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Low Serum Homoarginine Is a Novel Risk Factor for Fatal Strokes in Patients Undergoing Coronary Angiography

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Background and Purpose—Low serum concentrations of the amino acid homoarginine have been associated with endothelial dysfunction and an increased risk of all-cause and cardiovascular mortality. We aimed to investigate whether homoarginine levels are also associated with fatal strokes and a history of nonfatal cerebrovascular disease.

Methods—Serum homoarginine was measured in 3305 participants of the Ludwigshafen Risk and Cardiovascular Health (LURIC) study who were referred to coronary angiography at baseline (1997 to 2000) and were followed up with respect to mortality.

Results—During a median follow-up time of 9.9 years, 991 patients died including 61 fatal (ischemic and hemorrhagic) strokes. In a binary logistic regression analysis, the odds ratio (with 95% CI) for fatal stroke per SD of homoarginine was 0.52 (0.37 to 0.73; $P<0.001$) and remained significant after multivariable adjustments (0.62 [0.42 to 0.91]; $P=0.014$). For previous cerebrovascular disease events, the multivariable adjusted OR per SD of homoarginine was 0.82 (0.70 to 0.96; $P=0.014$).

Conclusions—Low homoarginine levels are a novel risk factor for fatal strokes and are reduced in patients with a history of cerebrovascular disease. Further studies are needed to explore the significance of homoarginine to risk stratification and therapeutic approaches in the prevention of strokes. **(*Stroke*. 2011;42:1132-1134.)**

Key Words: amino acids ■ cerebrovascular ■ homoarginine ■ mortality ■ prospective

Homoarginine is an amino acid that seems to be mainly synthesized from lysine in the kidney.[1] Previous studies suggest a role of homoarginine in the metabolism of the vasodilator nitric oxide.[2–5] Homoarginine has been shown to serve as a substrate for nitric oxide synthase and has been associated with endothelial function.[2] Homoarginine may also play a role in insulin secretion, inhibition of platelet aggregation, and blood pressure regulation.[3–5] In the Ludwigshafen Risk and Cardiovascular Health (LURIC) study, we have shown that low homoarginine concentrations are associated with an increased risk of all-cause and cardiovascular mortality.[6] These data among patients referred to coronary angiography were confirmed by similar results in hemodialysis patients.[6] Whether homoarginine levels are also associated with risk of strokes has not been examined so far. Hence, we investigated in the LURIC study whether serum homoarginine levels are associated with risk of strokes.

Methods

Baseline examinations of the LURIC cohort (1997 to 2000) and follow-up procedures have been published previously with some disease classifications being updated meanwhile.[6,7] In brief, the LURIC study consists of 3316 white patients who were referred to coronary angiography at a tertiary care center in southwest Germany. Written informed consent was obtained from all study participants and the "Ärztekammer Rheinland-Pfalz" gave ethical approval for the study. Previous cerebrovascular disease events were defined as a documented history of a foregoing transient ischemic attack, prolonged ischemic deficit, or cerebral infarction. Serum homoarginine was determined in 3305 study participants by means of a high-performance liquid chromatography method, as previously described.[6] Binary logistic regression analyses of patients with fatal stroke versus the remaining study cohort were performed with the SD of homoarginine (derived from the entire cohort) as an explanatory (independent) variable. Several possible confounders including established risk factors of stroke were stepwise included as indicated.[8] Similarly, we calculated logistic regression analyses with a dichotomous outcome variable for the presence or absence of a history of cerebrovascular disease events at baseline. Statis-

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Table 1. Baseline Characteristics for Patients With Fatal Stroke and the Remaining Study Cohort

	Fatal Stroke	Remaining Cohort
Number	61	3244
Homoarginine, μmol/L	2.07±0.83	2.58±1.06
Age, years	70.2±9.0	62.5±1.1
Female, percent	41.0	30.2
Body mass index, kg/m^2	26.8±3.7	27.5±4.1
High-density lipoprotein cholesterol, mmol/L	0.96±0.26	1.01±0.28
Low-density lipoprotein cholesterol mmol/L	2.98±0.85	3.03±0.88
Diabetes mellitus, percent	57.4	39.6
Systolic blood pressure, mm Hg	152±27	141±23
Active smokers, percent	9.8	19.8
Cystatin C, mg/L	0.98 (0.84–1.23)	0.91 (0.81–1.06)
Previous cerebrovascular disease event, percent	68.9	8.0
Cardiovascular disease, percent	83.6	77.7
Atrial fibrillation, percent	11.9	12.1
Left ventricular hypertrophy, percent	9.8	8.0
C-reactive protein, mg/L	4.3 (1.7–14.4)	3.4 (1.3–8.6)
Antihypertensive medication, percent	88.5	86.8
Statins, percent	39.3	47.0
Died, percent	100.0	28.7

Continuous data are shown as means±SD or medians with interquartile range, as appropriate.

tical analyses were performed by SPSS Version 17.0 (SPSS Inc, Chicago, IL) and a probability value <0.05 was considered statistically significant.

Results

The homoarginine concentration (mean±SD) in the entire LURIC cohort was 2.42±1.05 μmol/L. Baseline characteristics are shown in Table 1. During a median follow-up period of 9.9 years, 991 patients died including 61 fatal strokes. In a binary logistic regression analysis, the OR (with 95% CIs) for fatal stroke per SD of homoarginine was 0.52 (0.37 to 0.73; $P<0.001$). This association remained statistically significant after adjustments for various possible confounders (Table 2). Unadjusted OR for a previous (nonfatal) cerebrovascular disease event at baseline (n=302) per SD of homoarginine was 0.67 (0.58 to 0.78; $P<0.001$). After multivariable adjustments (according to Model 4 in Table 2), this association remained significant with 0.82 (0.70 to 0.96; $P=0.014$).

Discussion

In patients referred to coronary angiography, we show that low serum homoarginine levels are an independent risk factor for fatal strokes and a history of cerebrovascular disease events.

Table 2. Risk for Fatal Stroke per SD of Homoarginine

Model	OR (95% CI)	P
Unadjusted	0.52 (0.37–0.73)	<0.001
Model 1*	0.63 (0.44–0.89)	0.009
Model 2†	0.57 (0.39–0.83)	0.003
Model 3‡	0.62 (0.42–0.91)	0.015
Model 4§	0.62 (0.42–0.91)	0.014

Binary logistic regression analyses for risk for fatal strokes with ORs (with 95% CI) per SD of homoarginine.

*Adjusted for age and sex.

†Additionally adjusted for systolic blood pressure, active smokers, cardiovascular disease, atrial fibrillation, left ventricular hypertrophy, antihypertensive medication, and diabetes mellitus.

‡Additionally adjusted for low-density lipoprotein and high-density lipoprotein cholesterol, cystatin C, body mass index, and C-reactive protein.

§Additionally adjusted for statin use.

A previous analysis of the LURIC cohort with a shorter follow-up time has shown that low homoarginine predicts mortality.[6] The current work is the first report on the association of homoarginine status and stroke risk. Underlying mechanisms remain to be explored but there exists accumulating evidence that homoarginine plays a role in the metabolism of nitric oxide, which is critically involved in the regulation of cerebral blood flow and cell viability.[9] Further studies suggest that homoarginine might play a role in the pathogenesis of stroke risk factors such as diabetes mellitus, arterial hypertension, or prothrombotic states.[3–6] Interestingly, the key enzyme for homoarginine synthesis, arginine: glycine amidinotransferase, is upregulated in the failing heart and is highly expressed in the brain.[1,10] Inborn errors of this enzyme lead to disturbances in energy metabolism, so-called creatine deficiency syndromes, which are associated with mental disorders.[11]

Our data are limited by the relatively low number of events, which preclude adequately powered analyses of specific causes of stroke deaths. Furthermore, we investigated a specific cohort of patients referred to coronary angiography and our results may not be generalizable. Despite careful adjustments for possible confounders, we cannot rule out residual confounding.

In summary, our results suggest that low serum homoarginine levels are a novel risk factor for strokes. Further studies are needed to elucidate whether homoarginine levels may help to improve risk prediction of strokes and whether homoarginine is a promising target for therapeutic approaches.

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Disclosures

None.

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