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-
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/m²). 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.

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
greater than the median was a predictor of future HF compared with an ESR less than or equal to the median (Table 2, middle column). A cumulative HF incidence plot for ESR split by the median is presented in Figure 2. When evaluating ESR as a diagnostic test for future HF (ESR greater than the median [6 mm/h] considered to be a positive test), the sensitivity was 48%, specificity 57%, positive predictive value 13%, and the negative predictive value was 89%. As a comparison, we calculated the corresponding values for hypertension (sensitivity 57%, specificity 59%, positive predictive value 16%, and negative predictive value 91%). Adjusting for established risk factors for HF (hypertension, diabetes, electrocardiographic left ventricular hypertrophy, smoking, BMI, serum cholesterol) and hematocrit, ESR remained a significant predictor of HF in both the dichotomous and the quartile Cox proportional hazards models (Table 2, right column).

Evidence of myocardial infarction during the follow-up was present in 411 of the subjects in the total cohort and in 107 of the 282 HF cases (38%). When adjusting for interim myocardial infarction in addition to the established baseline risk factors for HF, an ESR in the highest quartile (compared with quartile 2; hazard ratio [HR] 1.46, 95% CI 1.04 to 2.05, \( p = 0.03 \)) and greater than the median (compared with less than or equal to the median; HR 1.35, 95% CI 1.06 to 1.72, \( p = 0.01 \)) remained significant predictors of future HF. In the subsample free from corticosteroids and anti-inflammatory analgesics, the results were essentially the same in all models (data not shown).

**DISCUSSION**

In this community-based cohort study of middle-aged men free from heart failure, myocardial infarction, and valvular disease at baseline, erythrocyte sedimentation was a signif-

### Table 1. Baseline Characteristics of the Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (Mean ± SD or %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of hypertension (%)</td>
<td>43</td>
</tr>
<tr>
<td>Prevalence of diabetes (%)</td>
<td>5.6</td>
</tr>
<tr>
<td>Electrocardiographic left ventricular hypertrophy (%)</td>
<td>1.7</td>
</tr>
<tr>
<td>Current cigarette smoking (%)</td>
<td>51</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.0 ± 3.2</td>
</tr>
<tr>
<td>S-cholesterol (mmol/l)</td>
<td>6.9 ± 1.3</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>43.4 ± 2.7</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
<td>7.8 ± 7.0 (median 6, range 1–83)</td>
</tr>
</tbody>
</table>

Values are means ± SD or %.

### Table 2. Incidence of Heart Failure in Relation to Erythrocyte Sedimentation Rate (ESR) in the Total Sample (n = 2,314) Free From Heart Failure (HF), Myocardial Infarction, and Valvular Disease at Baseline, Unadjusted and Adjusted for Established Risk Factors

<table>
<thead>
<tr>
<th>Established risk factors for HF</th>
<th>Unadjusted Hazard ratio for HF (95% CI)</th>
<th>Adjusted for Established Risk Factors and Hematocrit Hazard Ratio for HF (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of hypertension</td>
<td>2.14 (1.69–2.71)‡‡</td>
<td>1.66 (1.29–2.13)‡‡</td>
</tr>
<tr>
<td>Prevalence of diabetes</td>
<td>1.77 (1.16–2.72)†</td>
<td>1.58 (1.03–2.44)*</td>
</tr>
<tr>
<td>Electrocardiographic left ventricular hypertrophy</td>
<td>5.42 (3.16–9.30)‡‡</td>
<td>4.52 (2.60–7.83)‡</td>
</tr>
<tr>
<td>Current cigarette smoking</td>
<td>1.51 (1.19–1.91)‡</td>
<td>1.70 (1.33–2.17)‡</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>1.59 (1.44–1.77)‡‡</td>
<td>1.48 (1.33–1.65)‡</td>
</tr>
<tr>
<td>S-cholesterol (mmol/l)</td>
<td>1.18 (1.06–1.32)†</td>
<td>1.09 (0.97–1.23)</td>
</tr>
</tbody>
</table>

Cox proportional hazards ratios for a 1-standard deviation increase in continuous variables or transfer from one level to another of categorical variables. For categorical variables, the level with the lowest incidence rate was used as the reference level. Data are hazard ratios (95% confidence intervals [CI], unadjusted or adjusted for established risk factors (hypertension, diabetes, electrocardiographic left ventricular hypertrophy, smoking, body mass index and serum cholesterol) and hematocrit. The values shown for established risk factors in the right column are acquired from the multivariable model incorporating erythrocyte sedimentation rate (ESR) split by the median. Any \( p \) values \( <0.05 \) are considered significant. *\( p < 0.05 \); †\( p < 0.01 \); ‡\( p < 0.001 \).
icant predictor of HF, taking established risk factors for HF and hematocrit at baseline and interim myocardial infarction during follow-up into account. Our observations indicate that inflammation might be an important factor that occurs early in the process leading to HF. This fact is further supported by the lag time of one decade before development of HF observed in this cohort (Fig. 2). The diagnostic capacity of ESR as a test for incident HF, in terms of sensitivity and specificity, was comparable with that of hypertension.

Previous studies. In the last decade, evidence of inflammation as a crucial part of the atherosclerosis process has emerged (1). Inflammation can be initiated in the vessels as a response to retained and modified low-density-lipoprotein cholesterol, injury, and infections. Other major risk factors for cardiovascular diseases, such as hypertension, diabetes, obesity, and smoking, also have been associated with a low-grade chronic inflammation (1,13). In recent years, the role of inflammation in the pathogenesis of HF has been investigated. Elevated levels of various inflammatory markers have been observed in patients with HF (14,15) and, in recent prospective studies, increased levels of C-reactive protein, TNF-alpha, and IL-6, markers of cytokine-mediated inflammation, predicted subsequent HF (5,6). Cesari et al. (5) used a study sample about as large as ours, whereas Vasan et al. (6) used a smaller sample with slightly more than 700 subjects. Both studies had much shorter follow-up (3.6 years and 5.2 years, respectively), and fewer HF cases (92 and 56 cases, respectively) than our study. The subjects in these studies were older (mean age, 74 and 78 years, respectively). The hazard ratios observed for high versus low levels of the studied cytokines in these studies were somewhat higher than for high versus low ESR in our study, but it is difficult to draw any firm conclusions about possible differences in the strengths of associations between the various inflammatory markers and HF because of the large differences in study design.

C-reactive protein, TNF-alpha, and IL-6 are specific markers of cytokine-mediated inflammation but provide no information about other (potentially equally or more important) aspects of inflammation. The ESR is a less-specific marker of systemic inflammation that is known to be elevated in many acute and chronic diseases characterized by tissue necrosis and inflammation. It is a simple and inexpensive laboratory test that is in widespread use and is easily accessible. In his classic report, Wood observed a low ESR in a small sample of patients with HF of different origins (16), but more recent studies have reported that in patients with manifest HF a high ESR is associated with a more severe stage of HF and a worse prognosis (14,15). The aforementioned studies have examined the association between ESR and already diagnosed HF (14–16), whereas the present study is the first to examine ESR as a predictor of subsequent incident HF.

Possible mechanisms. The ESR has repeatedly been found to be a predictor of subsequent coronary heart disease in longitudinal studies (2–4). Nonetheless, in the present study the association between ESR and HF remained significant, even after adjusting for interim myocardial infarction, which may indicate that inflammation could directly impair myocardial function. Previous studies have shown that proinflammatory cytokines, such as TNF-alpha, can depress myocardial contractility (17) and affect left ventricular remodeling through local induction of matrix metalloproteinases (18,19). Inflammation also can induce endothelial dysfunction in small vessels (20), resulting in an impaired coronary flow reserve and impaired left ventricular function.

Strengths and limitations. The strengths of this study include the large population, the long follow-up period, and the detailed characterization of the cohort. Furthermore, all HF cases were validated, limiting the inclusion of false-positive cases. Some limitations to this study exist. Because we only examined men of the same age with a similar ethnic background, this study has an unknown generalizability to women and other age and ethnic groups. Furthermore, because this study was initiated in the 1970s and the HF diagnosis was based on a review of medical records, it was not possible to differentiate between systolic and diastolic heart failure as echocardiography was not available at the time of diagnosis for many of the cases. At that time, ESR was the only measured inflammatory marker; thus, it was not possible to directly compare ESR and other inflammatory markers as predictors of HF in this study.

Conclusions. Inflammation measured as ESR was a significant predictor of HF, independent of established risk factors for HF, including an interim myocardial infarction, after almost three decades of follow-up in a population-based sample of middle-aged men. Further research is warranted to determine potential gender and ethnic variations of the relation between inflammation and HF incidence and to compare ESR with other markers of inflammation as predictors of incident congestive heart failure.

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REFERENCES


