Inhibition of active lymph pump by simulated microgravity in rats

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Inhibition of active lymph pump by simulated microgravity in rats. Am J Physiol Heart Circ Physiol 290: H2295–H2308, 2006. First published January 6, 2006; doi:10.1152/ajpheart.00260.2005.—During spaceflight the normal head-to-foot hydrostatic pressure gradients are eliminated and body fluids shift toward the head, resulting in a diminished fluid volume in the legs and an increased fluid volume in the head, neck, and upper extremities. Lymphatic function is important in the maintenance of normal tissue fluid volume, but it is not clear how microgravity influences lymphatic pumping. We performed a detailed evaluation of the influence of simulated microgravity on lymphatic diameter, wall thickness, elastance, tone, and other measures of phasic contractility in isolated lymphatics. Head-down tail suspension (HDT) rats were used to simulate the effects of microgravity. Animals were exposed to HDT for 2 wk, after which data were collected and compared with the control non-HDT group. Lymphatics from four regional lymphatic beds (thoracic duct, cephalic, mesenteric, and femoral lymphatics) were isolated, cannulated, and pressurized. Input and output pressures were adjusted to apply a range of transmural pressures and flows to the lymphatics. Simulated microgravity caused a potent inhibition of pressure/stretch-stimulated pumping in all four groups of lymphatics. The greatest inhibition was found in cervical lymphatics. These findings presumably are correlated to the cephalic fluid shifts that occur in HDT rats as well as those observed during spaceflight. Flow-dependent pump inhibition was increased after HDT, especially in the thoracic duct. Mesenteric lymphatics were less strongly influenced by HDT, which may support the idea that lymph hydrodynamic conditions in the mesenteric lymphatic during HDT are not dramatically altered.

lymphatic vessels; thoracic duct; lymphatics

The earth’s gravity exerts a pervasive effect on the human body’s fluid pressure gradients and regional volume distribution (58). When humans are exposed to a microgravity environment, many body functions are altered. Notably, the normal head-to-foot hydrostatic pressure gradients are eliminated and body fluids shift toward the head, resulting in a diminished fluid volume in the legs, facial edema, and increased fluid volume in the upper extremities (17, 27, 36, 56, 58). The facial puffiness common among astronauts and cosmonauts can persist wholly or partially for the duration of space missions lasting days, weeks, and months (14, 18, 27). Another important impact of microgravity is immune dysfunction. Both short- and long-term spaceflights have been associated with a number of effects related to immune dysfunction.

The facial edema and increased upper extremity tissue fluid volume associated with microgravity are thought to result in part from elevated capillary blood pressure, reduced capillary colloid osmotic pressure, and a net transvascular fluid filtration (46, 58). However, these considerations do not take into account the important influences that lymphatic function has on interstitial volume regulation (55). Historically lymphatic function has been thought to be one of the critical safety factors preventing and resolving edema. Thus the upper body edema encountered during exposure to microgravity may also reflect an altered ability of lymphatic vessels to transport excessive interstitial fluids from the tissues to the venous circulation, particularly given the persistence of the condition. Any other disorders connected with an insufficiency of lymphatic ability to evacuate extracellular fluid cause tissue edema and post-edema complications, including impairment of immune function (48, 53).

The transport of fluid from the interstitium to venous blood is dependent in part on the ability of the lymphatics to actively pump fluid, because the normal net pressure gradient from the interstitium to the great veins opposes passive flow. Additionally, effective lymph transport depends on the normal function of the lymphatic valves to prevent lymph backflow when the pressure gradient does not favor central flow. Although these valves are anatomic hallmark structures of lymphatic vessels, the details of their precise roles in lymphatic function have not been well documented. This active lymph pump depends on the intrinsic phasic contractions of the lymphatic smooth muscle. The pumping activity is known to be extremely sensitive to lymph fluid dynamics, i.e., lymphatic pressure and flow (19, 21, 33, 40, 43). Stretch of the lymphatic due to increased transmural pressure has long been known to stimulate the active lymph pump and is thought to be one of the principal intrinsic regulators of lymphatic pump function (see Refs. 3, 19, 22, and 49 for review). On the other hand lymph flow, via shear, is known to be a powerful inhibitor of the active lymph pump (21, 28, 34, 35). Additionally, we recently demonstrated (20) that the influence of lymph dynamics on the active lymph pump is differentially regulated, dependent on the regional patterns of lymph dynamics. During head-down tail suspension (HDT) and microgravity the central venous pressure increases and the gradient of interstitial to venous pressure becomes even more unfavorable to passive flow (5, 51).

To assess whether the contractile function of lymphatic vessels is altered by microgravity, the HDT rat was used as a model to study this phenomenon on Earth. The HDT rat is used as a surrogate for microgravity exposure because this model induces the cephalic fluid shift that occurs in microgravity (10, 24, 47, 59) and HDT rats manifest many of the adaptations that...
are characteristic of human exposure to microgravity, including hypovolemia (37, 51), immune dysfunction (1, 8, 9, 50, 52, 57), resting and exercise tachycardia (32), a diminished capacity to elevate vascular resistance (32, 44), orthostatic hypotension (31), and a reduced aerobic capacity (13, 44). Comparative analysis of metabolic and structural shifts in rats after 14 days of microgravity aboard biosatellite Cosmos-2044 and their tail-suspended synchronous controls demonstrated a high correlation of changes in bones and muscles for both experimental groups of animals and provided valuable evidence that HDT can be used as a model of the microgravity effects in ground-based studies (26).

The critical roles of lymphatic pumping in body fluid regulation and immune function and the extremely limited information on the influences of microgravity on lymphatic contractile activity drove our interest to investigate lymphatic pumping behavior in different regional lymphatic vessels under the influence of stimulated microgravity. Previous work demonstrated that actual and simulated microgravity can adversely affect smooth muscle contractile function in arteries (12, 25, 45), arterioles (11), veins (16), and the uterus (7). We hypothesized that microgravity could also alter lymphatic muscle contractility. We studied the intrinsic sensitivity of the active lymph pump to pressure and flow in rat lymphatic vessels isolated from four different regions of the lymphatic vasculature (thoracic duct, cervical, mesenteric, and femoral lymphatics) after 14 days of exposure to HDT.

MATERIALS AND METHODS

Animals, HDT Model, and Surgical Procedures

The animal facilities used for these studies have been accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International and adhere to the regulations, policies, and principles detailed in the Public Health Service Policy for the Humane Care and Use of Laboratory Animals (1996) and the Department of Agriculture’s Animal Welfare Regulations (Animal Welfare Act, 9 CFR, 1985, 1992). All animal procedures performed for this study were reviewed and approved by the Texas A&M University Institutional Animal Care and Use Committee and conform to the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals [DHHS Pub. No. (NIH) 85-23, Revised 1985, Office of Science and Health Reports, DRR/NIH, Bethesda, MD 20892].

To study the influences of simulated microgravity on the active lymph pumps we investigated the contractile activity of lymphatics from 74 male Sprague-Dawley rats (weighing between 250 and 400 g). Six- to eight-month-old rats were obtained from Harlan and housed in an environmentally controlled room maintained at 23 ± 2°C. The animals were given food (commercial rat chow) and water ad libitum. Rats were randomly divided between control (n = 27) and HDT (n = 47) groups. The hindlimbs of the HDT animals were elevated to an approximate spinal angle of 40 – 45° from horizontal (10, 59). The animals were injected with pentobarbital sodium (120 mg/kg body wt ip). A 4-cm-long midline abdominal incision was made through the skin, underlying fascia, and abdominal muscle layers. A small loop of small intestine, 6 – 7 cm in length, was exteriorized through the incision. A section of the mesentery containing lymphatic vessels was exteriorized and continuously suffused with a modified Tyrode-physiological saline solution. Suitable lymphatics were found and cleared of all surrounding tissues. Sections of the mesenteric lymphatics 1 – 1.5 cm in length were carefully dissected and used for experiments. After the mesenteric, cervical, and femoral lymphatics were isolated, the rats were euthanized with pentobarbital sodium (120 mg/kg body wt ip).

To isolate the cervical lymphatics, the rats were anesthetized with a combination of a fentanyl-droperidol solution (0.3 ml/kg im) and diazepam (2.5 mg/kg im). A 4-cm-long midline abdominal incision was made through the skin, underlying fascia, and abdominal muscle layers. A small loop of small intestine, 6 – 7 cm in length, was exteriorized through the incision. A section of the mesentery containing lymphatic vessels was exteriorized and continuously suffused with a modified Tyrode-physiological saline solution. Suitable lymphatics were found and cleared of all surrounding tissues. Sections of the mesenteric lymphatics 1 – 1.5 cm in length were carefully dissected and used for experiments. For isolation of femoral lymphatics, all anesthesia and euthanasia procedures were the same as those used to obtain the cervical lymphatic segments. The skin was removed from the entire ventral surface of the rat’s neck. The underlying fascia layers and superficial muscles were dissected in the area near the connection of the external and internal jugular veins. Cervical lymphatics were identified as comparatively large lymphatic trunks between the internal and external jugular veins located on the cephalic side of their confluence deeper than the level of veins. These lymphatic vessels formed a sharp angle with the external jugular vein and were sometimes found under the external jugular vein. Sections of cervical lymphatics 1 – 1.5 cm in length were carefully dissected and used for experiments.
Later during the experiments, we measured the diameters of all lymphatic vessels used for these studies. At a transmural pressure of 3 cmH2O, the average resting/diastolic diameters were 448 ± 27 (thoracic duct), 385 ± 28 (cervical lymphatics), 117 ± 26 (mesenteric lymphatics), and 123 ± 28 (femoral lymphatics) μm.

Isolated Vessel Procedures and Techniques

Once exteriorized, each lymphatic segment was transferred to a chamber filled with chilled (0–4°C) albumin-physiological salt solution (APSS; in mM: 145.00 NaCl, 4.7 KCl, 2.0 CaCl2, 1.17 MgSO4, 1.2 NaH2PO4, 5.0 dextrose, 2.0 sodium pyruvate, 0.02 EDTA, and 3.0 MOPS, with 10 g/l bovine serum albumin). The isolated lymphatic was cannulated and tied onto two carefully matched glass micropipettes (90- to 120-μm tip diameter for mesenteric and femoral lymphatics, 300–350 μm for cervical lymphatics, and 400–450 μm for thoracic ducts). Great care was used to prepare and select sets of resistance-matched pipettes for experiments with controlled imposed flow. For each experiment we chose pairs of pipettes with matching diameters and tip lengths and tested them to ensure that the difference between their measured electrical resistances did not exceed 10% (29) so as to not alter the transmural pressure when varying flow through their measured electrical resistances did not exceed 10% (29) between their measured electrical resistances did not exceed 10% (29). For each experiment we chose pairs of pipettes with matching diameters and tip lengths and tested them to ensure that the difference between their measured electrical resistances did not exceed 10% (29) so as to not alter the transmural pressure when varying flow through the vessel. These glass pipettes were connected to independently adjustable pressure reservoirs. Once cannulated, the vessel was slowly warmed over 60 min to ~25°C. Slight positive pressure (2–3 cmH2O) was applied to the vessel to detect leaks and to ensure that the vessel was undamaged and untwisted. The vessel was set to its approximate in situ length and positioned above the glass coverslip comprising the chamber bottom. The isolated vessel preparation was then transferred to the stage of a microscope. The pressurizing system was calibrated such that an intraluminal pressure of 0 cmH2O was accepted when levels of colored solutions in input and output reservoirs did not allow solutions to enter or exit the input or output pipettes. Both pipettes were positioned in the middle of an isolated vessel chamber, and the chamber was filled by solution as it would be during the experiment. The vessel was set to an equilibrium pressure of 1 cmH2O and warmed further to 37–38°C. Once tone and spontaneous contractions were observed, the vessel was allowed to equilibrate at 1 cmH2O for an additional 15 min. A video camera and a high-resolution monitor were used to observe the lymphatic, and a video recorder was used to record all experiments. The lymphatic diameters (outer and inner) were later measured from the videotape with a videomicroimeter and techniques described previously (61–63). To evaluate the characteristics of the lymph pump we used cardiac pump analogies to define lymphatic systolic and diastolic outer diameters in reference to the lymphatic contractile cycle (2, 62). At the end of each experiment, the passive (relaxed) diameters and average lymphatic wall thicknesses (expressed as % of the outer diameter, %WT) were measured at each pressure after the vessels were exposed for 15 min to nominally calcium-free APSS supplemented with EDTA (3.0 mM).

From the lymphatic diameters the following lymph pump parameters were calculated: contraction amplitude (difference between systolic and diastolic outer diameters), contraction frequency, ejection fraction (fraction of end-diastolic volume ejected during lymphatic contraction), and fractional pump flow (a size-independent index of lymph pump flow, calculated as ejection fraction times contraction frequency, equating to fractional change in lymphatic volume per minute). The data were collected in 5-min intervals at each set of inflow/outflow pressures. Because of the anatomic, regional, and individual variations between lymphatic vessels, to compare the changes in diameters during the lymphatic contractile cycle the diastolic and systolic diameters were normalized to the passive lymphatic diameters in calcium-free APSS at the corresponding transmural pressure and presented as a percentage of the passive diameter. The differences between the diastolic outer diameters and the corresponding passive outer diameters in calcium-free APSS were used to measure the changes in the “resting” myogenic tone in lymphatics during the experiments. Thus an increase in tone is represented as a decrease in the normalized diastolic diameter. To evaluate the influence of HDT on compliance of the lymphatics, we calculated the incremental Young’s modulus of elastance (E′), which is inversely related to vascular compliance under passive conditions over the range of pressures studied (39).

Experimental Protocol and Statistics

The inflow and outflow pipettes were attached to independently adjustable pressure reservoirs by three-way stopcocks. Care was taken to ensure that there were no air bubbles in the tubing or the pipettes. To evaluate pressure-induced changes in contractile activity of selected lymphatics, all vessels were exposed to a range of transmural pressures (1, 2, 3, 5, and 7 cmH2O) with no imposed flow. To determine the flow-induced changes in lymphatic contractions, the vessels were exposed to sets of imposed flows. Imposed flows through the isolated lymphatics were generated with techniques previously used in isolated arterioles and venules (29). Because lymphatic vessels are very sensitive to changes in transmural pressure, it was important to maintain a constant net transmural pressure at any given set of imposed flows (19–21, 33, 40). Briefly, this was accomplished by raising the pressure on the inflow end of the isolated vessel and lowering the pressure on the outflow end of the isolated vessel by identical amounts so as to create a pressure gradient of 0–5 cmH2O across the input to output ends of the vessel (29). For example, for a transaxial pressure gradient of 1 cmH2O and a transmural pressure of 3 cmH2O, we set input pressure to 3.5 cmH2O and output pressure to 2.5 cmH2O. Because we showed previously that flow inhibits the active lymph pump (21) and different vessel types display different pump/pump maximums (20, 38), we wanted to study the impact of flow in each vessel type at the transmural pressure at which maximum pumping occurred. For studies on thoracic duct, we chose 3 cmH2O as the mean transmural pressure, which is the pressure at which these lymphatic vessels displayed maximal active pumping. For other lymphatics we used 5 cmH2O as the mean transmural pressure. The numbers of lymphatic vessels used in the reported data are shown separately for each group of experiments, where n depicts the number of vessels used for each experimental protocol. Only one vessel was taken from each animal, so in most cases the pressure- and flow-induced responses were determined once for each vessel. Statistical analyses were determined by ANOVA, analysis of covariance, regression analysis, and Student’s t-test (JMP software version 5.0.1.2 for Windows) and considered significant at P < 0.05.

RESULTS

Influences of HDT on Transmural Pressure-Induced Changes in Active Lymphatic Pumping

In the present study we compared the contractile behavior of isolated thoracic duct (n = 5/15, control and HDT rats, respectively), cervical (n = 6/8), mesenteric (n = 7/13), and femoral (n = 6/9) lymphatics under the influence of transmural pressures from 1 to 7 cmH2O in control and HDT groups of animals. We present as examples the changes in lymphatic pumping parameters that occurred at transmural pressures of 3 and 7 cmH2O. These are the transmural pressures at which all lymphatics selected for study exhibit maximal or submaximal pumping (20). Values obtained at all the pressures selected for study are presented in Figs. 1–4 and Table 1.

Normalized diastolic and systolic diameters. Figure 1 presents the comparison of normalized diastolic and systolic diameters in the four different lymphatic vessels at different transmural pressures in control and HDT groups. In the thoracic duct, simulated microgravity (HDT) caused a significant

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increase in normalized diastolic diameter at all levels of transmural pressure (10% increase at 3 cmH2O and 9% at 7 cmH2O). These changes represented a 63% and 69% reduction in resting tone at 3 and 7 cmH2O transmural pressure, respectively. In addition to these changes in diastolic diameter, the lymphatic wall thickness %WT of the thoracic duct increased by 65% (from 4.5% to 7.5%) after HDT.

In cervical lymphatics, HDT induced quite different changes in lymphatic diameter. We found only a slight trend for HDT to increase normalized diastolic diameters, which was not statistically significant at any level of transmural pressure. This indicates that tone in cervical lymphatics remained unchanged after HDT. The wall thickness of the cervical lymphatics increased by 42% (%WT rose from 8.6% to 12.3%) after HDT. \( E_s \) of the cervical lymphatics was not significantly altered by HDT. Normalized cervical systolic diameters were increased in HDT rats (12% increase at 3 cmH2O and 7% increase at 7 cmH2O). These changes in diameters led to a dramatic reduction of the contraction amplitude in cervical lymphatics after 2 wk of HDT. At transmural pressures of 3 and 7 cmH2O, contraction amplitude was decreased 86% and 76%, respectively, from values seen in control vessels. On average, for all pressure levels contraction amplitude was inhibited in HDT cervical lymphatics by 84%.

The normalized diastolic diameter of HDT mesenteric lymphatics exhibited a pattern similar to that found in the thoracic duct. HDT increased normalized diastolic diameters at all investigated levels of transmural pressure (Fig. 1; 6% increase at 3 cmH2O and 2% increase at 7 cmH2O). The changes in resting diameter represents a 45% and 24% reduction in tone at 3 and 7 cmH2O of transmural pressure, respectively. Mesenteric lymphatic wall thickness decreased by 40% (%WT from 13.0% to 7.7%) after HDT. \( E_s \) of the mesenteric lymphatics from control rats varied from 0.28 \( \times \) 10^6 dyn/cm^2 at 2 cmH2O to 21.65 \( \times \) 10^6 dyn/cm^2 at 7 cmH2O. However, HDT did not produce significant changes in \( E_s \) of the thoracic duct. Thoracic duct normalized systolic diameters were also significantly increased at all transmural pressures in HDT animals (38% increase at 3 cmH2O and 15% at 7 cmH2O). As a result of these diameter changes, the amplitude of the phasic contractions was diminished after 2-wk HDT exposure. The differences between the blue lines in Fig. 1 demonstrate the lymphatic contraction amplitude in control rats, and the differences between red lines demonstrate the contraction amplitude in HDT animals. At 3 and 7 cmH2O, the contraction amplitude in the thoracic duct was reduced by 68%. The average contraction amplitude for all pressure levels was inhibited in HDT thoracic duct by 63%, indicating a negative inotropic effect.

### Table 1. Influence of simulated microgravity on transmural pressure-induced changes in lymphatic diameters

<table>
<thead>
<tr>
<th>Transmural Pressure, cmH2O</th>
<th>Thoracic Duct ((n = 5/15))</th>
<th>Cervical Lymphatics ((n = 6/6))</th>
<th>Mesenteric Lymphatics ((n = 7/13))</th>
<th>Femoral Lymphatics ((n = 69))</th>
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<td>DD C</td>
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<td>306 (\pm) 37</td>
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Values (in \(\mu\)m) are means \(\pm\) SE for \(n\) rats [control group (C)/head-down tail suspension (HDT) group]. DD, diastolic diameter; SD, systolic diameter.
However, HDT did not significantly alter $E_s$ in femoral lymphatics. Normalized systolic diameters were increased 9% at 3 cmH$_2$O and 4% at 7 cmH$_2$O in HDT femoral lymphatics. These changes caused a decrease of contraction amplitude after HDT. At 3 and 7 cmH$_2$O the contraction amplitude was reduced 72% and 55%, respectively, from control. On average, for all pressure levels the contraction amplitude in HDT femoral lymphatics was inhibited 72%. Table 1 presents changes in all the values of normalized diastolic and systolic diameters due to HDT.

**Contraction frequency.** HDT caused negative chronotropic effects on pumping in all four groups of lymphatic vessels. In thoracic duct, the HDT-induced inhibition of frequency was comparatively small, although this vessel has a low sensitivity of contraction frequency to pressure even under control conditions (20). At 3 and 7 cmH$_2$O of transmural pressure, the contraction frequency of HDT thoracic ducts was reduced 43% and 19%, respectively, from control. On average, contraction frequency in HDT thoracic ducts was inhibited by 35%. In cervical lymphatics, the chronotropic inhibition was significantly higher than in thoracic ducts. Contraction frequencies in cervical lymphatics were diminished by 81% and 77% at transmural pressures of 3 and 7 cmH$_2$O, respectively.

The average decrease in frequency due to HDT in cervical lymphatics was 80%, whereas the sensitivity of the cervical lymphatics contraction frequency to transmural pressure was decreased by 70% after HDT. Mesenteric lymphatics also exhibited a frequency decrease tied to exposure to HDT. At pressures of 3 and 7 cmH$_2$O, contraction frequencies were inhibited 32% and 26%, respectively, in these vessels. Average HDT-induced inhibition of frequency in mesenteric lymphatics was 33%, although there was no significant change in the sensitivity of the mesenteric lymphatics contraction frequency to transmural pressure. In femoral lymphatics, HDT also caused a negative chronotropic effect. Contraction frequency was decreased by 48% and 49% at transmural pressures of 3 and 7 cmH$_2$O, respectively. On average, the contraction frequency was diminished in femoral lymphatics by 48% and the sensitivity of the contraction frequency to transmural pressure was diminished by 53%. Figure 2 compares the HDT-induced inhibition in contraction frequency for all four lymphatics at all pressures tested.

**Ejection fraction.** Figure 3 presents a comparison of HDT-induced changes in ejection fraction for all four groups of lymphatics studied. In all lymphatic vessels, we observed an HDT-induced inhibition of ejection fraction, which was a sign...
of the strong negative inotropic effect on lymphatic muscle. At both 3 and 7 cmH$_2$O of transmural pressure, the ejection fractions of HDT thoracic ducts were decreased by 69%. On average, for all transmural pressure levels ejection fractions in HDT thoracic ducts were inhibited 66%. In cervical lymphatics, inotropic inhibition was greater than in thoracic ducts. On average, this parameter was reduced by 83% in cervical lymphatics. Ejection fraction in HDT mesenteric lymphatics was 45 and 50% less than control at transmural pressures of 3 and 7 cmH$_2$O, respectively. The average HDT-induced inhibition of ejection fraction in mesenteric lymphatics was by 49%. In HDT femoral lymphatics, ejection fraction was decreased by 69% and 54% at transmural pressures of 3 and 7 cmH$_2$O, respectively. On average, ejection fraction was inhibited in femoral lymphatics by 59%.

**Fractional pump flow.** Fractional pump flow is an index of the effectiveness of lymphatic pumping irrespective of vessel size that reflects the combined effect of the chronotropic and inotropic reactions of the lymphatic vessels. The longstanding precept of lymphatic pump function indicates that pump flow increases as transmural pressure increases. As presented in Fig. 4, all lymphatics had generally similar changes in the patterns of fractional pump flows after the period of simulated microgravity. In HDT thoracic duct, fractional pump flow was inhibited by 66% and 51% at 3 and 7 cmH$_2$O, respectively. In cervical lymphatics the HDT-induced inhibition of lymphatic pumping was greater than in thoracic duct. Fractional pump flow was diminished by 89% at 3 cmH$_2$O of transmural pressure and by 85% at 7 cmH$_2$O. In HDT animals, mesenteric lymphatic fractional pump flow was inhibited by 51% and 53% at 3 and 7 cmH$_2$O, respectively. In HDT femoral lymphatics, fractional pump flow was reduced 74% at 3 cmH$_2$O and 61% at 7 cmH$_2$O compared with the control group. On average, fractional pump flow in HDT lymphatics was inhibited 58% in thoracic duct, 89% in cervical lymphatics, 54% in mesenteric lymphatics, and 71% in femoral lymphatics.

**Influences of HDT on Imposed Flow-Induced Changes in Active Lymphatic Pumping**

In the present study we compared the contractile behavior of thoracic duct (n = 8/6, control and HDT rats, respectively), cervical (n = 5/6), mesenteric (n = 6/7), and femoral (n = 6/5) lymphatics under the influence of increasing imposed flow (produced by an axial pressure gradient from 0 to 5 cmH$_2$O) in control and HDT groups of animals. We present changes in lymphatic pumping, which occurred in the presence of an imposed flow with axial pressure gradients from 1 to 5 cmH$_2$O. These values of imposed flow were previously shown to be the flows at which all lymphatics selected for study demonstrated the initial or maximal degree of flow-induced inhibition in pumping (20). Values obtained at all imposed flows selected for study are presented in Figs. 5–8.
Flow-induced reactivity was altered differently by HDT in lymphatic vessels from the four investigated regions of the body. Figure 5 presents the comparison of normalized diastolic and systolic diameters in lymphatic vessels at different levels of imposed flow gradients in control and HDT groups. In thoracic duct, simulated microgravity caused a large increase in normalized diastolic and systolic diameters at all levels of imposed flow gradients. At the lowest imposed flow gradient tested (1 cmH\textsubscript{2}O) in HDT thoracic ducts, the normalized diastolic diameters were increased 3.9% of the passive diameter (representing a 70% reduction in resting tone). At a relatively high imposed flow gradient (5 cmH\textsubscript{2}O), HDT induced an increase in normalized diastolic diameter that also resulted in a 70% decrease in tone. Thus HDT produces nearly a complete loss of resting tone and an increased sensitivity of the flow-induced inhibition of both phasic and tonic contractions in thoracic duct. The HDT-induced changes in normalized systolic diameters during imposed flow were also very dramatic. Thoracic duct normalized systolic diameters in HDT were increased significantly at all levels of imposed flows. For example, during the low imposed flow gradient of 1 cmH\textsubscript{2}O, the systolic diameter increased by 10.4% of passive diameter in HDT thoracic duct. At higher imposed flows, systolic diameters of HDT thoracic ducts rose essentially to the level of their corresponding diastolic diameters. The lymphatic diameter changes led to an intensive inhibition of lymphatic phasic contraction amplitude even at relatively low imposed flows. In comparison with thoracic ducts from control animals, the contraction amplitude after HDT was diminished by 81% at the imposed flow gradient of 1 cmH\textsubscript{2}O. At the imposed flow gradients from 3 to 5 cmH\textsubscript{2}O, phasic contractions of the thoracic duct in HDT were completely absent.

In HDT rats, the normalized diastolic diameters of the cervical lymphatics remained unchanged despite elevations of the imposed flow gradient. However, the normalized diastolic diameters were smaller than those in the control group at low (1 cmH\textsubscript{2}O) and high (5 cmH\textsubscript{2}O) imposed flows (representing a 63–81% increase in tone accordingly). This is in stark contrast to the reductions in tone observed in the thoracic duct of HDT animals. Normalized systolic diameters of cervical lymphatics in HDT animals were essentially the same as the corresponding diastolic diameters, and the contraction amplitude was decreased to virtually zero at all investigated levels of imposed flow. In comparison with control, the contraction amplitude was reduced by 80% during an imposed flow gradient of 1 cmH\textsubscript{2}O and by 58% at an imposed flow gradient of 5 cmH\textsubscript{2}O. The average reduction of contraction amplitude in HDT cer-

Fig. 3. Influence of HDT on pressure-induced changes in ejection fraction of rat lymphatic vessels. *Significant differences (P ≤ 0.05) between ejection fractions in control and HDT groups.
vascular lymphatics at all investigated levels of imposed flow was by 72% compared with control vessels.

In mesenteric lymphatics, HDT exposure altered the flow-dependent changes of lymphatic diameters in the same manner as seen in thoracic ducts. Simulated microgravity caused a marked increase in normalized diastolic and systolic diameters at all levels of imposed flow gradient. At the low imposed flow gradient of 1 cmH₂O, normalized diastolic diameter was increased by 9.5% (73% decrease in tone) in HDT mesenteric lymphatics compared with control. At the high imposed flow gradient of 5 cmH₂O, HDT caused a 6.6% increase in normalized diastolic diameter (67% decrease in tone). HDT also induced an increase in normalized systolic diameter in these vessels at all levels of imposed flow. For instance, at a flow gradient of 1 cmH₂O, the systolic diameters increased 33.4% in HDT mesenteric lymphatics. At a flow gradient of 5 cmH₂O, the systolic diameters were increased 9.5%. Contraction amplitude was decreased by 51% and 22% at imposed flow gradients of 1 and 5 cmH₂O, respectively. Therefore, on average, the contraction amplitude in mesenteric lymphatics was reduced by 39%.

In femoral lymphatics HDT did not cause significant changes in the normalized diastolic or systolic diameters during the imposed flow gradient elevations. However, because of subtle changes, the average contraction amplitude in HDT femoral lymphatics, which was comparatively low in respect to other lymphatics, decreased by 35%.

**Contraction frequency.** Figure 6 shows the comparison of contraction frequencies for lymphatic vessels at different values of imposed flow gradients in control and HDT animals. In thoracic ducts, HDT induced significant attenuation of the contraction frequency during low flow (decreased 81%) and completely abolished lymphatic contractions at higher imposed flows. In HDT cervical lymphatics, the pattern of flow-induced changes in frequency was somewhat different than in HDT thoracic duct. At a flow gradient of 1 cmH₂O, the contraction frequency in HDT lymphatics was 70% lower than in control vessels. However, at higher imposed flow gradients (3–5 cmH₂O) we observed the same contraction frequencies for both HDT and control cervical lymphatics. In mesenteric lymphatics HDT also altered the flow-induced frequency responses. Contraction frequency was diminished in the HDT group by 67% to 63% at imposed flow gradients of 1 and 5 cmH₂O, respectively. On average, the lymphatic contraction frequency in HDT animals decreased in mesenteric lymphatics by 65% compared with control. Interestingly, in femoral lymphatics the pattern of HDT-induced changes in the contraction frequency in response to flow was opposite to that seen in
cervical lymphatics. In HDT femoral lymphatics we found no significant differences in lymphatic contraction frequency at the low (1 cmH2O) imposed flow gradient, whereas at higher flows it was decreased on average by 76%.

**Ejection fraction.** Figure 7 shows the comparison of ejection fractions in the four groups of lymphatic vessels at different levels of imposed flow pressure gradients in control and HDT groups. In thoracic ducts, simulated microgravity decreased ejection fraction by 80% at the imposed flow gradient of 1 cmH2O. During higher imposed flows we did not observe phasic contractile activity in HDT thoracic ducts. In cervical lymphatics after 2 wk of HDT, ejection fraction was also 80% lower than in control vessels at a imposed gradient of 1 cmH2O. At high flows we did not observe any further reductions in the ejection fraction in cervical lymphatics from the HDT group or any significant differences between the low ejection fractions in HDT and control groups. In mesenteric lymphatics, HDT caused principally the same pattern of changes in ejection fraction during the imposed flow elevations. At low flows (1 cmH2O gradient) ejection fraction in the HDT group was 51% lower than control, whereas at higher flows we observed no significant differences between the comparatively high ejection fractions seen in both HDT and control mesenteric lymphatics. In femoral lymphatics, the ejection fraction after HDT was slightly (but not significantly) decreased at all levels of imposed flow.

**Fractional pump flow.** Figure 8 presents the comparison of fractional pump flows in all four groups of lymphatic vessels at different values of imposed flow gradients in control and HDT groups. After a 2-wk period of HDT, all lymphatics selected for this study demonstrated profound differences in flow-induced reactivity of the active lymph pumps. In HDT thoracic duct, fractional pump flow was inhibited by 97% at a flow gradient of 1 cmH2O and was completely abolished at higher values of imposed flow. In HDT cervical lymphatics, fractional pump flow was 84% lower than control at an imposed flow gradient of 1 cmH2O, but at higher flows active lymphatic pumping was also extremely low, with no significant differences between the two groups. In the HDT mesenteric lymphatics, as a result of the chronotropic and inotropic influences of HDT, fractional pump flow remained unchanged at all imposed flow elevations. In femoral lymphatics of HDT rats, fractional pump flow was inhibited at all levels of imposed flow, with an average decrease of 62%.

**DISCUSSION**

To date, no studies have been conducted to assess the effects of microgravity on lymphatic vessel contractile function. This study is principally the first detailed investigation of the influences of HDT on two main lymphatic regulatory mechanisms: stretch- and shear-dependent regulation of the intrinsic spontaneous contractile activity. HDT decreased the stretch-activated myogenic stimulation and altered the flow-mediated inhibition in all of the active lymph pumps to differing degrees regionally. We conclude that simulated microgravity pro-
Fig. 6. Influence of HDT on imposed flow-induced changes in contraction frequency of rat lymphatic vessels. *Significant differences ($P \leq 0.05$) between contraction frequencies in control and HDT groups.

Fig. 7. Influence of HDT on imposed flow-induced changes in ejection fraction of rat lymphatic vessels. *Significant differences ($P \leq 0.05$) between ejection fractions in control and HDT groups.
foundly inhibited the active lymph pump in all four regions of the lymphatic network studied. However, it is likely that this inhibition of lymph pumping is not solely due to changes in the hydrodynamic conditions and their effects on regulation of the lymphatic pump or to generalized muscle atrophy during prolonged inactivity. We propose that this inhibition may be partially responsible for the shifts of body fluids and impairment of immune function that are observed in long-term microgravity.

There are only a few reports worldwide of investigations of Earth-based simulations of microgravity on lymph dynamics. In two papers, Bulekbaeva et al. (5, 6) reported the short-term effects of simulated microgravity on lymph flow observed during experiments lasting up to 30 min. In antorthostatic conditions (body rotation with a 30° head-down tilt), lymph flow in the dog thoracic duct had a threefold increase in the first minute of rotation and came back to normal values near the tenth minute of rotation. The thoracic duct lymph flow was reduced approximately 30% after the first 10 min of tilt and then came back to normal values in the next 10 min. However, the left cervical lymphatic trunk had a very different response to the same conditions. Opposite to the thoracic duct, lymph flow from the left cervical lymphatic trunk immediately fell twofold in the first minute of rotation and remained decreased during all 30 min of rotation time. After return of body position back to normal, cervical lymph flow was slightly but not significantly elevated in the next 30 min. The authors explained these transient changes in central lymph flow by the direct redistribution of body fluids to the cranial part of body due to the gravitational influences and reflex constriction of the thoracic duct because of the increased central venous pressure. Later, this group published a short report (4) concerning their attempts to investigate long-term effects of simulated microgravity on the contractile activity of rat thoracic ducts. After 14 days of HDT of rats at an angle of 45°, thoracic ducts were isolated from animals. One-lymphangion segments of thoracic duct were sutured at both ends, and contractions of these preparations were observed with tracings recorded under isometric conditions. Inhibition of contractile activity in the thoracic duct by HDT was observed. The frequency of contractions was reduced approximately 13% compared with the control group, whereas the amplitude of contractions exhibited a profound fivefold decrease. Although we observed the same general trends, unfortunately, the technique of isometric registration of contractile activity in nonperfused lymphatic segments has many technical limitations (e.g., impossibility of controlling intraluminal pressure and volume). Importantly, the intralymphatic volume and accordingly intralymphatic pressure in the thoracic duct were not controlled in these studies. Because of the powerful effect of pressure/stretch on lymphatic pumping function, it is difficult to interpret these data and determine the real direction and degree of influence of simulated microgravity on lymphatic pumping in conditions with unknown/unregulated transmural pressures.

In the present study we evaluated the effects of an earth-bound simulation of microgravity, HDT, on a critical component of lymphatic function, the active lymph pump. We studied anatomic and biomechanical characteristics, contractile activity, and pumping capabilities of isolated lymphatics in response to the normal stimulatory factor pressure/stretch and the
mesenteric lymphatics, in which wall thickness significantly increased some signs of structural remodeling in the lymphatics. The reduction of tone in these vessels would result in decreases in lymph outflow resistance. It also resulted in increased wall thickness in three of the four lymphatics, with the exception of mesenteric lymphatics, in which wall thickness significantly declined. Distensibility, as judged by its inverse relationship to $E_{\text{a}}$, was only altered by HDT in the mesenteric lymphatics. We demonstrated a potent inhibition of active lymph pumps by simulated microgravity in all four types of rat lymphatic vessels studied: thoracic duct, cervical, mesenteric, and femoral lymphatics. This was generally expressed as reductions in the pressure-induced stimulation of the active lymph pump and potentiation of the flow-induced inhibition of the active lymph pump. We observed the greatest inhibition of the active lymph pump by HDT in cervical lymphatics (90% inhibition) and a strong inhibition in hindlimb lymphatics (70% inhibition), whereas mesenteric lymphatics and thoracic duct still exhibited 40–50% of normal pump function. We believe that the inhibitory effects of HDT on lymphatic pumping are complex and that the changes in active pumping for the examined lymphatic beds reflect the effects of numerous integrated HDT-induced physical, neural, and humoral influences on lymphatic contractile function. The general HDT-induced reduction in lymphatic pumping could partially be related to general inhibitory influences of microgravity on muscle contractile function (18, 26). However, it is highly likely that the direct effects of altered lymph dynamic conditions on lymphatics during HDT are also an important cause of lymphatic pump inhibition. The normal pressure gradient along the lymphatic network starts near zero or perhaps subatmospheric in the initial lymphatics and rises in the central direction in the anesthetized rat (64). The hydrostatic indifference point (HIP) for the lymphatic system has never been measured in this or any other lymphatic model. However, the outflow pressure of the lymphatic system, i.e., the central venous pressure in the great veins of the upper thorax, is just beyond the HIP for the venous blood (45, 54, 60). Thus the pressure against which the lymphatics must move lymph is likely to be slightly elevated. As others (15, 30, 33) have clearly demonstrated, altering the outflow pressure against which the lymphatic system must move lymph by even a few centimeters of H$_2$O will increase lymph pressure upstream and dramatically alter lymph hydrodynamics and pumping. If this is true, then the lymphatic system may not possess a HIP, because all lymphatic pressures may rise as a result of any increase in the central venous pressure in the great veins of the upper thorax. What may be more important in this lymphatic model is the degree of change in lymph pressures during HDT in the four lymphatics studied. Given the inherently low lymph pressures observed in situ and the normal pressure gradients found along the lymphatic network due to the combined effect of the hydrostatic pressure column, valves, and pumps, the differences in the degree of HDT-induced inhibition of the lymph pump found in the different lymphatic vessels may be associated with regional variations in the lymph dynamic conditions during HDT. However, further validation of this suggestion is needed.

For example, gravity is an important factor responsible for passive lymph transport from the region of the head and neck in animals as well as humans. Conversely, gravitational forces oppose passive lymph transport from the lower body despite the prevalence of the lymphatic valves. For cervical lymphatics, HDT eliminates the positive influence of gravitational force on lymph flow (in many physiological situations gravitation acts in this region in the same direction as lymph flow) and will likely result in an increase in cervical lymph pressure based on the position of the lower body lymph column with respect to the neck and the probable increase in outflow resistance due to elevated central venous pressure. As a result of the lack of passive gravitational support of lymph flow in this region, chronic overdistension of cervical lymphatics by lymph during HDT may occur. We believe that such a chronic HDT-induced increase in diastolic lymphatic volume in cervical vessels could be an important factor that inhibits the cervical active lymph pump during microgravity, particularly given the normal hydrostatic position of these vessels in the lymphatic tree. Figures 1 and 2 demonstrate the fact that the HDT-induced inhibition of the amplitude and frequency of the phasic contractions in cervical lymphatics was greater than in all other three groups of lymphatic vessels. For example, HDT produced 84% inhibition of contraction amplitude and 80% inhibition of contraction frequency in cervical lymphatics vs. 50% and 33% inhibition in mesenteric lymphatics, respectively. On the basis of these results, we believe that the cephalic fluid shift is a potent inhibitor for both passive and active cervical lymphatic pumps. Thus the facial edema observed during spaceflights (14, 18, 27) may be directly linked to the decreased lymphatic drainage of this region, which leads to increased lymph and interstitial pressures. In addition, the flow-induced inhibition of the active pump in cervical lymphatics was stronger after a 2-wk period of HDT. As presented in Figs. 5–8, parameters of cervical lymphatic contractility were decreased during the periods of the imposed flow elevations in HDT vs. control, perhaps because of alterations in the endothelium-dependent mechanisms responsible for this effect.

The smallest changes in active lymphatic pumping due to HDT were found in mesenteric lymphatics. Because the majority of lymph in the body is formed in the gut lymphatic net (23) and the mesenteric lymphatics are nearer the venous HIP (45, 60), the conditions of lymph dynamics in this region are likely least dependent on the position of the body and the influences of gravitational forces but are strongly connected with gastrointestinal function. The position of mesenteric lymphatics in the abdominal cavity, and consequently their horizontal orientation, varies many times during the day because of intestinal motility. The filling of mesenteric lymphatics depends dramatically on the levels of intestinal digestion and adsorption. Because of this we believe that the inhibition of the active lymph pump we saw in this region of body was primarily an indication of a general inhibition of the active lymph pumps induced by HDT. This suggestion has been supported by our findings that flow-dependent sensitivity of these lymphatics remained basically unchanged by HDT in these vessels (Fig. 8). This could be additional evidence supporting the idea that lymph dynamic conditions principally do not change in the mesenteric lymphatic net during HDT. Interestingly, the mesenteric lymphatics were also the only
lymphatic bed in which wall thickness did not increase as a result of HDT; in fact, it fell by 40%.

Opposite to the mesenteric lymphatics, the contractile activity of femoral lymphatics depends on the position of hindlimb and skeletal muscle activity. During HDT, the hindlimb is in a postural position that would allow gravitational forces to favor the movement of lymph centrally. Increased lymphatic pressure patterns that are connected with increased muscle activity have been demonstrated by Olszewski and Engeset (42), and the transport capacity of the lymphatics from this area directly adjusts to their fluid load (41). Hydrodynamic fluid and pressure shifts and decreased skeletal muscle activity in this region of body during HDT are additional factors that may amplify HDT-induced inhibition of the femoral active lymph pump. For instance, we observed 72% inhibition of contraction amplitude and 48% inhibition of contraction frequency in femoral lymphatics vs. 50% and 33% inhibition in mesenteric lymphatics, respectively.

In the thoracic duct, stretch-induced active lymph pumping was altered to approximately the same degree as in the mesenteric lymphatics. We believe that HDT-induced inhibition of pumping in thoracic duct primarily reflects the general inhibition of lymphatic muscle by simulated microgravity, the cause of which still remains unclear, although an increase in the thoracic duct stretch due to a chronically elevated lymph pressure cannot be ruled out. However, it is important to note that the flow-induced sensitivity in thoracic duct, very high under control conditions, was noticeably increased after 2 wk of HDT. We believe that HDT provides an additional passive gradient in the thoracic duct, which increases flow in this lymphatic trunk. This increased gradient for passive lymph flow in the thoracic duct results in a diminished need for an active lymph pump. This enlarged passive flow may chronically increase the shear stress in the thoracic duct and augments the flow-induced sensitivity for pump inhibition in thoracic duct after HDT. The reduction in active pumping activity in thoracic duct leads to an effective reduction in the outflow resistance, which could in turn augment passive lymph outflow as indicated in our previous studies (21).

In summary, we performed for the first time a detailed evaluation of the influence of simulated microgravity on isolated lymphatic contractile function. Using the HDT rat as a model, we found that simulated microgravity caused a potent inhibition of pressure/stretch-induced responses in isolated lymphatics from all four investigated regional lymphatic beds (thoracic duct, cervical, mesenteric, and femoral lymphatics). The most potent inhibition was found in the cervical lymphatics. These findings presumably reflect the influence of the cephalic fluid shifts that occur in HDT rats as well as those observed during spaceflight. Sensitivity of the isolated lymphatics to flow-dependent inhibition was also potentiated, especially in the thoracic duct and neck. Mesenteric lymphatics were less influenced by simulated microgravity, which supports the idea that lymph hydrodynamic conditions do not dramatically change in the mesenteric lymphatic net during HDT. These studies were conducted with isolated vessels, which allowed us to determine how the inherent sensitivity of the vessels to pressure and flow changed chronically. However, isolated vessel studies do not measure the changes in lymph pressure and/or flow that occur acutely or chronically in situ during HDT. Additionally, the isolated vessel studies by design do not include the role of neural and humoral alterations that may occur in situ. These important considerations need to be addressed in future studies to further define the process that is occurring in lymphatic function during HDT. Thus further investigations are required in this important but still underestimated and thus underdeveloped area of physiology to determine how the pressure gradients along the lymphatic network change during HDT in situ. Additionally, studies of how lymphatic vessels adapt their contractile function to chronic changes in lymph pressure and flow are needed. Discovery of the physiological regulatory mechanisms and development of compensatory measures that can maintain lymph flow during the microgravity will be beneficial to the prevention of lymphatic and immune dysfunction in astronauts during the proposed long-term interplanetary space missions.

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