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 ($\pm$ standard deviation) uric acid levels were 390 ± 131 $\mu\text{mol/L}$ in patients who died versus 353 ± 86 $\mu\text{mol/L}$ among survivors (hazard ratio 1.48 per 100 $\mu\text{mol/L}$; 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 $\mu\text{mol/L}$; 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 $\geq 416 \mu\text{mol/L}$ (7.0 mg/dL) in men and $\geq 357 \mu\text{mol/L}$ (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

Categorical 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 $357 \pm 92 \mu\text{mol/L}$ (6.0 ± 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 $\mu\text{mol/L}$; 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 ($\geq 410 \mu\text{mol/L}$) 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,

TABLE 1. Clinical characteristics of study cohort and univariable relationship to mortality

Characteristic	All patients (n = 1140)	All-cause mortality			P value
		Alive (n = 1014)	Died (n = 126)	Hazard ratio (95% CI)	
Age, y	66 (59–71)	65 (58–71)	70 (65–75)	2.18 (1.73–2.74)*	<.001
Risk factors and medical history					
Male	893 (78%)	795 (78%)	98 (78%)	0.94 (0.62–1.43)	.776
Current smoker	112 (10%)	98 (10%)	14 (11%)	1.14 (0.66–1.99)	.641
Diabetes	126 (11%)	107 (11%)	19 (15%)	1.42 (0.87–2.31)	.162
Hypertension	504 (44%)	446 (44%)	58 (46%)	1.00 (0.70–1.41)	.978
Body mass index	27.8 ± 3.9	27.9 ± 3.9	27.2 ± 3.6	0.79 (0.63–1.00)	.053
Prior CABG	26 (2%)	20 (2%)	6 (5%)	2.21 (0.97–5.01)	.059
Previous MI (>7 d)	484 (42%)	424 (42%)	60 (48%)	1.14 (0.80–1.61)	.479
LVEF < 50%	394 (35%)	333 (33%)	61 (48%)	1.78 (1.25–2.53)	.001
NYHA functional class III or IV	757 (66%)	678 (67%)	79 (63%)	0.89 (0.62–1.28)	.543
Additional major cardiac procedure	117 (10%)	91 (9%)	26 (21%)	2.64 (1.71–4.06)	<.001
Bypass time (15 min)	79 (62–97)	79 (61–96)	86 (67–113)	1.14 (1.08–1.19)	<.001
Crossclamp time (15 min)	44 (33–54)	44 (33–54)	45 (35–63)	1.15 (1.07–1.24)	<.001
Off-pump surgery	102 (9%)	94 (9%)	8 (6%)	0.76 (0.37–1.55)	.442
EuroSCORE	4 (2–6)	3 (2–5)	6 (4–8)	1.34 (1.26–1.43)	<.001
Renal function					
Creatinine (mg/dL)	1.21 ± 0.48	1.18 ± 0.39	1.41 ± 0.90	1.49 (1.28–1.75)†	<.001
Estimated GFR (mL/min/1.73 m ²)	64.8 ± 14.7	65.6 ± 14.2	58.1 ± 17.1	0.73 (0.65–0.81)‡	<.001
Uric acid (μmol/L)	357 ± 92	353 ± 86	390 ± 131	1.48 (1.25–1.74)§	<.001
Quartile of uric acid level					
Quartile 1	278 (24%)	248 (25%)	30 (24%)	1	–
Quartile 2	281 (25%)	257 (25%)	24 (19%)	0.80 (0.47–1.37)	.42
Quartile 3	295 (26%)	274 (27%)	21 (17%)	0.67 (0.38–1.17)	.16
Quartile 4	286 (25%)	235 (23%)	51 (41%)	1.79 (1.14–2.81)	.01
Hyperuricemia	284 (25%)	237 (31%)	47 (37%)	1.92 (1.33–2.75)	<.001

CABG, Coronary artery bypass grafting; MI, myocardial infarction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; GFR, glomerular filtration rate; CI, confidence interval; EuroSCORE, European System for Cardiac Operative Risk Evaluation. *HR per decade. †HR per mg/dL. ‡HR per 10 mL/min/1.73 m². §HR per 100 μmol/L. ||See text for details.

1.02–2.13; $P = .04$). Similarly, in a model including all the variables in Table 2, but with hyperuricemia replacing uric acid as a continuous variable, there was a trend toward hyperuricemia independently predicting mortality (HR 1.35; 95% CI, 0.93–1.96; $P = .11$).

Secondary Analyses

Cardiovascular mortality. Preoperative uric acid level was a univariable predictor of cardiovascular death (HR 1.51 per 100 μmol/L; 95% CI, 1.27–1.79; $P < .001$). In a multiple Cox regression model including all variables, selected as described above, uric acid was a predictor of cardiovascular death (HR 1.27 per 100 μmol/L; 95% CI, 1.07–1.51; $P = .008$). In a model with only EuroSCORE and uric acid, the HR was 1.33 per 100 μmol/L (95% CI, 1.13–1.57; $P = .001$). Patients with uric acid levels in the upper quartile had an HR of 1.89 for cardiovascular death (95% CI, 1.29–2.76; $P = .001$) even after correction for their EuroSCORE.

Patients undergoing isolated CABG. Of 1023 patients undergoing isolated CABG, 100 (10%) died during fol-

low-up. Preoperative uric acid levels remained univariable predictors of all-cause mortality in this subgroup (HR 1.30 per 100 μmol/L; 95% CI, 1.06–1.59; $P = .01$). They remained independent predictors after correction for EuroSCORE (HR 1.21 per 100 μmol/L; 95% CI, 1.00–1.46; $P = .049$). However, although a similar trend was observed ($P = .18$), they failed to achieve statistical significance in a model including all variables (except the EuroSCORE and crossclamp time), selected as described above.

Mortality at 30 days. Twenty-three patients (2%) died within 30 days of surgery. Preoperative uric acid levels

TABLE 2. Multivariable predictors of mortality

Characteristic	Hazard ratio	95% CI	P value
Age (per 10 y)	1.93	1.53–2.43	<.001
Creatinine (per mg/dL)	1.42	1.18–1.72	<.001
Bypass time (per 15 min)	1.10	1.04–1.16	<.001
Left ventricular ejection fraction <50%	1.67	1.17–2.39	.005
Uric acid (per 100 μmol/L)	1.25	1.06–1.47	.009

CI, Confidence interval.

TABLE 3. Baseline characteristics according to the quartile of preoperative uric acid levels

Characteristic	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P value
	70–299 $\mu\text{mol/L}$ n = 278	300–349 $\mu\text{mol/L}$ n = 281	350–409 $\mu\text{mol/L}$ n = 295	410–830 $\mu\text{mol/L}$ n = 286	
Age (y)	64 (58–71)	65 (57–70)	66 (59–70)	68 (62–74)	<.001
Male	182 (65%)	225 (80%)	255 (86%)	231 (81%)	<.001
Creatinine (mg/dL)	1.12 $\pm$ 0.57	1.14 $\pm$ 0.39	1.24 $\pm$ 0.56	1.32 $\pm$ 0.31	<.001
eGFR (mL/min/1.73 m ²)	68.9 $\pm$ 15.2	68.1 $\pm$ 12.9	64.6 $\pm$ 13.7	57.8 $\pm$ 14.4	<.001
Body mass index	26.7 $\pm$ 3.8	27.4 $\pm$ 3.6	28.3 $\pm$ 3.7	28.6 $\pm$ 4.3	<.001
Hypertension	125 (45%)	113 (40%)	132 (45%)	134 (47%)	.43
Diabetes mellitus	43 (15%)	27 (10%)	19 (6%)	37 (13%)	.20
Smoker	32 (12%)	27 (10%)	32 (11%)	21 (7%)	.16
Previous myocardial infarction	118 (42%)	116 (41%)	122 (41%)	128 (45%)	.59
LVEF < 50%	82 (29%)	76 (27%)	105 (36%)	131 (46%)	<.001
NYHA functional class III or IV	196 (71%)	178 (63%)	188 (64%)	195 (68%)	.61
EuroSCORE	4 (2–5)	3 (2–5)	3 (2–5)	4 (2–7)	.004

eGFR, Estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

were predictors of 30-day mortality (odds ratio 1.74 per 100 $\mu\text{mol/L}$; 95% CI, 1.23–2.47; $P = .002$). In a multivariable model that also included the EuroSCORE, the odds ratio for death at 30 days was 1.41 greater for every 100 $\mu\text{mol/L}$ increase in uric acid levels (95% CI, 1.00–2.00; $P = .05$). The small number of events limits the ability to undertake further modeling.

Late mortality. Uric acid levels remained predictive of late mortality (defined as deaths that occurred more than 30 days after surgery, $n = 103$): HR 1.41 per 100 $\mu\text{mol/L}$; 95% CI, 1.17–1.71; $P < .001$. This remained the case in a model that included the EuroSCORE (HR 1.29 per 100 $\mu\text{mol/L}$; 95% CI, 1.08–1.55; $P = .006$) and in a further model including all variables (except the EuroSCORE and crossclamp time), selected as described above (HR 1.24 per 100 $\mu\text{mol/L}$; 95% CI, 1.03–1.50; $P = .03$).

DISCUSSION

The current data demonstrate that elevated levels of serum uric acid are common among patients undergoing CABG

and are strongly and independently predictive of increased mortality in this setting. The excess hazard of death was concentrated among patients with uric acid levels in the upper quartile whose risk of death during a median follow-up of 4.5 years was increased by 76%, even after adjustment for their preoperative EuroSCORE.

Previous Studies

No previous studies have addressed the utility of serum uric acid in predicting the outcome of CABG. Several large epidemiologic studies have, however, demonstrated a strong relationship between uric acid and cardiovascular outcome.^{3,9,10} Although elevated levels of uric acid are associated with cardiovascular risk factors, including components of the metabolic syndrome such as obesity, diabetes mellitus, and hypertension, the majority of studies have demonstrated that their predictive value is independent of these.^{3,24} In high-risk patients, or patients with preexisting cardiovascular disease, high levels of uric acid are associated with a particularly poor outcome. As observed in the current

FIGURE 1. Quartiles of uric acid and mortality.

cohort, the excess risk is generally concentrated among patients with the highest levels.^{3,9}

Potential Mechanisms

The adverse outcome associated with elevated levels of uric acid may be multifactorial. Some of the prognostic utility may relate to its ability to integrate the effects of several other factors that determine a worse outcome. Certainly, conditions such as diabetes, hypertension, and renal dysfunction, all of which predispose to hyperuricemia, are well known to confer an adverse prognosis. However, the prognostic utility of uric acid is independent of these factors, suggesting that other mechanisms may be involved.

Data from the Atherosclerosis Risk in Communities study suggest that levels of uric acid are related to carotid intima-media thickness, a direct measure of atherosclerotic burden.²⁵ Elevated uric acid levels may also induce platelet lysis and increase adhesiveness.^{6,7} In addition, recent data have shown that uric acid levels are strongly and independently associated with elevations of inflammatory markers, including the leukocyte and neutrophil count, C-reactive protein, and proinflammatory cytokines.⁸ Several of these have, in turn, been associated with a poorer outcome in patients undergoing CABG.

Uric acid is formed from xanthine in a reaction catalyzed by xanthine oxidoreductase.²⁶ This enzyme exists in 2 interconvertible forms: xanthine oxidase and xanthine dehydrogenase.²⁷ Xanthine oxidoreductase has many complex actions, including the production of reactive oxygen species.^{27,28} Thus, it plays an important role in ischemia-reperfusion injury, including that after cardiac surgery. It is conceivable that high levels of uric acid identify patients with high xanthine oxidoreductase activity and who are, therefore, at particular risk of perioperative reperfusion injury. Indeed, allopurinol, a competitive inhibitor of xanthine oxidase that is commonly used to treat hyperuricemia, may have a role in perioperative myocardial protection.²⁸⁻³⁰

Study Strengths and Limitations

This is a single-center study with the inherent limitations. It does, however, assess the outcome of a large cohort of consecutive patients, allowing the use of all-cause mortality as the objective primary end point. The absence of data regarding other, nonfatal, outcomes is a limitation, as is the reliance on a single measurement of uric acid.

The incidence of diabetes mellitus in the study cohort is lower than might be expected. This diagnosis was based on a clinical history of the condition and may, therefore, be an underestimate. The lack of data regarding a clinical history of gout and drug therapy are further limitations. Unfortunately, these data were not collected prospectively, and the medical records of the majority of patients who have died have been destroyed. It is not possible, therefore, to correct

for the effects of medication, and in particular treatment with diuretics.

Despite these limitations, the current data demonstrate for the first time a strong and independent relationship between preoperative levels of uric acid, particularly those in the upper quartile, and mortality after CABG. Further work is required to corroborate these findings and confirm whether incorporation of this easily measured biomarker can improve the prognostic accuracy of existing or novel methods of preoperative risk stratification. Likewise, it remains uncertain whether elevated levels of uric acid are mediators or merely markers of increased mortality. More research, therefore, is required before treatment of uric acid can be recommended specifically to reduce cardiovascular risk in this setting.

CONCLUSIONS

The current study confirms that elevated uric acid levels are a marker of increased risk after cardiac surgery. Although no causal mechanism can be inferred, high levels may be associated with an increased risk of reperfusion injury and a variety of factors that determine both early and long-term outcome, such as inflammatory cell and platelet activation, increased atherosclerotic burden, and increased prevalence of major cardiovascular risk factors.

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