

EFFECT OF ACUTE CARDIAC LYMPH STASIS ON METABOLIC CORONARY ADAPTATION IN THE DOG

F. Solti, V. Nemeth, A. Juhasz-Nagy

Clinic of Cardiovascular Surgery, Semmelweis University Medical School
Budapest, Hungary

ABSTRACT

Surgical blockade of cardiac lymph drainage was performed in dogs to examine the effect of acute cardiac lymph stasis on coronary adaptive mechanisms. Coronary blood flow (CBF) was measured using an electromagnetic flow probe on the left anterior descending (LAD) artery. Metabolic autoregulatory capacity was assessed by eliciting reactive hyperemic responses after flow interruptions of 10-60 second duration and by administering submaximal doses (250-500µg) of adenosine, the putative transmitter of reactive hyperemia, into the left heart. The effect of lymph stasis was tested in two experimental groups, one hour and 48 hours after lymph obstruction and the data compared to control dogs.

Although cardiac lymph stasis did not notably affect baseline arterial pressure and CBF, both reactive hyperemic response and adenosine-induced coronary vasodilation were reduced significantly (equal to or less than 50% control). On occasion, a complete absence of autoregulation was observed. These findings suggest that cardiac lymph stasis decreases vascular responsiveness to physiologic vasodilator stimuli and/or retards diffusion of biologically unstable substance(s) presumably involved in autoregulation. Persistently impaired coronary autoregulation in the lymphedematous heart may contribute to progressive ischemic damage as for example after myocardial infarction.

Experimental obstruction of lymph drainage from the heart adversely affects structural elements of coronary blood vessels (15). As early as the 1950's, Foldi et al (7), suggested a causal relation between experimentally induced cardiac lymphedema and myocardial ischemic damage. To date,

however, quantitative information on the interrelation between myocardial blood flow regulation and lymph obstruction is lacking. Accordingly, we examined the dog heart after acutely obstructing cardiac lymph flow to characterize functional alteration of coronary adaptation to reactive hyperemia and instillation of adenosine, the putative vasorelaxant transmitter.

MATERIALS AND METHODS

Experiments were performed in adult mongrel dogs (13-28 kg), anesthetized with sodium pentobarbital (30-35 mg/kg, IV) and ventilated through a cuffed endotracheal tube with room air using a volume-cycled respirator. The chest was entered through the left fourth intercostal space and the pericardium was opened anterior to the phrenic nerve from its base to the diaphragm. The left anterior descending (LAD) coronary artery was utilized for measurement of coronary blood flow (CBF). The artery was freed proximal to its first major oblique branch and a flow probe of appropriate diameter (usually 2 mm) circumferentially applied. The probe was connected to a Statham SP 2202 electromagnetic flowmeter. Phasic and mean flow curves were registered on a four-channel Hellige recorder. Systemic blood pressure in the abdominal aorta was continuously measured using a Statham transducer (P 23

Db) inserted through a catheter introduced via a femoral artery. A separate catheter was inserted into the left atrium through the auricular appendage for administration of adenosine.

Coronary vasodilator capacity was determined before and after obstruction of cardiac lymph drainage. Initially, lymphatics on the heart surface were visualized by intramyocardial injections of a small amount (0.3-0.5 ml) of 0.5% Evans blue (T-1824) using a 23 gauge needle. Obstruction of cardiac lymph flow was as thorough as possible and included ligation of the two collecting lymphatic trunks of the heart, ligation of the pretracheal and cardiac lymph nodes, ligation of the mediastinal lymph nodes connecting the cardiac lymph system and that of the thoracic duct, and ligation of the thoracic duct near its entrance into the left subclavian vein.

Experimental preparations were divided into two groups of six dogs each. In the first group the change of coronary adaptive capacity was tested one hour after cardiac lymphatic obstruction. In the second group, the control procedures, including application of measuring devices, were performed under aseptic conditions. Lymphatics were obstructed as described. Thereafter, the canulas and the flow probe were removed, the chest (but not the pericardium) was closed, and the effect of lymphatic obstruction was tested under pentobarbital anesthesia 48 hours after the first operation. Successful measurements were made in six and five dogs in each group respectively with one dog having to be excluded from the second group because of malfunction in flow recordings.

Coronary responses to exogenous adenosine were determined by rapid intraauricular injections of the nucleoside into the left heart in doses of 250-500 μ g, dosages thought to have near maximal vasodilator activity (11). The response was characterized both by peak flow change and computing the maximum values of mean vascular conductance (CBF/mean aortic pressure).

Metabolic autoregulatory capacity of the coronary circulation was determined by eliciting reactive hyperemic responses. For

this purpose CBF was interrupted by means of a thread loop distal to the flow probe for 10, 30 and 60 seconds, respectively. The hyperemic reaction which followed release of the occluder, was assessed using four parameters: 1) flow excess, i.e. the volume of CBF flow in excess of control flow calculated as the difference between total hyperemic flow and the product of the control flow and the duration of hyperemia; 2) repayment, i.e. the ratio of flow excess to flow debt or in effect the volume of flow that the heart is deprived of by occlusion; 3) peak flow rate, i.e. the percent increase of flow at maximal hyperemia; 4) time-to-peak, i.e. the elapsed period before the hyperemic response reached its maximum after coronary artery release.

In previous experiments performed in four sham-operated dogs and in other studies carried out in this laboratory (12) these parameters including vasodilator responses had been followed and found to be stable for at least three hours.

Values in the text and tables are mean \pm SEM. Statistical evaluation was by Student's t-test for paired data.

RESULTS

Typical tracings in Fig. 1, taken from two representative experiments, illustrate the adenosine-induced coronary vasodilation in controls and in dogs with cardiac lymphatic blockade at one hour (A) and 48 hours (B). Mechanical insufficiency of cardiac lymph flow was without notable effect on baseline arterial pressure or CBF, but nonetheless lowered significantly the vasoactive response at each interval. Table 1 summarizes the overall data. Because average coronary response elicited by the 250 μ g dose of adenosine was within ten percent of that elicited by 500 μ g dose suggesting maximum vasodilation, coronary vasodilator responses obtained with 500 μ g adenosine are shown in Table 1. The

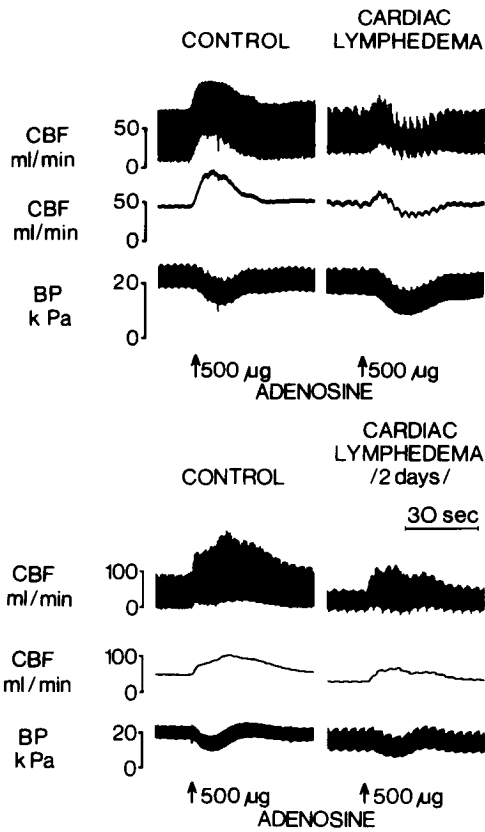


Fig. 1: Decrease of adenosine-induced coronary vasodilation in cardiac lymphedema 1 hour (above) and 48 hours (below) after lymph-obstructive surgery. From above downwards in each block: phasic and mean coronary blood flow (CBF) in left anterior descending coronary artery; arterial blood pressure (BP). 1kPa = 7.5 mmHg

degree of reduction of vasodilator responses to adenosine was nearly identical in each experimental group (although baseline CBF was higher in the second group, the average weight of the dogs was also greater).

Similar results were obtained in these dogs when studying reactive hyperemic responses of the coronary bed. Typical tracings are shown in Fig. 2 and overall data summarized in Table 2. Statistical evaluation (Table 2) reveals reduced coronary autoregulation in "lymphedematous hearts." The volume of flow excess was markedly diminished compared with peak hyperemia and, moreover, there was considerable delay in achieving flow maximums (Fig. 2). The inhibitory effect of impaired cardiac lymph drainage on reactive hyperemic vasodilation was greater than accounted for by slight changes in resting cardiovascular values (see Table 1). Accordingly, repayment of flow debt was also reduced significantly. Forty-eight hours after cardiac lymphatic blockade, the impaired hyperemic response was less impressive and less uniform than one hour after lymphatic blockade. Thus, after 48 hours, two dogs exhibited only a modest reduction (~15%) in the hyperemic response. On the other hand, the greatest autoregulatory inhibition was also observed at this time (Fig. 3).

Table 1
Effect of Cardiac Lymphedema On Adenosine-Induced Coronary Vasodilation[§]

		Lymphedema, 1 hour [†]		Lymphedema, 48 hours [‡]	
		Basic Level	Change	Basic Level	Change
Coronary blood flow (ml·min ⁻¹)	A	22.7±1.7	+34.0±5.8	36.5±1.8	+53.9±7.1
	B	24.7±3.4	+15.8±7.9 ^b	30.6±5.7	+28.4±12.5 ^b
Mean arterial pressure (kPa*)	A	15.6±1.6	-3.9±1.0 ^a	17.1±1.0	-3.7±0.6 ^a
	B	14.0±2.0	-1.7±0.5 ^a	16.9±0.8	-2.4±0.6 ^a
Vascular conductance (%)	A	100±0	+240±29 ^a	100±0	+219±19 ^a
	B	124±13	+97±29 ^{ab}	84±15	+98±34 ^{ab}

[†] n = 6, body weight = 15.7±1.1 kg

[‡] n = 5, body weight = 23.1±1.8 kg

[§] 500 µg adenosine into the left heart

A control state

B lymphedema

^a statistically significant change (p < 0.05) from basic level

^b statistically significant change (p < 0.05) from control state

* 1 kpa ≅ 7.5 mmHg

DISCUSSION

Besides myocardial damage, cardiac lymph stasis induces structural derangements in small coronary blood vessels (e.g. endothelial swelling, subendothelial plasma imbibition, intramural fibrinoid necrosis) (16,21,27). These findings support earlier observations by Foldi et al (5-7) of abnormal electrocardiograms and serum enzymes following interference with cardiac lymph flow, derangements similar to that associated with insufficient coronary blood flow. Later, other workers, reached similar conclusions (9,10,15,17,22,26). On the other hand, understanding of functional derangements corresponding to structural changes in the coronary system with lymph stasis is lacking. In our short-term experiments, blockade of cardiac lymph flow failed to effect arterial pressure. Moreover, resting hemodynamics of coronary blood flow were also minimally affected. Baseline levels, however, are not sufficient and it is equally important to ascertain whether vascular reactivity (e.g. adap-

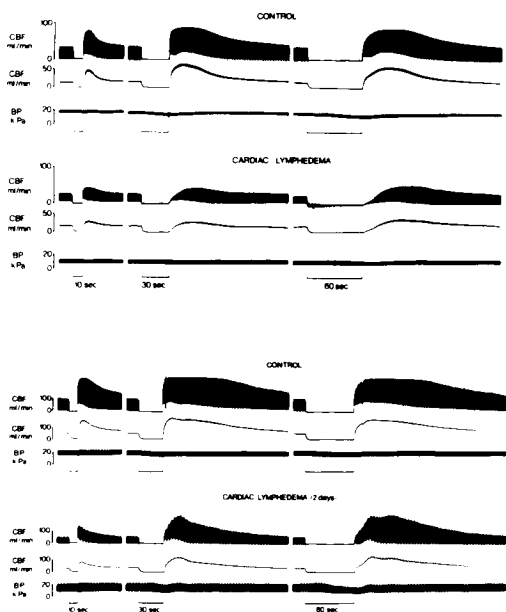


Fig. 2: Typical reactive hyperemic response 1 hour (above) and 48 hours (below) after lymph-obstructive surgery. Abbreviations as in Fig. 1.

Table 2
Effect of Cardiac Lymphedema on Reactive Hyperemic Responses in the Coronary Circulation

Time of occlusion (sec)	Lymphedema, 1 hour [†]			Lymphedema, 48 hours [‡]		
	10	30	60	10	30	60
Flow excess (ml)	A 13.6±2.7 B 6.5±1.3 ^a	A 45.6±9.3 B 19.1±4.1 ^a	A 77.2±14.5 B 34.8±5.8 ^a	A 27.7±7.3 B 16.7±9.5	A 86.9±18.9 B 42.6±19.6 ^a	A 117.0±23.2 B 66.4±30.0 ^a
Repayment (%)	A 368±75 B 188±42 ^a	A 403±71 B 176±53 ^a	A 347±56 B 164±43 ^a	A 462±107 B 295±117	A 459±92 B 289±88 ^a	A 329±67 B 234±77 ^a
Peak flow rate (Δ%)	A 176±25 B 119±25	A 199±29 B 130±28	A 211±34 B 142±24	A 228±31 B 148±42	A 226±30 B 206±55	A 227±39 B 245±69
Time to peak (sec)	A 5.6±0.6 B 7.2±0.8 ^a	A 12.7±1.1 B 18.2±2.7 ^a	A 21.5±1.5 B 32.3±3.7 ^a	A 7.1±1.2 B 13.1±4.3	A 15.6±1.7 B 28.6±6.9 ^a	A 23.4±5.5 B 39.0±9.2 ^a

[†] n = 6

[‡] n = 5

A control state

B lymphedema

^a statistically significant change (p < 0.05) from control state

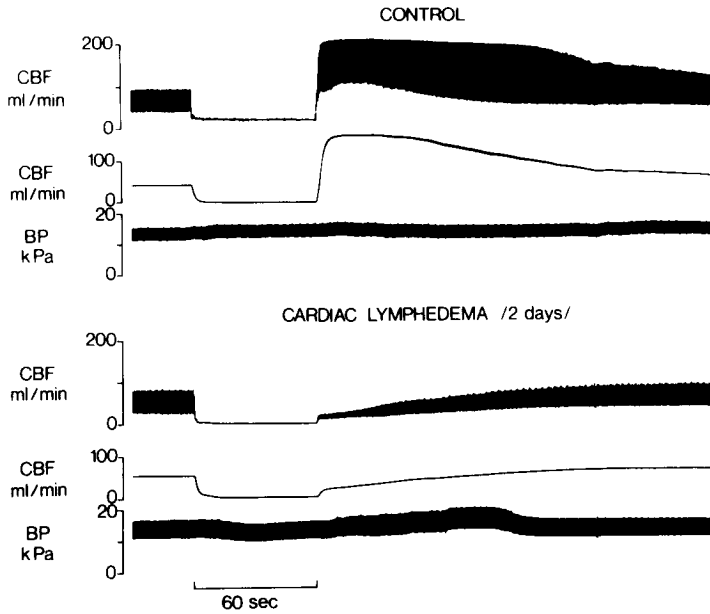


Fig. 3: Complete loss of reactive hyperemia 48 hours after lymph-obstructive surgery. Note similar resting flow in both states of the experiment, but extremely slow blood flow recovery with lymph stasis.

tive vasodilation or metabolic autoregulation) is otherwise effected (1). In the present study this issue was addressed first by administering adenosine, the putative vasorelaxant adaptive transmitter, in doses sufficient to exert maximal or near maximal vasodilation, and second by subjecting a selected region of the left ventricle to brief periods of ischemia and eliciting reactive hyperemic responses. In both acute and short-term cardiac lymph stasis both types of coronary circulatory reactions were similarly and significantly reduced; on occasion a total inhibition occurred (Fig. 3).

These findings suggest after cardiac lymphatic obstruction, certain myocardial regions may sustain ischemic damage when heightened oxygen demand is unable to be met by an appropriate augmentation in coronary blood flow. This supposition also suggests considerable heterogeneity of microcirculatory blood flow in the heart during restricted lymph drainage, a finding supported by earlier work (21).

Although flow limitations in the cor-

onary circulation were remarkably consistent after acute (~1 hour) lymph obstruction, after 48 hours the findings were less consistent and tended to normalize. Most likely, it is impossible to sustain total obstruction of lymph flow from the myocardium. Thus collateral lymphatics (15), lymphaticovenous communications and even arteriovenous shunts (18,21) probably compensate in some subjects after attempted complete ablation of lymph drainage.

In light of these abnormal hemodynamics, it is reasonable to ask what is the mechanism impaired in coronary autoregulation during lymph stasis? A partial answer derives from a comparison of reactive hyperemic responses. From Table 2, it appears that the least compromised was the magnitude of peak hyperemic overshoot (i.e., reactivity of the larger conductive vascular segments to mechanical stimuli or so-called Bayliss effect). On the other hand, reduced hyperemic volume-flow and decreased response to adenosine favors abnormal reactivity in vascular pathways

downstream to large conductive arteries (i.e. affected mechanisms are "metabolic" or "chemical" in contrast to "mechanical"). Thus, adenosine receptors are sparse in large and abundant in small coronary branches (19). Because of the key role of tissue elements adjacent to small coronary arterial branches in metabolic adaptation, these concepts do not exclude physico-chemical or even geometrical changes of the interstitium in adaptive impairment. Whether one accepts Berne's adenosine theory of metabolic coronary autoregulation (3) or a broader "extracellular hypothesis" (2), it is evident that free diffusion of transmitter agents from myocardium to vascular muscle cells is prerequisite to vasodilator reactivity. Even a slight increase in the distance between these two structural elements may diminish the potency of a vasodilator, especially a biologically unstable substance like adenosine. In fact, a major difficulty of the "adenosine theory of vasodilation" (3,4) is whether this unstable nucleoside, formed by adenosine nucleotides in cardiac cells, can persist as adenosine in the interstitium and induce coronary arterial relaxation. Interstitial edema further casts doubt on this and other pathomechanisms postulated for autoregulation including role of endothelium (8) and vascular smooth muscle (23,24). These explanations are consistent with loss of coronary autoregulatory adaptive capacity after both cardiac lymphatic obstruction and sudden extracellular expansion with physiologic salt solution (2). Taken together, reactive hyperemia, while a predictable response not easily influenced by pharmacologic manipulation (e.g. there is no specific blocking drug), is adversely affected by deranged ionic composition of the arterial wall (22-24). Interdependence of these two phenomena (coronary autoregulation and interstitial drainage of the heart) raises the spectre of lymphatic drainage as a critical factor in pathologic cardiac conditions. For example, obstruction of cardiac lymphatics aggravates myocardial ischemia (3,20), and undrained interstitial fluid may therefore be an underestimated force in adversely affecting adjustments in coronary

blood flow and, accordingly, the degree and extent of myocardial damage during ischemic infarction.

REFERENCES

1. Adiado, DM, A Juhász-Nagy: Effets hemodynamiques de l'inosine sur le coeur normal et pathologique. *Rev. Med.* 18 (1977), 209-220.
2. Belloni, FL: The local control of coronary blood flow. *Cardiovasc. Res.* 13 (1979), 63-85.
3. Berne, RM: The role of adenosine in the regulation of coronary blood flow. *Circ. Res.* 35 (1980), 807-813.
4. Feigl, EO: Coronary Physiology. *Physiol. Rev.* 63 (1983), 1-205.
5. Foldi, M, P Braun, M Papp, I Horvath: Changes in serum transaminase activity following myocardial damage due to lymphatic congestion. *Nature* 183 (1959), 1333-1334.
6. Foldi, M, G Romhányi, I Rusznyak, F Solti, G Szabo, A Temesváry: Wirkung von venöser und Lymphstauung auf die Herzmuskulatur. *Acta Med. Hung.* 7 (1955), 33-48.
7. Foldi, M, G Romhányi, I Rusznyak, F Solti, G Szabo: Über die Insuffizienz der Lymphstromung des Herzen. *Acta Med. Hung.* 6 (1954), 61-75.
8. Furchgott, RF: Role of endothelium in response of vascular smooth muscle. *Circ. Res.* 53 (1983), 557-573.
9. Guski, H, P Buntrock, H Brasemann, I Marx: The effect of lymphostasis on the isolated working rat heart. *Experientia* 30 (1974), 1452-1455.
10. Jacobs, G, F Kleinschmidt, L Benesch, W Lenz, G Uhlig, F Huth: Tier-experimentelle Untersuchungen des kardialen Lymphgefäß-systems. *Thoraxchirurgie* 24 (1976), 453-467.
11. Kekesi, V: Adenosine sensitivity of canine coronaries reduced by calcium-displacement with lanthanum. *Adv. Physiol. Sci.* 27 (1981), 119-131.
12. Kekesi, V, A Juhász-Nagy: Pharmacologic assessment of the functional state in the stenosed coronary circulation of the dog. *Acta Physiol. Hung.* 59 (1982), 147-153.
13. Kline, IK, AJ Miller, R Pick, LN Katz: The effect of chronic impairment of cardiac lymph flow on myocardial reactions after coronary artery ligation in dogs. *Am. Heart J.* 68 (1964) 515-523.
14. Maroko, RP, P Libby, CM Bloor, SE Sobel, E Braunwald: Reduction by hyaluronidase of myocardial necrosis following coronary artery occlusion. *Circulation* 46 (1972), 430-437.
15. Miller, AJ: Lymphatics of the Heart. Raven Press, New York, 1982.
16. Nagy, Z, H Jellinek, B Veress, A Kocze, A Balint, F Solti: Effect of experimental lymph congestion on coronary artery permeability in the dog. *Acta Morph. Hung.* 17 (1969), 1967-170.

17. Pick, R, A Miller, G Glick: Myocardial pathology after cardiac venous and lymph flow obstruction in the dog. *Am. Heart J.* 87 (1974), 627-632.
18. Rusznyak, I, M Foldi, G Szabo: Lymphatics and lymph circulation. Pergamon Press, New York, 1960.
19. Schnaar, R, H Sparks: Response of large and small coronary arteries to nitroglycerine, NaNO₂, and adenosine. *Am. J. Physiol.* 223 (1972), 223-228.
20. Solti, F, M. Iskum, Z Nagy, A Hartai, B Veress, I Huttner, T Kerenyi: The effect of mechanical lymph flow insufficiency on cardiac necrosis as a result of coronary ligation. *Cor Vas* 10 (1968), 68-73.
21. Solti, F, G Ungvary, P Glovicski, M Sebestyen, T Tatrai, G Toreky: The effect of cardiac lymphostasis on the microcirculation of the heart. *Lymphology* 14 (1981), 122-126.
22. Sun S, J Lie: Cardiac lymphatic obstruction; ultrastructure of acute-phase myocardial injury in dogs. *Mayo Clin. Proc.* 52 (1977), 785-792.
23. Szentivanyi, M, A Juhasz-Nagy: The physiological role of the coronary constrictor fibres. II. The role of vasomotors in metabolic adaptation of the coronaries. *Quart. J. Exp. Physiol.* 48 (1963), 105-118.
24. Szentivanyi, M, A Juhasz-Nagy: Functional coronary rigidity as an experimental model of angina pectoris. *Acta Physiol. Hung.* 30 (1966), 241-260.
25. Szlavy, L, D Adams, H Hollenberg, H Abrams: Cardiac lymph and lymphatics in normal and infarcted myocardium. *Am. Heart J.* 100 (1980), 323-331.
26. Ullal, S, T Kluge, F Gerbode: Functional and pathologic changes the heart following chronic cardiac lymphatic obstruction. *Surgery* 71 (1972), 328-334.
27. Veress, B, HJellinek, I Huttner, T Kerenyi, F Solti, M Isum, A Hartai, J Nagy: Uber die morphologie der lymphstauerungsbedingten Koronarveränderungen. *Frankf. Z. Pathol.* 75 (1966), 331-335.