Published in final edited form as:

Eur J Cardiovasc Nurs. 2008 March ; 7(1): 52–58.

Relation of Depression, Natural Killer Cell Function, and Infections after Coronary Artery Bypass in Women

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Abstract

Background—After hospital discharge for coronary artery bypass grafting (CABG), infection is a common cause of morbidity. Although depression has been associated with immune dysfunction, its role in post-CABG infection is unknown.

Aims—The purpose of this study was to: 1) compare natural killer cell cytotoxicity (NKCC) and post-hospitalization infections in depressed and non-depressed women after CABG; and 2) test whether NKCC mediated the relationship between post-discharge depression and infections.

Methods—Sixty-seven women recovering from CABG were assessed for depression prior to hospital discharge and followed for six months. Major depression was identified by a structured clinical interview. Infections were identified by patient report using the Modified Health Review and by medical chart audit.

Results—Compared to non-depressed women after CABG, women with major depression had reduced NKCC, more all-cause infections, and more self-reported illnesses. Although NKCC did not mediate the relationship between depression and wound (i.e. incisional) infections after CABG, it did mediate the relationship between depression and non-wound infections, including pneumonias and upper respiratory infections.

Conclusions—For the first six months after CABG, women with major depression are at increased risk for infections. Natural killer cell cytotoxicity may be related to this phenomenon, particularly to non-wound infections.

Keywords

depression; coronary artery bypass; infection; women

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In cardiac patients, depression is common and dangerous. (1,2) Those undergoing coronary artery bypass grafting (CABG) are particularly susceptible, with depressive symptoms reported commonly both before and after surgery. (3-6) Reports of clinical depression are rare, with postoperative major depression (MD) reported in 17% to 20% of CABG patients and minor depression in an additional 27%. (7,8) In contrast, the 12-month prevalence of MD in community samples is from 5.5% to 10.8%. (9,10) With approximately 306,000 patients undergoing CABG annually in the United States, (11) we can expect approximately 61,000 to suffer MD and an additional 82,000 to experience minor depression annually. Depression-related mortality and morbidity after CABG are high, with increased cardiac events, postoperative complications, and costs reported in depressed versus non-depressed patients. (7,12-14)

Although a causative link between depression and morbidity has proved elusive, immune dysfunction has been implicated. It is established that natural killer cell cytotoxicity (NKCC) is diminished in MD. (15,16) Natural killer (NK) cells, first-responders in innate immunity, are active against viral infections and play a role in acquired immunity by stimulating T-cell activation. (17) Despite the early role of NK cells in immune responses to infection, clinical outcomes of diminished NKCC in MD have not been explored.

A significant source of morbidity after CABG is infection, which occurs in up to 27% of patients, is most common after hospital discharge, and is a leading cause of rehospitalization and mortality. (18-20) Although there are no reports linking clinical depression directly to infection after CABG, such an association is likely. Natural killer cells constitute a first line defense against pathogens. In vulnerable hosts, such as CABG patients, who are frequently elderly and stressed by surgery, impaired NKCC may provide an early “window of opportunity” for colonized pathogens to invade and disrupt tissues. However, the role of NKCC in post-hospitalization infectious illnesses has not been investigated in CABG patients.

In women after CABG, depression is prevalent and is associated with poorer outcomes. Thus, the objective of this study was to investigate the relationship of depression, NKCC, and clinical outcomes in women after CABG. The specific aims of this study were to 1) compare NKCC and documented post-hospitalization infections in depressed and non-depressed women after CABG; and 2) test whether NKCC mediated the relationship between clinical depression at hospital discharge and infections during the first six post-hospitalization months.

METHODS

Design

A longitudinal design was used, in which post-CABG women with major and minor depression were compared to those without depression from hospital discharge to six months after discharge.

Sample and Setting

Women were recruited from two tertiary care centers in a major metropolitan area. Following approval by institutional review boards, women were invited to participate if they were ≤ 75 years old, having first-time CABG, English-speaking, available for follow-up, and without documented perioperative infection, malignancy or autoimmune disease. One hundred seventeen women met initial eligibility requirements and 75 agreed to participate. Only those who completed follow-up measures, including six months of monitoring, ($n = 67$) were included in this report. There were no demographic or clinical differences between patients who completed the study and those who dropped out ($p > .05$).

Procedures

This investigation conforms with the principles outlined in the Declaration of Helsinki.(21) Prior to hospital discharge, informed consent was obtained and a research nurse administered the Mini Mental Status Exam (MMSE). After confirming a MMSE score ≥ 24 , consistent with a lack of cognitive impairment (22,23), the interviewer administered the Diagnostic Interview and Structured Hamilton (DISH) and a demographics form, obtained a blood specimen and conducted a chart audit. For those women not depressed at hospital discharge, a second DISH interview was scheduled 2 to 4 weeks later. All patients received monthly telephone calls from a single research assistant blinded to depression status who administered the Modified Health Review (MHR). Hospital and clinic records were reviewed by blinded research assistants to identify complications, documented infectious illnesses, and the number and type of health care contacts. Based on the guidelines used by the Society of Thoracic Surgery, wound (i.e. incisional) infections were identified as present if any of three criteria were met: 1) incision and drainage required; 2) positive culture consistent with clinical findings; 3) treatment with antibiotics required.(24) Other infections were identified as present if there was a confirmatory diagnosis and if active treatment (i.e., antibiotic therapy) was documented.

Instruments

DISH—The DISH is a semistructured interview for diagnosing depression in medically ill patients.(25) Embedded in the DISH is the 17-item Hamilton Depression Rating Scale (HDRS), in which the interviewer rates subjects' symptoms. Scores range from 0 to 52, with higher scores indicating greater severity. In validation studies, the DISH and the Structured Clinical Interview for DSM-IV resulted in 88% agreement ($K = .86$).(25) Interrater reliability testing yielded 93% agreement between DISH and clinician diagnosis and diagnostic agreement across symptom clusters ($K = .75$).(25,26) In the current study, interrater reliability between interviewers was 90%.

MHR—The MHR is a structured interview for periodic assessment of infectious illness (27-29). The MHR determines the number of illnesses incurred and includes only symptoms likely to indicate an infectious etiology.(28) Each symptom is weighted according to its probability for indicating infection. Symptom scores are totaled for each illness and those with scores ≥ 3 are counted as infectious. (28) The MHR was selected because it has proven reliability and validity in measuring bacterial and viral infections likely to be associated with NKCC dysfunction and to occur during CABG recovery. The MHR compared favorably with physician diagnosis (Cohen's kappa of .77).(28) For interrater and test-retest reliability, Cohen's kappa of .87 and .76 respectively have been reported.(28) In the current study, Cronbach's alpha was 0.69. To aid patient recall, data were collected monthly and summed to achieve 3-month and 6-month totals.

Flow cytometry—The numbers of lymphocytes were determined by flow cytometry on whole blood samples. Cells were stained with fluorochrome-conjugated antibodies (PD Biosciences, San Jose, CA) to detect surface markers for all T cells (CD3), T-helper cells (CD4), cytotoxic T cells (CD8), and NK cells (CD56 and CD16) and quantitated in a FACSCAN (Becton-Dickinson Immunocytometry Systems, San Jose, California).

⁵¹Cr-release assay—Blood specimens were obtained in the early morning and delivered to the lab within two hours for immediate processing. Assays were performed according to standard protocols.(30) Briefly, specimens were fractionated on Ficoll-Hypaque, and the buffy layer was harvested, washed and resuspended in RPMI 1640 supplanted with 10% fetal calf serum. Nonadherent lymphocytes were obtained by sequential incubation on plastic tissue culture dishes followed by incubation on nylon wool column at 37° C for one hour. Nylon wool column-eluted lymphocytes were washed with medium three times and gradually diluted to a

concentration of 1×10^7 cells/ml in phosphate-buffered saline. Nonadherent lymphocytes were washed in phosphate-buffered saline and used immediately. Standard effector-to-target cell ratios (12.5:1, 25:1, 50:1) of nonadherent lymphocytes were incubated with ^{51}Cr -labeled K562 target cells (American Type Culture Collection, Manassas, VA) for four hours. Supernatants were harvested; radioactivity was determined by a gamma-counter. The percentage of ^{51}Cr released at each effector-to target cell ratio was calculated to give percent specific cytotoxicity, calculated as:

$$\% \text{ cytotoxicity} = \frac{\text{experimental cpm} - \text{spontaneous cpm}}{\text{total cpm} - \text{spontaneous cpm}} \times 100$$

where experimental cpm (counts per minute) = target cell counts released after incubation with effector cells, spontaneous cpm = target cell counts of cells incubated in medium alone, and total cpm = experimental cpm + spontaneous cpm.

Analysis

Measures of central tendency were used to describe the sample. Group comparisons between depressed and on non-depressed women were conducted using analysis of variance. For comparisons of immune variables, the time from surgery to blood sampling (in days) was used as a covariate to control for effects of surgery. Because wound and non-wound infection are likely to vary in etiology, we evaluated the relationships of depression and NKCC to all-cause infection, wound infections only, and other non-wound infections. Bivariate correlations were measured for NKCC with depression status (major, minor, none) and HDRS scores. To test whether NKCC mediated the relationship of MD to infections documented by chart audit, linear regressions were performed as recommended by Baron & Kenny (31) and Bennett. (32) To summarize, for each type of infection (all, wound, other), 3 separate regressions were performed to test whether: 1) presence of MD was associated with NKCC; 2) presence of MD was associated with infections; and 3) NKCC was (a) associated with infections and (b) its presence in the equation reduced the significance of the relationship between MD and infections.

RESULTS

Demographic and clinical characteristics are summarized in Table 1. Clinical events occurring during hospitalization are presented in Table 2. Within the first month after CABG, 28 (41.8%) women had clinical depression; 15 had MD, while 13 had minor depression. Three women, all with past histories of depression, were on antidepressants preoperatively. Of those, two were not depressed after CABG and one had minor depression. Women with minor depression were younger than non-depressed women; those with MD were more likely to have a history of depression than non-depressed women (Table 1). Compared to non-depressed women, those with MD had more febrile episodes during hospitalization (Table 2). There were no differences in clinical treatments at 6 months (Table 3).

There were no group differences in white blood cell counts or in the percentage of total lymphocytes or CD56 cells. However, with a 50:1 effector-to-target ratio, NKCC differed between groups, with lower levels found among women with MD compared to non-depressed women (Figure 1). Similarly, women with MD differed from non-depressed women in the number of self-reported illnesses and in the number of illnesses that limited normal activities. Nineteen documented infections occurred in 17 (25.4%) patients. Pneumonias and upper respiratory infections were the most prevalent, accounting for 10 (52.6%) infections. Of these cases, three (30%) required hospitalization. Most of the remaining infections involved leg and sternal incisions (36.8% and 5.3%, respectively). Compared to patients with MD, those without

depression and those with minor depression experienced fewer non-wound and all-cause infections (Figure 3).

Bivariate relationships between NKCC and depression status yielded a significant correlation only for presence of MD ($r = .353$, $p = .032$). There were no relationships of NKCC to depressive symptoms (HDRS scores) or to minor depression. However, NKCC was related to all-cause infections ($r = -.355$, $p = .016$) and to non-wound infections ($r = -.334$, $p = .023$). The evaluation of relationships among MD, NKCC (target:effector ratio of 50:1), and documented infections showed that NKCC mediated the relationship of MD and non-wound infections (Figure 3). Specifically, three separate linear regressions showed that 1) MD was a significant predictor of NKCC (adjusted $R^2 = 0.10$, $p = .032$); 2) MD was a significant predictor of non-wound infections (adjusted $R^2 = 0.144$, $p = .005$); and 3) when considered together, (a) both NKCC (adjusted $R^2 = 0.178$, $p = .038$) and MD (adjusted $R^2 = 0.072$, $p = .047$) contributed significantly to changes in the number of documented non-wound infections, and (b) the significance of MD was lower, with a change in percent variance explained from 14.4% to 7.2%, when it was considered together with NKCC than when it was considered alone. When age, presence of diabetes, and antidepressant use (all of which may affect immune response) were included in the regressions, the relationships remained unchanged. For wound and all-cause infections, the same relationships were not evident.

DISCUSSION

The findings of this study add to the body of knowledge regarding depression after CABG in two ways. First, they document that MD is associated with increased non-cardiac illnesses, specifically pneumonias and upper respiratory infections, among women after CABG. Second, the current findings link both MD and downregulation of immune function, specifically NKCC, to these illnesses.

The relationship of clinical depression to increased mortality and morbidity in cardiac patients has been widely reported. (33) There have been numerous reports of both increased all-cause and cardiac mortality related to post-CABG depression. (7,34-36) Depression has been reported as an independent predictor of post-CABG cardiac morbidity, including such events as new myocardial infarctions, cardiogenic shock, pulmonary edema, and unstable angina. (7,36-38) The current study contributes to existing data in that the sample was exclusively female and focused on infectious illness after CABG. Previous findings have been based on samples including a majority of men. In one previous study, in which the sample was 33% female, both female sex and MD were independently related to adverse cardiac events after CABG, although no interaction between sex and depression was reported. (7) In a secondary analysis of the same study, investigators reported that non-cardiac events after CABG were unrelated to MD. (7) Thus, the current study is among the first to report a positive relationship of MD to increased non-cardiac illnesses after CABG. In the current study, women with MD experienced more total self-reported non-cardiac illnesses than non-depressed women. These illnesses were consistent with infections, such as upper respiratory and urinary tract infections, colds and flu. Depressed women recovering from CABG perceived these illnesses to be more functionally limiting than did their non-depressed counterparts. In addition, compared to non-depressed women, those with MD experienced more documented non-wound infections, emergency room visits, and routine primary care visits.

Other investigators have speculated that depressed post-CABG patients experience increased cardiac events because they are less likely to follow medical advice or engage in positive self-care behaviors. (39) It is also possible that depressed patients may report minor illnesses more often than non-depressed patients. A recent study found support for this possibility, in that

depressed patients had 2.1 times the number of doctor visits compared to controls, and depression was related to illness expression and the appraisal of illness consequences.(40)

Although not previously documented in post-CABG patients, the finding that NKCC mediated the relationship of MD to pneumonias and upper respiratory infections is consistent with what is known about the role of NK cells in pathogen surveillance. We were not able to ascertain the etiology of the infections in our study. However, many community-acquired upper respiratory infections are of viral origin. (41) Thus, it is logical that a NKCC dysfunction would provide fertile ground for these types of infections. The finding is also consistent with recent reports that cardiac patients who scored highest on a self-report depression measure exhibited high rates of seropositivity to three common latent viruses; those patients with the most severe symptoms were most likely to be seropositive to all three pathogens.(42)

While reduced NKCC has been reported in otherwise healthy depressed individuals, its effect on health outcomes has not been extensively reported. In a single study of community-dwelling caregivers of Alzheimer Disease sufferers, depressed caregivers experienced more days of infectious illness than non-depressed caregivers.(27) The current finding that NKCC mediated the relationship between MD and non-wound infections in CABG patients provides initial evidence that depression-related reductions in NKCC have clinical significance medically ill individuals and underscores the need to identify and treat depression in the medically ill.

The correlational design of this study precludes any causal inferences regarding the relationships we found. However, we have demonstrated a unique pattern of association consistent with a mediational role of NKCC in the relationship of MD to post-CABG infection. A possible explanation is that severe depression acts as a form of chronic stress, which is believed to play a role in decreased immune responses.(43) Researchers hypothesize that chronic stress is associated with hypothalamic-pituitary-adrenal axis hyperactivity and subsequent desensitization of glucocorticoid receptors on macrophages and lymphocytes, via increased activity of inflammatory prostaglandin pathways.(44) These changes lead to decreased cell-mediated immune responses by reducing the expression of transferrin receptors on lymphocytes, including NK cells. Alternatively, it is possible that post-CABG infection leads to increased levels of inflammatory mediators, which contribute to depression, with NKCC dysfunction being a downstream side effect. The fact that both the depression and NKCC dysfunction we observed preceded temporally the reported infections supports the former, rather than the latter, hypothesis. Further study is needed to explain these relationships.

Our study has both strengths and weaknesses. A major strength of the study was the use of a diagnostic interview to establish depression. Because the sample was small, we were not able to evaluate the role of other potentially mediating variables, such as cortisol or norepinephrine. The small sample may have limited our ability to find a mediating relationship of NKCC to minor depression and some types of infections. Also, since we studied only women who underwent CABG, our findings are not generalizable to men. Because we used self-reports of infectious illness episodes, there may have been a report bias favoring over-reporting of symptoms. Conversely, since we used chart reviews to identify post-hospitalization illnesses, the number of health care provider identified illnesses may have been underreported.

As other investigators have noted, depression is often considered to be a normal reaction to the severe circumstances frequently accompanying CABG surgery. Thus, it may be untreated.(7) Together with data from other studies, the current findings underscore the importance of identifying and treating post-CABG depression, particularly in women. The current study also highlights the prevalence of infectious illness in women after CABG. While these illnesses may be transient, they are significant to patients, who report impaired functional. Finally, the current study extends previous findings by identifying biological pathways, i.e. reduced

NKCC, by which MD is related to post-operative illnesses, particularly those of non-cardiac origin.

Acknowledgements

Supported by NIMH 5 K01 MH01700

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Figure 1.
Natural Killer Cell Cytotoxicity across Groups. White = Not Depressed; Striped = Minor Depression; Black = Major Depression. Major Depression vs. Not Depressed: * $p < .05$

Figure 2.

Clinical Outcomes across Groups. White = Not Depressed; Striped = Minor Depression; Black = Major Depression. Major Depression vs. Not Depressed: * $p < .05$; ** $p < .005$

Figure 3.

Infections across Groups. White = Not Depressed; Striped = Minor Depression; Black = Major Depression. Major Depression vs. Not Depressed: * $p < .05$; ** $p < .005$

Figure 4.
Mediator Effect of Natural Killer Cell Cytotoxicity on Relationship of Depression Status and Non-Wound Infections.

Table 1
Comparison of Demographic and Clinical Characteristics

	Not Depressed (n = 39)	Minor Depression (n = 15)	Major Depression (n = 13)	P*
	M ± SD	M ± SD	M ± SD	
Age (years)	64.3 ± 10.3	54.5 ± 18.2**	60.7 ± 8.5	0.04
Body mass index	31.5 ± 7.0	29.5 ± 7.2	30.9 ± 4.6	0.60
Ejection fraction (%)	60.8 ± 19.8	51.5 ± 15.8	58.6 ± 12.3	0.36
Cardiopulmonary bypass time (minutes)	71.3 ± 38.7	81.4 ± 56.9	69.6 ± 45.1	0.74
Bypass grafts	2.7 ± 0.8	2.5 ± 1.0	2.5 ± 1.0	0.55
Hospital days	6.9 ± 4.6	6.9 ± 3.4	8.3 ± 4.9	0.59
	N (%)	N (%)	N (%)	
≤ High School education	15 (38.5)	8 (53.3)	8 (61.5)	0.29
Married	19 (48.5)	9 (73.7)	6 (46.2)	0.22
Ethnicity:				0.73
Caucasian	22 (56.4)	9 (60.0)	7 (53.8)	
African American	9 (23.1)	2 (13.3)	1 (7.7)	
Latina	6 (15.4)	4 (26.7)	3 (23.1)	
Other	2 (5.2)	0	2 (14.4)	
Preoperative risk category:				0.31
Good	3 (7.7)	4 (26.7)	1 (7.7)	
Fair/poor	27 (69.2)	9 (60.0)	10 (76.9)	
High/Extremely high	9 (23.1)	2 (13.4)	2 (14.4)	
Diabetic	21 (53.8)	9 (60.0)	8 (61.5)	0.85
Current Smoker	3 (8.1)	3 (20.0)	2 (18.4)	0.46
History of depression	6 (15.4)	5 (33.3)	7 (53.8) [§]	0.02
On antidepressants	2 (5.7)	1 (6.7)	0 (0.0)	0.65

* Among all three groups

** Compared to Not Depressed, p = .01

[§] Compared to Not Depressed, p = .002

Table 2
Group Comparisons of In-Hospital Complications

	Not Depressed (n = 39) M ± SD	Minor Depression (n = 15) M ± SD	Major Depression (n = 13) M ± SD	P*
Total complications	1.3 ± 1.4	1.5 ± 1.5	2.2 ± 1.7	0.17
Total infections	0.03 ± 0.17	0.17 ± 0.58	0.62 ± 0.96	0.12
	N (%)	N (%)	N (%)	
Perioperative MI	10 (25.6)	3 (20.0)	4 (30.8)	0.80
Respiratory insufficiency	3 (7.7)	1 (6.7)	2 (15.4)	0.67
Postoperative fever	1 (2.6)	1 (6.7)	4 (30.8)**	0.009
Septicemia	1 (2.6)	1 (6.7)	1 (7.7)	0.68
Urinary tract infection	3 (7.7)	0	2 (15.4)	0.31
Sternal infection	0	0	1 (7.7)	0.21

* Among all three groups

** Compared to Not Depressed, p < .005

Table 3**Group Comparison of Clinical Therapies at 6 Months**

	Not Depressed (n = 39) N (%)	Minor Depression (n = 15) N (%)	Major Depression (n = 13) N (%)	P*
On antidepressants	4 (10.3)	1 (6.7)	2 (15.4)	0.75
On aspirin	22 (56.4)	9 (60)	6 (46.2)	0.74
On beta-blockers	21 (53.8)	8 (53.3)	7 (53.8)	0.99
On hormone replacement therapy	4 (10.5)	4 (26.)	3 (23.1)	0.29
On statins	23 (59.0)	11 (73.3)	8 (19.4)	0.62
Attended cardiac rehabilitation	8 (21.0)	2 (13.3)	2 (15.4)	0.77