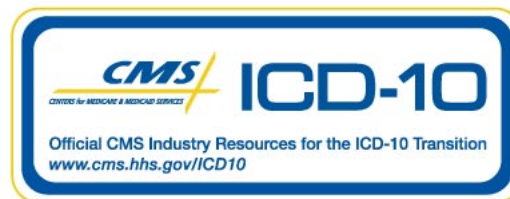


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J. Am. Coll. Cardiol. 1998;31;1555-1560

This information is current as of February 12, 2012

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Modulation of Circulating Cellular Adhesion Molecules in Postmenopausal Women With Coronary Artery Disease

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Objectives. The present study examined the association of estrogen (E_2) and the inflammatory response of endothelium in coronary artery disease (CAD) by measuring circulating cellular adhesion molecules (cCAMs) in subjects with atherosclerosis.

Background. Atherosclerotic plaque demonstrates features similar to inflammation. Endothelial cell activation by inflammatory cytokines induces expression of cellular adhesion molecules (CAMs), thereby perhaps augmenting leukocyte adhesion and recruitment and subsequent development of atherosclerosis. The incidence of CAD is lower in women; this may be due to the cardioprotective effects of E_2 .

Methods. Conservative eligible subjects with CAD admitted for cardiac catheterization were studied. The groups evaluated were men, postmenopausal women receiving E_2 replacement therapy (ERT), postmenopausal women not receiving ERT and premenopausal women. Control groups included men and women without CAD. Preprocedural blood samples were drawn from all groups.

Measurements of cCAMs, E-selectin, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 were performed by enzyme-linked immunoabsorbant assay. E_2 levels were assessed by radioimmunoassay.

Results. We observed a statistically significant increase in all cCAMs in men with CAD and postmenopausal women with CAD not receiving ERT compared with postmenopausal women with CAD receiving ERT. Premenopausal women with CAD and postmenopausal women with CAD receiving ERT had a significant increase in VCAM-1 alone compared with the female control group.

Conclusions. A possible mechanism by which E_2 exerts one of its cardioprotective effects is by limiting the inflammatory response to injury by modulating the expression of CAMs from the endothelium.

(J Am Coll Cardiol 1998;31:1555-60)

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Pathologic examination has demonstrated similarities between inflammation and atherosclerosis (1). The endothelial cell contributes actively to the development of local vascular immune and inflammatory responses. Intercellular adhesion between vascular endothelial cells and circulating leukocytes initiates many of these responses (2). The modulation of leukocyte-endothelial adhesion is thought to be mediated by cellular adhesion molecules (CAMs), which include E-selectin, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) and -2. These molecules are

associated with enhanced leukocyte adhesion, as well as enhanced surface thrombogenicity and intravascular coagulation, observed in early atherosclerosis (3). Recently soluble isoforms of CAMs have been measured in the circulation and correlated with disease activity. Increased levels of soluble E-selectin have been demonstrated in patients with polyarteritis nodosum, scleroderma, giant cell arteritis, sepsis and diabetes mellitus (4). This suggests endothelial activation in these patients because the expression of E-selectin is only found on activated endothelium. The soluble ICAM-1 and VCAM-1 levels have been reported to be elevated in patients with cancer, inflammatory disease and infection (5-8). In addition, a recent report demonstrated abnormal levels of CAMs in the circulation in atherosclerosis (9).

The incidence of coronary atherosclerosis in premenopausal women is half that observed in age-matched men (10). After menopause the incidence of cardiovascular disease increases, but estrogen (E_2) replacement therapy (ERT) significantly reduces this risk. The protective effect of E_2 is not completely understood. E_2 affects cholesterol metabolism; however, the magnitude of the lipid changes cannot fully

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Manuscript received November 14, 1997; revised manuscript received February 9, 1998, accepted March 4, 1998.

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Abbreviations and Acronyms

CAD	= coronary artery disease
CAM	= cellular adhesion molecule
cCAM	= circulating cellular adhesion molecule
cE-selectin	= circulating E-selectin
cICAM-1	= circulating intercellular adhesion molecule-1
cVCAM-1	= circulating vascular cell adhesion molecule-1
E ₂	= estrogen
ERT	= estrogen replacement therapy
ICAM-1	= intercellular adhesion molecule-1
VCAM-1	= vascular cell adhesion molecule-1

account for the observed cardiovascular protective effects (11,12).

E₂ is a steroid hormone whose response is mediated by specific intracellular receptors (13). The hormone initiates diverse physiologic responses by binding to its receptor in the target cell, and E₂ receptors have been demonstrated in endothelial cells (14). Modulation of transcription of CAMs in vitro by E₂ through its receptor has functional implications for leukocyte adhesion to endothelial cells (14). This relation in turn could influence development of atherosclerosis.

The purpose of the present study was to evaluate the association of ERT and the inflammatory response of the endothelium in coronary artery disease (CAD) by examining circulating cellular adhesion molecules (cCAMs) in subjects with atherosclerosis. This investigation into the relation between inflammation and atherosclerosis in the presence of ERT may provide insight into the cardioprotective effect of the hormone.

Methods

Subjects. Consecutive subjects with clinical evidence of CAD admitted for cardiac catheterization between July 1996 and September 1997 were screened for entry into the present study. CAD was defined as lumen irregularities or stenoses >50% in at least one vessel. The subjects were divided into four groups: 1) men, 2) postmenopausal women receiving oral ERT in the form of a conjugated equine E₂, 3) postmenopausal women not receiving ERT, and 4) premenopausal women. Control groups included volunteer medical center employees, men and premenopausal women, all with no clinical evidence of CAD by history. One hundred seventy-five subjects were evaluated for the present study. Exclusion criteria included acute myocardial infarction, hemodynamic instability, the use of progesterone, ERT by topical application, recent viral illness, active inflammatory or connective tissue disease and clinically significant systemic illness. Menopause was defined as >6 months since last menses. At least 6 months of therapy was required for inclusion in the study group receiving ERT. Physical examination, blood pressure, electrocardiography, complete blood count, clinical chemistry and liver and renal function tests were performed before entry in

the present study. The control groups were evaluated for clinically significant CAD by history and physical examination. The study protocol was approved by the Human Investigation Committee, Yale University School of Medicine. Written informed consent was obtained from all subjects before inclusion in the study.

Protocol. Subjects who fulfilled entry criteria and agreed to participate in the present study were entered in a consecutive manner over a 14-month (July 1996 to September 1997) period. On entry into the study a data sheet for clinical and cardiac risk profile was completed. Potential subjects had preprocedural blood samples drawn on the morning of their procedure and were entered into the study if significant CAD was present at catheterization. Significant disease was defined as at least one vessel with >50% angiographic stenosis. Coronary angiograms were read in a double-blind manner. Serum samples were stored at -20°C. Because of differences in the absolute levels for circulating ICAM-1, VCAM-1 and E-selectin (cICAM-1, cVCAM-1 and cE-selectin), cCAM data were normalized to measured cCAM levels in premenopausal control subjects and expressed as the percent increase over control values when all three cCAMs were compared between groups.

Laboratory assays. All serum samples were stored at -20°C and assayed in duplicate (E₂ levels) or triplicate (cCAM levels). Circulating E₂ levels were measured using a commercially available radioimmunoassay (Diagnostic Products Corporation), according to the manufacturers' instructions. The intraassay and interassay coefficients of variation were 5.8% and 6.0%, respectively, for E₂. The E₂ antiserum is specific for 17beta-estradiol, with low cross-reactivity to other steroids. A standard curve was included with all assays, and concentrations of E₂ were determined and expressed as pmol/liter.

Enzyme-linked immunoabsorbant assay (ELISA) for circulating cellular adhesion molecules was performed with commercially available ELISA kits for cE-selectin, cICAM-1 and cVCAM-1 (R & D Systems). There was no cross-reactivity with other adhesion molecules. Dilution curves of the serum samples were parallel to standard dilution curves. The interassay and intraassay coefficients of variation were <8%, as determined in human serum. The normal ranges of cCAMs in our study were obtained from 20 healthy male volunteers (cICAM-1 245 ± 58 ng/ml; cVCAM-1 640 ± 165 ng/ml; cE-selectin 44 ± 29 ng/ml) and 20 women (cICAM-1 225 ± 50 ng/ml; cVCAM-1 475 ± 145 ng/ml; cE-selectin 35 ± 19 ng/ml) and are in accordance with those published (15); normal men were noted to have increased levels of all cCAMs compared with premenopausal female control subjects; however, the increase was not statistically significant. This observation also has been previously reported (16).

Statistical analysis. Results are expressed as mean value ± SD. Differences among the groups were compared by a one-way factorial analysis of variance and then by the Tukey test for multiple comparisons. Correlations between serum E₂ levels and cCAM levels were examined using simple linear

Table 1. Study Groups and Estradiol Levels

	No. of Subjects	Estradiol (pmol/liter) (mean ± SD)
Premenopausal control	20	320 ± 60
Premenopausal CAD(+)	10	300 ± 69
Postmenopausal CAD(+), ERT(+)	25	150 ± 65
Postmenopausal CAD(+), ERT(-)	50	30 ± 24*
Male control	20	38 ± 10*
Male CAD(+)	50	20 ± 8*

*p < 0.05 versus premenopausal women and women receiving ERT. CAD = coronary artery disease; ERT = estrogen replacement therapy; (+) = with disease or receiving therapy; (-) = without disease or not receiving therapy.

regression analysis by the least squares method. The differences were considered statistically significant at p < 0.05.

Results

Clinical characteristics. Table 1 summarizes the subject and control groups and their mean E₂ level ± SD. There was a significant difference (p < 0.05) in E₂ levels in men and postmenopausal women with CAD not receiving ERT compared with the other groups. The E₂ levels in both of these groups are consistent with measurements reported for postmenopausal women. Both groups of premenopausal women had comparable E₂ levels despite control women being younger. The E₂ level in postmenopausal women with CAD receiving ERT was lower than that measured in the premenopausal groups. All ERT had a daily dosing schedule, significant fluctuations in levels were not observed.

The clinical characteristics are summarized in Table 2. The age of postmenopausal women was not significantly different between groups receiving or not receiving ERT. There were no statistically significant differences in the cardiac risk factors of hypertension, cigarette use, diabetes mellitus and total cholesterol/low density lipoprotein. A small, but statistically significant, increase in the use of lipid-lowering agents in men with CAD compared with women with CAD was observed. There

was a statistically significant difference in high density lipoprotein and triglyceride levels in postmenopausal women with CAD receiving ERT compared with men with CAD and postmenopausal women with CAD not receiving ERT.

Linear regression analysis demonstrated a significant correlation for a biologic system between E₂ levels in women and cCAMs: cE-selectin (y = -0.043x + 38.847, r² = 0.333, p < 0.05); cICAM-1 (y = -0.418x + 348.518, r² = 0.339, p < 0.05); cVCAM-1 (y = -0.697x + 784.418, r² = 0.276, p < 0.05).

cCAM Levels. Figure 1 demonstrates the absolute levels (ng/ml) of cE-selectin, cICAM-1, and cVCAM-1 in the groups studied. The levels of cICAM-1 and cE-selectin are significantly higher in men with CAD and postmenopausal women with CAD not receiving ERT compared with the other groups. The increase in all cCAMs is comparable in men with CAD and postmenopausal women with CAD not receiving ERT. The level of cVCAM-1 is significantly elevated in all groups with CAD.

cCAM levels in postmenopausal women with CAD receiving or not receiving ERT. The association of ERT and cCAMs in postmenopausal women with CAD is shown in Figure 2. All data for cCAM levels were normalized to cCAM levels in control premenopausal women and expressed as the percent increase in cCAMs over this baseline. There is a statistically significant increase in cE-selectin, cICAM-1 and cVCAM-1 in postmenopausal women with CAD not receiving ERT compared with postmenopausal women with CAD receiving ERT. Thus ERT is associated with a decrease in all cCAM levels in postmenopausal women with CAD. The increase in cE-selectin and cICAM-1 in postmenopausal women with CAD receiving ERT is not statistically significant compared with the premenopausal control group; however, the elevation in cVCAM-1 is significant.

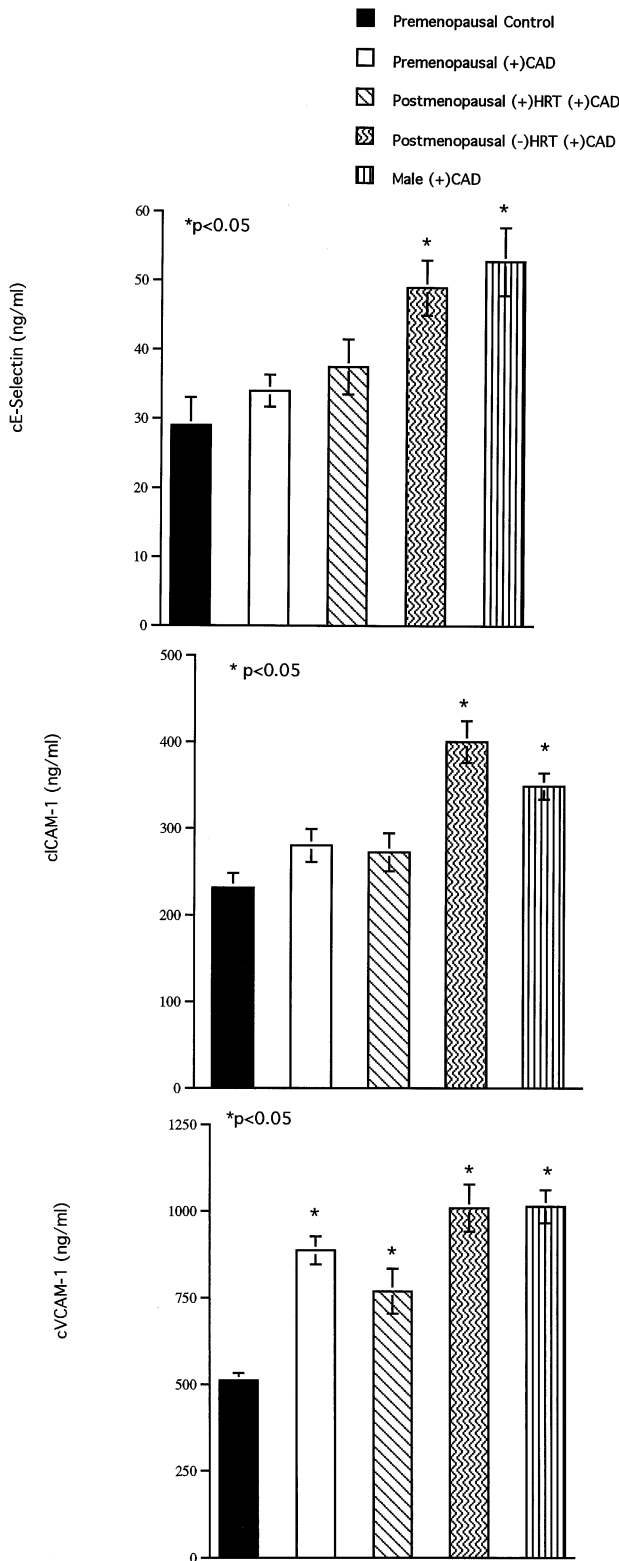
cCAM levels in men with CAD. There is a statistically significant increase in the levels of all cCAMs (cE-selectin, cICAM-1 and cVCAM-1) in men with CAD compared with male control subjects (Fig. 3). The basal expression of cCAMs in male control subjects is greater than that observed in female

Table 2. Clinical Characteristics

	Premenopausal Control (n = 20)	Premenopausal (+)CAD (n = 10)	Postmenopausal (+)ERT, (+)CAD (n = 25)	Postmenopausal (-)ERT, (+)CAD (n = 50)	Male Control (n = 20)	Male (+)CAD (n = 50)
Age (yr)	33 ± 6	43 ± 5	62 ± 10	60 ± 15	29 ± 8	55 ± 16
Anti-HTN medication	0%	20%	68%	50%	10%	63%
Smoke	5%	50%	48%	50%	10%	50%
DM	0%	20%	34%	30%	0%	20%
Cholesterol (mg/dl)	186 ± 24	220 ± 23	200 ± 30	218 ± 34	205 ± 34	219 ± 30
HDL (mg/dl)	49 ± 3	36 ± 4	39 ± 4	30 ± 3*	40 ± 5	32 ± 3.7*
LDL (mg/dl)	118 ± 12	130 ± 10	129 ± 14	140 ± 16	130 ± 15	139 ± 11
TGs (mg/dl)	148 ± 58	228 ± 68	180 ± 66	250 ± 63*	214 ± 30	230 ± 28*
Lipid medication	0	0	20%	20%	0	37%†

*p < 0.05 versus postmenopausal women with coronary artery disease (CAD) receiving estrogen replacement therapy (ERT). †p < 0.05 versus postmenopausal women with CAD. Data presented are mean value ± SD or percent of patients. DM = diabetes mellitus; HDL = high density lipoprotein; HTN = hypertension; LDL = low density lipoprotein; TG = triglycerides.

Figure 1. cCAM levels (ng/ml) in all study groups. **Top,** cE-selectin. **Middle,** cICAM-1. **Bottom,** cVCAM-1. All assays were performed in triplicate. HRT = hormone replacement therapy (ERT); + = with; - = without. * $p < 0.05$ versus premenopausal control subjects.



control subjects; this is not statistically significant and has been previously described (16).

Discussion

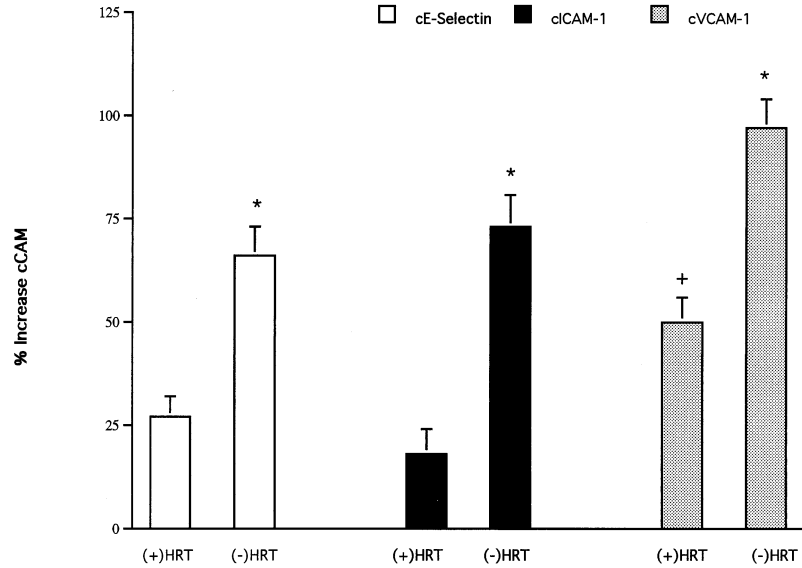
Studies of atherosclerotic lesions in human coronary arteries and aortas demonstrate an increased expression of ICAM-1 and E-selectin on endothelial cells adjacent to sites of inflammatory cell infiltrates (3). The effects of E_2 on the development of atherosclerosis have demonstrated inhibition of myointimal proliferation with injury (17), platelet aggregation (18), foam cell formation (19) and increased arterial smooth muscle prostacyclin production (20). E_2 also influences the expression of plasminogen activator inhibitor type 1 (21).

Statistical significance. We demonstrate that ERT in postmenopausal women with CAD is associated with a statistically significant decrease in the levels of cE-selectin, cICAM-1 and cVCAM-1 compared with postmenopausal women with CAD not receiving ERT and men with CAD. This suggests a possible alteration in the expression of CAMs in atherosclerosis that may be associated with ERT. These findings support *in vitro* data, which demonstrated E_2 treatment of human endothelial cells inhibited cytokine-induced expression of CAMs (14). This investigation suggests one of the protective roles of E_2 may be the regulation of CAM expression in atherosclerosis, which may be detected by the circulating levels of these molecules.

Exclusion of postmenopausal women receiving combined E_2 /progesterone therapy avoided possible effects of the progestational agent on the amount of E_2 receptor present or interactions with other steroids and receptors. Women receiving ERT by patch administration were not enrolled because of differences in biologic effects from the route of administration (22). Clinical characteristics and cardiac risk profiles were generally similar among the study groups. There were differences in the overall age of the groups, the use of lipid-lowering agents (increased in the men with CAD), and high density lipoprotein/triglyceride levels in premenopausal women and postmenopausal women receiving ERT.

Potential mechanisms. Few studies have investigated the hormonal regulation of CAM expression. A previous report showed that dexamethasone interacts with the glucocorticoid receptor and results in reduction of interleukin-1-induced E-selectin mRNA levels (23). Another study has reported reduced VCAM-1 mRNA and membrane protein levels in E_2 -pretreated, interleukin-1-activated cells (24). E_2 markedly inhibits interleukin-1-induced endothelial CAM transcription in endothelial cells, also reflected in decreased membrane protein expression and cytokine-induced leukocyte adhesion (14). The importance of cCAMs in various inflammatory diseases has been investigated (25,26). The association of CAMs in their tissue form with atherosclerosis has been described. Elevation of adhesion molecules in the tissue are usually associated with increased circulating levels (25,26). The present report demonstrates for the first time, that E_2 , which suppresses induction of these adhesion molecules *in vitro*, is associated with decreased levels of cCAMs *in vivo*. Speculation

Figure 2. cCAM levels in postmenopausal women with CAD receiving ERT [(+)HRT] versus those not receiving ERT [(-)HRT]. The data presented were normalized to cCAM levels in the premenopausal control group and expressed as the percent increase in cCAM. All assays were performed in triplicate. HRT = hormone replacement therapy. * $p < 0.05$ versus postmenopausal women with CAD receiving ERT. † $p < 0.05$ versus premenopausal control subjects.



on a possible mechanism for the decreased levels of adhesion molecules in the circulation with ERT, on the basis of our in vivo and in vitro studies, would include 1) downregulation of the gene transcription of the molecules, 2) subsequent decreased surface expression on the endothelium, and 3) finally, a decreased level found in the circulation. E₂ may exert part of its cardioprotective effects by modulating the systemic expression of cCAMs. Blann et al. (26) demonstrated elevation of these molecules in inflammatory vascular diseases, ischemic heart disease and peripheral vascular disease.

Study limitations. Limitations of this study are that we cannot rule out other possible mechanisms for the measured differences in cCAM levels. The mechanisms by which adhe-

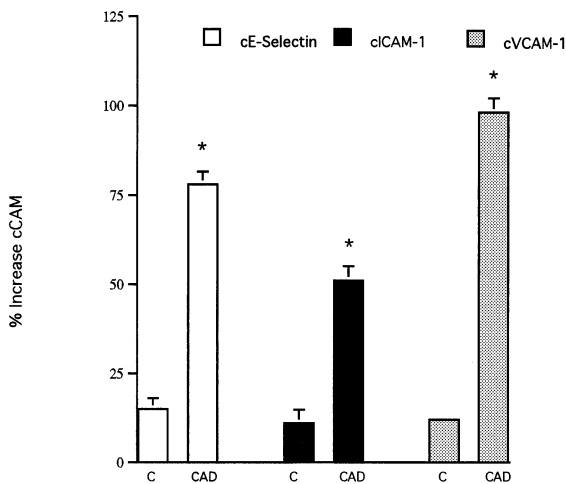
sion molecules are shed, released and cleared from the circulation probably affect circulating levels. These mechanisms remain unclear and are currently under investigation.

The oxidative modification of low density lipoprotein has been suggested as initiating the development of atherosclerotic lesions. In animal models antioxidants inhibit the development of atherosclerosis (27). E₂ may have antioxidant properties (28). It is possible that the decreased levels of cCAMs measured in the present report are a result of an antioxidant effect of ERT on low density lipoprotein. However, the major form of E₂ in conjugated equine E₂, the ERT preparation used by women enrolled in the present study, is estrone, which has weak antioxidant properties compared with 17beta-estradiol (29).

The effect of ERT on lipid metabolism as a possible mechanism for our observations cannot be eliminated. Decreased E₂ production with menopause results in an increase in low density lipoprotein cholesterol and lipoprotein(a) levels in women. The use of oral ERT has been associated with an increased high density lipoprotein and decreased low density lipoprotein cholesterol levels. In both animal and human studies E₂ effects on high density lipoprotein and triglyceride levels have been associated with a decrease in plaque formation and death from myocardial infarction (30). ERT may result in a more favorable lipid profile, resulting in overall plaque stability with decreased inflammation and subsequent CAM induction and expression. Further prospective investigations into changes in plaque composition and lipid metabolism as a result of ERT are ongoing and will be necessary to address these issues.

The clinical relevance of cCAMs and the mechanisms controlling the release of cCAMs is an area of active investigation. However, our data suggest that E₂ may be exerting its cardioprotective effect, in part, by decreasing the inflammatory response associated with atherosclerosis.

Figure 3. cCAM levels in men. The data presented were normalized to cCAM levels in the premenopausal control group and expressed as the percent increase in cCAM. All assays were performed in triplicate. * $p < 0.05$ versus male control subjects.



We express gratitude to the Cardiology Fellows for assistance with patient enrollment and sample collections. We are grateful to the nursing and technical staff of the Yale New Haven Hospital Cardiac Catheterization Laboratory and The Shoreline Office of Yale Cardiology for assistance in sample collection.

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