Uric acid levels and outcome from coronary artery bypass grafting

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Objective: Elevated uric acid levels have been associated with an adverse cardiovascular outcome in several settings. Their utility in patients undergoing surgical revascularization has not, however, been assessed. We hypothesized that serum uric acid levels would predict the outcome of patients undergoing coronary artery bypass grafting.

Methods: The study cohort consisted of 1140 consecutive patients undergoing nonemergency coronary artery bypass grafting. Clinical details were obtained prospectively, and serum uric acid was measured a median of 1 day before surgery. The primary end point was all-cause mortality.

Results: During a median of 4.5 years, 126 patients (11%) died. Mean (± standard deviation) uric acid levels were 390 ± 131 μmol/L in patients who died versus 353 ± 86 μmol/L among survivors (hazard ratio 1.48 per 100 μmol/L; 95% confidence interval, 1.25–1.74; $P < .001$). The excess risk associated with an elevated uric acid was particularly evident among patients in the upper quartile (≥410 μmol/L; hazard ratio vs all other quartiles combined 2.18; 95% confidence interval, 1.53–3.11; $P < .001$). After adjusting for other potential prognostic variables, including the European System for Cardiac Operative Risk Evaluation, uric acid remained predictive of outcome.

Conclusion: Increasing levels of uric acid are associated with poorer survival after coronary artery bypass grafting. Their prognostic utility is independent of other recognized risk factors, including the European System for Cardiac Operative Risk Evaluation.

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Uric acid is produced by purine metabolism. Higher levels are found in patients with vascular disease and in those with major cardiovascular risk factors, such as hypertension, diabetes mellitus, obesity, hyperinsulinemia/insulin resistance, and renal dysfunction.[1-3] Hyperuricemia is also associated with multiple biological effects, several of which are detrimental to cardiovascular health. These include oxidative stress, generation of free radicals, impaired endothelial function, increased platelet adhesiveness, and higher levels of inflammatory markers.[1,4-8]

Many, although not all, epidemiologic studies have suggested that high levels are independently predictive of cardiac and all-cause mortality in healthy populations.[3,9-11] In patients who are at high risk of or who have established vascular disease, an independent association has been more clearly established.[3,12-19] The relationship between uric acid levels and the outcome from surgical revascularization has not, however, been previously examined. Given the relationship between uric acid and other major risk factors, the effects of hyperuricemia on platelet and endothelial function, the putative role of products of purine breakdown in reperfusion injury, and the prognostic utility of increased levels in other settings, we hypothesized that elevated uric acid levels would predict a worse outcome from coronary artery bypass grafting (CABG). The current study tests this hypothesis.

MATERIALS AND METHODS

Ethical approval for the study was granted by the local research ethics committee. Between April 2000 and September 2002, 1221 consecutive patients underwent CABG at Aberdeen Royal Infirmary. Patients who underwent emergency surgery or surgery within 1 week of an acute myocardial infarction (n = 61) were excluded, as were 20 subjects who had no preoperative uric acid measurement. The study cohort consisted of the remaining 1140 patients.

Baseline clinical data, including medical history, cardiac risk factors, operative details, New York Heart Association functional class, and the European System for Cardiac Operative Risk Evaluation (EuroSCORE),[20] were collected prospectively by an experienced full-time data collector. Serum samples were collected a median of 1 day (interquartile range 1–2 days) preoperatively, and uric acid measured using the ADVIA 1650 General

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Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CI = confidence interval
EuroSCORE = European System for Cardiac Operative Risk Evaluation
HR = hazard ratio

Chemistry Analyzer (Siemens Diagnostics Solutions, Tarrytown, NY). Hyperuricemia was defined as $\geq$ 416 μmol/L (7.0 mg/dL) in men and $\geq$ 357 μmol/L (6.0 mg/dL) in women.[21,22] Renal function was measured, and the glomerular filtration rate was estimated from the Modification of Diet in Renal Disease equation.[23]

Follow-up

Patients were followed up using computerized hospital records and a vital events search performed by the General Register Office for Scotland. The primary end point was all-cause mortality. Secondary end points were a) cardiovascular mortality, b) all-cause mortality in patients undergoing isolated CABG, c) all-cause 30-day mortality, and d) late (>30 days) mortality. Cause of death was defined as cardiovascular if this was listed on the death certificate as the primary cause or a contributory factor.

Statistics

Categoric data are expressed as number (%) and continuous variables as mean (standard deviation) if normally distributed or median (interquartile range) if skewed. The influence of potential risk factors was explored using Cox regression, and hazard ratios (HRs) are presented with 95% confidence intervals (CIs). An a priori decision to include risk factors in multiple Cox regression models was based on univariate P values less than .25 or an estimated univariate HR greater than 2. Model fit was assessed using the log-likelihood and inspecting residuals. Models are presented and discussed for uric acid as a continuous variable, in quartiles, and as a dichotomous variable (''hyperuricemia''). Comparisons of baseline characteristics among patients with uric acid levels in differing quartiles were made using the chi-square test and analysis of variance as appropriate. Binary logistic regression was used for 30-day mortality, and odds ratios plus 95% CI are presented. Statistical analyses were performed using SPSS version 15.0 for Windows (SPSS, Chicago, IL).

RESULTS

The study cohort was predominantly male with a median age of 66 years (Table 1). A total of 1023 patients underwent isolated CABG, with 59 patients having 1 vessel grafted, 342 patients having 2 vessels grafted, 522 patients having 3 vessels grafted, and 100 patients having more than 3 vessels grafted. The remaining 117 patients had more complex procedures in addition to CABG. These included 107 valve replacements/repairs (80 aortic valve replacements, 26 mitral valve replacements/repairs, and 1 combined aortic and mitral valve operation). The remaining 10 complex procedures consisted of CABG in combination with left ventricular aneurysmectomy (n = 6), myxoma resection (n = 2), aortic root surgery (n = 1), and pericardiectomy (n = 1). In 1038 patients, surgery was performed using cardiopulmonary bypass. The remaining 102 patients underwent ''off-pump'' surgery.

The mean uric acid level was 357 $\pm$ 92 μmol/L (6.0 $\pm$ 1.5 mg/dL). Hyperuricemia was present in 284 subjects (25%). Vital status was available for all patients. During a median of 4.5 (3.8–5.2) years, 126 patients (11%) died (primarily or partly from cardiovascular causes in 107).

Univariable Predictors of All-Cause Mortality

Serum uric acid was a univariable predictor of mortality (Table 1). Other univariable predictors included age, impaired left ventricular systolic function, requirement for a major cardiac procedure in addition to CABG, bypass or crossclamp time, renal function, and the EuroSCORE.

Multivariable Predictors of All-Cause Mortality

All prognostic variables in Table 1 were considered for inclusion in a multiple Cox regression model, except the EuroSCORE (which is a composite that includes several of these parameters) and crossclamp time (which is closely related to, but inferior in terms of prognostic utility to, bypass time). In the most parsimonious regression model, uric acid levels remained independently predictive (Table 2). In a further model, including uric acid and the EuroSCORE only, both were independent predictors of mortality (HR for EuroSCORE 1.33 per unit increase; 95% CI, 1.25–1.42; $P <$ .001; HR for uric acid 1.32 per 100 μmol/L; 95% CI, 1.13–1.54; $P = .001$).

Quartiles of Serum Uric Acid Levels

Male patients were more likely to have elevated preoperative serum uric acid levels. Patients with higher levels also tended to be older and to have poorer renal function, a higher body mass index, impaired left ventricular systolic function, and a higher EuroSCORE (Table 3). The excess risk associated with an elevated uric acid was particularly evident in patients in the upper quartile (Table 1 and Figure 1). The HR associated with a serum uric acid level in this quartile ($\geq$410 μmol/L) was 2.18 (95% CI, 1.53–3.11; $P <$ .001 vs all other quartiles combined).

Further regression models were developed, similar to those described above but replacing uric acid as a continuous variable with uric acid in the upper quartile (vs all other quartiles). In the first of these, including all variables in Table 2, the upper quartile of preoperative uric acid levels remained independently predictive (HR 1.56; 95% CI, 1.08–2.26; $P =$ .02). In a model with the EuroSCORE alone, the hazard associated with a uric acid level in the upper quartile was 1.76 (95% CI, 1.23–2.52; $P = .002$).

Hyperuricemia

Hyperuricemia closely approximates the upper quartile of uric acid in the current cohort and is also associated with a worse survival (Table 1). In a regression model that included hyperuricemia and EuroSCORE only, the former was an independent predictor of death (HR 1.48; 95% CI,

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