Change in Lymph Flow during Low-Grade Fever and Febrile Fever under Experimental Conditions

K. A. Triandafilov, L. V. Plaksina, A. M. Farkhutdinov, F. I. Mukhutdinova, and M. M. Minnebaev

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 147, No. 3, pp. 276-278, March, 2009
Original article submitted November 20, 2008

Experiments on rats showed that low-grade fever is accompanied by a decrease in the central lymph flow rate, which results from inactivation of lymphangion components in lymphatic microvessels of the small intestine mesentery. Lymph flow rate was shown to increase during pyrogenal-induced fever, which did not depend on the duration of the disease.

Key Words: *lymph flow; microlymphocirculation; low-grade fever; fever*

The lymphatic system is a key humoral component of various pathological processes. One of the functions of the lymphatic system is the maintenance of homeostasis by means of drainage and detoxication. The long-term or strong exposure to some factors that cause lymphatic insufficiency is accompanied by the exhaustion of compensatory reserves of this system [9,13].

Here we studied the state of lymph flow during low-grade fever and febrile fever of different duration.

MATERIALS AND METHODS

Experiments were performed on 102 albino rats weighing 200-230 g. Low-grade fever was induced by administration of complete Freund's adjuvant (CFA, Difco Laboratories), which consisted of 0.1% killed and dried *Mycobacterium butiricum*. CFA in a dose of 0.15 ml was injected into the hind-paw [8] pads to cause a long-term temperature response [10]. Fever was induced by repeated (3, 5, and 10 times) intramuscular injection of pyrogenal in a dose of 100 mg/kg. Control animals received an equivalent volume of the apyrogenic solution (similar scheme of treatment). The rats were anesthetized with sodium ethaminal in a dose of 50 mg/kg. Lymph flow rate was estimated from lymph outflow per unit time. The ostium of the thoracic lymphatic duct (TLD) was punctured at the site of opening into the venous angle. Vital microscopy was used to estimate the following parameters of lymph microcirculation in rats with CFA-induced low-grade fever: contractile activity of myocytes in the wall and valve cusps of lymphatic microvessels (LM) in the small intestine mesentery [1]; amplitude of contractions; and diameter of the lumen [2]. The animals were killed by administration of a narcotic drug in the lethal dose. The results were analyzed by parametric Student's *t* test.

RESULTS

CFA-induced low-grade fever was accompanied by a 22.7% decrease in lymph flow rate in TLD. However, lymph flow rate in rats with pyrogenal-induced fever was shown to increase at the stage of temperature rise and 3rd stage of the pathological process (by 1.5 and 1.7 times, respectively; Table 1). This parameter remained high after repeated injection of LPS (by 1.7-1.9 times).

Studying the microlymphocirculation showed that low-grade fever is accompanied by a decrease

Department of Pathophysiology, Kazan State Medical University, Tatarstan. ***Address for correspondence:*** fimka54@mail.ru. K. A. Triandafilov

0007-4888/09/1473-0305

TABLE 1. Lymph Flow Rate in the Thoracic Duct of Rats with Low-Grade Fever and Pyrogenal-Induced Febrile Fever (10^{-2} ml/100 g/sec, *M*±*m*)

Control	Febrile fever, pyrogenal administration (times)					Low-grade fever
	single	stage of temperature rise, t°	stage of temperature reduction, t°			
			3-fold	5-fold	10-fold	
0.49±0.04 *n*=11	0.75±0.07* *n*=8	0.83±0.09* *n*=8	0.85±0.06* *n*=8	0.88±0.09** *n*=7	0.92±0.10* *n*=8	0.33±0.02* *n*=14

Note. Here and in Table 2: *$p<0.05$ compared to the control.

in the frequency of myocyte contractions in the wall of LM (by 1.4 times) and reduction of vasomotion amplitude (by 45%; Fig. 1). The diameter of LM lumen was increased by 27.5%. Functional activity of valve cusps in the lymphangion remained unchanged under these conditions.

An increase in the central lymph flow rate during pyrogenal-induced fever is probably related to the increased contractile activity of lymphangion components in LM [4] due to the effect of biologically active substances and transmitters [6,14]. An initial increase in lymph flow rate under the influence of histamine (high concentration in experimental fever [5]) is associated with a modulatory effect of this substance on motor activity of LM. Further changes are related to the increased production of lymph, which results from high permeability of exchange microvessels. A high-intensity release of fluid from the interstitial space into the lymphatic bed contributes to elevation of intravascular pressure. The resultant increase in contractile activity is followed by lymph flow acceleration. The increase in lymph circulation during febrile fever is also associated with hypoxia, activation of the sympathoadrenal system, and secretion of glucocorticoids from the adrenal glands. The observed changes play a role in the pathogenetic mechanisms of this disorder [3].

As differentiated from pyrogenal-induced fever, the reduction of lymph flow in TLD during experimental low-grade fever is probably related to a decrease in the frequency and amplitude of LM vasomotion. Published data show that the concentration of some cytokines in the blood increases during CFA-induced low-grade fever [7]. Interleukin-1 has an inhibitory effect on the release of fluid from the interstitial space into lymphatic vessels. This cytokine decreases the frequency of contractions and tone of lymphatic vessels and causes vasodilation. Moreover, the sensitivity of lymphatic vessels to variations in intravascular pressure is reduced under the influence of interleukin-1. A decrease in the contraction frequency of lymphatic vessels contributes to the reduction of lymph flow. These changes are accompanied by discoordination of vasomotion [11,12]. It should be emphasized that drainage of fluid and proteins from the interstitial space has an important role in the regulation of extravascular fluid level. Low-grade fever is accompanied by the decrease in contractile activity of LM, which results in resorption dysfunction of the lymphatic system.

As distinct from pyrogenal-induced fever, CFA-induced low-grade fever is followed by lymph flow insufficiency. This state is probably associated with abnormalities in the neurohormonal mechanisms for resorption and transport of interstitial fluid in lymphatic vessels. The formation of lymph is impaired under these conditions. Neurohormonal discoordination may be accompanied by dysfunction of the nervous system, including the receptors, intraorgan and extraorgan nerve fibers, central and peripheral synapses, *etc*. These data indicate that the process of lymph flow should be stimulated under conditions of low-grade fever.

TABLE 2. Functional Activity of Lymphangion Components in LM of the Small Intestine Mesentery in Rats with Experimental Low-Grade Fever (*M*±*m*)

Parameters	Control	Low-grade fever
Contraction frequency of the wall, min	8.10±1.03 (*n*=10)	5.75±0.87* (*n*=9)
Contraction frequency of valve cusps, min	5.70±0.76 (*n*=6)	6.10±0.53 (*n*=9)
Amplitude of wall contractions, %	23.5±6.4 (*n*=10)	16.3±4.4* (*n*=10)
Diameter of the lumen, m	138±4 (*n*=10)	176±6 (*n*=10)

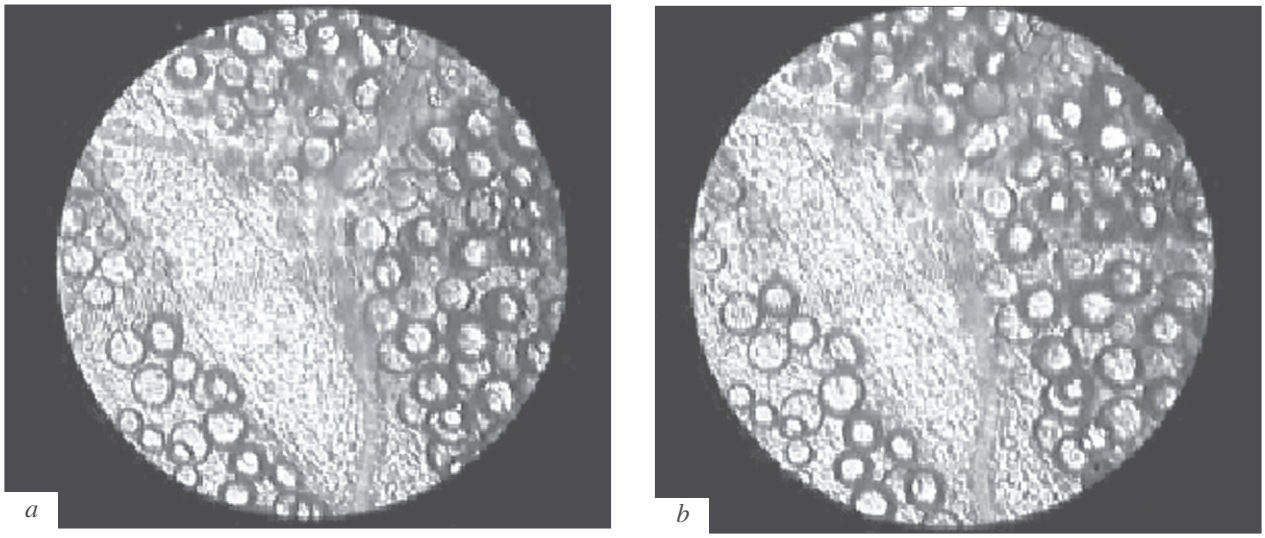

Fig. 1. Biomicroscopy of phasic contractions of LM wall in the small intestine mesentery of rats with CFA-induced low-grade fever. Relaxation of the wall (*a*); and contraction of the wall (*b*). Lens, ×10; ocular, ×12.5.

REFERENCES

1. P. N. Aleksandrov and V. K. Khugaeva, *Patol. Fiziol. Eksper. Ter.*, No. 4, 65-67 (1989).
2. G. E. Bril', E. I. Galanzha, S. S. Ul'yanov, *et al.*, *Ros. Fiziol. Zh.*, **87**, No. 5, 600-607 (2001).
3. V. N. Gourine, *Mechanisms of Fever* [in Russian], Minsk (1993).
4. F. I. Mukhutdinova, D. R. Tagirova, and D. A. Mukhutdinov, *Regionar. Krovoobr. Mikrotsirk.*, **6**, No. 2, 78-84 (2007).
5. F. I. Mukhutdinova, *Lymphatic System and Fever Response* [in Russian], Kazan (2008).
6. S. V. Petrov, *Regionar. Krovoobr. Mikrotsirk.*, **1**, No. 4, 62-67 (2002).
7. I. N. Semenenya, *Zdravookhranenie (Belarus')*, No. 4, 12-14 (2000).
8. I. N. Semenenya, *Problem of Low-Grade Fever: Basic Aspects* [in Russian], Minsk (2002).
9. V. K. Khugaeva, *Kardiologiya*, No. 8, 64-70 (1996).
10. V. N. Gourine, I. N. Semenenya, and A. V. Gourine, *J. Therm. Biol.*, **20**, No. 5, 405-407 (1995).
11. C. A. Hanley, R. M. Elias, H. Z. Movat, and M. G. Johnston, *Microvasc. Res.*, **37**, No. 2, 218-229 (1989).
12. A. Ledeboer, R. Binnekade, J. J. Breve, *et al.*, *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, **282**, No. 6, R1762-R1772 (2002).
13. D. C. Zawieja, *Microcirculation*, **12**, No. 1, 141-150 (2005).
14. J. Zhang, H. Li, and R. Xiu, *Clin. Hemorheol. Microcirc.*, **23**, Nos. 2-4, 349-353 (2000).