

| Variable | 1h rep | p-value | 1.5h rep | p-value | 2h rep | p-value | interaction of Epo and rep | p-value |
|---|---|---|---|---|---|---|---|---|
| White BCC | +24.01%+13.38% | 0.1012 | +22.09%+9.11% | 0.0351 | +20.17%+12.94% | 0.0902 | +14.63%+5.40% | 0.0080 |
| Red BCC | +1.45%+3.31% | 0.6589 | +0.37%+3.02% | 0.9048 | -0.70%+4.68% | 0.8844 | +0.81%+1.79% | 0.6446 |
| Hematocrit | +0.14%+2.89% | 0.9626 | -0.61%+2.37% | 0.8072 | -1.37%+4.05% | 0.7485 | +0.24%+1.38% | 0.8586 |
| MCH | +0.01%+1.29% | 0.9904 | +0.67%+0.80% | 0.3549 | +1.34%+1.08% | 0.1509 | -0.36%+0.47% | 0.4430 |
| RbcDW2 | -1.85%+4.24% | 0.6703 | -1.64%+2.53% | 0.5159 | -1.43%+3.34% | 0.6078 | -1.06%+1.43% | 0.4733 |
| Platelet DW | +1.60%+0.80% | 0.0765 | +1.36%+0.58% | 0.0205 | +1.13%+0.74% | 0.1152 | +0.37%+0.37% | 0.0615 |
| Platelet-crit | -16.47%+10.40% | 0.0921 | -13.74%+7.01% | 0.0158 | -11.01%+7.34% | 0.0882 | -6.88%+3.69% | 0.0615 |
| Urea | +21.42%+7.84% | 0.0115 | +20.11%+7.25% | 0.0059 | +18.80%+9.44% | 0.0709 | +15.64%+4.04% | 0.0003 |
| Creatinine | -0.10%+9.78% | 0.9904 | -4.84%+5.78% | 0.3721 | -9.59%+7.74% | 0.1509 | -2.62%+3.49% | 0.4430 |
| Uric acid | +10.13%+15.10% | 0.4917 | +15.86%+10.21% | 0.1408 | +21.59%+15.45% | 0.1940 | +9.33%+6.16% | 0.1264 |
| Total protei | -0.02%+2.47% | 0.9904 | -1.27%+1.51% | 0.3721 | -2.52%+2.03% | 0.1509 | -0.68%+2.48% | 0.4430 |
| ALT | +18.89%+12.42% | 0.1372 | +7.63%+18.94% | 0.6396 | -3.63%+25.19% | 0.8617 | +8.03%+11.36% | 0.4698 |
| *y*GT | -19.35%+18.58% | 0.2362 | -12.70%+13.11% | 0.3541 | -6.06%+19.96% | 0.7800 | -4.62%+7.97% | 0.5534 |
| ALP | +0.20%+18.57% | 0.9904 | +10.70%+12.78% | 0.3549 | +21.20%+17.11% | 0.1509 | +5.79%+7.72% | 0.4430 |
| ACP | +0.06%+5.79% | 0.9904 | +3.11%+3.71% | 0.3172 | +6.16%+4.97% | 0.1509 | +1.68%+2.23% | 0.4430 |
| CPK | +0.15%+14.09% | 0.9904 | +7.91%+9.44% | 0.3549 | +15.67%+12.65% | 0.1509 | +4.28%+5.70% | 0.4430 |
| LDH | +0.08%+7.92% | 0.9904 | +4.48%+5.35% | 0.3549 | +8.89%+7.17% | 0.1509 | +2.42%+3.22% | 0.4430 |
| Sodium | +0.72%+0.74% | 0.3054 | +0.21%+0.63% | 0.7136 | -0.29%+1.09% | 0.7670 | -0.11%+0.38% | 0.7531 |
| Potassium | -6.17%+4.94% | 0.1540 | -2.21%+3.66% | 0.5134 | +1.74%+5.43% | 0.7299 | +0.18%+2.22% | 0.9338 |
| Phosphorus | +1.92%+5.25% | 0.6982 | +3.95%+3.35% | 0.2100 | +5.98%+4.81% | 0.2930 | +2.45%+2.01% | 0.2168 |
| Magnesium3 | +1%+6.20% | 0.8596 | -1.09%+3.34% | 0.7248 | -3.19%+3.90% | 0.3729 | -0.19%+1.93% | 0.9197 |
| Amylase4 | +6.50%+9.15% | 0.4161 | +5.04%+6.12% | 0.3831 | +3.59%+8.42% | 0.6649 | +4.36%+3.65% | 0.2258 |
| Progesteron | -0.20%+18.65% | 0.9904 | -8.86%+10.58% | 0.3549 | -17.53%+14.15% | 0.1509 | -4.79%+6.39% | 0.4430 |
| Mean | +1.91%+9.88% | 0.5997 | +2.45%+8.98% | 0.3835 | +2.99%+10.61% | 0.3685 | +2.12%+5.61% | 0.4282 |

**TABLE 2:**
**Weight and platelet counts and Std. Dev. of groups**

| Groups | Variable | Mean | Std. Dev |
|---|---|---|---|
| A | Weight | 243 g | 45.77724 g |
| | Plt | 1003.2 103/μL | 143.9852 103/μL |
| B | Weight | 262 g | 31.10913 g |
| | Plt | 956 103/μL | 196.8389 103/μL |
| C | Weight | 242.8 g | 29.33636 g |
| | Plt | 932.3 103/μL | 345.6543 103/μL |
| D | Weight | 243 g | 32.84644 g |
| | Plt | 985.6 103/μL | 238.1079 103/μL |

**TABLE 3:**
**Statistical significance of mean values difference for groups (DG) after statistical standard t test application.**

| DG | Variable | Difference | p-value |
|---|---|---|---|
| A-B | Weight | -19 g | 0.2423 |
| | Plt | 47.2 103/μL | 0.2668 |
| A-C | Weight | 0,2 g | 0.9900 |
| | Plt | 70.9 103/μL | 0.4870 |
| A-D | Weight | 0 g | 1.0000 |
| | Plt | 17.6 103/μL | 0.8219 |
| A-C | Weight | 19,2 g | 0.2598 |
| | Plt | 23.7 103/μL | 0.8310 |
| A-D | Weight | 19 g | 0.1011 |
| | Plt | -29.6 103/μL | 0.6755 |
| C-D | Weight | -0,2 g | 0.9883 |
| | Plt | -53.3 103/μL | 0.6773 |

**TABLE 4:**
**The alteration trends of erythropoietin in connection with reperfusion time.**

| Change | 95% c. in. | Reperfusion time | p-values t-test | glm |
|---|---|---|---|---|
| -70.9 103/μL | -319.6696 103/μL - 177.8696 103/μL | 1h | 0.4870 | 0.5568 |
| -20.65 103/μL | -172.7879 103/μL - 131.4879 103/μL | 1.5h | 0.7312 | 0.7850 |
| +29.6 103/μL | -175.6472 103/μL - 234.8472 103/μL | 2h | 0.6755 | 0.7654 |
| +3.05 103/μL | -149.2356 103/μL - 155.3356 103/μL | reperfusion time | 0.9627 | 0.9679 |
| -1.572727 103/μL | -93.40496 103/μL - 90.2595 103/μL | interaction | | 0.9725 |

count. The 3 independent variables were the Epo administration or no, the reoxygenation time and their interaction. Inserting the rats' mass as independent variable at glm, a no significant correlation appeared with platelet count (p=0.5418), so as to further investigation was not required. The statistical analysis was performed by Stata 6.0 software [Stata 6.0, StataCorp LP, Texas, USA].

## RESULTS

The glm resulted in: Epo administration non-significantly decreased the plt count by 20.65 $10^3$/μL [-172.7879 $10^3$/

**TABLE 5:**
**The (%) alteration trends of erythropoietin in connection with reperfusion time.**

| Change | +SD | Reperfusion time | p-values |
|---|---|---|---|
| -7.32% | +13.11% | 1h | 0.5219 |
| -2.14% | +8.04% | 1.5h | 0.7581 |
| +3.04% | +10.78% | 2h | 0.7204 |
| +0.31% | +7.89% | reperfusion time | 0.9653 |
| -0.16 | +4.76% | interaction | 0.9725 |

μL - 131.4879 $10^3$/μL] (P= 0.7850). This finding was in accordance with the results of standard t-test (p=0.7312). Reoxygenation time non-significantly increased the plt count by 3.05 $10^3$/μL [-149.2356 $10^3$/μL - 155.3356 $10^3$/μL] (P= 0.9679) also in accordance with standard t-test (p=0.9627). However, epo administration and reoxygenation time together produced a non significant combined effect in decreasing the plt count by 1.572727 $10^3$/μL [-93.40496 $10^3$/μL - 90.2595 $10^3$/μL] (P= 0.9725). Reviewing the above and table 3, the tables 4 and 5 sum up concerning the alteration influence of Epo in connection with reoxygenation time.

## DISCUSSION

Hypoxia may influence plt counts. Chen H et al counted[5] decreased platelet count within first 3 days but increased gradually after the first postoperative week in IR sheep. Granulocyte-platelet and monocyte-platelet aggregates reached the peak at postoperative day 2. Lessiani G et al reported[6] persistent platelet activation as well in vivo indexes of residual thromboxane biosynthesis, oxidative stress and platelet-derived inflammation in critical IR limb patients. Lev EI et al found[7] favorable effects of statins on platelet counts during ischemia. Vilahur G et al associated[8] short-term myocardial ischemia with higher ($P < 0.001$) local recruitment of renders platelets deposition more susceptible to activation in pigs. Elkind MS characterized[9] patients at increased risk of ischemic events by diffuse immunologically mediated activation of platelets. Schuerholz T et al counted[10] significantly higher platelet counts compared with baseline values only in short-term ischemia after kidney transplantation. Nemeth N et al counted[11] higher platelet counts in short-term IR groups of outbred rats. Götz AK et al found[12] significantly reduced platelet counts in coronary effluent and demasked intracoronary transient formation of micro aggregates between PMN and plt after global heart ischemia in pigs. Witczak B et al provided[13] more platelet transfusions ($p < 0.02$) in chronic renal failure patients underwent to cardiovascular operation. Scheinichen D et al found[14] significantly decreased GPIIb/IIIa expression on circulating platelets in kidney transplantation preservation group than healthy volunteers. A significantly reduced P-selectin expression was found in the long-term preservation group than short-term one. Gresele P et al increased[15] platelet activation in vivo in acute short-term hyperglycemia. Verstraete M et al found[16] that platelet aggregation is due to activation of the platelet glycoprotein (GP IIb/IIIa) receptor on platelet surface. Nurden P et al showed[17] abciximab to be about 3.66 times more crowded on the surface of thrombin-activated platelets than nonstimulated ones in ischemic cardiovascular disease. Hayreh SS et al produced[18] vasospasm followed by transient, complete occlusion or impaired blood flow in the central retinal artery and/or PCA; developing ischemic disorders of the retina and optic nerve head, when platelets were aggregated in atherosclerotic monkeys. Zhu BQ et al found[19] significantly higher ϖ-3 fatty acid levels in platelets of rats fed 8 weeks of fish oil, compared with control ones ($p < 0.05$) appearing to correlate with infarcts size reduction. Sokolov EI et al showed[20] depressed platelets antiaggregant and latent disseminated intravascular platelets microcoagulation that tended to progress under emotional mental stress in coronary ischemia patients.

Also, Epo may influence plt counts. Kirkeby A et al counted platelets from[21] Epo-treated rats (50 μg/kg) but not carbamyl-CEPO-treated (50 μg/kg) ones showing an elevated plasma level of soluble P-selectin (sP-selectin) and significantly increased aggregatory responses to collagen in platelet-rich plasma (PRP) and an attenuated response in whole blood aggregometry and thrombelastography (TEG) platelet mapping. Tang YD et al increased significantly the platelet count at 5 days by a 400-U/kg dose[22] after Epo IV administration compared with placebo (P = .014) in some clinical acute

ischemic disease populations. Homoncik M et al decreased platelet counts[23] on day 28 (p= 0.007) in patients with chronic hepatitis C received 10,000 IU Epo x 3 /week than placebo. Epo promoted however an increase in platelet reactivity. Borawski J et al induced increased platelet counts in patients receiving 4-week maintenance hemodialysis combined with[24] recombinant human Epo (rHuEpo). Beguin Y et al have shown to increase platelet counts after moderate[25] stimulation treatment with rHuEpo, but they tended to normalize after 1-2 weeks. Large, chronic, intense Epo stimulation doses even caused thrombocytopenia. In the latter case, there appears to be a diphasic response to Epo, the initial positive response (a stimulation of platelet production) being followed by thrombocytopenia. Epo-induced thrombocytopenia is the result of an inhibition of platelet production. Stem-cell competition between erythroid and platelet precursors appears to be the cause of these phenomena in situations of prolonged, intense stimulation by Epo. In vitro data support the existence of a common erythrocytic and megakaryocytic precursor. Pirisi M et al administered a short-term[26] course (7-20 days) of rhEpo 4000 U daily SQ in patients with chronic liver disease and platelet count < 85,000/ml. After treatment the increase of platelet count in the rhEpo group was significant compared either with baseline values ($p < 0.005$) or with placebo ones ($p < 0.02$). When treatment was discontinued, the platelet count reverted to baseline in a few weeks. In conclusion, rhEpo treatment transiently corrected mild thrombocytopenia. McDonald TP et al increased platelet counts administering large, acute[27] doses of Epo in mice. Therefore, they tested the hypothesis that Epo injected in large, chronic doses (a total of 80 U of EPO over a 7-day period) might cause thrombocytopenia, decreased thrombocytopoiesis, ie, decreased platelet counts, percent 35S incorporation into platelets, and total circulating platelet counts (TCPC) ($P < 0.0005$). Femoral marrow megakaryocyte number was significantly ($P < 0.005$) reduced in normal and splenectomized mice treated with Epo. Therefore, they show that large, chronic doses of Epo increase erythropoiesis and decrease thrombocytopoiesis. Conversely, acute thrombocytopenia causes increased thrombocytopoiesis and decreased erythropoiesis. These findings support the hypothesis of competition between precursor cells of the erythrocytic and megakaryocytic cell lines (stem-cell competition) as the cause of thrombocytopenia in Epo-treated mice. Shikama Y et al observed an 18%+12% increase[28] in platelet counts in intact mice, whereas an increase of 31%+15% in splenectomized mice injected with a total of 50 U rEpo over 5 days. The factor also elicited a significant increase in bone marrow megakaryocytic size of the same magnitude in both groups but not in numbers of megakaryocytes and megakaryocytic progenitors. These findings suggest that Epo has an effect on thrombocytopoiesis, functioning as a late stimulator in short-term administration, However, the induced increases in both parameters, platelet counts and megakaryocytic size, are transient and declined after 5 days. Platelet counts returned to normal levels in intact mice 15 days after initiation of the injection. Yonemura Y et al found significant[29] thrombocytosis (a 30-40% increase over the control level) only in rats received a daily dose of 200 U/day. The size of the marrow megakaryocytes also increased dose-dependently but not the megakaryocyte numbers. Significant thrombocytosis was already present as early as day 1 at 24 h after initiating the Epo injections. These results suggest that in vivo administration of rHuEpo stimulates the maturation of mature as well as immature megakaryocytes already present in bone marrow. Sánchez Casajús A et al attained a significant[30] increase of platelet counts in patients with chronic renal failure subjected to hemodialysis for 12 weeks at an initial doses of 50 U/Kg with r-HuEpo. Hebbel RP et al manifested minimal increases in plasma Epo without thrombocytopenia at moderately high altitude (3,100 m) in striking[31] subjects.

## CONCLUSION

Epo administration whether it interacted or not with reoxygenation time has non significant decreasing short – term trends on plt count. Perhaps, a longer study time than 2 hours or a higher Epo dose may reveal more significant effects.

## ACKNOWLEDGMENT

This study was funded by Scholarship by the Experimental Research Center ELPEN Pharmaceuticals (E.R.C.E), Athens, Greece. The research facilities for this project were provided by the aforementioned institution.

## AUTHORS INPUT

**TC:** analyzed output data**, PC:** developed analytical tools **TK:** edited the manuscript,**TA :**commented on the manuscript, **ZG:** administered the experiment**, PA :**designed the experiment

**Conflict of interest:** Authors declare non inflict of interest.

## REFERENCES

1. Tsompos C, Panoulis C, Toutouzas K, Zografos G, Papalois A. The Acute Effect of Erythropoietin on Red Blood Cells Count During Hypoxia Reoxygenation in Rats. Literati Journal of Pharmaceutical Drug Delivery Technologies; 2016; 02(01): 3-7.
2. Tsompos C, Panoulis C, Toutouzas K, Triantafyllou A, Zografos G et al. (2016) The Acute Effect of Erythropoietin on Red Blood Cell Distribution Width Levels during Hypoxia-Reoxygenation Injury in Rats. J Anal Pharm Res 2(2): 00014.
3. Tsompos C, Panoulis C, Toutouzas K, Zografos G, Papalois A. The effect of erythropoietin on magnesium during ischemia reperfusion injury in rats. Revista Romana de Neurologie 2014;13(1):17-22.
4. Tsompos C, Panoulis C, Toutouzas K, Zografos G, Papalois A. The Effect of Erythropoietin on Amylase Levels during Ischemia Reperfusion Injury in Rats. Journal of Postgraduate Medicine Education and Research 2016;50(1):18-21.
5. Chen H, Zhou J, Sun H, et al: Short-term in vivo preclinical biocompatibility evaluation of FW-II axial blood pump in a sheep model. ASAIO J. 2011 May-Jun;57(3):177-82.
6. Lessiani G, Vazzana N, Cuccurullo C, et al: Inflammation, oxidative stress and platelet activation in aspirin-treated critical limb ischaemia: beneficial effects of iloprost. Thromb Haemost. 2011 Feb;105(2):321-8.
7. Lev EI, Kornowski R, Vaknin-Assa H, et al: Effect of previous treatment with statins on outcome of patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. Am J Cardiol. 2009 Jan 15;103(2):165-9.
8. Vilahur G, Hernández-Vera R, Molins B, et al: Short-term myocardial ischemia induces cardiac modified C-reactive protein expression and proinflammatory gene (cyclo-oxygenase-2, monocyte chemoattractant protein-1, and tissue factor) upregulation in peripheral blood mononuclear cells. J Thromb Haemost. 2009 Mar;7(3):485-93.
9. Elkind MS. Why now? Moving from stroke risk factors to stroke triggers. Curr Opin Neurol. 2007 Feb;20(1):51-7.
10. Schuerholz T, Weissig A, Juettner B, t al: Ex vivo microvesicle formation after prolonged ischemia in renal transplantation. Thromb Res. 2007;120(2):231-6.
11. Nemeth N, Lesznyak T, Szokoly M, et al.: Allopurinol prevents erythrocyte deformability impairing but not the hematological alterations after limb ischemia-reperfusion in rats. J Invest Surg. 2006 Jan-Feb;19(1):47-56.
12. Götz AK, Zahler S, Stumpf P, et al: Intracoronary formation and retention of micro aggregates of leukocytes and platelets contribute to postischemic myocardial dysfunction. Basic Res Cardiol. 2005 Sep;100(5):413-21.
13. Witczak B, Hartmann A, Svennevig JL. Multiple risk assessment of cardiovascular surgery in chronic renal failure patients. Ann Thorac Surg. 2005 Apr;79(4):1297-302.
14. Scheinichen D, zu Vilsendorf AM, Weissig A, et al: Reduced P-selectin expression on circulating platelets after prolonged cold preservation in renal transplantation. Clin Transplant. 2003 Oct;17(5):444-50.
15. Gresele P, Guglielmini G, De Angelis M, et al: Acute, short-term hyperglycemia enhances shear stress-induced platelet activation in patients with type II diabetes mellitus. J Am Coll Cardiol. 2003 Mar 19;41(6):1013-20.
16. Verstraete M. Synthetic inhibitors of platelet glycoprotein IIb/IIIa in clinical development. Circulation. 2000 Feb 15;101(6):E76-80.
17. Nurden P, Poujol C, Durrieu-Jais C, et al: Labeling of the internal pool of GP IIb-IIIa in platelets by c7E3 Fab fragments (abciximab): flow and endocytic mechanisms contribute to the transport. Blood. 1999 Mar 1;93(5):1622-33.
18. Hayreh SS, Piegors DJ, Heistad DD. Serotonin-induced constriction of ocular arteries in atherosclerotic monkeys. Implications for ischemic disorders of the retina and optic nerve head. Arch Ophthalmol. 1997 Feb;115(2):220-8.
19. Zhu BQ, Sievers RE, Sun YP, et al: Is the reduction of myocardial infarct size by dietary fish oil the result of altered platelet function? Am Heart J. 1994 Apr;127(4 Pt 1):744-55.
20. Sokolov EI, Baluda MV, Novikova IV, et al: Disorders in the status of the vessel-thrombocyte and plasma links of the hemostatic system in the pathogenesis of disseminated intravascular coagulation in ischemic heart disease. Kardiologiia. 1986 Sep;26(9):59-63.
21. Kirkeby A, Torup L, Bochsen L, et al: High-dose erythropoietin alters platelet reactivity and bleeding time in rodents in contrast to the neuroprotective variant carbamyl-erythropoietin (CEPO). Thromb Haemost. 2008 Apr;99(4):720-8.
22. Tang YD, Rinder HM, Katz SD. Effects of recombinant human erythropoietin on antiplatelet action of aspirin and clopidogrel in healthy subjects: results of a double-blind, placebo-controlled randomized trial. Am Heart J. 2007 Sep;154(3):494.e1-7.
23. Homoncik M, Sieghart W, Formann E, et al: Erythropoietin treatment is associated with more severe thrombocytopenia in patients with chronic hepatitis C undergoing antiviral therapy. Am J Gastroenterol. 2006 Oct;101(10):2275-82.
24. Borawski J, My?liwiec M. Effects of recombinant erythropoietin therapy on circulating endothelial markers in hemodialysis patients. Clin Appl Thromb Hemost. 2002 Jan;8(1):77-84.
25. Beguin Y. Erythropoietin and platelet production. Hematologica. 1999 Jun;84(6):541-7.
26. Pirisi M, Fabris C, Soardo G, et al: Thrombocytopenia of chronic liver disease corrected by erythropoietin treatment. J Hepatol. 1994 Sep;21(3):376-80.
27. McDonald TP, Clift RE, Cottrell MB. Large, chronic doses of erythropoietin cause thrombocytopenia in mice. Blood. 1992 Jul 15;80(2):352-8.
28. Shikama Y, Ishibashi T, Kimura H, et al: Transient effect of erythropoietin on thrombocytopoiesis in vivo in mice. Exp Hematol. 1992 Feb;20(2):216-22.
29. Yonemura Y, Kawakita M, Fujimoto K, et al: Effects of short-term administration of recombinant human erythropoietin on rat megakaryopoiesis. Int J Cell Cloning. 1992 Jan;10(1):18-27.
30. Sánchez Casajús A, Barrau J, Gómez Alamillo C, et al: Initial response to treatment with erythropoietin in anemia caused by chronic renal insufficiency. Sangre (Barc). 1990 Feb;35(1):82-4.
31. Hebbel RP, Eaton JW, Kronenberg RS, et al: Human llamas: adaptation to altitude in subjects with high hemoglobin oxygen affinity. J Clin Invest. 1978 Sep;62(3):593-600.