Is left ventricular hypertrophy a low-level inflammatory state? A population-based cohort study.

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A population-based cohort study

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Abstract

Background and Aims: Cross-sectional studies have shown that chronic sub-clinical inflammation is associated with left ventricular hypertrophy (LVH), but results are conflicting. We investigated the association between baseline LVH and high-sensitivity C-reactive-protein (CRP) values, both cross-sectionally and after a six-year-follow-up, in a population-based cohort (*n*=1564) and a subgroup from this cohort (*n*=515), without obesity, diabetes, metabolic syndrome or any drugs.

Methods and Results: ECG tracings at baseline were interpreted according to the Cornell voltage-duration product criteria: 166/1564 subjects (10.6%) showed LVH. Patients with baseline LVH showed increased BMI, waist circumference, blood pressure, and a worse metabolic pattern. Their CRP values both at baseline and at follow-up were almost two-fold higher than in patients without LVH. Similar results were found in the healthier sub-sample. In a multiple regression model, CRP at follow-up was directly associated with baseline LVH (expressed as Cornell voltage-duration product) in the whole cohort (β=0.0003;95%CI 0.0002-0.0006;$p<0.001$) and in the sub-sample (β=0.0003;0.0002-0.0004;$p<0.001$), after adjusting for age, sex, BMI, waist circumference, smoking, exercise levels, blood pressure and baseline CRP values.

Conclusion: Baseline LVH, which is associated with systemic inflammation, predicts increased CRP values at follow-up, independently of cardiovascular and metabolic risk factors, both in a population-based cohort and a healthier sub-sample. The inflammatory consequences of LVH might be an intriguing subject for further researches.

Key words: C-reactive protein, left ventricular hypertrophy, metabolic syndrome, waist circumference

Abbreviations: C-reactive protein (CRP), Electrocardiogram (ECG), Homeostasis Model Assessment-Insulin Resistance (HOMA-IR), left ventricular hypertrophy (LVH), Metabolic syndrome (MS), National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATPIII).

Introduction

Left ventricular hypertrophy (LVH) is an independent predictor of cardiovascular morbidity and mortality [1-2]. Pathophysiological mechanisms underlying these associations might be abnormalities in the coronary vessels [3], or platelets [4], a prothrombotic condition [5], endothelial dysfunction, and systemic inflammation, which could lead to accelerated atherosclerosis [6-7]. Furthermore, LVH is a manifestation of target organ damage from coexistent risk factors, such as hypertension, overweight, and diabetes.

Previous studies have shown that LVH was cross-sectionally associated with fibrinogen, C-reactive protein (CRP) and soluble tumor necrosis factor (TNF) receptor values [7-14]. It has been hypothesized that LVH itself may be an inflammatory state in animal [15] and human studies [10, 16]. Ventricular wall stress produces an increase in cytokine levels, which may induce and amplify the inflammatory response [17].

Most human studies were performed in selected cohorts (patients with resistant hypertension, chronic hemodialysis, or type 2 diabetes) or were cross-sectional [7-14]; the latter were therefore unable to derive a temporal or causal relationship between inflammatory markers and LVH. Furthermore, the results of these studies are conflicting, because in multivariable-adjusted models, the relation is no longer significant [11-13]. Thus, the association of LVH with inflammation might be mediated by clinical risk factors that are themselves related to an inflammatory state.

Electrocardiogram (ECG) patterns of LVH were found to be associated with cardiovascular risk [18-19]. The ECG is a simple, non-invasive, low-cost, and reproducible test. In addition, its accuracy in diagnosing LVH was recently confirmed in obese patients [20]. In particular, the Cornell voltage-duration product [21], and the Perugia criteria [22], when compared with echocardiography, give the best sensitivity and specificity for LVH diagnosis and have a better prognostic value in predicting cardiovascular risk [20-25].

In this study, we hypothesized that LVH is a pro-inflammatory state and we investigated the possible association between baseline LVH and high sensitivity C-reactive-protein (CRP) values both cross-sectionally and after a mean six-year-follow-up in a population-based cohort and a normal-weight subgroup from this cohort, without diabetes, metabolic syndrome, or any other known concurrent medical condition requiring drugs.

Methods

Study population

The Caucasian patients (*n*=1,877) aged 45-64 years of six family physicians were invited to participate in a metabolic screening in 2001-2003. These subjects were representative of the Local Health Units of the province of Asti (North-western Italy); 1658 (88.3%) subjects agreed to participate and provided written informed consent, while 219 patients declined. Both participants and non-participants were similar to the resident population of a corresponding age range, with respect to the percentage of males, level of education, prevalence of known diabetes, and residence in a rural area [26].

The study was approved by the local Ethics Committee. All procedures conformed to the Helsinki Declaration principles.

Patients with baseline rhythm disorders, bundle branch blocks or other conduction abnormalities, acute or chronic coronary artery disease, previous myocardial infarction, cardiovalvular disease, digitalis use and known acute or chronic infection or inflammation were excluded (*n*=94). In particular, cardiovascular disease and acute or chronic infection/inflammation were identified based on documented events that were recorded by the family physician (i.e. angina, previous myocardial infarction, coronary artery by-pass graft or other invasive procedures to treat coronary artery disease, transient ischemic attacks, strokes, gangrene, amputation, vascular surgery, intermittent claudication, absent foot pulses and abnormal brachial and posterior tibial blood pressure using Doppler techniques, heart failure requiring pharmacological treatment or hospital admission, fever and acute infections within the previous month, autoimmune, connective tissue disease, and/or

chronic diseases of the lung, liver, and kidneys). At baseline, vascular disease was evaluated by the Rose questionnaire in all patients [26]. A final total of 1564 patients were included in this study. From the whole cohort, individuals with the metabolic syndrome (339/1564-21.7%), diabetes (84/1564-5.4%), BMI≥25 kg/m^2 (917/1564-58.6%) and all those treated with any drugs (including anti-hypertensive treatment) were excluded, thus obtaining a sub-sample of 515 subjects.

In the morning and after fasting, weight, height, waist circumference, and blood pressure were measured, and glucose, insulin, total cholesterol, HDL-cholesterol, triglyceride, creatinine and high-sensitivity-CRP levels were determined. If the serum glucose value was ≥6.1 mmol/L, a second fasting glucose determination was performed.

Patients completed the Minnesota-Leisure-Time-Physical-Activity questionnaire [27].

Two blood pressure measurements were performed with mercury sphygmomanometers with appropriate cuff sizes after a ten-minute rest in the sitting position, and the values reported are the means of the two measurements. All patients underwent baseline 12-lead ECG (record speed 25 mm/s, standard calibration 1.0 mV/cm). The tracings were interpreted blindly by a cardiologist with experience in ECG reading. Another physician blindly analyzed the QRS complex axis and duration, R wave amplitude in leads aVL, V_5 and V_6, S wave amplitude in V_1, V_2 and V_3, and strain pattern in V_5 and V_6 in all ECG tracings.

From January to November 2008, patients were contacted for a follow-up visit. Deaths occurred in 54/1564 (3.45%) subjects during follow-up. The remaining 1510 patients had weight, waist circumference, and blood pressure measurement taken, as well as a blood sample for the determination of fasting glucose, lipids and CRP values.

Laboratory methods have been described previously [26, 28-29]. Quantitative measurement of insulin in serum was performed with an immunoradiometric assay kit (Radim, Italy). To better investigate differences in insulin levels at both the beginning of the study and the follow-up, insulin was measured in both samples simultaneously. Serum creatinine values were measured by Jaffé

method. The intra-assay and inter-assay coefficients of variation were 0.7% and 2.3% respectively, with stability during the study period.

All samples were run in blind.

Definitions

Hypertension was considered if 140≤systolic blood pressure or 90 mmHg≤diastolic blood pressure, and if patients were on antihypertensive treatment, regardless of their blood pressure values. Pulse pressure was the difference between systolic and diastolic blood pressure.

Insulin resistance was estimated by the Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) [30], and a HOMA-IR≥2 μmol/L×mmol/L was considered as a cut-off for decreased insulin sensitivity [31]. MS was defined according to the criteria of the National Cholesterol Education Program's-Adult Treatment Panel III (NCEP-ATP III) [32]. Increased waist circumference corresponded to >88 cm (females) and >102 cm (males),according to NCEP criteria [32]. Diabetes was diagnosed when two glucose values were ≥7.0 mmol/l, if known diabetes was recorded by the family physician [33], and/or there was concomitant anti-diabetic treatment, regardless of the measured glucose values.

The physical activity level was calculated as the product of the duration and frequency of each activity (in hours/week), weighted by an estimate of the metabolic equivalent of the activity (MET), and summed for the activities performed.

Baseline LVH was diagnosed according to the Cornell voltage-duration product: {[R_{aVL} +S_{V3} (plus 8 mm in females)] × QRS duration} with a threshold value of 2440 mm·ms [21]. Furthermore, the Perugia score [22] was also used: S_{V3} + R_{aVL} > 2.4 mV (men) and >2 mV (women), and/or Romhilt-Estes score ≥5, and/or left ventricular strain pattern (defined as a convex ST-segment depression with asymmetric T-wave inversion opposed to QRS complex in leads V_5 or V_6).

Incident cardiovascular disease was based upon documented events, which were recorded by the family physician (angina, myocardial infarction, coronary artery by-pass graft or other invasive

procedure to treat coronary artery disease, heart failure requiring pharmacological treatment or hospital admission).

Statistical analyses

Values in the text are means ± standard deviation (SD), unless otherwise indicated. Since the distribution of HOMA-IR, CRP, insulin, and triglyceride values was positively skewed, their values were log-transformed, in order to approximate a normal distribution. The log-transformed values of these variables were used in all analyses. For an easy interpretation, the median and inter-quartile range of non-transformed values were reported.

The Student's t test and the χ^2-test were performed to assess differences in continuous and categorical variables, respectively.

Multiple regression analyses were used to evaluate the associations between CRP values at follow-up and baseline variables (one model for each baseline variable) after adjustments for age, sex, BMI, waist circumference, smoking habit, exercise level and baseline CRP values. The association between CRP at follow-up and baseline LVH (expressed as Cornell voltage-duration product) was analyzed in the same model, after further adjusting for mean blood pressure values, pulse pressure and (in the whole cohort) presence of the MS. ANCOVA was used to evaluate the association between baseline LVH and CRP at follow-up, after controlling for baseline CRP values and age, sex, BMI, diabetes, hypertension, mean blood pressure, pulse pressure, HOMA-IR levels.

A multiple logistic regression analysis was used to estimate the odds of being in the highest quartile of CRP values at follow-up (dependent variable) relative to the presence of obesity, increased waist circumference, metabolic syndrome, diabetes, HOMA-IR ≥2 μmol/L×mmol/L, hypertension, after adjusting for age, sex, smoking habit, exercise level and baseline CRP. The association between baseline LVH (presence *vs* absence) and CRP at follow-up was analyzed in the same model, after further adjustments for BMI, mean blood pressure values, pulse pressure and presence of the MS. One model for each baseline variable was performed.

A two-sided p-value of <0.05 was considered to be statistically significant (SAS, version 9.0; SAS Institute, Cary, NC).

Results

The mean follow-up time was 6.1±0.34 years. LVH was identified at baseline in 166/1564 subjects (10.6%). Patients with baseline LVH showed increased values for age, BMI, waist circumference, blood pressure, and percentage of males, and had a significantly worse metabolic pattern, both at baseline and after follow-up (Table 1). CRP values both at baseline and after follow-up were almost two-fold higher in patients with baseline LVH.

In the sub-sample without MS, age, BMI, waist circumference, blood pressure, and percentage of males were significantly higher in those with LVH at baseline; many of these differences were reduced after follow-up (Table 2). About 23% of these subjects showed blood pressure values within hypertensive ranges although not treated with anti-hypertensive treatment. Most of those individuals with baseline LVH (95.4%) were thus hypertensive patients neither recognized nor properly treated. CRP values were about 1.5-fold higher in subjects with baseline LVH.

CRP at baseline was significantly associated with baseline LVH in a multiple regression analysis, after adjusting for age, sex, waist circumference, smoking, exercise, mean blood pressure values, pulse pressure, both in the whole sample (β=0.0002; 95%CI 0.0001-0.0003, p<0.001) and in the healthy sub-sample (β=0.0002; 0.00006-0.0003; p=0.002).

CRP values at follow-up were significantly associated with many baseline metabolic variables in the entire cohort (Tab. 3). In a multiple regression model, CRP at follow-up was directly associated with BMI, waist circumference, diastolic blood pressure, fasting insulin, HOMA-IR, baseline CRP, and LVH, and was inversely associated with HDL-cholesterol (Tab. 3, left). In the sub-sample, CRP at follow-up was directly associated with BMI, waist circumference, baseline CRP, and LVH and was inversely associated with HDL-cholesterol (Table 3, right).

The association between hsCRP at follow-up and baseline LVH remained highly significant ($p<0.001$), by using ANCOVA, after controlling for baseline CRP values and age, sex, BMI, diabetes, hypertension, mean blood pressure, pulse pressure and HOMA-IR levels (data not shown). The highest CRP quartile was ≥3 mg/L in the whole cohort and ≥ 1.2 mg/L in the sub-sample. In a linear logistic regression model, subjects with higher CRP quartiles at follow-up were more likely to have obesity, MS, diabetes, increased waist circumference, hypertension and LVH at baseline in the whole cohort (Figure 1, black bars) and baseline LVH in the healthier sub-sample (Figure 1, white bars). Among those patients with baseline CRP values<3 mg/L from the whole cohort, 3.1% and 21.2% of those without and with baseline LVH, respectively, developed CRP values at follow-up in the highest quartile ($p<0.001$).

In a multiple logistic regression analysis, being in the highest quartile of CRP values at follow-up was predicted by the following baseline variables: increased waist circumference, diabetes, MS, and LVH in the whole cohort (Table 4, left) and by baseline LVH in the sub-sample (Table 4, right).The associations between CRP at follow-up and baseline LVH were attenuated after adjusting for waist circumference (OR=1.96; 1.02-3.78; 0.04 and OR=2.76; 1.19-6.39; p=0.02 in the whole cohort and sub-sample, respectively), suggesting, as expected, that central body fat tissue is a recognized site of cytokine production, influencing CRP levels.

Associations between CRP at follow-up and baseline LVH did not change, after further adjustment for lipid parameters, HOMA-IR and creatinine values.

These results were highly concordant, when the Perugia score was used to define baseline LVH. Both in the whole cohort and in the sub-sample, patients with LVH showed increased BMI, waist circumference, blood pressure values, and a worse metabolic pattern, and their CRP values at follow-up were almost two-fold higher than in patients without LVH (Appendix). In a multiple logistic regression model, CRP at follow-up was directly associated with baseline LVH in the whole cohort (OR=3.01; 95%CI 2.19-4.15; $p<0.001$) and in the sub-sample (OR=5.63; 95%CI 2.92-10.9;

$p<0.001$), after adjusting for age, sex, smoking, exercise levels, BMI, baseline CRP values, mean blood pressure values and pulse pressure.

Data, based on either criterion, did not change significantly either after excluding the 56 individuals with CRP values at follow-up >10mg/L and the 27 patients who developed a vascular disease during follow-up.

Discussion

Both in a population-based cohort and in a healthier sub-sample from this cohort, baseline LVH is associated with systemic inflammation, and its presence predicts increased CRP values after a six-year follow-up, independently of cardiovascular risk factors and waist circumference.

LVH is a strong predictor of adverse cardiovascular outcome [1-2]. The inter-relationship between the activation of systemic inflammation and LVH might be one of the mechanisms implied, given the well known association between accelerated atherosclerosis and inflammation [6]. Cross-sectional independent associations of LVH with elevated levels of inflammation markers have been reported previously [7-17]. LVH has been hypothesized to interact with endothelial dysfunction, cytokines, insulin resistance, and hemodynamics to increase inflammation markers [12]. Stretched myocardium and LV overload are associated with cytokine production and higher circulating levels of inflammatory markers [17]. It has been demonstrated that hemodynamic overloading and myocardial stretch are sufficient to provoke de novo TNFα mRNA and protein expression in the heart [34] The severity of hemodynamic pressure overload correlated with citokine levels and chronic pressure overload may serve as a greater stimulus for cytokine production as compared to volume overload [17]. In most of the cross-sectional studies, the authors suggested that systemic low-grade inflammation may predict the occurrence of LVH [7-11, 13-14]. However, speculations about the temporal and causal relationships between inflammation and LVH development should be addressed by prospective studies. Our prospective data add a little piece to the existing knowledge: LVH is per se a pro-inflammatory factor and may contribute to a pro-inflammatory status, as well

as other chronic conditions do, such as insulin resistance, central obesity, microalbuminuria and chronic renal failure.

Large cross-sectional population-based studies found that the association between elevated CRP values and LVH did not persist in multivariate analyses after adjustment for cardiovascular risk factors and BMI [11-13]. This potentially suggests either that increased inflammation and LVH are epiphenomena of the augmented hemodynamic load that is associated with hypertensive status or that higher levels of inflammatory markers in LVH are a consequence of coexistent risk factors, such as hypertension, obesity, and diabetes. Unlike previous studies, which were cross-sectional, we found that baseline LVH was a strong predictor of high CRP values at follow-up, independently of waist circumference, which only attenuated the associations that were found. The relationship between baseline LVH and CRP at follow-up is independent of other important potential confounders, including BMI, insulin resistance, blood pressure, lipid levels and age. These confounders are, in turn, associated with markers of inflammation. Intriguingly, among those patients with baseline CRP values<3 mg/L, 3.1% and 21.2% of those without and with baseline LVH, respectively, developed CRP values in the highest quartile at follow-up.

It is noteworthy that, in the sub-sample without drug therapy, MS, obesity and diabetes, having LVH at baseline conferred a more than three-fold higher risk of having the highest CRP values after a six-year follow-up. This prospective association suggests that baseline LVH may precede further increases in inflammatory parameters in asymptomatic subjects in the absence of obesity, overt metabolic diseases and diabetes, thus explaining the well known association of LVH with incident cardiovascular diseases [1-2, 12, 14].

Limitations

Due to the low number of deaths or incident vascular events, our study was underpowered to detect differences in rates between the groups. We could not completely exclude either coronary atherosclerosis or other heart diseases in our study sample. Furthermore echocardiographic examinations were not available. Many studies have confirmed the high specificity of ECG criteria

for the diagnosis of LVH [20-25] and the usefulness of ECG-determined LVH as a predictor of cardiovascular morbidity and mortality [35-36].

The Perugia criteria have shown good sensitivity and specificity for the diagnosis of baseline LVH [20, 22-23], but the Cornell voltage-duration product might be even better in terms of specificity [21, 24-25]. The fact that similar findings were obtained using two different criteria for the diagnosis of LVH strengthens the results of our study. Furthermore, differences among LVH categories for several laboratory and clinical variables, which were measured in blind, were consistent with the LVH condition.

Associations between CRP and baseline LVH might be affected by confounding variables because of associations with other risk factors (i.e. up-regulation of cytokines, as a result of other not measured conditions) or because of reverse causation (e.g. the inflammatory process as a cause of LVH). Furthermore, data on sub-clinical atherosclerotic disease, which may be present and may have confounded the results, were not available. ECG tracings at follow-up were not available, thus it is not possible from our data either establishing a cause-effect relationship between inflammation and LVH, or analyzing changes in LVH. Nevertheless, the strong associations that were found in the healthier subgroup make the possibility of a confounding effect less likely. Even if these results should be considered hypothesis-generating only, they could be worthy of further explorations.

Only a single measurement of CRP was performed, and the variability in CRP measurements over time could influence the association between baseline LVH and CRP. However, random misclassification should have weakened the associations found, biasing the results to the null hypothesis.

Although we did not use more invasive methods to evaluate insulin resistance, HOMA is considered to be a well-validated index of insulin sensitivity [37].

Conclusion

In a population-based cohort without clinically overt cardiovascular disease and in a sub-sample without drug therapy, MS, obesity and diabetes, baseline LVH is prospectively associated with

increased CRP values. Screening patients for LVH, therefore, might be useful not only for distinguishing high-cardiovascular-risk individuals, independently of associated co-morbidities as already known [1-2], but for identifying those who are predisposed to a pro-inflammatory state, too. Although there are potential limitations for our results, these data intriguingly suggest to focus on the inflammatory consequence of LVH. In addition, if these observations are confirmed in other analyses, there will be a need for additional research to determine whether patients with LVH will benefit from specific treatment, such as, pleiotropic anti-hypertensive drugs or anti-inflammatory drugs.

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Figure 1 legend. Association between quartiles of CRP values at follow-up and prevalence of baseline clinical conditions in the whole cohort (black bars) and in the sub-sample (white bars).

A: obesity; B: MS; C: diabetes; D: increased waist circumference; E: hypertension; F: Baseline LVH. Patients with diabetes, the MS, on drugs (including anti-hypertensive treatment) and with BMI≥25 kg/m^2 were excluded from the sub-sample. In the whole cohort: 1=lower quartile (*n*=386; CRP<0.64 mg/l); 2= second quartile (*n*=377; CRP≥ 0.64 and ≤1.0 mg/l); 3= third quartile (*n*=372; CRP>1 and <3 mg/l); 4=higher quartile (*n*=375; CRP≥3 mg/l). In the whole cohort, p for trend by a linear logistic regression <.001 (A); <.001 (B); =.008 (C); =<.001 (D); =.02 (E); and <.001 (F). In the sub-sample: 1=lower quartile (*n*=128; CRP≤0.6 mg/l); 2= second quartile (*n*=125; CRP>0.6 and <1 mg/l); 3= third quartile (*n*=123; CRP≥1 and <1.2 mg/l); 4=higher quartile (*n*=127; CRP≥1.2 mg/l).

In the sub-sample, p for trend =.77 (E); and <.001 (F).

Table.1 Characteristics in the whole cohort at baseline and at follow-up, according to the presence of left ventricular hypertrophy at baseline

	At baseline			At follow-up		
	LVH at baseline			LVH at baseline		
	yes	No	P	Yes	No	P
Number	166	1398		155	1355	
Males (%)	55.4	44.4	.007	54.2	44.0	.02
Age (y)	55.7±5.7	54.3±5.6	.002	61.7±5.7	60.4±5.6	.007
Actual smokers (%)	20.0	24.5	.43	20.0	24.2	.51
Metabolic equivalent activity (hr/wk)	22.7±10.7	21.5±10.5	.16	23.0±10.8	21.5±10.5	.10
BMI (kg/m^2)	28.3±5.3	26.3±4.5	<.001	28.5±5.5	26.5±4.4	<.001
Waist circumference (cm)	96.8±12.6	90.2±12.7	<.001	97.9±12.8	91.7±12.4	<.001
Systolic BP (mmHg)	140.7±16.8	132.7±15.6	<.001	140.5±17.6	134.0±16.7	<.001
Diastolic BP (mmHg)	87.4±10.2	82.7±9.1	<.001	85.5±9.4	82.5±9.3	<.001
Fasting glucose (mmol/L)	5.9±1.5	5.7±1.6	.27	5.6±0.9	5.6±1.3	.78
Fasting insulin (pmol/L)[a]	42.3 (27.6)	40.8 (16.8)	<.001	51.5(39.5)[b]	42.8(33.8)[c]	.03
HOMA-IR (μmol/L×mmol/L)[a]	1.9 (1.5)	1.7 (0.9)	<.001	2.1 (2.0)[b]	1.7 (1.4)[c]	.01
Total cholesterol (mmol/L)	5.7±1.1	5.6±1.0	.48	5.7±0.9	5.7±1.0	.97
HDL cholesterol (mmol/L)	1.5±0.3	1.6±0.3	.27	1.4±0.4	1.5±0.4	.03
LDL cholesterol (mmol/L)	3.4±1.0	3.3±0.9	.63	3.6±1.0	3.6±1.0	.94
Triglycerides (mmol/L)[a]	1.4 (0.8)	1.3 (0.8)	.02	1.4 (0.7)	1.3 (0.8)	.02
Creatinine (μmol/l)	70.1±18.6	71.1±32.4	0.71	77.8±16.3	75.3±14.8	0.06
CRP (mg/L)[a]	2.2 (3.8)	1.2 (2.0)	<.001	2.9 (4.1)	1.0 (1.6)	<.001
Anti-hypertensive therapy (%)	31.3	22.1	.008	41.3	29.7	.003
Diabetes (%)	5.4	5.4	.98	5.8	6.2	.85

BP= blood pressure; mean ±standard deviation [a]median (inter-quartile range); [b]data available in 126 subjects; [c]data available in 941 subjects

Table.2 Characteristics in the sub-sample at baseline and at follow-up, according to the presence of left ventricular hypertrophy at baseline

	At baseline			At follow-up		
	LVH at baseline			LVH at baseline		
	yes	No	P	yes	No	P
Number	43	472		42	461	
Males (%)	53.5	36.2	.03	52.4	36.2	.04
Age (y)	55.6±5.9	52.8±5.5	.002	61.6±6.0	59.0±5.5	.003
Actual smokers (%)	16.3	28.2	.08	16.7	28.0	.15
Metabolic equivalent activity (hr/wk)	21.2±8.6	22.5±10.5	.42	21.3±8.6	22.4±10.5	.49
BMI (kg/m^2)	23.2±1.7	22.3±1.9	.003	23.6±1.8	22.8±2.2	.03
Waist circumference (cm)	86.4±8.1	80.1±9.1	<.001	88.1±5.4	82.0±9.4	<.001
Systolic BP (mmHg)	134.9±11.8	124.5±12.4	<.001	132.0±13.7	124.7±14.3	.001
Diastolic BP (mmHg)	83.9±9.4	78.3±7.2	<.001	80.4±7.3	78.2±7.6	.08
Fasting glucose (mmol/L)	5.4±0.7	5.2±0.7	.23	5.2±0.7	5.2±0.7	.88
Fasting insulin (pmol/L)[a]	39.0 (5.4)	38.4 (5.4)	.65	36.0(17.3)[b]	32.5(22.7)[c]	.80
HOMA-IR (μmol/L×mmol/L)[a]	1.5 (0.3)	1.5 (0.2)	.31	1.3 (0.5)[b]	1.3 (0.9)[c]	.65
Total cholesterol (mmol/L)	5.7±1.1	5.5±1.0	.13	6.0±0.8	5.6±1.0	.02
HDL cholesterol (mmol/l)	1.7±0.4	1.7±0.4	.73	1.5±0.5	1.6±0.4	.32
LDL cholesterol (mmol/L)	3.4±0.9	3.2±0.9	.23	3.8±1.0	3.4±1.0	.02
Triglycerides (mmol/L)[a]	1.2 (0.4)	1.1 (0.5)	.21	1.1 (0.8)	1.1 (0.7)	.40
Creatinine (μmol/l)	68.7±13.5	69.7±39.5	0.86	74.3±12.8	71.8±14.5	0.29
CRP (mg/L)[a]	1.2 (2.3)	0.8 (1.1)	.001	1.5 (2.1)	1.0 (0.6)	<.001
Anti-hypertensive therapy (%)	-	-		16.7	5.6	.006

BP= blood pressure; mean ±standard deviation

[a]median (inter-quartile range); [b]data available in 37 subjects; [c]data available in 292 subjects

Table.3. Association of CRP values at follow-up with baseline variables in the whole cohort and in the sub-sample at regression analyses

	Whole cohort		Sub-sample	
Baseline variables	**Crude[a]**	**Adjusted**	**Crude[a]**	**Adjusted**
	β; 95%CI; p	**β; 95%CI; p**	**β; 95%CI; p**	**β; 95%CI; p**
CRP (mg/L)	0.66; 0.62 0.70;<.001	0.66; 0.62 0.70;<.001[b]	0.53; 0.47 0.59;<.001	0.52; 0.46 0.58;<.001[b]
BMI (kg/m^2)	0.06; 0.05 0.07;<.001	0.04; 0.03 0.05;<.001[c]	0.07; 0.03 0.11;.002	0.06;0.002 0.10;.001[c]
Waist circumference (cm)	0.019; 0.015 0.022;<.001	0.02; 0.016 0.024;<.001[c]	0.02; 0.01 0.03;.<.001	0.02;0.01 0.03;<.001[c]
Systolic BP (mmHg)	0.006; 0.002 0.01;<.001	0.002; -0.001 0.005;.29[d]	-0.004; -0.01 0.002;.22	-0.002;-0.008 0.004;.44[d]
Diastolic BP (mmHg)	0.01; 0.004 0.016;<.001	0.005; 0.0001 0.01;.04[d]	-0.002; -0.012 0.008;.70	0.002; -0.008 0.001;.73[d]
Fasting glucose (mmol/L)	0.08; 0.04 0.11;<.001	0.008; -0.02 0.04;.58[d]	0.12; 0.002 0.24;.04	0.05; -0.05 0.15;.36[d]
Fasting insulin (pmol/L)	0.23; 0.17 0.29;<.001	0.17; 0.04 0.30;.02[d]	0.07; -0.05 0.19;.22	-0.03; -0.27 0.33;.87[d]
HOMA-IR(μmol/L×mmol/L)	0.23; 0.17 0.29;<.001	0.12; 0.01 0.23;.04[d]	0.10; -0.02 0.22;.11	0.05; -0.24 0.34;.76[d]
Total cholesterol (mmol/L)	0.03; -0.02 0.08;.23	0.02; -0.02 0.06;.38[d]	0.003; -0.08 0.11;.94	0.009; -0.06 0.08;.81[d]
HDL cholesterol (mmol/L)	-0.35; -0.51 -0.19;<.001	-0.19; -0.33 –0.05;.008[d]	-0.36; -0.58 –0.14;.002	-0.21: -0.42 0.001; 0.06[d]
LDL cholesterol (mmol/L)	0.05;- 0.01 0.11;.09	0.04; -0.01 0.09;.13[d]	0.04; -0.06 0.14;.33	0.04; -0.04 0.12;.38[d]
Triglycerides (mmol/L)	0.30; 0.18 0.42;<.001	0.09; -0.01 0.19;.10[d]	0.16; -0.04 0.36;.13	0.05; -0.13 0.23;.58[d]
Baseline LVH	0.0005; 0.0004 0.0006; <.001	0.0003; 0.0002 0.0006; <.001[e]	0.0004; 0.0003 0.0005;<.001	0.0003; 0.0002 0.0004; <.001[f]

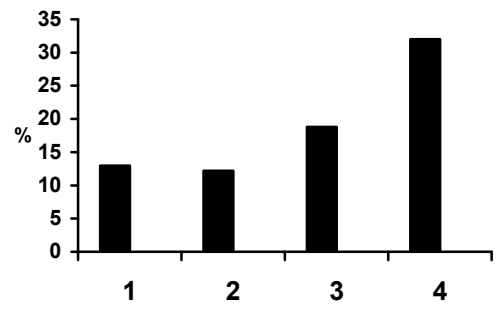
[a]association between log-CRP values at follow-up and each baseline variable by univariate regression analyses (one model for each baseline variable) [b]association between log-CRP values at follow-up and baseline CRP by multiple regression analyses, after adjustment for age, sex, BMI, waist circumference, smoking habit and exercise level [c]association between log-CRP values at follow-up and each baseline variable by multiple regression analyses, after adjustment for age, sex, smoking habit, exercise level and baseline CRP (one model for each baseline variable) [d]the same model as above described, additionally adjusted for BMI and waist circumference (one model for each baseline variable) [e]association between log-CRP values at follow-up and baseline LVH by the same model as above described, additionally adjusted for BMI, waist circumference, mean blood pressure values and pulse pressure, and presence of the MS [f]association between log-CRP values at follow-up and baseline LVH by the same model as above described, additionally adjusted for BMI, waist circumference, mean blood pressure values and pulse pressure.

Table.4. Odds ratios and 95% confidence intervals of having CRP values in the highest quartile at follow-up in the whole cohort and in the sub-sample in a multiple logistic regression analysis

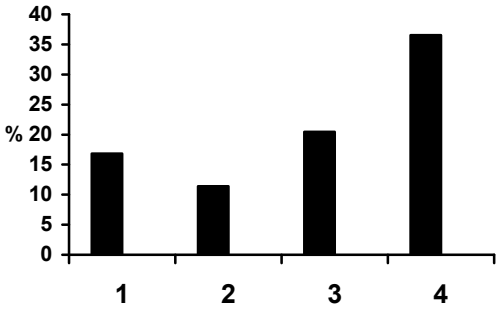
Baseline variables	Whole cohort OR (95% CI) p[a]	Sub-sample OR (95% CI) p[a]
Obesity	0.92 (0.60-1.41) .70	-
Increased waist circumference[b]	2.60 (1.52-4.47) <.001	-
Metabolic syndrome	1.56 (1.03-2.37) .03	-
Diabetes	2.55 (1.08-5.98) .03	-
HOMA-IR ≥2μmol/L×mmol/L	1.27 (0.86-1.87) .23	0.80 (0.37-1.74) .57
Hypertension	1.20 (0.78-1.85) .40	0.54 (0.28-1.05) .07
Baseline LVH	2.78 (1.84-4.20) <.001[c]	3.28 (1.49-7.20) .003 [d]

[a]multiple logistic regression analyses, after adjustments for age, sex, smoking, exercise level and baseline CRP (a model for each baseline variable)
[b]waist circumference >88 cm (females) and >102 cm (males),according to the National Cholesterol Education Program's Adult Treatment Panel III criteria [28]
[c]multiple logistic regression analyses, after adjustment for age, sex, smoking, exercise levels, BMI, baseline CRP values, mean blood pressure values and pulse pressure, and presence of the MS
[d]multiple logistic regression analyses, after adjustment for age, sex, smoking, exercise levels, BMI, baseline CRP values, mean blood pressure values and pulse pressure.

Figure 1.



A



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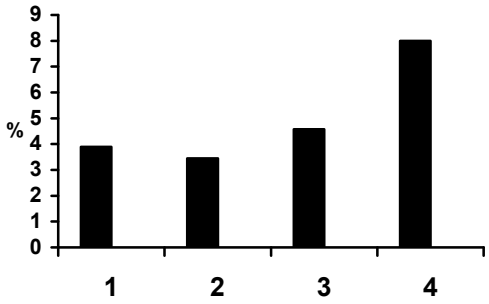

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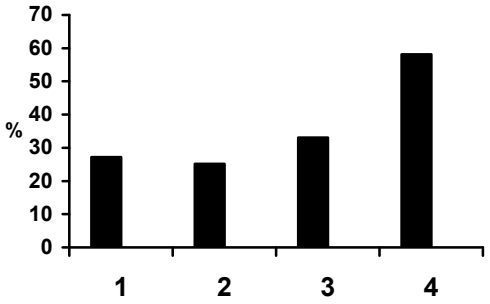

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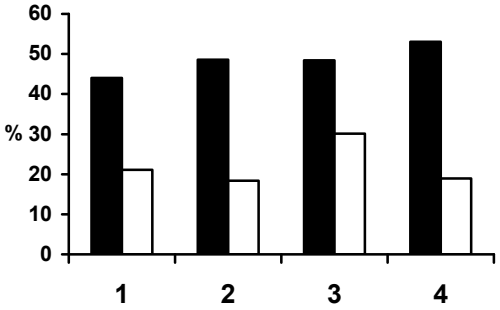

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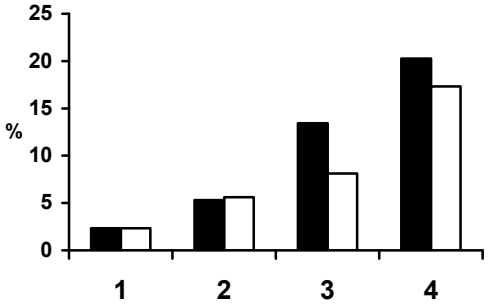

F