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Inflammatory cytokines and the possible immunological role for lipoproteins in chronic heart failure

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Abstract

Aims: We studied the clinical and immunological importance of fasting cholesterol, HDL, LDL and triglycerides in patients with chronic heart failure in relation to plasma concentrations of tumor necrosis factor-α (TNFα), soluble TNF receptor-1 and -2 (sTNF-R1 and -R2), and a ratio potentially indicating recent endotoxin bioactivity (soluble [s] CD14/total cholesterol). *Methods and results:* Fifty-eight stable, non-oedematous patients with established heart failure and 19 controls were studied prospectively. Concentrations of sTNF-R1 and sCD14 were higher in patients than in controls (1238±96 vs. 632±72 pg/ml, $P=0.005$ and 3401±120 vs. 2775±139 pg/ml, $P=0.007$, respectively), whereas those of TNFα (9.3±1.1 vs. 6.7±0.6 pg/ml) and sTNF-R2 (2464±145 vs. 1920±303 pg/ml) were not. Cholesterol (5.6±0.1 vs. 5.5±0.2 mmol/l) and LDL (3.5±0.1 vs. 3.6±0.2 mmol/l) were not different (both $P>0.75$). Patients had lower HDL (1.10±0.04 vs. 1.4±0.06 mmol/l, $P=0.0004$) and higher triglycerides (2.1±0.1 vs. 1.1±0.1 mmol/l, $P=0.0006$). Aetiology and the presence of cardiac cachexia did not influence the lipid profile. Correlations in patients: cholesterol vs. TNFα ($r=-0.40$, $P=0.003$), vs. sTNF-R1 ($r=-0.24$, $P=0.08$), vs. sTNF-R2 ($r=-0.29$, $P<0.04$); sCD14 vs. TNFα ($r=0.44$, $P=0.005$), vs. sTNF-R1: ($r=0.65$, $P<0.0001$), vs. sTNF-R2 ($r=0.59$, $P<0.0001$). The sCD14/cholesterol ratio related powerfully to TNFα ($r=0.60$), sTNF-R1 ($r=0.74$), and sTNF-R2 ($r=0.65$, all $P<0.0001$). This sCD14/cholesterol ratio emerged as the strongest predictor of TNFα, sTNF-R1 and -R2 (all $P<0.01$), independently of renal and hepatic function, and conventional measures of disease severity. A cholesterol level <5.2 mmol/l ($n=18$) significantly predicted a poor clinical outcome ($P<0.04$, RR 3.5, 95% CI 1.1–11.0) independently of peak VO_2 ($P=0.07$), NYHA class ($P=0.08$), aetiology ($P=0.14$), and age, body wasting, sodium, LVEF, heart rate, and blood pressure (all $P>0.20$, follow-up 12 months, event rate 26%). *Conclusion:* Our data supports previous findings that lower, rather than higher cholesterol levels are associated with poor clinical outcome in patients with chronic heart failure. This relationship is unrelated to heart failure aetiology, and suggests that the classic risk profile is not longer relevant in established heart failure. The little-recognised ability of all lipoprotein fractions to bind endotoxin and to serve as natural buffer substances may explain this relationship between lower lipoprotein levels, higher cytokine concentrations and impaired prognosis.

Keywords: Chronic heart failure; Cytokines; Lipoproteins; Immune activation; Prognosis; Endotoxin

1. Introduction

Following the first publication by Levine et al. [1] in 1990, increased concentrations of tumour necrosis

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factor-α (TNFα) and other inflammatory cytokines in patients with advanced chronic heart failure (CHF) have subsequently been confirmed by others [2,3]. Different mechanisms have been proposed to explain this up-regulation of cytokines in CHF, including myocardial production [4] and the release of cytokines due to lipopolysaccharide (LPS) challenge from the gastro-intestinal tract [5]. Recently, we have demonstrated that oedematous heart failure patients exhibit higher LPS plasma levels than non-oedematous patients and healthy controls [6]. Accordingly, Vonhof et al. [7] were able to show an increased TNFα release in full blood samples from patients with CHF after stimulation with LPS ex vivo.

There is no doubt that lipid-lowering therapy reduces mortality and morbidity in patients with coronary artery disease [8–10], and reduces the incidence of CHF [11]. However, once CHF is established, the functional importance of serum lipids is unclear. While the natural assumption would be that a lipid profile that is adverse in coronary artery disease would also be adverse in CHF, recent work has suggested that the exact opposite might be the case [12,13]. One possible explanation for such a paradoxical role for lipids in established heart failure is their known property to bind bacterial LPS [14]. This may be important in limiting the degree of immune activation, which has now been recognised as an important component of the pathophysiology of CHF. If this hypothesis were true, then higher levels of cholesterol would be expected to be associated with less prominent immune activation. The primary objective of the present study was therefore to explore whether total cholesterol, HDL and LDL relate to inflammatory cytokines such as TNFα, soluble TNF-receptor 1 (sTNF-R1) and soluble TNF-receptor 2 (sTNF-R2), and a ratio potentially indicating recent endotoxin bioactivity (endotoxin action per unit lipoprotein: soluble [s] CD14/total cholesterol). The other objective was to examine the prognostic impact of lipoprotein pattern in CHF.

2. Methods

2.1. Study population and characteristics

Measurements were made in 58 stable, non-oedematous male patients with mild to severe heart failure and in 19 healthy male control subjects of similar age (Table 1). The diagnosis of CHF was based on a history of heart failure of at least 6 months with typical symptoms, reduced exercise capacity, and imaging evidence of impaired left ventricular function. No patient was limited by exertional angina. The aetiology of CHF was ischaemic in 36 patients and non-ischaemic cardiomyopathy in 22 patients. Patients were excluded if they had clinical signs of infection, of secondary metabolic disorders affecting lipid metabolism (e.g. thyroid disease, liver disease, nephrotic syndrome, and diabetes mellitus), or if they were being treated with β-blockers, corticosteroids, or lipid-lowering drugs. Patients with myocardial infarction within the previous 12 months, severe chronic renal failure (creatinine>250 μmol/l) or excessive alcohol intake were also excluded.

All subjects performed a maximal treadmill exercise test (modified Bruce protocol, Amis 2000, Odense, Denmark) for measurement of peak VO_2 (ml/kg/min) [15]. In patients, the left ventricular ejection fraction (LVEF) was measured by radionuclide ventriculography. All patients were followed up in our heart failure clinic. We planned a follow up of one year focusing on event-free survival (events being defined as heart transplantation and death) and total mortality seperately. All participants had given written informed consent. The study protocol was approved by the Ethics Committee of the Royal Brompton Hospital.

2.2. Laboratory measurements

Blood samples were collected in the morning, between 9 and 10 am, after an overnight fast of at least 12 h. Venous blood samples (25 ml) were drawn following a supine rest for at least 20 min. After immediate centrifugation, aliquots were stored at −70°C until analysis. Commercially available ELISA test kids were used for the assessment of TNFα (Medgenix, Fleurus, Belgium: sensitivity 3.0 pg/ml, test not influenced by soluble TNF receptors), sTNF-R1 (sensitivity 25 pg/ml), sTNF-R2 (sensitivity 2 pg/ml, both kits R&D Systems, Minneapolis, MN, USA) and sCD14 (IBL, Hamburg, Germany: sensitivity 1 ng/ml). Blood samples were also drawn to measure fasting glucose and insulin as described elsewhere [16].

Table 1
Clinical characteristics of chronic heart failure patients and healthy control subjects[a]

Variable	Patients (n=58)	Controls (n=19)	P-value unpaired t-test
Age (years)	60±1	59±2	
BMI (kg/m^2)	25.6±0.5	25.4±0.8	
Systolic blood pressure (mm/Hg)	116±2	128±3	0.01
Diastolic blood pressure (mm/Hg)	73±1	82±2	0.002
Resting heart rate (bpm)	81±3	67±5	0.09
Peak VO_2 (ml/kg/min)	16.2±0.7	36.4±1.2	<0.0001
VE/VCO_2-slope	37.1±1.8	26.5±1.0	0.009
Sodium (mmol/l)	138±0.4	139±1.0	0.01
Potassium (mmol/l)	4.0±0.05	3.9±0.04	
Urea (mmol/l)	31.3±22.3	5.8±0.3	
Fasting insulin (pmol/l)	77.5±8.2	34.1±6.1	0.009
Fasting glucose (mmol/l)	5.7±0.2	5.2±0.1	
Cortisol (nmol/l)	420±15	376±35	
LVEF (%)	26±3		
NYHA class	2.7±0.1		
NYHA class I [n]	5		
NYHA class II [n]	14		
NYHA class III [n]	31		
NYHA class IV [n]	8		
Medication [n]			
Diuretics	50		
ACE inhibition	44		
Digoxin	17		
Warfarin	18		
Oral nitrates	15		
Amiodarone	14		
Aspirin	15		

[a] Values presented as mean±S.E., all P-values <0.20 are given.

Quantitative determination of total cholesterol concentration in serum was performed using Cholesterol Reagent, in conjunction with Synchron CX Systems CX MULI™ Calibrator (Beckman Coulter, Inc., Fullerton, CA, USA). The measurement of HDL cholesterol was done by a direct homogenous assay without the need for any offline pretreatment or centrifugation steps (Synchron CX® Systems). Triglycerides measurements were performed with the Triglycerides GPO Reagent with Synchron CX Systems CX MULI™ Calibrator (Beckman Coulter) by a timed-endpoint method. LDL was calculated from the following formula: LDL=total cholesterol−(HDL+0.45 triglycerides). These measurements are routine analyses of the Royal Brompton Hospital.

2.3. Statistical analysis

Results are presented as mean±standard error of the mean (S.E.). Unpaired Student's t-test and ANOVA were used for intergroup comparisons. Due to the skewed distribution, concentrations of TNFα, sTNF-R1, sTNF-R2 and the ratio sCD14/cholesterol were compared by the Mann–Whitney U-test. When ANOVA showed significance, Fisher's post hoc test was applied. A probability value of $P<0.05$ was considered statistically significant. To analyse relationships between variables, regression analyses were performed (skewed variables were logarithmic transformed). As multiple correlations were performed, we considered only P-values <0.01 as statistically significant. The Cox-proportional hazards model was used to assess the association of variables to total mortality and event-free survival. A commercially available statistical software program was used (StatView 5.0, Abacus Concepts Inc., Berkeley, USA). If blood results were below the detectable limit of a test, the lowest limit of detectability was recorded.

3. Results

3.1. Lipoproteins and immune activation

In patients with CHF, a serum lipid profile that would be considered adverse in coronary artery disease patients was associated with a less abnormal immune status. There was an inverse correlation between total cholesterol and TNFα ($r=-0.40$, $P=0.003$), sTNF-R1 ($r=-0.24$, $P=0.08$) and sTNF-R2 ($r=-0.29$, $P<0.04$). LDL and triglycerides were inversely related to TNFα ($r=-0.30$, $P=0.03$ and $r=-0.31$, $P<0.03$, respectively), and LDL related also to sTNF-R2 ($r=-0.31$, $P<0.03$). We found relationships between sCD14 concentrations ($n=41$) and cytokines (TNFα: $r=0.44$, $P=0.005$; vs. sTNF-R1: $r=0.65$, $P<0.0001$; vs. sTNF-R2: $r=0.59$, $P<0.0001$). Amongst the controls, there was no significant relationship. The clinical characteristics and cytokine and lipid values are presented in Tables 1 and 2.

3.2. Soluble CD14/total cholesterol ratio

The sCD14/total cholesterol ratio was significantly higher in patients than in controls ($P<0.04$, Fig. 1). All three cytokines had strong positive correlations with the sCD14/total cholesterol ratio in the total group of subjects studied (TNFα: $r=0.57$, sTNF-R1: $r=0.70$ and sTNF-R2: $r=0.67$, all $P<0.0001$). This relationship was predominantly among CHF patients (Table 3 and Fig. 2). The correlations were somewhat stronger in patients due to ischaemic aetiology, but remained significant (all $P<0.01$) irrespective of aetiology except for sTNF-R2 (in patients with idiopathic dilated cardiomyopathy: $r=0.44$, $P=0.11$). In forward-backward stepwise regression, the sCD14/

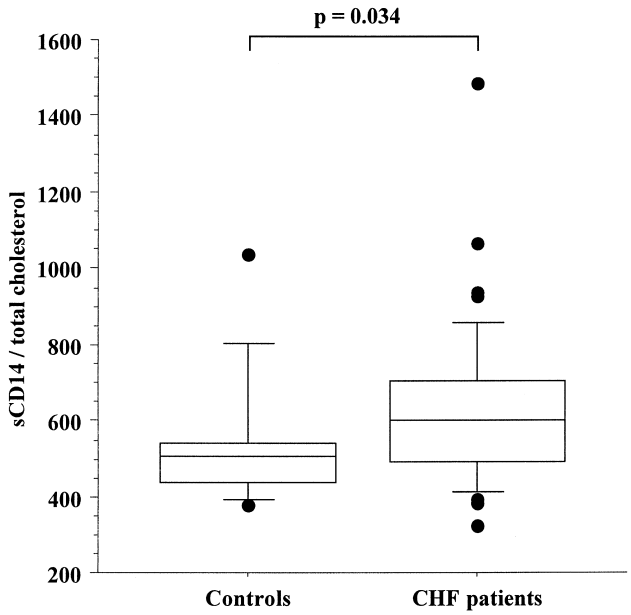

Fig. 1. The ratio sCD14/total cholesterol in chronic heart failure patients and healthy volunteers. Box plots displayed the 10th, 25th, 50th, 75th and 90th percentiles. *P*-value obained by Mann-Whitney *U*-test.

Table 2
Baseline characteristics of healthy control subjects and patients subgrouped by aetiology and cardiac cachexia[a]

Variable	Controls ($n=19$)	All patients ($n=58$)	*P*-value	dCHF ($n=22$)[b]	iCHF ($n=36$)	*P*-value	ncCHF ($n=39$)	cCHF ($n=19$)	*P*-value
TNFα (pg/ml)	6.7±0.6	9.3±1.1	0.27	10.8±2.6	8.4±0.9	0.31	6.3±0.4	14.6±2.6	0.0002
sTNF-R1 (pg/ml)	632±72	1238±96	0.005	1315±188	1190±105	0.54	1017±96	1649±170	0.0008
sTNF-R2 (pg/ml)	1920±303	2464±145	0.11	2777±287	2274±149	0.09	2282±167	2790±262	0.09
sCD14 (pg/ml)	2775±139	3401±120	0.007	3662±218	3270±140	0.12	3173±145	3677±184	0.03
Total Cholesterol (mmol/l)	5.5±0.2	5.6±0.1	0.76	5.4±0.3	5.7±0.2	0.45	5.6±0.2	5.5±0.2	0.67
HDL (mmol/l)	1.4±0.06	1.10±0.04	0.0004	1.12±0.07	1.08±0.04	0.57	1.05±0.04	1.18±0.07	0.08
LDL (mmol/l)	3.6±0.2	3.5±0.1	0.99	3.5±0.2	3.6±0.1	0.65	3.6±0.1	3.6±0.2	0.87
Triglycerides (mmol/l)	1.1±0.1	2.1±0.1	0.0006	1.9±0.3	2.2±0.2	0.29	2.3±0.2	1.6±0.2	0.04
Creatinine (μmol/l)	92±2	121±5	0.003	131±11	115±5	0.15	116±6	132±9	0.16
Albumin (g/l)	44.8±0.6	43.7±0.4	0.17	43.2±0.8	44.0±0.5	0.37	44.6±0.8	43.3±0.5	0.14
Total protein (g/l)	66.8±0.6	69.8±0.5	0.005	69.2±1.1	70.2±0.6	0.34	68.9±0.6	71.8±0.8	0.01

[a] Values presented as mean±S.E.

[b] dCHF: heart failure due to dilated cardiomyopathy; iCHF: heart failure due to coronary artery disease; ncCHF: non-cachectic heart failure patients; cCHF: cachectic heart failure patients.

Table 3
Cytokine concentrations in patients with chronic heart failure in relation to total cholesterol, sCD14 and the ratio sCD14/total cholesterol[a]

Variable	Total cholesterol	Soluble CD14	sCD14/total cholesterol
TNFα (pg/ml)	$r=-0.40$, $P=0.003$	$r=0.44$, $P=0.005$	$r=0.60$, $P<0.0001$
sTNF-R1 (pg/ml)	$r=-0.24$, $P=0.08$	$r=0.65$, $P<0.0001$	$r=0.74$, $P<0.0001$
sTNF-R2 (pg/ml)	$r=-0.29$, $P<0.04$	$r=0.59$, $P<0.0001$	$r=0.65$, $P<0.0001$

[a] Cytokines and the ratio sCD14/total cholesterol were logarithmic transformed due to skewed distribution.

total cholesterol ratio emerged as the strongest predictor of TNFα, sTNF-R1 and sTNF-R2 concentrations (Table 4), independently of peak VO_2, body mass index, creatinine, LVEF, NYHA class and age.

3.3. Clinical outcome

All patients were followed up for 12 months. Nine patients died and 6 patients underwent heart transplantation (5 of whom were alive at 12 months follow-up). In univariate Cox-proportional hazards analysis for event-free survival, independent predictive value was found for peak VO_2 ($P=0.0004$), NYHA class ($P=0.002$), and creatinine ($P<0.02$). Patient age, LVEF, sodium, albumin, total protein, resting heart rate and resting blood pressure had no significant predictive power (all $P>0.10$). A cholesterol level <5.2 mmol/l predicted impaired event-free survival ($P<0.009$, RR 3.9, 95% CI 1.4–11.1 (Fig. 3)), after correction for aetiology $P=0.011$ (RR 3.8, 95% CI 1.4–10.9). In multivariate analysis using established cut-offs for risk stratification in CHF (peak $VO_2<14$ ml/kg/min, NYHA class III+IV) and the presence of cardiac cachexia, a cholesterol

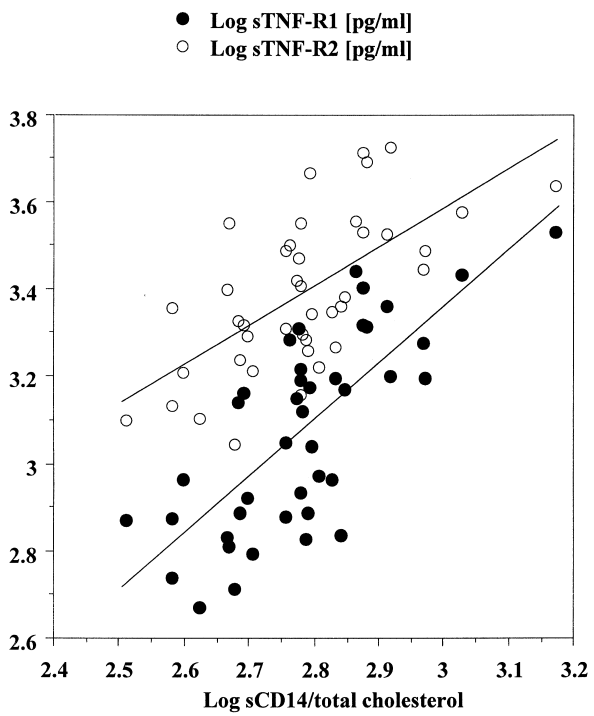

Fig. 2. Correlations between the ratio sCD14/total cholesterol, soluble tumor necrosis factor receptor-1 (sTNF-R1), and soluble tumor necrosis factor receptor-2 (sTNF-R2) in patients with heart failure (values logarithmic transformed).

Table 4
Forward stepwise and multiple regression analysis of the association between TNFα, sTNF-R1 and sTNF-R2 and the ratio sCD14/total cholesterol in 41 patients with chronic heart failure[a]

	TNFα	sTNF-R1	sTNF-R2
Stepwise regression	*F* (partial correlation)		
Step 1			
sCD14/cholesterol	21.1 (0.60)	44.2 (0.73)	28.4 (0.65)
Peak VO_2	4.8 (−0.34)	8.1 (−0.42)	1.8 (−0.21)
BMI	4.6 (−0.33)	1.4 (−0.20)	1.4 (0.19)
Creatinine	0.3 (0.1)	5.4 (0.36)	10.5 (0.47)
Step 2			
BMI	4.9 (−0.35)	1.5 (−0.20)	1.0 (0.17)
Creatinine	0.1 (0.04)	4.7 (0.34)	
Peak VO_2			1.1 (−0.18)
Multiple regression	*t*-Value (*P*)		
sCD14/cholesterol	2.9 (0.007)	4.7 (<0.0001)	4.0 (0.0003)
Peak VO_2	−2.1 (0.04)	−2.6 (0.012)	−0.9 (0.36)
BMI	−2.2 (0.03)	−1.6 (0.12)	1.0 (0.32)
Creatinine	0.5 (0.63)	2.5 (0.018)	3.1 (0.003)
Adjusted R^2	0.45	0.65	0.53
Joint predictive value	$r=0.71$	$r=0.83$	$r=0.76$

[a] $F>4.00$ with $P<0.05$.

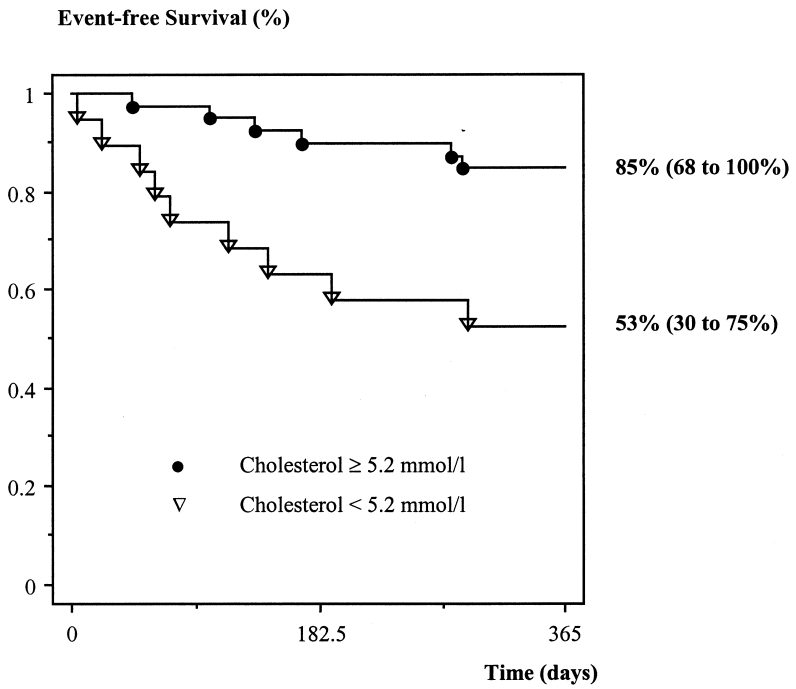

Fig. 3. Kaplan Meier curve for 365-day event-free survival according to the cholesterol cut off of <5.2 mmol/l. Event-free survival (%) and 95% confidence intervals (95% CI) are given.

level <5.2 mmol/l significantly predicted a poor clinical outcome ($P=0.036$, RR 3.5, 95% CI 1.1–11.0) independently of peak VO_2 ($P=0.07$), NYHA class ($P=0.08$), aetiology ($P=0.14$), and body wasting. After correction for impaired renal function (top tertile of creatinine) a cholesterol level <5.2 mmol/l remained the only independent and significant predictor for a poor clinical outcome ($P=0.04$, RR 3.3, 95% CI 1.05–10.58). When outcome was restricted to mortality, this cholesterol cut-off also significantly predicted 365 day mortality ($P=0.02$, RR 5.3, 95% CI 1.3–22.2) independently of peak VO_2<14 ml/kg/min ($P=0.02$) and aetiology ($P=0.13$). In patients who died, the sCD14/cholesterol ratio was highest (819±294 vs. 588±157, $P=0.007$) and correlated most strongly with systemic TNFα concentrations ($r=0.88$, $P=0.009$).

3.4. Aetiology

There was no difference between patients with ischaemic and non-ischaemic aetiologies in lipoprotein fractions ($P>0.20$) or cytokines (all $P>0.10$, Table 2). Nor was there any difference between aetiological groups in age, BMI and peak VO_2 (all $P\geq0.20$).

3.5. Cachectic state

To analyse whether the presence of cardiac cachexia relates to a specific lipoprotein profile, we compared the data of patients with and without cachexia (Table 2). There was no significant difference in the levels of the measured lipoproteins except for lower triglycerides in cachectic patients ($P=0.04$). Total protein was elevated in cachectic patients as were TNFα, sTNF-R1 and sCD14.

4. Discussion

Our first finding is confirmation of the paradox that lower total cholesterol levels predict significantly worse clinical outcome in patients with CHF rather than better, independently of established prognosticators. Second, the pattern of lipid fractions was independent of aetiology and of the presence of body wasting. These findings imply that the classic risk profile does not apply in patients once CHF is

established. Third, the ratio of sCD14/total cholesterol, indicative of recent LPS bioactivity, strongly related to cytokine concentrations. Fourth, the observed relationship between lower cholesterol levels, higher cytokines and increased mortality may be explained by the currently little-recognised role of lipoproteins in binding to LPS to reduce its toxicity and prevent unbalanced cytokine production.

4.1. Lipoproteins in chronic heart failure

In healthy individuals and coronary artery disease patients, high levels of cholesterol are established predictors of increased morbidity and mortality [8,9]. Coronary artery disease is a frequent cause of CHF [17], and it has been shown that the occurrence of CHF is reduced by long-term treatment with simvastatin [11]. Nevertheless, only limited data are available on lipoprotein levels once CHF is established, and their pathophysiological role has not yet been clarified. Vredevoe et al. [12] reported in a subset of patients with idiopathic dilated cardiomyopathy (n= 109, NYHA III/IV) that lower total cholesterol, LDL, HDL and TG levels were the strongest predictors of mortality in multivariate analysis considering 13 clinical variables. In a second study, comparing the perioperative mortality in patients with severe CHF supported by a left ventricular assist device (n=45, NYHA IV), very low levels of total cholesterol were associated with a significantly higher mortality [13]. This is in concert with the observation from a third study which demonstrated that in a group of CHF patients requiring implantation of a mechanical support device, those who died had persistently elevated cytokine concentrations and were more susceptible to infections [18], although lipoprotein levels have not been reported. We have now demonstrated that a cholesterol level $<$5.2 mmol/l which would conventionally be considered to be a positive feature [19] predicted a worse rather than a better 1-year event-free survival, independently of disease aetiology, peak VO_2, age, NYHA functional class, the presence of cardiac cachexia, or established markers of CHF severity. Cachectic and non-cachectic CHF patients did not differ in their total cholesterol, LDL and HDL levels. Additionally, patients with idiopathic aetiology had virtually the same lipoprotein levels like patients with CHF due to coronary artery disease. Hepatic synthetic capacity was not a confounding factor with albumin levels not being significantly different between patient groups. Indeed, total protein was higher in patients than in controls. Another potentially confounding factor like low fasting insulin levels was found to be higher in patients than in controls which is consistent with previous findings in a stable heart failure population [20]. Additionally, the fasting cortisol and glucose levels were not different between groups [20,21].

4.2. Potential immunological role of lipoproteins

Evidence is available from animal models of endotoxaemia [22–24] and in-vitro experiments [25,26] that lipoproteins may modulate TNFα release by binding LPS. In humans, a variety of acute and chronic diseases have been reported to present immune dysfunction together with alterations in lipoproteins [27–29]. In our study, TNFα, sTNF-R1 and sTNF-R2 concentrations correlated inversely and significantly with total cholesterol and positively with sCD14 in patients with chronic heart failure, suggesting an underlying relationship. The strongest relationship with the cytokines was observed with the sCD14/total cholesterol ratio. The correlations remained significant in all patient subgroups and a trend was found even in controls. A possible explanation could be suggested from the two different pathways of endotoxin clearance in vivo. First, endotoxin is transferred via a specific endotoxin-binding protein to lipoproteins, which are capable of binding endotoxin, resulting in a loss of bioactivity and a diminished inflammatory response [30]. Second, endotoxin is transferred to the membrane-bound CD14 receptor on circulating immune-competent cells, which results, via Toll-like receptor protein signalling, in subsequent cytokine release [31]. In our patient population, a lower cholesterol level (as a measure of the lipoprotein totality) was independently and significantly related to a poor clinical outcome. The strongest correlation between the ratio of sCD14/total cholesterol and TNFα occurred amongst the patients who died. Therefore, we believe that the property of lipoproteins to bind endotoxin may potentially explain the observed inverse relationship between high cytokine concentrations, low lipid levels and impaired survival. This relationship has

already been recognised in septic and critically ill patients [29,32] and has been linked to systemic endotoxaemia [27]. Hypocholesterolaemia also significantly predicted increased mortality in patients with acute renal failure [33].

The present pilot study, although it was prospective, was relatively small. The influence of early protein-energy malnutrition on cholesterol levels cannot be excluded, although the albumin levels did not differ between groups. The measurement of prealbumin might have given a more accurate estimation of the nutritional state. It would be interesting to see whether ultrasensitive CRP is correlated with cytokines and mortality predictive. Therefore, our findings are limited in terms of statistical power and subgroup analysis. Our conclusion needs to be confirmed by studying larger heart failure populations in more detail. There is clearly a need for a large-scale, randomised study on lipid-lowering therapy in CHF, which may be helpful in further evaluating the link between low cholesterol levels and survival in CHF. In particular, it would be also interesting to see results of statin intervention trials in respect to therapeutically lowered lipids and mortality in patients with ischaemic heart disease who subsequently developed CHF.

5. Conclusions

Chronic heart failure is a progressive syndrome characterised by an overall neurohumoral imbalance affecting hormonal pathways, immunological competence and metabolism. Serum lipids may serve as immunological buffer substances to counteract systemic inflammatory responses. Prognosis is poorest in those whose cholesterol is low (rather than high) in stark contrast to the findings in coronary artery disease patients. This relation is independent of aetiology. Our study is evidence for the clinical importance of the in vitro observation that lipoproteins can buffer bacterial endotoxin.

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