Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 45, No. 11, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.02.066

Inflammation, as Measured by the Erythrocyte Sedimentation Rate, Is an Independent Predictor for the Development of Heart Failure

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OBJECTIVES Our objective was to explore inflammation, measured as erythrocyte sedimentation rate (ESR), as a predictor for the development of heart failure (HF).

BACKGROUND In recent years, evidence of the importance of inflammation in the pathophysiology of HF has emerged, and various inflammatory markers have been found to predict future HF. Erythrocyte sedimentation rate is an inexpensive and easily accessible marker of systemic inflammation, but to this date it is unknown whether ESR predicts subsequent HF.

METHODS In a community-based prospective study of 2,314 middle-aged men free from HF, myocardial infarction, and valvular disease at baseline, ESR was analyzed in multivariable models together with established risk factors for HF (hypertension, diabetes, electrocardiographic left ventricular hypertrophy, smoking, obesity, and serum cholesterol) and hematocrit.

RESULTS A total of 282 men developed HF during a median follow-up time of 30 years. In Cox proportional hazards analyses, ESR was an independent predictor of HF (hazard ratio 1.46 for highest quartile vs. the lowest, 95% confidence interval 1.04 to 2.06). This observation remained significant when also adjusting for interim myocardial infarction during follow-up.

CONCLUSIONS Erythrocyte sedimentation rate was a significant predictor of HF, independent of established risk factors for HF, and interim myocardial infarction after three decades of follow-up in a population-based sample of middle-aged men. Our findings indicate that inflammation occurs early in the process leading to HF and that ESR could be used to evaluate this process. (J Am Coll Cardiol 2005;45:1802–6) © 2005 by the American College of Cardiology Foundation

In recent years, the association between inflammation and cardiovascular diseases has gained considerable interest (1). Several systemic markers of inflammation, including erythrocyte sedimentation rate (ESR), have been found to be predictors of coronary heart disease (2–4). C-reactive protein, tumor necrosis factor (TNF)-alpha, and interleukin (IL)-6, all markers of cytokine-mediated inflammation, have all been shown to predict incident heart failure (HF) (5,6), but to this date, there are no studies of the possible association between ESR and future HF. The ESR is a well-validated and inexpensive tool for evaluating inflammation (including aspects of inflammation other than cytokine-mediated reactions) and is available at every outpatient clinic.

Thus, our aim was to analyze ESR as a possible predictor of heart failure during a median follow-up time of 30 years in a community-based sample of middle-aged men free from HF, previous acute myocardial infarction, and valvular disease at baseline. Because ESR is a known predictor of coronary heart disease, a secondary aim was to analyze whether it predicted HF independently of an interim myocardial infarction during the follow-up period.

METHODS

Study sample. The study used the Uppsala Longitudinal Study of Adult Men (ULSAM) cohort, to which all 50-year-old men living in Uppsala county in 1970 to 1974 were invited. Of the 2,841 invited men, 82% (2,322 men) participated in the investigation (7). The ULSAM study is described in detail on the Internet (8). None of the subjects had been diagnosed with HF in the hospital discharge register before baseline. Seven subjects were excluded because of previous myocardial infarction and one subject because of valvular disease at baseline; thus, 2,314 men were eligible for the investigation. In a secondary analysis, we excluded all subjects receiving treatment with corticosteroids (n = 7) or potentially anti-inflammatory analgesics (n = 16). All subjects gave written consent, and the Ethics Committee of Uppsala University approved the study.

Examinations at baseline. Examinations performed when the subjects were 50 years of age (7) included a structured interview; a questionnaire; blood sampling (after an over-

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Manuscript received December 14, 2004; revised manuscript received February 16, 2005, accepted February 22, 2005.

Abbreviations and Acronyms

BMI = body mass index
CI = confidence interval
ESR = erythrocyte sedimentation rate
HF = heart failure
HR = hazard ratio
ICD = International Classification of Diseases
IL = interleukin
TNF = tumor necrosis factor
ULSAM = Uppsala Longitudinal Study of Adult Men

night fast) for glucose, lipid, and ESR determinations; an electrocardiogram; and a physical examination with determinations of supine blood pressure and anthropometric measurements.

The ESR was determined by Westergren's method. Body mass index (BMI) was calculated as weight (in kg) divided by height (in m) squared (kg/m^2). The presence of hypertension at baseline was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, and/or the use of antihypertensive medication. The presence of diabetes at baseline was defined as fasting blood glucose ≥6.1 mmol/l and/or the use of oral hypoglycemic agents or insulin. Electrocardiographic left ventricular hypertrophy was defined as high amplitude R-waves according to the revised Minnesota code (9) together with a left ventricular strain pattern (10). The presence of valvular disease (International Classification of Diseases [ICD]-8 codes 394-396 and 424, ICD-9 codes 394-397 and 424, or ICD-10 codes I05-I08 and I34-I37) and previous myocardial infarction (ICD-8 code 410, ICD-9 code 410, or ICD-10 code I21) were assessed from the hospital discharge register.

Follow-up and outcome parameter. The subjects had a median follow-up time of 29.6 years (range, 0.04 to 32.7 years), contributing to 59,122 person-years at risk. The possible HF cases were selected by linking the ULSAM participants to the hospital discharge register using the Swedish unique personal identification numbers. As a possible diagnosis of heart failure, we considered ICD heart failure codes 427.00, 427.10, 428.99 (ICD-8), 428 (ICD-9), and I50 (ICD-10) and hypertensive heart disease with heart failure, I11.0 (ICD-10), which were allowed in any of the six possible diagnosis positions. Three hundred forty-six men had a hospital discharge register diagnosis of HF between the entry to the ULSAM study and the end of 2002. The medical records from the relevant hospitalization were reviewed by two physicians (E.I. and L.L.), blinded to the baseline data, who classified the cases as definite, questionable, or miscoded. The classification relied on the definition proposed by the European Society of Cardiology (11). After this validation, 282 cases of definite HF were included in the present study. None of the subjects was lost to follow-up.

Statistical methods. Data are given as means ± SD and percent. Proportional hazards assumptions were confirmed both graphically and by Schoenfeld's tests. Cumulative hazard curves according to ESR levels were established by the Nelson-Aalen estimation method (12). Inspecting HF incidence rates in quartiles of ESR, an apparent threshold level at the median was observed (Fig. 1). On the basis of this, we assessed ESR as a nominal variable, both as four groups (quartiles) and as two groups (above vs. below or at the median). In the quartiles models, the lowest HF incidence was observed in the second quartile of ESR (Fig. 1), which was used as a reference level. The prognostic value of ESR for HF incidence was investigated using Cox proportional hazards analyses. We investigated three sets of models in a hierarchical fashion: 1) unadjusted analyses; 2) multivariable-adjusted analyses using the following baseline covariates: hypertension, diabetes, electrocardiographic left ventricular hypertrophy, smoking, BMI, serum cholesterol, and hematocrit; and 3) covariates as in model 2, with the addition of interim myocardial infarction during follow-up.

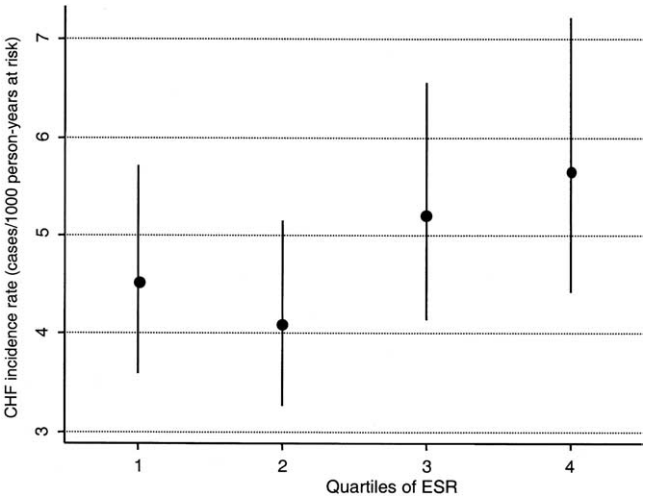

Figure 1. Incidence rates of congestive heart failure (CHF) by quartiles (quartile 1, erythrocyte sedimentation rate [ESR] = 1 to 3 mm/h; quartile 2, 4 to 6 mm/h; quartile 3, 7 to 10 mm/h; quartile 4, 11 to 83 mm/h) of ESR. **Lines** indicate 95% confidence intervals.

Hematocrit was included as a covariate in models 2 and 3, together with the established risk factors for HF, to adjust for the red blood cell characteristics, leaving ESR to reflect mainly systemic inflammation. Two-tailed 95% confidence intervals (CIs) and p values are given, with $p < 0.05$ regarded as significant. All analyses were specified a priori. Statistical software package STATA 8.2 (Stata Corp., College Station, Texas) was used.

RESULTS

The incidence rate for HF during the follow-up period was 4.8/1,000 person-years at risk. Table 1 shows the participant characteristics at baseline. In unadjusted Cox proportional hazards analyses, ESR was significantly associated with HF incidence, with the highest hazard ratio observed in the highest quartile of ESR compared with the reference level (Fig. 1, Table 2 middle column). In addition, an ESR