Anger in Young Men and Subsequent Premature Cardiovascular Disease

The Precursors Study

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Background: Anger can trigger myocardial ischemia and may be an independent risk factor for coronary heart disease, but its effect on early compared with late onset of disease is unclear.

Methods: We performed a prospective study of 1055 men followed up for 32 to 48 years to examine the risk of premature and total cardiovascular disease (CVD) associated with anger responses to stress during early adult life. Highest level of anger was defined as a self-report of all 3 possible anger reactions to stress (expressed or concealed anger, gripe sessions, and irritability) on a checklist questionnaire administered in medical school. Premature disease was defined as events before age 55 years.

Results: During a median follow-up period of 36 years, 205 men developed CVD (cumulative incidence at 76 years, 34.5%), of whom 77 men developed premature disease (cumulative incidence before 55 years, 7.9%). The highest level of anger was associated with an increased risk of premature CVD (adjusted relative risk, 3.1; 95% confidence interval, 1.1-8.6), including premature coronary heart disease (relative risk, 3.5; 95% confidence interval, 1.1-11.8) and premature myocardial infarction (relative risk, 6.4; 95% confidence interval, 1.8-22.3), compared with lower levels of anger. When CVD events after age 55 years were included, there was no longer a statistically significant association between anger and CVD.

Conclusion: High level of anger in response to stress in young men is associated with an increased risk of subsequent premature CVD, particularly myocardial infarction.

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Despite effective therapies and preventive efforts, coronary heart disease (CHD) remains the primary cause of morbidity and mortality, with 15% of CHD deaths occurring before age 65 years. Anger and hostility have been related to an increased risk of cardiovascular disease. The association of anger with heart disease may be mediated acutely through catecholamine release and increased cardiovascular reactivity. Chronically, anger may influence risk through established cardiac risk factors, such as hypertension or depression. Secondary prevention programs designed to reduce stress and anger in persons with CHD show a decreased incidence of recurrent ischemic events. If confirmed, these findings would provide strong evidence that the association between anger and CHD is causal.

Most prospective studies of the effect of anger on CHD have focused on middle-aged or older populations. Only 2 studies have prospectively assessed the risk of CHD associated with anger in young adults: a study of male medical students followed up for 25 years showed that higher levels of anger were associated with an increased incidence of CHD, whereas another study of college men followed up for 33 years found no such relationship. Such studies assume that anger is a trait that remains constant over time and affects CHD incidence uniformly throughout follow-up. In these studies, change in expression of anger at younger vs older ages was not accounted for, and no distinction was made between early vs late onset of disease. Because some cardiovascular disease (CVD) risk factors are more prevalent at older ages, anger may play a lesser role in CHD at older ages.

The Johns Hopkins Precursors Study, a longitudinal study of 1337 medical students initiated by Caroline Bedell Thomas, MD, in 1946, affords the unique opportunity to study prospectively the long-term relationship of anger responses in young adulthood to cardiovascular health before and after middle age and to adjust...
SUBJECTS AND METHODS

STUDY POPULATION

While they were in medical school, participants in the Johns Hopkins Precursors Study underwent a standardized medical examination and completed questionnaires about their personal and family history, health status, health behaviors, and reaction to stress.22,23 The cohort has been followed up after graduation by annual mailed questionnaires, with an average response rate of 90% over every 5-year period. Vital status of nonrespondents was ascertained by telephoning them, contacting family members, scanning obituaries, and systematically searching the National Death Index (last search in 1997). Vital status is known for more than 99% of the cohort. Self-reports of measures of personal health and disease by this cohort have been extremely accurate.24 It was not customary to obtain informed consent during the period in which the baseline data were collected. After the Joint Committee on Clinical Investigation was established at our institution, the follow-up protocol was reviewed and approved.

The study sample originally consisted of 1337 members of the graduating classes of 1948 to 1964. Excluded from this analysis were the small number of women (n=121), those who did not answer the questions about anger reactions to stress in medical school (n=133), those who reported CVD before graduation (n=2), and those who died in medical school or were unavailable for follow-up (n=26), leaving 1055 men for analysis.

MEASURES OF ANGER

Information on reactions to stress was obtained by means of the Habits of Nervous Tension Questionnaire (HNT).22 In response to the question, “Whenever you find yourself in situations of undue pressure or stress, how do you usually react?” respondents could check any of 27 items. After factor analysis and ς correlation matrix determination, 3 items were defined as indicating anger: “expressed or concealed anger,” “irritability,” and “gripe sessions.”25

The HNT was readministered as part of the 1992 questionnaire, a mean of 43 years after graduation. Although only 3 men reported all 3 anger items at baseline and in 1992, responses to the anger items remained clustered together at both assessments. Consequently, the same anger construct was identified in both assessments.26

The validity of the anger measure was supported by its association with the Multidimensional Anger Inventory questionnaire27 completed by 700 men (84.8% of those alive) in 1988. Anger at baseline was significantly correlated with total Multidimensional Anger Inventory score and Anger-In, Anger-Arousal, Hostile Outlook, and Range of Anger-Eliciting Situations factor-derived scales; the correlation coefficients ranged from 0.10 (P=.007) on the Hostile Outlook factor to 0.18 (P<.001) on the total Multidimensional Anger Inventory score. Men with all 3 anger responses in medical school who completed the Multidimensional Anger Inventory (n=16) also had higher scores on each subscale of the inventory than did those with fewer anger responses; given the small sample size, this association was statistically significant only for the overall score (P= .01).

COVARIATES

Information about body weight, height, smoking, alcohol consumption, hypertension, hyperlipidemia, parental health history, diabetes mellitus, and clinical depression was gathered at baseline and during follow-up from annual questionnaires and medical records. Hypertension was defined as a blood pressure of 160/105 mm Hg or greater on 1 annual questionnaire, 140/90 mm Hg on at least 2 readings 1 week or more apart, or pharmacologic treatment of hypertension. Body mass index was defined as weight in kilograms divided by the square of height in meters. Starting with the class of 1949, nonfasting serum cholesterol was measured during medical school.25 Premature parental CHD was defined as development of CHD before age 55 years in a participant’s father or before age 65 years in his mother.28

Number of cigarettes smoked per day was categorized as follows: 0, 1 to 10, 11 to 20, 21 to 39, and 40 or more. Alcohol consumption, hypertension, hyperlipidemia, parental health history, diabetes mellitus, and clinical depression was gathered at baseline and during follow-up from annual questionnaires and medical records. Hypertension was defined as a blood pressure of 160/105 mm Hg or greater on 1 annual questionnaire, 140/90 mm Hg on at least 2 readings 1 week or more apart, or pharmacologic treatment of hypertension. Body mass index was defined as weight in kilograms divided by the square of height in meters. Starting with the class of 1949, nonfasting serum cholesterol was measured during medical school.

RESULTS

Characteristics of the cohort are presented in Table 1 by number of anger responses. Most participants were white, smoked during medical school, drank alcohol, and had no parental history of premature CHD by the end of follow-up. Levels of serum cholesterol, body mass index, and mean blood pressures were similar across anger groups.

Of the 1055 men who answered the HNT in medical school, 229 men reported experiencing expressed or concealed anger; 169, gripe sessions; and 99, irritability. Twenty-one men reported the highest level of anger (all 3 anger items) in response to stress.

Median total follow-up for the cohort was 36 years (range, 4-48 years). Their average age in 1995 (n=921) was 64.5 years (range, 54-93 years). The cumulative incidence of CVD was 34.5% at age 76 years (n=205), with a median age at onset of 56 years. Of the 205 men who developed CVD, 145 men had CHD (94 with MI), and 59 men reported stroke; 128 men (62.4%) had medical records confirming their diagnoses. The cumulative incidence of premature CVD was 7.9% (n=77), with a median age at onset of 49 years. Of the 77 men with premature CVD, 56 had CHD (34 with MI), and 13 reported premature stroke.

The Figure presents the Kaplan-Meier incidence plot of CVD according to number of anger responses. Few men reported all 3 anger responses, and only 6 CVD events occurred in this group. Although the number of events was small, the incidence of CVD was significantly higher for those with the highest level of anger compared with those with lower levels of anger. The difference in CVD incidence between the groups decreased after age 55 years.

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consumption was categorized as current, former, or none. Depression was defined as self-reported clinical depression lasting more than 2 weeks and not related to grief.

OUTCOME MEASURES

The main outcomes for this analysis were incidence of premature CVD, defined as events before age 55 years, and total CVD after graduation from medical school through December 31, 1995. At the end of follow-up, 99.9% of the cohort was aged 55 years or older. Cardiovascular disease was defined as follows: CHD, composed of myocardial infarction (MI), sudden death, angina, chronic ischemic heart disease, and other coronary disease that required coronary bypass surgery or percutaneous coronary interventions; hypertensive heart disease; congestive heart failure; cerebrovascular disease; atherosclerosis; aortic aneurysm; peripheral vascular disease; and arterial embolization.

Diagnoses of CVD were assessed by annual questionnaires inquiring about medical conditions in checklist format and by medical records submitted by participants or their health care providers. Information on treatment was assessed throughout follow-up. Diagnoses were assigned by a committee of 5 physicians after review of all available information.

STATISTICAL ANALYSIS

The primary independent variable was the highest level of anger, defined as having all 3 self-reported reactions of anger to stress on the baseline HNT survey. A lower level of anger, defined as having any one of the anger reactions, was not examined with this analysis. The relationship of the highest level of anger with covariates was examined with t tests, analysis of variance, and χ² tests. Relationships of the highest level of anger and the number of reported anger reactions with subsequent incidence of premature and total CVD outcomes were examined with Kaplan-Meier analysis and the log-rank test to assess statistical significance. Age was the time variable used in all survival analysis.

Cox proportional hazards analysis was used to estimate relative risk (RR) and 95% confidence intervals (CIs) and to determine whether associations with premature and total CVD were independent of covariates. Covariates included serum cholesterol level, body mass index, alcohol use, and parental history of premature CHD, as well as cigarette smoking, hypertension, diabetes, and depression occurring during follow-up. The effects of a change in cigarette-smoking status and the development of hypertension, diabetes, and depression during follow-up were assessed by including time-dependent covariates for these variables in Cox models. To account for possible secular trends in anger level and incidence of CVD, Cox models were stratified according to calendar time: 1948 through 1957 and 1958 through 1964. Time-dependent covariates were also used to test the proportionality assumption. Relationships of each anger reaction alone and paired combinations of the anger reactions with subsequent premature and total CVD incidence were examined.

Because the small number of cases in the highest anger group limited power, bivariate analysis was performed with serum cholesterol level, body mass index, parental history of premature CHD, cigarette smoking, hypertension, diabetes, depression, and alcohol use. Multivariate models were also constructed including all variables. To ascertain whether any relationship of anger with CVD was mediated through associations with depression and anxiety, measures of these psychological states were derived from the HNT. These depression and anxiety constructs did not include any of the anger items and were used in Cox models as continuous variables.

To examine potential physiologic mechanisms of anger, the association of the HNT anger measure with vascular reactivity was examined with analysis of variance and t tests. Vascular reactivity was defined as the systolic blood pressure response to the cold pressor test administered to 1028 men (97.4%) during the baseline examination in medical school. Alpha levels of less than .05 based on a 2-tailed test were used to define statistical significance. All analyses were performed with the SAS statistical package, version 6.12 (SAS Institute Inc, Cary, NC).

Inspection of the data suggests that the effect of anger on cardiovascular risk is different in the early years than in the late years of follow-up. Although the proportionality assumption was confirmed by statistical analysis, power was limited.

In univariate analysis, the highest level of anger was associated with a greater incidence of subsequent premature CVD events, particularly MI (Table 2). The RR of premature MI was 3-fold higher for those who reported the highest level of anger than for those who reported lower levels. There was no statistically significant association between the highest level of anger and premature stroke (RR, 4.3; 95% CI, 0.6-32.9), although the number of premature strokes was small (n = 13) and CIs were correspondingly wide. When each anger reaction was examined separately, the small number of events may have limited power. None of the risk estimates with a single anger item or in pairwise combination were statistically significant.

In bivariate analysis with traditional CVD risk factors listed in Table 1, the highest level of anger remained independently associated with increased risk of premature MI, CHD, and CVD, although the 95% CI frequently included 1.0 for CHD (data not shown). In multivariate analysis including all risk factors, despite concerns of limited power, anger remained an independent predictor of premature MI, CHD, and CVD (Table 2).

Anger was related to the HNT measures of depression (P < .001) and anxiety (P = .006). In multivariate analysis adjusting for HNT depression and anxiety measures, the highest level of anger remained independently associated with risk of premature MI (RR, 3.9; 95% CI, 1.1-13.4). Results were similar for premature CVD and CHD.

When all cases of CVD, before and after age 55 years, were analyzed as an outcome, the highest level of anger was associated with a slightly increased risk of CVD that was not statistically significant (Table 2). When CVD events within the first 55 years of age were censored, there was no association between the highest level of anger and any CVD outcome, suggesting no relationship between anger at baseline and CVD occurring at older ages.
A high level of anger demonstrated a trend toward greater vascular reactivity as assessed during medical school. Men with all 3 anger reactions (n=21) had a slightly greater increase in systolic blood pressure in response to the cold pressor test (15.2±8.5 mm Hg) than those with fewer anger reactions (n=1007; 12.1±8.4 mm Hg; P=.03). Men with 2 or fewer anger responses had similar mean changes in systolic blood pressure (no anger responses, 12.3±8.4 mm Hg; 1 anger response, 12.0±8.0 mm Hg; 2 anger responses, 11.5±9.9 mm Hg; P=.68).

The present study isolates the powerful effect of a high level of anger in young men on subsequent incidence of premature CVD, particularly MI, during 48 years of follow-up. These increased risks were present only for premature CVD events, but similar trends were seen for CVD during all of the follow-up period. The relationship between the highest level of anger and incident CVD was specific, as 1 or 2 anger responses were not associated with increased risk of subsequent premature CVD. Moreover, no specific anger reaction was more or less predictive than another. Adjustment for other CVD risk factors did not substantially change the RR of premature CVD associated with anger. Although the number of premature events was small in this cohort, the relationship of a high level of anger with premature disease was statistically significant. We did not have the power to differentiate threshold effect vs a dose-response relationship.

Previous prospective studies, most conducted in midlife with a follow-up of less than 10 years, have shown a relationship between anger or hostility and increased risk of CVD.11-21 A recent analysis in the Atherosclerosis Risk in Communities Study sample demonstrated a dose-response relationship between anger and CHD.19 Similar to the current study, the increased risk of CHD was statistically significant only in individuals with high trait anger, particularly those who were normotensive. The longest study, with 27 years of follow-up, observed that higher scores on the abbreviated Cook-Medley Hostility Scale in 50-year-old men and women predicted subsequent acute MI.15 Only 2 previous prospective studies have been carried out in young persons. One analysis of 255 medical students found hostility predictive of CHD, but only hypertension was available as a covariate.20 Another study found no relationship but did not differentiate early from late events.21

Although the exact mechanism by which anger may cause premature CVD remains unclear, anger may have a role in underlying atherogenesis as well as triggering clinical events. Angry people have increased platelet reactivity and hyperaggregability.30 Anger also increases cardiovascular reactivity as manifest by increased catecholamine levels, heart rates, and blood pressure.31,32 High levels of anger during anger recall have produced coronary vasoconstriction of narrowed arteries, but not of nonnarrowed arteries.31 In patients with stable coronary artery disease, anger recall reduced left ventricular ejection fraction and cardiac output, and increased diastolic blood pressure and peripheral vascular resistance, more than exerci-
cise or other psychological stressors.34-36 In our cohort, vascular reactivity was not associated with CVD.37 However, men with the highest level of anger tended to have greater vascular reactivity than men with lower levels. This association suggests that the group with highest anger differs physiologically from those with lower anger levels. Additional physiological responses should be studied to determine mediators of the anger-CVD association.

One explanation for our findings may be that those who experienced a coronary event at a young age already had premature coronary atherosclerosis that was further exacerbated by a high level of anger. Another possibility is that anger assessed in young adulthood may not predict CVD events after age 55 years because other CVD risk factors become more important later in life or the level of anger changes over time. Additional follow-up in this cohort to ascertain CVD events after 1992, when anger was assessed for a second time, will aid in sorting out these competing hypotheses.

Potential limitations of this study should be discussed. Because the number of men with the highest level of anger was small, misclassification of 1 person can make a large difference. Moreover, our results are strictly generalizable to white men of high socioeconomic status. Nonetheless, the RR estimates are likely generalizable because potential biases, such as socioeconomic factors, would tend to affect those with and those without the highest level of anger to a similar degree. Because this analysis included only men, however, these results cannot be applied to women. As in most observational studies, anger responses were based on subjective assessment by respondents and not on observation during an interview. The correlation of the anger construct with vascular reactivity was not associated with CVD.29 However, another anger measure later in life and similar structure in factor analysis in assessments separated by decades supported this construct validity. Furthermore, the association of anger with incident CVD was not explained by its relationship with depression and anxiety.

In this study, the highest level of anger assessed with a brief self-administered questionnaire indicated an elevated risk for premature MI and other premature CVD events. Community studies in older populations have observed that secondary prevention efforts to reduce stress and anger may lead to decreased incidence of recurrent ischemic events.11,37,38 Whether knowledge about anger can be translated into effective primary prevention strategies in younger populations needs to be determined.

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REFERENCES


Table 2. Cumulative Incidence and Relative Risks of Premature and Total Cardiovascular Disease, Associated With Highest Level of Anger Response to Stress Compared With Lower Levels of Anger*

<table>
<thead>
<tr>
<th>Disease and Anger Level</th>
<th>No. of Cases</th>
<th>Cumulative Incidence Before Age 55 y, %</th>
<th>Crude RR (95% CI)</th>
<th>Adjusted RR (95% CI)†</th>
<th>No. of Cases</th>
<th>Cumulative Incidence at Age 70 y, %</th>
<th>Crude RR (95% CI)</th>
<th>Adjusted RR (95% CI)†</th>
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<tr>
<td>Highest</td>
<td>4</td>
<td>20.2†</td>
<td>2.9 (1.1-8.0)‡</td>
<td>3.1 (1.1-8.6)‡</td>
<td>6</td>
<td>37.9</td>
<td>1.7 (0.7-3.7)</td>
<td>1.5 (0.7-3.4)</td>
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<td>Lower</td>
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<td>7.6</td>
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<td>1.0</td>
<td>199</td>
<td>28.9</td>
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<td>Highest</td>
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<td>14.8</td>
<td>3.0 (0.9-9.5)</td>
<td>3.5 (1.1-11.8)‡</td>
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<td>Lower</td>
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<td>13.6</td>
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*P<.05.
†P=.05.


