Cardiovascular stress response and coronary artery disease: Evidence of an adverse postmenopausal effect in women

C. Noel Bairey Merz, MD,[a] Willem Kop, PhD,[b] David S. Krantz, PhD,[b] Karin F. Helmers, PhD,[c] Daniel S. Berman, MD,[a] and Alan Rozanski, MD[d] ***Los Angeles, Calif.; Bethesda, Md.; Toronto, Ontario, Canada; and New York, N.Y.***

Objectives To test the hypothesis that postmenopausal women demonstrate greater vascular instability, measured by enhanced cardiovascular stress responses during mental stress, compared with men and premenopausal women.

Background Recent data suggest that estrogen plays a role in regulating vascular tone. The possible consequences of estrogen deficiency during menopause on systemic vascular reactivity is largely unexplored.

Methods One hundred subjects (84 men and 16 women) underwent mental stress testing with radionuclide ventriculography. Study subjects included 19 normal volunteers, 23 control subjects with chest pain syndromes or hypertension but without coronary artery disease, and 58 coronary artery disease subjects. The subjects performed a series of three mental stress tasks, during which hemodynamic data and radionuclide ventriculograms were obtained.

Results Overall, women demonstrated greater hemodynamic responses during mental stress measured by changes in heart rate, systolic and diastolic blood pressure, and double product compared with those of men (all $p < 0.05$). Women with coronary artery disease demonstrated greater heart rate, diastolic blood pressure, and double product stress responses than their male counterparts (all $p < 0.05$). Women of postmenopausal age demonstrated significantly greater systolic blood pressure reactivity than men or premenopausal women ($p < 0.05$).

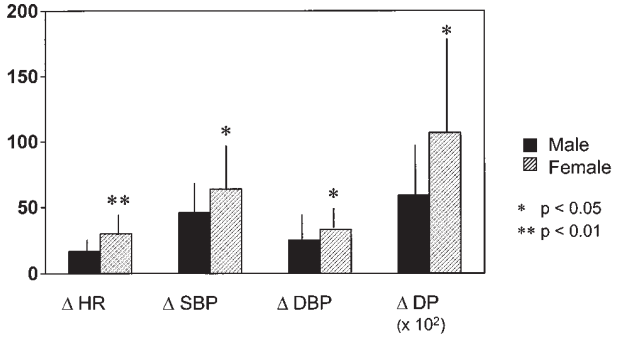
Conclusions Women of postmenopausal age have greater cardiovascular responses to stress than men or premenopausal women. These findings suggest an additional mechanism by which estrogen deficiency conveys a poor prognosis in female patients with coronary artery disease. (Am Heart J 1998;135:881-7.)

Evidence suggests that women with coronary artery disease have a worse prognosis when compared with men.[1,2] Although older age and more adverse risk factor profiles among women with coronary artery disease may account for some of this difference, several large prospective studies have demonstrated persistently poorer outcomes among women when compared with men after correction for these baseline differences.[1,2] It is important to note that 92% of coronary artery disease morbidity among women is experienced in the postmenopausal age group, where coronary artery disease prevalence and case-fatality rates rapidly accelerate when compared with that of premenopausal women.[3]

The operative factors behind the postmenopausal acceleration of coronary artery disease in women are not fully understood. Adverse changes in lipoprotein profiles associated with declining endogenous estrogen levels appear to account for approximately only 25% to 50% of the increased postmenopausal risk.[4] Animal and human studies have suggested that estrogen deficiency is associated with altered vasomotor reactivity[5] and that estrogen replacement normalizes this condition.[6] Indeed, labile vasomotor tone characterized by "flushing" is a clinical hallmark of menopause for many women. Although it is known that both systemic and

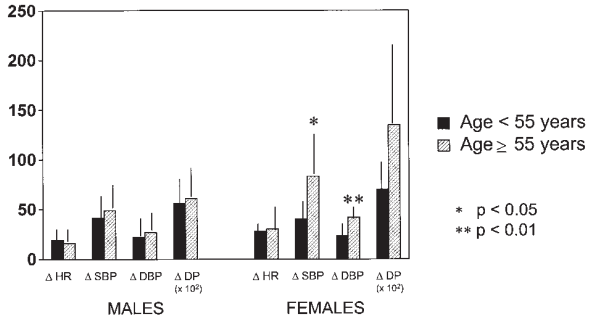
From the [a]Division of Cardiology, Department of Medicine and Department of Nuclear Medicine, Cedars-Sinai Research Institute, Cedars-Sinai Medical Center, and the Department of Medicine, University of California School of Medicine; the [b]Department of Medical and Clinical Psychology, Uniformed Services University of the Health Sciences; [c]York University; and [d]St. Luke's/Roosevelt Hospital Center, Columbia School of Physicians and Surgeons.
Submitted July 8, 1997; accepted Oct. 10, 1997.
Supported in part by grants from the Division of Cardiology, Department of Medicine, and the Division of Nuclear Cardiology, Department of Nuclear Medicine, Cedars-Sinai Medical Center; the John D. and Catherine T. MacArthur Foundation; the National Heart, Lung and Blood Institutes, grants no. 232HL07380 and HL47337; the CIBA-Geigy Corporation, Summit, N.J., and Capintec, Inc., Ramsey, N.J.
The opinions and assertions expressed herein are those of the authors and are not to be construed as reflective of the views of the U.S.U.H.S. or the U.S. Department of Defense.
Presented in part at the 64th Annual Scientific Sessions of the American Heart Association, Nov. 12, 1991, Anaheim, Calif.
Reprint requests: C. Noel Bairey Merz, MD, Preventive and Rehabilitative Cardiac Center, Cedars-Sinai Medical Center, 444 S. San Vicente Blvd., Suite 901, Los Angeles, CA 90048.
E-mail:merz@csmc.edu.
0002-8703/98/$5.00 + 0 **4/1/87837**

Figure 1



Mean values ± standard deviation for Δ heart rate (Δ *HR*, expressed as beats/min), Δ systolic blood pressure (Δ *SBP*, expressed as mm Hg), Δ diastolic blood pressure (Δ *DBP*, expressed as mm Hg), and Δ double product (Δ *DP*, calculated as Δ [heart rate × systolic blood pressure]) for men (*n* = 84) and women (*n* = 16).

Figure 2



Mean values ± standard deviation for Δ HR, Δ SBP, Δ DBP, and Δ DP, as described in Figure 1, for men <55 years (*n* = 38) and ≥55 years (*n* = 46), and for women <55 years (*n* = 6) and ≥55 years (*n* = 10).

coronary arterial walls contain estrogen receptors,[7] the possible consequences of estrogen deficiency on systemic vascular stress responses is largely unexplored.

Cardiovascular stress response, defined as the change in heart rate and blood pressure in response to structured stimuli, has been demonstrated to be a predictor of atherosclerosis[8] and cardiac events[9,10] as well as myocardial ischemia in the laboratory[11] and during daily life.[12] We hypothesized that postmenopausal women would demonstrate greater vascular instability, measured by larger cardiovascular stress responses during mental stress, than men and premenopausal women in a group of subjects who underwent laboratory mental stress with radionuclide ventriculography.

Methods

The study represents a retrospective analysis of 100 consecutive subjects (84 men and 16 women) who underwent research protocol mental stress testing examining triggered myocardial ischemia with radionuclide ventriculography in our laboratory. These subjects included 19 normal volunteers, 23 control subjects with chest pain syndromes or hypertension but without known coronary artery disease, and 58 patients with coronary artery disease. Coronary artery disease was documented by a prior cardiac event or coronary angiography demonstrating ≥50% luminal diameter stenosis in one or more major epicardial coronary arteries (*n* = 44) or a high (≥80%) likelihood of disease (*n* = 14) based on Bayesian analysis of age, sex, symptoms, risk factors, and the results of a prior treadmill exercise test.[13] Control subjects had no documented coronary artery disease and a low (<20%) likelihood of disease.

The study protocol was approved by the medical center institutional review board and all subjects gave written informed consent.

Laboratory stress testing

Patients were asked to withhold β-blocking medication for 48 hours, calcium channel blockers for 24 hours, and long-acting nitrates on the day of testing. Patients were injected with 25 mCi of in vitro labeled technetium 99m red blood cells. Three-channel ECG and heart rate were continuously monitored throughout the study and 12-lead ECGs were obtained at rest and before each mental stress task, at 2-minute intervals during each mental stress task, and every minute of the recovery periods. Blood pressure was recorded at rest and before each mental stress task, every 2 minutes during each mental stress task, and at 2-minute intervals during recovery by use of an automated cuff (Critikon Dynamapp, Model #1846SS). Before data collection was initiated, blood pressure measurements were taken with both the automated cuff and the standard mercury sphygmomanometer to ensure that the automated blood pressure assessments were accurate.

Mental stress

Subjects were asked to relax for 12 to 15 minutes with the room lights off, after which baseline studies were obtained. Subjects then performed a series of three mental stress tasks, with 5-minute rest periods between tasks. Mental arithmetic: Subjects were instructed to subtract serial sevens from a four digit number for 5 minutes while being harassed about their speed or accuracy. Stroop Color Word Task: Subjects were presented with a rapid series of slides for 3 minutes, displaying the written names of colors (i.e., green) with the letters appearing in a nonmatching color (i.e., blue). Subjects were required to state out loud the color used to display the word,

Table I. Population demographic and clinical variables

	Healthy volunteers		Controls		Coronary artery disease	
	Men (*n* = 15)	Women (*n* = 4)	Men (*n* = 17)	Women (*n* = 6)	Men (*n* = 52)	Women (*n* = 6)
Age (yr)	29 ± 7	27 ± 7	52 ± 12	58 ± 23	61 ± 10	63 ± 18*
Age ± 55 yr (%)	0	0	47	67	73	100*
HTN (%)	0	0	41	50	48	50*
Prior MI (%)	0	0	0	0	21	33
Angina (%)	0	0	29	50	73	100*
Med withdrawal (%)	0	0	6	17	56	67
β-Blocker withdrawal (%)	0	0	6	17	33	33

Angina, Chronic angina; *Med withdrawal,* antianginal medication, including β-blockers, calcium channel agents, or nitrates withdrawn before testing; *HTN,* hypertension; MI, myocardial infarction.
*Main effect for coronary artery disease.

rather than the word itself. Simulated Public Speaking: Subjects were asked to give a 5 minute speech in front of two observers regarding his or her personal faults or undesirable habits. The subject was instructed to speak frankly and specifically and to maintain eye contact with the observers. At the end of each mental task, the subjects were asked to rate their feelings of tension, interest, anxiousness, arousal, challenge, and anger on a five-point scale.

Radionuclide ventriculography

After multiple-view resting gated equilibrium blood pool ventriculography was performed, the camera was positioned in the left anterior oblique angle that best separated the left and right ventricles while the subject reclined supine at a 45-degree angle during mental stress testing. After repeat resting images before each mental task, mental stress task images were obtained in the last 2 minutes of each task. The gamma camera used for acquisition was equipped with a $^1/_4$-inch sodium iodide crystal and an all-purpose parallel hole collimator. Twenty frames of equal duration were acquired during the cardiac cycle, resulting in approximately 100,000 counts per frame.[14] After spatial and temporal smoothing, segmental wall motion was assessed visually on the rest and mental task by use of a continuous loop video display. Two experienced observers scored five segments by consensus with a five-point scale: 3 = normal, 2 = mild hypokinesis, 1 = marked hypokinesis, 0 = akinesis, and –1 = dyskinesis. A "stress-induced wall motion worsening score" was calculated as the sum of the five segmental scores at rest minus the sum of the segmental scores at peak stress. An ischemic response was defined as a stress-induced wall motion worsening score of ≥1. We have previously documented the validity and utility of these methods for the measurement of inducible myocardial ischemia.[11] Left ventricular ejection fraction was calculated after end-diastolic, end-systolic, and background regions were manually assigned by a computer operator blinded to the clinical data.[14]

Statistical analysis

Data are expressed as either mean values ± standard deviation or as proportions. To determine the magnitude of hemodynamic response, difference scores were calculated from baseline to the task at which the subject displayed the highest rate pressure product, calculated by the following formula: heart rate (measured in beats/min) × systolic blood pressure (measured in mm Hg). Analysis of the results including all mental stress tasks was not significantly different from the results presented and is not considered further. Analysis of variance (ANOVA) was used to examine differences in hemodynamic response with sex as a two-level between-subjects factor (men vs women) and diagnostic group as a three-level between-subjects factor (normal volunteers vs control subjects vs patients with coronary artery disease), and age as a covariate. Subgroup differences were further examined using post hoc unpaired *t* tests (with pooled or separate variance estimates when appropriate) or nonparametric tests (Mann-Whitney and Kruskal-Wallis). Comparisons of proportions were performed using chi-square tests. A p value of ≤0.05 was considered statistically significant.

Results

The sample population demographic and clinical variables are shown stratified by sex in Table I. Patients with coronary artery disease were older and more likely to be hypertensive. Ten of 16 (63%) of the women overall and six of six (100%) of the women with coronary artery disease were ≥55 years, an age by which 95% of U.S. women are postmenopausal.[15] None of the women were taking hormonal replacement therapy.

There were no differences in baseline characteristics among the men and women (Table I), although women as a group had a higher resting heart rate compared with men (Table II). Normal volunteers had lower baseline systolic and diastolic blood pressure than did

Table II. Baseline hemodynamics according to group

	Healthy volunteers		Controls		Coronary artery disease	
	Men (*n* = 15)	Women (*n* = 4)	Men (*n* = 17)	Women (*n* = 6)	Men (*n* = 52)	Women (*n* = 6)
HR (beats/min)	63 ± 11	70 ± 7	66 ± 9	74 ± 8	65 ± 11	73 ± 11*
SBP (mm Hg)	121 ± 11	106 ± 16	127 ± 18	130 ± 25	129 ± 25	139 ± 17
DBP (mm Hg)	74 ± 10	59 ± 9	81 ± 13	77 ± 11	80 ± 17	87 ± 12
DP ($\times 10^2$)	77 ± 17	75 ± 18	84 ± 19	97 ± 27	83 ± 22	100 ± 19

HR, Heart rate; *HTN*, hypertension; *DBP*, diastolic blood pressure; *DP*, double product (calculated as HR × SBP); *SBP*, systolic blood pressure.
*Main effect for sex.

patients with coronary artery disease and controls ($p < 0.05$). However, analysis of covariance revealed that these lower baseline differences were entirely explained by the age differences between the groups. The presence of coronary artery disease also did not account for any baseline hemodynamic differences after adjustment for age.

No sex differences were observed in either the specific task that produced the greatest hemodynamic change or in the subjective ratings of task-induced anxiety, anger, interest, challenge, or tension.

Sex differences in cardiovascular stress response

Mental stress induced significant increases in the heart rate, blood pressure, and double product compared with baseline (all $p < 0.01$). Women demonstrated significantly greater hemodynamic stress responses than men, including heart rate, diastolic blood pressure, and double product (all Mann-Whitneys $p < 0.05$)(Fig. 1).

Subgroup analyses revealed that normal female volunteers had elevated heart rate responses compared with normal male volunteers. No significant sex differences in hemodynamic stress response were observed in the control group, whereas female coronary artery disease patients had significantly higher heart rate, systolic and diastolic blood pressure, and double product responses to mental stress (Table III). Analyses of variance with sex and coronary artery disease status as between-subjects factors and covarying for age confirmed that women had higher heart rate, systolic and diastolic blood pressure, and double product responses than did men ($p < 0.01$), whereas no interaction between sex and coronary artery disease status or a main effect of coronary artery disease status on hemodynamic response was noted. Although mental stress–induced systolic blood pressure response was substantially higher in women in the control and coronary disease groups, these differences did not reach statistical significance, likely because of the small sample size.

To specifically examine sex differences in the effects of postmenopausal age on mental stress–induced reactivity, hemodynamic responses in patients ≥55 years old were compared to responses of subjects <55 years of age, taking into account the effects of coronary artery disease status. Analysis of variance showed that women of postmenopausal age had higher systolic blood pressure and double product responses than men or premenopausal women ($p_{interaction} = 0.05$). A similar but nonsignificant interaction was found between age and gender for heart rate and diastolic blood pressure. This pattern of results remained the same when statistically controlling for baseline hemodynamics. Given the small sample size and differing standard deviations, nonparametric analysis of variance was used, which confirmed that postmenopausal women ($n = 10$) had higher systolic and diastolic blood pressure and double product responses than premenopausal women ($n = 6$), men ≥55 years of age ($n = 46$), and men <55 years of age ($n = 38$) (all $p < 0.05$). As shown in Fig. 2, women ≥55 years had significantly higher systolic and diastolic blood pressure responses to mental stress compared with women <55 years (t test$_{\text{separate variance estimates}}$ $p < 0.05$). Age did not affect cardiovascular reactivity in men.

Cardiovascular stress response and radionuclide ventriculographic ischemia

Inspection of radionuclide ventriculographic response to mental stress demonstrated overall similar left ventricular ejection fraction changes among the women and men, respectively, in the normal subjects (–1% ± 12% vs 5% ± 6%, p = NS) and control subjects (0% ± 4% vs 1% ± 3%, p = NS). Women, however, demonstrated a greater heterogenous left ventricular ejection fraction response and two (50%) normal female subjects had a left ven-

Table III. Cardiovascular stress response according to group

	Δ HR (beats/min)	Δ SBP (mm Hg)	Δ DBP (mmHg)	Δ DP (×102)
Normal volunteers				
Male (*n* = 15)	20 ± 12	34 ± 11	11 ± 11	52 ± 25
Female (*n* = 4)	30 ± 4*	37 ± 26	22 ± 12	70 ± 32
Control subjects				
Male (*n* = 17)	19 ± 11	39 ± 15	26 ± 10	58 ± 27
Female (*n* = 6)	27 ± 24	71 ± 47	34 ± 12	110 ± 90
Patients with coronary artery disease				
Male (*n* = 52)	15 ± 11	51 ± 32	28 ± 14	61 ± 36
Female (*n* = 6)	32 ± 12†	82 ± 42	44 ± 10*	140 ± 60†

HR, Heart rate; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure; *DP*, double product (calculated as HR × SBP).
*$p < 0.05$ compared with men.
†$p < 0.01$ compared with men.

tricular ejection fraction fall of ≥7%, a finding that was not observed in any of the male normal subjects or control subjects. Stress-induced wall motion worsening scores were within normal limits for the normal and control subjects and not significantly different between the women and men.

The coronary artery disease patients demonstrated a trend toward a greater left ventricular ejection fraction change among the women compared to that of the men (–3 ± 8 vs 2 ± 6, $p = 0.09$), although a similar proportion of women and men demonstrated left ventricular ejection fraction falls of >5% (17% vs 12%, p = NS). Mental stress triggered an ischemic response in 37 of the 58 coronary artery disease patients (64%), including two of six (33%) of the women and 35 of 52 (65%) of the men (p = NS). No associations were found between the magnitude of hemodynamic response to mental stress and the inducibility of myocardial ischemia. Among the patients demonstrating mental stress–induced ischemia, women demonstrated a trend toward a more pronounced decrease in left ventricular ejection fraction during mental stress compared with the men (11% ± 9% vs 1% ± 7%, respectively, $p < 0.06$) but not in the stress-induced wall motion worsening score (5.0 ± 1.4 vs 3.5 ± 2.4, respectively, p = NS).

Discussion

These results demonstrate that women (particularly women with coronary artery disease) have greater cardiovascular responses to mental stress than do men. Also of importance, cardiovascular stress responses appear to be greatly enhanced among women of postmenopausal age compared with those of men and premenopausal women, especially with regard to blood pressure. Although in this small data set the observed enhanced cardiovascular reactivity among the postmenopausal women was not associated with a greater frequency of induced myocardial ischemia, we cannot discount the possibility that this enhanced hemodynamic stress response may have an adverse effect in terms of triggering cardiac events.

The mechanisms responsible for the greater cardiovascular stress responses among women compared with men are unknown. Prior studies among healthy populations have demonstrated that young women have a higher heart rate reactivity than do young men,[16,17] similar to our findings among the normal volunteer subjects. These sex-related differences have been found to emerge at the time of adolescence, suggesting that reproductive hormones play a role in their determination.[18] Two prior studies that evaluated older healthy subjects have reported findings similar to ours with regard to elevated blood pressure reactivity during mental stress among postmenopausal women when compared with premenopausal women.[19,20] Owens et al.[19] have demonstrated that these group differences correlate with low serum estradiol levels but not plasma catecholamine levels, suggesting that estrogen deficiency plays a role in elevating cardiovascular reactivity among postmenopausal women. Alternatively, poor physical exercise habits or comorbid conditions such as hypertension that are prevalent in older women may result in greater cardiovascular reactivity because of deconditioning.

Elevated cardiovascular reactivity can have adverse consequences, both in terms of enhancing the atherosclerotic process and in triggering cardiac events such as myocardial infarction and cardiac death. These data, as well as previous data from our laboratory[21] and others,[22] demonstrate that elevated cardiovascular reactivity is associated with greater falls in left ventricular ejection

fraction, independent of the presence of coronary artery disease. Work in animals has also demonstrated that elevated cardiovascular reactivity, measured by heart rate surges in cynomolgus monkeys in response to a threatening stimulus, is associated with greater atherosclerosis,[8] possibly through mechanisms of greater endothelial injury and subsequent cholesterol infiltration. Studies in human beings have shown that elevated blood pressure reactivity is associated with future cardiac events such as myocardial infarction and sudden death,[9,10] possibly through an association with coronary artery vasoconstriction[23] and resultant myocardial ischemia[24] or triggering of atherosclerotic plaque rupture.[25] The current results' lack of concordance with our previous results demonstrating an association between elevated cardiovascular reactivity and myocardial ischemia[24] is likely the result of our small subgroup sample sizes.

The current study findings help further our understanding of women with coronary artery disease. Although previous studies have found that women with coronary artery disease have a more adverse prognosis when compared with men,[1,2] a biologic basis for this has not been clearly elucidated. More advanced age and adverse baseline risk factor profiles among women as compared with men appear to account for some of this difference.[1,2] Sex-related differences in the management of coronary artery disease[26] may also play a role, although recent analyses question this.[27,28] The current study findings support an additional explanation for these sex-related differences in outcomes. Our results suggest the hypothesis that enhanced hemodynamic responses to stress in postmenopausal women with coronary artery disease may place women at greater risk for adverse cardiac events, possibly via triggering of plaque rupture or myocardial ischemia. Pertinent to the current study findings, Williams et al.[5] demonstrated that surgical menopause via bilateral oophorectomy elevates coronary artery vascular reactivity in cynomolgus monkeys. Work in both animals[5] and human beings[6] has documented that subsequent estrogen replacement re-establishes normal vasomotor responses in coronary and brachial arteries among estrogen-deficient female subjects.

Limitations

The current study has several limitations. First, we did not have serum hormonal determinations on the women to confirm their premenopausal or postmenopausal status and thus used an age criteria for this purpose. This limitation precludes drawing any direct conclusions regarding a relationship between low estrogen levels and elevated cardiovascular reactivity from our data, although previous work has documented this relationship.[19] Second, our age cutoff of 55 years for postmenopausal status is a conservative estimate that possibly may have excluded some younger women that were postmenopausal. It is possible that larger group differences would have been observed with a less conservative age cutoff. Testing with prospective identification of menopausal status is clearly indicated. Third, we tested the premenopausal women in our study without regard to the phase of their menstrual cycle. Although previous work by Stoney et al.[29] suggests that cardiovascular response to stress does not vary according to the phases of the menstrual cycle, firm conclusions regarding this have not been drawn. Finally, our retrospective analysis, cross-sectional study design, lack of women <55 years with coronary artery disease, and small subgroup sample sizes limited the generalizability of our results. Further prospective work assessing cardiovascular response to stress with larger numbers of women is needed to adequately test this hypothesis.

Implications

Previous work has hypothesized a vascular reactivity mechanism to in part explain the adverse cardiovascular effects of estrogen deficiency in women. These results provide preliminary support for this as a biologic mechanism and suggest that elevated cardiovascular response to stress may contribute to more adverse outcomes in postmenopausal women with coronary artery disease. Accordingly, estrogen replacement therapy may improve outcomes in postmenopausal women with coronary artery disease by reducing the cardiovascular response to stress. Studies have demonstrated that estrogen treatment improves coronary[6] and brachial[30] artery vasoreactivity, as well as exercise duration,[31] in postmenopausal women. Further prospective work is needed to explore the relationship between serum hormone level, hemodynamic and vasomotor responses, and cardiac mortality among women with coronary artery disease, as well as the possible therapeutic effect of estrogen treatment.

References

1. Greenland P, Reicher-Reiss H, Goldbourt U, Behar S. In-hospital and 1-year mortality in 1524 women after myocardial infarction: comparison with 4315 men. Circulation 1991;83:484-91.

2. Tofler GH, Stone PH, Muller JE, Willich SN, Davis VG, Poole WK. Effects of gender and race on prognosis after myocardial infarction: adverse prognosis for women, particularly black women. J Am Coll Cardiol 1987;9:473-82.
3. Eaker ED, Chesebro JH, Sacks FM, Wenger NK, Whisnant JP. American Heart Association medical/scientific statement on cardiovascular disease in women. Circulation 1993;88:1999-2009.
4. Barrett-Connor E, Bush TL. Estrogen and coronary heart disease in women. JAMA 1991;265:1861-7.
5. Williams JK, Adams MR, Klopfenstein HS. Estrogen modulates responses of atherosclerotic coronary arteries. Circulation 1990;81:1680-7.
6. Reis SE, Gloth ST, Blumenthal RS, Resar JR, Zacur HA, Gerstenblith G, et al. Ethinyl estradiol acutely attenuates abnormal coronary vasomotor responses to acetylcholine in postmenopausal women. Circulation 1994;89:52-60.
7. Lin AL, McGill HC, Shain SA. Hormone receptors of the baboon cardiovascular system. Circ Res 1982;50:610-6.
8. Manuck SB, Kaplan JR, Clarkson TB. Behaviorally induced heart rate reactivity and atherosclerosis in cynomolgus monkeys. Psychosom Med 1983;45:95-108.
9. Sparrow D, Tifft CP, Rosner B, Weiss S. Postural changes in diastolic blood pressure and the risk of myocardial infarction: the normative aging study. Circulation 1984;70:533-7.
10. Alderman MH, Ooi WL, Madhavan S, Cohen H. Blood pressure reactivity predicts myocardial infarction among treated hypertensive patients. J Clin Epidemiol 1990;43:859-66.
11. Rozanski A, Bairey CN, Krantz DS, Friedman J, Resser KJ, Morell M,et al. Mental stress and silent myocardial ischemia in coronary artery disease patients. N Engl J Med 1988;318:1005-12.
12. Blumenthal JA, Jiang W, Waugh RA, Frid DJ, Morris JJ, Coleman RE, et al. Mental stress-induced ischemia in the laboratory and ambulatory ischemia during daily life: association and hemodynamic features. Circulation 1995;92:2102-8.
13. Diamond GA, Staniloff HM, Forrester JS, Pollack BH, Swan HJC. Computer assisted diagnosis in the noninvasive evaluation of patients with suspected coronary artery disease. J Am Coll Cardiol 1983;1:444-55.
14. Rozanski A, Berman DS, Gray R, Diamond G, Raymond M, Prause J, et al. Preoperative prediction of reversible myocardial asynergy by postexercise radionuclide ventriculography. N Engl J Med 1982;307:212-6.
15. Krailo MD, Pike MC. Estimation of the distribution of age at natural menopause from prevalence data. Am J Epidemiol 1983;117:352-9.
16. Stoney CM, Matthews KA, McDonald RH, Johnson CA. Sex differences in lipid, lipoprotein, cardiovascular, and neuroendocrine responses to acute stress. Psychophysiology 1988;25:645-56.
17. Weidner G, Friend R, Ficarrotto TJ, Mendell NR. Hostility and cardiovascular reactivity to stress in women and men. Psychosom Med 1989;51:36-45.
18. Matthews KA, Stoney CM. Influence of sex and age on cardiovascular responses during stress. Psychophysiology 1988;50:46-56.
19. Owens JF, Stoney CM, Matthews KA. Menopausal status influences ambulatory blood pressure levels and blood pressure changes during mental stress. Circulation 1993;88:2794-802.
20. Saab PG, Matthews KA, Stoney CM, McDonald RH. Premenopausal and postmenopausal women differ in their cardiovascular and neuroendocrine responses to behavioral stressors. Psychophysiology 1989;26:270-80.
21. Bairey CN, de Yang L, Berman DS, Rozanski A. Comparison of physiologic ejection fraction responses to activities of daily living: implications for clinical testing. J Am Coll Cardiol 1990;16:847-54.
22. Becker LC, Pepine CJ, Bonsall R, Cohen JD, Goldberg AD, Coghlan C, et al. Left ventricular, peripheral vascular, and neurohumoral responses to mental stress in normal middle-aged men and women: reference group for Psychophysiological Investigations of Myocardial Ischemia (PIMI) Study. Circulation 1996;94:2768-77.
23. Yeung A, Vekshtein VI, Krantz DS, Vita JA, Ryan TJ, Ganz P, Selwyn AP. The effect of atherosclerosis on the vasomotor response of coronary arteries to mental stress. N Engl J Med 1991;325:1551-6.
24. Krantz DS, Helmers KF, Bairey CN, Nebel LE, Hedges SM, Rozanski A. Cardiovascular reactivity and mental stress-induced myocardial ischemia in patients with coronary artery disease. Psychosom Med 1991;53:1-12.
25. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. Circulation 1989;79:733-43.
26. Steingart RM, Packer M, Hamm P, Coglianese ME, Gersh B, Geltman EM, et al. Sex differences in the management of coronary artery disease. N Engl J Med 1991;325:226-30.
27. Bickell NA, Pieper KS, Lee KL, Mark DB, Glower DD, Pryor DB, et al. Referral patterns for coronary artery disease treatment: gender bias or good clinical judgment? Ann Intern Med 1992;116:791-7.
28. Mark DB, Shaw LK, DeLong ER, Califf RM, Pryor DB. Absence of sex bias in the referral of patients for cardiac catheterization. N Engl J Med 1994;330:1101-6.
29. Stoney CM, Owens JF, Matthews KA, Davis MC, Caggiula A. Influences of the normal menstrual cycle on physiologic functioning during behavioral stress. Psychophysiology 1990;27:125-35.
30. Lieberman EH, Gerhard MD, Uehata A, Walsh BW, Selwyn AP, Ganz P, et al. Estrogen improves endothelium-dependent flow-mediated vasodilation in postmenopausal women. Ann Intern Med 1994;121:936-41.
31. Rosano GMC, Sarrel PM, Poole-Wilson PA, Collins P. Beneficial effect of oestrogen on exercise-induced myocardial ischaemia in women with coronary artery disease. Lancet 1993;342:133-6.