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Prospective Study of C-Reactive Protein, Homocysteine, and Plasma Lipid Levels as Predictors of Sudden Cardiac Death

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Background—Sudden cardiac death (SCD) is an important cause of mortality even among apparently healthy populations.

However, our ability to identify those at risk for SCD in the general population is poor, and more specific markers are needed.

Methods and Results—To compare and contrast the relative importance of C-reactive protein (CRP), homocysteine, and lipids as long-term predictors of SCD, we performed a prospective, nested, case-control analysis involving 97 cases of SCD among apparently healthy men enrolled in the Physician's Health Study. Of these plasma markers measured, only baseline CRP levels were significantly associated with the risk of SCD over the ensuing 17 years of follow-up (P for trend=0.001). The increase in risk associated with CRP levels was primarily seen among men in the highest quartile, who were at a 2.78-fold increased risk of SCD (95% CI 1.35 to 5.72) compared with men in the lowest quartile. These results were not significantly altered in analyses that (in addition to the matching variables of age and smoking status) controlled for lipid parameters, homocysteine, and multiple cardiac risk factors (relative risk for highest versus lowest quartile 2.65, 95% CI 0.79 to 8.83; P for trend=0.03). In contrast to the positive relationship observed for CRP, neither homocysteine nor lipid levels were significantly associated with risk of SCD.

Conclusions—These prospective data suggest that CRP levels may be useful in identifying apparently healthy men who are at an increased long-term risk of SCD. (*Circulation*. 2002;105:2595-2599.)

Key Words: death, sudden ■ inflammation ■ lipids ■ risk factors

In the United States, 250 000 sudden cardiac deaths (SCDs) occur every year, constituting \approx 50% of all coronary heart disease (CHD) deaths.¹ Although the presence of overt CHD markedly increases the risk of SCD,² over half of the SCD victims do not have clinically recognized CHD before death.³ CHD risk factors are predictive of SCD in this segment of the population; however, single risk factors, including lipids, are limited in their ability to identify specific individuals who are at high risk of SCD.^{3,4} Therefore, there is a need for additional markers of SCD risk.

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Several novel risk factors for atherosclerosis have recently been proposed, including C-reactive protein (CRP) and homocysteine levels. Several lines of research indicate that chronic inflammation and thrombosis play a major role in the initiation and progression of atherosclerosis and in the conversion of a stable atherosclerotic plaque to an unstable potentially occlusive lesion. Markers of inflammation (most notably, CRP) have been found to predict future risk of

myocardial infarction (MI) in several populations.⁵⁻⁷ Homocysteine, a nutritional marker associated with premature atherothrombosis, also predicts future risk of MI and CHD death in observational studies.⁸

Because atherosclerosis underlies most cases of SCD found in men^{9,10} and because acute plaque rupture with associated thrombosis is found in a significant proportion of SCD victims,^{11,12} CRP and/or homocysteine levels may aid in the identification of those at risk for SCD in apparently healthy populations. Although this use has been suggested for CRP,¹³ neither hypothesis has been specifically examined. The Physicians' Health Study of 22 071 apparently healthy men followed for an average of 17 years presented a unique opportunity to compare and contrast the potential value of CRP, homocysteine, and lipids as long-term predictors of SCD.

Methods

The methods of the Physicians' Health Study have been described in detail elsewhere.¹⁴ Briefly, 22 071 male physicians who were aged 40 to 84 years in 1982 and who had no history of MI, stroke,

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Dr Ridker is named as a coinventor on patents related to the use of inflammatory biomarkers in cardiovascular disease.

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transient ischemic attack, or cancer were assigned at random to aspirin, β -carotene, both active drugs, or both placebos; a 2-by-2 factorial design was used. At baseline, the physicians completed questions on health status and risk factors for cardiovascular disease. Information on cardiovascular events was updated every 6 months for the first year and annually thereafter through brief follow-up questionnaires.

Before randomization, between August 1982 and December 1984, potential participants were asked to provide baseline blood samples, which were collected in EDTA and processed for long-term storage at -80°C . Of the randomized study participants, 14 916 (68%) provided baseline blood samples. At the time of blood collection, during the prerandomization run-in period, all study participants were taking active oral aspirin.

End-Point Confirmation and Selection of Controls

The end point of SCD was ascertained in a 2-step process. First, deaths of any cause were generally reported by postal authorities or next-of-kin and were confirmed for a cardiovascular cause through end-point committee review of medical records obtained from hospitals and attending physicians. Mortality follow-up was 99%. The next of kin was interviewed regarding the circumstances surrounding the death if it was not adequately documented in the medical records.

Second, to ascertain the specific end point of SCD, medical records and reports from next of kin for all cardiovascular deaths (excluding strokes) were reviewed again by 2 cardiologists unaware of exposure status. In this second review, SCD was defined as death within 1 hour of symptom onset and/or a witnessed cardiac arrest or abrupt collapse not preceded by >1 hour of symptoms that precipitated the terminal event. There was no other probable cause of death other than cardiac suggested by history or autopsy. To increase the specificity for "arrhythmic death," we excluded anyone who had evidence of collapse of the circulation (hypotension, exacerbation of congestive heart failure, and/or altered mental status) before the disappearance of the pulse.¹⁵ Unwitnessed deaths that could have occurred within 1 hour of symptom onset and that had autopsy findings consistent with an SCD (ie, acute coronary thrombosis or severe coronary artery disease without myocardial necrosis or other pathological findings to explain death) were considered probable SCDs.

Each participant who provided an adequate baseline blood sample for analysis and who had a confirmed SCD during follow-up was matched with 2 control subjects. Because relationships with MI have already been documented for both CRP⁶ and homocysteine¹⁶ in this cohort, we excluded those cases ($n=22$) with a documented MI, leaving 97 cases of SCD for this analysis. Controls were study participants with adequate baseline blood samples who were free of confirmed cardiovascular disease at the time of case ascertainment. Controls were randomly selected from the study participants who met the matching criteria of age (± 1 year), length of study follow-up (6-month intervals), and smoking status (past smoking, current smoking, or never smoked). For 2 cases, only 1 adequate control could be found. With these criteria, 192 matched controls were evaluated in this analysis.

Measurement of CRP, Homocysteine, and Lipids

Baseline plasma samples were thawed and assayed for high-sensitivity CRP with the use of latex-enhanced immunonephelometric assays on a BN II analyzer (Dade Behring).¹⁷ Total cholesterol (TC), triglyceride, HDL cholesterol (HDL-C), and LDL cholesterol (LDL-C) levels were measured on a Hitachi 911 analyzer (Roche Diagnostics) with reagents from Roche Diagnostics and Genzyme. Plasma levels of homocysteine were measured by using high-performance liquid chromatography (Bio-Rad).¹⁸ Blood specimens were analyzed in blinded triplets, with the position of the case's specimen varied at random within the triplets to reduce the possibility of systemic bias and to decrease interassay variability.

TABLE 1. Baseline Characteristics of the Study Participants

Characteristic	SCD Cases (n=97)	No SCD (n=192)	P
Age, y	59.6 \pm 8.7	59.5 \pm 8.6	Matching factor
Body mass index, kg/m ²	25.5 \pm 3.2	25.1 \pm 3.4	0.35
Vigorous exercise <1 time/wk, n (%)	25 (26.0)	48 (25.4)	0.91
Smoking, n (%)			
Current	10 (10.3)	19 (9.9)	Matching factor
Past	45 (46.4)	89 (46.4)	
Never	42 (43.3)	84 (43.8)	
Reported history, n (%)			
Diabetes	11 (11.3)	6 (3.2)	0.005
High cholesterol*	12 (13.6)	29 (17.8)	0.40
Hypertension†	46 (48.9)	48 (25.7)	0.001
Parental history of MI before age 60 y, n (%)	19 (20.4)	6 (3.1)	0.001
Alcohol intake, n (%)			
$<$ Weekly	33 (34.4)	46 (24.2)	0.003
Weekly	27 (28.1)	94 (49.5)	
Daily	36 (37.5)	50 (26.3)	
Aspirin assignment, n (%)	39 (40.2)	103 (53.7)	0.03

Values are mean \pm SD or number (percentage).

*Self-reported high-cholesterol, cholesterol level ≥ 240 mg/dL, or taking cholesterol-lowering medications.

†Self-reported systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or taking antihypertensive medication.

Statistical Analysis

Means or proportions for baseline cardiac risk factors were calculated for cases and controls. The significance of associations was tested with the χ^2 statistic for categorical variables and with the Student *t* test for continuous variables. The median values for each plasma marker were first compared between case and control groups by using the nonparametric Wilcoxon rank sum test. After dividing the subjects into quartiles based on the distribution of control values, we then performed logistic regression analysis, conditioned on the matching variables of age and smoking, to compute the relative risks of SCD associated with increasing levels of CRP, lipid parameters, and homocysteine. Tests for trend for each plasma marker were performed by assigning the median value to each quartile and then modeling this as a continuous variable in separate conditional regression models.

For those plasma markers that were found to be associated with SCD in the age- and smoking-adjusted models, the conditional logistic regression model was adjusted further to determine the independent contribution of each plasma marker on the risk of SCD. First, the other plasma markers were entered simultaneously into the conditional logistic regression model to determine the independent effect of each marker (multivariate model 1). Then, the potential confounding variables of hypertension, body mass index, family history of premature atherosclerosis, diabetes, alcohol intake, and exercise frequency were added to this multivariate model (multivariate model 2). All probability values are 2-tailed, and all CIs were computed at the 95% level (SAS Version 8.2, SAS Institute).

Results

Table 1 shows baseline characteristics of the 97 study subjects who died suddenly from cardiac causes (86 definite and 11 probable) and the 192 matched controls. The men who died suddenly were significantly more likely to have a history

TABLE 2. Baseline Plasma Levels of CRP, Lipids, and Homocysteine Among Cases and Controls

Variable	Plasma Level, Median (Interquartile Range)		<i>P</i> *
	Cases (n=97)	Controls (n=192)	
CRP, mg/dL	0.17 (0.07–0.36)	0.10 (0.06–0.22)	0.01
Homocysteine, μ mol/L	11.2 (9.5–14.0)	11.5 (9.8–13.3)	0.93
TC, mg/dL	223 (196–247)	218 (189–245)	0.51
LDL-C, mg/dL	141 (121–165)	142 (117–159)	0.19
HDL-C, mg/dL	44 (38.5–51.1)	46 (40.5–55.1)	0.11
Triglycerides, mg/dL	128 (85–174)	118 (85–162)	0.61
TC/HDL-C ratio	4.97 (4.00–6.05)	4.63 (3.85–5.60)	0.05

*Wilcoxon rank sum test.

of hypertension and diabetes or a parental history of coronary artery disease. These men were also less likely to drink moderate amounts of alcohol or to have been randomized to aspirin. Because of matching, cases and controls were similar with respect to age and smoking status. The mean time to SCD was 9.2 years (range 0.7 to 16.8 years). As shown in Table 2, although there was some degree of overlap in the interquartile range, the median plasma level of CRP was significantly higher at baseline in cases than in controls ($P=0.01$). In contrast, the median homocysteine level was similar in cases and controls. Of the lipid parameters, only the TC/HDL-C ratio differed significantly between cases and controls ($P=0.05$).

Table 3 displays the relationship of baseline plasma levels of CRP, lipid parameters, and homocysteine to subsequent risk of SCD. Of the plasma markers measured, CRP was the most strongly associated with risk of SCD (P for trend <0.001). The increase in risk associated with CRP levels was primarily seen among men in the highest quartile, who were at a 2.78-fold increased risk of SCD (95% CI 1.35 to 5.72) compared with men in the lowest quartile. If we assume that the distribution of CRP levels in the controls is reflective of the entire cohort, 56% of the risk of SCD in this population would be estimated to be attributed to having a CRP level in the highest quartile (attributable risk percent). Again, the baseline homocysteine level was not related to subsequent risk of SCD. Of the lipid parameters, the TC/HDL-C ratio was the most strongly associated with the risk of SCD, although the P for trend value across quartiles was of

borderline significance ($P=0.06$). Baseline plasma levels of TC, LDL-C, and triglycerides were not significantly associated with SCD risk.

On the basis of the results of the age- and smoking-adjusted analyses, we further evaluated the independent contribution of both CRP and TC/HDL-C ratio to SCD risk. The positive relationship between both of these variables and the risk of SCD was not materially altered in analyses that controlled for other plasma markers simultaneously (multivariate model 1, Table 4). CRP remained strongly associated with SCD risk (P for trend=0.004), and there continued to be a trend toward an increase in risk associated with the TC/HDL-C ratio (P for trend=0.09). When cardiac risk factors were additionally entered into the model (multivariate model 2, Table 4), the significant positive relationship between CRP levels and SCD persisted (P for trend=0.03); however, the relationship between TC/HDL-C was markedly attenuated and no longer approached significance (P for trend=0.28). Again the elevation in risk associated with CRP levels was primarily limited to the highest quartile. In a post hoc analysis, the men in the fourth quartile of CRP were compared with those in the lower 3 quartiles, and the multivariate relative risk of SCD in the highest quartile was significantly elevated at 2.79 (95% CI 1.06 to 7.34, $P=0.04$).

Discussion

In this prospective, nested, case-control study of apparently healthy male physicians, baseline plasma CRP levels were positively associated with risk of SCD over the ensuing 17 years of follow-up. The relationship remained significant even after controlling simultaneously for homocysteine, lipids, and multiple cardiac risk factors. Compared with men in the lowest quartile of CRP, the men in the highest quartile were at a 2.8-fold increased risk of SCD in age- and smoking-adjusted analyses, and these results were not materially altered in multivariate analyses. In contrast, neither homocysteine nor lipid levels were significantly associated with risk of SCD. Of the lipid parameters, the TC/HDL-C ratio was the most strongly associated with risk of SCD; however, this relationship was not significant in either the age- and smoking-adjusted or multivariate analysis.

These data raise both clinical and pathological issues. One clinical implication of these data is that markers of inflammation may be useful in identifying men at higher risk for

TABLE 3. Age- and Smoking-Adjusted RR of SCD Associated With Baseline Plasma Levels of CRP, Lipids, and Homocysteine

Variable	RR (95% CI) by Quartile				<i>P</i> for Trend
	1	2	3	4	
CRP	1.0	1.12 (0.51–2.46)	1.19 (0.55–2.61)	2.78 (1.35–5.72)	<0.001
Homocysteine	1.0	0.73 (0.38–1.45)	0.61 (0.29–1.28)	1.06 (0.51–2.20)	0.98
TC	1.0	1.50 (0.73–3.06)	1.38 (0.70–2.74)	1.43 (0.70–2.95)	0.37
LDL-C	1.0	1.59 (0.80–3.15)	0.91 (0.44–1.89)	1.48 (0.75–2.91)	0.56
HDL-C	1.0	0.72 (0.36–1.45)	0.65 (0.33–1.25)	0.63 (0.31–1.26)	0.17
Triglycerides	1.0	0.87 (0.43–1.77)	1.03 (0.52–2.04)	1.01 (0.52–1.97)	0.87
TC/HDL-C ratio	1.0	1.07 (0.51–2.26)	1.24 (0.61–2.50)	1.89 (0.92–3.86)	0.06

RR indicates relative risk.

TABLE 4. Multivariate RR of SCD According to Baseline Blood Levels of CRP and TC/HDL-Ratio

	Quartile of Plasma Marker				P for Trend
	1	2	3	4	
CRP					
Median level (range)	0.04 (0.2–0.5)	0.08 (0.06–0.10)	0.16 (0.11–0.22)	0.44 (0.23–3.34)	
Multivariate 1, RR (95% CI)	1.0	1.15 (0.49–2.68)	1.44 (0.61–3.42)	3.36 (1.45–7.81)	0.004
Multivariate 2, RR (95% CI)	1.0	0.67 (0.19–2.44)	1.14 (0.34–3.80)	2.65 (0.79–8.83)	0.03
TC/HDL-C ratio					
Median level (range)	3.34 (2.25–3.84)	4.21 (3.85–4.62)	5.09 (4.63–5.60)	6.30 (5.61–8.81)	
Multivariate 1, RR (95% CI)	1.0	1.23 (0.54–2.78)	1.21 (0.47–3.11)	2.21 (0.84–5.87)	0.09
Multivariate 2, RR (95% CI)	1.0	1.54 (0.48–4.97)	1.09 (0.30–3.90)	2.14 (0.56–8.23)	0.28

Multivariate model 1 controlled simultaneously for plasma CRP, homocysteine, triglyceride, and TC/HDL-C ratio levels in quartiles. Multivariate model 2 controlled for plasma variables listed above in multivariate model 1 and for aspirin treatment assignment, history of hypertension, alcohol consumption (\leq monthly, weekly, or daily), parental history of MI before age 60 y, history of diabetes, body mass index (<25 kg/m², 25–30 kg/m², or >30 kg/m²), and vigorous exercise ($<$ weekly or \geq weekly).

SCD who have no obvious signs of CHD many years before the fatal event. Because $>50\%$ of all SCD victims do not have a history of clinically recognized CHD,³ improved identification of those at risk will hopefully improve our ability to prevent SCD. The observed long-term association between CRP and SCD also raises the possibility that intervention at an early stage in the development of disease process might be important for prevention. Individuals with elevated CRP levels, especially those in the highest quartile, might benefit from more aggressive long-term dietary, lifestyle, and coronary risk factor modification than would be the standard of care in a primary prevention population.

These data also raise important clues regarding the pathophysiological mechanism underlying the association between CRP and SCD. Given the length of time between the measurement of CRP and subsequent SCD in the present study (mean time to SCD was 9.2 years), it is likely that the effects of inflammation on SCD are mediated through a chronic process. The most obvious chronic process whereby inflammation may be involved in the pathogenesis of SCD is in the development of coronary atherosclerosis, which underlies $\approx 80\%$ of all cases of SCD.^{9,10} CRP levels have been consistently associated with a variety of atherosclerotic end points in healthy populations^{6–7,19}; however, none of these studies has examined the specific end point of SCD. One study of patients with angina pectoris found that CRP levels were directly correlated with the incidence of a combined end point of MI and SCD, but because of the small numbers of those experiencing SCD, that study was unable to examine the effect on this end point separately.²⁰ In the present study, we excluded those cases ($n=22$) with a documented MI and, therefore, were able to specifically examine the end point of SCD independent of the known association with MI. Of note, the association between CRP and SCD was similar to that previously reported for MI,⁶ which is consistent with a common physiology underlying these 2 acute coronary syndromes.

Apart from their role in the development of underlying atherosclerosis, it is also possible that mediators of inflammation, such as CRP, may have direct long-term effects on ischemic, failing, or even normal myocardium that may be

proarrhythmic. CRP levels have been associated with the development of arrhythmias in a small number of patients after coronary artery bypass surgery²¹ and with atrial fibrillation in a recently reported case-control study.²² Also, in autopsy cases of SCD for whom no macroscopic cause of death can be found, isolated areas of myocardial fibrosis and inflammation are often seen.²³ These areas of inflammation and resulting fibrosis could predispose an individual to SCD by serving as a substrate for reentry. Finally, because markers of inflammation have also been associated with congestive heart failure severity²⁴ and mortality,²⁵ these markers may also be elevated in the presence of asymptomatic left ventricular dysfunction, the most powerful predictor of SCD risk.

Several limitations of the present study warrant consideration. First, our analysis was based on a single baseline determination of each plasma marker; therefore, we were unable to account for changes in these markers over time. In addition, because most of the events occurred later in the study, we were limited in our ability to assess the effects on short-term risk. This limitation could account for the relatively null results observed for lipid parameters and homocysteine if the majority of their effects are on short-term risk or if the levels changed significantly over the course of the study because of changes in dietary habits and/or the use of lipid-lowering agents. For example, in this same cohort, homocysteine levels were associated with MI over the short term¹⁶ but not over a longer follow-up period.²⁶ Finally, even though the present study is the largest we know of to examine the association between these plasma markers and the risk of SCD in apparently healthy men, our power to detect small to moderate effects is still limited by the small number of cases. This may account for the absence of a statistically significant association between TC/HDL-C and SCD.

In summary, these prospective data suggest that CRP levels may be useful indicators of long-term risk of SCD in apparently healthy men. These data are in agreement with those for other atherosclerotic end points,^{5–7,19} and together, they support a role for CRP in the assessment of cardiovascular risk in healthy populations.²⁷ This assessment of risk may be particularly important in reducing mortality from SCD. Because more than half of all SCDs occur as the first

manifestation of ischemic heart disease³ and because survival rates after out-of-hospital cardiac arrest continue to be poor,²⁸ improved identification of those at risk before the event is crucial. CRP, when used in combination with other cardiac risk factors, may improve the prediction of risk among apparently healthy individuals.

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