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CLINICAL PAPER

Early high-dose erythropoietin therapy and hypothermia after out-of-hospital cardiac arrest: A matched control study☆

Alain Cariou[a,h,k,*], Yann-Erick Claessens[b,h,i], Frederic Pène[a,h,i], Jean-Sebastien Marx[c], Christian Spaulding[d,h,k], Cyrla Hababou[g], Nicole Casadevall[e,h], Jean-Paul Mira[a,h,i], Pierre Carli[c,h], Olivier Hermine[f,h,j]

[a] *Medical Intensive Care Unit, Cochin Hospital, Paris Cedex, France*
[b] *Department of Emergency Medicine, Cochin Hospital, 27 rue du Faubourg Saint-Jacques, Paris, France*
[c] *SAMU 75, Necker Hospital, Paris, France*
[d] *Cardiology Department, Cochin Hospital, Paris, France*
[e] *Haematology Laboratory, Hotel-Dieu Hospital, Paris, France*
[f] *Haematology Department, Necker Hospital, Paris, France*
[g] *Janssen-Cilag Orthobiotech France, Issy-les-Moulineaux, France*
[h] *Paris Descartes University, Paris, France*
[i] *INSERM U567, Cochin Hospital, Paris, France*
[j] *CNRS UMR 8143, Necker Hospital, Paris, France*
[k] *INSERM U909, Sudden Death Epidemiology Unit, Paul Brousse Hospital, Villejuif, France*

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Summary
Aim: To test the possible neuroprotective effect of early high-dose erythropoietin-alpha (Epo-alpha) after out-of-hospital cardiac arrest (OHCA).
Methods: A matched control study. Following resuscitation with mild hypothermia after OHCA, participants received a first dose of Epo-alpha followed by four additional injections within 48 h (40,000 IU intravenously each injection). Plasma Epo-alpha levels were measured at different time points. Outcome and adverse events were assessed up to day 28 and were compared with those of matched-paired controls.

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* Corresponding author at: Medical Intensive Care Unit, Cochin Hospital, 27 rue du Faubourg Saint-Jacques F-75679, Paris Cedex 14, France. Tel.: +33 1 58 41 25 01; fax: +33 1 58 41 25 05.
E-mail address: alain.cariou@cch.aphp.fr (A. Cariou).

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Results: In all 18 participants received Epo-alpha and were compared with 40 matched controls. Pharmacokinetic variables were similar to those previously reported for healthy people or for persons treated with usual dosages of Epo. At day 28, survival rates among the Epo-treated group and the controls (55% versus 47.5%, $p = 0.17$) and rates of full neurological recovery (55% versus 37.5%) did not differ significantly. Incidences of thrombocytosis in the Epo-treated group and controls were 15% and 5%, respectively; an arterial vascular thrombosis was observed in one case (5%) from the Epo-treated cohort.
Conclusions: Among victims of OHCA treated with Epo-alpha and hypothermia, we observed a high survival rate, with no minor cerebral sequels but potential haematological side effects. Future studies of Epo should pay particular attention to these findings.

Introduction

Usually out-of-hospital cardiac arrest (OHCA) is followed by post-anoxic encephalopathy leading to a post-resuscitation neurological deficiency that is either transient or definitive and represents the major cause of death in these cases.[1] Currently, apart from mild-induced hypothermia, no other treatment has shown any ability to decrease the consequences of cerebral ischaemia due to cardiac arrest.[2,3]

The main role of erythropoietin (Epo) is to support erythropoiesis, and this hormone has been used for many years to prevent anaemia in different pathological conditions. Numerous preliminary data suggested a neuroprotective effect of Epo in various experimental models, particularly after neuron damage related to ischaemia-reperfusion stress.[4,5] However, a recent animal study showed no effect of Epo on survival and cerebral recovery after cardiac arrest even with pre-treatment.[6] Among humans, preliminary data have suggested that Epo could improve the neurological outcome after stroke,[7] but to our knowledge Epo has never been tested in the setting of cardiac arrest. Furthermore, even if Epo and cooling may both lead to specific complications, there are no data showing that these treatments are safe when used together. In this pilot study, we tested the safety and pharmacokinetics of early administration of high-dose Epo-alpha for persistently comatose people successfully resuscitated from OHCA and treated with mild hypothermia. In addition, we tried to estimate the potential risks and benefits of Epo treatment by comparing Epo-treated people with matched controls.

Methods

Patient population

The following inclusion criteria were applied: age between 18 and 75 years; witnessed OHCA of presumed cardiac origin; delay between collapse and onset of cardiopulmonary resuscitation (CPR; 'no flow') less than 10 min; delay between onset of CPR and return of spontaneous circulation (ROSC; 'low flow') less than 50 min; and persistent coma with Glasgow Coma Scale (CGS) less than 7 after ROSC (re-checked and confirmed immediately before injection of Epo). Exclusion criteria were: cardiac arrest of non-cardiac aetiology (i.e. trauma, sepsis, acute respiratory failure); previous Epo treatment; pregnancy; and evidence of rapidly fatal underlying condition.

Study design and method

This was a monocentric, open-labelled study performed between November 2003 and May 2004. Patients were included in the field by the pre-hospital medical emergency team (SAMU 75) and then referred to the 24-bed Cochin University Hospital intensive care unit (ICU). Protocol and consent procedures were approved by the ethics review committee of the Cochin University Hospital, in accordance with the European Guidelines for Good Clinical Practice. In accordance with French law, the next of kin were orally informed about the trial by the pre-hospital emergency team at the time of inclusion, and written consent was systematically obtained from participants' next of kin within 24 h. Furthermore, written consent was obtained from all survivors.

As the first step, we studied the effects of high-dose Epo-alpha for 20 consecutive patients who had been successfully resuscitated by the emergency medical service (EMS). These participants received a first dose of Epo-alpha as soon as possible after stable ROSC, followed by an additional injection every 12 h during the first 48 h after ICU admission (40,000 IU intravenously each injection). This dosage was chosen in accordance with the dose regimen previously used in animal experiments demonstrating neuroprotective effects of Epo.[8] Collected data included demographics, clinical characteristics, biological features, treatment and outcome. Severity was assessed by the Simplified Acute Physiologic Score 2 (SAPS 2).[9] Mortality and neurological outcome were recorded at day 28. All unexpected events were assessed in order to detect potential side effects of high-dose Epo administration.

As the second step, we compared the outcomes observed among the prospective Epo-treated cohort with the outcomes observed among case-matched historical controls. These controls, all treated by mild hypothermia, were selected from our local cardiac arrest database by an independent investigator blinded to patient outcome. The investigator selected matched control patients admitted to our ICU after OHCA during the same time period (2003—2004), using the following criteria: age, SAPS 2, no flow and low flow intervals, number of electric shocks and total adrenaline (epinephrine) dosage required during initial resuscitation. In order to improve the quality of the comparison, at least two matched controls were selected for each Epo-treated person.

Table 1 Glasgow—Pittsburgh Cerebral Performance Category (CPC) scale

CPC level 1	Normal ability or minimal disability (good cerebral performance, conscious, alert, able to work and lead a normal life)
CPC level 2	Moderate cerebral disability (conscious, sufficient cerebral function for part-time work in sheltered environment or independent activities of daily life. May have hemiplegia, seizures, ataxia, dysarthria, dysphasia or permanent memory or mental changes)
CPC level 3	Severe disability (conscious, dependent on others for daily support because of impaired brain function)
CPC level 4	Severe disability (coma, vegetative state, no cognition, verbal or psychological interactions with environment)
CPC level 5	Death (or brain death)

Outcome assessment

Neurological performance was assessed at each time point according to the Glasgow—Pittsburgh Cerebral Performance Category (CPC) scale which is commonly used in this setting (Table 1).[3,10,11] This assessment was performed on admission and each day between days 1 and 7, and at days 14, 21 and 28. For participants who were no longer in the hospital at the end of follow-up, this evaluation was performed by telephone interview with the participant and/or family members.

Concomitant treatments

Epo-alpha administration was the single intervention performed in the prospective cohort. All other therapeutic options were left to the physician's discretion and were collected in the database. According to our local practices, post-OHCA adults are treated with mild hypothermia between 32 °C and 34 °C for 24 h, followed by progressive re-warming. Temperature is continuously monitored with a bladder temperature probe. Our local practices also target a mean arterial blood pressure between 65 mm Hg and 75 mm Hg, and include sedation with adjusted doses of midazolam, morphine and pancuronium to prevent shivering during induced hypothermia, as well as strict adherence to normal ranges for serum sodium, colloid osmotic pressure, glucose and arterial CO_2 content. Since acute coronary syndrome is the most frequent cause of cardiac arrest among adults, coronary angiograms were performed routinely and were followed when indicated by percutaneous coronary interventions.[12]

Laboratory tests

Among the Epo-treated group, blood samples were drawn daily from day 1 to day 7 and weekly from day 7 to day 28 for determination of haemoglobin concentration, haematocrit level and white blood cell and platelet counts, in order to detect Epo-induced haematological changes.

Pharmacokinetic study

To describe the pharmacokinetics of the product, Epo-alpha concentrations were measured in blood samples drawn just before and at 2 h, 4 h, 6 h, 8 h, 10 h, 12 h, 24 h, 36 h, 48 h, 72 h, 78 h, 84 h and 96 h after the first administration of Epo-alpha. Pharmacokinetic variables were determined from the plasma concentration—time curves, on day 1 at 2—12 h after the first Epo-alpha administration, and on day 2 at 48—96 h, corresponding to 48 h after the fifth administration of Epo-alpha. Pharmacokinetic analyses were performed by model-independent methods using Win Nonlin software (Professional Edition, Version 1.5; Scientific Consulting, Cary NC, USA). The following variables were determined: peak of Epo-alpha plasma concentration after the first and the fifth injection (C_{max}); area under the concentration—time curve (AUC); and clearance (Cl) calculated from dose/AUC for the first injection. Volume of distribution (Vss) was calculated using statistical moment theory, with AUC. Terminal half-life ($t_{1/2}$) was computed from the 0.693/elimination rate constant estimated on a minimum of four data points after the first and the fifth injection.

Statistical analysis

Cardiac arrest data and outcome were documented according to the Utstein style.[13] Continuous variables were expressed as median value and interquartile range (IQR, 25th and 75th percentiles) or mean ± standard deviation (S.D.). Categorical variables were reported as numbers and proportions. Variables from independent samples were compared using either the Mann—Whitney *U*-test for continuous variables, a chi-squared test or Fisher's exact test for categorical variables. Paired data were compared using the Wilcoxon rank sum test; *p* values below 0.05 were considered statistically significant. Statistical analysis was performed with SPSS software Version 10.0 (SPSS, Chicago, IL, USA).

Results

The pre-hospital rescue team enrolled 20 persons initially. Two of these were excluded from the study at ICU admission as having an unrecognised extra-cardiac cause of arrest; one arrest was due to massive pulmonary embolism and the other to asphyxia secondary to aspiration pneumonia. Both individuals died at ICU admission within the first 6 h. Thus, 18 cases were analysed as the Epo-treated group. These people (16 men and 2 women) had a median age of 59 (56—69) years, a median SAPS 2 of 61 (50—73) and received the first Epo injection as soon as possible after stable ROSC (Table 2). All were similarly treated with mild hypothermia during the first 24 h. The leading cause of OHCA was acute coronary syndrome, and early coronary angiography at admission identified significant coronary disease with recent occlusion in 12 cases (67%), as shown in Table 3. The median value of the delay between cardiac arrest occur-

Table 2 Participant characteristics

Characteristic	Epo-treated group ($n = 18$)	Controls ($n = 40$)	p value
Median age in years (IQR)	59 (56—69)	58 (51—65)	0.23
Gender, n M/F	16/2	39/1	0.16
Median SAPS 2 (IQR)	61 (50—73)	65 (52—73)	0.42
Smokers, n (%)	13 (72.2)	22 (55)	0.18
CAD, n (%)	5 (27.8)	12 (30)	0.76
Hypertension, n (%)	11 (61.1)	14 (35)	0.054
Diabetes, n (%)	0	6 (15)	0.062
HC, n (%)	7 (38.9)	18 (45)	0.59

IQR, interquartile range; M, male; F, female; SAPS 2, Simplified Acute Physiologic Score 2; CAD, coronary artery disease; HC, hypercholesterolaemia.

Table 3 Clinical features of cardiac arrests

Feature	Epo-treated group ($n = 18$)	Controls ($n = 40$)	p value
Median no flow, min (IQR)	6 (3—10)	3 (0—5)	0.053
Median low low, min (IQR)	19 (14—25)	15 (10—28)	0.94
Electrical shocks, n (%)	3 (1—5)	2 (1—5)	0.72
Median epinephrine, mg (IQR)	2 (0—7)	3 (0—8)	0.68
VF/pulseless VT, n (%)	16 (89)	32 (78)	0.64
PEA/asystole, n (%)	2 (11)	8 (20)	0.70
Median first temp (°C) (IQR)	36.2 (35.4—36.5)	35.9 (65—36.4)	0.17
Median interval CA to first Epo IV injection, min (IQR)	62 (42—75)	—	—

IQR, interquartile range; VF, ventricular fibrillation; VT, ventricular tachycardia; temp, temperature; PEA, pulseless electrical activity; CA, cardiac arrest; IV, intravenous.

rence and ROSC ('no flow' + 'low flow') was 24.5 (19—60) min and the median time between cardiac arrest and the first Epo-alpha injection administrated by the EMS was 62 (42—75) min.

The mean (±S.D.) plasma Epo-alpha concentration—time profile is depicted in Figure 1. The pharmacokinetic parameters are presented in Table 4, showing individual data. The Epo-alpha concentrations measured 2 h after the first administration of 40,000 IU were considered as the C_{max} since no samples were drawn earlier. The concentration—time plasma profiles followed a mono-exponential decline after the first and fifth administrations, for 2 h to 12 h and for 48 h, respectively. As shown in Table 3, C_{max} and $t_{1/2}$ remained constant after multiple doses.

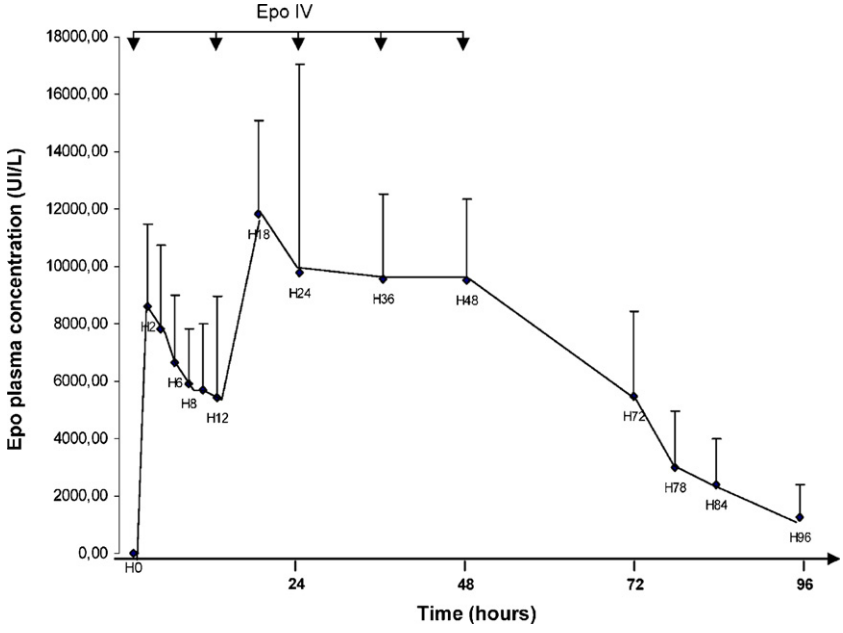

Figure 1 Mean (S.D.) plasma Epo-alpha concentration—time profile among Epo-treated population. H, hours from admission.

In all, 40 patients were selected from our local OHCA database to represent matched controls. As expected, there was no significant difference between the Epo-treated group and controls, either in term of baseline (Table 2) or cardiac arrest characteristics (Table 3). According to the CPC scale measured at day 28, no significant difference was noted between Epo-treated patients and matched controls; survival rates of patients with a CPC level between 1 and 4 were 55% versus 47.5%, $p = 0.17$. Among the controls, 15 of 40 (37.5%) survived to attain full neurological recovery (CPC level 1), whereas all survivors (55%) in the Epo-treated population reached the same CPC level 1 at the end of follow-up; however, this difference was not statistically significant (Figure 2).

A lower mean haemoglobin level was observed among the Epo-treated group than among the controls on admission, i.e. 12.8 (11.9—14.0) versus 14.3 (13.6—15.3), $p = 0.001$ and on day 2, i.e. 13.2 (11.8—14.4), $p = 0.037$. However, the mean haemoglobin level among the Epo-treated group was higher than among the controls at day 14, i.e. 10.4 (10.1—11.3) versus 9.3 (9.0—9.9), $p = 0.012$. A similar evolution was observed regarding haematocrit level (Table 5). None of the Epo-treated group received an intravenous transfusion during their ICU stay, whereas 2 of 40 controls (5%) required red blood cell transfusions because of progressive anaemia (haemoglobin level <9 g/dl). At day 1, leukocytes were lower among the Epo-treated group than among the controls, i.e. 12.0 (10.1—18.7) versus 19.7 (14.3—22.1), $p = 0.005$. No significant difference between the two groups was observed regarding platelet counts over time. A thrombocytosis (platelet count >500 $\times$ 10^3 platelets per mm^3) was observed among 3 of the 18 people (15%) in the Epo-treated cohort versus 2 of the 40 controls (5%). Thrombocytosis was temporally associated with an arterial vascular thrombosis (coronary stent thrombosis) in one case (5%) from the Epo-treated cohort. Regarding possible other effects of high-doses of Epo in this setting, seizures were observed in a similar proportion of Epo-treated group and the control group (25% versus 30%, not significant).

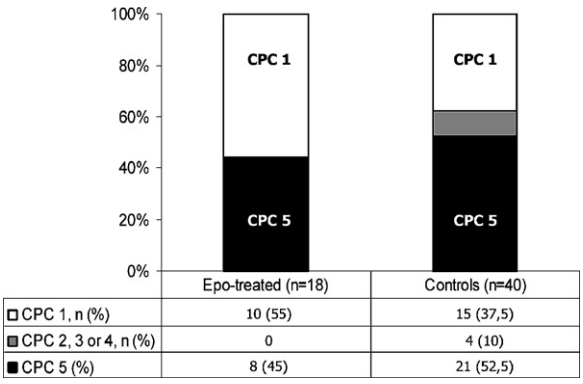

Figure 2 Outcome at day 28 of Epo-treated group and controls according to the Glasgow—Pittsburgh Cerebral Performance Category (CPC) scale. Among the four non-CPC 1 survivors in the control group, three scored CPC 2 and one scored CPC 4.

Table 4 Pharmacokinetic analysis in Epo-treated group

Participants	First injection					Fifth injection	
	C_{max} (UI/l)	AUC (h UI/l)	$t_{1/2}$ (h)	Cl (ml/min)	Vss (l)	C_{max} (UI/l)	$t_{1/2}$ (h)
1	9820	158579	10.5	4.2	4.1	11516	14.4
2						12687	13.6
3							
4	10693	259015	14.8	2.6	3.5		
5	8369	94988	7.1	7.0	4.8	5562	6.3
6	4044	41188	5.8	16.2	10.4	12738	10.3
7	9404	192179	13.3	3.5	4.1	8029	12.7
8	11449					10298	na
9	5164	102833	12.1	6.5	7.2	10411	11.8
10							
11	6482	83833	6.8	8.0	5.6	8242	na
12	10901					9548	10.4
13	10424	143875	9.0	4.6	3.8	10028	10.0
14	9138	90955	6.4	7.3	4.5	7993	7.5
15	10136	114572	7.2	5.8	4.1	5407	8.9
16	7611	176266	13.6	3.8	4.8	15672	12.8
17	11855	113605	5.5	5.9	3.2	8554	11.2
18	11025	181809	10.6	3.7	3.7	7274	
Mean	9101	134809	9.4	6.1	4.9	9597	11.5
S.D.	2341	57763	3.2	3.5	2.0	2784	3.3

C_{max}, maximal concentration; AUC, area under curve; Cl, clearance; Vss, volume of distribution; $t_{1/2}$, terminal half-life; S.D., standard deviation; na, not available.
Where no result is shown, there was either no sample or an insufficient number of samples.

Table 5 Median haematological outcomes (interquartile ranges)

	Haemoglobin (g/dl)			Haematocrit (%)			Platelets ($\times 10^9$ per mm^3)			WBC ($\times 10^9$ per mm^3)		
	Epo-treated	Controls	*p* value	Epo-treated	Controls	*p* value	Epo-treated	Controls	*p* value	Epo-treated	Controls	*p* value
Day 1	12.8 (11.9–14.0)	14.3 (13.6–15.3)	0.001	38.1 (35.4–42.9)	42.0 (40.1–45·1)	0.006	208 (172–242)	247 (179–306)	ns	12.0 (10.1–18.7)	19.7 (14.3–22.1)	0.005
Day 2	13.2 (11.8–14.4)	14.4 (13.1–15.5)	0.037	39.1 (34.5–42.6)	41.0 (38.2–45.0)	0.058	188 (159–229)	190 (132–248)	ns	14.2 (10.8–19.1)	14.7 (10.8–22.1)	ns
Day 3	11.3 (10.5–13.4)	12.9 (11.4–14.1)	ns	33.8 (30.8–4.5)	37.4 (33.8–41.4)	ns	193 (159–219)	166 (131–209)	ns	16.3 (17.0–22.9)	14.8 (8.7–17.3)	ns
Day 4	10.7 (9.4–11.5)	11.2 (10.5–12.0)	ns	31.0 (27.9–33.7)	32.0 (31.0–34.8)	ns	179 (128–194)	149 (117–182)	ns	12.3 (10.1–15.6)	11.1 (9.1–15.0)	ns
Day 5	10.2 (9.6–11.2)	10.4 (10.0–11.4)	ns	30.0 (28.1–31.2)	30.0 (28.4–33.0)	ns	148 (118–236)	145 (96–178)	ns	10.7 (8.9–12.2)	10.7 (8.7–13.8)	ns
Day 6	9.6 (8.6–10.6)	9.9 (9.5–11.6)	ns	29.7 (24.9–33.4)	29.0 (27.3–33.3)	ns	165 (118–237)	159 (109–192)	ns	8.3 (6.7–11.8)	10.3 (7.5–12.3)	ns
Day 7	10.5 (8.6–11.3)	10.0 (9.4–11.0)	ns	30.7 (25.6–33.0)	29.0 (26.8–31.2)	ns	162 (134–323)	175 (119–228)	ns	9.0 (7.2–12.4)	7.7 (6.9–10.5)	ns
Day 14	10.4 (10.1–11.3)	9.3 (9.0–9.9)	0.012	30.6 (30.2–33.3)	27.6 (27.0–28.0)	0.014	448 (399–670)	555 (504–1022)	ns	8.8 (7.7–12.7)	11.2 (9.8–18.1)	ns
Day 21	12.0 (10.0–13.0)	NA	–	36.0 (28.0–39.0)	NA	–	299 (262–410)	NA	–	5.9 (5.6–7.0)	NA	–
Day 28	12.0 (11.0–12.0)	NA	–	35.0 (31.0–36.0)	NA	–	175 (171–332)	NA	–	5.8 (5.1–6.0)	NA	–

WBC, white blood cells; NA, not available; ns, non-significant.

Discussion

To our knowledge, this is the first study assessing the feasibility and safety of high-dose Epo-administered during the acute phase to OHCA victims treated by mild hypothermia. In these prospectively treated patients, we observed a high survival rate with no or minor cerebral sequels but we also detected some potential adverse effects.

Survival with complete neurological recovery after cardiac arrest depends on several interventions during the chain of survival, and includes both pre- and post-admission factors. Pre-admission factors (mostly related to age, physiological status and resuscitation variables) are usually considered to be predominant but obviously cannot be modified by post-resuscitation care.[14] In contrast, post-admission factors and the final outcome may be influenced significantly by the quality of post-resuscitation care, which should include when possible a neuroprotective strategy such as mild hypothermia. Unfortunately, despite promising experimental results, all large clinical trials testing neuroprotective drugs after OHCA have been unsuccessful.[10,15,16]

Besides its well-known erythropoietic effect, Epo also modulates a broad array of cellular processes and is now considered to have potential applicability in a variety of disorders that include cerebral ischaemia, myocardial infarction and chronic congestive heart failure.[5] Various *in vivo* and *in vitro* experimental models have demonstrated Epo-induced neuronal and vascular protection in the nervous system.[17,18] Hence, animal models testing Epo during cerebral hypoxia—ischaemia showed a reduction in ischaemia-induced learning disability, increased neuronal survival and development of ischaemic tolerance.[19,20] Of note, in models of both focal and global cerebral ischaemia, Epo reduced cerebral infarction and was able to protect sensitive hippocampal neurons from injury.[21–24]

It has also been demonstrated that Epo does not require intrathecal administration to provide effective neuroprotection. Systemic delivery of recombinant human Epo reduced cerebral infarct volume by about 75% in a rodent model of middle cerebral artery stroke.[24] However, this protective effect is questionable, since a recent animal study showed no effect of Epo on survival and cerebral recovery after cardiac arrest even with pre-treatment.[6] Ehrenreich and co-workers consecutively assessed safety and efficacy among humans of recombinant human Epo for treatment of ischaemic stroke.[7] In the safety study, 13 patients received Epo intravenously (33,000 IU) once daily for 3 days after a stroke. No safety concerns were identified. Efficacy was assessed in a double-blind, randomised proof-of-concept trial, in which 40 patients received either Epo or saline after stroke. Treatment with Epo was strikingly associated with an improvement in neurological outcome. A strong trend toward reduction in infarct size among Epo-treated people as compared with controls was also observed by magnetic resonance imaging. Our results are consistent with the effects of Epo observed in most animal studies and among persons with stroke. However, since our main goal was only to provide valuable information in order to design future efficacy studies, the present study was not designed or powered to reach conclusions on efficacy.

Our results afford important information regarding potential side effects. The chosen dosage (200,000 IU over

48 h) is twice that used by Ehrenreich and co-workers for people with stroke.[7] This dosage, which was among the highest tested in clinical trials at the time the study was designed, was chosen in accordance with the dosages previously used in animal experiments demonstrating neuroprotective effects of Epo.[8] Using this high-dose of Epo, the only unexpected haematological event was a rise in platelet counts in 3 of 18 cases, which was associated with a coronary vascular thrombosis in 1 case. Whether Epo can be incriminated in the genesis of these events is questionable. Although megakaryocytic progenitors express Epo-R, Epo does not play a critical role in megakaryopoiesis. However, it cannot be ruled out that high-dose Epo, in association with other factors including hypothermia, cytokines and factors produced during inflammation, may act synergistically to enhance platelet production and coagulation activation. It is indeed well-established that the post-resuscitation phase is associated with a sepsis-like syndrome and with major coagulation abnormalities.[25,26] These inflammatory and coagulation abnormalities may have been partially or totally incriminated in the genesis of the thrombocytosis and vascular thrombosis observed in our Epo-treated group.

We also noted seizures in five cases in the Epo-treated group, but they were considered due to post-anoxic cerebral insult since these events are common in this setting, as reflected by the high rate of seizures observed in our control group and in other studies.[27,28] Thus, future studies aiming to test the efficacy of such a high dosage of Epo-administered very early over a short period to people with OHCA should pay particular attention to these findings.

Our study also presents new data about Epo pharmacokinetics when used in high-doses over a short time. To date, the pharmacokinetics of Epo-alpha after intravenous administration have been mostly studied among healthy people[29–32] and among people with anaemia due to chronic renal failure.[33–35] Regarding total Cl and Vss, our findings are consistent with these previous studies. The plasma elimination half-life calculated at steady-state after the fifth administration suggests that the pharmacokinetic behaviour of Epo-alpha is not modified after repeated intravenous administrations. Thus, pharmacokinetic variables obtained among survivors of cardiac arrest appear similar to those reported among healthy people or among people with anaemia due to impaired renal function and treated with lower doses of Epo-alpha.

There are several limitations to our study. First, since the study was designed as a pilot mainly focusing on safety concerns, the small number of participants and the absence of a randomised control group both preclude any firm conclusion about the efficacy of Epo treatment in this setting. Further larger clinical studies with a blinded, randomised design is be required to clarify this potential benefit. Second, we did not assess availability of Epo in cerebrospinal fluid (CSF) after intravenous infusion because we considered that lumbar punctures could have been deleterious for our patients, most of whom were treated with anti-thrombotic agents. However, the results of the safety study performed by Ehrenreich and co-workers confirmed that intravenous administration of a total of 100,000 IU of Epo after a documented stroke increased CSF Epo levels by a factor of 60—100. It can be predicted that the higher dosage of Epo used in our study provided at least similar CSF Epo concentrations. Finally, the use of an expensive treatment such as Epo for a large population of patients carrying a poor prognosis may be questioned. In future studies, the cost of Epo treatment in this setting should be evaluated in conjunction with its potential ability to decrease the incidence of cerebral damage after OHCA.

In conclusion, to our knowledge we assessed for the first time the feasibility and safety of Epo treatment in conjunction with hypothermia at the acute phase of OHCA. We observed a high survival rate with no or minor cerebral sequels, but we did detect several side effects focusing on vascular thrombosis. On the basis of these results, we believe that future studies aiming to test the efficacy of such a high dosage of Epo-administered in conjunction with mild hypothermia in the acute phase of OHCA should pay particular attention to these findings.

Conflict of interest

A. Cariou received honoraria from OrthoBiotech France when engaged as a speaker, and C. Hababou, was previously an employee from OrthoBiotech France (a manufacturer of erythropoietin). No other potential conflict of interest has occurred since this work was initiated.

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