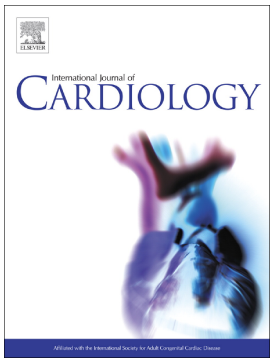

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Joint Effect of Blood Pressure and C-Reactive Protein and the Risk of Sudden Cardiac Death: A Prospective Cohort Study

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Abstract

Background: Both blood pressure and C-reactive protein (CRP) are each independently related to mortality risk. However, the combined effect of systolic blood pressure (SBP) and CRP on sudden cardiac death (SCD) risk has not been studied.

Patients and Methods: We studied the joint impact of SBP and CRP and the risk of SCD in the Kuopio Ischemic Heart Disease prospective cohort study of 1953 men aged 42-61 years with no history of ischemic heart disease. Baseline investigations were conducted between

March 1984 and December 1989. SBP and CRP were measured. SBP was divided based on median values to low and high (median cutoffs 132mm Hg) and CRP as low and high (median cut-off 1.30 mg/L). Hazard ratios (HRs) with confidence intervals (CIs) were calculated after multivariate adjustment.

Results: Subjects were followed-up for 23.2 years, and 137 SCDs occurred. In this study, elevated SBP (>132mmHg) combined with elevated (CRP >1.30mg/L) were associated with SCD risk. Adjustment for age, examination year, alcohol consumption, BMI, energy expenditure during exercise, total cholesterol, HDL-cholesterol, type 2 diabetes, smoking, antihypertension medication and aspirin use, the risk of SCD remained statistically significant (HR, 2,73, 95% CI, 1.62-4.60, p <.001). Further adjustment for socio-economic status, years of education and history of cardiovascular disease in a family the results were only slightly changed (HR, 2.65, 95% CI, 1.57-4.49, p <.001).

Conclusions: In our male cohort study, the joint effect of high SBP together with increased CRP levels is a risk predictor of SCD compared with low SBP and CRP.

Keywords C-reactive protein; Men; Sudden cardiac death; Systolic blood pressure

Introduction

Sudden cardiac death (SCD) may occur momentarily after the onset of the symptoms without typical warning signs, thus leaving very limited time for any type of medical intervention (1). Due to the wide-scale public health implications, prevention remains to be the most viable approach to reduce the risk of SCD in the general population (2). Although the occurrence of

SCD is relatively low in the common population, the absolute numbers are high among asymptomatic subjects.

Hypertension is an established risk factor for various cardiovascular diseases including SCD. Similarly, C-reactive protein (CRP), a marker of inflammatory process, and has also been associated with various cardiovascular events (3-6). Among subjects with elevated blood pressure, increased CRP have been observed. Furthermore, it is known that inflammation plays a role in the development of hypertension (6-11). Increased CRP levels are linked to reduced nitric oxide production in endothelial cells (9-10) which may result in excess production of endothelin and vasoconstriction (12-13). It has been assumed that hypertension may be in part associated with inflammatory diseases. Consistently, long-term hypertension may further lead to harmful left ventricular hypertrophy (LVH), a known risk predictor for SCD (14). Therefore, this study was designed to determine if elevated blood pressure together with CRP is a risk predictor for SCD in the Finnish male population without diagnosed coronary heart disease (CHD).

Study Population

The Kuopio Ischemic Heart Disease (KIHD) risk factor study, is prospective cohort study designed to study atherosclerotic cardiac events in men from Finland. The subjects included 42-61 years of age living in the city of Kuopio and its surrounding communities. Baseline investigations were performed between March 01, 1984, and December 31, 1989. In all 2682 men were included in the overall study. Our analysis included 1953 men with complete data on SCD, covariates and no history of CHD. The study was approved by the Research Ethics Committee of the University of Eastern Finland. Each participant gave a written informed consent to participate in the study.

Assessment of risk markers and biochemical measurements

The standard blood pressure definition was used for blood pressure measurements. Blood pressure was assessed at 5, 10, and 15 minutes after 15 minutes of supine rest; one standing blood pressure measurement was taken after being for rest for 1 minute; 10 minutes of seated rest with BP measured at minutes 5 and 10 (15). The mean of these values was used as mean blood pressure. A professional nurse measured blood pressure using a sphygmomanometer (Hawksley, United Kingdom) in a resting seated position in a quiet room from 8:00 to 10:00 a.m (15). Hypertension at rest was either hypertension confirmed by the current use of antihypertensive medication and/or SBP >140 mm Hg and/or DBP >90 mm Hg.

At baseline various examinations including physical examinations, collection of blood samples and the collection of self-administered questionnaires was done. Body mass index (BMI) was calculated after measuring height and body weight of the subjects. Blood samples were taken according to the protocol in the mornings between 8 and 10 a.m. after an overnight fast. Subjects were also asked to abstain from alcohol consumption for 3 days and smoking for 12 hours before blood collection. Collected serum samples were frozen at −80 °C before analyses of lipids and biochemical analytes. Serum CRP was analyzed using an immunometric assay (Immulite High Sensitivity C-Reactive Protein Assay; DPC, Los Angeles, CA, USA). Fasting plasma glucose (FPG) was measured using the standard glucose dehydrogenase method (Merck, Darmstadt, Germany). Assessments of alcohol consumption, smoking, history of various health conditions, education, and socioeconomic status; subjects were asked to complete health and lifestyle questionnaires (15-18). Physical energy expenditure of various physical activities were assessed using the validated KIHD physical

activity questionnaire. Left ventricular hypertrophy (Sokolow-Lyon index) was recorded from the electrocardiogram (ECG) at rest.

Classification of Sudden Cardiac Death

All the information on fatal cardiac events used for classifying were interviews, hospital documents, death certificates, autopsy reports and medico-legal reports and interviews (18). Deaths that occurred till the end of 2017 were included after checking health and hospital documents including death certificates.

SCD was classified as death that occurred either within 1 hour after the onset of symptoms or within 24 hours after sudden onset of a change in symptoms when autopsy report revealed a non-cardiac cause of sudden death. Sudden out-of-hospital deaths were also defined based on all information at disposal including interviews (18). Non-cardiac comorbidities, deaths due to aortic aneurysm rupture, pulmonary embolism, cardiac rupture or tamponade, and cancer deaths were all excluded. The final conclusions were made using available clinical data such as symptoms, investigative and ECG findings, cardiac biomarkers, autopsy findings, use of medications and defibrillator use and data available with the paramedic staff. Complete information was further cross-checked by two physicians (18). For classification purposes independent events committee were-blinded to the data available.

Statistical analysis

We examined SBP and CRP and the other risk factors for SCD by covariate analysis and the risk of SCD with Cox proportional hazard modeling. To study the joint associations of SBP and CRP, with SCD risk, the median values of SBP and CRP were divided into four categories of low/high. Low SBP (<132mm Hg) and low CRP (<1.30mg/L) were used as a reference. We used three sets of covariates: Model (1) consisted of age and examination year;

Model (2) consisted of Model 1 together with type 2 diabetes, BMI, alcohol consumption, energy expenditure, total cholesterol, serum HDL cholesterol, smoking, antihypertensive medication and aspirin use; and Model (3) consisted of Model 1and 2 together with socioeconomic status, education, and history of cardiovascular diseases in the family. Furthermore, in another model we analyzed if CRP was less than 10 mg/L in another model. Relative risk estimates (HRs, hazard ratios) were adjusted for risk factors and estimated as antilogarithms of coefficients from multivariable models. All tests for statistical significance were defined as p-values of <.05 and were 2-sided. The Kaplan-Meier method was used to assess the cumulative survival for SCD. Statistical analysis was performed by using IBM, SPSS Statistics, version 25.0 for Windows (IBM Armonk, New York).

Results

Baseline characteristics

Over an average follow-up of 23.2 years, 137 SCD cases were documented. The baseline characteristics of subjects in the groups are presented in Table 1. The mean age of men was 52 years, while SBP was 134mmHg (median 132 mmHg). Mean serum CRP levels were 2.2 mg/L (median 1.3 mg/L) respectively. In model 3, after further adjustment SBP and CRP levels, significant risk markers for SCD were age (p=.008), alcohol consumption (p=.002), smoking (p=.006) and alcohol consumption (p<.001), and socioeconomic status (p=.010). Among men with high SBP combined with high CRP (>132mmHg and >CRP of >1.30mg/L) had high BMI, consumed more alcohol, had higher total cholesterol, had more cases of type 2 diabetes, used more of antihypertensive but had lower education status as compared to other groups.

Systolic blood pressure, C-reactive protein, and sudden cardiac death

Elevated SBP combined with elevated CRP levels was related the risk of SCD. In an age and examination year adjusted model, when we compared high SBP combined with high CRP (>132 mmHg and >1.30 mg/L) with combined low levels of SBP combined with CPR (<132mmHg, <1.30 mg/L reference group) 4.0-fold risk (95% CI 2.44-6.53, p<.001) was observed. Further adjustment for alcohol consumption, BMI, energy expenditure during exercise, serum total cholesterol, serum HDL-cholesterol, type 2 diabetes, smoking, antihypertension medication and aspirin use, the risk of SCD remained statistically significant (HR, 2,73, 95% CI, 1.62-4.60, p <.001) (Table 2). Progressive adjustment (Model 3) for socio-economic status, years of education and history of cardiovascular disease in a family the results were only slightly changed (HR, 2.65, 95% CI, 1.57-4.49, p <.001). The Kaplan-Meier cumulative survival curves for SCD according to the groups of SBP and CRP levels are shown in Figure 1.

The risk of SCD was also significantly increased in the group of low SBP (<132mmHg) combined with high CRP >1.30 mg/L, was (HR 1.73, 95% CI, 1.20-2.48, p=.003). However, the respective risk was not increased in men with high SBP (>132mg Hg) combined with low CRP of (<1.30mg/L) (HR 1.30, 95% CI, 0.89-1.91, p=.17).

Increase in systolic blood pressure, C-reactive protein and sudden cardiac death

We investigated the role of increased SBP when CRP was less than 10 mg/L at baseline. Subjects were divided into groups depending on their SBP. In the SCD risk analyses, men with a mean SBP of 121 mmHg (range 121-132 mmHg) together with mean CRP of 1.52 mg/L (range 0.10-9.97 mg/L) was the reference group. Among men with mean SBP of 147 mmHg (range 132-203 mmHg) and mean CRP of 1.72mg/L range (1.0-2.98 mg/L) the HR for SCD was 2.12-fold (95% CI, 1.26-3.56, p=.005) higher as compared to the reference group after adjustment for all used risk factors including anti-hypertensive medication,

aspirin use and LVH. Similarly, the HR was 3.80-fold (95% CI, 2.03-7.12, p<.0001) among men with mean SBP of 148 mmHg (range 132-213mmHg) and mean CRP of 4.9 mg/L (range 3.0-9.8 mg/L) highest versus the lowest levels.

Different blood pressure, C-reactive protein and sudden cardiac death

For further investigations among men with CRP>2 and blood pressure of over 140/90 the risk was (HR 2.65, 95 % CI 1.54-4.57, p <0.001) as compared the group with CRP<2 and blood pressure <140/90 in a multivariate adjusted model. Similarly, among subjects with CRP >2 and blood pressure over 135/85 the results were similar (HR 3.36, 95 % CI 1.63-6.94, p <0.001) as compared to the reference group CRP <2 and blood pressure < 135/85 mmHg.

Discussion

The joint impact of high SBP and increased CRP is strong risk predictor for SCD among men with no apparent CHD in the beginning of the study. After taking into consideration previously known risk factors in addition to socio-economic status, years of education, history of cardiovascular disease in a family and LVH, the associations between the main exposures and SCD remained robust and strong.

Coronary artery obstruction is one of the most important underlying factors in SCD. It has been suggested that both myocardial as well as electrical abnormalities are likely to influence the risk of SCD (19). Hypertension usually leads to LVH over time, especially if blood pressure level is not controlled during the treatment period, and thus LVH may lead to the risk of SCD (14). Although elevated blood pressure and clinical hypertension are established risk factors for SCD, little is known about the synergistic effects of hypertension and systemic inflammation, including information on serum CRP levels, and the risk of SCD. It is suggested that elevated blood pressure and high levels of CRP may have been interacting

with increasing risk of adverse cardiovascular events. Furthermore, it is known that inflammation plays a role in hypertension development (6-11). Ventricular arrhythmias are commonly observed in hypertensive patients (14, 20-21). LVH also leads to longer action potential duration, an increase in dispersion of repolarization, and also increase in the vulnerability to arrhythmia induction (22,23). CHD together with hypertension may cause LVH that may contribute to SCD (24, 25). LVH predicts helps in future malignant arrhythmias such as ventricular ectopies leading to SCD. Decreased blood flow due to epicardial narrowing of the coronary arteries and decreased vasodilatory reserve may cause hypertensive subjects more vulnerable to ischemic effects (26). The myocardium in subjects with hypertension are more likely to experience malignant arrhythmias, which may lead to arrhythmias increasing the risk of SCD compared to the normotensives having a stable myocardium.

We had 16% of the participants with CRP levels 3.0 mg/L and above. This may due to either differences in the distribution of CRP or the different assays used for analyses. Higher levels of CRP may also raise SBP by reducing nitric oxide production in endothelial cells (9-12) which may lead to vasoconstriction and increase the production of endothelin (12-13). This process may further cause platelet activation, leukocyte adherence, oxidation, and thrombosis (10-13), which has been shown to increase atherosclerotic properties by modifying angiotensin type-1 receptor expression (13), leading to high blood pressure and hypertension. These changes are all indicative of coronary artery disease leading to hypertension (12-13, 28). Hypertension commonly causes that may cause left ventricular hypertrophy (LVH), left atrial enlargement, diastolic dysfunction, and neuro-hormonal changes. These all further lead arrhythmias such as atrial fibrillation (AF) as well as ventricular arrhythmias, known risk factors for SCD. Furthermore, LVH an established risk predictor for SCD especially in the presence of myocardial ischemia, scar tissue, and AF. Inflammation and oxidative stress play

an important role that further arrhythmias, and SCD. Due to the public health burden of elevated blood pressure and its global impact, prevention of hypertension appears to be an important population-level tool to prevent the risk of SCD (24, 29-30).

The strengths of our prospective study are the long-term follow-up of this representative cohort. The aim of the long-term study design includes a representative sample of the male Caucasian population, however, these results need to be studied in different age groups and females. The assessment of prevalent clinical conditions was based on self-administered questionnaires is a limitation of the study. However, all the questionnaires were checked by study physician and this methodology is widely used in population-based studies. Our study being an observational study may have been affected by other residual confounding factors and the regression bias, underrating the observed associations, since blood pressure and CRP were collected only at the baseline assessment. These single observations may have changed during follow-up over the time.

In conclusion, the joint effect of high systolic blood pressure and CRP is a strong risk predictor for SCD. It seems that the risk seems more due to more increases in SBP than CRP, although more studies are needed to study this aspect. Studies at population level and clinical trials are needed to confirm our findings and explore the mechanistic pathways underlying the observed findings.

Disclosures

Declarations of interest: none

Conflicts of interests

All the authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Conflicts of interest/Competing interests: None declared.

Acknowledgement of grants: none

"The authors report no relationships that could be construed as a conflict of interest".

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Table 1. Baseline characteristics of middle-aged men with no history of ischemic heart disease. Values indicate mean ± SD unless otherwise informed.

Variable	All subjects	SBP ≤132 mmHg CRP <1.30 mg l^{-1}	SBP ≤132 mmHg CRP ≥1.30 mg/L	SBP >132 mmHg CRP <1.30 mg/L	SBP >132 mmHg CRP ≥1.30 mg/L	P-value Between groups
n	1953	545	427	431	550	
SCD (*n*)	137	21	19	29	68	
Age	52 ± 5.3	52 ± 5.5	52 ± 5.3	53 ± 5.2	53 ± 5.0	<.001
Year of examination	1987 ± 1.7	1987 ± 1.6	1987 ± 1.6	1986 ± 1.7	1986 ± 1.7	.007
Years of education	9.0 ± 3.6	9.6 ± 3.9	8.9 ± 3.6	8.9 ± 3.6	8.6 ± 3.3	<.001
Socioeconomic status	12 ± 5.1	11 ± 5.2	12 ± 5.2	11 ± 5.1	12 ± 4.9	<.001
BMI	27 ± 3.5	25 ± 2.7	27 ± 3.4	27 ± 3.0	28 ± 3.9	<.001
Alcohol consumption (g $week^{-1}$)	74 ± 118	62 ± 102	73 ± 105	61 ± 122	98 ± 135	<.001
LTPA (kcal day^{-1})	138 ± 169	144 ± 166	119 ± 145	149 ± 160	138 ± 192	.051
Serum total cholesterol (mmol l^{-1})	5.9 ± 1.0	5.8 ± 1.0	5.8 ± 1.1	5.8 ± 1.0	6.0 ± 1.0	.002
HDL-cholesterol (mmol l^{-1})	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	<.001
Diabetes (% of yes: FPG >6.9 mmol l^{-1} or medication)	4.7	1.7	4.4	4.6	7.8	<.001
Smoker (% of yes: smoked less than a month ago)	30	24	42	19	34	<.001
Uses drugs for hypertension (% of yes)	14	6.6	11	15	24	<.001
Uses acetylsalicylic acid (% of yes)	5.8	5.0	5.9	4.6	7.6	.162
CVD in family (% of yes)	80	78	78	81	84	.103
Left ventricular hypertrophy (% of yes)	0.9	0.4	0	1.1	1.8	.033

Abbreviations. SBP: Systolic blood pressure. CRP: Serum high-sensitive C-reactive protein. SCD: Sudden cardiac death. BMI: Body mass index. LTPA: Leisure-time physical activity. HDL: High-density lipoprotein. FPG: Fasting plasma glucose. CVD: Cardiovascular disease including hypertension.
Notes. The *p*-values are for the analysis of variance or Kruskal-Wallis test. Family refers to mother, father, and siblings.

Table 2. Hazard ratios for Sudden Cardiac Death among Men with Systolic blood pressure combined with C-reactive protein

SBP combined with CRP	Hazards Ratio	95% Confidence interval		P-value
SBP <132mm hg and CRP <1.30 mg/L	1,02	0,54	1,93	,94
SBP <132mm hg and CRP ≥1.30 mg/L	1,46	0,82	2,60	,19
SBP >132mm hg and CRP <1.30 mg/L	2,73	1,[illegible]	4,59	<.001
Age, (years)	1,06	1,02	1,10	,003
Year of examination	0,91	0,81	1,02	,113
Body mass index (kg/m^2)	1,05	1,00	1,10	,050
Alcohol consumption grams/week	1,00	1,00	1,00	,001
Energy expenditure (kcal/day)	1,00	0,99	1,00	,453
Serum total cholesterol, (mmol/l)	1,15	0,98	1,34	,074
Serum HDLcholesterol, (mmol/l)	0,76	0,40	1,42	,390
Type 2 diabetes mellitus	1,68	0,90	3,14	,101
Cigarette smokers (pack-years)	1,75	1,21	2,54	,003
Use of anti-hypertensive medication	1,36	0,89	2,08	,154
Use of acetylsalicylic acid	0,81	0,35	1,84	,611

Abbreviations. SBP: Systolic blood pressure. CRP: Serum high-sensitive C-reactive protein. SCD: Sudden cardiac death. BMI: Body mass index. LTPA: Leisure-time physical activity. HDL: High-density lipoprotein.. CVD: Cardiovascular disease including hypertension.

Figure 1. The Kaplan-Meier cumulative survival curves for sudden cardiac death according to median of systolic blood pressure and C-reactive protein levels.

SBP was categorized as low and high (median cutoff 132mm Hg) and CRP as low and high (median cut-off of 1.30 mg/L).

Hightlights:

- Little is known about the combined effect of blood pressure and C-reactive protein on acute sudden cardiac death risk.
- This study shows that the combined effect of high systolic blood pressure and CRP is associated increased risk of future sudden cardiac death compared with low SBP and low CRP levels.
- The combined effect of high systolic blood pressure and CRP is associated increased risk of future sudden cardiac events and both the factors may help while starting the therapy.

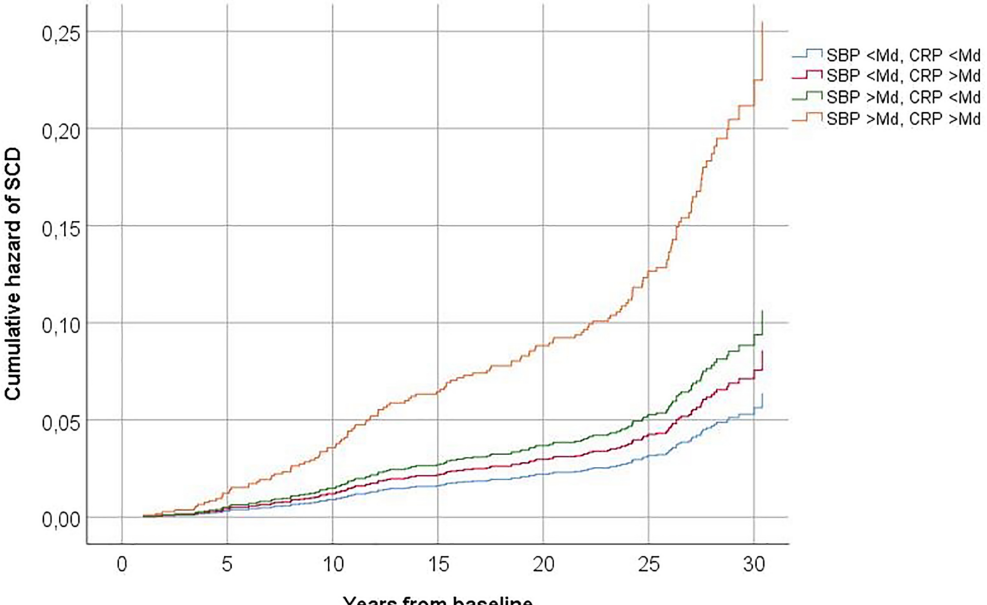
Cumulative hazard of SCD
0,25
0,20
0,15
0,10
0,05
0,00
0
5
10
15
20
25
30
Years from baseline
SBP <Md, CRP <Md
SBP <Md, CRP >Md
SBP >Md, CRP <Md
SBP >Md, CRP >Md

Figure 1