

Cardiovascular Reactivity and the Course of Immune Response to an Acute Psychological Stressor

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This study evaluated the temporal nature of cellular immune responses, as well as the effects of cardiovascular reactivity on immune responses after exposure to an acute psychological stressor. Lymphocyte subsets and lymphocyte proliferative response to phytohemagglutinin were assessed at baseline and at 5 and 21 minutes after stressor onset in the experimental group and at the same time points in a nonstressor control group. By 5 minutes after stressor onset, the number of CD8 suppressor/cytotoxic T and CD16/56 natural killer cells increased and proliferative response to phytohemagglutinin decreased. These changes were maintained at 21 minutes. Those subjects showing the greatest cardiovascular reactivity had the largest immune alterations. These data did not indicate that gender significantly moderated immune responses. Results are consistent with the hypothesis that sympathetic activation mediates stressor-induced quantitative alterations of peripheral blood lymphocyte subpopulations and nonspecific mitogen stimulated proliferation.

Key words: cardiovascular reactivity; gender; acute psychological stressor; cellular immune response.

INTRODUCTION

It is well documented that lymphocyte numbers and functions are influenced by acute laboratory stressors (1-6). Typical immune alterations include decreased proliferative responses to mitogens and increased numbers of circulating natural killer (NK) and CD8 suppressor/cytotoxic T cells (7). Some data suggest that these immune changes are mediated by sympathetic nervous system activation after stressor exposure (4, 6). A sympathetic mediation explanation, however, would be bolstered if data showed that immune alterations occurred very rapidly after stressor onset and that they occur predominantly in individuals who show the greatest reactivity to the stressor.

With regard to the speed of immune response, there is evidence that changes in numbers of specific lymphocyte subsets in circulation appear as early as 8 minutes after stressor onset (3) and that functional changes occur by 12 minutes (5). Because these changes occur so rapidly, there is a low probability that they are driven by activation of the hypothalamic-pituitary-adrenal axis. It takes approximately

30 minutes from stressor onset for cortisol to reach its peak levels (8), so increases in cortisol do not adequately explain immune changes in response to laboratory stressors lasting 12 or 20 minutes. In fact, evidence shows immune alterations in the absence of changes in serum cortisol (3-4). Moreover, where changes in serum cortisol are detected, they are unrelated to immune changes (6).

The sympathetic nervous system [SNS], on the other hand, is activated immediately when exposed to a stressor and is associated with release of norepinephrine and epinephrine. Infusion of epinephrine has been shown to produce rapid changes in lymphocyte proliferation and circulating lymphocyte subsets (9-10). Thus, if SNS activation mediates the rapid immune changes observed in laboratory stress studies, data should show that immune alterations occur earlier than previous reports suggest. Therefore, we examined quantitative and functional immune changes 5 and 21 minutes after stressor onset. We expected that by 5 minutes, subjects exposed to an acute stressor would show decreased proliferative responses to mitogen as well as increased numbers of NK and CD8 cells in circulation.

Although the SNS responds very quickly to a stressor, sympathetic responsivity to stressors varies widely among individuals (11-12). Thus, investigators have examined relations between sympathetic and immune responses to stress. For example, Manuck et al. (4) found that proliferative response decreased and the number of CD8 cells increased after exposure to an acute stressor but only in individuals who also showed heightened SNS activation in response to the stressor. Others have examined rela-

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tions between cardiovascular reactivity and immune changes and have demonstrated that high cardiovascular reactors show greater decreases in proliferative response than low reactors (6). In this study, we also examined reactivity differences, and we expected that high cardiovascular reactors would show greater immune alteration than low reactors by 5 minutes after stressor onset.

Finally, we explored gender differences in immune response after exposure to an acute stressor. A substantial amount of literature describes gender differences in responses indicative of SNS activation to acute behavioral and psychological stressors (13–15). When exposed to acute stressors, men exhibit greater increases in systolic blood pressure and urinary epinephrine excretion than women, whereas women exhibit greater increases in heart rate than men (15–18). Because SNS activation is hypothesized to mediate immune responses after acute stressors, one might also expect gender differences in the immune responses themselves. No studies have asked this question, so we explored gender differences in cellular immune response to an acute psychological stressor. Because data collected in studies with rigorous within subjects designs show that menstrual cycle phase does not affect cardiovascular responses to acute stressors (19–24), we addressed this question without regard to cycle stage.

METHODS

Subjects

Forty-one subjects (22 men and 19 women) aged 18 to 29 years (mean = 22.3, SD = 2.5) participated in this study. Subjects were recruited through newspaper and electronic bulletin board advertisements asking for volunteers for a study assessing the effects of stress on cardiovascular health and on the immune system. Eligibility for participation was determined by a standard telephone screening procedure. Volunteers who reported chronic (e.g., diabetes, high blood pressure (BP)) or current acute (e.g., upper respiratory infection) health problems or a history of psychiatric problems (e.g., depression, anxiety) were excluded from the study. Subjects were nonsmokers and denied use of illicit drugs and prescription or nonprescription medications, with the exception of nine women (five experimental, four control) who reported use of oral contraceptives (OCs). All subjects provided informed consent and were paid \$40 for their participation.

Procedures

Subjects were randomly assigned to either a stress (10 men and 10 women) or control (12 men and 9 women) condition. In the stress condition, blood was drawn before, during, and immediately after termination of an acute laboratory stressor. BP and heart rate (HR) were assessed during the baseline and task pe-

riods. The same measurements were obtained in the control condition, although these subjects rested during the time that experimental subjects were exposed to the stressor. Subjects fasted for 12 hours before attending the laboratory sessions that started at either 8 or 10 a.m. Equal numbers of stress and control subjects were run at each time point.

On arrival at the laboratory, subjects were taken to a temperature-controlled chamber. An occluding cuff was placed on the subject's dominant arm and connected to a vital signs monitor (Critikon Dinamap 8100, Critikon Inc., Tampa, FL) for automated measurement of systolic and diastolic BP (in mm Hg). HR was recorded via an electrocardiogram. A nurse inserted a 20-gauge intravenous catheter into the antecubital vein of the nondominant arm, and connected it to an exfusion pump via a short length of sterile heparinized tubing. A 30-minute rest period followed insertion of the catheter, at the end of which 25 ml of blood was drawn. During the last 6 minutes of the rest period, BP was recorded four times (every 90 seconds), and HR was recorded over 12 30-second intervals. These measures were averaged to reflect resting baseline conditions.

At this point, control subjects were instructed to continue to sit quietly for 21 minutes while the experimental group performed a 21-minute computerized version of the Stroop Color-Word Interference Test (25–26). Subjects indicated their responses by pressing one of four microswitches on a keypad under pressure of time and against a distractor (random color names generated by computerized voice synthesis). To enhance task participation, subjects were offered a monetary incentive based on their level of performance. In addition, halfway through the task (10.5 minutes) the experimenter said via an intercom: "I'm interrupting you because you're halfway through your time on this task and have made only \$4.25. The average subject earns between \$13 and \$15, so you're running below average. It looks as though you could really increase your performance by speeding up a little." During task performance BP was recorded 14 times (every 90 seconds) and HR was recorded over 42 30-second intervals. Task HR and BP measures were averaged to yield a single task mean.

Immune Measures

Blood for immune assessment was drawn three times: at the end of baseline, 5 minutes, and 21 minutes. Immune assays included lymphocyte proliferative response to phytohemagglutinin (PHA) and the numbers of specific lymphocyte subsets circulating in peripheral blood.

Mitogen stimulation A whole blood assay was conducted to establish a dose response curve for PHA at final concentrations of 0.5, 2.5, 5.0, and 10.0 $\mu\text{g/ml}$. Blood was diluted 1:10 with RPMI-1640 tissue culture medium, supplemented with 10 mM hepes, 2 mM glutamine, and 50 μg gentamicin per ml. One hundred- μl of diluted whole blood was added to a 96-well, flat-bottomed culture plate containing 100 μl of PHA solution prepared in RPMI in one of the four final concentrations. Background proliferation was measured by incubating cells in RPMI only. Each assay was performed in quadruplicate. Plates were incubated for 120 hours at 37°C in air and 5% CO_2 . Eighteen hours before the end of incubation, the wells were pulsed with 1 μCi tritiated thymidine and harvested for counting. The difference in counts per minute between stimulated and unstimulated samples was determined separately for each concentration. Difference scores are used in the analyses.

Lymphocyte subsets Circulating populations of T cell subsets, B cells, and NK cells were assessed in whole blood using dual

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TABLE 1. Stressor Exposure, Cell Numbers, and Proliferative Responses

| | Baseline | | 5 Minutes | | 21 Minutes | |
|-------------------------|----------|-------|-----------|-------|------------|-------|
| | × | SD | × | SD | × | SD |
| Cell numbers | | | | | | |
| CD4 cells | | | | | | |
| Stress | 917 | (412) | 922 | (390) | 919 | (546) |
| Control | 784 | (238) | 793 | (238) | 759 | (214) |
| CD8 cells | | | | | | |
| Stress | 590 | (247) | 681 | (268) | 703 | (411) |
| Control | 482 | (175) | 493 | (173) | 474 | (152) |
| CD16/56 cells | | | | | | |
| Stress | 173 | (96) | 268 | (148) | 288 | (125) |
| Control | 126 | (45) | 137 | (54) | 139 | (50) |
| CD19 cells | | | | | | |
| Stress | 292 | (120) | 298 | (130) | 278 | (131) |
| Control | 223 | (76) | 223 | (82) | 211 | (72) |
| Proliferative response* | | | | | | |
| Stress | 924 | (299) | 801 | (253) | 830 | (305) |
| Control | 1009 | (233) | 974 | (217) | 1074 | (268) |

* Optimal concentration × 1000.

color fluorescence analysis with a FACSCAN flow cytometer. Lymphocyte subsets were analyzed using monoclonal antibodies labeled with either fluorescein (FITC) or phycoerythrin (PE) to quantify CD4⁺ (helper T), CD8⁺ (suppressor/cytotoxic T), CD3⁺CD19⁺ (B), and CD3⁺CD16⁺56⁺ (NK) cells. Isotype controls labeled with FITC or PE were used to assess nonspecific binding. Absolute number of cells was calculated from the complete blood count.

RESULTS

Experimental vs. Control Subjects

Baseline comparability. A series of 2 (Group: stress, control) × 2 (Gender: male, female) ANOVAs investigated potential group or gender differences on baseline cardiovascular and immune measures. Results showed only one group difference; the stress group had a somewhat higher number of CD19 B cells in circulation than the control group (292 vs. 223 cells/mm³; $F(1, 36) = 4.62, p < .05$). Gender differences consistent with other literature were found for baseline systolic BP (men 117 mm Hg; women 111 mm Hg; $F(1, 36) = 7.21, p < .05$) and heart rate (men 66 bpm; women 73 bpm; $F(1, 36) = 5.86, p < .05$). In addition, a repeated measures ANOVA showed a main effect for gender for baseline lymphocyte proliferative response to PHA ($F(1, 34) = 8.25, p < .01$). Separate univariate ANOVAs at each concentration indicated that the proliferative response among women was lower at all four concentrations of mitogen (means collapsing across concentrations; men 897,000 cpm; women 693,000 cpm; F 's (1,33) > 4.20, p 's < .05). Gender did not interact with group assignment on any of the vari-

ables included in the analyses.¹

Cardiovascular response to the stressor. To confirm that the task had the desired stress effect on subjects' cardiovascular responses, a series of 2 (Group) × 2 (Gender) ANCOVAs were done. Covariates were baseline values of each measure. Results indicated that subjects in the stress condition showed greater cardiovascular responses than subjects in the control condition on all three-measures: systolic BP (all task means are adjusted for baseline; 125 vs. 114 mm Hg; $F(1, 36) = 61.51, p < .001$), diastolic BP (71 vs. 63 mm Hg; $F(1, 36) = 33.46, p < .001$), and HR (81 vs. 69 bpm; $F(1, 34) = 41.17, p < .001$). There were no main effects for gender nor any interactions of gender with group assignment on any of the cardiovascular response measures.

¹ Although we did not focus on the effects of the menstrual cycle in this study, we did collect information on cycle phase that we describe for the reader's interest. Specifically, of the 10 women, five reported using OCs, two were in the follicular phase of their cycles (determined by serum levels of estrogen and progesterone), and three were in the luteal phase. Of the nine control women, four reported using OCs and five were in the follicular phase. There were no baseline differences between OC users, women in the follicular phase, or women in the luteal phase in terms of any cardiovascular or immune measure. There were not enough women exposed to the stressor to differentiate OC users in follicular phase from luteal phase in terms of cardiovascular and immune responses to the stressor. Examining the differences between OC users and nonusers, however, showed that OC users had greater systolic BP responses but did not differ in diastolic BP or HR responses. Moreover, there were no differences between OC users and nonusers in any of the immune responses.

Immunologic response to the stressor. A series of 2 (Group) \times 2 (Gender) \times 2 (Time: 5 minutes, 21 minutes) repeated measures ANCOVAs examined group and gender differences in numbers of specific lymphocyte subsets after exposure to the stressor (Table 1). Covariates were baseline values of each measure. Results showed a main effect for group assignment for the number of CD8 ($F(1, 35) = 7.70, p < .01$) and NK cells ($F(1, 35) = 23.41, p < .001$). Increases over baseline values in numbers of both subsets were evident at both 5 and 21 minutes. The interaction of time with group assignment was not reliable, which suggests that immune alterations at 21 minutes were similar to those at 5 minutes. Control subjects showed no increases or decreases on these immune parameters over any period. Stressor exposure did not reliably affect the number of CD19 B cells or CD4 helper T cells in circulation. Finally, there were no main effects of gender nor any interactions of gender with group assignment.

Proliferative response to PHA was evaluated with a 2 (Group) \times 2 (Gender) \times 2 (Time) \times 4 (Concentration) repeated measures ANCOVA with baseline values covaried. The analysis showed the expected effect for mitogen concentration ($F(3, 101) = 9.93, p < .001$), which indicates increased proliferation as concentration of mitogen increased, until the highest concentration of mitogen where proliferation decreased somewhat. There was also an effect for group assignment ($F(1, 33) = 15.63, p < .001$), but no interaction with concentration, which suggests that effects of stressor exposure were similar across all four concentrations of mitogen. Thus, Figure 1 illustrates the effect of stressor exposure for a representative concentration, as well as the optimal concentration, that is the concentration of mitogen that stimulated the greatest amount of proliferation across all subjects (see Table 1 for group means). Relative to baseline, subjects in the stress condition showed decreased proliferative responses at 5 minutes and 21 minutes. Time did not interact with group assignment, which suggests that immune alterations were similar at 21 minutes. Control subjects did not show reliable changes from baseline in proliferative response. No effects for gender nor any interactions reached significance.

Earlier work suggested that stressor-induced decreases in proliferative response might reflect inhibitory influences of the stressor-induced increase in the number of CD8 cells (4). To examine this hypothesis, we conducted a 2 (Group) \times 2 (Gender) \times 2 (Time) \times 4 (Concentration) repeated measures ANCOVA. Covariates were baseline PHA values as well as residualized scores reflecting changes in

number of CD8 cells from baseline to 5 and 21 minutes. Results showed that the effect for group assignment remained ($F(1, 31) = 7.88, p < .01$), which suggests that increased CD8 cell numbers do not fully account for decreased proliferative responses 5 and 21 minutes after stressor onset.

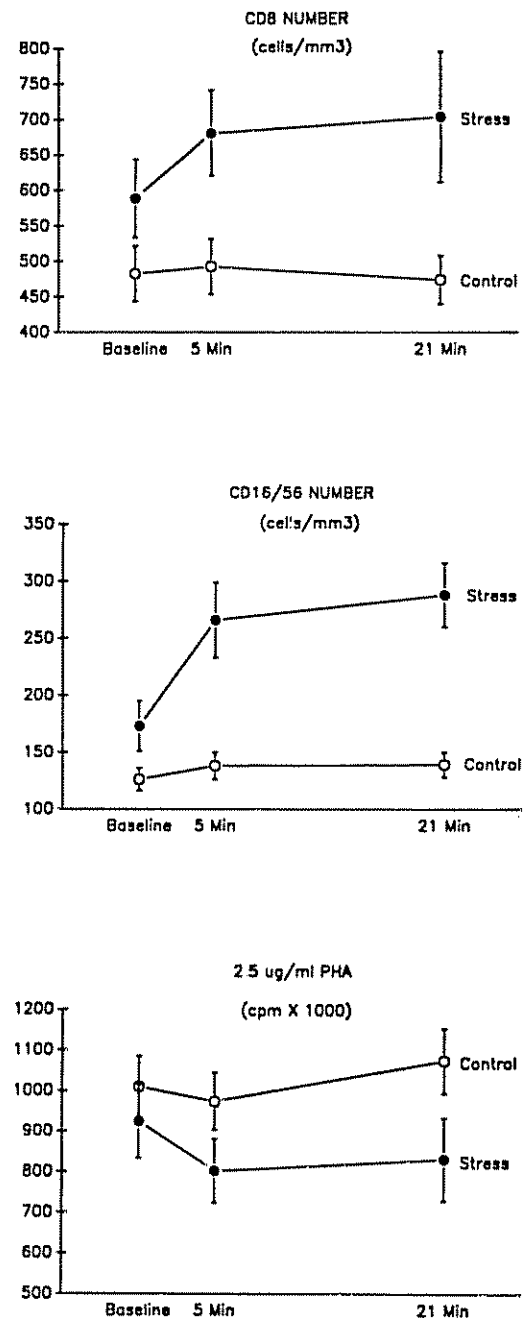


Fig. 1. Number (cells/mm³) of CD8 and CD16/56 NK cells in circulation and proliferative responses (cpm \times 1000) to the optimal concentration of PHA, as a function of group assignment and time since stressor onset are illustrated. Vertical bars are \pm one standard error of the mean.

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High Reactors vs. Low Reactors vs. Control Subjects

Reactivity classification. To determine individual differences in cardiovascular response to the stressor, residualized scores reflecting changes in systolic BP, diastolic BP, and HR were calculated across gender. Subjects falling above the median on reactions to at least two of the three parameters were classified as "high cardiovascular reactors" (HCR) ($N = 10$; three men and seven women), and the remainder were classified as "low cardiovascular reactors" (LCR) ($N = 10$; seven men and three women). ANOVAs indicated that there were no baseline differences between HCR, LCR, or control subjects in terms of the number of CD8 ($F(2, 37) = 1.79, p > .10$) or NK cells ($F(2, 37) = 2.44, p > .10$) or proliferative response to PHA ($F(2, 32) = 1.60, p > .10$).

Immunologic response to the stressor. A series of 3 (Group) \times 2 (Gender) \times 2 (Time) repeated measures ANCOVAs investigated the effect of reactivity classification on changes in the numbers of CD8 and NK cells after exposure to the stressor. Covariates were the baseline value of each measure. Results showed a main effect for reactivity classification in both cases: number of CD8 ($F(2, 33) = 7.17, p < .01$) and NK cells ($F(2, 33) = 16.29, p < .001$). Group means are provided in Table 2 and the effects are illustrated in Figure 2.

By 5 minutes both HCR and LCR showed increased numbers of CD8 and NK cells. The interaction of time with reactivity classification was not reliable, which suggests that these immune alterations were similar at 21 minutes. However, as Figure 2 illustrates, relative to control subjects and adjusting for baseline levels, HCR had higher numbers of CD8 and NK cells at 5 minutes and 21 minutes ($F(1,$

$25) > 10.9, p < .01$). In contrast, at both 5 and 21 minutes, results of ANCOVA showed that LCR differed from control subjects only on number of CD16/56 cells ($F(1, 25) = 8.14, p < .01$).

Proliferative responses to PHA were evaluated with a 3 (Group) \times 2 (Gender) \times 2 (Time) \times 4 (Concentration) repeated measures ANCOVA, with baseline values covaried. The analysis again showed the expected effect for mitogen concentration ($F(3, 95) = 8.26, p < .001$). There was also an effect for reactivity classification ($F(2, 31) = 5.12, p < .05$) but no interaction with concentration, which suggests that effects were similar across all four mitogen concentrations. Figure 2 illustrates the effect for the optimal concentration of mitogen (see Table 2 for group means). Both HCR and LCR showed decreased proliferative responses at 5 minutes. That time did not interact with reactivity classification suggests that the decreased proliferative response was maintained at 21 minutes. However, adjusting for baseline values, the results of ANCOVAs suggested that, relative to control subjects, HCR showed decreased proliferative response at both 5 and 21 minutes ($F(1, 25) = 8.54, p < .01$), whereas LCR did not ($F(1, 23) = 4.12, p > .05$).

DISCUSSION

This study provides evidence of the temporal nature of immune responses and extends past work with respect to the effects of cardiovascular reactivity on immune responses after exposure to an acute psychological stressor. First, with respect to timing of immune response, we have shown increased numbers of CD8 and NK cells in circulation and

TABLE 2. Reactivity Classification, Cell Numbers, and Proliferative Responses

| | Baseline | | 5 Minutes | | 21 Minutes | |
|-------------------------|----------|-------|-----------|-------|------------|-------|
| | x | SD | x | SD | x | SD |
| Cell numbers | | | | | | |
| CD8 cells | | | | | | |
| High reactor | 639 | (272) | 778 | (270) | 828 | (504) |
| Low reactor | 539 | (223) | 584 | (240) | 578 | (260) |
| Control | 482 | (175) | 493 | (173) | 474 | (152) |
| CD16/56 cells | | | | | | |
| High reactor | 189 | (117) | 322 | (154) | 328 | (133) |
| Low reactor | 157 | (73) | 213 | (127) | 248 | (109) |
| Control | 126 | (45) | 137 | (54) | 139 | (50) |
| Proliferative response* | | | | | | |
| High reactor | 800 | (340) | 677 | (264) | 755 | (355) |
| Low reactor | 1078 | (142) | 958 | (127) | 925 | (213) |
| Control | 1009 | (233) | 974 | (217) | 1074 | (268) |

* Optimal concentration \times 1000.

decreased proliferative response to PHA by 5 minutes after stressor onset. Further, no increases or decreases are found 16 minutes later: that is, the immune changes are maintained at 21 minutes. It is important to emphasize that we have replicated effects for immune parameters where effects of

acute stressors have previously been found: decreased proliferative responses and increased numbers of NK and CD8 cells (7).

The rapidity of immune response is consistent with the hypothesis that SNS activation mediates immune changes in the face of acute stressors. As indicated, infusion of epinephrine results in immune alterations similar to those found in this study (9-10). Although some argue that acute effects of SNS activation on mitogen stimulated lymphocyte proliferation primarily reflect changes in trafficking patterns, it is noteworthy that decreases in proliferative response at 5 and 21 minutes were not attenuated when the increase in number of CD8 cells was controlled. Thus, it seems that cellular function and number are independently affected within 5 minutes of stressor onset.

The explanation that SNS activation mediates immune changes in the face of an acute stressor is strengthened by the fact that, relative to control subjects, individuals classified as high reactors showed greater short-term immune change than low reactors. These reactivity effects are consistent with others that have been found (4, 6). The form of the reactivity effect, however, was dependent on the specific immune outcome. That is, only high reactors differed from control subjects in the number of CD8 cells in circulation and in proliferative response to PHA. However, both high and low reactors differed from control subjects in the number of NK cells in circulation. These differences suggest that the mechanism driving changes in the number of NK cells may differ from the mechanism driving the other immune responses. It may be, for example, that proliferative response to PHA and number of CD8 cells in circulation are mediated primarily adrenergically, whereas the number of NK cells is also affected by the release of other stressor-elicited hormones (e.g., opioids).

We found no strong evidence for a moderating effect of gender on immune response to the acute stressor. We also did not confirm findings of other studies showing gender differences in cardiovascular response to acute stressors (13-15). However, some evidence suggests that the gender relevance of a stressor moderates cardiovascular responses to it (27; but see 18). Perhaps, then, men and women showed similar cardiovascular responses because the Stroop Color-Word task is perceived as gender neutral unless instructions highlight gender relevance (18). Alternatively, two studies suggest that OC use is related to higher blood pressure responses to acute stressors (28-29). Post-hoc analyses with our data confirm that women in the experimental

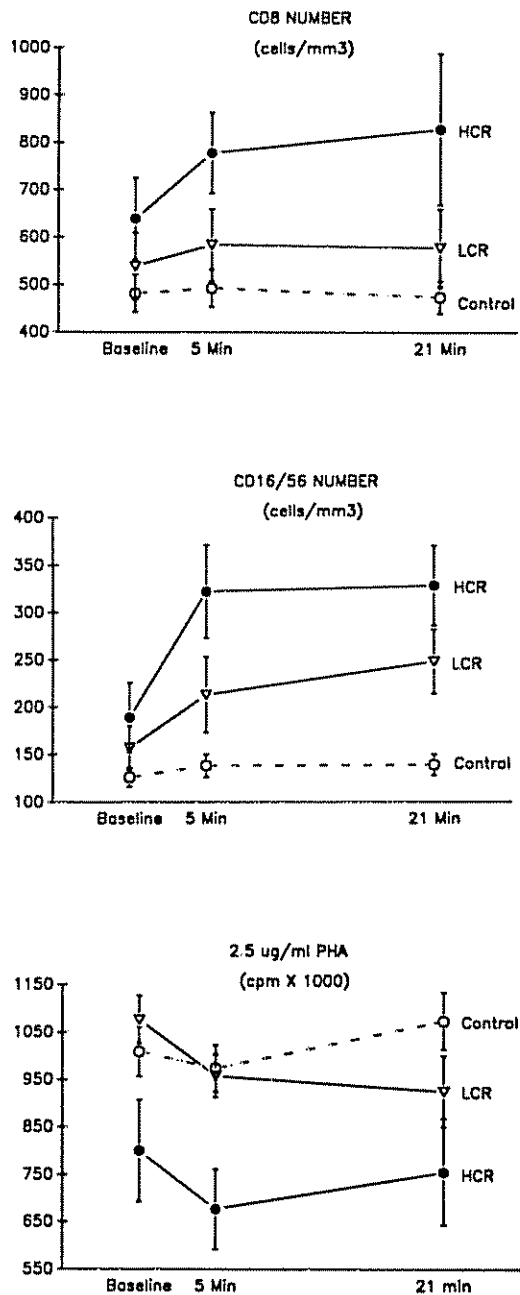


Fig. 2. Number (cells/mm³) of CD8 and CD16/56 NK cells in circulation and proliferative responses (cpm × 1000) to the optimal concentration of PHA, as a function of cardiovascular reactivity and time since stressor onset are illustrated. Vertical bars are ± one standard error of the mean.

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group who used OCs ($N = 5$) showed greater systolic BP responses than women who did not ($N = 5$). However, there were no differences in immune response nor any baseline cardiovascular or immune differences between OC users and nonusers. The elevation in systolic BP response in OC users might, therefore, have obscured any potential gender difference in systolic BP response. OC use, however, does not account for the lack of difference in heart rate response typically found. Our initial question though, was whether there were gender differences in immune response after exposure to an acute stressor regardless of menstrual cycle phase, and these data do not support the notion that gender moderated immune responses. However, because we addressed this issue only in a preliminary way, more systematic study of the question is necessary.

In summary, we investigated the temporal nature of the immune response, as well as the effects of cardiovascular reactivity on the immune response, after exposure to an acute psychological stressor. We found increased numbers of CD8 and NK cells in circulation and decreased proliferative responses to PHA by 5 minutes after stressor onset. Subjects high in cardiovascular reactivity showed greater immune alteration on these parameters than subjects low in cardiovascular reactivity. These data are consistent with the explanation that SNS activation mediates immune changes when individuals are confronted with an acute psychological stressor.

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ANNOUNCEMENT

Psychonephrology 1994

The 9th International Conference on Psychonephrology will be held in New York City, October 7 to 9, 1994. This is a biennial conference devoted to psychosocial and ethical issues surrounding patients on forms of dialysis and recipients of renal transplants. It will consist of Plenary Sessions, Concurrent Large Sessions, and Small Discussion Groups in which the latest developments in this area are discussed. The conference also provides a forum in which participants present scientific and scholarly work in our Free Communications Section. Abstracts for consideration should be 300 words or less and addressed to the Conference Coordinator. Send abstracts and inquiries to: Dr. Norman B. Levy, Liaison Psychiatry Division, New York Medical College, Valhalla, NY 10595. Telephone (914)285-8424; FAX (914)285-1965.