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Natural Killer Cell Activity and Lymphocyte Function During and After Coronary Artery Bypass Grafting in Relation to the Endocrine Stress Response

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The effects of elective coronary artery bypass grafting (CABG) and the associated endocrine stress response on natural killer (NK) cell activity in peripheral blood, the distribution of lymphocyte subpopulations, and the phytohemagglutinin (PHA)-induced lymphocyte transformation were studied in 20 patients anesthetized with either etomidate-high dose fentanyl (75–125 $\mu g \cdot kg^{-1}$) or midazolam-low dose fentanyl (<20 $\mu g \cdot kg^{-1}$). The endocrine response to surgery was measured as changes in serum cortisol, plasma epinephrine, and norepinephrine. Compared with control values, a significant increase of NK cell activity was found in both groups prior to induction of anesthesia, followed by a decrease after induction until initiation of cardiopulmonary bypass (CPB) and a gradual increase to levels exceeding controls during CPB. Postoperatively, NK cell activity and the lymphocyte transformation to PHA stimulation were significantly depressed for at least 1–3 days. These changes were accompanied by severe lymphopenia affecting the T-lymphocytes (T3, T4, and T8) and the NK cells (Leu 11). Apart from a delayed cortisol increase in the etomidate group, the endocrine response showed a similar pattern in the two groups. Compared with control values, a significant decrease in the serum cortisol until CPB could be demonstrated, followed by a significant increase persisting for at least 6 days postoperatively. The plasma catecholamines showed a steep rise and, consequently, a significant increase during CPB, followed by a gradual return to control values in the postoperative period. The results indicate that, in patients undergoing CABG, immune surveillance is impaired prior to CPB and during the early postoperative period. The mechanisms underlying the fluctuations in NK cell activity and lymphocyte function are complex, but the results suggest that the endocrine stress response may be of major importance. (Key words: Anesthetics, intravenous: etomidate; fentanyl; midazolam. Hormones: catecholamines; cortisol; endocrine stress response. Immune response: distribution; lymphocyte function; natural killer cell activity; subpopulations. Surgery: cardiac. Sympathetic nervous system: catecholamines.)

NATURAL KILLER (NK) CELLS are a subpopulation of lymphocytes showing spontaneous cytotoxicity directed against a variety of target cells, such as tumor cells, virus infected cells, and primitive normal cells.[1,2]

Previous investigations concerning the effect of different kinds of surgery and anesthesia have indicated an enhanced NK cell activity following premedication and during anesthesia and surgery,[3–6] followed by a pronounced reduction for 3–6 days after major surgery,[3,5,7,8] and only slight changes in relation to minor surgery.[9]

The mechanisms underlying the fluctuations in NK cell activity are unknown, but it has been suggested that the endocrine stress response is of importance.[8] Serum cortisol and plasma epinephrine are prominent markers of this response, and several studies have demonstrated that cortisol and epinephrine exert opposite effects on the NK cell system, with epinephrine enhancing,[10,11,12] and cortisol inhibiting, the activity *in vitro* and *in vivo*.[13]

Cardiac surgery with cardiopulmonary bypass (CPB) evokes a marked, persistent, and fairly well-defined endocrine stress response,[14–17] and appears to present ideal conditions for a clinical study of the relation between NK cell activity and the hormonal response to anesthesia and surgery. Several investigations have documented that open-heart surgery affects the immune defense with decreased lymphocyte transformation to various mitogens and microbial antigens,[18,19,20] impaired phagocytic function,[21] decreased number and activity of T-suppressor lymphocytes,[22] reduced serum immunoglobulins,[23] and lymphopenia and neutrophilia.[18]

Thus far, only one study has been published on NK cell activity after open-heart surgery.[7] However, this study focused exclusively on the postoperative period, and gave no indication of NK cell function during surgery and CPB or the relation to the endocrine stress response. The present prospective study was designed to examine the effects of coronary artery bypass grafting (CABG) and CPB on NK cell activity and lympho-

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cyte function in relation to the endocrine stress response.

Materials and Methods

Subjects and Protocol

After approval by the Regional Ethical Committee on Human Research, 22 adult patients scheduled to undergo CABG participated in the study. Informed consent was obtained as part of the preoperative visit. All patients demonstrated normal or only slightly impaired left ventricular function at coronary angiography with left ventricular end-diastolic pressures (LVEDP) less than 15 mmHg and ejection fractions greater than 50%. The administration of β-adrenergic and calcium-entry blocking agents was continued until the morning of operation. Premedication consisted of diazepam, 0.25 mg/kg orally, morphine sulfate, 0.2 mg/kg, and scopolamine, 0.003 mg/kg intramuscularly, 60–90 min before the scheduled time of operation.

Three venous and two arterial catheters were inserted percutaneously using local analgesia, and electrocardiographic monitoring was established before induction. One of the arterial catheters was reserved for blood sampling. The patients were randomly allocated to two groups.

In group I, general anesthesia was induced with etomidate, 0.3 mg/kg, and fentanyl, 3.5 μg/kg, and muscle relaxation was achieved with pancuronium bromide, 0.1 mg/kg. The patients were mechanically ventilated with a Servo ventilator with oxygen/air to maintain Pa_{O_2} above 125 mmHg and Pa_{CO_2} between 35–42 mmHg. Before sternotomy, 75–125 μg/kg of fentanyl was administered, and anesthesia was maintained with a continuous infusion of etomidate and fentanyl at a rate adjusted to the clinical needs of the patients.

In group II, general anesthesia was induced with midazolam, 0.15 mg/kg, and fentanyl, 3.5 μg/kg. Muscle relaxation was achieved and controlled ventilation instituted as in group I. Before sternotomy, up to 20 μg/kg of fentanyl was administered. Anesthesia was maintained with a continuous infusion of midazolam at a basal rate of 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$ and the addition of halothane and nitrous oxide adjusted to the clinical needs of the patients.

CPB was performed during generalized hypothermia (28° C) using a disposable bubble oxygenator (Polystan, Great Britain) with a prime volume of 2500 ml heparinized Ringer's solution. Perfusion flow was maintained above $2.2\ l \cdot m^{-2} \cdot min^{-1}$. Cardiac arrest was induced by a cardioplegic solution containing potassium, magnesium, and procaine.[24] A nitroglycerin infusion was used to control the mean arterial pressure.

TABLE 1. Schedule of Blood Sampling

Sample No.	Sampling Time
1	The day before operation
2	After insertion of arterial and venous catheters but before induction of anesthesia
3	10 min after tracheal intubation
4	10 min after sternotomy
5	Just before initiation of CPB
6a	10 min after beginning CPB
6b	40 min after beginning CPB
6c	70 min after beginning CPB, or 2 min after initiation of partial CPB
6d	100 min after beginning CPB, or 2 min after initiation of partial CPB
7	15 min after termination of CPB
8	During skin closure
9	First postoperative day
10	Third postoperative day
11	Sixth postoperative day

From each patient, 13 or 14 samples were taken dependent on the duration of CPB. CPB = cardiopulmonary bypass.

Postoperatively, controlled ventilation was continued for 5–10 h, and all patients remained in the intensive care unit for 2–3 days.

Considering the influence of catecholamines on the immune defense,[10,11] and the fact that administration of catecholamines would interfere with the catecholamine analyses, patients requiring inotropic agents at the termination of CPB or to support cardiac performance at any stage were excluded from the study.

Sampling of arterial blood for determination of NK cell activity, distribution of lymphocyte subpopulations, blood leucocyte counts, and lymphocyte blastogenesis to phytohemagglutinin (PHA), and for measurements of total serum cortisol, plasma epinephrine, and norepinephrine was done as shown in table 1. The total number of samples taken from each patient varied with the duration of CPB. All preoperative and postoperative samples were obtained between 9 and 11 A.M.

Natural Killer Cell Cytotoxicity Assay

Separation of mononuclear cells, cryopreservation, and determination of NK cell cytotoxicity were performed as described in detail previously.[3]

Briefly, mononuclear cells were isolated by Ficoll-Hypaque (Lymfoprep®, Nyegaard & Co., Oslo) gradient centrifugation. The cells were cryopreserved and stored in liquid nitrogen until all specimens from each patient could be tested at the same time against K 562 target cells in a 6-h ^{51}Cr-release assay. Lymphocyte viability tested by trypan blue exclusion exceeded 95% both before and after cryopreservation, and the recovery of cytotoxicity was about 85% when the specimens were kept at room temperature for 5–6 h before test-

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ing. All assays were performed in duplicate at effector-to-target cell ratios of 50:1, 25:1, and 12.5:1, with the results representing the first-mentioned ratio. NK cell activity was expressed as percentage cytotoxicity according to the expression:

$$\% \text{ cytotoxicity} = \frac{\text{cpm experimental release} - \text{cpm spontaneous release}}{\text{cpm maximum release} - \text{cpm spontaneous release}} \times 100,$$

where cpm is counts/min. Spontaneous release was the radioactivity released from target cells in the growth medium, and maximum release was the radioactivity released when the target cells were frozen and thawed three times in distilled water. The spontaneous release never exceeded 20% of the maximum release. The analytical "within" variation of the NK cytotoxicity assay was estimated by 20 simultaneous measurements of one specimen of mononuclear cells. The coefficient of variation (CV) was 5%. The interindividual and intraindividual variations were calculated from two consecutive "day-to-day" samples from 24 healthy volunteers. The interindividual CV was 58%, while the intraindividual CV was 13%.

Leucocyte and Differential Counts

The total peripheral blood leucocyte counts were made by Coulter Counter S (Coulter® Electronics, England), and the differential counts were performed using an automated differential cell counter (Model 360, Hematrach® Geometric Data, England).

Lymphocyte Subpopulations

For determination of lymphocyte subpopulations, the lymphocytes were thawed in a 37° C water bath, washed three times in TC-199 medium (Gibco, Bio-Cult, Glasgow, Scotland), and, finally, adjusted to 0.5×10^6 cells/test tube in 0.5 ml TC-199 medium. After centrifugation at 500 × g for 10 min, the supernatant was removed from the tubes.

The relative percentage of the lymphocyte subpopulations was then estimated by the use of the monoclonal antibodies OKT3, OKT4, OKT8 (Ortho-Mune®, Ortho Diagnostic Systems, Inc., New Jersey, U.S.A.), B1 (Coulter Clone®, Coulter Immunology, Florida, U.S.A.), and Leu 11 (Becton Dickinson®, Becton Dickinson Monoclonal Center, Inc., California, U.S.A.) reacting selectively with T cells, T-helper cells, T-suppressor cells, B cells, and NK cells, respectively.

One batch of lyophilized antibody was reconstituted in 1 ml of distilled water, diluted with RPMI-1640 medium (Gibco-Europe) to a ratio of 1:40, and supplemented with a suspension medium of 5% heat inactivated fetal calf serum. The lymphocytes were mixed with 100 μl of each preparation of monoclonal antibody and incubated for 45 min at 4° C. The cells were then washed twice in TC-199 medium supplemented with 2.5% heat inactivated human AB-serum and mixed with 100 μl of fluorescein-conjugated goat anti-mouse IgG antibody (GAM-FITC, Coulter® Immunology) diluted to a ratio of 1:40 in the above mentioned suspension medium and incubated for 45 min at 4° C. After two washings, the cells were fixed in 250 μl fixation medium containing 1.5% formaldehyde and 2.5% inactivated human AB-serum in TC-199 medium. After resuspension, 3 μl of each cell suspension were transferred to microtrays and finally covered with paraffin oil. Cells reacting with the different monoclonal antibodies were enumerated employing fluorescence microscopy. Slides were scored in a blinded fashion and duplicate enumerations averaged for each sample.

Mitogen-induced Lymphocyte Transformation

After thawing and washing, the cells were adjusted to 10^6 cells/ml in RPMI-1640 medium supplemented with Hepes, 25 μmol/ml; glutamine, 2 μmol/ml; penicillin, 100 μg/ml; streptomycin, 100 μg/ml; and 25% heat inactivated fetal calf serum. A sample of 100 μl of the cell suspension containing 10^5 cells was pipetted into the wells of sterile microtiter plates (Nunc InterMed, Roskilde, Denmark). To each culture, 50 μl of phytohemagglutinin mitogen (PHA) in two different concentrations were added, resulting in final PHA/suspension dilutions of 1:50 and 1:75. To the control cultures, 50 μl of culture medium were added instead of PHA.

All cultures, performed in triplicate, were incubated at 37° C in an atmosphere of 5% CO_2 in air for 4 days. Twenty-four hours before harvesting, 0.04 μCi of ^{14}C-thymidine (The Radiochemical Centre, Amersham, United Kingdom) in a volume of 20 μl isotonic saline was added to each well. The cultures were harvested with a multiple cell-culture harvester (Skatron, Liebyen, Norway), and the thymidine uptake was measured using an automated beta-scintillation counter (LKB, Wallac, Turku, Finland). The results were expressed as cpm in the stimulated cultures minus cpm in the corresponding unstimulated cultures. Median values of the triplicates were used for each culture.

Serum Cortisol, Plasma Epinephrine, and Norepinephrine

Serum cortisol concentrations were determined by a competitive protein binding technique.[25] The sensitiv-

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TABLE 2. Comparative Demographic and Clinical Data of Patient Groups

Group	Anesthesia	n	Sex (Female/male)	Age (Yr)	Weight (kg)	Duration of Anesthesia Before Surgery (Min)	Duration of Operation (Min)	Duration of Cardiopulmonary Bypass (Min)
I	Etomidate/high-dose fentanyl	10	2/8	52 (38-65)	75 (61-91)	28 (20-45)	240 (180-275)	103 (47-162)
II	Midazolam/low-dose fentanyl	10	3/7	58 (48-67)	71 (56-84)	28 (20-50)	259 (195-300)	117 (77-159)

Values are means with ranges indicated in parentheses. No significant differences between groups.

ity of the assay was 13 nmol/l. The intraassay and interassay coefficient of variation was 3.5% and 6.2%, respectively.

Plasma catecholamines were measured by a single isotope-derivate assay.[26] The sensitivity of the assay was 1 pg of epinephrine and 2 pg of norepinephrine. The coefficients of variation was 11% for epinephrine and 7% for norepinephrine.

STATISTICAL ANALYSIS

The GENSTAT system was used for the statistical analysis of the data on a digital computer. The subprogram used was a three-way analysis of variance (MANOVA) with the factors: patient, time, and treatment. Inspection of residuals suggested a logarithmic transformation for the variables: NK cell activity, lymphocyte count, serum cortisol, plasma epinephrine and norepinephrine, and the lymphocyte subpopulations. For the transformed variables, mean values and standard errors of the mean (SEM) were calculated. The antilogarithm was applied to the corresponding confidence limits to obtain the confidence limits in the untransformed scale. Values of $P \leq 0.05$ were considered to indicate statistical significance.

Results

Two patients, one from each group, requiring epinephrine infusion to support cardiac performance after CPB, were excluded from the study according to the protocol. The course of one of these patients has been described elsewhere.[27]

The remaining 20 patients were distributed with ten in each group, and there was no significant difference between groups with regard to demographic data, duration of anesthesia before surgery, duration of CPB, and duration of operation (table 2).

The changes in NK cell activity are shown in figure 1. No significant differences were found between the groups. Compared with control values, the activity increased significantly during premedication before induction of anesthesia. During anesthesia until initiation of CPB, the activity was decreased, followed by a gradual increase during CPB to about control levels but significantly higher than pre-bypass values. After termination of CPB and surgery, the activity declined and remained significantly reduced for at least 1 (group II) and 3 days (group I) postoperatively.

The percentage of segmented neutrophils and lymphocytes are presented in figure 2. The changes induced were almost identical whether the percentage or the absolute numbers were used, and there were no significant differences between the groups. Compared with control values, a significant leucocytosis with neutrophilia and lymphopenia was shown in the pre-bypass and postoperative period.

The distribution of lymphocyte subpopulations was determined on the day before surgery (−1), and on the first (1) and sixth (6) postoperative day. The percentages of the total number of lymphocytes reacting with the monoclonal antibodies characterizing the subsets are given in table 3, while figure 3 illustrates the calculated absolute numbers. The postoperative lympho-

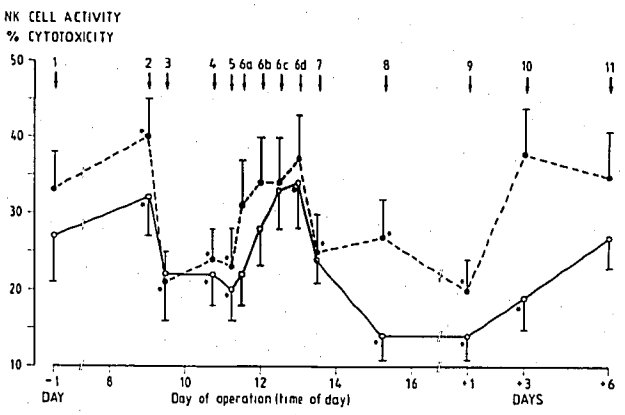

FIG. 1. Natural killer (NK) cell activity expressed as % cytotoxicity (mean ± SEM, n = 10) before, during, and after coronary artery bypass grafting in patients receiving etomidate-high dose fentanyl (○) or midazolam-low dose fentanyl (●). The shaded area represents the period of cardiopulmonary bypass. Arrows indicate time points of sampling. *Significant difference ($P \leq 0.05$) from preoperative value (sample 1, day −1).

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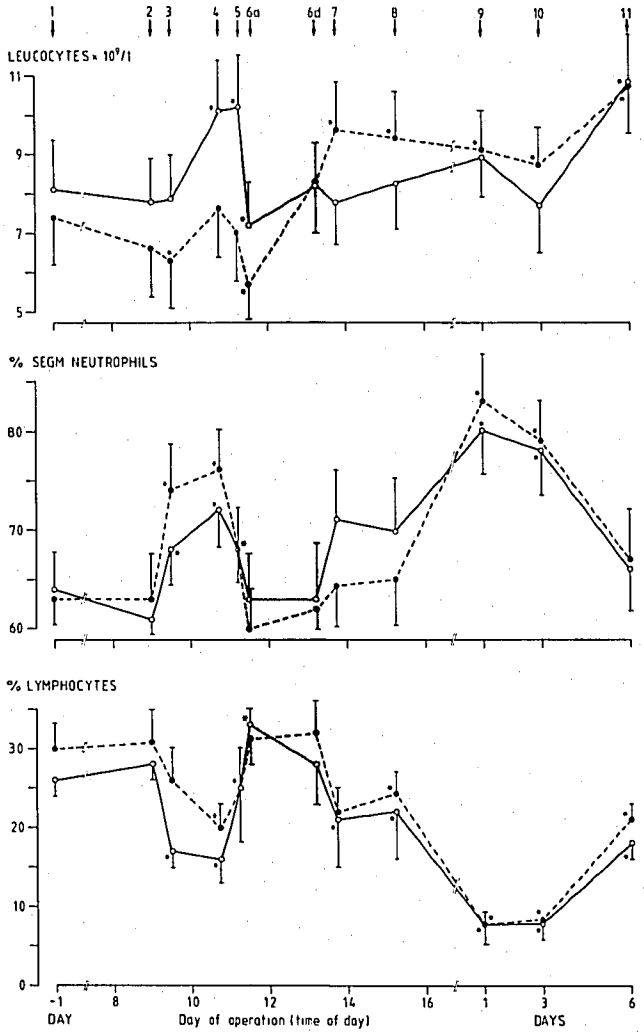

FIG. 2. Number of leucocytes and percentage of segmented neutrophils and lymphocytes in peripheral blood (mean ± SEM, n = 10) before, during, and after coronary artery bypass grafting in patients receiving etomidate-high dose fentanyl (O) or midazolam-low dose fentanyl (●). The shaded area represents the period of cardiopulmonary bypass. Arrows indicate time points of sampling. *Significant difference ($P \leq 0.05$) from preoperative value (sample 1, day −1).

penia was associated with a significant decrease in the number of all T-subsets and the NK cells, while the B lymphocytes remained unchanged. The response was identical for the two groups.

Compared with preoperative values the lymphocyte transformation to PHA stimulation was significantly depressed during CPB, and for at least 1 (group I) and 3 days (group II) postoperatively. There were no differences between the groups.

The changes in the plasma catecholamine and serum cortisol concentrations are shown in figure 4. Apart from a significant reduction of serum cortisol in the etomidate group from just before initiation of CPB until the first postoperative day, no differences could be demonstrated between groups. Serum cortisol was significantly decreased compared with control values until just before initiation of CPB. During CPB, a gradual rise and eventually a significant increase could be shown in group II. From the first postoperative day and throughout the study, serum cortisol remained significantly increased. A steep and significant rise in the plasma catecholamines during CPB, gradually returning to control values postoperatively, could be demonstrated.

Discussion

Both humoral and cellular factors may influence the NK cell activity during and after anesthesia and surgery.[2,8,28] The main purpose of the present study was to evaluate the interaction between NK cell activity, the endocrine stress response, the lymphocyte function, and the distribution of lymphocyte subpopulations presenting humoral and cellular aspects. There have been no previous studies of this interaction during cardiac surgery and CPB.

The influence of the integrated endocrine stress response on NK cell activity appears to be complex, and is not clarified in detail. However, there have been studies indicating that selective increases in epinephrine enhance NK cell activity,[10–12] while increases in cortisol suppress the activity *in vivo* and *in vitro*.[13]

The results of the present study are consistent with these findings.

Before induction of anesthesia, a slight but significant increase in plasma epinephrine and decrease in serum cortisol, with a concurrent increase in NK cell activity, was shown. Anxiety is accompanied by similar changes in the plasma epinephrine concentration, more pronounced in arterial than in venous blood.[29] The augmentation of NK cell activity at this point may thus be attributed to anxiety, even though all patients were heavily premedicated and appeared sedated and relaxed.

The marked increase of plasma catecholamines and the more gentle increase of serum cortisol in group II during CPB agree with other studies.[14–17] and represent a generalized stress response to CPB. In the etomidate-high dose fentanyl group (group I), the cortisol response was suppressed and delayed. This probably reflects the depth of high-dose fentanyl anesthesia which may affect the cortisol response to the stress of CPB,[14] or it may be caused by the well-recognized inhibitory effect of etomidate on the adrenocortical function.[30] However, the disparity in the cortisol levels did not influence the immune response, which was almost identical in the two groups. During CPB, the large increase in

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epinephrine levels seemed to overwhelm the relatively small increase in cortisol levels, thereby resulting in enhanced NK cell activity. In contrast, the lymphocyte function estimated by PHA-stimulation was suppressed during CPB, suggesting a selective effect of epinephrine on the NK cell system.

In the postoperative period, it appeared that the increase in cortisol levels superseded the fading catecholamine response, with a resulting decrease in NK cell activity. Concurrent with, and probably related to, the peak values of serum cortisol, the lymphocyte transformation to PHA was decreased on the first postoperative day. The postoperative decrease in NK cell activity is consistent with the findings after major surgery in previous studies.[3,5,7] Ryhänen *et al.* demonstrated impairment of the NK cell activity immediately after open heart surgery, but gave no indication of the relation to the endocrine stress response.[7]

The decline in the number of circulating NK cells estimated by the monoclonal antibody Leu 11 has not been demonstrated before. This depletion or redistribution of NK cells from the peripheral blood is probably a major contributing factor to the impaired postoperative NK cell activity. The changes in the number of circulating lymphocytes bear no direct relation to changes in NK cell activity or the lymphocyte response to PHA stimulation, since the respective assays are performed on a fixed number of mononuclear cells from peripheral blood.

CABG resulted in lymphopenia and an altered balance between the circulating lymphocyte subpopulations, with a reduction in the percentage, as well as the total number, of the T-cell and NK cell subsets on the first postoperative day. These findings are similar to another study using monoclonal antibodies to monitor lymphocyte subsets after upper urinary tract surgery.[31] In contrast, Hansbrough *et al.* did not find changes in the relative percentage of T-cells and B-cells after cholecystectomy, while the T-helper cell fraction decreased with a simultaneous increase of the T-suppressor cell fraction.[32] However, neither the type of anesthesia nor of the surgery are comparable in the existing studies, and this may explain the conflicting results.

It is well established that the combination of anesthesia and surgery is associated with a diminished immunocompetency and suppression of the cell-mediated and humoral immunity.[33-35] However, the contribution of the anesthetic agents used remains controversial. Both clinical and *in vitro* investigations have demonstrated that the effect of anesthesia *per se* on the NK cell system is limited to a reversible, short-term inhibition, which appears to be insignificant in relation to the postoperative changes in NK cell activity.[36,37] In the clinical circumstances of the present study, it was not possible to

TABLE 3. Distribution of Lymphocyte Subpopulations Before and After Coronary Artery Bypass Grafting

Group No. Anesthesia	T Lymphocytes (OKT3)			T-helper Cells (OKT4)			T-suppressor Cells (OKT8)			B Lymphocytes (B1)			NK Cells (Leu 11)		
	Sample No.			Sample No.			Sample No.			Sample No.			Sample No.		
	1	9	11	1	9	11	1	9	11	1	9	11	1	9	11
Group I: etomidate/ high-dose fentanyl	59.1 ± 3.4	39.9* ± 4.1	46.7* ± 2.7	43.0 ± 1.8	28.9* ± 2.9	39.1* ± 2.6	21.0 ± 2.3	22.8 ± 2.1	20.6 ± 1.7	8.9 ± 1.3	16.8* ± 2.4	10.9 ± 1.2	8.7 ± 1.4	12.1* ± 2.1	7.3 ± 0.7
Group II: midazolam/ low-dose fentanyl	54.9 ± 5.9	32.0* ± 3.0	47.9 ± 6.7	34.9 ± 3.2	23.5* ± 2.6	35.3 ± 4.7	19.1 ± 2.3	20.3 ± 2.7	20.7 ± 3.2	7.6 ± 1.8	12.7* ± 1.5	7.1 ± 1.0	7.9 ± 1.0	10.8* ± 2.1	7.4 ± 1.1

Values are percentage (mean ± SEM, n = 10) of the total lymphocyte population reacting with the monoclonal antibodies characterizing T lymphocytes (OKT3), T-helper cells (OKT 4), T-suppressor cells (OKT8), B lymphocytes (B1), and NK cells (Leu 11). Determinations were made on the day before operation (sample 1, day −1), on the first postoperative day (sample 9, day 1), and on the sixth postoperative day (sample 11, day 6).
* Significant difference ($P \leq 0.05$) from sample 1.

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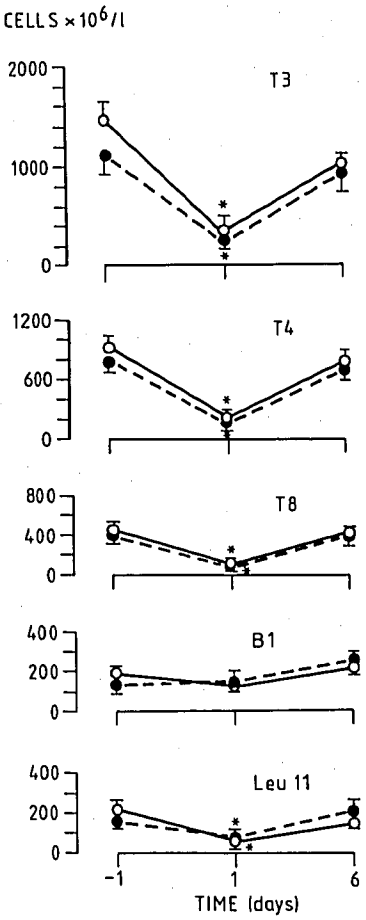

FIG. 3. Number of cells in peripheral blood (mean ± SEM, n = 10) reacting with the monoclonal antibodies characterizing T lymphocytes (OKT3), T-helper cells (OKT4), T-suppressor cells (OKT8), B lymphocytes (B1), and NK cells (Leu 11) before and after coronary artery bypass grafting in patients receiving etomidate-high dose fentanyl (O) or midazolam-low dose fentanyl (●). Measurements were performed on the day before operation (−1), and on the first (1) and sixth (6) postoperative day. *Significant difference ($P \leq 0.05$) from preoperative value (−1).

distinguish between the effects of anesthesia and surgery. In spite of the different endocrine response evoked by etomidate-fentanyl and midazolam-fentanyl anesthesia, the changes in immune function during anesthesia and surgery were identical indicating that the effects of anesthesia were insignificant. On the other hand, two very similar intravenous techniques were employed, and another design using more diverse anesthetics would possibly have yielded more specific differences.

The NK cell system has a key position in the defense against certain microbial infections and growth of tumor cells.[1,38] In the present investigation, no untoward clinical consequences attributable to the alterations in NK cell activity could be demonstrated. Whether the changes in NK cell function induced by anesthesia and surgery under certain circumstances increase the susceptibility to postoperative infection or contribute to the dissemination of solid tumors in patients undergoing cancer surgery remains to be settled.

In summary, we have shown that CABG and CPB induce changes in the NK cell activity. The findings suggest that the changes result from a complex interaction involving epinephrine and cortisol, and probably other variables. Further investigations are necessary to clarify the underlying mechanisms in detail, to determine the clinical implications, and to ascertain whether a further suppression of the endocrine stress response to CABG and CPB could modify the alterations in immune surveillance.

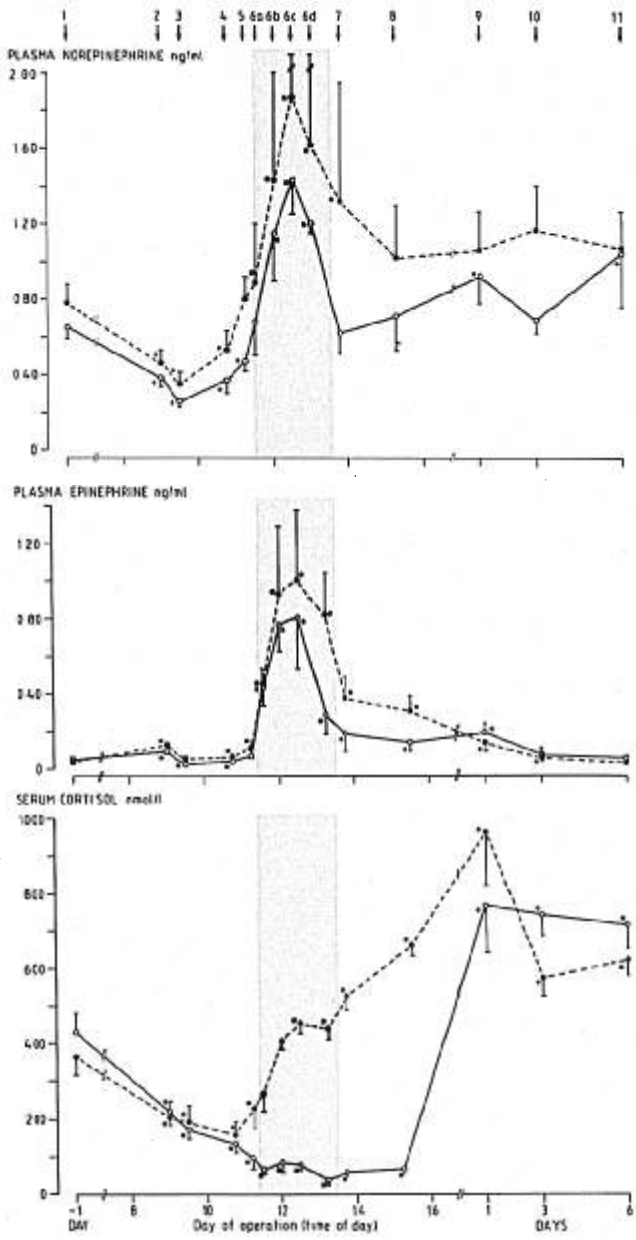

FIG. 4. Concentration of norepinephrine and epinephrine in plasma and cortisol in serum (mean ± SEM, n = 10) before, during, and after coronary artery bypass grafting in patients receiving etomidate-high dose fentanyl (O) or midazolam-low dose fentanyl (●). The shaded area represents the period of cardiopulmonary bypass. Arrows indicate time points of sampling. *Significant difference ($P \leq 0.05$) from preoperative value (sample 1, day −1).

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