# Lipid Composition in Rats with Nonischemic Chronic Heart Failure

**A. V. Sidorov, V. N. Fedorov, E. V. Sal'nikov, and M. M. Fateev**

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 148, No. 7, pp. 23-26, July, 2009
Original article submitted October 31, 2008

The initial stages of nonischemic chronic heart failure in rats (model of oleothorax) were accompanied by the development of dyslipidemia. This state was characterized by an increase in total cholesterol concentration (due to the fraction of low-density lipoproteins) and atherogenicity index. The concentrations of plasma total cholesterol and low-density lipoproteins were shown to decrease in animals with severe course of nonischemic chronic heart failure. These changes were accompanied by a decrease in the atherogenicity index. Intragastric administration of cholesterol had little effect on the lipid composition of blood plasma in rats, irrespective of the severity of heart failure.

**Key Words:** *chronic heart failure; cholesterol; lipoproteins*

Dyslipidemia often accompanies the development of chronic heart failure (CHF) in patients. In medical practice, lipid metabolism disorders during CHF are believed to be associated with changes in coronary heart disease (CHD). This state is pathogenetically related to atherogenic dyslipidemia [4]. In other words, dyslipidemia is often considered as an independent process not related to CHF. However, it seems unlikely that CHF, a systemic disorder involving the whole organism, does not affect lipid metabolism. It can be hypothesized that the pathogenetic role of dyslipidemia significantly varies with the transition from CHD to CHF. There are contradictory data on the qualitative changes in blood plasma lipids during CHF of various functional classes [1,6]. It is impossible to evaluate the contribution of heart failure into the pathogenesis of comorbid dyslipidemia in patients with various underlying diseases. This problem can be solved by studies on animals with experimental disorders.

Here we studied the lipid composition of blood plasma during experimental CHF, which was etiologically unrelated to CHD or arterial hypertension.

Department of Pharmacology, Department of Biology, Department of Normal Physiology, Yaroslavl State Medical Academy, Russia. ***Address for correspondence:*** fateev52@mail.ru. M. M. Fateev

## MATERIALS AND METHODS

CHF in rats was induced by administration of silicon oil into the pleural cavity [8,10]. This approach allows us to increase gradually the severity of disease in experimental animals. This experimental model reproduces a progressive type of CHF, but excludes the effect of underlying diseases (dyslipidemia, CHD, and arterial hypertension) on the course of this disorder. Absorption of silicon oil from the pleural cavity and effect of this oil on the lipid composition of blood plasma should be excluded due to its inertness [8]. This conclusion was confirmed after thoracotomy and measurement of the total volume of silicon oil.

Experimental CHF was induced in rats of 4 groups under hexenal anesthesia (100 mg/kg intraperitoneally). Group 1 animals ($n$=13) received two injections of silicon oil as follows: (1) 1.5 ml silicon oil per 100 g body weight into each pleural cavity; and (2) 1 ml silicon oil per 100 g body weight into each pleural cavity (30 days after the 1st treatment).

Experimental CHF in group 2 animals ($n$=13) was induced as described for group 1 specimens. These rats also received daily injections of 10% oil emulsion of cholesterol (CH, 0.5 ml per 100 g body weight intraperitoneally) starting from the 2nd day after the

0007-4888/09/1481-0017 

1st intrapleural injection of silicon oil to the end of observations.

Group 3 animals ($n$=15) received the 3rd injection of silicon oil in a dose of 1 ml per 100 g body weight (into each pleural cavity) on day 60 after the 2nd injection of silicon oil.

Experimental CHF in group 4 animals ($n$=15) was induced as described for group 3 specimens (3-fold intrapleural injection of silicon oil into the pleural cavities). These rats also received daily injections of 10% oil emulsion of CH (intraperitoneally) starting from the 2nd day to the end of observations.

Therefore, the severity of CHF was greater in rats of groups 3 and 4. The duration of experiments was 60 days (groups 1 and 2) or 120 days (groups 3 and 4). Blood lipid composition was studied by the end of experiments. Two groups of intact rats (10 animals per group) of the same age served as the control. All animals were housed under similar conditions and received standard diet (pelleted food).

The concentrations of total CH, high-density lipoprotein (HDL) CH, and triacylglycerides (TG) in blood plasma were measured by the enzymatic colorimetric method with standard kits (Human). The amount of low-density lipoprotein (LDL) CH was evaluated as the difference between the concentrations of total CH, HDL CH, and very low-density lipoprotein (VLDL) CH. The content of VLDL CH was calculated as the TG/2.2 ratio [3]. The index of plasma atherogenicity was calculated as the difference between the concentrations of total CH and HDL CH divided by the concentration of HDL CH [7].

The differences were significant at $p<0.05$ (Student's $t$ test).

## RESULTS

Total CH concentration in blood plasma from CHF rats was shown to increase by 12% after 2-fold injection of silicon oil into the pleural cavity ($p<0.05$ compared to intact animals). Elevation of total CH concentration was mainly related to a 19% increase in the content of LDL CH ($p<0.05$ compared to intact animals). The concentrations of HDL CH, VLDL CH, and TG remained practically unchanged. The atherogenicity index increased by 17% (Table 1). Variations in the lipid composition in group 2 animals were similar to those in intact specimens. The concentration of total CH, content of LDL CH, and atherogenicity index in these animals increased by 22, 35, and 23%, respectively ($p<0.05$). The amount of TG, VLDL CH, and HDL CH did not change under these conditions. No differences were found between groups 1 and 2.

The increase in the concentrations of LDL CH and total CH in blood plasma from rats with moderate CHF was probably related to a decrease in activity of liver enzymes that play a role in the catabolism of CH and lipoproteins [7]. For example, activation of lipid peroxidation (LPO) is followed by the inhibition of microsomal hydroxylase (key enzyme in CH catabolism) [2]. Oxidative stress can be induced by hyperactivation of the sympathoadrenal system, particularly during suppression of antioxidant defense enzymes. These changes are observed during CHF [2,9]. LPO plays an important role in the pathogenesis of cardiovascular diseases, because free radicals are involved in the modification of LDL increasing their atherogenic potential [5,12].

Qualitatively different changes in lipid composition of blood plasma were revealed in animals with severe CHF (Table 2). Total CH concentration in these rats decreased by 27% ($p<0.05$ compared to intact animals), which mainly resulted from a sharp decrease in the content of LDL CH (by 53%, $p<0.05$). Similarly to animals with moderate CHF, variations in the concentrations of HDL CH, VLDL CH, and TG were insignificant in rats with severe disorder (as compared to intact specimens). The atherogenicity index in animals with severe CHF decreased by 43% ($p<0.05$). Additional treatment of group 4 animals with CH emulsion had no effect on the lipid composition of blood plasma (compared to group 3 rats). The concentration of total CH, content of LDL CH, and atherogenicity index in group 4 animals decreased by 24, 49, and 42%, respectively, compared to intact rats ($p<0.05$). The concentrations of TG, VLDL CH, and HDL CH remained practically unchanged in these rats.

The data on animals with severe CHF are consistent with the results of clinical trials. A negative correlation was found between the concentration of total CH in blood plasma from CHF patients and functional class of the disease [1,6].

It remains unclear why the concentration of CH correlates negatively with the severity of CHF. The endotoxin-lipoprotein theory [15] postulates that CH-rich lipoproteins have a protective effect and neutralize endotoxins of pathogenic intestinal bacteria, which circulate in the blood during intestinal obstruction and dysbacteriosis under conditions of reduced pump function of the heart in congestive CHF. In the absence of sufficient amounts of LDL, endotoxins activate CD14 receptors on the surface of monocytes and mast cells. They stimulate the synthesis and release of proinflammatory cytokines in the circulation (*e.g.*, tumor necrosis factor-α). These cytokines contribute to the progression of heart failure [11,13].

Our results indicate that intragastric administration of CH produced less pronounced effect on the lipid composition in rats with severe experimental CHF than in animals with moderate disease. These data

**TABLE 1.** Lipid Content (mol/liter) during Experimental CHF Produced by Twofold Injection of Silicon Oil into the Pleural Cavities (*M*±*m*)

| Group | Total CH | HDL CH | LDL CH | VLDL CH | TG | Plasma atherogenicity index |
|---|---|---|---|---|---|---|
| Intact | 1.981±0.080 | 0.431±0.033 | 1.039±0.062 | 0.510±0.024 | 1.122±0.044 | 3.60±0.21 |
| 1 | 2.219±0.061* | 0.427±0.020 | 1.234±0.070* | 0.557±0.026 | 1.225±0.046 | 4.20±0.23* |
| 2 | 2.426±0.121* | 0.448±0.051 | 1.406±0.104* | 0.571±0.021 | 1.257±0.035 | 4.42±0.30* |

**Note.** Here and in Table 2: *$p<0.05$ compared to intact rats.

**TABLE 2.** Lipid Content (mol/liter) during Experimental CHF Produced by Threefold Injection of Silicon Oil into the Pleural Cavities (*M*±*m*)

| Group | Total CH | HDL CH | LDL CH | VLDL CH | TG | Plasma atherogenicity index |
|---|---|---|---|---|---|---|
| Intact | 2.048±0.131 | 0.443±0.026 | 1.131±0.140 | 0.477±0.022 | 1.050±0.034 | 3.62±0.43 |
| 3 | 1.494±0.104* | 0.490±0.045 | 0.535±0.061* | 0.468±0.042 | 1.030±0.084 | 2.05±0.32* |
| 4 | 1.552±0.153* | 0.498±0.042 | 0.575±0.080* | 0.481±0.041 | 1.058±0.082 | 2.11±0.50* |

indirectly confirm the theory of hypocholesterolemia due to abnormal intestinal absorption at the stage of dystrophic changes during progressive CHF. Possible impairment of synthetic processes in the liver (target organ in CHF) should be taken into account.

Our results indicate that the initial stage of experimental nonischemic CHF in rats is accompanied by blood dyslipidemia. This state manifested in the elevation of total CH concentration (due to the fraction of LDL) and increase in the atherogenicity index of blood plasma. The development of severe CHF is accompanied by a decrease in the concentrations of total CH and LDL CH and reduction of the atherogenicity index. Intragastric administration of CH for 60-120 days had little effect on the lipid composition of blood samples from rats with CHF of different severity.

## REFERENCES


1. G. P. Arutyunov and F. T. Ageev, *Zh. Serdechn. Nedostatochn*., **4**, No. 4, 206-212 (2003).
2. I. A. Volchegorskii, I. I. Shaposhnik, E. N. Alekseev, and N. V. Kharchenkova, *Klin. Med*., No. 8, 36-40 (2003).
3. V. S. Kamyshnikov, *Clinical-and-Biochemical Laboratory Diagnostics* [in Russian], Minsk (2003), Vol. 2.
4. Yu. A. Karpov and E. V. Sorokin, *Stable Coronary Heart Disease: Strategy and Approach to Therapy* [in Russian], Moscow (2003).
5. V. Z. Lankin, V. P. Lupanov, A. A. Lyakishev, *et al*., *Kardiologiya*, No. 6, 87-90 (1991).
6. V. Yu. Mareev, *Consilium Medicum*, **1**, No. 3, 109-146 (1999).
7. A. N. Okorokov, *Diagnostics of Internal Diseases* [in Russian], Moscow (2002), Vol. 6.
8. N. N. Pyatnitskii and Yu. A. Blinkov, *Kardiologiya*, No. 1, 143-144 (1970).
9. R. I. Stryuk and I. G. Dlusskaya, *Adrenoreactivity and Cardiovascular System* [in Russian], Moscow (2003).
10. V. N. Fedorov, A. V. Yal'tsev, O. V. Danilova, *et al*., *Pat. Fiziol. Eksper. Ter*., No. 3, 7-9 (2005).
11. B. R. Gordon, T. S. Parker, D. M. Levine, *et al*., *Ann. Pharmacother*., **37**, Nos. 7-8, 943-950 (2003).
12. J. He, L. G. Ogden, L. A. Bazzano, *et al*., *Arch. Intern. Med*., **161**, No. 7, 996-1002 (2001).
13. L. C. Hudgins, T. S. Parker, D. M. Levine, *et al*., *J. Lipid Res*., **44**, No. 8, 1489-1498 (2003).
14. M. Rauchhaus, A. L. Clark, W. Doehner, *et al*., *J. Am. Coll. Cardiol*., **42**, No. 11, 1933-1940 (2003).
15. M. Rauchhaus, A. J. Coats, and S. D. Anker, *Lancet*, **356**, No. 9233, 930-933 (2000).