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Low Vitamin D Status: A Contributing Factor in the Pathogenesis of Congestive Heart Failure?

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OBJECTIVES This study was designed to evaluate the association between vitamin D status and congestive heart failure (CHF).

BACKGROUND Impaired intracellular calcium metabolism is an important factor in the pathogenesis of CHF. The etiology of CHF, however, is not well understood.

METHODS Twenty patients age <50 years and 34 patients age ≥50 years with New York Heart Association classes ≥2 and 34 control subjects age ≥50 years were recruited. N-terminal pro-atrial natriuretic peptide (NT-proANP), a predictor of CHF severity; vitamin D metabolites; and parameters of calcium metabolism were measured in fasting blood samples collected between November 2000 and March 2001.

RESULTS Both groups of CHF patients had markedly increased serum levels of NT-proANP ($p < 0.001$), increased serum phosphorus levels ($p < 0.001$), and reduced circulating levels of both 25-hydroxyvitamin D ($p < 0.001$) and calcitriol ($p < 0.001$). Albumin-corrected calcium levels were reduced and parathyroid hormone levels were increased in the younger CHF patients compared with the controls (both p values <0.001). Moreover, parathyroid hormone levels tended to be higher in the elderly CHF patients than in the controls ($p = 0.074$). In a nonlinear regression analysis 25-hydroxyvitamin D and calcitriol were inversely correlated with NT-proANP ($r^2 = 0.16$; $p < 0.001$ and $r^2 = 0.12$; $p < 0.01$, respectively). The vitamin D genotype at the BmsI restriction site did not differ between the study groups.

CONCLUSIONS The low vitamin D status can explain alterations in mineral metabolism as well as myocardial dysfunction in the CHF patients, and it may therefore be a contributing factor in the pathogenesis of CHF. (J Am Coll Cardiol 2003;41:105–12) © 2003 by the American College of Cardiology Foundation

Congestive heart failure (CHF) is a cardiac dysfunction syndrome characterized by a reduced left ventricular ejection fraction (LVEF) in association with water and sodium retention. Muscle weakness and early fatigue are the two major symptoms of CHF patients. The prevalence of CHF is approximately 1% to 3% in Western societies (1,2). Morbidity and mortality of CHF increase progressively with age (3,4).

The etiology of CHF is not well understood. Obviously, an altered intracellular handling of ionized calcium (Ca^{2+}) seems to play an important role in the impaired contractility of the myocardium (5). In isolated myocytes from patients with terminal heart failure, systolic Ca^{2+} transients were found to be markedly reduced, diastolic Ca^{2+} levels were increased, and the rate of diastolic decay of Ca^{2+} was slowed compared with heart cells from healthy subjects (6). Consequently, digitalis and beta-blockers are frequently used medications for secondary prevention. They are able to improve contractility by increasing myocardial intracellular Ca^{2+} levels (7) and by improving intracellular Ca^{2+} utilization (8).

In a recent observational study in patients with severe CHF, both vitamin D deficiency and hyperparathyroidism were common findings (9). Interestingly, vitamin D plays a pivotal role in cardiac function. Cardiac muscle cells possess a vitamin D receptor and a calcitriol-dependent Ca^{2+} binding protein (10,11). Moreover, a calcitriol-mediated rapid activation of voltage-dependent Ca^{2+} channels exists in cardiac muscle cells (12). Consequently, calcitriol administration can normalize the impaired contractility of the myocardium that is observed under experimental vitamin D deficiency (13,14). Calcitriol also suppresses synthesis and secretion of the atrial natriuretic peptide (ANP) in cardiac muscle cells (15). Circulating levels of the N-terminal pro-ANP (NT-proANP) are massively increased in CHF patients and are thus a predictor of disease severity (16).

On the basis of these preliminary data, it can be hypothesized that low circulating levels of vitamin D metabolites are contributing to the pathogenesis and/or the symptomatology of CHF. To support this postulate, we performed a case-control study in younger and older CHF patients.

METHODS

Participants and study design. Fifty-four patients admitted for investigation or treatment of CHF were recruited at the Heart and Diabetes Center North Rhine-Westfalia

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Abbreviations and Acronyms

Ca^{2+}	= ionized calcium
CHF	= congestive heart failure
CI	= cardiac index
LVEF	= left ventricular ejection fraction
NT-proANP	= N-terminal pro-ANP
NYHA	= New York Heart Association
25OHD	= 25-hydroxyvitamin D
PCWP	= pulmonary wedge pressure
PTH	= parathyroid hormone
TNF	= tumor necrosis factor
UV	= ultraviolet
VDR	= vitamin D receptor

(geographic latitude: 52°N) between November 2000 and March 2001. Patients were ambulatory or hospitalized for not longer than two days. They were classified by New York Heart Association (NYHA) functional class according to their cardiac symptoms. Only patients with NYHA classes ≥2 were included. Moreover, LVEF was determined by echocardiogram. Cardiac index (CI) and pulmonary wedge pressure (PCWP) were assessed using right ventricular cardiac catheterization. Left ventricular ejection fraction values <35%, CI values >2 l/min/m^2, and PCWP values >20 mm Hg are regarded as clinically unfavorable. Patients were then divided into group I (<50 years; n = 20) and group II (≥50 years; n = 34) to evaluate possible age-related effects. Control group III consisted of 34 elderly (≥50 years) free-living subjects. Exercise capacity was assessed by a questionnaire based on NYHA functional classification (17). Subjects were recruited between November 2000 and March 2001 by an advertisement in several senior groups in Bonn, Germany (geographic latitude 51°N). Participants of group III were matched for gender, age, and body mass index with group II (Table 1). All control subjects had an unlimited exercise capacity (NYHA class <2). Exclusion criteria were serum creatinine level >2 mg/dl, serum aspartate aminotransferase level >35 U/l, therapy with glucocorticoids or anticonvulsants, and intake of vitamin D supplements (hospital document/questionnaire).

One blood sample was obtained from the antecubital vein of each subject after a 12-h overnight fast. Aliquots of whole blood, plasma, and serum were frozen consecutively at −20°C until analysis. All participants gave written informed consent to the study, which was approved by the Ethics Committee of the University of Bonn.

Biochemical analysis. Blood hormone and cytokine analyses are summarized in Table 2. Serum Ca^{2+} and phosphorus as well as serum albumin concentrations were assessed using atomic absorption spectrometry (Ca^{2+}) and colorimetric test kits (phosphorus and albumin; BioMerieux, Nürtingen, Germany), respectively. Coefficients of variation were below 2.5%. Total serum Ca^{2+} was corrected with ±0.32 mg for each 0.5 mg deviation of concomitant serum albumin from a normal mean of 4.14 mg (18). Vitamin D binding protein was measured by single radial immunodiffusion (coefficient of variation = 10.8%; Immundiagnostik, Bensheim, Germany). Serum creatinine was determined enzymatically (test kit: Boehringer, Mannheim, Germany). Creatinine clearance (ml/min) was estimated according to the Crockroft-Gault formula (19):

$$\frac{(140 - \text{age} \times (\text{wt kg})}{72 \times \text{serum creatinine (mg/dl)}}$$

Table 1. Characteristics of the Study Groups

	CHF Patients <50 years (n = 20)	CHF Patients ≥50 years (n = 34)	Controls ≥50 years (n = 34)
Age (yrs)	38.9 ± 7.9	64.1 ± 6.4	68.9 ± 5.2
Male (%)	60.0	61.8	61.8
BMI (kg/m^2)	26.3 ± 5.1	25.6 ± 3.8	25.1 ± 2.9
Coronary heart disease (%)	15	44.1	0
Hypertension (%)	0	32.4	41.2
Diabetes (%)	10	23.5	2.9
Drug therapy (%)			
Digitalis	60	68	0
Beta-blocker	75	65	5
Vasodilators (including ACE inhibitors)	85	81	11
Diuretics*	85	100	9
Loop diuretics	65	100	0
Thiazide diuretics	40	41	9
Aldosterone antagonists	80	77	0
LVEF (%)	33.9 ± 17.5	29.8 ± 11.1	n.d.
CI (l/min/m^2)	2.17 ± 0.51	2.04 ± 0.52	n.d.
PCWP (mm Hg)	22.0 ± 8.4	20.6 ± 8.5	n.d.
Aspartate-aminotransferase (U/l)	10.2 ± 6.5	10.9 ± 4.8	11.9 ± 5.9
Creatinine (mg/dL)	0.98 ± 0.26	1.06 ± 0.36	0.90 ± 0.24

Several patients were taking different kinds of diuretics; n.d. = not determined
ACE = angiotensin-converting enzyme; BMI = body mass index; CHF = congestive heart failure; CI = cardiac index; LVEF = left ventricular ejection fraction; PCWP = pulmonal capillary wedge pressure.

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Table 2. Blood Hormone and Cytokine Analyses

Parameter	Method	Interassay CV	Normal Range	Manufacturer
25-hydroxyvitamin D	RIA	11.0% (n = 40)	50–200 nmol/l	DiaSorin, Stillwater, Minnesota
Calcitriol*	Solid-phase extraction/ ELISA	9.0% (n = 20)	37–137 pmol/l	Immundiagnostik, Bensheim, Germany
Intact parathyroid hormone*	ELISA	7.9% (n = 8)	10–60 pg/ml	DRG Diagnostics, Marburg, Germany
N-terminal propeptide of atrial natriutrtic peptide†	RIA	8.5% (n = 20)	0.11–0.60 mmol/l	Biotop Oy, Oulu, Finland
Tumor necrosis factor alpha[3]	ELISA	7.6% (n = 15)	0–20 pg/ml‡	DRG Diagnostics, Marburg, Germany

*Serum samples; †plasma samples; ‡mean values 6 pg/ml.
CV = coefficient of variation; ELISA = enzyme-linked immunosorbent assay; RIA = radioimmunoassay.

Results were reduced by 15% to calculate the creatinine clearance of female subjects.

The restriction fragment length polymorphism for the vitamin D receptor (VDR) gene at the BsmI site was measured with the polymerase chain reaction by using the method and primers described by Morrison et al. (20). The presence of a polymorphic restriction site was designated as b, whereas the absence of this site was designated as B.

Statistics. All statistical evaluations were performed with the Statistical Package for Social Sciences (SPSS), version 10 (Chicago, Illinois). Normal distribution of the data was tested by the Kolmogorov-Smirnov test. Normal distribution was considered if p values were above 0.05. Data were then evaluated using an analysis of variance (ANOVA) (normal distributed data) or by the Kruskall-Wallis test (non-normal data; serum parathyroid hormone, PTH). In the case of significant differences between subgroups, post hoc analyses were based on the Tukey test (normal distributed data) or on the Mann/Whitney U-test. The chi-square test was used to test differences in the genotype of the vitamin D receptor between the study groups. Pearson's correlation coefficient r (normal distributed data), Spearman's rank correlation coefficient r_s (non-normal data), and nonlinear regression analyses were used to assess interrelationships. A p value <0.05 (two-tailed test) was considered statistically significant. Data are expressed as mean ± SD.

RESULTS

Serum levels of 25-hydroxyvitamin D (25OHD), calcitriol (Fig. 1), Ca^{2+}, Ca^{2+}C, phosphorus, and PTH (Table 3) revealed highly significant differences between the study groups (ANOVA; all p values <0.001).

Concentration of 25OHD was lower in both patient groups compared with the elderly control group (Fig. 1). Moreover, both groups of CHF patients had lower serum calcitriol levels, lower serum Ca^{2+} levels, and higher phosphorus levels than the controls (Fig. 1, Table 3). Reduced albumin-corrected serum Ca^{2+}levels were, however, observed only in the younger CHF patients. Serum PTH levels were significantly increased in the younger CHF patients compared with the controls, whereas PTH concentrations tended to be higher ($p = 0.074$) only in the elderly CHF patients compared with the controls. Two of the 34 elderly CHF patients and nine out of the 20 younger CHF patients, but none of the controls, had hypocalcemia (serum $Ca^{2+} < 8$ mg/dl). Serum vitamin D binding globulin levels were similar in all groups studied. Patients with CHF and controls did not differ in the distribution of the genotype for the VDR gene at the BsmI site (Table 3).

Both age groups of CHF patients had markedly higher plasma levels of NT-proANP than controls (Fig. 2). Even in the control subjects, however, the NT-proANP levels of 0.96 ± 0.37 nmol/l were slightly higher than the normal values published for healthy adults (0.11 to 0.60 nmol/l, ages 20 to 55 years). Mean serum albumin levels were significantly lower in the CHF patients compared with the controls, but they were still in the normal range of 4.0 to 5.4 g/dl (Table 3). Tumor necrosis factor (TNF)-alpha was significantly increased in the elderly patient group compared with their age-matched controls ($p < 0.001$). The TNF-alpha levels of the younger patients did not differ from the elderly controls. The levels were, however, markedly higher than the generally accepted mean normal concentrations of 6 pg/ml for healthy middle-aged subjects. Creatinine clearance was highest in the young CHF patients (Table 3).

Calcitriol was correlated with albumin-corrected Ca^{2+} ($r = +0.48$; $p < 0.001$) and was inversely related to PTH ($r_s = -0.22$; $p < 0.05$). Concentration of 25OHD was correlated with albumin ($r = +0.24$; $p < 0.05$) and vitamin D binding globulin ($r = +0.28$; $p < 0.025$) and was inversely related to PTH ($r_s = -0.45$; $p < 0.001$), phosphorus ($r = -0.33$; $p < 0.01$), and TNF-alpha ($r = -0.25$; $p < 0.025$). Circulating levels of NT-proANP showed a nonlinear correlation with 25OHD (Fig. 3), TNF-alpha ($r^2 = 0.27$, $p < 0.001$; regression equation: NT-proANP = $-1.8 \cdot \text{TNF-alpha}^{1.258}$), and calcitriol ($r^2 = 0.12$, $p < 0.01$; regression equation: NT-proANP = $4.372 \cdot \text{calcitriol}^{-0.769}$). Data in Figure 3 indicate that 25OHD levels above 40 ng/ml would be necessary to reduce NT-proANP levels of almost all subjects close to the normal range of 0.11 to 0.60 nmol/l.

DISCUSSION

This study could demonstrate that reduced circulating levels of 25OHD and also reduced calcitriol concentrations (Fig. 1) are a typical feature in CHF patients. The associated increase of serum phosphorus and PTH as well as the reduced serum Ca^{2+} levels of the CHF patients (Table 3)

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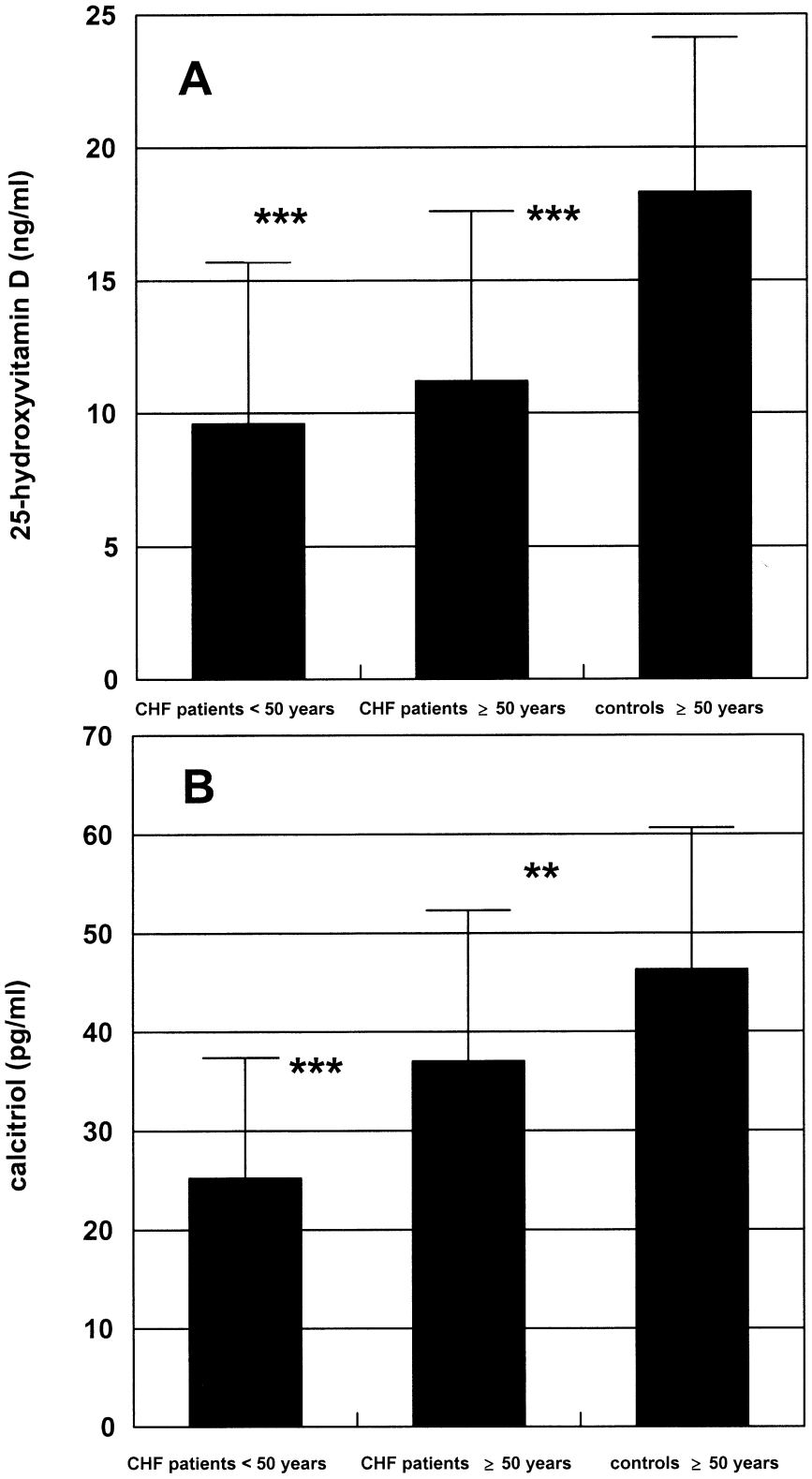

Figure 1. Circulating concentrations (mean ± SD) of 25-hydoxyvitamin D **(A)** and calcitriol **(B)** in congestive heart failure (CHF) patients and in elderly healthy controls (≥50 years). Main effects of study groups were observed (analysis of variance; $p < 0.001$). ***Significant differences between CHF patients and elderly controls, $p < 0.001$ (post hoc Tukey test); **Significant difference between CHF patients and elderly controls, $p < 0.025$ (post hoc Tukey test).

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Table 3. Biochemical Parameters and Vitamin D Receptor Genotype of Patients With Congestive Heart Failure and of Elderly Controls

	CHF Patients <50 years (n = 20)	CHF Patients ≥50 years (n = 34)	Controls ≥50 years (n = 34)
Albumin (g/dl)	4.61 ± 0.65	4.39 ± 0.58†	5.02 ± 0.30
Intact PTH (pg/ml)	69.3 ± 53.6†	54.6 ± 64.0‡	31.4 ± 43.1
Ca^{2+} (mg/dl)	7.96 ± 0.76†	8.72 ± 0.72§	9.16 ± 0.64
Ca^{2+}C (mg/dl)	7.72 ± 0.64†	8.56 ± 0.64	8.64 ± 0.72
Phosphorus (mg/dl)	4.38 ± 1.02†	4.14 ± 1.02†	3.49 ± 0.46
DBP (mg/dl)	55.6 ± 12.2	54.8 ± 13.1	59.7 ± 13.5
TNF-alpha (pg/ml)	17.5 ± 11.7	20.6 ± 9.1†	14.0 ± 6.3
Creatinine clearance (ml/min)	118 ± 45†	77 ± 29	83 ± 32
VDR genotype (BB/Bb/bb in %)	35/55/10	26.5/56/17.5	41/41/18

Main effects of study groups were observed for albumin, Ca^{2+}, Ca^{2+}C, phosphorus, and creatinine clearance (analysis of variance [analysis of variance]; all p values < 0.001), for TNF-alpha (analysis of variance; $p < 0.025$) and for parathyroid hormone (Kruskall Wallis test; $p < 0.001$). †Significant differences between CHF patients and elderly controls, $p < 0.001$ (post hoc Tukey test or Mann Whitney *U* test); ‡borderline significance compared to elderly controls ($p = 0.074$); §significant differences between CHF patients and elderly controls, $p < 0.025$ (post hoc Tukey test or Mann Whitney *U* test).

Ca^{2+} = calcium; Ca^{2+}C = albumin corrected calcium; CHF = congestive heart failure; DBP = vitamin D binding globulin; PTH = parathyroid hormone; TNF = tumor necrosis factor; VDR = vitamin D receptor.

can be seen as a consequence of the low vitamin D status (21). The differences in circulating levels of NT-proANP (Fig. 2) confirm the classification of patients and controls by NYHA functional classes (16).

We measured serum Ca^{2+} levels by atomic absorption spectrometry, which is regarded as the gold standard. Moreover, our study design allowed samples batching, and the fasting blood drawing guaranteed that serum Ca^{2+} concentrations were unaffected by dietary Ca^{2+} intake. Because sufficient amounts of extracellular activator Ca^{2+} are mandatory for the first step in myocardial contraction (22), adequate influx of activator Ca^{2+} is questionable in the young CHF patients with low serum levels of albumin-corrected Ca^{2+} (Table 3). In addition, the low calcitriol levels of the young *and* of the elderly CHF patients (Fig. 1) might also impair calcitriol-dependent intracellular genomic actions, such as Ca^{2+} binding protein synthesis (10), and non-genomic actions of Ca^{2+} metabolism, such as calcitriol-dependent activation of adenylate cyclase (23,24). Low adenylat cyclase activity can result in an impaired extracellular Ca^{2+} influx (2,25), decreased Ca^{2+} re-uptake into the sarcoplasmic reticulum (26), and reduced Ca^{2+}

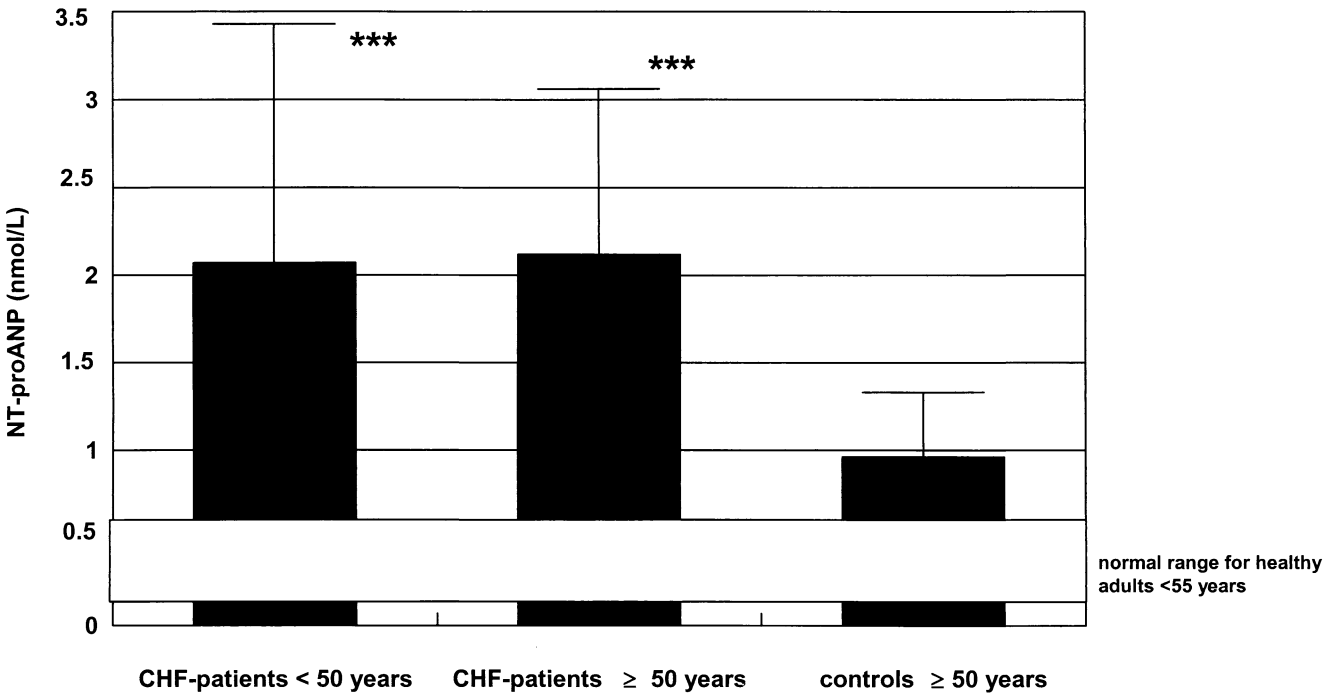

Figure 2. Blood concentrations (mean ± SD) of N-terminal pro-atrial natriuretic peptide (NT-proANP) in congestive heart failure (CHF) patients and in elderly healthy controls (≥50 years). Main effects of study groups were observed (analysis of variance; $p < 0.001$). ***Significant differences between CHF patients and elderly controls, $p < 0.001$ (post hoc Tukey test).

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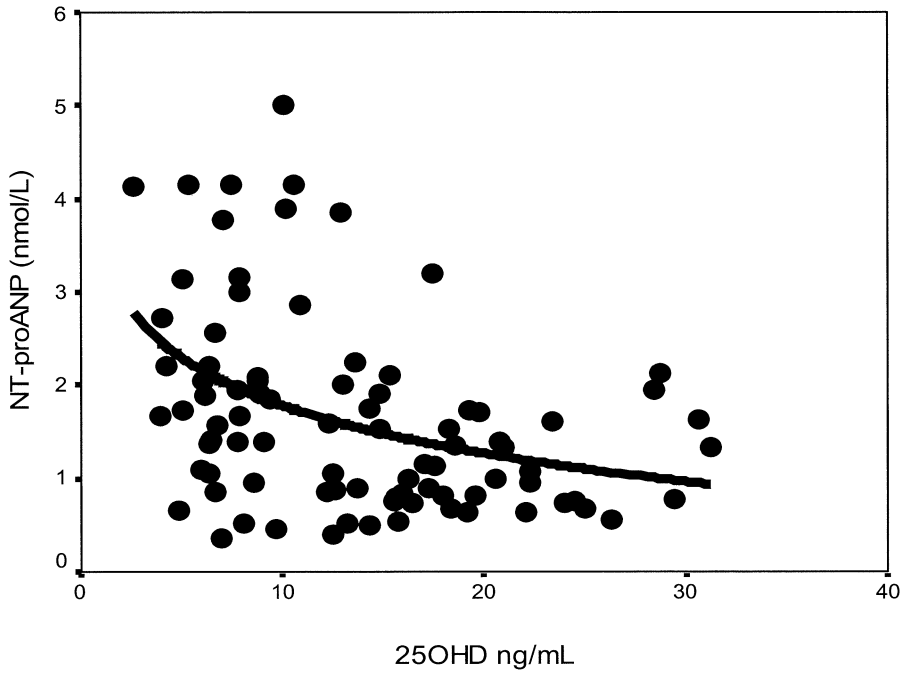

Figure 3. Association between serum N-terminal pro-atrial natriuretic peptide (NT-proANP) and serum 25-hydroxyvitamin D values ($r^2 = 0.16$; $p < 0.001$; regression equation: NT-proANP $4.14 \cdot 25OHD^{-0.741}$).

liberation from the sarcoplasmic reticulum (27). The latter alteration is considered an important pathogenic factor of the impaired contractility in cardiomyopathy (6,28).

The pathogenesis of low calcitriol levels in CHF patients is uncertain. Some earlier studies brought evidence forward that reduced serum calcitriol levels are the result of low circulating 25OHD levels (29,30). It has recently been suggested that TNF-alpha may also suppress calcitriol synthesis (31). We found an inverse association of TNF-alpha with 25OHD (results section), indicating that low 25OHD levels are involved in activation of the TNF-alpha system. Because the creatinine clearance was highest in the young CHF patients (Table 3), it seems rather unlikely that an impaired kidney function was responsible for a reduced renal 1-alpha hydroxylation of 25OHD in the CHF patients compared with the controls.

25OHD has several independent effects on muscle cells. Uptake of $^{45}Ca^{2+}$into cultured cardiac muscle cells is increased by physiologic concentrations of 25OHD (32). The 25OHD activity in cardiac muscle cells is on a molar basis 222 times lower than that of calcitriol (32). However, at serum concentrations of the two metabolites as those found in our study groups (Fig. 1), these relative molar potencies indicate that from 58% to 64% of the circulating vitamin D activity is contributed by 25OHD. On the basis of the molar potencies of 25OHD and calcitriol and the serum concentrations of the two vitamin D metabolites, the circulating vitamin D activity is 68% in the elderly CHF patients and only 54% in the younger CHF patients compared with the control subjects. Moreover, intracellular Ca^{2+} re-uptake into the sarcoplasmic reticulum is reduced in experimental vitamin D deficiency (33), which is obviously not mediated by calcitriol but probably by 25OHD (27). In addition, intracellular accumulation of phosphate by muscle might be directly increased by 25OHD (34), an effect that may be blunted in the case of low circulating 25OHD levels.

We cannot definitively rule out that diuretic therapy of CHF patients (Table 1) has contributed to the low serum Ca^{2+} levels. A renal Ca^{2+} leak should, however, result in an increased serum calcitriol level. Moreover, some case reports of patients with untreated rickets and with untreated osteomalacia suffering from heart failure (35–37) support our hypothesis that low serum levels of vitamin D metabolites might be an important cause of the reduced serum Ca^{2+} levels and of the cardiac dysfunction. In these earlier case reports a rapid normalization of the hypocalcemia and cardiac symptoms was observed after therapy with Ca^{2+} and vitamin D (metabolites), and in combination with the administration of diuretics such as furosemide and spironolactone (35–37). The inverse nonlinear correlation of 25OHD and calcitriol with NT-proANP (Fig. 3 and Results section) support our hypothesis that the severity of CHF is increased at low serum levels of vitamin D metabolites.

In Europe, circulating levels of 25OHD largely depend on exposure to ultraviolet (UV) light, namely UV B light (38). Normally, serum 25OHD decreases with age (36) because the capability of the skin to produce previtamin D after UV B irradiation declines with age (39). It is thus an unexpected finding that even in the younger CHF patients the vitamin D status is lower than in elderly controls. From the inclusion criteria of our study we can rule out an impaired liver function of the CHF patients (Methods

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section). Possible explanations for the low circulating 25OHD levels may thus be a genetic abnormality of the hepatic 25-hydroxylase activity, an increased 25OHD catabolism, or an insufficient UV B exposure and/or inadequate dietary vitamin D intake. In this context, it may well be that a disease-related reduction in outdoor activity contributes to the low vitamin D status. Granted the pivotal role of an adequate vitamin D status for the systemic and myocardial Ca^{2+} metabolism, the CHF patients might enter into a circulus vitiosus.

There is growing evidence that circulating 25OHD levels >40 ng/ml are necessary to achieve full physiologic vitamin D actions (40,41). The inverse association between NT-proANP and 25OHD in our study groups (Fig. 3) supports this earlier assumption. Not all subjects with relatively low 25OHD levels, however, had high NT-proANP levels (Fig. 3). Thus, additional factors might increase susceptibility to CHF.

Vitamin D acts through the highly specific vitamin D receptor. The mechanisms by which the receptor protein mediates the cellular vitamin D actions are a subject of intense research. In other vitamin-D-related diseases such as osteoporosis and diabetes mellitus, the genotype of the vitamin D receptor at the BmsI restriction site was associated with disease prevalence (20,42). There is, however, obviously no relationship between the vitamin D genotype at the BmsI restriction site and susceptibility to CHF (Table 3).

Our data of alterations in circulating vitamin D metabolites and in systemic mineral metabolism in CHF patients (Fig. 1 and Table 3) and the cellular alterations in Ca^{2+}metabolism found by others (6) are very similar to those observed in essential hypertension (43). Therapy of hypertension has successfully been performed by increasing circulating 25OHD levels through UV B irradiation (44) or by oral vitamin D supplementation (45). Consequently, a clear rationale for interventional trials with vitamin D in combination with a Ca^{2+}supplement in chronic CHF would exist.

In conclusion, this case-control study provides evidence for an association between a low vitamin D status and CHF severity. Moreover, data encourage future investigations on the relationship between vitamin D status and the early onset of CHF observed in the subgroup of young patients.

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