Heart Failure

Ursodeoxycholic Acid in Patients With Chronic Heart Failure

A Double-Blind, Randomized, Placebo-Controlled, Crossover Trial

Stephan von Haehling, MD, PhD,† Joerg C. Schefold, MD,‡ Ewa A. Jankowska, MD, PhD,§ Jochen Springer, MD,¶ Ali Vazir, MBBS, PhD,# Paul R. Kalra, MD,**, Anja Sandek, MD,* Günter Fauler, MD,† Tatjana Stojakovic, MD,† Michael Trauner, MD,** Piotr Ponikowski, MD, PhD,§ Hans-Dieter Volk, MD, PhD,§¶ Wolfram Doehner, MD, PhD,*¶¶ Andrew J. S. Coats, DM,¶ Philip A. Poole-Wilson, MD,# Stefan D. Anker, MD, PhD## Berlin, Germany; Wroclaw, Poland; London, Norwich, and Portsmouth, United Kingdom; Graz and Vienna, Austria; and Rome, Italy

Objectives

This study sought to assess the effects of ursodeoxycholic acid (UDCA) on endothelial function and inflammatory markers in patients with chronic heart failure (CHF).

Background

Endothelial dysfunction is commonly observed in patients with CHF, and it contributes to the limitation in exercise capacity that accompanies this condition. Bacterial lipopolysaccharide may trigger proinflammatory cytokine release and promote further endothelial dysfunction. UDCA, a bile acid used in the treatment of cholestatic liver disease, has anti-inflammatory and cytoprotective properties and may contribute to the formation of mixed micelles around lipopolysaccharide. These properties may help to improve peripheral blood flow in patients with CHF.

Methods

We performed a prospective, single-center, double-blind, randomized, placebo-controlled crossover study of UDCA in 17 clinically stable male patients with CHF (New York Heart Association functional class II/III, left ventricular ejection fraction <45%). Patients received in random order 500 mg UDCA twice daily for 4 weeks and placebo for another 4 weeks. The primary endpoint was post-ischemic peak peripheral arm blood flow as assessed by strain-gauge plethysmography.

Results

Sixteen patients completed the study. UDCA was well tolerated in all patients. Compared with placebo, UDCA improved peak post-ischemic blood flow in the arm (+18%, p = 0.038), and a trend for improved peak post-ischemic blood flow in the leg was found (+17%, p = 0.079). Liver function improved: compared with placebo, levels of y-glutamyl transferase, aspartate transaminase, and soluble tumor necrosis factor alpha receptor 1 were lower after treatment with UDCA than after placebo (all p < 0.05). There was no change in 6-min walk test or New York Heart Association functional class, and levels of tumor necrosis factor and interleukin-6 were unchanged or increased compared with placebo.

Conclusions

UDCA is well tolerated in patients with CHF. UDCA improves peripheral blood flow and is associated with improved markers of liver function. (Ursodeoxycholic Acid in Chronic Heart Failure; NCT00285597) (J Am Coll Cardiol 2012;59:585–92) © 2012 by the American College of Cardiology Foundation
The pathophysiology of heart failure is not merely restricted to pump failure; marked abnormalities of the musculoskeletal, renal, neuroendocrine, and immune systems are seen (1). Endothelial dysfunction is a key aspect of chronic heart failure (CHF) that contributes to the patient's clinical symptoms (2) and may thus have direct effects on quality of life. Proinflammatory cytokines are involved in endothelial dysfunction (1), disease progression, and the development of muscle wasting (3,4). Tumor necrosis factor (TNF)-α appears to be the most important cytokine in this context. However, therapeutic approaches to block the overproduction of TNF-α using specific antibodies have largely failed (5–7).

**Materials and Methods**

**Patient recruitment and endpoints.** We prospectively studied 17 clinically stable patients with CHF who were recruited from the Royal Brompton Hospital specialist heart failure clinic (London, United Kingdom) with a diagnosis of CHF according to then current guidelines of the European Society of Cardiology (17) and a left ventricular ejection fraction <45%. The etiology of heart failure was coronary artery disease or diastolic cardiomyopathy. Subjects with exertional angina, signs of peripheral or pulmonary edema, clinical signs of infection, severe neuromuscular disease, rheumatoid arthritis, significant renal dysfunction (serum creatinine >250 μmol/l), or cancer were excluded. We also excluded patients younger than 18 years of age and those with a history of unstable angina, myocardial infarction, or stroke within 3 months before the study.

The study was of a crossover design, randomized, placebo-controlled and double-blind. None of the investigators involved in clinical and laboratory assessments were aware of the patients' treatment allocation at any time during the study. The study design is depicted in Figure 1. After baseline assessment, patients were randomly assigned to either therapy with UDCA (500 mg twice daily) or matching placebo for 4 weeks. This treatment period was followed by a washout period of another 4 weeks during which the patients did not receive any study medication. Finally, patients underwent another 4 weeks of treatment during which each patient received the opposite treatment. Assessments of all parameters were performed at baseline and after each of the 2 treatment periods (UDCA and placebo). UDCA capsules and matching placebo were donated as an unrestricted grant from the manufacturer (Dr. Falk Pharma GmbH, Freiburg, Germany). The manufac-

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One hypothesis holds that proinflammatory cytokine activation is a consequence of altered gut wall morphology and barrier function (8,9). Thus, endotoxin, otherwise known as lipopolysaccharide (LPS), a cell-wall component from gram-negative bacteria, may enter the circulation either through the edematous gut wall during periods of heart failure decompensation or simply as a consequence of an altered intestinal morphology (1). The inhibition of LPS might be clinically more meaningful than targeting single downstream cytokines (9,10). Ursodeoxycholic acid (UDCA), a bile acid used in patients with cholestatic liver diseases, is an interesting candidate in this respect because it appears to be able to form mixed micelles around LPS leading to its detoxification (11,12). UDCA is a physiologic constituent of human bile that has been used in cholestatic liver disease such as primary biliary cirrhosis (13). The drug has been on the market in Japan since the 1950s and in Western countries since the mid-1980s (14). Its structure was first elucidated in 1936 by Iwasaki (15). In the 1970s, it became clear that UDCA is able to dissolve gallstones (16).

We hypothesized that short-term administration of UDCA to patients with CHF would yield improvements in peripheral blood flow as a consequence of decreases in proinflammatory cytokines. We performed a randomized, placebo-controlled, double-blind, crossover trial of UDCA in stable CHF patients.
urer had no role in the design or in the conduct of the trial and was not involved in the analysis of the data.

The primary endpoint of the study was post-ischemic peak arm blood flow after UDCA treatment versus placebo. Secondary endpoints included changes in post-ischemic peak leg blood flow, New York Heart Association (NYHA) functional class and 6-min walk test as well as cellular markers of immune function, serum levels of proinflammatory cytokines, and LPS-stimulated cytokine production. Previous randomized trials had shown that a dose of 10 to 15 mg/kg/day (mean dose 1,018 mg/day) is safe and effective in reducing rejection rates in patients undergoing liver transplantation (18–20). The dose used in our study reflects this earlier experience. The local ethics committee approved the study, and all subjects gave written informed consent.

**Blood collection and cytokine assessments.** Citrated venous blood was collected early in the morning from an antecubital vein after the patient rested in the supine position for 15 min and processed within 1 h. After blood collection, serum samples were immediately centrifuged and stored at −80°C until final analysis. Serum levels of interleukin-6, TNF-α, and soluble tumor necrosis factor-α receptor 1 (sTNFR-1) were determined using commercially available high-sensitivity enzyme-linked immunosorbent assay kits (Quantikine HS, R&D Systems, Minneapolis, Minnesota). The lower limits of detection are 0.039 pg/ml, 0.106 pg/ml, and 7.8 pg/ml, respectively.

Whole blood 1-ml aliquots diluted 1:1 with RPMI 1640 supplemented with 10 U/ml heparin were placed in 1.5-ml Eppendorf tubes. *Escherichia coli*–derived endotoxin (serotype 0111:B4) was added to achieve final concentrations of 0.1, 1, 10, and 100 ng/ml. Dilutions, aliquoting, and stimulations were performed under sterile conditions. A nonstimulated sample served as control. Whole blood samples were incubated for 6 h in a humidified atmosphere (37°C, 5% CO₂). After incubation, the samples were centrifuged at 1,500 rpm for 5 min. The supernatants were harvested and stored at −80°C until final assessment. Cell viability was >90% as assessed using trypan blue exclusion. Concentrations of TNF-α in cell culture supernatant were measured by standard enzyme-linked immunosorbent assay kits (R&D Systems) according to the manufacturer’s instructions. The lower limits of detection were 15 pg/ml. All samples were frozen at −80°C until analysis. All samples were analyzed in duplicate and thawed only once for immediate analysis.

**Assessment of bile acids from serum.** All bile acids (cholic acid, deoxycholic acid, chenodeoxycholic acid, lithocholic acid, UDCA) were assessed as unconjugated acids and as taurine and glycine conjugates using a tandem mass spectrometry method as described previously (21). All subfractions of the bile acids (free acids and their corresponding conjugates) were analyzed by 3 different multiple–reaction monitoring experiments within 1 high-performance liquid chromatography run. High-performance liquid chromatography was performed on a reversed-phase (C18) column that used a methanol/water gradient for chromatographic solution of isobaric bile acids. Quantitation was done by the use of deuterated internal standards and correlation of peak area ratios in linear regression.

**Blood flow assessment.** We used strain-gauge venous occlusion plethysmography (EC4, D.E. Hokanson, Inc., Bellevue, Washington) to assess arm and leg blood flow (provided in ml × 100 ml⁻¹ × min⁻¹), as described previously (22). This technique involves tying a strain gauge, a thin, stretchable, mercury-filled elastic tube, around the entire circumference of the limb. Because all patients enrolled in the study were right-handed, all measurements were performed at the largest part of the patient’s right arm or right leg, respectively. Resting blood flow was assessed after 15 min of rest in the supine position with the right leg comfortably rested and slightly elevated. Stimulated peak blood flow during reactive hyperemia was assessed immediately after relief from 3 min of total ischemia, which was induced by external compression of the respective limb using an inflatable cuff 30 mm Hg above systolic blood pressure. Thereafter, blood flow was measured in 10-s intervals for 2 min. The flow rate was recorded with a plethysmograph. The highest flow results were considered to be the peak blood flow.

**Statistical analysis.** Data are presented as mean ± SD. The primary (post-ischemic peak arm blood flow) and secondary endpoints were analyzed for the presence of a period or carryover effect as recommended by Hills and Armitage (23). No such effect was found (with the exception of a period effect for alkaline phosphatase [AP], and the results are therefore presented together in this order: baseline, treatment, and placebo. Simple regression, Student unpaired and paired t tests, and the chi-square test were used as appropriate. Repeated-measures analysis of variance was used to analyze the effects of increasing doses of LPS ex vivo. A p value <0.05 was considered significant.

**Results**

We enrolled 17 male patients with CHF of NYHA functional classes II and III. Patient baseline demographic data are provided in Table 1 and patient medications in Table 2. Eight patients were allocated to the UDCA first and 9 patients to the placebo first treatment arm. Compliance was 100%, as assessed by counting the returned UDCA capsules. UDCA was well tolerated in all study subjects, and there were no significant differences between subjects in the 2 treatment groups with the exception of a slightly higher aspartate transaminase (AST) level in the group that received UDCA first (Table 1). During the first days of participation, 1 subject withdrew consent. Unblinding revealed that the patient was on placebo, and the patient was withdrawn from all further analyses.

**Blood flow assessment and clinical variables.** After UDCA treatment, no significant difference was detected in
resting arm or leg blood flow (both \( p > 0.7 \)) (Fig. 2).

Compared with the placebo phase, UDCA improved peak blood flow significantly: UDCA treatment increased postischemic blood flow by 18% in the arm (\( p = 0.038 \)), and there was a trend toward an increase of 17% in the leg (\( p = 0.079 \)) (Fig. 2). This was not associated with an improvement in NYHA functional class or 6-min walk test (Table 3).

**Laboratory parameters, bile acids, and cytokines.** Compared with placebo, treatment with UDCA yielded a significant increase in serum levels of tauro-UDCA and glyco-UDCA (Table 3). There was a mean 16-fold increase in UDCA, and a mean 67-fold increase in the serum levels of all UDCA subfractions combined. Details on the other bile acids are provided in the Online Table. No correlation was detected between forearm blood flow and total or any of the subfractions of UDCA (all \( p > 0.05 \)). We found significant reductions in γ-glutamyl transferase (GGT) and AST serum levels with UDCA treatment when comparing serum values assessed after UDCA and placebo (Table 3). There was also a significant reduction in serum AP (Table 3). However, there was a significant period effect of AP (\( p = 0.02 \)). No changes in the serum concentrations of sodium, potassium, creatinine, uric acid, total protein, albumin, C-reactive protein, bilirubin, high-density lipoprotein, low-density lipoprotein, and total cholesterol were noted (all \( p > 0.15 \)).

After UDCA treatment, we detected significant correlations between total UDCA and AST (\( r^2 = 0.48, p = 0.005 \)) or total bilirubin (\( r^2 = 0.29, p = 0.03 \)). No such relationship was detected between total UDCA and AP, GGT, or C-reactive protein (all \( p > 0.1 \)). Furthermore, we detected a significant decrease in serum levels of sTNFR-1 after UDCA treatment compared with placebo (Table 3). No such changes were noted for interleukin-6 or TNF-α (Table 3).

**Ex vivo whole blood stimulation experiments.** Whole blood samples from patients with CHF released increasing amounts of TNF-α when stimulated with increasing doses of LPS (data not shown). This was also true at baseline and after the treatment period with either UDCA or placebo (repeated-
measures analysis of variance; all \( p < 0.0001 \)). No significant difference was noted between the amounts of TNF-\( \alpha \) released after any LPS dose when comparing assessments after UDCA and placebo treatment (all \( p > 0.3 \)).

**Full blood count.** Absolute numbers of leukocytes, neutrophils, and lymphocytes were significantly lower after UDCA treatment than after placebo (Table 3). After UDCA treatment, the number of neutrophils was lower than after placebo (Table 3). Likewise, after UDCA treatment, the number of lymphocytes was lower compared with placebo (Table 3). No such difference was noted for monocytes, eosinophils, or basophils (all \( p > 0.15 \)). No change was detected for hemoglobin concentration between UDCA treatment and placebo (Table 3). In addition, we detected significant relationships between total UDCA and the absolute number of white blood cells \( (r^2 = 0.34, p = 0.02) \) or the absolute number of lymphocytes \( (r^2 = 0.29, p = 0.03) \) after UDCA treatment.

**Discussion**

We show that 4 weeks of treatment with UDCA 500 mg twice daily significantly increases post-ischemic blood flow in the arm. In addition, there was a trend toward increased post-ischemic blood flow in the leg. These changes were associated with significantly lower serum levels of sTNFR-1 and significant reductions in the absolute numbers of neutrophils and lymphocytes after UDCA treatment compared with placebo. Additionally, we noted a reduction in GGT and AST serum levels. However, these changes were not reflected in improvements in the 6-min walk test or NYHA functional class in our small study. No change was noted in LPS-stimulated TNF-\( \alpha \) secretion in peripheral blood ex vivo.

UDCA treatment at the dose used in this study is well tolerated in patients with CHF, in whom the drug has not been used previously. Measurement of serum levels of bile acids may be useful to assess patient compliance.

For many years, reduced peripheral blood flow has been recognized to be one of the major factors limiting the exercise capacity of patients with CHF (24). Although angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are known to improve endothelial function in cardiovascular illnesses and in heart failure, exercise limitation remains a major issue, particularly in patients with CHF. Bile acids are known to have vasodilatory properties (25), and the finding that UDCA has beneficial effects on peripheral blood flow merits attention. The level of improvement in peripheral blood flow observed in our study is similar to that observed with diuretic therapy in decompensated heart failure (26) or with other drugs such as allopurinol (27). Earlier studies had shown that liver function may have a role in patients with CHF because 2 studies found bilirubin to be a strong prognostic marker in patients with heart failure (28,29).

Deficiency in nitric oxide is associated with endothelial dysfunction, and TNF-\( \alpha \) and other proinflammatory cytokines have been associated with its development (2). Our study was not designed to establish the underlying mechanism; however, a direct induction of nitric oxide by UDCA does not appear likely. This is in line with an earlier study in 11 patients with coronary artery disease in whom 6 weeks of treatment with UDCA yielded a significant improvement in nitric oxide–independent endothelial vasodilation as assessed by strain-gauge plethysmography in the forearm (30). These investigators infused acetylcholine and nitroprusside.
to test endothelium-dependent and endothelium-independent vasodilation, respectively, and suggest that the anti-inflammatory properties of UDCA might be responsible for their findings (30). Indeed, an effect that interferes with TNF-α production or its (soluble) receptors appears possible.

We found significantly lower levels of sTNFR-1 after UDCA treatment than after placebo. Although we cannot exclude the possibility of a chance finding, sTNFR-1 is indeed thought to better reflect long-term TNF-α exposure than TNF-α itself (31). One of the properties of UDCA is that it, like cholesterol, maintains membrane stability and prevents membrane damage induced by mechanical and chemical stress (32). Bile salts are present in bile as mixed micelles that act as solubilizers and emulsifiers of cholesterol, bilirubin, lecithin, fat-soluble vitamins, and also for LPS (33). UDCA is present in human bile in small amounts, forming about 3% of human bile (14). UDCA has membrane-stabilizing and antiapoptotic effects (34). Apart from effects on proinflammatory mediators, it is also possible that these indirect effects are involved in the improved blood flow found in our study, although we could not detect a direct relationship between serum levels of total UDCA or its subfractions.

Indeed, Bährle et al. (35) reported that UDCA might have beneficial effects after cardiac transplantation. In their study, they compared 21 cardiac allograft recipients receiving UDCA for cyclosporine-induced cholestasis (500 mg twice daily, for >8 weeks) with 31 cardiac transplant patients not receiving UDCA. They found that during the first 6 months after transplantation, the number of acute rejection episodes was significantly lower in the UDCA group compared with the control group (p = 0.005) (35). This effect may be due to the immunomodulatory properties of UDCA, which include suppression of the production of cytokines like TNF-α and interferon-γ but also modulation of T-cell and B-cell function (36). This is in line with our findings because leukocyte counts decreased with UDCA treatment compared with placebo. An elegant study was presented by Aouad et al. (12), who showed that ligation of the common bile duct in Lewis rats yielded significantly elevated levels of LPS in the bloodstream compared with control animals. This finding was highly suggestive that bile acids are able to hold bacterial components back in the intestine. Indeed, application of chenodeoxycholic acid to rats in this study was still associated with significantly reduced plasma LPS levels (12). Because elevated levels of LPS are present in patients with CHF (10), the improvement in post-ischemic blood flow observed in our study may be due to the formation of mixed micelles containing UDCA around LPS. Consequently, fewer proinflammatory
mediators were released into the bloodstream, which brings about an improvement in nitric oxide–independent endothelial function. However, because not all measured proinflammatory mediators were affected, it is unlikely that this pathway is the only one involved in the benefits seen with UDCA treatment. Indeed, alternate mechanisms may have an even stronger impact on the clinical effects of UDCA seen in our study, and further testing of the role of LPS in heart failure is warranted.

The fact that UDCA treatment in our study was associated with a significant reduction in serum AST and GGT highlights the fact that an effective dose was used. However, the dose of UDCA used in our study (1,000 mg/day) may still have been too low to translate an improvement in endothelial function into an improvement in clinical variables such as the 6-min walk test. The dose used in patients with primary biliary cirrhosis, for example, is usually 10 to 16 mg/kg of body weight per day (i.e., 700 to 1,600 mg/day) (13). Another possibility is that the duration of treatment in our study was too short to achieve clinical improvements (e.g., enhanced skeletal muscle function).

Study limitations. The number of patients was small, and multiple statistical comparisons were performed, increasing the likelihood that these results may be due to chance. Although the implementation of a crossover design potentiates its statistical power, the addition of a second baseline assessment before the initiation of the second treatment period might have provided additional information, especially because some of our findings were the result of changes in the placebo group compared to baseline measures, rather than changes in the UDCA group per se. UDCA was administered for a comparatively short time, and it is not clear whether a longer time frame may have potentiated the effects of UDCA. Although UDCA was well tolerated in our study, it is noteworthy that rare but typical side effects of UDCA include constipation, nausea, and indigestion. It remains a matter of speculation whether the fact that serum levels of GGT and AST were reduced by UDCA treatment highlights the fact that pathophysiological relevant doses were used.

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Reprint requests and correspondence: Dr. Stephan von Haehling, Applied Cachexia Research, Department of Cardiology, Charité Medical School–Campus Virchow-Klinikum, 13353 Berlin, Germany. E-mail: stephan.von.haehling@web.de.

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Key Words: blood flow • cytokines • heart failure • inflammation • ursodeoxycholic acid.

APPENDIX

For supplementary text, tables, figures, and references, please see the online version of this article.