CHOLESTEROL AND CHLORIDE IN ACUTE HEART FAILURE

Bojana Radulović1, Ines Potočnjak2, Sanda Dokoza Terešak2, Matias Trbušić2,3, Nada Vrkić2,4, Azra Huršidić Radulović5, Neven Štarčević6, Milan Milošević7, Vesna Degoricija2,3 and Saša Frank8

1Zagreb University Hospital Centre, Zagreb, Croatia; 2Sestre milosrdnice University Hospital Centre, Zagreb, Croatia; 3University of Zagreb School of Medicine, Zagreb, Croatia; 4University of Zagreb Faculty of Pharmacy and Biochemistry, Zagreb, Croatia; 5Occupational Medicine Office, Zagreb, Croatia; 6Sveti Duh University Hospital, Zagreb, Croatia; 7Andrija Štampar School of Public Health, University of Zagreb School of Medicine, Zagreb, Croatia; 8Institute of Molecular Biology and Biochemistry, Centre of Molecular Medicine, Medical University of Graz, Graz, Austria

SUMMARY – Detecting predictors of poor outcome is crucial for understanding the underlying pathophysiology of heart failure (HF) and thus creating new therapeutic concepts. It is well established that low serum lipid levels are associated with unfavorable outcomes in HF patients. Several studies examined the association between serum lipids and established predictors of mortality in HF patients. The aim of the present study was to examine the association of serum lipid and chloride concentrations, as well as their impact on survival in acute heart failure (AHF). The present study was performed as a prospective, single-centre, observational research. The study included 152 patients with AHF. Spearman’s correlation coefficient revealed a significant positive correlation of serum chloride levels with serum levels of total cholesterol ($\rho=0.221$, $p=0.006$), low-density lipoprotein cholesterol (LDL-c) ($\rho=0.187$, $p=0.015$) and high-density lipoprotein-cholesterol (HDL-c) ($\rho=0.169$, $p=0.038$). Binary logistic regression revealed a significant association of chloride, total cholesterol and LDL-c serum levels measured at admission with hospital survival (OR 1.077, CI 1.01-1.154, $p=0.034$), (OR 1.731, CI 1.090-2.748, $p=0.020$) and (OR 1.839, CI 1.033-3.274, $p=0.038$), respectively, as well as with 3-month survival (OR 1.065, CI 1.002-1.131, $p=0.042$), (OR 1.625, CI 1.147-2.303, $p=0.006$) and (OR 1.711, CI 1.117-2.622, $p=0.014$), respectively. In conclusion, positive statistical association between serum cholesterol (total cholesterol, LDL-c and HDL-c) and chloride levels may suggest their similar modulation by AHF pathophysiology. Serum levels of total cholesterol, LDL-c and chloride contribute to patient survival.

Key words: Heart failure; Cholesterol, LDL; Cholesterol, HDL; Lipids; Chloride

Introduction

Heart failure (HF) has been in the focus of interest of cardiovascular studies because of its high prevalence, wide spectrum of etiology and incomplete under-
Paradoxically, a well-known fact is that low serum levels of total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c) and triglycerides have been associated with worse outcomes in HF studies. This phenomenon is part of the so-called reverse epidemiology in HF, whereby the risk factors of poor clinical outcome and mortality in the general population, such as obesity, hypercholesterolemia, and high blood pressure, have been associated with better survival. As a result of those studies, the level of total cholesterol has become part of the predictive models for HF survival such as the Seattle Heart Failure Model. Several studies investigated the connection between serum lipid levels with previously established predictors of outcome in HF patients, aiming at elucidating the pathophysiology of lipids in HF. However, no study so far has explored the association of serum lipid and chloride levels.

Hyponatremia is also considered to have a predictive value for survival in HF patients. Nevertheless, studies in the past years showed that serum chloride levels were independently and inversely associated with mortality in HF patients and that chloride could predict development of hyponatremia in these patients, thus making chloride the main electrolyte for predicting outcome in HF patients. The pathophysiology of hypochloremia in HF is still unknown. Exploration of the association between serum lipid and chloride levels could generate new knowledge concerning HF pathophysiology. Therefore, the present study investigated the association between serum chloride and lipid levels and their impact on survival in acute heart failure (AHF) patients.

**Patients and Methods**

**Study design and patients**

The study was a prospective, single-centre, observational research conducted over 16 months and concluded at the beginning of 2015. It included 152 consecutive adults hospitalized for AHF through Emergency Department, Sestre milosrdnice University Hospital Centre. The study was designed and conducted in accordance with the principles of the Declaration of Helsinki and approved by the hospital Ethics Committee. A written informed consent was obtained from the patients. Inclusion required patients older than 18 years with a primary diagnosis of AHF, which was confirmed within 24 hours of admission by N-terminal pro-brain natriuretic peptide (NT-proBNP) values and echocardiography. The patients were categorized by clinical presentation of HF and ejection fraction (EF).

**Data collection**

At first encounter in emergency department, sociodemographic status, past medical history, signs and symptoms, as well as chest radiography and electrocardiography were obtained in each patient. Echocardiography was performed on the first day post admission. Blood samples were obtained from medial cubital vein for routine laboratory assays at admission (complete blood count, metabolic and electrolyte panel, blood urea nitrogen, creatinine, lipid profile, and NT-proBNP). Standard serum electrolytes, renal panel and serum lipids were tested on Beckman Coulter instrument AU 2700, 2007 (Brea, CA, US) and Architect c8000, Abbott 2013 (Chicago, IL, US). Elecsys e411 (Roche Diagnostics GmbH, Mannheim, Germany) measured the level of Nt-proBNP. Admission chloride, total plasma cholesterol, LDL-c, HDL-c and triglycerides were defined as values obtained on presentation at emergency department. Hypochloremia was defined as serum concentration of chloride lower than 98 mmol/L. Total cholesterol lower than 5 mmol/L was considered normal, and so was the value of LDL-c lower than 3 mmol/L. HDL-c concentration higher than 1.2 mmol/L in women and higher than 1.00 mmol/L in men was set as normal. Serum concentration of triglycerides higher than 1.7 mmol/L was a high value.

All data were recorded on days 2, 3 and 7 of hospital stay, and follow up measurements were performed at three months.

**Statistical analysis**

The MedCalc™ v. 15.1 (MedCalc Software, Belgium) software was used for statistical assessment. Kolmogorov–Smirnov test determined the distribution of quantitative data. After determination, non-parametric or parametric statistical tests were utilized as appropriate. The median and interquartile ranges were used to display interquartile ranges.
quencies were used for categorical variables. Spearman correlation coefficients were calculated to assess the correlation of serum chloride and lipid levels. Binary logistic regression analysis was performed to study the impact of chloride, lipids, statin treatment and EF on hospital and 3-month mortality. The level of statistical significance was set at $p<0.05$.

### Results

A total of 152 patients were included in the study conducted during a 16-month period. Most of the patients had a positive past medical history of hypertension (89.5%), metabolic syndrome (55.9%) and type 2 diabetes mellitus (51.7%). Twenty-five (16.5%) patients had hypochloremia (Cl <98 mmol/L) at admission. Hospital mortality was 14.5% (n=22) and after 3-month follow up, mortality was 27.4% (n=40). Patient general information is shown in Table 1.

As shown in Figure 1, serum chloride levels were significantly correlated with serum levels of total cholesterol (Fig. 1A), LDL-c (Fig. 1B) and HDL-c (Fig. 1C), but not with serum triglyceride levels (Fig. 1D).

Interestingly, in contrast to chloride, serum sodium levels correlated significantly with chloride levels but not with serum lipid levels (Table 2).

As revealed by binary logistic regression analyses, the levels of serum chloride, total cholesterol and LDL-c measured on the first day of hospitalization
showed a significant positive association with both hospital and 3-month survival of AHF patients (Table 3). No association was found for serum HDL-c and triglycerides (Table 3), or for statin therapy before hospitalization and EF (not shown).

Multiple logistic regression models were made with serum sodium, chloride and cholesterol levels, therapy and outcome. Although they were significant and explained more than 60% of variance, only the association of total cholesterol and in-hospital survival remained significant (Table 4).

Discussion

In the present study, we found a statistical positive correlation between serum cholesterol and chloride concentrations. Additionally, we found that patients with higher serum cholesterol levels had higher both hospital and 3-month survival. Similar was found for serum chloride levels, namely, patients with higher serum chloride levels had higher both hospital and 3-month survival. Numerous studies in the last ten years revealed higher mortality in HF patients with lower total cholesterol levels6-8. In contrast, only few studies acknowledged low serum chloride levels as a predictor of poor outcome in HF patients12-14. To our knowledge, no study so far has addressed the association of serum chloride and cholesterol levels in AHF. The relationship between serum chloride and cholesterol concentrations in AHF might suggest a similar mode of their regulation by AHF pathophysiology. This new knowledge might help getting better insight into the

Fig. 1. Correlation of serum chloride with various lipid levels.

Correlation of serum chloride and (A) total cholesterol; (B) LDL-c; (C) HDL-c; and (D) triglyceride levels was calculated using Spearman’s correlation coefficients; \( \rho \) = correlation coefficient; LDL-c = low-density lipoprotein cholesterol; HDL-c = high-density lipoprotein cholesterol.
There are several theories regarding the connection of low serum lipid levels and poor outcome in HF. According to one of these theories, low cholesterol levels are associated with a decreased ability of serum to cope with endotoxins, resulting in an increased inflammatory response in HF patients. There are also several theories trying to explain low lipid levels in HF. The majority of these theories are based on the assumption that decreased calorie intake and impaired intestinal nutrient absorption might cause low lipid levels in a state of increased resting energy consumption. Some recent studies implicated venous congestion and thereby associated reduced overall intestinal absorption, including that of dietary lipids, being an underlying mechanism for low serum lipid levels in HF. Indeed, an inverse relationship between serum lipid levels and right ventricle end diastolic diameter (an indicator of the chronic volume overload status in HF) argues for the role of venous congestion in lowering serum lipids in HF. However, it is unclear why serum chloride and not serum sodium levels are associated with serum cholesterol levels, knowing that the intake of both sodium and chloride is equally affected in bowel edema.

The positive statistical correlation between serum cholesterol and chloride levels found in the present study suggests that there might be similar pathophysiological mechanisms that modulate their levels in AHF. Accordingly, decreased total cholesterol, LDL-c and HDL-c levels might be governed by the mechanisms implicated in the pathophysiology of chloride disorders in HF. It has been established that WNK signaling is involved in chloride sensing, regulation of renin-angiotensin-aldosterone system, sodium transport, hypertension and regulation of diuretic activity. Given the critical role of chloride in a number of important regulatory systems, one cannot exclude its role in the regulation of cholesterol homeostasis in AHF. Further investigation in a greater number of patients would be interesting.

**Study strengths and limitations**

The study had a uniform and structured algorithm and protocol for hospitalized AHF patients and extensive data collection with pre-planned goals. The study topic is new, as it has never been considered or

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### Table 3. Binary logistic regression analysis of laboratory parameters, and in-hospital and 3-month survival

| Variable            | In-hospital survival | 3-month follow up survival |
|---------------------|----------------------|----------------------------|
|                     | OR       | 95% CI              | p value | OR       | 95% CI              | p value |
| Chloride (mmol/L)   | 1.077    | 1.010 - 1.154       | 0.034   | 1.065    | 1.002 - 1.131       | 0.042   |
| Total cholesterol (mmol/L) | 1.731 | 1.090 - 2.748       | 0.020   | 1.625    | 1.147 - 2.303       | 0.006   |
| LDL-c (mmol/L)      | 1.839    | 1.033 - 3.274       | 0.038   | 1.711    | 1.117 - 2.622       | 0.014   |
| HDL-c (mmol/L)      | 2.563    | 0.596 - 11.022      | 0.206   | 2.410    | 0.775 - 7.491       | 0.129   |
| Triglycerides (mmol/L) | 1.830 | 0.682 - 4.914       | 0.230   | 1.658    | 0.809 - 3.398       | 0.167   |

OR = odds ratio; CI = confidence interval; LDL-c = low-density lipoprotein cholesterol; HDL-c = high-density lipoprotein cholesterol; significant associations depicted in bold.

### Table 4. Multivariate logistic regression analysis of in-hospital and 3-month survival according to serum chloride and total cholesterol levels

| Variable            | In-hospital survival | 3-month follow up survival |
|---------------------|----------------------|----------------------------|
|                     | OR       | 95% CI              | p     | Events | OR       | 95% CI              | p     |
| Chloride (mmol/L)   | 1.046    | 0.928 - 1.179       | 0.459 | 22/152 | 1.016    | 0.919 - 1.123       | 0.508 | 57/145 |
| Total cholesterol (mmol/L) | 1.680 | 1.020 - 2.770       | 0.041 | 1.016    | 0.957 - 2.049       | 0.742 | 57/145 |

The model was adjusted for age, serum sodium and statin therapy; CI = confidence interval; Events = number of events/number of patients; OR = odds ratio.
investigated. Nevertheless, the number of patients enrolled in the study was small. The study could not establish whether low cholesterol or low chloride was the cause or merely marker of AHF pathophysiology.

**Conclusion**

Positive statistical association between serum cholesterol (total cholesterol, LDL-c and HDL-c) and chloride levels might suggest their similar modulation by AHF pathophysiology. Serum levels of total cholesterol, LDL-c and chloride contribute to survival in AHF patients. Further larger studies are needed to confirm and elaborate our findings.

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Sažetak

KOLESTEROL I KLORIDI U AKUTNOM ZATAJIVANJU SRCA

B. Radulović, I. Potočnjak, S. Đokoza Terešak, M. Trbušić, N. Vrkić, A. Huršidić Radulović, N. Starčević, M. Milošević, V. Degoricija i S. Frank

Otkrivanje pokazatelja lošijeg ishoda u bolesnika s akutnim zatajivanjem srca je od velike važnosti za razumijevanje njegove patofiziologije, a time i za otkrivanje novih terapijskih pristupa. Poznato je da su niske koncentracije lipida u serumu povezane s lošijim ishodom u bolesnika s akutnim zatajivanjem srca. Brojne studije su pokušale utvrditi vezu između koncentracije lipidida u serumu i ostalih prediktora lošijeg ishoda u bolesnika s akutnim zatajivanjem srca. Cilj istraživanja bio je istražiti povezanost koncentracije lipidida i klorida u serumu kod bolesnika sa zatajivanjem srca te njihov utjecaj na preživljenje. Studija je provedena u obliku prospektivnog opservacijskog istraživanja u jednom bolničkom centru. U istraživanju je bilo uključeno 157 bolesnika s akutnim zatajivanjem srca. Spearmanovi koeficijenti korelacije su pokazali značajnu pozitivnu povezanost koncentracije klorida i ukupnog kolesterola (ρ = 0,221, p = 0,006), lipoproteina male gustoće (LDL-c) (ρ = 0,187, p = 0,015) i lipoproteina velike gustoće (HDL-c) (ρ = 0,169, p = 0,038). Binarnom logističkom regresijom je uočena statistički značajna povezanost koncentracije klorida, ukupnog kolesterola i LDL-c u bolesnika s akutnim zatajivanjem srca prilikom prijma bolesnika u bolnicu i unutarbolničkog preživljenja (OR 1,077, CI 1,01-1,154, p = 0,034), (OR 1,731, CI 1,090-2,748, p = 0,020) i (OR 1,839, CI 1,033-3,274, p = 0,038), kao i preživljenja nakon tri mjeseca (OR 1,065, CI 1,002-1,131, p = 0,042), (OR 1,625, CI 1,147-2,303, p = 0,006) i (OR 1,711, CI 1,117-2,622, p = 0,014). Zaključno, pozitivna statistička povezanost između koncentracije kolesterola u serumu (ukupni kolesterol, LDL-c i HDL-c) i koncentracije klorida može ukazivati na njihovu sličnu ulogu u patofiziologiji akutnog zatajivanja srca. Koncentracija ukupnog kolesterola, LDL-c i klorida u serumu sudjeluju u preživljenju bolesnika.

Ključne riječi: Srčano zatajivanje; LDL-kolesterol; HDL-kolesterol; Lipidi; Klorid