Lymphology 34 (2001) 124-134

# PHYSIOLOGY OF HUMAN LYMPHATIC CONTRACTILITY: A HISTORICAL PERSPECTIVE

A.A. Gashev, D.C. Zawieja

Department of Medical Physiology, College of Medicine, Texas A&M University System Health Science Center, College Station, Texas, USA

"On emptying them [lymphatics] in the living animal, I have seen them contract so much that it was with the greatest difficulty I could distinguish them from the fibres."

Albrecht van Haller
(circa 1750)

*ABSTRACT*

*The lymphatic system is a transport system that has important roles in fluid/ macromolecule homeostasis, lipid absorption, metastasis and immune function. It accomplishes these roles via the generation of a regulated lymph circulation which is dependent upon valves and pumps to overcome the normal fluid pressure gradients. Lymphatic contractility plays crucial roles in the regulation and generation of lymph transport. Whereas our understanding of lymphatic contractility in humans is somewhat limited, a number of studies both in situ and in vitro have provided important insights into the presence and modulation of lymphatic contractility. These studies have clearly demonstrated that lymphatic vessels from a number of different human tissues possess both tonic and phasic changes in contractility. These changes in contractility are presumably involved in the generation and regulation of lymph flow. It has been shown that human lymphatic contractility can be influenced by a number of neural and humoral agents as a means to control lymph transport. However our understanding of the physical and chemical factors which regulate both the spontaneous pumping activity and the vessel tone are more limited. An understanding of the factors which regulate human lymph transport could provide valuable information on human biology that could be of benefit to the treatment and prevention of diseases.*

The lymphatic system is an organized network of vessels and lymphoid tissues that plays a crucial role in fluid and macromolecular transport/homeostasis, lipid absorption and immunity. The functioning of the lymphatic system depends upon a controlled circulation of lymph through this vascular and nodal network. Over the past 25 years, our knowledge of the core concepts of the physiology of lymph transport has grown more complete. Numerous *in vivo* and *in vitro* studies of lymphatic transport in many different tissues and species have been performed and reported. The lymphatic system moves fluid, macromolecules and formed elements from within the interstitial spaces into the primary lymphatics in the form of lymph. From these lymph capillaries, the lymph is propelled throughout a complicated network of lymphatic vessels, through numerous lymph nodes and eventually into the blood of the great veins. Because of the prevailing gradient of fluid pressures the flow of lymph can only be accomplished with the involvement of numerous pumps and valves.

Lymphatic vessels can be divided up into morphological/functional units termed lymphangions (1). A lymphangion is defined as the section of a lymphatic vessel between two adjacent lymphatic valves. Lymphangions have highly organized endothelial and smooth muscle layers in their walls. The presence of spontaneous oscillatory contractile activity has been seen in lymphatic vessels from many regions of the lymphatic system in many different species. The spontaneous contractile activity of lymphangions is initiated by action potentials, apparently arising within cells in the smooth muscle layer. It has been established that this "pumping" of the lymphatic vessels is one of the most important mechanisms for generating lymph flow. The phases of lymphangion contractile activity that lead to the movement of lymph toward the venous circulation are similar to the phases of contractile activity of the heart chambers. It is known that lymphangions have inherent autoregulatory mechanisms, such as stretch and endothelium-dependent responses, that modulate lymph pumping. Interstitial tissue forces, such as those produced during respiration, intestinal motility, tissue deformation, skeletal muscle activity and others, can influence the highly compliant lymphatics within that tissue to generate and alter lymph transport. The lymph pump also has complicated systems of extrinsic control, both neural and humoral, to match lymphatic pumping to the different physiological activities in the different parts of the body. Thus changes in the lymphatic contraction/relaxation state via the intrinsic/extrinsic pumping mechanisms or neural/humoral controllers can lead to changes in lymph circulation. Lymph flow can also be modulated by altering the resting diameter or "basal tone" of the lymphatics through the controlled tonic contraction/relaxation of the lymphatic smooth muscle. These changes in lymphatic tone can be activated either neurally or humorally, altering thereby lymph outflow resistance and modulating lymph flow through these vessels. Summaries of the physiology of lymphatic transport can be found in numerous reviews and articles (2-13).

Despite this body of work, there are still several important issues regarding lymph transport in humans that must be addressed. Generally the number of studies conducted in the area of human lymph transport is significantly smaller than those performed in other species. In particular, our understanding of the lymph pump in man is more limited. Also the different techniques and approaches used in these investigations can lead to different and sometimes opposing conclusions. In addition, although the regulation of lymphatic contractile behavior has some common features in all species, the differences among species can be notable. For these reasons, the use of data obtained in animal studies for the understanding of human lymphatic physiology, and pathology, may be problematic. Thus, the main aims of this review are; to present the state of the art of the physiology of human lymphatic pumping mechanisms, to summarize the current observations of human lymphatic contractility, and to look towards the future of this important yet unsettled area of human biology. This paper is organized to present the findings in historical order from the *in vivo* studies first followed by the data obtained *in vitro*.

## *PRESSURE MEASUREMENTS AND OBSERVATIONS OF CONTRACTILE ACTIVITY OF HUMAN LYMPHATICS IN VIVO*

Over the years, there have been many limitations that restrict our ability to investigate the contractile activity of the human lymphatics. The first evidence of contractile activity in human lymphatic vessels was obtained when investigators directly observed lymphatics during surgery. This evidence includes direct visual observations of the contractions, as well as

records of rhythmic intralymphatic pressure fluctuations that were independent of extrinsic forces.

The first study describing the presence of intrinsic contractility in human lymphatics in the modern era was published in 1956. Kinmonth and Taylor (14) described the visual observation of contractions of the thoracic duct and the large retroperitoneal lymphatics during surgical manipulations. The frequency of these contractions was 4-6 per minute. The authors indicated that the contractions were independent of respiratory movements. During these operations, the lymphatic contractions were filmed for demonstration purposes using cinematography film. Szegvari et al (15) described visual observations of lymphatic vessels of the leg prepared for lymphangiography in 1963. In all cases investigated they found spontaneous, rhythmic lymphatic contractions with frequencies of 4-5 per minute. Photos of a leg lymphatic vessel before and during a contraction were shown. In 1964, these authors (16) described more of their investigations. During lymphangiography, they made a 3 cm long transverse incision on the back of a foot of 20 patients with malignancies to observe the subcutaneous lymphatic vessels. These vessels were filmed for 30-50 min with a stereomicroscope. According to their observations, the lymphangions contracted 4 to 5 times a minute on average. They observed that the lymphangion contracted not only transversally, but also longitudinally. Motor activity of lymphangions was uniformly observed in each of the 20 patients studied. They also found that the lymphangions were highly sensitive to mechanical stimuli. Lymphatic contractions were stimulated by touching the surrounding tissues and after application of a NaCl solution. In the response to one drop of 0.5% procaine, the lymphatic first contracted slightly, and then dilated after a lapse of 8 to 10 seconds. Histamine and adrenaline applied locally in dilutions of $10^{-5}$M caused contractions of the lymphatics lasting 5 to 7 minutes. In 1964 Nusbaum et al (17) described the rhythmic expulsion of contrast compound from the thoracic duct into the venous system that was independent of breathing. In 1965 Edwards et al (18) reported radiographic observations of spontaneous contractility in the thoracic duct after injection of radiotracer into the foot. Waves of contraction were observed in the thoracic duct that were independent of respiration, segmental in nature and propagated up the duct. The contraction frequency in these experiments varied from 1 to 4 waves per minute.

Tilney and Murray, in 1968 (19), described experiments utilizing chronic (from 2 to 8 weeks) thoracic duct cannulation. The end-lymphatic pressure tracing showed "intrinsic ductal contractions" at a frequency of 5/minute that were unrelated to either respiration or heart rate. They demonstrated pressure fluctuations of about 5-10 mmHg in amplitude from a basal level near 30 mmHg. In 1973, Kinnaert (20) reported recordings of pressure waves in the cervical portion of the thoracic duct during a lymph drainage procedure. In 2 out of 8 patients, the pressure waves were independent of breathing and heart rate, with a frequency of 4-5 per minute. In 1968 Olszewski et al (21) reported the spontaneous movements of lymph vessels in man. Two cases of lymphedema of the lower limb were presented, in which contractions of lymph vessels were observed during lymphography and after surgical exposure during a lympho-venous anastomosis operation. Later Olszewski and Engeset (22, 23) measured intralymphatic pressures in the subcutaneous lymph trunks of healthy individuals. The lower leg subcutaneous lymph vessels were cannulated against the direction of lymph flow. The approximate lymphatic diameter ranged between 0.1 and 0.4 mm. The external end of cannula was connected to a pressure transducer to obtain pressure measurements. The zero level of pressure was set at the level of the internal opening of the cannula.

Lymph end pressures and lymph flow rates were measured. Pressure within the cannula was equilibrated to atmospheric pressure, then the stopcock was closed and pressure immediately increased to 5-25 mmHg. All pressure fluctuations in these experiments started from these resting values. Lymph pulse pressure ranged from 1 to 40 mmHg. At higher-pressure values, the frequency of contractions was higher. The rhythmic pressure pulsations were composed of groups of waves with 30-60 s intervals between each contraction. In each group of waves there were at least two but usually four to seven pulses. In all cases the lymph "pressure waves" were completely asynchronous with arterial pulse rate, respiratory movement and movements of leg muscles.

In later investigations, Olszewski and Engeset (24) performed lymphatic cannulations using T-shape tubes to measure the intraluminal lateral pressures. At rest, the mean lateral systolic pressure in the lymphatics with free lymph flow was 13.5±8.01 mmHg, lymph pulse amplitude was 8.8±4.6 mmHg and contraction frequency was 2.42±1.88/min. These values all rose sequentially from a horizontal rest position, to a horizontal position with flexing of the foot, to an upright rest position, to upright with a rising toe position. In the last case these values were: peak pressure 23.8±6.15 mmHg, lymph pulse amplitude 9.67±4.08 mmHg, contraction frequency 5.5±1.04/min. During these measurements of lateral pressures, the pressure level in between the pulse waves was always low, between zero and a few mmHg. The authors calculated mean lymph flow by measuring the movement of a tiny air bubble introduced into tubing inserted into both ends of leg lymph vessel. It was 0.25±0.04 ml/h (0.004 ml/min) in the horizontal position at rest, and 0.76±0.26 ml/h (0.012ml/min) in the upright position rising on toes. Lymph flow measured during the contraction phase was 1.62±0.64 ml/h (0.027 ml/min) at rest and close to the same value during skeletal muscular activity. During muscle activity or massage, the mean lymph diastolic, systolic and pulse pressures, contraction frequency and mean lymph flow did not increase significantly. Lymph flow was only observed during the pulse waves, and there was no flow in the period between the pulses, although massaging was continued. The authors explained the relatively high values of pressures by stating "lymphatics of the human limb should have a higher pumping capacity because of the large tissue mass of the extremity and a higher vascular resistance due to the increased length of vessels and gravitational forces" (24). Generally, there was a trend towards higher pressures in the larger vessels. They also noted that "even at 0 mmHg, contractions continued at a low frequency" (24). In 1982 this group measured lymph flow using an optical flowmeter (25). They recorded volume lymph flow and lymph pressure in the human leg. Each pressure wave (amplitude was near 4 mmHg) ejected a volume of about 0.001 ml.

In 1979 Seki (26) investigated the lymphatics of the human leg with lymphoradiography. Small amounts of a radioactive solution were injected into lymphatics at the back of the foot and radioactivity was recorded continuously for 30-40 minutes in either the inguinal region or at the thigh on the same side. Radioactivity measurements showed many spikes with a frequency of about 1/min. This frequency increased after moving the subjects from a supine position to the sitting position. Because these spikes were asynchronous with respiratory movement and arterial pulse, Seki concluded that the rhythmic spikes were due to oscillatory lymph flow attributable to the contractility of lymphatics. Armenio et. al used diagnostic lymphangiography of the lower limbs for the observation of contractile activity in human lymphatics in 1981 (27, 28). The authors made serial radiograms at 8-15 second intervals of the lower limbs of patients with malignancies or lower limb edema. In 26 out of 35 patients intrinsic spontaneous contractility was shown. All the patients that

demonstrated contractility were studied while lying in the supine position, avoiding any movement. The authors observed that usually groups of 2-4 lymphangions contracted simultaneously. Diastole was always significantly longer than systole. The contraction frequency was variable: sometimes contractions were every 20 sec, but usually they occurred every 30-120 sec. In only a few instances did the contractile activity move centripetally, resembling a peristaltic wave. They measured the linear velocity of lymph flow in a single experiment, observing the centripetal movement of an air bubble in the lymph vessel in consecutive radiograms. The measured velocity was 0.18 mm/sec.

Stranden and Kramer measured lymph pressures in superficial leg lymphatics in 1982 (29). Subcutaneous lymphatics were cannulated approximately 15 cm above the ankle joint. Intralymphatic end pressure waves were recorded and ranged between 30 and 40 mmHg. They wrote, "when the cannula was connected to the pressure transducer the intralymphatic pressure gradually increased. After the pressure had reached a threshold, rhythmic pulsations appeared. The threshold pressure varied between 5 and 15 mmHg" (29). The mean 24-hour lymph flow was 1.24±0.9 ml/h. In 1985 Aas et al (30) investigated the conditions of lymph flow in the human lower leg, using injections of radioactive human serum albumin. They found fluctuations of radioactivity using scintigrams and concluded that these fluctuations represented contractions of the different lymph vessel segments. In 1989 Sjoberg et al (31) described the measurement of lymphatic pressures in the human lower leg. They catheterized subcutaneous lymphatics in a retrograde direction. They found rhythmic pressure waves with a frequency 2.4±0.5/min at rest and 5.4-5.8±0.7/min during exercises. The amplitude of these pressure waves was 3.2-4.7 mmHg. These amplitudes were not consistently altered during exercises or running. The authors noted that they did not know if they measured end- or lateral pressures, because they did not know anything about the absence or presence of the branches in the region of the cannula.

In 1990 Gashev et al (4) made a visual analysis of lymphograms performed using a modified Kinmonth method (32). They found evidence of the presence of contractile activity of human leg deep-lymphatic collectors. They assumed that loss of contrast media in part of the vessels was due to the contractions of the lymphangions. But the contracted lymphangions did not completely empty; some portion of the contrast compound remained inside the vessel in the lymphangion near the input valve. This was described as the end-systolic volume. It was possible to determine how many lymphangions were involved in the contractile wave during one time period (the time of exposure was 5 sec). This number varied from 1 to 4 lymphangions and was dependent on the length of the contracted lymphangions. They found that if the diameter of the visible part of vessels was the same in all visible lymphangions, the length of the previously relaxed part of the vessel was similar to the length of vessel involved in the next contracted segment. This gave rise to the possibility that the ejected volume of the previous lymphangion could initiate contractions in 1 to 4 of the next lymphangions. In other words, the ejected volume of one lymphangion was enough to activate the contractions of the next one long lymphangion or 2-4 short lymphangions. In 1991 Krylov et al (33) published measurements of lymphatic pressure before lymphography and during an operation for lymphovenous anastomosis. Before lymphography, they catheterized the inflow end of the more central lymphatic vessels and measured the end-lymphatic pressure. The values of these pressures measured on the dorsum of hand and on the dorsal surface of foot were low, 0.86-1.1 mmHg. Then, they catheterized the outflow end of the more peripheral lymphatics in the leg and in the hand. In the

distal catheterization, pressure waves were recorded that were about 2-20 mmHg in amplitude from basal levels of 8-17 mmHg. The authors visibly correlated the elevations of lymph pressure with the contractions of lymphatic vessel.

In 1993 Zaugg-Vesti and others published (34) the measurements of lymphatic capillary pressure in healthy volunteers and in patients with primary lymphedema. Pressure was measured using the servo-null technique in the distal forefoot proximal to the base of the first and second toe. Mean lymph capillary pressure was 7.9±3.4 mmHg in the controls and 15.0±5.1 mmHg in patients with edema. The authors found pressure fluctuations of more than 3 mmHg. In their next investigation (35), Bollinger's group categorized the types of pressure fluctuation waves into two patterns: rhythmic low-amplitude (3.7±0.9 mmHg) waves with a frequency identical to respiration and spontaneous nonrhythmic, low frequency (1.24±0.64/min) waves with a higher amplitude (5.6±1.3 mmHg). However in 50 % of healthy controls no pressure fluctuations were observed. In 1996, Fischer et al published (36) data concerning measurements of flow velocity in the lymphatic capillaries of the foot dorsum. After injection of 10 microliters of fluorescent dextran they determined flow velocity on the video screen by direct measurement of the advancement of the fluorescent lymph. Peak flow velocity recorded during the first 45 s after dye injection was 0.51 mm/s (0.27 and 0.61 mm/s for lower and upper quartiles respectively). Resting velocity was 9.7 µm/s (6.9 and 14.2 µm/s for lower and upper quartiles respectively). In other work (37), this group described the influence of postural changes on cutaneous lymph capillary pressure at the dorsum of the foot. Mean lymph capillary pressure was 9.9±3.0 mmHg in the sitting and 3.9±4.2 in the supine position. Spontaneous low frequency pressure fluctuations occurred 89% of the time during sitting and in 54% of those in a supine position. They also described (38) pulsatile lymph flow seen during clinical observation of a chronic, traumatic lymph fistula. The authors concluded that this was due to the contractile activity of lymph collectors.

## *INVESTIGATIONS OF CONTRACTILE ACTIVITY OF HUMAN LYMPHATICS IN VITRO*

Many limitations have prevented lymphatic biologists from obtaining mechanistic information about the contractile activity of human lymphatics *in vitro*. Only a few scientists worldwide have published data from experiments using isolated parts of human lymphatics. The first report on human lymphatic *in vitro* experiments was published in the Proceedings of the Symposium "New Trends in Basic Lymphology" in 1966. Mislin (1) reported that he had isolated a mesenteric lymph vessel that exhibited spontaneous contractile activity from a recently deceased child. A series of studies were published in the 80's concerning aspects of arachidonic acid metabolism in human lymphatics. While these studies did not specifically evaluate the effects of arachidonic acid metabolites on pumping, they did look at the impact of these agents on tonic contractions. In 1980 (39) Mannheimer et al described the ability of human lymphatics taken from the dorsal pedis region to generate prostacyclin ($PGI_2$) in amounts that were high in comparison to vascular tissue of various species. In 1984 (40, 41) this same group found other arachidonic acid metabolites in human lymphatic tissue samples. They saw little or no effect of $PGI_2$ or $PGE_1$ on the tone of small isolated human lymphatic rings but described an increase in tone after $PGH_2$ administration. In 1986 (42) they described the increase in lymphatic tone seen after leukotriene $C_4$ administration. Later (43) these authors dissected lymphatics from lower legs obtained after trauma amputation. Experiments were performed on the small

rings that were cut from these vessels. It was established that prostaglandins $E_1$ and $I_2$ had no significant effect on tonic lymphatic contractility, whereas the thromboxane agonist U46619 and prostaglandin $F_{2\alpha}$ induced a rise of lymphatic tone.

Potashov et al (44) reported their investigations of the lymphatic vessels that were taken from 98 patients with lymphedema of the legs. During lymphography performed using a modified Kinmonth method (32), they obtained small specimens of lymphatic vessels. After extirpation, these vessels were investigated in a standard organ bath for isolated vessels. Constant recordings of longitudinal tension were performed under isometric conditions. Spontaneous rhythmic contractile activity was found in most of these vessels. The frequency of the contractions was 1-3/min. The application of additional longitudinal tension, 10 mM KCl, $3x10^{-9}$ M histamine, $3x10^{-9}$ M noradrenaline, or serotonin increased the frequency of the contractions in the spontaneously active vessels. These factors could also initiate contractile activity in inactive vessels. Transmural electrical stimulation caused tonic contractile responses. The administration of $\alpha$-adrenoblockers significantly decreased the tonic contractile responses to the transmural electrical stimulation. Morphological investigation of these specimens showed that in the vessels with spontaneous contractile activity, the structure of the lymphangion wall was relatively normal. In the inactive vessels taken from patients with high levels of edema, the authors found partial or complete atrophy in the smooth muscle layers in lymphangion wall, a significant decrease in the number of smooth muscle cells and other pathological changes.

In 1995 Borisova et al (45) summarized the data from their experiments conducted on isolated lymphangions from the human leg. These studies were performed under isometric conditions and measured the changes of tension. The spontaneous contractile activity of these lymphangions exhibited a contraction frequency of 3-4/min. Besides these phasic contractions, slow fluctuations of the basal tension were also seen. Noradrenaline either initiated contractions in quiescent vessels or increased their frequency at concentrations of $3x10^{-9}$ M or higher. The maximum chronotropic effect of noradrenaline was observed at concentration $3x10^{-5}$ M. The frequency of the contractions increased 232.6±22.7% above basal values. Adrenaline and isoprenaline in the same concentrations decreased the frequency of contractions. These effects were blocked by the _-antagonist Inderal. In low concentrations ($3x10^{-9}$ – $3x10^{-8}$ M) histamine caused an increase in the frequency and amplitude of the contractions, as well as the level of basal tension. But in higher concentrations ($3x10^{-7}$ – $3x10^{-5}$ M) the effects were the opposite. Serotonin ($2.5x10^{-9}$ – $2.5x10^{-5}$ M) caused a dose-dependent increase of the frequency and amplitude of contractions. The maximum effects were seen at $2.5x10^{-5}$ M and caused frequency to rise to 190.0±22.6% of basal frequency and the contraction amplitude to increase to 288.1±40.6% of basal amplitude. The $S_2$-receptor blocker, metizergid prevented all these effects. It was also determined that heparin in the doses 0.3-25 ED/ml decreased the frequency and amplitude of the phasic contractions as well as the level of the basal tension.

In 1987 Sjoberg et al (46) published data obtained in isolated rings from human lymphatics. Lymphatics with an outer diameter 0.2-0.4 mm were removed from the superficial groin during operations in 21 patients (one with lymphedema). Histochemically no nerves were identified with either specific catecholamine fluorescence or immunoreactivity to tyrosine hydroxylase or dopamine $\beta$-hydroxylase. Ring preparations of the lymphatics were mounted isometrically in tissue baths and contractions were recorded after administration of $K^+$ (124mM), acetylcholine, selected amines and prostanoids. Noradrenalin, adrenalin, dopamine,

**TABLE 1**
**The Regions of Human Body Where the Evidence of Lymphatic Contractile Activity Were Obtained**

| Body Region | Method | Spontaneous Contractility | References |
|---|---|---|---|
| Chest (thoracic duct) | Visual observations | + | (14) |
| | Observations during lymphography | + | (17,18) |
| | Lymph pressure measurements | + | (19,20) |
| Mesentery | Recordings of the length changes in isolated vessel | + | (1) |
| Hand | Lymph pressure measurements and visual observations | + | (33) |
| Groin | Recordings of tension of lymphatics rings | - | (46,47) |
| Leg | Visual observations | + | (15,16) |
| | Observation during lymphangiography | + | (4,26-28) |
| | Scintigraphy | + | (30) |
| | Lymph pressure and/or flow measurements | + | (21-25,29,31,33) |
| | Recordings of longitudinal tension of isolated vessels | + | (44,45) |
| | Recordings of tension of lymphatics rings | - | (43,48) |
| Foot | Fluorescence microlymphography | + | (36) |
| | Recordings of tension of lymphatic rings | - | (40-42) |
| | Lymph pressure measurements | + | (34,35,37) |

and acetylcholine had no or only weak contractile effects. In some segments, serotonin induced contractions. Prostaglandin $E_2$ showed no contractile effect but prostaglandin $F_{2\alpha}$ induced contraction in most of the tested lymphatics. In the lymphatic segment from the patient with lymphedema, a slightly greater contractile response to noradrenaline and serotonin was observed. Overall the results suggest an absence of sympathetic innervation and contraction-mediating $\alpha$ adrenergic receptors in human superficial groin lymphatics, and support the concept that certain prostanoids are important regulators of human lymphatic contractility. It must be noted that in all these experiments, vessel segments were first prewashed with a $K^+$-rich solution (2-6 times) and then $K^+$-induced contractions were evoked before any applications of drugs. Later, Sjoberg et al (47) described the depression of the thromboxane-induced contractions by thromboxane receptor antagonists. It's interesting to note that the authors carried out their experiments on the day after dissections. They observed $K^+$-induced contractions but wrote, "no spontaneous contractions were observed on the vessels" (47). The next paper from Sjoberg & Steen (48) was devoted to the contractile

properties of lymphatics from the human lower leg. Vessels were dissected from healthy volunteers. The extirpated vessels were about 5 mm long and had diameters of 0.2 mm *in situ*. They investigated contractile responses to $K^+$-rich solution of ring segments. In the lower leg lymphatics, noradrenaline induced phasic contractions at $10^{-7}$ – $10^{-5}$ M with a maximum frequency of 5-13/min at $10^{-6}$ M. The beta-blocker, propranolol $3X10^{-7}$ M and $10^{-6}$ M did not influence the noradrenaline-induced phasic contractions but the alpha-antagonist phentolamine $10^{-6}$ M abolished them. Phasic contractions were also elicited by 5-hydroxytryptamine, prostaglandin $F_{2\alpha}$ and thromboxane $A_2$-mimetic U-44069.

## *SUMMARY AND CONCLUSIONS*

In summary, there is strong documentation of the presence of spontaneous contractile activity in human lymphatic vessels. This evidence has been obtained using many different techniques; including visual observations, measurements of lymph pressure fluctuations in catheterized lymphatics, and limited data from isolated lymphatic sections *in vitro* (*see Table 1*). This spontaneous contractile activity presumably results in the changes in lymph pressure needed to produce lymph flow. The mechanisms by which this pumping activity is regulated is still poorly understood. We know that some factors can change lymph flow by modulating human lymphatic contractility, i.e. adrenergic and nonadrenergic regulation. However, our knowledge of the mechanisms which generate and regulate lymphatic pumping activity in humans is far from complete. Notably the following important information is limited or missing:

1. The biomechanical properties of human lymphatic vessels and valves;
2. The shape and the ionic nature of the muscle excitation leading to contraction in human lymphatics;
3. The propagation and coordination of contractile waves in human lymphatic vessels;
4. The pressure – flow relationships in human lymphatics during the contractile cycle;
5. The presence and the potential mechanisms of stretch- and flow-dependent changes in lymphatic contractile function;
6. The importance and mechanisms of neural and humoral control of lymphatic contractions;
7. The interactions between the venous and lymphatic systems in the regions of the thoracic duct and lymph nodes;
8. The presence, importance and mechanisms of contractile activity of human lymph nodes.

In general most of our understanding of the mechanisms responsible for controlling human lymphatic pump function is limited primarily to observational data. More detailed analyses of the homeostatic regulation of human lymph transport will benefit from more mechanistic experimental approaches. These early studies have provided important documentation of the presence of spontaneous contractile pumping activity in most human lymphatics and has given valuable insights into the possible neural/humoral agents which can modulate that pumping function. However, studies of this nature could provide the scientific and medical community with valuable information on human biology that could potentially be of great benefit to the treatment and prevention of human diseases.

## *REFERENCES*

1. Mislin, H: Structural and functional relations of the mesenteric lymph vessels. New Trends in Basic Lymphology; Proceedings of a Symposium held at Charleroi (Belgium); July 11-13, 1966. Experientia. Suppl. 14 (1966), 87-96.
2. Atchison, DJ, MG Johnston: Role of extra- and intracellular Ca2+ in the lymphatic myogenic response. Am. J. Physiol. 272 (1997), R326-33.
3. Benoit, JN, DC Zawieja: Gastrointestinal lymphatics. In: *Physiology of the Gastrointestinal Tract*, L. Johnson, (ed.), Raven Press, New York, 1994, pp. 1669-92.

4. Gashev, AA, RS Orlov, AV Borisov, et al: The mechanisms of lymphangion interaction in the process of the lymph movement [Russian]. Fiziologicheskii Zhurnal Imeni I.M. Sechenova 76 (1990), 1489-508.
5. McHale, NG: Lymphatic innervation. Blood Vessels 27 (1990), 127-36.
6. McHale, NG: The lymphatic circulation. Ir. J. Med. Sci. 161 (1992), 483-6.
7. Ohhashi, T, S Yokoyama: Nitric oxide and the lymphatic system. Jap. J. Physiol. 44 (1994), 327-42.
8. Schmid-Schonbein, GW: Microlymphatics and lymph flow. Physiological Reviews 70 (1990), 987-1028.
9. Szuba, A, SG Rockson: Lymphedema: Anatomy, physiology and pathogenesis. Vascular Medicine 2 (1997), 321-6.
10. Von der Weid, PY, DF Van Helden: Functional electrical properties of the endothelium in lymphatic vessels of the guinea-pig mesentery. J. Physiol. 504 (1997), 439-51.
11. Witte, CL, MH Witte: Disorders of Lymph Flow. Acad. Radiol. 2 (1995), 324-334.
12. Zawieja, DC, KL Davis, R Schuster, et al: Distribution, propagation, and coordination of contractile activity in lymphatics. Am. J. Physiol. 264 (1993), H1283-91.
13. Zawieja, DC: Lymphatic microcirculation. Microcirculation 3 (1996), 241-3.
14. Kinmonth, JB, GW Taylor: Spontaneous rhythmic contractility in human lymphatics. J Physiol. 133 (1956), 3P.
15. Szegvari, M, A Lakos, F Szontagh, et al: Spontaneous contractions of lymphatic vessels in man. Lancet 7294 (1963), 1329.
16. Szegvari, M, A Lakos, F Szontagh, et al: The active function of the subcutaneous lymphatic vessels of the human lower extremity. Acta Medica Academiae Scientiarum Hungaricae 20 (1964), 209-13.
17. Nusbaum, M, S Baum, RC Hedges, et al: Roentgenographic and direct visualization of thoracic duct. Archives of Surgery 88 (1964), 127-35.
18. Edwards, JM, MH Gough, JB Kinmonth, et al: Spontaneous contractility of the human thoracic duct. J. Physiol. 177 (1965), 41P-42P.
19. Tilney, NL, JE Murray: Chronic thoracic duct fistula: operative technic and physiological effects in man. Annals of Surgery 167 (1968), 1-8.
20. Kinnaert, P: Pressure measurements in the cervical portion of the thoracic duct in man. Brit. J. Surg. 60 (1973), 558-61.
21. Olszewski, WL, S Kruszewski, J Sokolowski, et al: Observations of movements of lymph vessels in patients with lymphoedema of the limbs [Polish]. Polski Tygodnik Lekarski. 23 (1968), 1345-47.
22. Olszewski, WL, A Engeset: Intrinsic contractility of leg lymphatics in man. Preliminary communication. Lymphology 12 (1979), 81-4.
23. Olszewski, WL, A Engeset: Lymphatic contractions. New Eng. J. Med. 300 (1979), 316.
24. Olszewski, WL, A Engeset: Intrinsic contractility of prenodal lymph vessels and lymph flow in human leg. Am. J. Physiol. 239 (1980), H775-83.
25. Sorensen, O, A Engeset, WI Olszewski, et al: High-sensitivity optical lymph flow-meter. Lymphology 15 (1982), 29-31.
26. Seki, K: Lymph flow in human leg. Lymphology 12 (1979), 2-3.
27. Armenio, S, F Cetta, G Tanzini, et al: Spontaneous contractility in the human lymph vessels. Lymphology 14 (1981), 173-8.
28. Armenio, S, F Cetta, G Tanzini, et al: Spontaneous contractility of the lymphatic vessels in man. [Spanish]. Angilogia 33 (1981), 325-7.
29. Stranden, E, K Kramer: Lymphatic and transcapillary forces in patients with edema following operation for lower limb atherosclerosis. Lymphology 15 (1982), 148-155.
30. Aas, M, A Skretting, A Engeset, et al: Lymphatic drainage from subcutaneous tissue in the foot and leg in the sitting human. Acta Physiol. Scand. 125 (1985), 501-11.
31. Sjoberg, T, L Norgren, S Steen: Contractility of human leg lymphatics during exercise before and after indomethacin. Lymphology 22 (1989), 186-93.
32. Kinmonth, JB: *The Lymphatics. Diseases, Lymphography and Surgery*. Edward Arnold Publisher, London, 1972.
33. Krylov, VS, NO Milanov, KG Abalmasov, et al: Endolymphatic pressure in the evaluation of the status of peripheral lymph flow in the extremities [Russian]. Khirurgiia. 6 (1991), 63-9.
34. Zaugg-Vesti, B, J Dorffler-Melly, M Spiegel, et al: Lymphatic capillary pressure in patients with primary lymphedema. Microvasc. Res. 46 (1993), 128-34.
35. Wen, S, J Dorffler-Melly, I Herrig, et al: Fluctuations of skin lymphatic capillary pressure in controls and in patients with primary lymphedema. Int. J. Microcirc. Clin. Experimental 14 (1994), 139-43.
36. Fischer, M, U Franzeck, I Herrig, et al: Flow velocity of single lymphatic capillaries in human skin. Am. J. Physiol. 270 (1996), H358-63.

37. Franzeck, UK, M Fischer, U Costanzo, et al: Effect of postural changes on human lymphatic capillary pressure of the skin. J. Physiol. 494 (1996), 595-600.
38. Fischer, M, UK Franzeck, A Bollinger: Rhythmic lymph extravasation from a lymph fistula [German]. Vasa. 25 (1996), 358-61.
39. Mannheimer, E, H Sinzinger, R Oppolzer, et al: Prostacyclin synthesis in human lymphatics. Lymphology 13 (1980), 44-6.
40. Sinzinger, H, J Kaliman, E Mannheimer: Arachidonic acid metabolites of human lymphatics. Lymphology 17 (1984), 39-42.
41. Sinzinger, H, E Mannheimer, J Kaliman: Regulation of human lymph contractility by prostaglandins and thromboxane. Lymphology 17 (1984), 43-5.
42. Sinzinger, H, J Kaliman, E Mannheimer: Effect of leukotrienes C4 and D4 on prostaglandin I2-liberation from human lymphatics. Lymphology 19 (1986), 79-81.
43. Sinzinger, H, A Oguogho, J Kaliman: Isoprostane 8-epi-prostaglandin F2 alpha is a potent contractor of human peripheral lymphatics. Lymphology 30 (1997), 155-9.
44. Potashov, LV, RS Orlov, AV Borisov, et al: Pathogenetic basis of the diagnosis and treatment of lymphedema of the lower extremities [Russian]. Kardiologiia 29 (1989), 63-6.
45. Borisova, RP, NA Bubnova, SV Petrov, et al: The importance of the theory of lymphangion for clinic [Russian]. In: *Lymphangion (Theory and Practice)*. Borisov, AV (ed.), State Medical Academy, St.-Petersburg, Russia, 1995, pp. 86-91.
46. Sjoberg, T, P Alm, K-E Andersson, et al: Contractile response in isolated human groin lymphatics. Lymphology 20 (1987), 152-60.
47. Sjoberg, T, K-E Andersson, L Norgren, et al: Antagonism of thromboxane receptor induced contractions in isolated human groin lymphatics. Lymphology 22 (1989), 135-40.
48. Sjoberg, T, S Steen: Contractile properties of lymphatics from the human lower leg. Lymphology 24 (1991), 16-21.

**Anatoliy A. Gashev, M.D., Ph.D.**
**Texas A&M University System Health Sciences Center**
**Department of Medical Physiology**
**336 Joe H. Reynolds Medical Building**
**College Station, Texas 77843-1114**