Uric Acid and Survival in Chronic Heart Failure
Validation and Application in Metabolic, Functional,
and Hemodynamic Staging

Stefan D. Anker, MD, PhD; Wolfram Doehner, MD; Mathias Rauchhaus, MD; Rakesh Sharma, MRCP; Darrel Francis, MRCP; Christoph Knosalla, MD; Constantinos H. Davos, MD, PhD; Mariantonieta Cicoira, MD; Waqar Shamim, MRCP; Michel Kemp, MD; Robert Segal, MD; Karl Josef Osterziel, MD; Francisco Leyva, MD; Roland Hetzer, MD; Piotr Ponikowski, MD; Andrew J.S. Coats, DM

Background—Serum uric acid (UA) could be a valid prognostic marker and useful for metabolic, hemodynamic, and functional (MFH) staging in chronic heart failure (CHF).

Methods and Results—For the derivation study, 112 patients with CHF (age 59±12 years, peak oxygen consumption \( \dot{V}O_2 \) 17±7 mL/kg per minute) were recruited. In separate studies, we validated the prognostic value of UA (n=182) and investigated the relationship between MFH score and the decision to list patients for heart transplantation (n=120). In the derivation study, the best mortality predicting UA cutoff (at 12 months) was 565 \( \mu \)mol/L (9.50 mg/dL) (independently of age, peak \( \dot{V}O_2 \), left ventricular ejection fraction, diuretic dose, sodium, creatinine, and urea; \( P<0.0001 \)). In the validation study, UA \( \geq 565 \) \( \mu \)mol/L predicted mortality (hazard ratio, 7.14; \( P<0.0001 \)). In 16 patients (from both studies) with UA \( \geq 565 \) \( \mu \)mol/L, left ventricular ejection fraction \( \leq 25% \) and peak \( \dot{V}O_2 \) \( \leq 14 \) mL/kg per min (MFH score 3), 12-month survival was lowest (31%) compared with patients with 2 (64%), 1 (77%), or no (98%, \( P<0.0001 \)) risk factor. In an independent study, 51% of patients with MFH score 2 and 81% of patients with MFH score 3 were listed for transplantation. The positive predictive value of not being listed for heart transplantation with an MFH score of 0 or 1 was 100%.

Conclusions—High serum UA levels are a strong, independent marker of impaired prognosis in patients with moderate to severe CHF. The relationship between serum UA and survival in CHF is graded. MFH staging of patients with CHF is feasible. (Circulation. 2003;107:1991-1997.)

Key Words: heart failure ■ prognosis ■ hemodynamics

Numerous parameters are capable of predicting prognosis in patients with chronic heart failure (CHF). Many of the modern parameters are only assessed by using research tests that are not widely available. There is a need for simple parameters that can be measured anywhere at low cost. Very few attempts have been made to develop scoring systems to predict prognosis in patients with CHF, but these are not simple enough for general application. For prognostication in CHF, the following 3 main areas of relatively independent importance emerge: (1) a hemodynamic factor (for example, left ventricular ejection fraction [LVEF]); (2) the patient’s functional status (eg, peak oxygen consumption [\( \dot{V}O_2 \)]); and (3) a metabolic factor, including the neuroendocrine and immunologic processes. Consequently, we have previously proposed a metabolic, functional, and hemodynamic (MFH) staging system for the assessment of prognosis in CHF. Such a system would depend on a straightforward metabolic marker. We propose that the latter could be serum uric acid (UA) levels.

See p 1951

In CHF, hyperuricemia (independent of kidney function and diuretic dose) is a marker of impaired oxidative metabolism and hyperinsulinemia, inflammatory cytokine activation, and impaired vascular function. The relationship of UA to kidney function and diuretic dose may additionally increase the value of UA as prognostic marker. In one study, it has been suggested that in CHF, UA levels reflect the degree of circulating xanthine oxidase (XO) activity. The XO system is an important source of oxygen free radicals. Additionally, via degradation of accumulated purines, UA is a general marker of cell death (see Figure 1). In CHF, weight
Figure 1. The interrelationship between hyperuricemia, XO, cell metabolism and insulin resistance (IR), tissue hypoxia, vascular dysfunction, cytokines, and oxygen free radicals in CHF. Feedback mechanisms cause increased XO activation and hence hyperuricemia. These complex interrelated mechanisms explain why UA levels are correlated with many different parameters and can serve as a metabolic marker with strong prognostic power. IR and tissue wasting (cell death) can cause accumulation of purine bodies and hence hyperuricemia. Increased activation of XO can be caused by tissue hypoxia, which itself is a consequence of vascular (and cardiac) dysfunction. Oxygen free radicals and inflammatory cytokines contribute to vascular dysfunction. Oxygen free radicals promote production of inflammatory cytokines and are themselves produced by XO. Impaired kidney function and diuretic treatment can also contribute to hyperuricemia. PPRP indicates pentose phosphate pathway; PPRP, phosphoribosylpyrophosphate.

loss is linked to impaired survival but also to hyperuricemia. We hypothesized that UA might be a widely available and powerful prognosticator. We also hypothesized that patients with high UA levels and low peak VO2 and LVEF would have a particularly poor prognosis.

Methods

We assessed the relationship between survival and UA in 112 extensively evaluated patients with CHF who (between April 1992 and August 1997) were prospectively recruited into a long-term metabolic study program (derivation sample). The local ethics committee approved this study. All patients gave informed consent. To validate our results, we used a patient sample comprising all CHF patients who (between April 1992 and August 1997) were prospectively recruited into a long-term observational study. In these patients, we tested the principal results and best cutoff values as derived from the derivation study. In these patients, we recorded the results of treadmill exercise testing and radionuclide ventriculography if these had been performed within 4 months of the UA assessment, provided patients had been clinically stable and not undergoing transplantation evaluation visit.

Follow-Up

Follow-up for survival (as of September 10, 2001) was available in February 2002 from the Office of National Statistics, where all patients had been flagged for reports of death. The study focused on all-cause mortality. Major events included heart transplantation (5 patients, 2 died, 3 still alive) or implantation of a permanent ventricular assist device (1 patient, subsequently died). Patients were censored alive at the time of these events.

MFH Score and Transplantation Evaluation

We retrospectively analyzed 120 consecutive patients (without major contraindications for heart transplantation) who underwent full assessment for heart transplantation eligibility in the German Heart Institute in Berlin between January and June 1999. In all patients, the MFH score was calculated retrospectively on the basis of results that were determined during the patients’ transplantation evaluation visit. At the time the responsible physicians had access to these individual results, they were not aware of the MFH score or of our data on UA and prognosis.

Statistics

All results are presented as mean±SD. Group differences were assessed by unpaired Student’s t tests. Cox proportional hazard analysis was used to assess the association between variables and mortality. Hazard ratio (RR) and 95% confidence interval (CI) for risk factors and significance levels for \( \chi^2 \) (likelihood ratio test) are given. Kaplan-Meier cumulative survival plots were constructed (StatView 4.5, Abacus Concepts). Because we considered sensitivity and specificity of equal importance, in ROC analyses, the best prognosticators for survival status were considered to be those parameters that gave the highest product of sensitivity and specificity for predicting death at the respective times.

Results

Derivation Study

The range of observed UA levels was between 187 and 930 μmol/L (UA <400 μmol/L; n=54 [30%]). During follow-up...
Anker et al Uric Acid and Survival in CHF 1993

Table 2. Predictors of Mortality in 112 Patients With CHF (Derivation Study): Cox Proportional Hazard Analysis

<table>
<thead>
<tr>
<th></th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis (Stepwise, Forward)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>χ²</td>
<td>P</td>
</tr>
<tr>
<td>UA, μmol/L</td>
<td>29.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urea, mmol/L</td>
<td>20.15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, y</td>
<td>14.55</td>
<td>0.0001</td>
</tr>
<tr>
<td>Peak VO₂, mL/kg per minute, n=108*</td>
<td>14.13</td>
<td>0.0002</td>
</tr>
<tr>
<td>LVEF, %, n=99</td>
<td>8.69</td>
<td>0.003</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>6.71</td>
<td>0.010</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>5.33</td>
<td>0.021</td>
</tr>
</tbody>
</table>

(51±39 months), 69 deaths were observed (12-month mortality, 24% [95% CI, 16 to 32]). Survivors had mean UA levels of 438±108 μmol/L (nonsurvivors, 544±163 μmol/L; P=0.0003).

UA (hazard ratio, 1.00498 [1.00322 to 1.00674]), urea, age, peak VO₂ (all P<0.001), LVEF (P=0.003), creatinine, sodium, and frusemide equivalent dose (all P<0.03) predicted mortality (Table 2). UA levels above the median (>484.5 μmol/L; RR 2.6 [95% CI, 1.6 to 4.3]; χ²=15.6; P<0.0001), in the highest tertile (>565 μmol/L; RR 3.9 [2.4 to 6.4], χ²=26.9; P<0.0001), and in the highest quartile (>595 μmol/L, RR 3.2 [1.9 to 5.4], χ²=17.8; P<0.0001) were all predictive of impaired survival. In ROC analyses, the best UA level for predicting survival status at 12 or 18 months was 565 μmol/L [9.50 mg/dL] (see the online Data Supplement).

Validation Study

These 182 outpatients were older than the derivation study patients, and they had a somewhat better LVEF (Table 1). Mean UA levels were 466±155 μmol/L (range, 106 to 1251 μmol/L, <400 μmol/L; n=64 [35%]). During follow-up (41±23 months), 59 deaths were observed (12-month mortality, 15% [10% to 20%]). Survivors had mean UA levels of 418±102 μmol/L (nonsurvivors, 565±195 μmol/L; P<0.0001). Also in the validation sample, UA levels predicted mortality (RR 1.00532 [1.00400 to 1.00666]; χ²=46.4; P<0.0001). For every 100-μmol/L increase in UA, the risk of death increased by 53% (31.7% risk increase for every 1 mg/dL increase in UA).

UA levels ≥565 μmol/L (RR 7.14 [4.20 to 12.15], χ²=43.5) strongly related to increased mortality (P<0.0001, Figure 2). The survival of patients with UA ≥565 μmol/L was 52% at 12 months [34% to 70%] and 36% at 24 months [18% to 53%]. In patients with UA <565 μmol/L, survival was 92% [88% to 96%] and 86% [80% to 92%] at 12 and 24 months, respectively. In a multivariate Cox model with 7 variables (n=113), only UA (P=0.0001), LVEF (P=0.04), and peak VO₂ (P=0.005) predicted prognosis (creatinine, sodium, urea, and age; all P>0.3).

Graded Relation Between UA and Survival

Considering all 294 patients with CHF, we found a graded relationship between serum UA and mortality in CHF (χ²=76.2, P<0.0001, Figure 3). Patients with normal UA (<400 μmol/L) had best survival (at 12 months, 93%) compared with patients with UA between 401 and 600 μmol/L (87%, RR 1.76 [1.11 to 2.78]), patients with UA between 601 and 800 μmol/L (54%, RR 6.27 [3.73 to 10.54]), and patients with UA >800 μmol/L (17%, RR 18.53 [9.18 to 37.42]).

Uric Acid, HFSS Score, and MFH Score

In 194 patients, data were available to calculate the 7-parameter HFSS score (mean, 8.56±1.24; see the online Data Supplement). The HFSS score had prognostic power at its 3 risk levels1 (χ²=39.1, P<0.0001) and as continuous variable (χ²=45.4, P<0.0001), which was similar to that of UA in these patients (χ²=54.0, P<0.0001). Both HFSS and UA predicted prognosis independently of each other, regardless of whether the parameters were treated as continuous or categorical variables (all P<0.0001). There was a continuous relationship between the estimated probability of death within 1 year and UA levels within each of the HFSS strata (Figure 4A). Applying the best UA cutoff (≥565 μmol/L) to the HFSS subgrouping improved the positive and negative discriminatory power for survival prediction in all HFSS strata (Figure 4B). The relationship between MFH score and survival is shown in Figure 5.

MFH Staging and Heart Transplantation (German Heart Institute Berlin)

The MFH score was determined in 120 patients with CHF (female, 15) with the following clinical characteristics: age 53±8 years, NYHA class 2.5±0.7, treadmill peak VO₂ 14.3±4.4 mL/kg per minute, LVEF 23±8%, and UA 469±145 μmol/L. Of 20 patients with MFH score 0 and 35 patients with MFH score 1, none was listed for heart transplantation. Of 47 patients with MFH score 2, 24 patients (51%) were listed, whereas 16 of 18 patients with MFH score 3 (89%) were listed for heart transplantation. The positive predictive value of not being listed for heart transplantation with MFH score 0 or 1 was 100%. By the end of 1999, of 40 patients listed for transplantation, 8 patients (20%) had been transplanted, 3 patients (7.5%) had received a ventricular assist device, and 13 patients (32%) had died.
Discussion

This study documents and validates that high serum UA levels are a strong, independent marker of impaired prognosis in patients with moderate to severe CHF. The relationship between serum UA and survival in CHF is graded. The assessment of UA provides information independently of and better than other well-established parameters, such as the clinical status, exercise capacity, and parameters of kidney function. In CHF, individualized treatment is needed to achieve optimal outcome. This requires reliable assessment of individual prognosis. One prognostic stratification system has previously been validated (the 7-parameter HFSS score1). This computer-based system may not be simple enough for routine application. We have now shown that UA predicts prognosis as well as and independently of the HFSS score. Adding UA to the HFSS score improves its prognostic power. We suggest in the light of its wide availability and very low cost that UA determination should be considered a routine measurement in the assessment and follow-up for patients with heart failure.

Hyperuricemia has been suggested to reflect raised XO activity in CHF.10 The XO enzyme system is an important source of oxygen free radicals.11 The latter provides the pathophysiological link of UA with a large variety of detrimental processes, including increased cytokine production, cell apoptosis, and endothelial dysfunction. In a prospective series of studies on patients with CHF, we have previously shown that hyperuricemia relates to many of these abnormalities6–9 independently of diuretic treatment and markers of kidney function. Therefore, serum UA may be a valid metabolic marker in CHF.

The activity of XO within the myocardium is discussed controversially. A significant source of confusion is the large interspecies variability in tissue expression of XO.16 For example, myocardial XO enzyme activity was found high in the dog17 and rat18 but low in the rabbit19 and pig.20 In humans, studies report myocardial XO activity to be either high,21 low,22 or undetectable.23,24 Although there is some considerable evidence that suggests that the enzyme XO may

### Table: Kaplan-Meier Survival Analysis

<table>
<thead>
<tr>
<th>UA Status</th>
<th>At Risk</th>
<th>Deaths</th>
<th>Cumulative Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UA &lt;565 µmol/l</td>
<td>151</td>
<td>143</td>
<td>130</td>
</tr>
<tr>
<td>UA ≥565 µmol/l</td>
<td>31</td>
<td>17</td>
<td>16</td>
</tr>
</tbody>
</table>

### Figure 2. Kaplan-Meier survival plot for 182 patients with CHF (validation study).

### Figure 3. The graded relationship between serum UA (in µmol/L) and survival in 294 CHF patients. Kaplan-Meier survival plot and hazard ratios are shown. *P=0.016 vs patients with UA <400 µmol/L. ****P<0.0001 vs patients with UA ≥400 µmol/L.
indeed be expressed in the human myocardium, 25–27 we believe that the effect may be local. No systemic effects from the myocardial activity of XO have been reported.

We propose to apply MFH assessments for staging of patients with CHF. It is widely accepted that an exercise test with gas exchange analysis is ideal to assess functional capacity of patients with CHF objectively. 28 When the main result of this test (peak VO₂ < 14 mL/kg per minute; yes or no) was complemented with the results of LVEF assessments (≤25%; yes or no) and a simple blood test (UA ≥ 565 μmol/L [9.50 mg/dL]; yes or no), we were able to distinguish 4 risk groups, ranging from very low mortality (MFH 0, 9% at 3 years) to extremely high mortality (MFH 3, 87.5% at 18 months). It appears logical that these patient groups may need different follow-up strategies. MFH staging may be helpful to guide in the decision of whether to transfer a patient to a heart transplantation center.

The application of our staging system needs to be additionally investigated. Peak VO₂ may be replaceable by simpler measures, such as the 6-minute walk distance. Equally, some might want to use higher LVEF cutoffs or replace LVEF with brain natriuretic peptide levels. The ultimate validation would be to test whether tailoring treatment with this (or any) staging system would improve morbidity and mortality compared with a scenario in which treatment is individualized but formal staging is not used. The role of a genetic predisposition as a potential fourth prognostic factor needs to be assessed in the future, but it is conceivable that the genetic status is already reflected in one of the other factors.

Whether UA could be used to diagnose heart failure or to predict the mode of death is not known. We suggest that UA could be used to monitor metabolic status in CHF and hence to monitor CHF therapy concerning metabolic effects. It has been shown that hyperuricemia in the general population is independently associated with all-cause, total cardiovascular, and ischemic heart disease mortality. 29 Therefore, assessing UA may be of general value in health and illness.
Changes in underlying therapy may impact the prognostic value of parameters. It may be a limitation, therefore, that in our studies relatively few patients were taking β-blockers. Preliminary analyses indicate that also in the ELITE II population, UA is a strong independent prognosticator, which is also independent of concomitant β-blocker therapy (unpublished observation, 2002). For patients with CHF, the direct effects of UA have not been assessed in detail. To therapeutically target UA, one could use uricosuric treatments (to increase excretion of UA) or one could inhibit production by increasing endogenous xanthine oxidase activity.

Emerging data suggest that the latter indeed may be beneficial in CHF.

Acknowledgments
Dr Anker is supported by a donation from Dr Hubert Bailey and the Vendarvell Fellowship. Applied Cachexia Research (SDA) is supported by a grant from the Charité ´Medical School, Berlin, Germany. The Department of Clinical Cardiology is supported by the British Heart Foundation.

References


Uric Acid and Survival in Chronic Heart Failure: Validation and Application in Metabolic, Functional, and Hemodynamic Staging
Stefan D. Anker, Wolfram Doehner, Mathias Rauchhaus, Rakesh Sharma, Darrel Francis, Christoph Knosalla, Constantinios H. Davos, Mariantonietta Cicoira, Waqar Shamim, Michel Kemp, Robert Segal, Karl Josef Osterziel, Francisco Leyva, Roland Hetzer, Piotr Ponikowski and Andrew J.S. Coats

_Circulation_. 2003;107:1991-1997; originally published online April 21, 2003;
doi: 10.1161/01.CIR.0000065637.10517.A0
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/107/15/1991

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2003/04/21/01.CIR.0000065637.10517.A0.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/