Deferoxamine infusion during coronary artery bypass grafting ameliorates lipid peroxidation and protects the myocardium against reperfusion injury: immediate and long-term significance

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Aims Previous reports have demonstrated enhanced myocardial protection and better post-ischaemic recovery using the oxygen free radical scavenger deferoxamine (DEF) during cardioplegia. The aim of this study was to test whether, in patients undergoing coronary artery bypass grafting (CABG), DEF i.v. infusion can reduce reperfusion injury on a short- and long-term basis.

Methods and results Forty-five consecutive male patients were randomly allocated to two groups: in group D (n = 25, age 60.8 ± 8.6 years), 4 g of DEF were infused for 8 h starting immediately after the induction of anaesthesia; in group C (n = 20, age 62.2 ± 6.4 years) dextrose solution was given for the same time as placebo. Haemodynamic monitoring and measurement of oxygen free radical production [by measuring thiobarbituric acid reactive substances (TBARS)] were carried out before and after CABG. Left ventricular ejection fraction (EF) and wall motion score index (WMSI) were measured before and after CABG and 12 months later. Haemodynamic measurements were similar in both groups before and after CABG. TBARS peaked at 4.8 ± 1.1 nmol/mL in group C, but remained unchanged (2.4 ± 0.9 nmol/mL) in group D (P = 0.01). At baseline, both the EF and WMSI were similar between the groups. Following CABG, EF increased more in group D (8.8 ± 8.4%) than in group C (1.3 ± 6.7%), P = 0.008, while WMSI decreased more in group D (-0.7 ± 0.3) than in group C (-0.2 ± 0.2), P = 0.0001. Dividing group D according to the pre-operative median EF value (38%), we observed that after 1 year follow-up, DEF infusion conferred more protection in patients with a lower EF (EF increased by 19.3 ± 6.2%, WMSI decreased by -1.1 ± 0.2) than in those with a higher EF (EF increased by 7.7 ± 4.5%, WMSI decreased by -0.8 ± 0.2), P = 0.001, respectively.

KEYWORDS
Reperfusion injury;
Free radicals;
Cardioprotection;
Stunned myocardium

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Introduction

Extracorporeal circulation of blood during cardiopulmonary bypass has been shown to induce the production of several pro-inflammatory molecules such as cytokines, chemokines, growth factors, and vasoactive substances. The ensuing systemic inflammatory response and the superimposed period of ischaemia–reperfusion are conditions that promote the production of oxygen-derived free radical species, which are able to initiate lipid peroxidation and a chain of events leading to cell membrane damage, tissue injury, and organ functional impairment. Iron overload, which is attributed to haemolysis, and the consistence of cardioplegia solutions, amplifies these events, as does the generation of the potent hydroxyl radical and the chain reactions involved in lipid peroxidation which require iron catalysis. Iron chelation with deferoxamine is capable of preventing the generation of hydroxyl radicals from superoxide ions by means of the Fe(II) to Fe (III)-driven Fenton reaction. Several experimental studies have so far indicated that the addition of the iron chelator deferoxamine to the cardioplegic solution prevents the generation of oxygen free radicals and preserves the endothelium-dependent relaxation of coronary arteries and skeletal muscle microvessels. Deferoxamine also reduces post-ischaemic CPK release, attenuates cardiac stunning, decreases the incidence of arrhythmias, and lessens the lung injury which is frequently seen after surgery. Furthermore, a small number of clinical trials have shown that cardioplegia with deferoxamine can reduce oxygen free radical activity and lipid peroxidation, attenuate apoptotic cell death, and preserve myocardial cells. However, these observations have not been translated into improved patient outcome. Moreover, pre-treatment with deferoxamine can significantly improve survival.

We aimed to test whether, in patients undergoing coronary artery bypass grafting (CABG), DEF i.v. infusion can reduce reperfusion injury on a short- and long-term basis.

Methods

Study population

Between March and December 2000, 45 male patients (61.4 ± 7.7 years old) with coronary artery disease (CAD), who underwent first-time elective CABG by the same surgeon (A.M.), were enrolled in the study. After having obtained an informed consent and approval of the hospital ethics committee, they were randomly assigned to two groups. In the deferoxamine group (group D, n = 25), a total amount of 4 g of deferoxamine was dissolved in 250 mL of 5% dextrose solution and continuously infused (at a rate of 31.2 ml/h) for 8 h, starting immediately after the induction of anaesthesia. The optimal regimen for intravenous infusion of deferoxamine remains to be established.

Previous studies during cardiopulmonary bypass have used a dose of 30 mg/kg although in β-thalassaemia major patients with cardiac disease, in whom there is much experience in this kind of treatment, the recommended dose is 50–100 mg/kg.16 For the former dose achieving steady state concentrations between 6 and 12 h.17 In this respect we decided to infuse 4 g in order to deal with a mean weight of 80 kg. In the control group (group C, n = 20) 250 mL of 5% dextrose solution were infused for the same period of time and infusion rate, as placebo. Patients with severely impaired left ventricular function [ejection fraction (EF) < 20%, insulin-dependent diabetes mellitus, neurological disease, liver dysfunction, or renal insufficiency were excluded. Demographic data were similar in both groups (Table 1).

Anaesthesia and surgical procedure

Anaesthesia, surgical procedures, mechanical ventilation, and cardiopulmonary bypass (CPB) were performed according to standard hospital protocols. The procedure involved separate preparation and administration of the pharmaceutical treatment in order to ensure that the people administering the treatment were not aware as to whether they were administering placebo or not. Patients received 1 mg of lorazepam orally the night before surgery and were pre-medicated with morphine 0.1 mg/kg, 1 h before anaesthesia. Anaesthesia was induced with fentanyl 20 µg/kg/min, midazolam 3 mg, etomidate 10–15 mg in incremental doses, and cis-atracurium 0.15 mg/kg, and maintained with a propofol infusion of 3 mg/kg/h, and additional doses of cis-atracurium. A nitroglycerine infusion of 1.5 µg/g/min was given to all patients. Mechanical ventilation was maintained with a tidal volume of 10–15 mL/kg at 10–12 breaths/min and a gas mixture of oxygen-air (FiO2 0.6–0.8). Ventilation parameters were modified in accordance with arterial blood gases. CABG was carried out through a full median sternotomy in all patients. CPB was achieved by cannulating the ascending aorta and right atrium. CPB was accomplished at moderate hypothermia (25–28°C) with a centrifugal pump (flow rate 1.2–2.2 L/min/m²) and a membrane oxygenator. Cardiac protection was achieved by infusing ante- and retrograde cold blood cardioplegia. Cardiac arrest was established by adding a high (65 mEq/L) and low (35 mEq/L) potassium dose in the cardioplegic solution.

Standard monitoring techniques included arterial, central venous, and Swan-Ganz catheters, inserted pre-operatively. Measurements of heart rate, systolic, diastolic, and mean arterial pressures, pulmonary artery pressure, central venous pressure, pulmonary capillary wedge pressure, and cardiac output by thermodilution were recorded immediately and 8 h after the induction of anaesthesia.

Assessment of lipid peroxidation

Thiobarbituric acid reactive substances (TBARS) are almost exclusively made of malondialdehyde, and its measurement remains the most frequently adopted index of lipid peroxidation. Thus, in vitro assessment of the plasma content of LDL-derived TBARS has been traditionally used to indirectly quantify the degree of lipid peroxidation. Plasma was separated

Conclusion

In patients undergoing CABG, DEF i.v. infusion ameliorates oxygen free radical production and protects the myocardium against reperfusion injury. Patients with a lower EF seem to benefit more by DEF i.v. infusion.
The LDL pellet was completely dissolved in 200 reagent followed by low-speed centrifugation (3000 r.p.m.) selective precipitation using 2 mL of an LDL-precipitating (0.6 mM) for 45 min at 37
vitro by incubating 100 mL of plasma with phenylhydrazine sing. To determine TBARS, lipid peroxidation was induced in anaesthesia, and the day after the end of the surgical procedure, 8 h after the induction of dialdehyde. TBARS were measured before and during bypass, at the amount of TBARS was derived from a standard curve for malon-dialdehyde. TBARS were centrifuged at 5000 r.p.m. for 20 min. The absorbance of the supernatant was measured at 532 nm with a Beckman spectrophotometer (Beckman Coulter Inc., Fullerton, CA, USA). The intensity of the pink coloration was read against a blank, and the
trophotometer (Beckman Coulter Inc., Fullerton, CA, USA). The intensity of the pink coloration was read against a blank, and the

Pre-operative medications

<table>
<thead>
<tr>
<th>β-blockers</th>
<th>20 (100)</th>
<th>25 (100)</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-inhibitors</td>
<td>18 (90)</td>
<td>21 (84)</td>
<td>0.8</td>
</tr>
<tr>
<td>Statins</td>
<td>10 (50)</td>
<td>13 (52)</td>
<td>0.4</td>
</tr>
<tr>
<td>Aspirin</td>
<td>20 (100)</td>
<td>25 (100)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Data are mean ± SD or n (%).

by centrifugation and immediately stored at −80°C until process-
ing. To determine TBARS, lipid peroxidation was induced in vitro by incubating 100 mL of plasma with phenylhydrazine (0.6 mM) for 45 min at 37°C. LDLs were then separated by selective precipitation using 2 mL of an LDL-precipitating reagent followed by low-speed centrifugation (3000 r.p.m.). The LDL pellet was completely dissolved in 200 µL NaOH (0.015 N) to which 1.2 mL 1% thiobarbituric acid in 10% acetic acid solution (pH 3.5) was added, and the mixture was incubated at 95°C for 45 min. After cooling at room temperature, samples were centrifuged at 5000 r.p.m. for 20 min. The absorbance of the supernatant was measured at 532 nm with a Beckman spectrophotometer (Beckman Coulter Inc., Fullerton, CA, USA). The intensity of the pink coloration was read against a blank, and the amount of TBARS was derived from a standard curve for malondialdehyde. TBARS were measured before and during bypass, at the end of the surgical procedure, 8 h after the induction of anaesthesia, and the day after.

Transoesophageal echocardiography

Immediately and 8 h after the induction of anaesthesia, transoesophageal echocardiography was performed by two independent experts who were blinded to patients’ clinical details. According to the American Society of Echocardiography and the Society of Cardiovascular Anaesthesiologists guidelines, transoesophageal imaging was accomplished by a multi-plane probe with a 5-MHz transducer attached to a Hewlett Packard (Sonos 2500, Philips Medical Systems, Andover, MA, USA) device. Image sequences were continuously stored on a VHS videotape. By adjusting the depth of the probe and at various degrees of tip anteflexion, transgastric cross-sectional short-axis images at papillary muscle level were obtained. Care was taken to obtain images perpendicular to the left ventricular long axis, showing a circular left ventricular cavity. Subsequently, the probe was gently pulled back into the oesophagus and a transverse four-chamber view and a sagittal two-chamber view were obtained by 90° rotation of the sector to visualize the more apical parts of the left ventricle. During acquisition of the transoesophageal views, foreshortening of the left ventricular cavity was avoided by maximal probe retroflexion without losing contact with the oesophageal wall. In addition, complete visualization of the apex was ascertained by ensuring that the length of the left ventricular cavity, measured from the mitral valve plane to the apical endocardium, was identical in the four-chamber and two-chamber views. To optimize the correspondence of transoesophageal echocardiography scans, the position of the probe was documented by noting the depth of the probe from the bite-guard for each of the four anatomical levels. Fine adjustments were made with regard to the shape of the papillary muscles to provide an image as close as possible to the baseline image.

Regional wall motion was evaluated using a 16-segment left ventricle model, as recommended by the American Society of Echocardiography and the International Anaesthesia Research Society. Myocardial segments were scored according to the following scale: 1 = normal or hyperkinetic myocardium, 2 = hypokinesia (i.e. reduced but not absent systolic wall thickening and inward wall motion), 3 = akinesia (i.e. absent wall thickening and wall motion), and 4 = dyskinesia (i.e. systolic outward movement of the endocardial border and absent systolic wall thickening or systolic wall thinning). The regional wall motion score index was calculated as the sum of scores for each segment divided by the total number of segments. Additionally, and according to the modified Simson’s rule technique, left ventricular end-diastolic and end-systolic volumes were calculated and the left ventricular ejection fraction (LVEF) was derived.
Follow-up study

We did a 12 month follow-up of the patients, consisting of a complete physical examination, a transthoracic echocardiogram, and a treadmill exercise stress test, to assess whether cardiac protection conferred by deferoxamine during CABG was sustained. In cases of reported chest pain a coronary angiogram was performed. All patients were on β-blockers, ACE-inhibitors, statins, and aspirin.

Statistical analysis

All data are expressed as mean ± SD. The power of test procedure was applied in order to determine sample size (45). The type of study was set for Student’s t-test of independent samples, at an alpha level = 0.05, power of test = 0.80, and a 0.8 ratio of control to study samples. We processed the results for all intended Student’s t-tests and found that the most stringent requirements were introduced by EF%. The SD of 8.0 and a discernible difference of means at the five units level for EF% was obtained during interim evaluation of the study, after including the first 20 patients. Analysis of variance for repeated measurements [EF%, wall motion score index (WMSI)] was performed using general linear model (GLM) repeated measures (SPSS for Windows version 10). Two classification variables (whether the patient belonged to the control group or not and whether his baseline EF% value exceeded 38) were introduced as factors. Type III sums of squares were used to evaluate the hypothesis, utilizing a repeated contrast for the main factors. Levene test for homogeneity of variance, Box’s M test of the homogeneity of the covariance matrices of the dependent variables, and Bartlett’s test of sphericity were utilized to determine the appropriate statistic. Estimated marginal means were used to provide estimates of predicted mean values for the cells in the model, and Bonferroni adjustment was applied to the confidence intervals obtained. Student’s t-test was used for comparing two independent samples. χ² test was used for discrete data. A two-tailed P value <0.05 was considered significant.

Results

There were no deaths in this series, probably due to the high quality of the care provided. Moreover, severely ill patients were excluded from the study.

Effect of deferoxamine on lipid peroxidation after CABG

Arterial specimens were obtained from the first 11 consecutive patients randomized to deferoxamine (six patients) or placebo (five patients). The iron-catalysed oxygen free radical production and subsequent lipid peroxidation, as assessed by measuring the plasma levels of TBARS, are shown in Figure 1. No significant difference in plasma TBARS was found between the two groups before operation. However, as expected, increased production of oxygen free radicals leading to lipid peroxidation was noted after CPB in the control group (plasma TBARS levels increased from 2.1 ± 0.7 nmol/mL to 4.8 ± 1.1 nmol/mL, P = 0.03). Of particular interest, the infusion of deferoxamine completely prevented oxygen free radical production in group D (plasma TBARS levels remained unchanged from 2.6 ± 0.6 nmol/mL to 2.4 ± 0.9 nmol/mL, not significant).

Effect of deferoxamine on cardiac stunning after CABG

Overall, patients tolerated CABG well, recovered completely, and were discharged in good condition. None required re-exploration for bleeding and none suffered from peri-operative myocardial infarction. Before CABG, troponin levels were similar between the groups (0.07 ± 0.06 ng/mL for group C and 0.06 ± 0.06 ng/mL for group D, however, after CABG troponin levels were higher in group C (2.8 ± 0.7 ng/mL) than in group D (2.3 ± 0.5 ng/mL), P = 0.02. Demographic, CAD risk factors, and post-operative data are shown in Table 1. At the intensive coronary care unit (ICU) the use of inotropes was similar in both groups, in terms of agent and dose infused. Liver (bilirubinaemia, transaminases) and renal function (urea and creatinine) were similar between the groups both before and after the surgical procedure.

The comparison of measured variables between the deferoxamine and the control group is shown in Table 2. More specifically, the LVEF increased more in the deferoxamine group rather than in the control group (P = 0.008), whereas the WMSI decreased more in the deferoxamine group rather than in the control group (P = 0.0002). There were no differences between the groups regarding pre- and post-operative heart rate, systolic blood pressure, pulmonary capillary wedge pressure, central venous pressure, and cardiac output. Interestingly, although CPB and aortic cross-clamping times were similar between the two groups, the cardioprotective effect of deferoxamine infusion during and after CABG resulted in a shorter ICU stay (P = 0.04) and hospital stay (P = 0.01) in group D patients compared with controls, Table 1. A higher incidence of supraventricular arrhythmias (12 patients, 60%),

![Figure 1 TBARS measurements before and during bypass, at the end of surgical procedure (end), at the intensive care unit (ICU), and the day after. Although at baseline TBARS were similar between the two groups, following CABG they doubled in the control group (P = 0.01), but remained unchanged in the deferoxamine group.](https://academic.oup.com/eurheartj/article-abstract/26/3/263/487143/1.1-nmol/mL-P-0.03). Of particular interest, the
Deferoxamine during CABG protects myocardium

Table 2 Comparison of the measured variables between control (n = 20) and deferoxamine (n = 25) groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Deferoxamine</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF1 (%)</td>
<td>38.8 ± 7.9</td>
<td>39.2 ± 8.2</td>
<td>0.9</td>
</tr>
<tr>
<td>EF2 (%)</td>
<td>40.3 ± 10.2</td>
<td>48 ± 6.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Δ-EF (%)</td>
<td>1.3 ± 6.7</td>
<td>8.8 ± 8.4</td>
<td>0.008</td>
</tr>
<tr>
<td>WMSI 1</td>
<td>2.4 ± 0.2</td>
<td>2.4 ± 0.2</td>
<td>0.8</td>
</tr>
<tr>
<td>WMSI 2</td>
<td>2.2 ± 0.3</td>
<td>1.7 ± 0.3</td>
<td>0.0002</td>
</tr>
<tr>
<td>Δ-WMSI</td>
<td>−0.2 ± 0.2</td>
<td>−0.7 ± 0.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>HR 1, beats/min</td>
<td>63.8 ± 6.9</td>
<td>62.4 ± 9.1</td>
<td>0.6</td>
</tr>
<tr>
<td>HR 2, beats/min</td>
<td>94.3 ± 11.7</td>
<td>93 ± 10.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Δ-HR, beats/min</td>
<td>30.5 ± 13.9</td>
<td>30.6 ± 14.4</td>
<td>0.9</td>
</tr>
<tr>
<td>SBP 1, mmHg</td>
<td>107.3 ± 14.0</td>
<td>105.5 ± 13.1</td>
<td>0.9</td>
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<tr>
<td>SBP 2, mmHg</td>
<td>107.9 ± 24.9</td>
<td>110 ± 10.1</td>
<td>0.7</td>
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<tr>
<td>Δ-SBP, mmHg</td>
<td>0.5 ± 29.4</td>
<td>4.5 ± 12.5</td>
<td>0.6</td>
</tr>
<tr>
<td>PWP 1, mmHg</td>
<td>11 ± 3.1</td>
<td>10.7 ± 2.7</td>
<td>0.4</td>
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<tr>
<td>PWP 2, mmHg</td>
<td>9.7 ± 1.7</td>
<td>10.3 ± 3</td>
<td>0.3</td>
</tr>
<tr>
<td>Δ-PWP, mmHg</td>
<td>−1.2 ± 3.4</td>
<td>−0.4 ± 2.3</td>
<td>0.3</td>
</tr>
<tr>
<td>CVP 1, mmHg</td>
<td>8.2 ± 1.7</td>
<td>8.1 ± 1.6</td>
<td>0.9</td>
</tr>
<tr>
<td>CVP 2, mmHg</td>
<td>6.7 ± 1.5</td>
<td>7.5 ± 1.5</td>
<td>0.09</td>
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<tr>
<td>Δ-CVP, mmHg</td>
<td>−1.5 ± 2.1</td>
<td>−0.6 ± 1.9</td>
<td>0.1</td>
</tr>
<tr>
<td>CO 1, L/min</td>
<td>2.8 ± 0.3</td>
<td>2.7 ± 0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>CO 2, L/min</td>
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<td>3.5 ± 0.2</td>
<td>0.03</td>
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<tr>
<td>Δ-CO, L/min</td>
<td>0.5 ± 0.3</td>
<td>0.8 ± 0.3</td>
<td>0.004</td>
</tr>
</tbody>
</table>

HR, heart rate; SBP, systolic blood pressure; PWP, pulmonary wedge pressure; CVP, central venous pressure; CO, cardiac output. The number 1 represents measurements before operation, and number 2 represents measurements in the ICU. Δ represents the difference between the second and the first calculation.

P = 0.0001, and non-sustained ventricular tachycardia (five patients, 25%), P = 0.0001, was observed in the control group compared with that observed in the deferoxamine group (two patients, 8%, presented supraventricular tachycardia and one patient, 4%, non-sustained ventricular tachycardia).

Effect of deferoxamine treatment according to pre-operative EF

Since low EF is considered an independent risk factor for major adverse events and influences plasma antioxidant capacity and lipid peroxidation after CABG, we further analysed the impact of deferoxamine treatment on post-bypass cardiac function in relation to pre-operative EF. To this end, we divided deferoxamine-treated patients according to the median value of pre-bypass EF (38%), into two subgroups: subgroup A with EF > 38% (n = 12), and subgroup B with EF < 38% (n = 13). If an EF improvement of ≥5% after CABG is considered significant then, as shown in Table 3, deferoxamine was particularly beneficial in patients with severe pre-operative left ventricular dysfunction in terms of improvement of both LVEF and WMSI.

Long-term effect of deferoxamine treatment

All patients were followed up for 12 months and during this time no major cardiac event was reported. Clinical examination in both groups showed no signs or symptoms of CAD. Similarly, stress tests showed no signs of unvascularized myocardium in any patient. In 10 out of 45 patients who reported chest pain, the coronary angiogram showed a patency of bypass grafts. Table 4 shows the long-term deferoxamine-related cardioprotection, as evaluated by echocardiography performed 12 months after CABG. Table 4 shows that the immediate beneficial effect of deferoxamine treatment on cardiac function after CABG is maintained during follow-up so that, by the end of the observation period, patients in group D had significantly (P < 0.0001) better preservation of left ventricular performance indices in terms of LVEF and WMSI compared with group C. It also shows that cardioprotection due to deferoxamine is apparently more evident in the subgroup of patients with a lower pre-operative EF (LVEF increased by 19.3 ± 6.2% and WMSI decreased by −1.1 ± 0.2) than in the subgroup with a better pre-operative EF (LVEF increased by 7.7 ± 4.5% and WMSI decreased by −0.8 ± 0.2, P = 0.001).

Discussion

This study demonstrates that, in patients undergoing elective CABG for the first time, the infusion of the free radical scavenger deferoxamine, for 8 h, starting immediately after the induction of anaesthesia, improves the post-ischaemic recovery of the left ventricle, mainly...
in those patients with the poorest pre-operative cardiac function. Of particular interest, this benefit remains for the 12 months of follow-up.

### Basis for the use of a free radical scavenger

Complete restoration of coronary flow is the goal of treatment for every patient who is operated on for CAD. However, complete restoration of coronary flow immediately after reperfusion witnesses a depression in left ventricular function with slow functional recovery, apparently caused by the deleterious effects of free radicals, which are mainly produced upon reperfusion. Free radicals are reactive chemicals with an unpaired electron in their outer shell and are derived from the re-introduction of oxygen after a period of ischaemia. This unpaired electron renders them very unstable and prone to react with other molecules in organic substrates in order to lose or gain an electron. The generated free radicals attack the lipid and protein components of the cell membrane, causing cardiac myocyte disruption and dysfunction. The heart is protected by an endogenous antioxidant system which varies between species and contributes to the elimination of free radicals. When the oxidative stress is profound, this endogenous system is insufficient in restoring normal conditions and it thus becomes necessary to provide exogenous antioxidant agents. According to the Habar–Weiss and Fenton reactions, iron (Fe) is involved in free radical production, reacting as Fe$^{3+}$ with O$_2$ and as Fe$^{2+}$ with H$_2$O$_2$, finally generating OH$^-$ and OH. Deferoxamine is a strong ferrum chelator without significant haemodynamic effects and is extensively used in cases of iron overload. In the present study, we used this agent in an attempt to improve the post-ischaemic recovery of left ventricular function by decreasing the generation of free radicals. In fact, left ventricular function was significantly improved in patients treated with deferoxamine in comparison with those treated with placebo, as confirmed by the improved WMSI and EF. This benefit seems to be due to the inhibition of free radical generation as is indicated by the circulating levels of TBARS, which decreased significantly in the deferoxamine-treated group following CABG.

### Previous clinical studies

Previous clinical studies have used specific leukocyte filters at the time of extracorporeal circulation in order to avoid the generation of free radicals from this source. Other workers have enriched their cardioplegic solutions with deferoxamine in order to eliminate free radical production. However, these biological observations have not been translated into an improved post-operative patient outcome. The possible reasons for the discrepancy between this study and others might be the fact that in our study all patients were treated for a longer period of time with higher doses of deferoxamine. This might suggest a longer protection against tissue damage associated with post-ischaemic reperfusion and inflammation and reduction of the post-bypass oxidative responsiveness of activated leukocytes. To our knowledge, this is the first clinical study of i.v. deferoxamine administration just before CABG which resulted in better post-ischaemic recovery of left ventricular function. Moreover, our results showed that, although the CPB time, aortic cross-clamping time, and haemodynamic parameters were similar between groups, in the deferoxamine group both the ICU stay and hospital stay were significantly shorter.

### Oxidative stress and poor left ventricular function

The results of this study suggest that deferoxamine infusion protects mainly the hearts with the poorest function. This is in keeping with previous reports which concluded that depressed heart function favours sustained...
free radical activity and consequently greater lipid peroxidation.\textsuperscript{3,36} Moreover, it is well recognized that a higher ATP content in the normal myocardium suggests a greater availability of energy in patients with higher LVEF values, thus making them more capable of repairing oxidative damage.\textsuperscript{37}

Clinical applications

This easy and safe therapeutic intervention may be extensively used in patients who are to be operated on and especially those with a poor pre-operative LVEF who are expected to have a more complicated post-operative period because of the slow recovery of an already-impaired left ventricle.

Study limitation

Spin trap probes convincingly demonstrate the generation of free radicals but this specific technique is used only in a limited number of experimental studies. However, easier methods, such as the circulating levels of malondialdehyde or TBARS, are currently used in many experimental and clinical studies. In this study, the TBARS measurements were done in a small sample of patients. However, since this measurement was performed randomly and both groups had a similar number of patients, it tends to minimize major mistakes in the interpretation of the results. Moreover, our major goal was to establish the clinical usefulness of deferoxamine in patients undergoing CABG. In this respect, when interim analysis showed that the selected dose of 4 g of deferoxamine was adequate to completely block oxygen free radicals, we decided not to measure TBARS further.

Conclusion

We have shown that deferoxamine i.v. infusion improves post-operative cardiac recovery and function, an effect which was sustained for at least 1 year of follow-up. The benefits of deferoxamine are particularly evident in patients with a lower pre-operative LVEF.

Acknowledgements

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References