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Original Contributions

HEART RATE AS A PROGNOSTIC FACTOR FOR CORONARY HEART DISEASE AND MORTALITY: FINDINGS IN THREE CHICAGO EPIDEMIOLOGIC STUDIES

ALAN R. DYER,[1] VICTORIA PERSKY,[1] JEREMIAH STAMLER,[1] OGLESBY PAUL,[2] RICHARD B. SHEKELLE,[3] DAVID M. BERKSON,[1] MARK LEPPER,[3] JAMES A. SCHOENBERGER[3] AND HOWARD A. LINDBERG[1]

Dyer, A. R. (Northwestern U. Medical School, Chicago, IL 60611), V. Persky, J. Stamler, O. Paul, R. B. Shekelle, D. M. Berkson, M. Lepper, J. A. Schoenberger and H. A. Lindberg. Heart rate as a prognostic factor for coronary heart disease and mortality: Findings in three Chicago epidemiologic studies. *Am J Epidemiol* 112:736–749, 1980.

The associations between heart rate and death from the cardiovascular diseases (CVD), coronary heart disease (CHD) and sudden death from CHD, along with death from all causes and non-cardiovascular causes, are examined for three groups of middle-aged white males: 1233 men aged 40–59 years followed for 15 years from the Chicago Peoples Gas Company study; 1899 men aged 40–55 years followed for 17 years from the Chicago Western Electric Company study; and 5784 men aged 45–64 years followed an average of five years from the Chicago Heart Association Detection Project in Industry. In univariate analyses, mortality from both cardiovascular and non-cardiovascular causes generally increases with increasing heart rate. In bivariate analyses, using the Cox regression model to control for age, heart rate is significantly related to mortality from all causes in each study, with the associations again due to both cardiovascular and non-cardiovascular causes. In multivariate Cox regression, controlling for age, blood pressure, serum cholesterol, cigarettes smoked per day and relative weight, heart rate is a significant risk factor for sudden CHD death and non-CVD death in two of the three studies, with the association with sudden death being U-shaped in one of the studies. Although heart rate may be an independent risk factor for sudden CHD death, the associations with other CVD death and non-sudden CHD death, in general, appear to be secondary to associations between heart rate and other cardiovascular risk factors.

coronary disease; death; death, sudden; heart rate; prospective studies

An unsolved problem in cardiovascular epidemiology and one that has received only scant attention in the literature is the role of resting heart rate as an independent risk factor for the adult cardiovascular diseases (CVD) in general and coronary heart disease (CHD) in particular. The present report examines the association between heart rate and death from CVD, CHD and sudden death from

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Abbreviations: CHD, coronary heart disease; CVD, cardiovascular diseases; ECG, electrocardiogram.

[1] Dept. of Community Health and Preventive Medicine, Northwestern U. Medical School, 303 East Chicago Ave., Chicago, IL 60611. (Send reprint requests to Dr. Alan R. Dyer at this address).

[2] Harvard Medical School, Boston, MA.

[3] Dept. of Preventive Medicine, Rush-Presbyterian-St. Lukes Medical Center, Chicago, IL.

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CHD, along with death from all causes and non-cardiovascular causes for middle-aged white males from three epidemiologic studies in Chicago: 1233 white males aged 40–59 years followed for 15 years from the Chicago Peoples Gas Company study; 1899 white males aged 40–55 years followed for 17 years from the Chicago Western Electric Company study; and 5784 white males aged 45–64 years followed an average of five years from the Chicago Heart Association Detection Project in Industry.

Materials and methods

Study populations

Chicago Peoples Gas Company study (*Gas Company study*). This is a longitudinal investigation of the natural history, epidemiology and etiology of adult CVD in males aged 40–59 on January 1, 1958. Of the 1594 male employees in this age range on that date, 1465 (91.9 per cent) underwent complete physical examination in 1958. This examination and other details of this study have been described at length elsewhere (1, 2). This paper reports on 1233 white males with complete baseline data who were free of definite CHD upon initial examination. For these men, heart rate was obtained from a resting electrocardiogram (ECG).

Chicago Western Electric Company study (*Western Electric study*). This is a long-term investigation of CHD begun during the fall of 1957 among men at that time aged 40–55 years employed by the Hawthorne Works of the Western Electric Company in Chicago. The 5397 men aged 40–55 employed at the works for more than two years as of 1957 were assigned an identification number by a randomizing process. Members of the randomly selected group were invited to participate voluntarily by being called from the random list. Those who accepted the invitation underwent a complete physical examination in 1957 or 1958. This examination and other details of this study have been published (3). The response rate among invited participants was 67 per cent. The group of 1899 men considered here consists of white males free of definite CHD on initial examination and with complete baseline data. Among the Western Electric study men, pulse rate was taken. Heart rate will be used here to mean both "heart rate" and "pulse rate."

Chicago Heart Association Detection Project in Industry (*Chicago Heart Association study*). From the fall of 1967 until early 1973 this study screened 39,665 young adult and middle-aged men and women, both white and black, employed by 85 firms in the greater Chicago area. The total labor force among these companies and institutions was over 75,000 persons. Thus, the volunteer rate for this screening effort was about 53 per cent. In all facilities, all employees were encouraged to participate irrespective of type of job or shift worked. The details of this screening examination have been published (4). Heart rate was measured to the nearest beat per minute during the initial phase of the study by measuring the R to R interval over three consecutive QRS complexes recorded on

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This work was done while Dr. Dyer was an Established Investigator of the American Heart Association.

an ECG strip chart. Subsequently, a heart rate meter was constructed; the meter performed the same measurement electronically and provided direct digital display. In between these two phases, however, there was a period when ECG strip charts—and, therefore, heart rates—were not obtained uniformly for all participants. To eliminate bias, the heart rates for all participants screened during this interim phase were treated as missing. Of the 39,665 men and women screened, 7577 were white males aged 45–64 years; 1254 of these 7577 were excluded from the analyses because of missing heart rate, 61 for missing other relevant variables, 415 for missing follow-up data, and 63 because of positive ECG evidence of a myocardial infarction at baseline. Thus, the cohort considered here consists of 5784 men.

Methods

The associations between heart rate and death from all causes, CVD, CHD, sudden death from CHD, and death from non-CVD were analyzed in these three studies utilizing both cross-classification and Cox regression (5). In the cross-classification analyses, for each study, heart rate was divided into approximate quintiles with the mortality rates then computed within each quintile. A χ^2 statistic was then used to test the hypothesis that the mortality rates were the same within each quintile of heart rate. If the results from this χ^2 test were statistically significant, another χ^2 statistic was computed to test the hypothesis that the association between heart rate and mortality was linear. (A description of this test is given in Fleiss (6, pp. 96–99)) In addition, because heart rate may be associated with increased risk of mortality only at very high or very low values, or at both, the mortality rates for those in the upper and lower 5 per cent of the distribution of heart rate were also obtained. A final χ^2 statistic was then computed to test the hypothesis that the mortality rate in the upper 5 per cent of the distribution was the same as that in the lower 95 per cent of the distribution. In the presentation of the results, only the χ^2 tests for the quintile comparison and the upper 5 per cent versus the lower 95 per cent are given.

The associations between heart rate and mortality with other variables controlled was assessed using the Cox life-table regression model. In these analyses, the association between heart rate and each cause of death was examined controlling only for age, and then for serum cholesterol, systolic blood pressure, cigarettes/day, and relative weight in addition to age, where relative weight is defined as per cent of ideal weight for height (7).

In the Gas Company study, these analyses were based on 15 years of follow-up; in the Western Electric study, 17 years; and in the Chicago Heart Association study, five years.

Results

In order fully to understand the associations between heart rate and mortality, it is first necessary to examine the associations between heart rate and other risk factors, particularly the three major risk factors for adult CVD, i.e., hypercholesterolemia, hypertension and cigarette smoking. Table 1 presents the correlations between heart rate and age, serum cholesterol, systolic and diastolic blood pressure, relative weight, and cigarettes/day for the men from each study. Consistently, heart rate is positively correlated with systolic and diastolic blood pressure and cigarette use. For age, serum cholesterol and relative weight, the correlations are either small or inconsistent. Thus, heart rate is positively associated with two of the three major risk factors, and weakly with the third, and it can be anticipated that any association between heart rate and mortality observed

TABLE 1

Correlations of heart rate with other risk factors—Chicago Peoples Gas Company study, Chicago Western Electric Company study, Chicago Heart Association Detection Project in Industry

Variable	Study		
	Peoples Gas Company	Western Electric	Chicago Heart Association
Age	0.0786	−0.0076	−0.0604
Serum cholesterol	0.0895	0.0681	0.0581
Systolic blood pressure	0.2244	0.2889	0.2742
Diastolic blood pressure	0.2302	0.2912	0.2273
Relative weight	0.0088	0.0121	0.0252
Cigarettes/day	0.1647	0.1084	0.2037

on univariate analysis will be decreased on multivariate analysis with these other risk factors controlled.

Univariate analyses

Table 2 presents the 15-year mortality rates per 1000 population for CVD, CHD and sudden CHD death, along with the rates for all causes and non-CVD by level of heart rate for the 1233 men from the Gas Company study. In this study, the 127 non-cardiovascular deaths include 75 attributable to cancer and 52 to other causes, including 11 from cirrhosis of the liver, 10 from pneumonia, eight from accidents, plus 23 from other causes. The distribution of heart rate was divided into approximate quintiles, with the highest and lowest quintiles then subdivided in order to provide the mortality rates within the upper and lower 5 per cent of the distribution of heart rate. For the quintile analysis, the χ^2 statistics indicate that the mortality rates are significantly different among the five heart rate groups for all but sudden death. For none of the endpoints with a significant χ^2 could the hypothesis of linearity be rejected, i.e., there were no significant non-linear associations. When the highest and lowest quintiles are subdivided, there is a marked increase in mortality for those in the upper 5 per cent of the distribution for CVD, CHD, sudden CHD and non-CVD. Although the χ^2 statistic for the comparison of the upper 5 per cent with the lowest 95 per cent is statistically significant for each of these endpoints and for all causes, the increased CVD and CHD mortality for those with baseline heart rates ≥ 94 beats/min is entirely due to sudden CHD death, since a subtraction of the mortality rates for sudden CHD from those for CVD and CHD indicate no increase in non-sudden CHD or CVD death for this group. Thus, the increased all causes mortality in this group reflects increased mortality from both sudden CHD and non-cardiovascular causes. In addition, although the numbers are small, there is an increased mortality from sudden death in the lowest 5 per cent of the heart rate distribution, suggesting a possible U-shaped relationship between heart rate and sudden death among the men in this study. (When compared to the mortality rate in the rest of the men, this increase is not statistically significant.) Thus, for the men in this study, there appears to be a strong association between heart rate and risk of death for both CVD and non-CVD, with the association being particularly strong for those in the upper 5 per cent of the distribution.

Table 3 gives the 17-year mortality rates for the 1899 men from the Western Electric study by level of heart rate. For the Western Electric study men, the 128 non-CVD deaths include 78 attributable to cancer and 50 to other causes, includ-

TABLE 2

15-year mortality, all causes and specific causes, by level of heart rate, in 1233 white males who were aged 40–59 years in 1958, in the Chicago Peoples Gas Company study, 1958–1973

Heart rate (beats/min)	*N*	All causes		Specific causes							
				CVD death		CHD death		Sudden death		Non-CVD death	
		No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
All	*1233*	*267*	*217*	*140*	*114*	*98*	*79*	*47*	*38*	*127*	*103*
≤55	55	9	164	6	109	4	73	3	55	3	55
56–60	175	26	149	14	80	8	46	3	17	12	69
≤60	230	35	152	20	87	12	52	6	26	15	65
61–69	311	57	183	31	100	24	77	7	23	26	84
70–74	159	32	201	12	75	6	38	5	31	20	126
75–79	299	71	237	40	134	29	97	15	50	31	104
≥80	234	72	308	37	158	27	115	14	60	35	150
80–93	158	41	259	22	139	14	89	5	32	19	120
≥94	76	31	408	15	197	13	171	9	118	16	211
5 groups χ^2		20.10‡		10.34*		11.53*		7.36		11.21*	
Upper 5% χ^2		17.48‡		5.65*		9.28†		14.24‡		10.14†	

* $p \leq 0.05$.
† $p \leq 0.01$.
‡ $p \leq 0.001$.

TABLE 3

17-year mortality, all causes and specific causes, by level of heart rate, in 1899 white males who were aged 40–55 years in 1957, in the Chicago Western Electric Company study, 1957–1974

Heart rate (beats/min)	*N*	All causes		Specific causes							
				CVD death		CHD death		Sudden death		Non-CVD death	
		No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
All	*1899*	*322*	*170*	*194*	*102*	*163*	*86*	*62*	*33*	*128*	*67*
≤60	98	12	122	8	82	8	82	2	20	4	41
61–70	299	44	147	25	84	24	80	10	33	19	64
≤70	397	56	141	33	83	32	81	12	30	23	58
71–75	359	41	114	23	64	19	53	7	19	18	50
76–80	473	80	169	47	99	37	78	13	27	33	70
81–89	367	76	207	48	131	40	109	16	44	28	76
≥90	303	69	228	43	142	35	116	14	46	26	86
90–99	202	48	238	28	139	23	114	9	45	20	99
≥100	101	21	208	15	149	12	119	5	50	6	59
5 groups χ^2		21.05‡		15.79†		11.35*		5.60		4.41	
Upper 5% χ^2		1.12		2.50		1.48		0.96		0.11	

* $p \leq 0.05$.
† $p \leq 0.01$.
‡ $p \leq 0.001$.

ing nine from cirrhosis of the liver, 14 from accidents, plus 27 from other causes. In the quintile analyses, the χ^2 statistics indicate that the mortality rates are significantly different for the five heart rate groups for CVD, CHD and all causes. Although the mortality rates from non-CVD are not significantly different for the five quintiles, the association between heart rate and all causes mortality reflects an increase in mortality from both CVD and non-CVD with increasing heart rate. Although the highest mortality occurs among men in the highest heart rate quintile, there is no increase in mortality for those with baseline heart rate $\geq$100 beats/min when compared to those with baseline values in the range 90–99 beats/min. In addition, none of the second set of χ^2 statistics is statistically significant. There is also no evidence of an increase in mortality in the lowest 5 per cent of the distribution of heart rate. Although the quintile with the lowest mortality was not the lowest heart rate quintile, none of the χ^2 tests for linearity for CVD, CHD and all causes indicated a significant non-linear association.

The 5-year mortality rates by level of heart rate for the 5784 men from the Chicago Heart Association study are listed in table 4. The 149 non-CVD deaths include 95 attributable to cancer and 54 to other causes, including 13 from accidents, seven from pneumonia, six from cirrhosis of the liver, plus 28 from other causes. In this study, only the mortality rates for all causes and non-CVD are significantly different for the five heart rate groups. For non-CVD death, the χ^2 test for linearity was statistically significant, indicating that the association between heart rate and non-CVD death is a non-linear one. This non-linear association is due primarily to the sharp increase in non-CVD death in the highest quintile of heart rate. As in the Gas Company study men, there is a marked increase in mortality for those in the upper 5 per cent of the distribution of heart rate for CVD, CHD and sudden CHD, which is due primarily to increased mortality from sudden CHD in this group. There is also a decrease in non-CVD mortality for those in the upper 5 per cent of the distribution, with the result that the all causes mortality rate shows no increase in this group. The χ^2 statistic for the upper 5 per cent versus the lower 95 per cent is statistically significant only for sudden CHD death. There is also some evidence of an increase in sudden CHD death in the lowest 5 per cent of the heart rate distribution, indicating that the association between heart rate and sudden CHD death in this study is U-shaped. (This increase is not, however, statistically significant when compared to the rest of the men.)

Multivariate analyses

Table 5 presents the coefficients and t values for heart rate from bivariate regression analyses using the Cox life-table regression model for the associations between heart rate and mortality for each of the studies. The second variable in these analyses is age. Because both CVD death and CHD death include sudden death from CHD, and CHD is included in CVD, CVD deaths have been divided into sudden CHD, non-sudden CHD, and CVD which is not also CHD. This further breakdown of CVD deaths was done because the U-shaped relationship between sudden death and heart rate in the Chicago Heart Association study will produce a Cox regression coefficient that is nearly zero, thus lowering the coefficients from the Cox regressions for all CVD and all CHD in that study.

The t value is used to test the hypothesis that the coefficient for heart rate, after adjusting for the association between the endpoint and age, is equal to zero, or that baseline heart rate is not related to subsequent survival. Based on a two-sided test of this hypothesis, the coefficient for heart rate is regarded as being signifi-

TABLE 4

5-Year mortality, all causes and specific causes, by level of heart rate, in 5784 white males aged 45–64 years, in the Chicago Heart Association Detection Project in Industry, 1967–1979

Heart rate (beats/min)	*N*	All causes		Specific causes							
				CVD death		CHD death		Sudden death		Non-CVD death	
		No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
All	*5784*	*307*	*53*	*158*	*27*	*134*	*23*	*50*	*9*	*149*	*26*
≤59	329	14	43	9	27	8	24	6	18	5	15
60–66	996	43	43	19	19	15	15	8	8	24	24
≤66	1325	57	43	28	21	23	17	14	11	29	22
67–72	1096	43	39	27	25	21	19	4	4	16	15
73–78	1111	67	60	37	33	31	28	14	13	30	27
79–86	1121	54	48	30	27	27	24	7	6	24	21
≥87	1131	86	76	36	32	32	28	11	10	50	44
87–99	883	68	77	25	28	22	25	6	7	43	49
≥100	248	18	73	11	44	10	40	5	20	7	28
5 groups χ^2		20.40‡		4.58		5.21		6.70		22.48‡	
Upper 5% χ^2		1.96		2.83		3.37		4.01*		0.06	

* $p \leq 0.05$.
† $p \leq 0.01$.
‡ $p \leq 0.001$.

TABLE 5

Coefficients and t values for the associations between heart rate and mortality adjusted for age—Chicago Peoples Gas Company study, Chicago Western Electric Company study and the Chicago Heart Association Detection Project in Industry

Cause of death	Study					
	Peoples Gas Company		Western Electric		Chicago Heart Association	
	Coefficient	*t*	Coefficient	*t*	Coefficient	*t*
All causes	0.02392	4.95‡	0.01878	4.25‡	0.01770	3.98‡
All CVD death	0.02172	3.22†	0.02123	3.78‡	0.01134	1.79
CVD, not CHD	0.00855	0.65	0.03598	2.83†	−0.01117	−0.64
All CHD death	0.02703	3.45‡	0.01805	2.89†	0.01505	2.21*
CHD, not sudden	0.01402	1.20	0.01727	2.17*	0.02062	2.45*
Sudden death	0.03957	3.75‡	0.01930	1.92	0.00518	0.45
Non-CVD death	0.02631	3.81‡	0.01491	2.08*	0.02416	3.87‡

* $p \leq 0.05$.
† $p \leq 0.01$.
‡ $p \leq 0.001$.

cantly different from zero at the 5 per cent level if $|t| \geq 1.96$. Based on this criterion, heart rate is significantly related to death from all causes in each of the three studies. In the Gas Company study, the significant association between heart rate and all causes mortality is due primarily to strong significant associations between heart rate and sudden CHD death and between heart rate and non-CVD death. Although the coefficients for all CVD death and all CHD death are significantly different from zero, the smaller coefficients for non-sudden CHD and other CVD indicate that the coefficients for all CVD and all CHD are significant largely because of the strong association between heart rate and sudden CHD. For the Western Electric study men, the only coefficient that is not significant is that for sudden death. The size of the coefficient is, however, similar to that for non-sudden CHD, which is significant. Thus, in the Western Electric study, the association between heart rate and all causes mortality reflects an association between heart rate and CVD, in general, plus a weak, but significant association between heart rate and non-CVD death. In the Chicago Heart Association study, the association between all causes mortality and heart rate is due to significant associations between heart rate and non-sudden CHD and heart rate and non-CVD death. The coefficients for non-sudden CHD are reasonably similar for the three studies, even though the coefficient in the Gas Company study is not significant.

Because of the possible U-shaped relationship between heart rate and sudden death in the Gas Company and Chicago Heart Association studies, heart rate squared was added to the Cox regression model for sudden death in these two studies. For the men in the Gas Company study, the coefficient for heart rate squared was not statistically significant. However, the *t* for the quadratic term in heart rate in the Chicago Heart Association study was 2.63, a value that is statistically significant at $p < 0.01$. (The likelihood ratio test, an alternative means of testing for significance in the Cox regression model, and one that may be more appropriate when the model includes a quadratic term, gave a *t* of 2.17, which is also statistically significant.)

Given the positive associations between heart rate and known risk factors, particularly blood pressure and cigarette use, it is not clear whether the associations noted above between heart rate and mortality are independent of the relationships between heart rate and other risk

factors, i.e., are the associations noted in the bivariate analyses secondary to associations between heart rate and blood pressure, heart rate and cigarette use, and heart rate and cholesterol?

In order to answer this question, Cox regression models were fit to the data from each of the studies utilizing the variables age, serum cholesterol, cigarettes/day, relative weight and systolic blood pressure, in addition to heart rate. Table 6 gives the coefficients and t values for the associations between heart rate and mortality adjusted for the other variables for each of the three studies. After adjustment for these other variables, the coefficient for death from all causes continues to be statistically significant only in the Gas Company study, although the coefficients are nearly significant for the other two studies. The only other associations between heart rate and mortality that continue to be significant after adjustment for these other risk factors are those with sudden death in the Gas Company study, and non-CVD death in the Gas Company and Chicago Heart Association studies. In the Gas Company study, the association between heart rate and sudden death is no longer strong enough to make the associations between all CVD and all CHD significant, the coefficients for non-sudden CHD and other CVD now being virtually zero. In the Western Electric study, although the association between heart rate and each of the cardiovascular endpoints is positive, none of the coefficients is statistically significant. The Chicago Heart Association study shows the strongest association between heart rate and non-sudden CHD, but the coefficient is not significantly different from zero. In addition, although there is a fairly strong negative association with other CVD, this coefficient is also not significantly different from zero.

In the Chicago Heart Association study, the significant quadratic association between heart rate and sudden death noted on bivariate analysis continued to be significant in the multivariate analysis when the other variables were included in the model, whether based on the coefficient for heart rate squared and its standard error ($t = 2.33$), or the likelihood ratio ($t = 1.96$).

Because heart rate is positively related to abnormalities in the ECG, Cox regression models with any ECG abnormality as a controlling variable were also run for sudden death in the Gas Company and Chicago Heart Association studies. (The correlation between heart rate and any ECG abnormality is 0.1179 in the Gas Company study and 0.1175 in the Chicago Heart Association study.) In the Gas

TABLE 6

Coefficients and t values for the associations between heart rate and mortality adjusted for age, serum cholesterol, blood pressure, relative weight and cigarettes/day—Chicago Peoples Gas Company study, Chicago Western Electric Company study and the Chicago Heart Association Detection Project in Industry

Cause of death	Study					
	Peoples Gas Company		Western Electric		Chicago Heart Association	
	Coefficient	t	Coefficient	t	Coefficient	t
All causes	0.01298	2.54*	0.00909	1.89	0.00900	1.87
All CVD death	0.00917	1.29	0.01085	1.76	0.00116	0.17
CVD, not CHD	−0.00068	−0.05	0.01839	1.31	−0.02712	−1.44
All CHD death	0.01341	1.61	0.00893	1.30	0.00567	0.78
CHD, not sudden	0.00011	0.01	0.00507	0.58	0.00908	1.00
Sudden death	0.02671	2.35*	0.01510	1.36	−0.00012	−0.01
Non-CVD death	0.01719	2.35*	0.00617	0.71	0.01730	2.54*

* $p \leq 0.05$.

Company study, the association between heart rate and sudden death continued to be significant in this analysis. For the Chicago Heart Association study, although the coefficient for heart rate squared continued to be statistically significant in this analysis ($t = 2.19$), the likelihood ratio statistic ($t = 1.84$) did not.

Although tables 5 and 6 suggest differences in the association between heart rate and mortality in the three studies, a χ^2 test of homogeneity used to test the hypothesis that the coefficients for a given endpoint are the same for the three studies did not give significant results for any endpoint in either the bivariate or the multivariate analyses.

Discussion

A previous analysis of the Gas Company study data based on 10 years of follow-up (8) suggested that heart rate is a risk factor for CHD independent of coexistent diseases, ECG abnormalities, and other risk factors. In contrast, a previous analysis of the Western Electric study data (3) found no significant difference in mean heart rate for those who developed the disease and those who did not. There was, however, a higher percentage of men with heart rate ≥90 beats/min among those with CHD than among those without. Both of these reports were based on cross-classification—univariate in the Western Electric study and both univariate and multivariate in the Gas Company study. The present report is an extension of these previous analyses, based on additional follow-up for each of these two studies, with the addition of the 5-year mortality data from the Chicago Heart Association study.

Other studies (9–15) which have examined the association between heart rate and the incidence of CHD have not yielded consistent findings. Four studies (9–12) noted a positive association between baseline heart rate and subsequent CHD incidence. In Glostrup County, Copenhagen (9), men who subsequently died of myocardial infarction within 10 years had significantly higher baseline heart rates on the average than those who survived 10 years without CHD. A study of 10,000 Israeli male government employees (10) revealed a highly significant association between baseline pulse rate and 5-year incidence of myocardial infarction. In addition, the Framingham Study (11) found that heart rate was significantly related to death from CVD, CHD and sudden death from CHD, as well as from all causes, in middle-aged white males. Finally, a case-control study of men aged 40–79 years from the Kaiser Permanente Medical Care Program (12) noted that high brachial pulse rate was a predictor of sudden cardiac death in five and one-half years of follow-up.

In contrast to these positive findings, three large studies found no significant associations between heart rate and incidence of CHD. Among middle-aged men in Sweden, Tibblin et al. (13) found no significant association between baseline heart rate and 10-year incidence of myocardial infarction, although the heart rate of men who died from ischemic heart disease tended to be higher than the heart rate of those who survived. Paffenbarger et al. (14) noted no difference in the rates of CHD death within 20 years in a study of 40,000 college students stratified by resting pulse into those above 90 beats/min and those below 90 beats/min. Finally Keys et al. (15), in a study of Minnesota business and professional men, noted no significant association between baseline pulse rate and the 20-year incidence of CHD.

In bivariate analyses with only age controlled, the results from the three studies presented here were consistent in showing a significant positive association between heart rate and all causes mortality and between heart rate and non-CVD mortality, although the association be-

tween heart rate and non-CVD death in the Western Electric study was weaker than in the other two studies. The studies were less consistent with respect to the associations between heart rate and death from CVD and CHD. In the Gas Company study, heart rate was significantly related to sudden death from CHD, but not to non-sudden CHD or other CVD. In the Western Electric study, heart rate was significantly related to non-sudden CHD and other CVD, and almost to sudden death. In the Chicago Heart Association study, heart rate was related to non-sudden CHD and to sudden CHD death in a quadratic relationship, but not to other CVD.

In the multivariate analyses, controlling for age, blood pressure, cigarettes smoked per day, serum cholesterol and relative weight, heart rate continued to be significantly related to non-CVD death and sudden death in both the Gas Company and Chicago Heart Association studies. None of the other associations noted above between heart rate and CVD death and CHD death continued to be significant in the multivariate analyses. This dampening of the association between heart rate and cause-specific CVD mortality was also noted in the Israeli study (16) and the Kaiser Permanente study (12). In Framingham (11), however, the significant associations noted on univariate analysis continued to be significant on multivariate analysis.

The fact that the associations between baseline heart rate and CVD death and CHD death dampen on multivariate analysis is due in part to the associations between heart rate and other cardiovascular risk factors. The strong correlations between heart rate and blood pressure noted in these three studies have been noted previously in both cross-sectional analyses (4, 17) and prospective analyses (18–20). In addition, several groups of investigators have noted an association between cigarette smoking and increased heart rate (21–24). Smaller but consistently positive associations between heart rate and serum cholesterol have also been reported (15, 24).

The data on sudden CHD death from the Gas Company and Chicago Heart Association studies suggest that heart rate may be an independent risk factor for sudden CHD death at both ends of the distribution of heart rate. In the Gas Company study, the positive association was restricted to those in the upper 5 per cent of the distribution of heart rate. In addition, there was a suggestion of increased risk at the low end of the distribution. In the Chicago Heart Association study, both the upper and lower 5 per cent of the distribution of heart rate had mortality rates that were sharply higher than those of the rest of the men. The size of the coefficient for heart rate and sudden death in the multivariate analysis in the Western Electric study, although not significantly different from zero, lends additional support to the hypothesis that high heart rate is an independent risk factor for sudden death from CHD.

The mechanism by which an elevated heart rate might predispose to sudden death has not been established. One possibility is that high heart rate may be a marker for decreased physical fitness (25, 26), which in turn may increase risk of sudden death as well as CHD. The literature (27–38) relating sedentary life style to CHD, however, is controversial and the mechanism by which decreased activity could be related to sudden death independent of the known risk factors and heart rate is not at all clear.

The fact that both very high and very low heart rates appear to be related to sudden death in the Chicago Heart Association study suggests that these extreme values may be symptomatic of other conduction disturbances which in turn would predispose to sudden death. If this were so, controlling for the presence of ECG abnormalities in the analysis

should dampen the association between heart rate and sudden death. However, the dampening of the association between heart rate and sudden death was only slight in both studies, when any ECG abnormality was included as a controlling variable in the multivariate analyses.

An alternative possibility is that increased heart rate is the result of enhanced neural activity, which in turn predisposes to a lowered threshhold for ventricular fibrillation and increased risk of sudden death (39, 40).

The association between heart rate and non-CVD death that persisted on using multivariate analysis in two of the three studies, has not, to our knowledge, been previously noted. We are currently carrying out further investigation to determine which causes of death appear to be related to heart rate. This will be the subject of a future report.

Although the results of these three studies may not appear to be particularly consistent, given the large standard errors of the coefficients from the Cox regression analyses, it is impossible to determine whether the differences in the strengths of the associations between heart rate and mortality for the three studies represent real differences, that might, for example, be related to the difference in volunteer rates for the three studies, or are simply the result of chance variation. A comparison of the coefficients did not show any statistically significant differences. Further, because heart rate was on the average measured closer to the time of death in the Chicago Heart Association study, with its shorter follow-up than the other two studies, one might anticipate stronger associations between heart rate and mortality in this study than the other two. In particular, the shorter follow-up in the Chicago Heart Association study might explain why a strong U-shaped relationship between heart rate and sudden death was observed in this study, but was only suggested in the Gas Company study, with its 15 years of follow-up, and was not present at all in the Western Electric study, with its 17 years of follow-up.

Thus, the results of these three studies suggest that high heart rate may be an independent risk factor for sudden death from CHD and death from causes other than the cardiovascular diseases. This latter association awaits further clarification.

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