Plasma B vitamins and their relation to the severity of chronic heart failure[1–3]

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ABSTRACT

Background: Total homocysteine (tHcy) has been linked to the severity of chronic heart failure (CHF). Elevated tHcy concentrations are mainly caused by folate and vitamin B-12 deficiencies.

Objective: We hypothesized that folate and vitamin B-12 deficiencies can explain the relation between tHcy and the severity of CHF.

Design: We investigated 987 CHF patients. All subjects underwent a physical examination and blood sampling. Cardiac catheterization was performed in 929 patients and echocardiography in 460 patients. Serum tHcy, folate, vitamin B-12, and *N*-terminal pro-B-type natriuretic-peptide (NT-proBNP) were measured and renal and hepatic function were studied.

Results: tHcy increased with increasing New York Heart Association (NYHA) classes of heart failure ($P < 0.001$) and correlated with the left ventricular ejection fraction (EF; $r = -0.150$, $P < 0.001$). Contrary to the hypothesis, vitamin B-12 ($P < 0.001$) increased with NYHA class ($P < 0.001$) and was negatively correlated with EF ($r = -0.080$, $P = 0.015$). Folate showed no relation with NYHA class or EF. Comparable results were obtained for NT-proBNP (tHcy: $r = 0.27$, $P < 0.001$; vitamin B-12: $r = 0.091$, $P = 0.004$; folate: $r = -0.045$, $P = 0.169$). The correlations between tHcy, EF, and NT-proBNP were significantly stronger in patients without coronary artery disease (CAD) than in those with CAD. Regression analysis showed that tHcy, but not B vitamins, is a strong predictor of EF and NT-proBNP.

Conclusions: This study showed that tHcy, but not folate and vitamin B-12, is related to clinical, echocardiographic, and laboratory variables of CHF, which indicates a relation between tHcy and the severity of CHF. This relation is stronger in patients without CAD. The lack of association of folate and the paradoxical relation of vitamin B-12 with CHF can possibly be explained by a disturbance in hepatic homeostasis. *Am J Clin Nutr* 2007;85:117–23.

KEY WORDS Chronic heart failure, homocysteine, folate, vitamin B-12, NT-proBNP, ejection fraction, coronary artery disease

INTRODUCTION

Despite an increased awareness of disease prevention, recent data from the Rochester Epidemiology Project clearly show that the incidence of chronic heart failure (CHF) has not decreased since 1991 (1). Current estimates for 2006 indicate a prevalence of 5 million CHF patients, an incidence of 550 000 new cases, 287 000 CHF-related deaths, and CHF-related costs of 29.6 billion dollars in the United States (2). From 1993 to 2003, death rates from CHF increased by 20.5%, whereas the total death rate decreased by 2.0% in the same period (2). A comparable situation exists in Western Europe (3–5). According to the European Society of Cardiology, the prevalence of symptomatic heart failure in Europe ranges between 0.4% and 2.0% (4). Data from the World Health Organization estimates a 1.4% prevalence of CHF in Europe, with a total number of 5.3 million affected persons (4). Consequently, CHF is an ongoing major health problem, and the prevention of CHF by identifying risk factors is still an important issue.

Recently, plasma total homocysteine (tHcy) has been suggested as a newly recognized risk factor for CHF (6–8). Experimental studies suggest that hyperhomocysteinemia is causally involved in CHF (9, 10). However, the underlying mechanisms are largely unknown. A major question that to be answered is whether tHcy acts via its atherogenic effects on coronary vessels or directly on the myocardium.

The particular importance of hyperhomocysteinemia is due to the most interesting therapeutic implications. Deficiencies of folic acid, vitamin B-12, vitamin B-6, or a combination thereof are the most common causes for mild-to-moderately-elevated tHcy concentrations in adults (11, 12). The prevalence of B vitamin deficiencies in Western countries without folic acid fortification increases with age, to 10% in persons aged >75 y (13–16). Moreover, it has repeatedly been shown that hyperhomocysteinemia can efficiently be treated via harmless and inexpensive supplementation with folic acid, vitamin B-12, and vitamin B-6 (12, 17, 18). However, reliable data about the role of these B vitamins in CHF do not exist (6). The demonstration of relations between various clinical, functional, and biochemical markers of CHF with the B vitamin status would help to understand the role of B vitamins and tHcy in CHF.

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We hypothesized that plasma tHcy, folate, vitamin B-12, and vitamin B-6 concentrations are associated with clinical, functional, and biochemical signs of CHF, indicating a relation between tHcy, B vitamins, and the severity of CHF. Moreover, we postulated that these associations are independent of the presence of coronary artery disease (CAD), which suggests direct actions of tHcy on the myocardium. Accordingly, we investigated the relations of plasma tHcy and B vitamins with clinical signs of CHF, left ventricular function, serum *N*-terminal pro-B-type natriuretic peptide (NT-proBNP), and coronary status (number of stenotic coronary vessels) in a large sample of well-characterized CHF patients.

SUBJECTS AND METHODS

Study design

The present study analyzed data from 987 consecutive CHF patients, who presented between October 2003 and September 2004 in the heart failure unit of the Department of Cardiology of the University Hospital of Saarland in Homburg, Germany. Patients were interviewed and examined by an experienced cardiologist who was blinded to the study. A detailed medical history, physical examination, and venous blood sampling were performed in all patients. Nine-hundred twenty-nine patients underwent a standardized cardiac catheterization according to the Guidelines for Coronary Angiography of the American Heart Association (19). Briefly, monoplane ventriculography was done in standard projection (right anterior oblique position, 30°/0°). The ejection fraction (EF) was calculated by end-diastolic and end-systolic left ventricular area with the use of an automated computer system. Additionally, a standard echocardiography was done in a subset of 460 patients. Anthropometric and clinical data for the subjects are summarized in **Table 1**. Informed consent was obtained from all study participants, and the study protocol was approved by the local ethical review board (reference no. 89/05).

Blood sampling and preanalytic handling of samples

Fasting venous plasma and serum were drawn into EDTA-containing tubes and serum tubes (without coagulant) at 0800 and transported immediately to our laboratory. The EDTA-containing plasma samples were placed on ice during transport. Within 45 min after blood sampling, serum and plasma were separated from the cellular blood components by centrifugation and stored at −20 °C until analyzed.

Laboratory analysis

tHcy was detected with an enzymatic fluorescence polarization immunoassay on an Axsym automated analyzer (Abbott, Wiesbaden, Germany). The intra- and interassay CVs for this method were <4.5% and 5.1%, respectively. Vitamin B-12 and folate were measured with commercial, competitive chemiluminescence immunoassays (Bayer Diagnostics, Fernwald, Germany) on an ACS Centaur automated analyzer (Bayer Diagnostics). The folate assay detects 5-methyltetrahydrofolate. The intra- and interassay CVs were <4.0% and <4.4% for vitamin B-12 and <5.3% and <5.5% for folate, respectively. Analysis of serum NT-proBNP was done with a chemiluminescence immunoassay on an Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany). The intra- and interassay imprecisions were <2.7% and <3.2%, respectively.

TABLE 1
Patient characteristics[1]

	All patients (n = 987)	Men (n = 685)	Women (n = 302)
Anthropometric data			
Age (y)	63 ± 12[2]	62 ± 12	65 ± 12[3]
Weight (kg)	81 ± 16	85 ± 14	74 ± 16[3]
Height (cm)	170 ± 8	174 ± 7	162 ± 6[3]
NYHA classification (n)			
I	362	270	92
II	389	253	136
III	201	136	65
IV	35	26	9
Blood pressure (mm Hg)			
Systolic	147 ± 27	145 ± 5	149 ± 28[4]
Diastolic	84 ± 12	83 ± 12	84 ± 13
Echography and catheterization			
EF (%)	38 ± 20	58 ± 21	65 ± 18[3]
FS (%)	19 ± 9	25 ± 9	29 ± 9[3]
LVDD (mm)	64 ± 10	58 ± 10	52 ± 8[3]
Laboratory analyses			
Homocysteine (μmol/L)	13.8 ± 7.5	14.2 ± 8.0	12.7 ± 6.2[3]
NT-proBNP (ng/L)	1245 ± 2768	1185 ± 2543	1373 ± 3224
Troponin T (mg/L)	0.26 ± 3.43	0.26 ± 3.93	0.25 ± 1.85
Creatinine (mg/L)	1.1 ± 0.4	1.1 ± 0.4	1.0 ± 0.5[3]
Cystatin C (mg/L)	1.1 ± 0.6	1.1 ± 0.5	1.2 ± 0.62
Glomerular filtration rate (mL/min)	74 ± 23	77 ± 22	68 ± 24[4]
Folate (mg/L)	6.9 ± 6.3	6.6 ± 6.2	7.5 ± 6.4[4]
Vitamin B-12 (ng/L)	379 ± 276	365 ± 222	411 ± 370
ASAT (U/L)	33 ± 35	35 ± 41	29 ± 20[3]
ALAT (U/L)	19 ± 23	20 ± 25	16 ± 17[3]
gGT (U/L)	52 ± 72	59 ± 80	36 ± 45[3]
Choline esterase (kU/L)	8.5 ± 2.0	8.4 ± 2.1	8.6 ± 1.8
C-reactive protein (mg/L)	6.0 ± 12.7	5.7 ± 11.3	6.6 ± 15.5
Cardiac disease risk factors (n)			
Current	178	144	34
Previous smokers	402	335	67
Hypertension	794	548	246
Coronary artery disease	656	490	166
Myocardial infarction	284	227	57
Stroke	80	60	20
Diabetes mellitus	236	151	85
Medication use (n)			
β-Blockers	799	569	230
Diuretics	650	491	164
ACE inhibitors	693	499	194
Digoxin, digitoxin	52	42	10
Antiarrhythmics	46	39	7
Aspirin	611	448	163
Statins	625	442	183
AT1-receptor inhibitors	97	60	37
Marcumar	89	70	19

[1] NYHA, New York Heart Association; EF, left ventricular ejection fraction; FS, fractional shortening; LVDD, left ventricular diastolic diameter; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; gGT, γ-glutamyltransferase; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; ACE, angiotensin converting enzyme.

[2] $\bar{x}$ ± SD (all such values).

[3,4] Significantly different from men (Mann-Whitney U test): [3] $P < 0.01$, [4] $P < 0.05$.

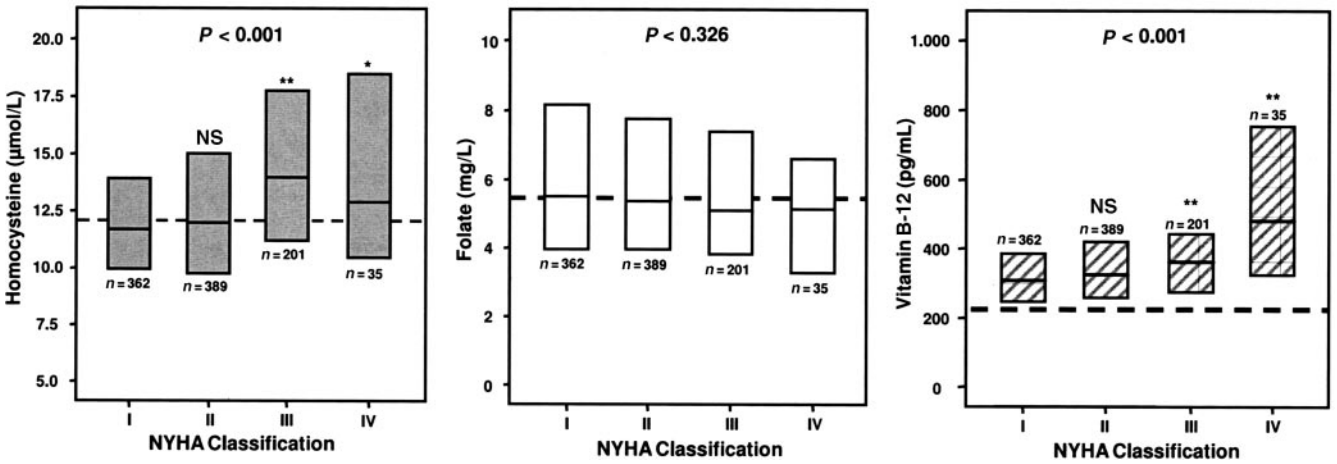

FIGURE 1. Boxplot (25th–75th percentile) of the relation between the New York Heart Association (NYHA) classification of heart failure and homocysteine, folate, and vitamin B-12. The *P* values in the panels were derived with a Kruskal-Wallis test. A *P* value <0.05 indicates a significant difference. If the Kruskal-Wallis test indicated a significant result, a Mann-Whitney *U* test was performed. *,**Significantly different from NYHA class I (Mann-Whitney *U* test): $^{*}P < 0.05$, $^{**}P < 0.001$. All *P* values were adjusted for multiple testing.

Because there is a strong negative correlation between tHcy and renal function, we also measured serum creatinine and cystatin C and calculated the glomerular filtration ratio according to the formula of the Modification of Diet in Renal Disease Study Group (20). In addition, vitamin B-12 status strongly depends on normal hepatic function (21–24). Vitamin B-12 concentrations from persons with a disturbance in hepatic homeostasis may be falsely high because they may include metabolically inactive cobalamin analogues (22, 24). Moreover, folate utilization strongly depends on the availability of active vitamin B-12. A reduced availability of active vitamin B-12 could depress folate utilization and result in a folate trap (25, 26). Because it is known that CHF may cause congestion of blood into the liver with an accompanying disturbance in hepatic function (27), we evaluated liver function on the basis of alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), γ-glutamyltransferase (gGT), choline esterase (CHE), and C-reactive protein (CRP). All of these variables were measured on a Hitachi 917 analyzer with the use of reagents from Roche Diagnostics. Intra- and interassay CVs for ALAT, CHE, and CRP were <5%.

Statistical analysis

Anthropometric data and descriptive statistics are provided as means ± SDs. Mean values were compared by using a Mann-Whitney *U* test. If >2 mean values were compared [eg, mean age in the 4 New York Heart Association (NYHA) classes of heart failure], we performed a Kruskal-Wallis test. Then, not normally distributed variables (tested by Kolmogorov-Smirnov test) were transformed logarithmically before further analysis. The logarithmically transformed variables were used in a Spearman correlation analysis. Finally, we calculated several multivariate linear regression models using log(EF), log(NT-proBNP), log(vitamin B-12), and log(ASAT) as dependent variables. A *P* value <0.05 was considered significant. Calculations were done with the software package SPSS (version 11.0 for WINDOWS; SPSS Inc, Chicago, IL).

RESULTS

tHcy, B vitamins, and NYHA class

Most of the patients investigated were classified as NYHA classes I ($n = 362$) and II ($n = 389$). The remaining patients were characterized as NYHA classes III ($n = 201$) and IV ($n = 35$), respectively. The median age increased significantly ($P = 0.004$) with increasing NYHA class (NYHA class I: 62 ± 12 y; NYHA class II: 64 ± 11 y; and, NYHA classes III + IV: 64 ± 12 y). Hypertension (80%) and CAD (66%) were the most prevalent cardiac risk factors. Diabetes mellitus was found in 24% of the subjects. As expected, β-blockers, diuretics, and angiotensin-converting enzyme inhibitors were the most frequently used pharmaceuticals. A detailed characterization of the patients is provided in Table 1.

Serum tHcy was lowest in subjects with NYHA class I and increased significantly with increasing NYHA class ($P < 0.001$; **Figure 1**). Median tHcy concentrations in subjects with NYHA classes I-II were ≤12 μmol/L, which represents the cutoff recommended by the German, Austrian, and Swiss consensus conference (12). However, median tHcy concentrations for subjects with NYHA classes III and IV exceeded this cutoff. Contrary to our hypothesis, circulating vitamin B-12 concentrations increased with increasing NYHA class ($P < 0.001$; Figure 1) and were clearly above the lower reference limit of the detection method used (lower reference limit: 211 ng/L) in all NYHA classes. No relation was observed between folate and NYHA class.

tHcy, B vitamins, and EF

Because NYHA class is a relatively rough tool for staging CHF patients, we analyzed the EF as a functional variable of cardiac pump function. Confirming our results obtained with the NYHA classification, EF decreased with increasing tHcy concentration (**Figure 2**). Correlation analysis showed a weak but highly significant association between EF and tHcy ($r = -0.150$, $P < 0.001$). This correlation was considerably stronger ($P <$ 0001) in patients without CAD than in those with CAD. The

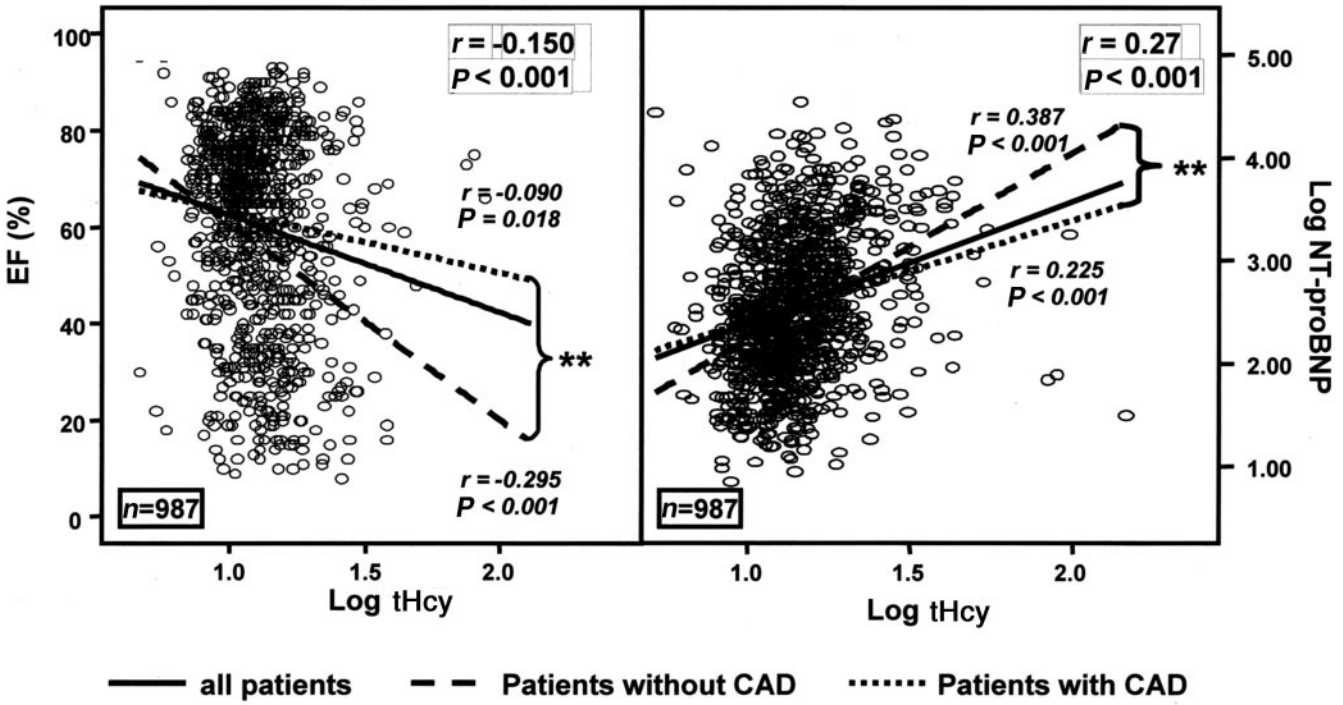

FIGURE 2. Pearson's correlation analysis of logarithmically transformed (log) total homocysteine (tHcy) and left ventricular ejection fraction (EF) and log *N*-terminal pro-B-type natriuretic-peptide (NT-proBNP). The larger *r* and *P* values in the upper right corner of each plot represent the overall analysis including all patients. The smaller *r* and *P* values close to the lines are the results of the separate analyses for CAD and non-CAD patients. **Significant difference between patients with and without CAD, $P < 0.01$ (multivariate regression analysis).

paradoxical relation between NYHA class and vitamin B-12 was also confirmed. However, the negative correlation between EF and vitamin B-12 was very weak ($r = -0.080$, $P = 0.015$), and the CAD patients did not differ from those of the non-CAD patients. No association was found between folate and EF ($r = -0.045$, $P = 0.169$).

tHcy, B vitamins, and NT-proBNP

To further substantiate our findings, we also measured NT-proBNP as a modern and sensitive marker of cardiac dysfunction with a high negative predictive value. tHcy showed a highly significant correlation with NT-proBNP that was significantly stronger in patients without CAD than in patients with CAD (Figure 2). Comparable with EF and NYHA class, vitamin B-12 was paradoxically correlated with NT-proBNP ($r = 0.091$, $P = 0.004$). However, the association was rather weak, and no significant difference between CAD and non-CAD patients was observed. NT-proBNP was not related to circulating folate concentrations ($r = -0.011$, $P = 0.73$).

Variables of hepatic function

Mean ASAT, ALAT, gGT, and CRP were within the sex-specific reference ranges (Table 1). Dividing subjects into those with vitamin B-12 concentrations below and above the median (379 ng/L), ASAT (29 compared with 37 U/L; $P < 0.01$), ALAT (16 compared with 22 U/L; $P < 0.01$), and gGT (44 compared with 60 U/L; $P < 0.01$) were significantly higher in the group with vitamin B-12 above the median, which indicated a slight disturbance in hepatic cell integrity.

Multivariate regression analyses

In a next step we calculated several multivariate regression models using EF and NT-proBNP as dependent variables. In the first 2 models we included tHcy, folate, vitamin B-12, age, sex, renal function (GFR), cardiac disease risk factors (eg, hypertension and diabetes mellitus), and medication use (eg, angiotensin-converting enzyme inhibitors, β-blockers, and diuretics) as independent variables (**Table 2**). These models confirmed a strong and highly significant relation between tHcy and NT-proBNP and between tHcy and EF. Moreover, the associations between vitamin B-12 and NT-proBNP and between vitamin B-12 and EF remained of borderline significance. Folate exhibited a weak but significant association with EF. To determine whether relevant differences existed between CAD and non-CAD patients, we performed 2 additional analyses including coronary status (number of stenotic coronary vessels) and interaction terms for tHcy, folate and vitamin B-12 into the models. In these models, tHcy was the strongest independent variable for NT-proBNP and EF in non-CAD patients. Moreover, the influence of tHcy on EF and NT-proBNP was significantly attenuated in CAD patients

To obtain more information about the missing or paradoxical relations of B vitamins with the severity of CHF, we subsequently introduced vitamin B-12 as a dependent variable in a multivariate regression model that also included ASAT, ALAT, gGT, CHE, and CRP (**Table 3**). In this model, ASAT was the strongest predictor of vitamin B-12. We then used ASAT as a dependent variable in the same regression model (Table 3), which yielded NT-proBNP as the strongest predictor of ASAT.

TABLE 2
Multivariate linear regression analysis with left ventricular ejection fraction (EF) and *N*-terminal pro-B-type natriuretic peptide (NT-proBNP) as dependent variables[1]

Model	Dependent variable	Independent variable of interest	Regression coefficient	SE	*P*
1[2]	$\log_{10}$NT-proBNP	$\log_{10}$(Hcy)	0.556	0.142	<0.001
		$\log_{10}$(Folate)	0.033	0.073	0.643
		$\log_{10}$(B12)	0.189	0.093	0.044
2[2]	$\log_{10}$ EF	$\log_{10}$(Hcy)	−0.127	0.045	0.005
		$\log_{10}$(Folate)	−0.049	0.022	0.030
		$\log_{10}$(B12)	−0.057	0.031	0.064
3[3]	$\log_{10}$NT-proBNP	$\log_{10}$(tHcy) w/o CAD	1.216	0.172	<0.001
		$\Delta\log_{10}$(tHcy) w/o CAD − $\log_{10}$(tHcy) with CAD	−0.590	0.180	0.023
		$\Delta\log_{10}$(Folate) w/o CAD − $\log_{10}$(Folate) with CAD	0.173	0.122	0.324
		$\Delta\log_{10}$(B12) w/o CAD − $\log_{10}$(B12) with CAD	0.081	0.145	0.576
4[3]	$\log_{10}$ EF	$\log_{10}$(tHcy) w/o CAD	−0.335	0.077	<0.001
		$\Delta\log_{10}$(tHcy) w/o CAD − $\log_{10}$(tHcy) with CAD	0.227	0.080	0.005
		$\Delta\log_{10}$(Folate) w/o CAD − $\log_{10}$(Folate) with CAD	0.027	0.053	0.611
		$\Delta\log_{10}$(B12) w/o CAD − $\log_{10}$(B12) with CAD	−0.045	0.044	0.306

[1] n = 987. CAD, coronary artery disease; B12, serum vitamin B-12; folate, serum folate; tHcy, total plasma homocysteine; w/o, without.
[2] Included independent variables: tHcy, glomerular filtration rate, B12, serum folate, age, sex, weight, height, hypertension, diabetes mellitus, β-blocker, diuretics, angiotensin converting enzyme, and aspirin.
[3] Included independent variables: coronary status (number of stenotic vessels), tHcy, glomerular filtration rate, B12, serum folate, age, and sex.

DISCUSSION

The main findings of the present study were the consistent associations of plasma tHcy with clinical (NYHA class), functional (EF), and laboratory markers (NT-proBNP) of CHF that were significantly stronger in patients without CAD than in those with CAD. Contrary to our hypothesis, folate and vitamin B-12 did not predict or paradoxically predicted these variables, which could possibly be due to a cardiohepatic syndrome in CHF patients that leads to a disturbance in vitamin B-12 status and consequently to insufficient folate utilization.

TABLE 3
Multivariate regression analysis with vitamin B-12 and aspartate aminotransferase (ASAT) as dependent variables[1]

Model	Dependent variable	Independent variable of interest	Regression coefficient	SE	*P*
1[2]	$\log_{10}$B12	$\log_{10}$(ASAT)	0.214	0.063	0.001
		$\log_{10}$(Creatinine)	0.198	0.063	0.002
		$\log_{10}$(Hcy)	−0.322	0.053	<0.001
		$\log_{10}$(Folate)	0.081	0.026	0.002
		$\log_{10}$(EF)	<0.001	0.00	0.865
		$\log_{10}$(CRP)	0.021	0.014	0.134
		$\log_{10}$(CHE)	−0.32	0.066	0.628
		$\log_{10}$(NT-proBNP)	0.22	0.014	0.114
		$\log_{10}$(ALAT)	−0.024	0.044	0.579
		$\log_{10}$(gGT)	0.029	0.023	0.196
2[3]	$\log_{10}$ASAT	$\log_{10}$(NT-proBNP)	0.030	0.008	0.001
		$\log_{10}$(ALAT)	0.481	0.018	<0.001
		$\log_{10}$(CRP)	0.22	0.008	0.007
		$\log_{10}$(Creatinine)	0.084	0.036	0.022
		$\log_{10}$(B12)	<0.001	0.00	0.865
		$\log_{10}$(Hcy)	0.024	0.031	0.448
		$\log_{10}$(EF)	0.000	0.000	0.627
		$\log_{10}$(gGT)	0.026	0.013	0.042
		$\log_{10}$(Folate)	0.070	0.015	0.931

[1] n = 989. ALAT, alanine aminotransferase; CHE, choline esterase; CRP, C-reactive protein; EF, left ventricular ejection fraction; folate, serum folate; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; tHcy, total plasma homocysteine; gGT, γ-glutamyltransferase; B12, serum vitamin B-12.
[2] Included independent variables: EF, NT-proBNP, tHcy, ALAT, ASAT, gGT, plasma creatinine, serum folate, B12, C-reactive protein, and CHE.
[3] Included independent variables: EF, NT-proBNP, tHcy, plasma creatinine, serum folate, B12, C-reactive protein, CHE, ALAT, and gGT.

tHcy and CHF

CHF is diagnosed by clinical, Echocardiographic, and laboratory analyses (2, 4, 28, 29). In agreement with a recent pilot study from our group (7), plasma tHcy was significantly related to NYHA class, EF, and NT-proBNP, which indicates a relation between tHcy and the severity of CHF. The strongest relation was found for tHcy and NT-proBNP, which is not surprising because NT-proBNP assessment is free of subjective modification, and elevations can frequently be found in diastolic dysfunction (30–33), where EF is normal, as well as in mild systolic dysfunction (34–36). In addition, modern concepts consider the heart to be a multifunctional and interactive organ that is part of a complex network (37, 38). Several studies have shown that BNP has antifibrotic and cytoprotective properties (39–42). Obviously, these counterregulatory actions of BNP are present before clinical symptoms and changes in EF occur and probably explain the strong prediction of NT-proBNP by tHcy. Contrary to NT-proBNP, changes in EF and NYHA class can easily be modified by subjective influences, have a limited reproducibility, and are dependent on the investigator's experience. The role of tHcy in CHF is substantiated by recent data from the Framingham Study, which show a strong increase in CHF incidence in healthy subjects with a tHcy concentration above the sex-specific median (8). Moreover, in animal experiments, isolated hyperhomocysteinemia in normotensive and hypertensive rats induced cardiac hypertrophy, fibrosis, and diastolic dysfunction which suggests a mechanistic role of tHcy for the pathogenesis of CHF (9, 10). Because CAD is one main cause of CHF and hyperhomocysteinemia is considered to be an independent risk factor for CAD, it can be speculated that the relation between tHcy and CHF is due to the atherogenic potency of tHcy. However, the present

results show a significantly stronger relation between tHcy and the clinical status of CHF in patients without CAD, which indicates direct pathomechanistic effects of tHcy on the myocardium.

B vitamins and CHF

Because tHcy concentrations are strongly dependent on folate and vitamin B-12 status, we suggest that circulating concentrations of these vitamins are also related to CHF. However, the present results show that folate and vitamin B-12 are poorly associated with CHF. Moreover, vitamin B-12 had a weak paradoxical relation with NYHA class, EF, and NT-proBNP that remained of borderline significance after multivariate adjustment (Table 2). A comparison of our findings with those of others is difficult because few other studies are available. However, some information on folate can be obtained by analyzing CHF statistics before and after the initiation of food fortification with folate in the United States in 1998. The Rochester Epidemiology Project shows that the incidence of CHF between 1991 and 2000 did not decrease (1). However, survival after onset of CHF has increased significantly. Gorelik et al (43) reported that folate intake did not differ between CHF patients and control subjects. Regarding vitamin B-12, one study showed a lower left ventricular EF among vitamin B-12–deficient patients (44). However, the significance of this effect was weak and the sample size was much smaller than in the present study.

Contrary to current concepts, we observed missing or paradoxical relations between B vitamin status, NYHA class, NT-proBNP, and EF, which suggests that tHcy, not B vitamins, is probably the pathomechanistically active component. However, what could be the reason for the missing or paradoxical relations of B vitamins with the clinical status of CHF? The vitamin B-12 status strongly depends on hepatic function (21–24). Vitamin B-12 concentrations in persons with a disturbance in hepatic homeostasis may be falsely high because of metabolically inactive cobalamin analogues that contaminate vitamin B-12 measurement (22, 24, 24). Moreover, folate utilization strongly depends on the availability of vitamin B-12. A reduced availability of active vitamin B-12 could depress folate utilization and result in a folate trap (25, 26). Because it is known that CHF may cause congestion of blood into the liver (27), we analyzed ALAT, ASAT, gGT, and CRP in relation to vitamin B 12. ASAT, ALAT, and gGT were significantly higher in subjects with vitamin B-12 concentrations above the median, which indicates a slight disturbance in hepatic cell integrity. Subsequently, we introduced vitamin B-12 as a dependent variable in a multivariate regression model (Table 3). In this regression analysis, ASAT was the strongest predictor of vitamin B-12, which confirmed that higher vitamin B-12 concentrations are possibly associated with a disturbance in hepatic cell integrity. We then included ASAT as a dependent variable in the same regression model (Table 3), which yielded NT-proBNP as the strongest predictor. On the basis of these analyses, it can be hypothesized that CHF causes a mild liver congestion that causes a disturbance in hepatic cell integrity and induces a release of hepatic vitamin B-12. Such a "cardiohepatic syndrome" could partially explain the missing or paradoxical relations between B vitamins and the severity of CHF.

The clinical effect of our results is not fully clear. Additional studies should analyze whether elevated tHcy concentrations in CHF patients are associated with a faster progression of the disease and a worse clinical outcome. If our hypothesis of a cardiohepatic syndrome in CHF patients is true, tHcy-lowering therapy with folate and vitamin B-12 might still be a promising therapeutic option that could help to reduce the progression of the disease and improve the clinical outcome. Preliminary data from our own pilot study suggest that folate supplementation can possibly lower elevated NT-proBNP (45). Moreover, Witte et al (46) recently reported a 13% reduction in left ventricular volume and a 5% increase in EF after 9 mo of high-dose micronutrient supplementation (including folate, vitamin B-12, and vitamin B-6) in CHF patients. However, an evidence-based recommendation to supplement CHF patients with B vitamins is not justified at the moment.

Conclusion

In conclusion, the present study showed that plasma tHcy is related to clinical, functional, and laboratory variables of CHF, which suggests a relation between tHcy and the clinical status of CHF patients. The observed effects are significantly stronger in patients without CAD, which argues against an exclusive atherogenic action of tHcy on vessel and indicates direct effects of tHcy on the myocardium. Folate and vitamin B-12 are not or paradoxically associated with CHF. Consequently, tHcy—and not B vitamins—is the active compound in CHF. The unexpected observations regarding folate and vitamin B-12 are possibly due a cardiohepatic syndrome in CHF. Future studies will be needed to clarify the mechanistic role of tHcy and B vitamins in CHF. Moreover, the effects of a tHcy-lowering treatment by B vitamin supplementation on the incidence of CHF and the progression of the disease should be investigated.

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MH was responsible for the conception and design of the study, analysis and interpretation of the data, draft of the manuscript, and final approval of the manuscript. SM was responsible for the conception and design of the study and analysis and interpretation of the data. IK was responsible for the conception and design of the study, analysis and interpretation of the data, and critical revision of the manuscript for important intellectual content. LG was responsible for the conception and design of the study and analysis and interpretation of the data. JK was responsible for the analysis and interpretation of the data. MB and WH were responsible for the conception and design of the study, analysis and interpretation of the data, critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted.

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