Neutrophilia and granulocyte colony-stimulating factor levels after cardiopulmonary bypass

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Purpose: The precise mechanism of neutrophilia after cardiac surgery is unknown. Granulocyte colony stimulating factor (G-CSF) can increase the number of leukocytes. The purpose of this study was to evaluate the relationship between serum G-CSF levels and peripheral blood leukocyte counts after cardiac surgery.

Methods: We prospectively studied 10 patients undergoing cardiac surgery (coronary artery bypass grafting) using cardiopulmonary bypass (CPB). Plasma G-CSF levels and neutrophil count were measured before induction of anaesthesia, at the end of surgery, and on the first postoperative day. These changes were compared with those in patients undergoing non-cardiac major surgery (control group).

Results: At the end of surgery, G-CSF levels increased ($P < 0.01$) in both groups, but were higher in the control than in the cardiac group ($3,250 \pm 690$ vs 194 ± 29.5 pg·ml⁻¹, respectively, mean $\pm$ SEM, $P < 0.01$). On the first postoperative day, G-CSF levels were still high in both groups, and were still higher in the control (710 ± 179 vs 122 ± 19.9 , respectively, $P < 0.01$). However, neutrophilia was greater in the cardiac group than in the control. G-CSF response correlated positively with neutrophilia in the control group ($r = 0.656$, $P < 0.05$) but not in the cardiac group.

Conclusions: Our results indicate that changes in leukocyte count following cardiac surgery are unique to patients undergoing CPB. G-CSF plays an important role as the mediator of neutrophilia after non-cardiac surgery, but not after cardiac surgery with CPB.

Objectif : Le mécanisme précis de la polynucléose neutrophile qui survient après une intervention en cardiochirurgie est inconnu. Le facteur stimulant la formation de colonies de granulocytes (FSC-G) peut augmenter le nombre de leucocytes. L'objectif de la présente étude était d'évaluer la relation entre les niveaux sériques de FSC-G et la numération leucocytaire du sang périphérique à la suite d'une intervention cardiaque.

Méthode : Nous avons mené une étude prospective auprès de 10 patients qui ont subi un pontage aorto-coronarien sous circulation extracorporelle (CEC). Les niveaux plasmatiques de FSC-G et la numération des neutrophiles ont été mesurés avant l'induction de l'anesthésie, à la fin de l'opération et au premier jour postopératoire. Les changements ont été comparés avec ceux qu'on a observés chez des patients qui ont subi une intervention importante, non cardiaque (groupe témoin).

Résultats : À la fin de l'opération, les niveaux de FSC-G ont augmenté ($P < 0,01$) dans les deux groupes, mais ont été plus élevés dans le groupe témoin que dans le groupe de cardiochirurgie ($3,250 \pm 690$ vs $194 \pm 29,5$ pg·ml⁻¹, respectivement, moyenne $\pm$ écart type, $P < 0,01$). Au premier jour postopératoire, les niveaux de FSC-G étaient encore élevés dans les deux groupes et toujours plus hauts chez les témoins (710 ± 179 vs $122 \pm 19,9$, respectivement, $P < 0,01$). Toutefois, la polynucléose neutrophile était plus marquée dans le groupe de cardiochirurgie que dans le groupe témoin. La réponse du FSC-G était en corrélation avec la polynucléose neutrophile dans le groupe témoin ($r = 0,656$, $P < 0,05$) mais non dans l'autre groupe.

Conclusion : Nos résultats indiquent que les changements de numération des leucocytes, à la suite d'une intervention cardiaque, sont uniques aux patients qui subissent une CEC. Le FSC-G joue un rôle important comme médiateur de la polynucléose neutrophile après une opération non cardiaque, mais pas après une intervention cardiaque sous CEC.

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NEUTROPHIL activation occurs in patients who have undergone cardiopulmonary bypass (CPB).¹ The process and consequences of neutrophil activation are complex and the data available are insufficient to explain the complex processes. Recently, it has become apparent that human granulocyte colony-stimulating factor (G-CSF) is the main regulator of the production as well as functional state of neutrophilic granulocytes.^{2,3} The purpose of this study was to determine the relationship between changes in neutrophil counts and G-CSF levels after CPB.

Methods

Ten patients (three male, seven female; mean age, 63.0 yr, range 47-75) undergoing cardiac surgery (coronary artery bypass grafting) using CPB were prospectively studied following informed consent and approval of the Human Subjects Committee.

Blood samples for the measurement of plasma G-CSF, total and differential leukocyte counts, were obtained prior to the induction of anesthesia, at the end of surgery, and on the first postoperative day. Total leukocyte and neutrophil counts were determined by routine laboratory methods. For the determination of serum G-CSF levels, the blood samples were analyzed using enzyme immunoassay.⁴

Another group of eight patients (two male, six female; mean age, 63.9 yr, range 55-83) who underwent major surgery (esophagectomy and esophageal reconstruction) without CPB were recruited as the control sample. Approval for the study was also obtained from the Human Subjects Committee.

A high-dose fentanyl (50-75 $\mu\text{g}\cdot\text{kg}^{-1}$)-oxygencurium bromide technique supplemented with diazepam and an inhalation agent, isoflurane (0.5-1.0%), was used in the cardiac surgery group. In the non-cardiac group, anesthesia was induced with thiamylal and maintained with isoflurane (1.5-2.0%) and nitrous oxide, and occasionally supplemented with low-dose fentanyl (0.1-0.2 mg).

All data were expressed as mean $\pm$ SEM. Differences between groups were examined for statistical significance using ANOVA, Fisher's Protected Least Significant Difference, Student's *t* test, and linear regression analysis. A *P* value less than 0.05 denoted the presence of a statistically significant difference.

Results

The characteristics of patients of both groups are shown in Table I. The amount of transfused blood during surgery was significantly lower ($P < 0.01$) in the cardiac group than in the non-cardiac group. In

TABLE I Patients characteristics.

	Cardiac Surgery	Non-Cardiac Surgery
n	10	8
Sex (M/F)	3/7	2/6
Age (yr)	63.0 $\pm$ 3.0	63.9 $\pm$ 3.2
Body weight (kg)	52.4 $\pm$ 4.3	57.0 $\pm$ 3.8
Duration of anesthesia (hr)	5.4 $\pm$ 0.5	11.5 $\pm$ 1.3*
Duration of operation (hr)	5.0 $\pm$ 0.3	10.8 $\pm$ 1.2*
Amount of bleeding (g)	534 $\pm$ 140	886 $\pm$ 147
Volume of blood transfusion (ml)	410 $\pm$ 143	1,125 $\pm$ 280*

Data are mean $\pm$ SEM. * $P < 0.01$, compared to the cardiac surgery group.

FIGURE 1 Changes in plasma granulocyte colony stimulating factor (G-CSF) concentrations after cardiac (n=10) and non-cardiac (n=8) surgery. Open squares: cardiac group, open circles: non-cardiac surgery. Data are mean $\pm$ SEM. * $P < 0.01$ vs the control group. † $P < 0.01$ vs the cardiac group.

addition, the duration of surgery and anesthesia were shorter in the cardiac group.

Basal G-CSF levels were $< 30 \text{ pg}\cdot\text{ml}^{-1}$ in all patients (Figure 1). At the end of surgery, G-CSF concentrations increased ($P < 0.01$) in both groups, and were higher in the non-cardiac than in the cardiac group ($3,250 \pm 690$ vs $194 \pm 29.5 \text{ pg}\cdot\text{ml}^{-1}$, respectively, $P < 0.01$). On the first postoperative day, G-CSF levels were still high in both groups, and were still higher in the non-cardiac group.

Both types of surgery resulted in massive leukocytosis in the peripheral blood on the first postoperative day, mainly attributed to an increase in the percentage of neutrophils (Table II). Statistical analysis showed higher increase in leukocyte and neutrophil counts in

TABLE II Total white blood cell count and percent of neutrophils.

	Cardiac Surgery	Non-Cardiac Surgery
Baseline		
Total leukocytes (cells-mm ³)	4,540 ± 437	5,700 ± 369
Neutrophils (%)	55.6	55.3
First Postoperative Day		
Total leukocytes (cells-mm ³)	13,570 ± 1,457*†	8,050 ± 681*
Neutrophils (%)	85.9	84.5

Data are mean ± SEM. * $P < 0.01$ vs basal value, † $P < 0.01$ vs non-cardiac group.

FIGURE 2 Correlation between plasma granulocyte colony stimulating factor (G-CSF) and white blood cell (WBC) counts in non-cardiac surgery group ($P < 0.05$, $r=0.656$).

the cardiac group than in the control group, contrary to the changes in G-CSF levels. There was a positive correlation between the G-CSF response to surgery and postoperative leukocyte counts in the non-cardiac group ($r=0.656$, $P < 0.05$, Figure 2). In contrast, no such correlation was identified in the cardiac group.

Discussion

Leukocytosis was noted in both groups of patients, although, the total white blood cell count and relative neutrophilia were greater in the cardiac than in the non-cardiac group. Pearl and coworkers⁵ demonstrated that the degree of leukocytosis correlated primarily with the extent of surgery. Our data showed that the extent of surgery according to the operation time and blood transfusion was greater in the non-cardiac group than in the cardiac group. These results suggest that the stress and trauma in the cardiac group were less than in the non-cardiac group. However, the level

of neutrophilia after cardiac surgery was greater than after non-cardiac surgery. Hence, the hematological changes that occur in cardiac surgery patients may be attributed to the CPB procedure rather than to the extent of surgical procedure itself.

Despite the uncomplicated perioperative courses, leukocytosis and neutrophilia are generally encountered after CPB.^{6,7} However, the complex mechanisms and mediators are not well understood. One may speculate that increased concentrations of G-CSF contributed to post-CPB leukocytosis. To confirm this, we investigated the relationship between changes in neutrophil counts and G-CSF levels in patients undergoing cardiac and non-cardiac major surgery. Our results demonstrated that plasma G-CSF levels correlated with neutrophil counts after non-cardiac major surgery, but not cardiac surgery. In contrast to leukocyte counts, G-CSF levels were lower in the cardiac surgery than in the non-cardiac surgery group. Patients undergoing cardiac surgery showed a greater increase in neutrophils, but a smaller increase in G-CSF. These results suggest that G-CSF may not play an important role as the mediator of neutrophilia in cardiac surgery. One reason for these results may be related to the two different anesthetics used in the present study. We used a high dose of fentanyl for cardiac surgery and isoflurane inhalation anesthesia for non-cardiac surgery. *In vitro* studies have shown that opioids, at higher concentrations, reduced hyperactivation of granulocytes and monocytes exposed to the stimulatory effects of plasma obtained from CPB patients.^{8,9} Therefore, the high-dose fentanyl in cardiac surgery might attenuate the surgical stress response better than inhalation anesthetics. This may well explain the suppressed G-CSF response in cardiac surgery. However, the use of different anesthetics could not explain the marked post-CPB neutrophilia.

In conclusion, our results suggest that G-CSF plays an important role as the mediator of neutrophilia in non-cardiac surgery, but not in cardiac surgery with CPB.

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