Symptoms of Anxiety and Risk of Coronary Heart Disease

The Normative Aging Study

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Background Several studies have suggested an increased risk of fatal coronary heart disease (CHD) among patients with panic disorder, phobic anxiety, and other anxiety disorders. We prospectively examined this association in the Normative Aging Study.

Methods and Results An anxiety symptoms scale was constructed out of five items from the Cornell Medical Index, which was administered to the cohort at baseline. During 32 years of follow-up, we observed 402 cases of incident coronary heart disease (137 cases of nonfatal myocardial infarction, 134 cases of angina pectoris, and 131 cases of fatal CHD—made up of 26 cases of sudden cardiac death and 105 cases of nonsudden death). A nested case-control design (involving 1869 control subjects who remained free of diagnosed CHD) was used to assess the association between anxiety and risk of CHD. Compared with men reporting no symptoms of anxiety, men reporting two or more anxiety symptoms had elevated risks of fatal CHD (age-adjusted odds ratio [OR]=3.20, 95% confidence interval [CI]: 1.27 to 8.09), and sudden death (age-adjusted OR=5.73, 95% CI: 1.26 to 26.1). The multivariate OR after adjusting for a range of potential confounding variables was 1.94 (95% CI: 0.70-5.41) for fatal CHD and 4.46 (95% CI: 0.92-21.6) for sudden death. No excess risks were found for nonfatal myocardial infarction or angina.

Conclusions These data suggest an association between anxiety and fatal coronary heart disease, in particular, sudden cardiac death. (***Circulation.* 1994;90:2225-2229.**)

Key Words • coronary disease • risk factors • aging

Several studies have suggested that chronic anxiety is associated with an increased risk of coronary heart disease.[1-3] Recently, two prospective cohort studies have found a strong association between self-reported symptoms of phobic anxiety and risk of fatal coronary heart disease (CHD).[4,5] In the Northwick Park Heart Study,[4] an ongoing cohort of 1457 British men, high levels of anxiety were associated with relative risks of fatal CHD of 3.77 (95% confidence interval [CI]: 1.64 to 8.64). In that study, the presence of anxiety was assessed using the Crown-Crisp index,[6] an 8-item self-rated scale that elicits common symptoms of phobic anxiety. Using the same index of phobic anxiety, Kawachi et al[5] prospectively examined the association of anxiety to risk of CHD in the Health Professionals Follow-up Study, an ongoing cohort of 33 999 US men aged 42 to 72 years in 1986. The relative risk of fatal CHD among men with the highest levels of anxiety was 2.45 (95% CI: 1.00 to 5.96) compared with men reporting no symptoms of anxiety. When fatal CHD was further categorized into sudden cardiac death and nonsudden cardiac death, the excess risk was confined to sudden death (relative risk among men with highest levels of anxiety=6.08, 95% CI: 2.35 to 15.73).

The postulated mechanisms through which anxiety may increase the risk of fatal CHD include hyperventilation during an acute attack, which could in turn induce coronary spasm,[7] or an acute attack of anxiety triggering an episode of fatal ventricular arrhythmias.[8,9] In the present study, we examined the association between symptoms of anxiety and risk of coronary heart disease in the Normative Aging Study, an ongoing prospective cohort study.

Methods

The Normative Aging Study is a longitudinal study of aging established by the Veteran Administration in 1961.[10] The study cohort consists of 2280 community-dwelling men from the Greater Boston area who were aged 21 to 80 years at the time of entry. Volunteers were screened at entry according to health criteria,[10] and were free of known chronic medical conditions at the start of follow-up.

Assessment of Exposures

In the first phase of screening, the Cornell Medical Index[11] was administered to all participants. We constructed a five-item anxiety symptom scale out of questions selected from the Cornell Medical Index. The five individual items selected were similar to items included in existing, validated psychological assessment scales, such as the Brief Symptom Inventory,[12] the Spielberger State-Trait Anxiety Inventory,[13] the Hamilton Rating Scale for Anxiety,[14] and the Crown-Crisp index.[6] We selected the following five items to construct our anxiety scale: "Do strange people or places make you afraid?"; "Are you considered a nervous person?"; "Are you constantly keyed up and jittery?"; "Do you often become suddenly scared for no good reason?"; and "Do you often break out in a cold sweat?" The items were selected in an a priori manner, i.e., before any

Received March 31, 1994; revision accepted July 2, 1994.

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analyses had been carried out. A positive response to any of these questions scored 1, while a negative response scored 0. Our anxiety symptom scale therefore ranged from 0 to 5, with higher scores indicating higher levels of anxiety. For the purposes of analysis, we categorized responses to our anxiety scale into scores of 0, 1, and 2 or more. These cut-points were arrived at from an a priori categorization of scores, based on an assessment of the score distribution in the whole cohort (in which 89.3% scored 0, 8.8% scored 1, and 1.9% scored 2 or more).

We assessed the validity of the scale we constructed against the Crown-Crisp experiential index,[6] which was the instrument used in the two previous prospective studies that suggested an association between anxiety and fatal coronary heart disease (ie, the Northwick Park Heart Study[4] and the Health Professionals Follow-up Study[5]). The Crown-Crisp index is an eight-item questionnaire, with possible scores ranging from 0 (no symptoms of phobic anxiety) to a maximum of 16. We administered the Crown-Crisp index to 936 members of the Normative Aging Study cohort and compared their scores to the responses to our own anxiety scale derived from the Cornell Medical Index (CMI). Men who scored 0, 1, and 2 or higher on the CMI-derived scale scored 2.01 (95% CI: 1.88 to 2.13), 2.77 (95% CI: 2.17 to 3.36), and 4.40 (95% CI: 3.38 to 5.41), respectively, on the Crown-Crisp index.

Measurement of Other Cardiovascular Risk Factors

The baseline examination in the Normative Aging Study also included a medical history, physical examination, and a variety of biochemical laboratory tests. Serum cholesterol was measured with the calorimetric method of Sperry.[15] Blood pressure was measured by an examining physician using a standard mercury sphygmomanometer with a 14-cm cuff. With the subject seated, systolic blood pressure and fifth-phase diastolic blood pressure were measured in each arm to the nearest 2 mm Hg. The average systolic and diastolic blood pressures in both arms were used for analysis. Cigarette smoking status (current, former, never) was determined by a trained interviewer. Current smokers were defined as men who smoked one or more cigarettes daily. Weight and height were measured with the participants wearing only socks and underpants. Body mass index (weight/height^2) was then calculated. Alcohol drinking habits were ascertained from responses to the Cornell Medical Index ("Do you usually take two or more alcoholic drinks per day?" Yes/No). Similar examinations were repeated every 3 to 5 years. The data were supplemented by information on cardiovascular illness from hospital records.

The subjects for the current study were a subgroup of 2271 men in the Normative Aging Study. Seven men were excluded because of incomplete baseline information on the Cornell Medical Index. In addition, two men were excluded because they had possible coronary heart disease at baseline. All exposures were assessed prospectively (ie, before the onset of coronary heart disease).

Assessment of Morbidity and Mortality

We used a case-control design nested within a prospective epidemiologic study. The cases in our study consisted of 402 men who developed incident coronary heart disease between the baseline exam and March 1993. The diagnostic categories of coronary heart disease under consideration include nonfatal myocardial infarction (n=137), angina pectoris (n=134), and CHD deaths (n=131). The criteria for myocardial infarction and angina pectoris were those used in the Framingham Heart Study.[16] Myocardial infarction was diagnosed only when documented by unequivocal electrocardiographic changes (ie, pathologic Q waves), by a diagnostic elevation of serum enzymes (serum glutamic-oxaloacetic transaminase and lactic dehydrogenase) together with chest discomfort consistent with myocardial infarction, or by autopsy. Angina pectoris was diagnosed when the subject reported recurrent chest discomfort lasting up to 15 minutes, which was distinctly related to exertion or excitement and was relieved by rest or nitroglycerin. Death from coronary heart disease was designated when a death certificate (coded according to the Eighth Revision of the International Classification of Diseases[17]) indicated an underlying cause of death coded to rubric 410-414. Fatal coronary heart disease was then further categorized into cases of sudden cardiac death, and nonsudden CHD deaths. Sudden cardiac death was defined as death within one hour of the onset of symptoms when no previous serious illness was reported and no other possible cause of death (other than coronary disease) was reported.

The controls in the study consisted of all subjects who remained free of coronary heart disease throughout follow-up (n=1869). Exposure and covariate data from controls were collected at baseline in the same manner as the cases.

TABLE 1. Distributions of Cardiovascular Risk Factors Among Coronary Heart Disease Cases and Disease-Free Control Subjects

Cardiovascular Risk Factor	CHD Cases	Control Subjects
N*	402	1869
Age (years)	45.1	41.2†
	(9.4)	(9.2)
High school education or less (%)	52.0	46.0‡
Mean anxiety score	0.14	0.13
	(0.44)	(0.43)
Body mass index (kg/m^2)	26.1	25.6†
	(3.0)	(2.8)
Current smokers (%)	41.6	39.2
Former smokers (%)	32.5	31.1
Systolic blood pressure (mm Hg)	126.8	123.1†
	(12.3)	(11.6)
Diastolic blood pressure (mm Hg)	78.6	76.7†
	(7.8)	(7.9)
Serum cholesterol level (mg/dL)	217.9	201.9†
	(47.6)	(44.0)
Family history of heart disease (%)	13.3	10.1
Two or more drinks of alcohol per day (%)	10.4	12.7

*Complete data on all cardiovascular risk factors were available on 375 CHD cases and 1706 disease-free control subjects.

†$P<.01$, comparing cases to controls; ‡$P<.05$, comparing cases with controls.

SD values in parentheses.

Data Analysis

We performed logistic regression using the Statistical Analysis System (SAS)[18] to estimate age-adjusted odds ratios of coronary heart disease according to levels of anxiety. We also performed multiple logistic regression analysis, controlling for a range of potential confounding variables including: age (years); body mass index (kg/m^2); smoking status (never, current, former); systolic and diastolic blood pressure (mm Hg); serum cholesterol level (mg/dL); family history of heart disease (yes/no); and two or more drinks of alcohol per day (yes/no).

Results

Of the 2271 men, 402 developed CHD over the follow-up period. Total CHD was further categorized

TABLE 2. Age-Adjusted and Multivariate Odds Ratios of Coronary Heart Disease According to Anxiety Symptoms Score (95% Confidence Intervals in Parentheses)

		Anxiety Symptoms Score		
		0	1	2 or More
Controls				
	N	1670	166	33
	mv-N*	1530	143	33
Cases				
Total CHD	n	358	34	10
	OR	1.00	0.94	1.50
			(0.63-1.38)	(0.72-3.09)
	mv-N	333	33	9
	mv-OR†	1.00	1.09	1.07
			(0.72-1.64)	(0.48-2.35)
Nonfatal MI	n	123	11	3
	OR	1.00	0.89	1.31
			(0.47-1.69)	(0.39-4.34)
	mv-n	111	11	3
	mv-OR	1.00	1.08	1.03
			(0.56-2.09)	0.30-3.57)
Nonfatal CHD‡	n	247	20	4
	OR	1.00	0.81	0.85
			(0.50-1.31)	(0.30-2.44)
	mv-n	230	20	4
	mv-OR	1.00	0.97	0.71
			(0.59-1.60)	(0.24-2.09)
Fatal CHD	n	111	14	6
	OR	1.00	1.27	3.20
			(0.70-2.29)	(1.27-8.09)
	mv-n	103	13	5
	mv-OR	1.00	1.32	1.94
			(0.70-2.47)	(0.70-5.41)

CHD indicates coronary heart disease and MI, myocardial infarction.
*Number of subjects in multivariate (mv) analyses.
†Odds ratio adjusted for age, body mass index, smoking (never, current, former), systolic and diastolic blood pressure, serum cholesterol level, family history of heart disease, and two or more drinks of alcohol per day (yes/no).
‡Nonfatal myocardial infarction, plus angina pectoris.
95% confidence intervals in parentheses.

into 137 cases of nonfatal myocardial infarction, 134 cases of angina pectoris, and 131 cases of fatal CHD. The cases of fatal CHD were made up of 26 cases of sudden death, and 105 cases of nonsudden cardiac death.

We compared the cardiovascular disease risk factor distributions of CHD cases and control subjects (Table 1). As expected, CHD cases were slightly older than disease-free control subjects, had somewhat higher body mass index, higher serum cholesterol levels, and higher systolic and diastolic blood pressure levels ($P<.01$ for all comparisons). We adjusted for all the potential confounding variables listed in Table 1 in multivariate analyses described below.

When we performed logistic regression, there were no increases in either the age-adjusted odds ratios or the multivariate odds ratios of total CHD, nonfatal MI, or nonfatal CHD (nonfatal MI and angina pectoris), according to levels of anxiety symptoms (Table 2). By contrast, the age-adjusted odds ratio for fatal CHD was elevated (OR=3.20, 95% CI: 1.27 to 8.09, among men who scored 2 or more on the anxiety symptoms scale compared with men who scored 0). Because high levels of anxiety are associated with cigarette smoking,[19] we adjusted the odds ratios for smoking habit as well as body mass index, systolic and diastolic blood pressure, serum cholesterol level, family history of heart disease, and an indicator variable for whether they drank two or more drinks of alcohol per day. When this was done, the estimate of the multivariate odds ratio for fatal CHD was attenuated and became nonsignificant (OR for 2 or more symptoms=1.94; 95% CI: 0.70-5.41). Because of

TABLE 3. Age-Adjusted and Multivariate Odds Ratios of Sudden Cardiac Death and Nonsudden Cardiac Death According to Anxiety Symptoms Score

		Anxiety Symptom Score		
		0	1	2 or More
Controls	n	1670	166	33
	mv-n	1530	143	33
Cases				
Sudden death	n	19	5	2
	OR	1.00	2.66	5.73
			(0.97-7.23)	(1.26-26.1)
	mv-n	18	5	2
	mv-OR†	1.00	2.96	4.46
			(1.02-8.55)	(0.92-21.6)
Nonsudden death	n	92	9	4
	OR	1.00	0.99	2.77
			(0.49-2.03)	(0.93-8.25)
	mv-n	85	8	3
	mv-OR	1.00	0.97	1.49
			(0.45-2.10)	(0.42-5.27)

*Number of subjects in multivariate (mv) analyses.
†Adjusted for age, smoking (never, current, former), systolic and diastolic blood pressure, serum cholesterol level, family history of heart disease, and two or more drinks of alcohol per day (y/n).
95% confidence intervals in parentheses.

missing data on covariates, the numbers of cases and control subjects in the multivariate analyses are slightly less than the corresponding numbers in the age-adjusted analyses.

When we examined diagnostic categories within fatal CHD, elevated odds ratios were found for sudden cardiac death. Although based on a small number of cases, the multivariate odds ratio was 2.96 (95% CI: 1.02-8.55) for men who scored 1 on the anxiety scale compared with men who scored 0; and 4.46 (95% CI: 0.92-21.6) for men who scored 2 or higher. There appeared to be little elevation in the risk for nonsudden causes of cardiac death (Table 3).

Discussion

There have been few epidemiologic studies of psychosocial risk factors for sudden cardiac death. Sudden death has proved to be a difficult endpoint to study using the case-control design, as investigators have been forced to make retrospective assessments of exposure from proxy respondents (since the index cases are, by definition, dead). Proxy respondents may be biased in their recall of anxiety levels in the index case. Even if it were feasible to carry out a study among "survivors" of sudden cardiac death (ie, individuals who have been resuscitated following an attack of ventricular fibrillation), it would be impossible to rule out reverse causation, in which the individual's anxiety level is raised as a result of their near-death experience. For these reasons, the association between anxiety and sudden cardiac death can only be reliably addressed using the prospective cohort design.

There now appear to be three such cohort studies—the Northwick Park Heart Study,[4] the Health Professionals Follow-up Study,[5] and the present study—that have found a strong association between anxiety and fatal CHD, in particular sudden cardiac death. To our knowledge, these are the only published prospective studies on the association between anxiety and sudden death.

A variety of plausible mechanisms have been identified that support a causal link between anxiety and risk of sudden cardiac death. In a series of clinical and electrophysiologic studies, Lown and colleagues identified precursors to fatal ventricular arrhythmia and sudden death, including intense psychologic stresses burdening daily life, and a proximate charged psychologic event which triggers the arrhythmia.[8,20,21] Katz et al[9] studied 38 patients with frequent premature ventricular beats (VPBs) (defined as more than 30 per hour) and found that they scored higher compared with an age- and sex-matched control group on several standardized instruments that measured levels of anxiety. Patients with frequent VPBs described themselves as "frightened, desperate, fearful, nervous," and more "tense, anxious, agitated, high strung, and jumpy."[9]

Diminished heart rate variability has been identified as a potent risk marker for sudden cardiac death in patients recovering from myocardial infarction,[22-24] as well as in apparently healthy subjects.[25,26] Recent evidence suggests that patients who are "highly anxious" on the Minnesota Multiphasic Personality Inventory,[27] as well as DSM-III-R defined panic disorder patients,[28,29] exhibit reduced heart rate variability compared to control subjects. Such findings suggest that individuals with severe anxiety may exhibit pathological alterations in cardiac autonomic control, which may place them at higher risk of ventricular arrhythmia and sudden cardiac death.

One limitation of our data is that they are based on small numbers of sudden death, resulting in imprecise

estimates of risk. However, the magnitude and specificity of the association are quite consistent across the three cohort studies that have been reported to date.[4,5] All three studies adjusted for a wide range of potential confounding factors in assessing the relationship of anxiety to risk of fatal CHD. Nonetheless, it is possible that some unmeasured confounding factor, such as diet or physical exercise, could explain the observed association. On the other hand, the specificity of the association between anxiety and sudden death makes confounding an unlikely explanation for the observed effect. If confounding by diet or exercise could explain the association, one would have expected a positive relationship of anxiety to nonfatal myocardial infarction, as well as to fatal CHD. In fact, the association was specific to fatal CHD (in particular to sudden cardiac death) in all three cohort studies. Finally, the magnitude of the observed association (relative risks ranging between 2.5 to 6) makes residual confounding unlikely to account for the findings.

In the present study, assessment of anxiety was made only once, at baseline. The average time to onset of myocardial infarction or angina was 15.3 years (SD, 6.7 years), and the average time to occurrence of sudden cardiac death was 17.5 years (SD, 8.3 years). It is possible that a proportion of subjects who were normal at baseline may have developed symptoms of anxiety during the interval leading up to the occurrence of coronary endpoints. This is likely to have introduced nondifferential misclassification with respect to exposure (anxiety) status, and therefore biased our results in the direction towards the null.

All three cohort studies to date have been based in male populations.[4,5] To the extent that anxiety and panic disorders are more common in women,[30] there is an urgent need for studies to be carried out in women. We are currently investigating this association in two separate cohorts representing over 200 000 women.

Finally, more information needs to be gathered on the psychological and psychiatric profiles of patients at risk of sudden cardiac death. Anxiety disorders are classified by DSM-III-R[30] into four major categories: panic disorder with and without agoraphobia, social phobia and other phobias (eg, simple phobia and agoraphobia without a history of panic attacks), generalized anxiety disorder, and obsessive compulsive disorder. In the present study, we relied on self-reports of anxiety symptoms, and made no further attempts to collect data to verify clinical diagnoses. We are, however, currently planning to carry out a study to collect such data from Normative Aging Study participants.

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