

## Prospective Randomized Comparison of Cefodizime versus Cefuroxime for Perioperative Prophylaxis in Patients Undergoing Coronary Artery Bypass Grafting

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The effects of cefodizime and cefuroxime on neutrophil phagocytosis and reactive oxygen production in 54 patients undergoing elective coronary artery bypass grafting were studied. Both drugs were administered twice at a dosage of 40 mg/kg of body weight (pre- and intraoperative). Phagocytic capacity was assessed by measuring the uptake of fluorescein isothiocyanate-labeled *Escherichia coli* and *Staphylococcus aureus* by flow cytometry. Reactive oxygen generation after phagocytosis was estimated by determining the amount of dihydrorhodamine 123 converted to rhodamine 123 intracellularly. In both groups the mean phagocytic ability for *E. coli* and *S. aureus* decreased during surgery (-21 and -8%, respectively, for the cefodizime group and -39 and -38%, respectively, for the cefuroxime group;  $P < 0.05$  for all). In the cefodizime group a normalization of mean *E. coli* and *S. aureus* neutrophil phagocytosis was seen on day 5 (+9 and -4% compared to preoperative values;  $P > 0.35$  for both), whereas in cefuroxime-treated patients phagocytic ability remained depressed (-37 and -31%;  $P < 0.04$  for both). In both groups mean neutrophil reactive oxygen intermediate (ROI) production after *E. coli* and *S. aureus* phagocytosis increased during cardiopulmonary bypass (+44 and +83%, respectively, in the cefodizime group and +58 and +73%, respectively, in the cefuroxime group;  $P < 0.05$  for all). One day after surgery *E. coli*- and *S. aureus*-driven neutrophil ROI production was not different from the preoperative values (-2 and +12%, respectively, for the cefodizime group and +7 and +15%, respectively, for the cefuroxime group;  $P > 0.15$  for all). Postoperative serum levels of the C-reactive protein on days 2 and 7 were lower in cefodizime-treated patients ( $19 \pm 6$  and  $4 \pm 2$  mg/liter versus  $23 \pm 6$  and  $11 \pm 5$  mg/liter;  $P < 0.05$  for both). In addition to cefodizime's antimicrobial activity during perioperative prophylaxis, its use in coronary artery bypass grafting can prevent procedure-related prolonged postoperative neutrophil phagocytosis impairment.

Surgery is known to lead to a deterioration in host defense mechanisms and an increase in susceptibility to infection after operation (35). Both nonspecific innate and specific cell-mediated immune functions are depressed (2, 10, 12, 24, 26, 32). In addition, effects due to anesthetics, to surgical trauma, to hemorrhage, to transfusion, or to any concomitant pharmacological therapy have all been implicated in surgery-related immune system dysfunction (5, 10, 12, 24, 26, 32). Moreover, it is known that cardiopulmonary bypass (CPB) activates complement (11, 15, 20, 38), leads to neutropenia (15), and impairs cell-mediated immunity (14, 28).

Only a few data on the impairment of neutrophil function during and after cardiac surgery exist, and no attempt has been made to modulate this immune response (1, 8, 12, 25). This would be unnecessary if there were no adverse effects resulting from surgery-related immune function impairment. However, the high mortality rate of nosocomial infections in patients after cardiac surgery, ranging from 30 to 70% (11, 19, 27) compared to 3 to 5% in other surgical patient populations (18), implies that there are obviously some adverse effects in aorto-coronary bypass grafting. Furthermore, nosocomial infections

and multiorgan failure in patients following CPB are frequently associated with opportunistic microorganisms (16, 27, 29) which additionally induce a dysregulation of the immune response (26, 40).

Cefodizime was shown to enhance various immune functions such as phagocytic function, B-lymphocyte responsiveness, and delayed hypersensitivity (22, 23). Cefodizime was shown to normalize infection-induced suppression of phagocyte function more rapidly than the comparator ceftriaxone (39). We investigated the influence of cefodizime versus cefuroxime prophylaxis in coronary artery bypass surgery on phagocytic ability and reactive oxygen production by monitoring the phagocytosis of two common pathogens (*Escherichia coli* and *Staphylococcus aureus*) by neutrophils (39).

### MATERIALS AND METHODS

**Patients.** With approval from the local ethics committee and written informed consent we studied 60 patients with catheter-confirmed coronary heart disease undergoing elective aortocoronary bypass grafting. Patients were randomly assigned according to a randomization table to two groups: (i) 30 patients receiving 40 mg of cefuroxime per kg of body weight 1/2 h prior to incision and a second dose of 40 mg/kg after disconnection of the extracorporeal circulation and (ii) 30 patients receiving 40 mg of cefodizime per kg 1/2 h prior to incision and a second dose of 40 mg/kg after disconnection of the extracorporeal circulation. Patients with concurrent infections and/or immunosuppression were excluded. A radial artery catheter and a jugular vein catheter were inserted under local anesthesia. Anesthesia was introduced with 0.15 mg of midazolam, 0.2 mg of etomidate, 5 to

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TABLE 1. Pre- and postoperative clinical data

Group or P value	Mean age (yr) $\pm$ SD	Sex (f/m) <sup>a</sup>	Weight (kg) $\pm$ SD	Height (cm) $\pm$ SD	No. of patients (%) with:				No. of smokers (%)	Lowest temp (°C) $\pm$ SD	Duration of hypothermia (min) $\pm$ SD	CRP <sup>b</sup> level (mean $\pm$ SD) on day:	
					Diabetes mellitus II	Arterial hypertension	Hypercholesterinemia	Chronic obstructive bronchitis				2	7
Cefuroxime (n = 25)	65.3 $\pm$ 10.9	4/21	84 $\pm$ 9	172 $\pm$ 7	7 (28)	8 (32)	12 (48)	3 (12)	17 (68)	32.95 $\pm$ 1.23	186 $\pm$ 41	23.3 $\pm$ 5.8	10.5 $\pm$ 5.3
Cefodizime (n = 29)	64.1 $\pm$ 9.0	4/25	79 $\pm$ 12	170 $\pm$ 8	8 (28)	6 (21)	12 (42)	4 (14)	22 (76)	32.99 $\pm$ 1.25	195 $\pm$ 47	19.2 $\pm$ 6.4	4.1 $\pm$ 2.1
P value	0.668	0.264	0.066	0.436	0.457	0.135	0.332	0.389	0.258	0.436	0.397	0.031	0.024

<sup>a</sup> f, female; m, male.

<sup>b</sup> CRP, C-reactive protein.

10  $\mu$ g of fentanyl, and 0.15 mg of pancuronium per kg and was maintained with supplemental doses of fentanyl, midazolam, and pancuronium.

The CPB equipment consisted of roller pumps and disposable membrane oxygenators (Bard HF 5701). The pump was primed with 2-liter lactated Ringer solution to which 100 ml of 20% mannitol and 1,000,000 iE of aprotinin were added. CPB was instituted at a flow rate of 2.5 liters/min/m<sup>2</sup> of body surface area after systemic heparinization. After cross-clamping of the aorta, blood cardioplegic solution (Beyersdorf) was administered. Concentrations of the C-reactive protein in serum were routinely measured on the second and seventh postoperative days to evaluate postoperative alterations in the inflammatory response. In patients with diabetes mellitus glucose levels were routinely measured six times daily and glucose levels were kept between 80 and 160 mg/dl (4.4 to 8.8 mmol/liter). For comparison of preoperative values, 30 subjects (hospital staff) were the normal controls.

**Neutrophil phagocytosis and reactive oxygen production.** Blood samples were taken before induction of anesthesia (i.e., before the administration of the first dose of the study drugs), 30 min after the start of CPB, 30 min after cessation of CPB, 60 min after admission to the intensive care unit, 24 h postoperatively, and 5 days after the procedure. Sterile 10-ml Vacutainer tubes containing sodium heparin (Becton Dickinson Vacutainer Systems, Rutherford, N.J.) were used. Samples were kept at room temperature until analysis. All assays were performed, blinded as to the prophylaxis administered, within 4 hours of obtaining the blood.

Neutrophil phagocytosis and reactive oxygen production were determined as described previously (29). Heat-killed *E. coli* ATCC 25922 was labeled with fluorescein isothiocyanate (FITC) (Sigma Chemicals, Munich, Germany). A 1-ml volume of 0.1 M carbonate buffer, pH 9.6, containing  $5 \times 10^6$  bacteria/ml and 3  $\mu$ g of FITC was incubated at 37°C for 30 min. The fluoresceinated bacteria were washed twice in cold Hanks' balanced salt solution (Biochrom KG, Berlin, Germany) and resuspended in 50% pooled human sera to a concentration of  $10^8$ /ml. The bacteria were stored at -20°C in aliquots until analysis.

Dihydrorhodamine (DHR 123) was purchased from Molecular Probes Inc. (Eugene, Ore.) and dissolved in *N,N*,dimethyl formamide (Sigma Chemicals) at a concentration of 3  $\mu$ g/ml.

**Phagocytosis assay.** One hundred microliters of heparinized whole blood was aliquoted to the bottom of a 5-ml tube. Before adding the bacteria, samples were incubated in an ice-water bath for 15 min in order to cool them down to 0°C. Thereafter, 10  $\mu$ l of precooled FITC-labelled *E. coli* was added and the mixture was incubated for 10 min at 37°C in a shaking water bath. The controls were left on ice. Afterwards, 100  $\mu$ l of precooled quenching solution (Orpegen, Heidelberg, Germany) was added and all samples were washed twice in phosphate-buffered saline (PBS; pH 7.4). Finally, 2 ml of fluorescence-activated cell sorter (FACS)-lysing solution (Becton Dickinson) was added and the mixture was incubated for 20 min. Thereafter, the samples were washed with PBS and resuspended with 100  $\mu$ l of PBS containing propidium iodide (PI) at a final concentration of 50  $\mu$ g/ml for DNA staining. The samples were kept on ice until analysis.

**Reactive oxygen intermediate (ROI) production.** After identical preincubation, blood samples were stimulated with 25  $\mu$ l of unlabelled *E. coli* ATCC 25922 ( $10^8$ /ml) at 37°C. After 10 min of incubation, 25  $\mu$ l of the DHR solution was added and the mixture was incubated for an additional 10 min. At the end of the second incubation, 2 ml of FACS-lysing solution was added and the mixture was incubated for 20 min at room temperature. Thereafter, the samples were washed with PBS and resuspended with 100  $\mu$ l of PBS containing PI at a final concentration of 50  $\mu$ g/ml for DNA staining. The samples were kept on ice until analysis.

**Flow cytometry.** The cells were analyzed within 30 min of adding PI on a standard FACScan flow cytometer (Becton Dickinson, Mountain View, Calif.). For each measurement, 10,000 events were collected. Green fluorescence (FL1) was obtained through a 530-nm-band-pass filter. Red fluorescence (FL2) was collected through a 575-nm-band-pass filter. Fluorescence compensation was done to correct any crossover between FITC, DHR 123, and PI fluorescence. For

analysis of ROI production, granulocytes were separated by setting a gate on the population. To set the gate, the forward scatter (size) and side scatter (granularity) of the cells were determined and recorded. To exclude cell debris and nonphagocytized bacteria, a live gate was set on PI-stained leukocytes in FL2 during acquisition. Thereby, the background scatter could be reduced. For analysis of ROI production, the shift to the right in FL1 (green) was determined. The amount of cleaved substrate was estimated by the mean fluorescence, determined by using the statistical option of the FACScan software.

Similarly, the amount of phagocytized bacteria was assessed by determining the mean fluorescence. The mean fluorescence channel readings of both assays were compared to those of an unstimulated and a 0°C control. Daily alignment and calibration of the instrument were done with fluorescence beads (Calibrite; Becton Dickinson). The beads were put into the same histogram channel every day.

**Statistical analysis.** Differences between and within groups were compared by using the Student's *t* test for independent and dependent samples. The Pearson correlation coefficient was used. All the analyses were two sided, and differences with a *P* value that was <0.05 were considered significant.

## RESULTS

**Clinical findings.** The demographic data are depicted in Table 1. A total of 60 patients were enrolled. Three patients in the cefuroxime group and one patient in the cefodizime group did not receive the second intraoperative dose, and follow-up blood samples were lost for two patients in the cefuroxime group. These patients were excluded from the analysis. For the remaining 54 patients there were no differences between the groups with respect to age, height, weight, gender distribution, concomitant disease, and cardiac risk factors. The total time on CPB was (mean  $\pm$  standard deviation [SD]) 105  $\pm$  25 min for the cefuroxime group and 100  $\pm$  25 min for the cefodizime group, and the aorta was clamped for an average of 60  $\pm$  16 min and 60  $\pm$  18 min, respectively (*P* > 0.05 for both). Postoperative levels of the C-reactive protein in serum on days 2 and 7 were lower in cefodizime-treated patients (19  $\pm$  6 and 4  $\pm$  2 mg/liter versus 23  $\pm$  6 and 11  $\pm$  5 mg/liter; *P* < 0.05 for both). There were two patients with urinary tract infections in the cefuroxime group and one patient with a urinary tract infection in the cefodizime group (*P* = 0.2). Three patients in the cefuroxime group developed nosocomial pneumonia and one patient in the cefodizime group developed pneumonia (*P* = 0.08). In addition, four patients in the cefuroxime group had fevers of >38.5°C with no local signs of infection and two patients in the cefodizime group had fevers (*P* = 0.09). All patients with infections and fever received additional courses of antibiotics according to the discretion of the treating physician. These patients had decreased neutrophil phagocytosis and ROI production on day 5 (-24 to -33% for the cefuroxime-treated patients and -28 to -36% for the cefodizime-treated patients compared to the rest of the group). One patient in the cefuroxime group died due to postoperative septicemia on day 17. This patient had bacteremia due to *E.*

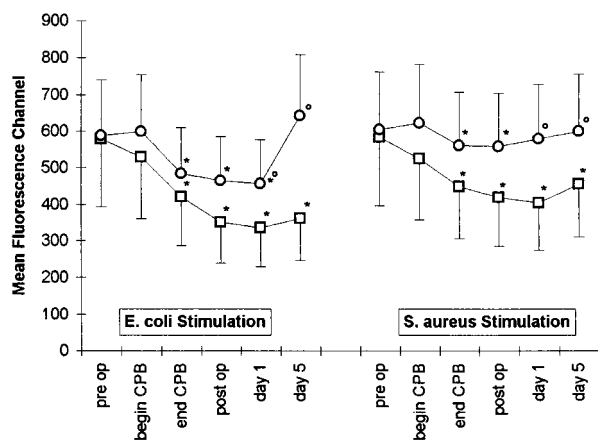


FIG. 1. Mean  $\pm$  SD fluorescence emission results for phagocytized FITC-labeled *E. coli* (left) and *S. aureus* (right) prior to, during, and after surgery for cefuroxime- (squares) and cefodizime (circles)-treated patients undergoing coronary artery bypass grafting. Asterisks indicate significant differences relative to preoperative values within the groups; small circles indicate significant differences between the groups.

*coli* on the second postoperative day and had been treated with ciprofloxacin. After initial improvement (respirator therapy, catecholamines) the patient deteriorated. A second bacteremia with methicillin-resistant staphylococci and *Enterococcus faecalis* was identified, and teicoplanin was administered. The patient finally died, in spite of adequate antimicrobial therapy, due to irreversible septic shock. A second patient in the cefodizime group was reanimated because of cardiac arrhythmia, subsequently entered a vegetative neurologic state, and died after a prolonged stay in the intensive care unit (94 days) due to acute respiratory distress syndrome.

**Ex vivo neutrophil phagocytic ability.** The perioperative kinetics of ex vivo neutrophil phagocytic ability are depicted in Fig. 1. The mean ( $\pm$ SD) fluorescence channel readings after neutrophil ingestion of labeled *E. coli* and *S. aureus* were  $578 \pm 212$  and  $584 \pm 256$ , respectively, for the cefuroxime group and  $588 \pm 265$  and  $605 \pm 267$ , respectively, for the cefodizime group. *E. coli* phagocytosis decreased in the cefuroxime group after CPB ( $420 \pm 206$ ) and remained depressed in the postoperative period ( $350 \pm 213$ ,  $336 \pm 174$ , and  $362 \pm 222$  on days 0, 1, and 5, respectively;  $P < 0.05$  for all). In the cefodizime group phagocytic ability decreased after CPB on postoperative days 0 and 1 ( $464 \pm 230$  and  $457 \pm 198$ ;  $P < 0.05$  for both) and was within the normal range 5 days after surgery ( $642 \pm 234$ ). There was a significant difference in *E. coli* neutrophil phagocytosis between both groups on postoperative day 1 ( $P = 0.027$ ) and day 5 ( $P = 0.013$ ). *S. aureus* phagocytosis was slightly decreased after CPB ( $560 \pm 255$ ) and on postoperative day 0 ( $558 \pm 257$ ) for the cefodizime group, whereas normal values were measured on days 1 ( $578 \pm 248$ ) and 5 ( $599 \pm 206$ ). In cefuroxime-treated patients phagocytic capacity decreased after CPB ( $449 \pm 160$ ) and on postoperative days 0, 1, and 5. A significant difference between the values for both groups existed on days 1 and 5 ( $P = 0.0016$  and  $P = 0.027$ , respectively). No correlation between neutrophil phagocytic ability and reactive oxygen production at the different time points existed ( $P > 0.05$  for all comparisons). In the normal controls *E. coli* and *S. aureus* neutrophil phagocytosis yielded a mean  $\pm$  SD fluorescence of  $589 \pm 54$  and  $612 \pm 72$ , respectively. These values were not significantly different from preoperative values.

**Ex vivo neutrophil ROI production.** The mean ( $\pm$ SD) fluorescence channel readings after neutrophil stimulation with *E. coli* and *S. aureus* were  $62 \pm 25$  and  $60 \pm 30$ , respectively, for the cefuroxime group and  $72 \pm 37$  and  $64 \pm 27$ , respectively, for the cefodizime group. *E. coli*- and *S. aureus*-stimulated neutrophil ROI production increased after initiation of surgery for both groups ( $98 \pm 50$  and  $103 \pm 48$ , respectively, for the cefuroxime group and  $104 \pm 53$  and  $116 \pm 54$ , respectively, for the cefodizime group; Fig. 2). A normalization of *E. coli*-driven ROI production was observed 1 h postoperative for the cefodizime group ( $81 \pm 46$ ) and on postoperative day 1 ( $50 \pm 22$ ) for the cefuroxime group. A normalization of *S. aureus*-driven ROI production was seen 1 h postoperative for the cefuroxime group ( $71 \pm 37$ ) and on postoperative day 1 ( $71 \pm 32$ ) for the cefodizime group. No significant differences between the groups were seen with respect to the perioperative kinetics of neutrophil ROI production ( $P > 0.05$  for all comparisons). *E. coli* and *S. aureus* neutrophil reactive oxygen production fluorescence emission values for healthy controls were (mean  $\pm$  SD)  $70 \pm 14$  and  $61 \pm 12$ . These values were not significantly different from preoperative values in patients.

## DISCUSSION

The alteration of the nonspecific host response by surgery (26) and/or antimicrobial therapy (9) has received increased interest in the past few years. A new aspect is the growing number of immunocompromised individuals in whom even a marginal influence on the host response may have a significant effect on clinical outcome. Older patients, patients with diabetes mellitus, and smokers are well recognized as being prone to both coronary heart disease and the impairment of immunoreactivity (28, 34, 38).

By using carefully standardized flow cytometry methods (4), we measured the phagocytic ability and generation of ROI of neutrophils under conditions that minimally disturb the normal microenvironment of these cells (3, 4). It has been demonstrated that isolation from whole blood can alter the expression of cell surface antigens and leukocyte functional behavior as well (5–7). In contrast to the practice in other studies, we did not separate blood leukocytes from their normal microenvironment before incubating them with bacteria (13, 31, 36).

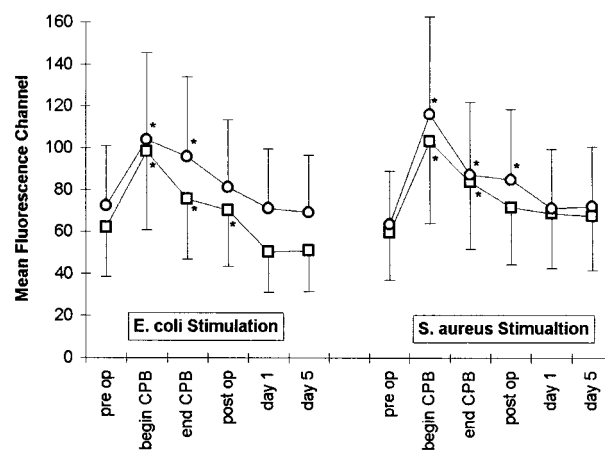


FIG. 2. Mean  $\pm$  SD fluorescence emission results for intracellularly generated rhodamine 123 in neutrophils after *E. coli* (left) and *S. aureus* (right) stimulation prior to, during, and after surgery for cefuroxime- (squares) and cefodizime (circles)-treated patients undergoing coronary artery bypass grafting. Asterisks indicate significant differences relative to preoperative values within the groups; small circles indicate significant differences between the groups.

Even so, because anticoagulation and temperature alterations were required for the experiments, the conditions were not entirely physiologic. However, it is unlikely that the addition of heparin and fluctuations in temperature preferentially influence the phagocytosis and ROI-producing abilities of cefodizime-exposed neutrophils as opposed to those of cefuroxime-exposed neutrophils.

In this study, cefodizime prophylaxis attenuated intraoperative neutrophil phagocytosis impairment and prevented a prolonged depression of neutrophil phagocytic ability in the postoperative period. A similar depression of neutrophil function has been described for patients with severe infections. For patients with severe infections cefodizime has been shown to restore normal neutrophil function more rapidly than the comparator ceftriaxone (39). In vivo models of experimental infections show that the prophylactic administration of cefodizime increases the survival of some strains of mice after challenge with even *Toxoplasma gondii* or *Candida albicans* (21, 39); its curative effect on infections due to members of the family *Enterobacteriaceae* is better than might be expected from its *in vitro* MICs relative to those of other expanded-spectrum cephalosporins (21). The exact mechanism of this additive (nonmicrobiological) effect of the drug remains speculative (30, 33). The duration of the beneficial effect of cefodizime could be due to a robust neutrophil host response during surgery, leading to lower postoperative bacterial burden. A similar effect has been seen in uremia where the depressed phagocytosis-related metabolic function was stimulated for up to 2 weeks (!) after the end of treatment (37).

Neutrophil reactive oxygen production increased significantly in both groups during surgery and decreased to preoperative values between days 0 and 1. We did not see differences with respect to neutrophil reactive oxygen production between the groups (Fig. 2).

There were several patients with postoperative infections in both groups. The patients with postoperative fever and/or localized infections had decreased neutrophil phagocytosis and ROI production on day 5, which corresponds to previous findings for patients with severe infections (39) or septicemia (40, 41). Because staphylococcal infections are among the most common after CPB, the higher MIC at which 50% of the isolates are inhibited of cefodizime compared to that of cefuroxime merits special attention. No difference in the incidences of infections between the two groups was seen; in particular no infections due to staphylococci were observed. However, since the lack of a difference could be due to the small sample size, this issue should be evaluated before clinical application of cefodizime in this setting.

Altogether, the present findings demonstrate a dynamic alteration of the activity of neutrophils during and after coronary artery bypass grafting. Antimicrobial prophylaxis with cefodizime attenuates the procedure-related depression of neutrophil phagocytosis and, in addition, prevents a further postoperative decline. These effects are associated with lower levels of acute-phase proteins. Whether this beneficial nonmicrobiological "side effect" of cefodizime could reduce the incidence of nosocomial infections, postoperative morbidity, and mortality and whether it could reduce hospital expenses needs to be elucidated.

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