High Homocysteine Levels Predict the Recurrence of Atrial Fibrillation After Successful Electrical Cardioversion

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SUMMARY

Recent data suggest that elevated plasma levels of homocysteine could be associated with atrial fibrillation (AF). The aim of our study was to investigate whether elevated plasma Hcy levels were predictive of the recurrence rate of AF after successful electrical cardioversion.

Eighty-three patients (63 ± 12 years, 61.4% men) with persistent AF lasting at least 7 days were included after successful electrical cardioversion. Echocardiography and plasma homocysteine assay were performed prior to cardioversion and patient baseline characteristics were obtained. Patients were monitored for a period of 18 months.

The patients were divided into two groups using a cut-off value for the last quartile of plasma homocysteine concentration ($> 14.4 \mu\text{mol/L}$). Kaplan Meier analysis showed a statistically significant difference in AF recurrence rates between both groups after 18 months ($P = 0.02$, log rank test). Cox proportional hazards multivariate analysis showed that predictors of AF recurrence were the duration of AF (OR 1.05, 95% CI 1.02-1.08, $P = 0.00$), treatment with amiodarone (OR 0.39, 95% CI 0.21-0.72, $P = 0.00$), and homocysteine level $\leq 14.4 \mu\text{mol/L}$ (OR 0.39, 95% CI 0.21-0.73, $P = 0.00$).

We found that the homocysteine levels determined prior to electrical cardioversion can predict recurrence of AF after successful restoration of sinus rhythm. (Int Heart J 2010; 51: 30-33)

Key words: Atrial fibrillation, Homocysteine, Cardioversion

In atrial fibrillation (AF) extensive structural and electrical remodelling of atrial tissue takes place.^{1,2)} It has been proven in previous studies that enhanced activity of matrix metalloproteinases (MMPs) may also be one of the mechanisms responsible for this.^{3,4)} It has been shown in animal studies that metalloproteinases in endocardial cells could be activated by homocysteine (Hcy).^{5,6)}

Elevated levels of Hcy are associated with an increased risk of coronary artery disease and cerebrovascular disease.⁷⁻⁹⁾ One study showed that elevated levels of Hcy are associated with the presence of nonvalvular AF.⁹⁾ Recently another study demonstrated an association between higher risk of cardiovascular events and higher Hcy levels in patients following radio frequency catheter ablation (RFA) for AF. However, no significant correlation between basal Hcy levels and the recurrence of AF after successful RFA could be found.¹⁰⁾ The aim of the present study was to investigate the association between Hcy levels and recurrent AF after successful electrical cardioversion (EC) of persistent AF.

METHODS

We retrospectively analysed the data of 83 consecutive

patients who underwent successful EC because of persistent AF (lasting > 7 days) between January 2005 and May 2006. Exclusion criteria were previous heart surgery or RFA of arrhythmic foci, an implanted pacing or defibrillating device, renal failure, and thyroid dysfunction. We collected and analysed patient data according to hospital ethics policy.

All patients were treated with anticoagulant therapy according to recent guidelines.¹¹⁾ Blood samples were drawn before EC from a basilic vein after an overnight fasting period. Plasma levels of Hcy were assessed by a chemiluminescence method (Immulite 2000, SIEMENS). Two-dimensional and Doppler echocardiographic measurements in classical projections were obtained by an experienced sonographer. Left atrial diameter taken from M-mode and ejection fraction, calculated by the Teicholz method, were used for analysis. EC was performed under sedation with propofol with up to two external monophasic (200 J, 300 J) or biphasic (100 J, 150 J) shocks. After the procedure, the patients were monitored for 24 hours and then another 12-lead ECG was recorded. After discharge the patients were monitored in our outpatient clinic by means of clinical examinations and 12-lead ECG. In the case of symptoms suggesting paroxysms of AF, 24-hour Holter monitoring was performed. Regular visits were scheduled every 3-6 months

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or in the case of any symptoms suggesting AF recurrence. The follow-up period lasted 18 months. Documented AF was considered as the study endpoint.

Hcy levels were divided in quartiles. The patients were divided into two groups using a cut-off value for the last quartile of plasma Hcy concentration. Continuous variables were compared using Student's *t* test or the Mann-Whitney U test. Proportional data were compared with a chi square test. A one-way ANOVA test was used for assessing the statistical significance where appropriate. We used Spearman's rank correlation coefficient for correlation analysis. Correlation between AF recurrence after 18 months and Hcy levels was examined by simple logistic regression. Survival curves for the incidence of AF recurrence were calculated with the Kaplan-Meier method and a log-rank test was

used to assess statistical significance. A Cox proportional hazards analysis was performed to determine the clinical predictors of AF recurrence. In multivariate analysis a step-wise forward method was used. A *P* value of < 0.05 was considered as statistically significant. Continuous variables are expressed as the mean $\pm$ SD and categorical variables as percentages. Statistical analysis was performed using the SPSS 13.0 statistical package (SPSS, Chicago, IL).

RESULTS

Eighty-three patients were included after the inclusion criteria were met. No patients were lost during follow-up. We did not observe any major cardiovascular events

Table. Main Patient Characteristics According to Homocysteine Levels

Patient characteristics	All patients (<i>n</i> = 83)	Low Hcy group ($\leq 14.4 \mu\text{mol/L}$) (<i>n</i> = 63)	High Hcy group ($> 14.4 \mu\text{mol/L}$) (<i>n</i> = 20)	<i>P</i>
Age (years)	63 $\pm$ 12	62 $\pm$ 10	65 $\pm$ 17	0.24
Sex (male)	51 (61.4%)	36 (57.1%)	15 (75.0%)	0.27
Duration of AF (months)	7 $\pm$ 10	6 $\pm$ 7	10 $\pm$ 15	0.10
LA diameter (mm)	52 $\pm$ 65	52 $\pm$ 66	53 $\pm$ 62	0.78
Ejection fraction (%)	51 $\pm$ 9	52 $\pm$ 9	49 $\pm$ 7	0.26
Mitral regurgitation (stage 2 or higher)	17 (20.5%)	13 (20.6%)	4 (20.0%)	1.0
Ischemic heart disease	9 (10.8%)	6 (9.5%)	3 (15.0%)	0.68
Arterial hypertension	56 (67.5%)	45 (71.4%)	11 (55.0%)	0.18
Diabetes mellitus	6 (7.2%)	3 (4.8%)	3 (15.0%)	0.15
Medication				
Beta blocker	23 (27.7%)	18 (28.6%)	5 (25.0%)	1.0
ACE inhibitor	56 (67.5%)	40 (63.5%)	16 (80.0%)	0.27
Amiodarone	64 (77.1%)	47 (74.6%)	17 (85.0%)	0.54
Sotalol	3 (3.6%)	3 (4.8%)	0 (0.0%)	1.0
Propafenone	15 (18.1%)	12 (19.0%)	3 (15.0%)	1.0
ARB	9 (10.8%)	8 (12.7%)	1 (5.0%)	0.68

Figure 1. The relationship between circulating levels of homocysteine and recurrent atrial fibrillation; box plots represent median levels with 25th and 75th percentiles and whiskers the 5th and 95th percentiles of homocysteine levels. (ANOVA test; *P* < 0.05)

Figure 2. Scatter plots of the correlation between left ventricular ejection fraction and homocysteine levels (*r* = -0.26, *P* = 0.02).

Figure 3. Kaplan-Meier curves showing freedom from atrial fibrillation recurrence in both groups according to homocysteine level (log rank test, $P = 0.02$).

or deaths during the observation period. Antiarrhythmic therapy was initiated before EC in all patients and then continued throughout the follow-up. Amiodarone was replaced by sotalol in 2 patients due to amiodarone related side effects (thyroid dysfunction).

AF recurrence occurred in 42 patients (50.6%) after 12 months and in 48 patients (58%) after 18 months. In patients with AF recurrence, plasma Hcy levels were significantly higher than in patients with persistent sinus rhythm ($P < 0.05$, Figure 1). We did not find a correlation between Hcy levels and the left atrial dimensions ($r = 0.19$, $P = 0.12$), however, there was a weak, but positive correlation between Hcy levels and left ventricular ejection fraction ($r = -0.26$, $P = 0.02$; Figure 2).

Hcy levels were divided into quartiles based on the distribution of this parameter in our population. According to the descriptions in previous reports,^{8,9)} we used a cut-off value for the last quartile of plasma Hcy concentration ($> 14.4 \mu\text{mol/L}$) to divide patients into two groups. Sixty-three patients were included in the group with low Hcy levels ($\leq 14.4 \mu\text{mol/L}$), while 20 patients formed a group with high Hcy levels ($> 14.4 \mu\text{mol/L}$). There were no significant differences in patient sex, age, other comorbidities, echocardiographic characteristics, and concomitant therapy between the 2 groups (Table). At 18 months follow-up, AF reoccurred in 32 (50.8%) patients in the low Hcy group and in 16 (80%) patients in the high Hcy group ($P = 0.03$). Survival analysis showed a statistically significant difference in AF recurrence rates between the groups ($P = 0.02$, log rank test, Figure 3). In the Cox univariate regression analysis, significant predictors of AF were male sex (OR 2.32, 95% CI 1.18-4.57, $P = 0.01$), duration of AF prior to EC (OR 1.04, 95% CI 1.01-1.07), Hcy level $\leq 14.4 \mu\text{mol/L}$ (OR 0.48, 95% CI 0.26-0.88, $P = 0.02$), and treatment with

amiodarone (OR 0.46, 95% CI 0.25-0.85, $P = 0.01$). In the multivariate model, we included duration of AF prior to EC, sex, treatment with ACE inhibitors and amiodarone, history of ischemic heart disease, arterial hypertension or diabetes, and Hcy levels. After adjustment for other potential confounders, Hcy level $\leq 14.4 \mu\text{mol/L}$ remained a statistically significant predictor of AF recurrence (adjusted OR 0.38, 95% CI 0.21-0.72, $P = 0.00$).

DISCUSSION

In the present study we found that Hcy levels were significantly elevated in the group of patients who developed AF during follow-up. Hcy levels turned out to be a statistically significant predictor for AF recurrence in survival analysis and retained its significance after adjustment for other possible confounders. Thus, our study further supports and extends existing data that there is a positive correlation between plasma levels of Hcy and AF.

There is only a limited amount of clinical data that deals with this subject. Only recently, Marcucci, *et al* showed that patients with AF were more likely to have elevated Hcy levels. They demonstrated an association between Hcy levels and left atrial diameter and also proved that elevated Hcy levels were an independent risk factor for ischemic complications during AF.⁹⁾ Shimano, *et al* investigated the potential association between Hcy levels and cardiovascular events or AF recurrence following RF catheter ablation in patients with AF. They also found that high Hcy levels are associated with the presence of AF and confirmed the role of Hcy as a risk factor for development of cardiovascular events. They were also able to prove a positive correlation between Hcy, left atrial diameter, and levels of type I collagen degradation marker, which could partly explain the mechanism responsible for structural remodelling of atria.¹⁰⁾ In line with both of the above-mentioned studies, we also found that Hcy levels significantly influenced AF. However, in contrast to both studies we did not find that Hcy levels were correlated with atrial dimensions, thus extending the pathological role of Hcy beyond left atrial enlargement. It seems that atrial remodelling with, but also without atrial enlargement, is the mechanism underlying the effect of Hcy on AF. Interestingly, we were able to prove a weak, but significant inverse correlation between Hcy and left ventricular ejection fraction. It has been postulated in previous studies that Hcy is associated with left ventricular dysfunction and heart failure, which can also be connected to increased AF occurrence.¹¹⁻¹³⁾

Still, based on available data it is not clear whether there is a causal relationship between elevated Hcy levels and atrial remodelling. It was postulated that activation of different MMPs can modulate extracellular matrix collagen disintegration, which can in turn cause the structural and hence electrical remodelling of human atria.^{3,4)} It was also proven that Hcy can upregulate the activity of MMPs 2 and 9.^{5,6)} Another experimental study showed that Hcy could cause electro-physiological disturbances of potassium currents in human atrial myocytes.¹⁴⁾ On the other hand, recent data also support the involvement of Hcy in oxidative stress and reduced nitric oxide bioavailability in animal heart tis-

sue.¹⁵⁾ Hence, hyperhomocysteinemia could be involved in the pathological processes in human atria accompanied by AF.

Hyperhomocysteinemia, which can result from both genetic and environmental influences,¹⁶⁻¹⁸⁾ is associated with increased risk of cardiovascular and cerebrovascular disease.^{7-9,19)} We were not able to investigate the cause of elevated Hcy levels in our patients. We also did not notice any major clinical adverse events, probably due to the small study group and relatively short observation period.

Our study has several limitations. It was retrospective, nonrandomised, and the study population was relatively small. It is possible that some short asymptomatic paroxysms of AF were not noticed. Echocardiographic measurements used in our study have only limited value; for more precise evaluation more exact methods like LA volume calculation and the Simpson method should be used. It is possible that concomitant medications could have had an impact on our results; however, there were no significant differences between the 2 groups regarding the medications used. Only a single Hcy measurement was obtained and no successive measurements during the follow-up period were performed. However, there are no data showing that modifying the level of Hcy could influence the level of AF recurrence. Hence, no firm conclusions could be drawn regarding different levels of Hcy in a single patient at this point.

Conclusions: Our study further supports the association between hyperhomocysteinemia and AF and also suggests that Hcy could be used as a prognostic marker of AF recurrence following successful cardioversion. Further investigation is needed to definitively clarify the role of Hcy in AF.

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