Venomotion modulates lymphatic pumping in the bat wing

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Dongaonkar RM, Stewart RH, Laine GA, Davis MJ, Zawieja DC, Quick CM. Venomotion modulates lymphatic pumping in the bat wing. Am J Physiol Heart Circ Physiol 296: H2015–H2021, 2009. First published March 27, 2009; doi:10.1152/ajpheart.00418.2008.—In skin, it is believed that lymph must be pumped by intrinsic contraction of lymphatic muscle, since investigators have not considered that cyclical dilation of venules could compress adjacent lymphatic microvessels. Because lymphatic vessels are sensitive to stretch, we hypothesized that venomotion not only can cause extrinsic pumping of lymph in nearby lymphatic vessels, but also can stimulate intrinsic contractions. Bat wing venules have pronounced venomotion and are in close proximity to lymphatic microvessels, and can be studied noninvasively without the confounding effects of anesthesia, surgical trauma, or contrast agents. Therefore, the interaction between venules and their paired lymphatic vessels in unanesthetized Pallid bats (n = 8) was evaluated by recording the diameters of both vessels. Four sets of observations suggested that lymphatic and venous contractions were partially coupled. First, venous dilation and contraction produced a significant change in lymphatic microvascular cross-sectional area. Second, lymphatic microvascular contractions were immediately preceded by a change in venular diameter. Third, venular and lymphatic vessel contraction frequencies were positively correlated (r = 0.75). Fourth, time delays between peak venular systole and onset of lymphatic microvascular contraction were negatively correlated with venomotion magnitude (r = −0.55) and velocity (r = −0.64). In a separate experiment, inhibiting venomotion resulted in a 54.3 ± 20.0% (n = 8) decrease in lymphatic contraction frequency. Furthermore, 85.7% (n = 56) of lymphatic vessels switch sides and lie adjacent to arterioles when venules were too small to exhibit venomotion. These results are consistent with both extrinsic pumping of lymph and stretch-induced lymphatic contraction and imply that intrinsic and extrinsic pumping can be coupled.

lymphangion; edema; interstitial fluid balance; venular-lymphatic coupling

LYMPHANGIONS. The segments of lymphatic vessels between two unidirectional valves, provide the structure that allows lymph to be propelled from the low-pressure interstitial space to the higher-pressure veins (46, 59). Although it is recognized that cyclical contraction of muscular lymphatic vessels can propel lymph, external compression is the only means of propulsion in the intestinal wall, skeletal muscle, heart, and lung, where lymphatic microvessels are devoid of lymphatic muscle (42). In these organs, lymph formation and propulsion depends solely on periodic extrinsic expansion and compression of lymphangions by surrounding tissues (31, 34). In organs such as skin, which are not surrounded by periodically contracting tissues, it is generally believed that intrinsic pumping is necessary to propel lymph. However, Schmid-Schönbein (41, 44) and colleagues suggested that, in addition to contractions of surrounding muscle, arteriolar vasomotion may also extrinsically propel lymph by compressing adjacent initial lymphatic vessels. Although venules can exhibit even greater cyclical contractions than arterioles, venomotion has not yet been identified as a source of extrinsic pumping of lymph.

Both lymphatic and venular systems are implicated in interstitial fluid balance. On the one hand, a primary function of venules is to modulate microvascular fluid pressure, and thus the driving pressure for transmicrovascular flux into the interstitium (11, 12, 19, 27). On the other, lymph, interstitial fluid that has entered the initial lymphatics, is transported via a system of converging conducting lymphatic vessels to the lymph nodes and then to the great veins of the neck (20, 46). Because lymph flow is inhibited by increases in central venous pressure (i.e., the lymphatic outlet pressure), venous and lymphatic functions are coupled at their outlets and at their inlets (17, 30). Although lymphatic microvessels may developmentally derive from venules (40, 45), share a similar structure, can be found within microns of each other (49, 59), and both play a critical role in regulating the local environment of the interstitium, venular and lymphatic microvascular functions are conventionally only described as indirectly coupled.

The intrinsic pumping of lymph is modulated by mechanical factors. First, tension in the filaments tethering lymphangions to the interstitium can passively enhance filling from upstream lymphangions or from the surrounding interstitium (5). Second, stretch of lymphatic muscle is known to enhance pacemaker activity and thus increase the frequency and strength of lymphangion contraction (2, 22, 35). This mechanism has been proposed to increase lymphangion pumping with increased tissue hydration (2). Furthermore, a rapid stretch is known to trigger contraction of vascular smooth muscle (37), which is one mechanism that can cause a lymphangion to contract after being filled by an upstream lymphangion. Because each mechanism allows a lymphatic vessel to respond to the mechanical forces in its immediate environment, venomotion of adjacent venules can potentially trigger contractions. Not only can common anesthetics, surgical trauma, and contrast agents complicate the study of mechanical modulators of lymphatic function, they can also reduce venomotion (7). Only the thin, translucent wing of bats allows noninvasive measurement of lymphatic and venular function without the confounding effects of surgery, anesthesia, or contrast agents. We therefore used the Pallid bat wing model to test the hypothesis that venomotion not only acts to extrinsically pump lymph but also to mechanically trigger intrinsic lymphatic contractions.
METHODS

Bat preparation. Since venomotion is diminished by common anesthetics (7), we utilized the unanesthetized bat wing model (53–56). Experimental procedures and animal care were performed in compliance with protocols approved by the Texas A&M University Institutional Animal Care and Use Committee. With a few notable exceptions, experimental procedures were similar to those employed by Widmer et al. (51, 52). Briefly, Pallid bats were maintained in a colony for over two years before experimentation. Because the bats were wild-caught, their ages were unknown. Bats were trained to participate in experiments without anesthesia, lying asleep in a plastic box with their wing extended outside of the box (51, 52). Following an established schedule, no bats in the colony were used for experimentation more than once per week, and no experiment lasted more than six hours. The wing was lightly pressed against a temperature-controlled glass plate (Olympus Tokai Hit) set at 27°C. Pairs of venules and adjacent lymphatic vessels were visualized with an intravital microscope (Olympus BX61WI) utilizing a water-immersion objective (×40, numeric aperture = 0.8; Olympus LUMPlanFl/IR) at ×400 total magnification, and the image was recorded at 30 frames/s via a digital video recorder (Panasonic KR222 S-Video Camera). The resulting image had a resolution of 700 × 480 pixels as displayed on screen. Video was recorded for at least 5 min to ensure a stable baseline (51, 52). The size of the captured video image was large enough for a venule and its paired lymphatic microvessel to be simultaneously visualized, ensuring that all venular and lymphatic motion can be captured simultaneously. This allowed synchronization of the measurements of diameter for a venule and corresponding lymphatic microvessel. The diameter of each venule and adjacent lymphatic microvessel was measured from each video frame (resulting in 30 data points/s) by manually manipulating custom video caliper software (LabView 7.1). Repeated measurements of a standard image revealed a caliper repeatability coefficient of 0.73 μm with 95% limits of agreement to be 0.037 ± 0.73 μm. Three sets of experiments were conducted, each with eight bats.

Procedures for correlating venomotion and lymphatic vessel contraction. In the first set of experiments, the role of naturally existing venomotion in lymphatic pumping was evaluated without any particular intervention. One pair of vessels consisting of a venule and an adjacent lymphatic microvessel was studied in each of eight bats (n = 8, 5 female and 3 male, 21.2 ± 3.2 g). The relative position of the pair was similar in all bats. The location selected for study was upstream of the first major arteriolar bifurcation between the fourth and fifth digits. Venules at this location averaged 90–110 μm in diameter and were located between arterioles and lymphatic microvessels. Lymphatic microvessels at this location averaged 12–25 μm in diameter. Consistent with previous reports (10, 47), all of these venules exhibited venomotion. Although lymphatic microvessels may exhibit a quiescent period (24), all of the lymphatic microvessels at this location exhibited spontaneous contractile activity. For each venomotion cycle, peak diastolic and systolic venular diameters (Δd) as well as corresponding lymphatic microvascular diameters (ΔDv) were recorded as a function of time. From these data, critical values were derived, including frequency of venular contraction (fΔd), frequency of lymphatic contraction (fΔDv), magnitude of the diameter change for each venule (Δd), rate of change of venous diameter during the venomotion cycle (ΔDv/Δt), and the time delay (Δt) between peak systolic venular diameter and the beginning of lymphatic vessel contraction. For each cycle, the venomotion period (T) was defined as the time between two consecutive venular dilations. Cross-sectional area (AΔd) of lymphatic microvessels was calculated from ΔDv, assuming a cylindrical conformation with circular cross section. To evaluate effectiveness of the extrinsic expansion and compression of the lymphatic microvessel by venomotion, only passive changes in the cross-sectional area were considered, and changes in lymphatic microvascular cross-sectional area due to active contraction were neglected. Active change in a lymphatic microvascular diameter was distinguished from a passive change by simultaneously tracking the walls of the lymphatic microvessel. During active contraction of the lymphatic microvessel, the walls moved in opposite directions toward each other. On the other hand, during passive compression, the walls moved in same direction away from the adjacent venule. The wall of the lymphatic microvessel next to the venule moved more than the other wall of the lymphatic microvessel, leading to a decrease in cross-sectional area.

Procedures to inhibit venomotion. In the second set of experiments, we evaluated the causal relationship between venomotion and lymphatic microvascular contractions by inhibiting venomotion. One pair of venules consisting of a venule and an adjacent lymphatic microvesSEL was studied in each of eight bats (n = 8, 6 female and 2 male, 20.5 ± 2.7 g) at the same location as the first set of experiments. Davis et al. (14) previously reported that an increase in venular transmural pressure can dilate venules and increase frequency of venomotion but significantly diminish the amplitude of venomotion. In the present study, venular transmural pressure was increased and venomotion was inhibited by completely occluding the venules downstream from the point of observation. Venules were selectively occluded using blunt glass micropipettes to compress the venules against the glass plate under the wing. Lymphatic microvessel contraction frequency before and after selective venular occlusion (with a 2-min equilibration period) were compared.

Procedures for determining the topology of the lymphatic network. In the third set of experiments, we determined whether lymphatic microvessels were located adjacent to venules that lacked venomotion. Seven pairs of venules consisting of a venule and adjacent lymphatic microvessel were studied in each of eight bats (n = 56, 7 female and 1 male, 22.2 ± 2.2 g). Lymphatic microvessels adjacent to venules with diameter >40 μm (exhibiting venomotion) were traced downstream through several branches to venules with diameter <25 μm (not exhibiting venomotion). It was noted whether the lymphatic microvessels at this level in the network switched sides to lie adjacent to arterioles.

Data analysis. A statistics software package (SAS Institute) was used for regression analysis and to perform t-tests. Correlation coefficients was determined between measured variables for each venule-lymphatic vessel pair. To determine whether the sample of correlation coefficients was significant, an overall correlation coefficient for the group was first obtained by Fisher’s Z Transformation. The significance of this overall correlation coefficient was determined by a one-sample t-test, used for comparing the mean of the sample with a hypothesized population mean of zero. A P value <0.05 was considered significant. All data are reported as means ± SD.

RESULTS

In each experimental subject, lymphatic microvessels were paired with venules exhibiting venomotion at the site of study. However, this was not the case further downstream; 85.7% of lymphatic microvessels (n = 56, 7/bat) were found to cross over and become paired with adjacent arterioles when venules did not exhibit venomotion (diameters <25 μm). All of the observed arterioles exhibited vasomotion, consistent with previous reports (3, 29, 41).

Figure 1 depicts the diameters of a representative venule and the adjacent lymphatic microvessel along with critical time points such as Δt (the time from b to c in Fig. 1) and T (the time from a to b in Fig. 1). On the left of c, the change in lymphatic microvascular diameter is passive, resulting from venular dilation and contraction. On the right of c, the change in lymphatic microvascular diameter is active, resulting from intrinsic lymphatic contraction. Passive changes in lymphatic microvascular diameters, such as those at a and b in Fig. 1, were used...
to evaluate the role of venomotion in extrinsic pumping of lymph. The oscillation of venular diameter exhibits a natural variation in the magnitude as well as the frequency. This natural variation in venomotion allowed correlation of changes in venular diameter to changes in lymphatic diameters without requiring a particular intervention.

Figure 2 indicates the relative incidence of different degrees of passive change in lymphatic microvascular cross-sectional area resulting from venomotion. A 58.5 ± 15.0% change in cross-sectional areas of lymphatic microvessels was observed as adjacent venules dilated and contracted in the absence of active lymphatic contraction.

We next attempted to characterize the impact of spontaneous venular contractions on active lymphatic contractions. The distribution of the number of lymphatic microvascular contractions occurring after the onset of venous contraction expressed relative to venomotion period (Fig. 3) illustrates that the lymphatic microvascular contractions were correlated with venular activity (i.e., with venular dilation and contraction). In fact, 86.4% of lymphatic microvascular contractions occurred in the first one-half of the venomotion period. Time point b in Fig. 3 corresponds to the peak venular systole (occurring within the first 21.0 ± 6.0% of the venomotion period).

We further analyzed the relationship between lymphatic microvascular contraction frequency and venomotion frequency (Fig. 4). The standardized slopes obtained from the linear regression of individual data sets indicated that venomotion frequency and lymphatic microvascular contraction frequency were positively correlated (overall correlation coefficient \( r = 0.75, P < 0.001 \)).

By analyzing the time delay (\( \Delta t \)) between peak venular systole and the beginning of lymphatic vessel contraction, the lymphatic muscle response was observed to vary with the magnitude and velocity of venomotion (Fig. 5). With increased magnitude of venomotion, the time delay (\( \Delta t \)) before the onset of lymphatic contraction was significantly reduced (overall correlation coefficient \( r = -0.55, P < 0.001 \); Fig. 5, A and B). Similarly, as the velocity of venomotion increased, the time delay (\( \Delta t \)) was significantly reduced (overall correlation coef-
Fig. 5. Time delay (Δt) between the onset of lymphatic microvascular contraction and peak venular systole were correlated to the magnitude (ΔDv) and velocity (dDv/dt) of changes in venular diameter. For clarity, vessels from bats 1 to 4 are plotted separately from vessels from bats 5 to 8. Time delay vs. magnitude of changes in venous diameters [for vessels from bats 1–4 (A) and for vessels from bats 5 to 8 (B)] suggests that, as the magnitude of venomotion increases, Δt is reduced (overall correlation coefficient r = −0.55, P < 0.001). Time delay vs. the velocity of vessel wall [in vessels from bats 1 to 4 (C) and in vessels from bats 5 to 8 (D)] suggests that, as the velocity of venomotion increases, Δt is reduced (overall correlation coefficient r = −0.64, P < 0.001).

**DISCUSSION**

The present work demonstrates that venomotion modulates the pumping of lymph by both compressing adjacent lymphatic microvessels (16) and mechanically triggering intrinsic lymphatic contractions. First, venous dilation and contraction produced a significant change in lymphatic microvascular cross-sectional area (Fig. 2). Second, lymphatic microvascular contractions were immediately preceded by a change in venular diameter (Fig. 3). Third, venular and lymphatic vessel contraction frequencies were positively correlated (r = 0.75; Fig. 4). Fourth, the time delay between the peak venular systole and the onset of lymphatic microvascular contraction was negatively correlated with venomotion magnitude (r = −0.55) and velocity (r = −0.64) (Fig. 5). Fifth, lymphatic microvessels were paired with venules that exhibited marked venomotion, but with arterioles when adjacent venules lacked venomotion. Sixth, a decrease in lymphatic contraction frequency was observed when venomotion magnitude was greatly diminished (Fig. 6). Taken together, these pieces of evidence are consistent with both extrinsic pumping of lymph by venules and mechanical triggering of intrinsic lymphatic contractions. These results also imply that, with venular-lymphatic coupling, extrinsic and intrinsic lymph pumping mechanisms not only coexist, but also are coupled.

**Evidence of the mechanical origin of venule-lymphatic coupling.** The possibility that venular and lymphatic contractions are both initiated by a common neural, electrical, or humoral factor must be addressed. First, venules and lymphatic microvessels in bats are not innervated (6, 28, 54). If a venule and an adjacent lymphatic microvessel were jointly innervated in the bat wing, there would have to be a consistent delay before the initiation of lymphatic contraction. However, such a consistent delay was not observed in the current study (Fig. 3). Second, there is no apparent connection between the muscular layers of venules and lymphatic microvessels to provide direct electrical conduction. With direct electrical conduction, it would be expected that venular and lymphatic contractions both increase or decrease. However, with complete venular occlusion, lymphatic microvascular contraction frequency decreased, even though venular contraction frequency increased (Fig. 6). Third, humoral factors may play a role in modulating both venular and lymphatic phasic contractions. Because venular EDRF was reported to dilate adjacent arterioles in 5–10 s (18), it is conceivable that nitric oxide produced in response to cyclical shear stress in venules may affect lymphatic vessels. In fact, nitric oxide is highly diffusible (traveling 3,300 μm²/s) (9, 49), and can conceivably traverse the short distance between venules and adjacent lymphatic microvessels. Because nitric oxide has been reported to lower lymphatic pacemaker activity (50), its production may depress the magnitude and frequency
of lymphangion contraction (36, 43, 58), which is inconsistent with the data in Figs. 4 and 5. None of these nonmechanical factors are consistent with all six observations presented above. In contrast, all six observations are consistent with the well-established phenomena of stretch-induced vascular muscle contraction (37).

Inhibiting venomotion to modulate lymphatic contraction. To ensure that the correlation of lymphatic vessel contraction with venomotion is causal and lymphatic vessel contractions are triggered by mechanical stimulation, an intervention was required. It was not possible to abolish venomotion pharmacologically without incidentally inhibiting lymphangion contraction, given the inability to dose venules independent from the nearby lymphatic vessels. Therefore, the intervention we adopted was inspired by Davis et al. (14), who reported that raising venular transmural pressure alters venomotion in the bat wing. A moderate increase in venular transmural pressure, such as would be expected in response to arteriolar dilation, enhances venomotion by increasing venular contraction frequency and amplitude. Further increases in venular transmural pressure, however, significantly decrease venular contraction amplitude and maintain contraction frequency (14). We therefore selectively occluded the venules to markedly raise their transmural pressures. Although venular transmural pressures were not measured, the occlusion produced venular dilation and reduced amplitude of venomotion by ~90%, thus selectively eliminating the mechanical source of lymphatic stimulation (Fig. 6A). It is possible that, in the process of occluding some venules, the adjacent lymphatic vessels may have been occluded. However, a previously reported increase in the lymphatic contraction frequency with elevated lymphatic transmural pressure (2, 22, 24, 35) was not observed in any of the vessels in the present study (Fig. 6). It is also possible that venular occlusion may have led to lowered tissue perfusion, and thus increased production of metabolites. However, blood flow-associated changes in lymphatic contractile activity in the bat wing are not mediated by metabolic factors (48). Similarly, there is a potential for venular occlusion to raise capillary hydrostatic pressure, and thus increase tissue hydration. The reported increases in lymphatic contraction frequency with elevated interstitial volume (23), however, were not observed in any of the vessels of the present study (Fig. 6). The reduced lymphatic microvascular contraction frequency associated with a decrease in magnitude of venomotion is most consistent with the conclusion that venomotion mechanically stimulates intrinsic contractions of adjacent lymphatic microvessels.

Methodological challenges to quantifying relative contribution of extrinsic pumping. There are a number of notable methodological limitations particular to our unique animal model. First, lymphatic microvessels in the bat wing may exhibit a quiescent period (24), which can make them difficult to locate without the use of contrast agents that might affect lymphatic function (1). However, in the present work, all locations studied revealed lymphatic microvessels that exhibited spontaneous contractions. Second, it was only possible to measure the diameter of lymphatic microvessels along the horizontal plane, and it was not possible to visualize the cross-sectional conformation. Assuming elliptical deformation with a constant minor diameter (i.e., vessels deform only along the horizontal plane), external expansion and compression would produce only a 36% change in the cross-sectional area, rather than the 58% predicted for vessels maintaining a circular shape. It is therefore possible that the assumption of circular cross-sectional area may overestimate the role of venomotion in extrinsic pumping of lymph. The 36% change in cross-sectional area is nonetheless significant relative to the 67% change reported for intrinsic contraction of lymphatic microvessels (2) (Fig. 2). Furthermore, use of the product of frequency and change in cross-sectional area as an index of lymph propulsion (2, 13, 14), \[ fV = 10 \pm 2 \text{ cycles/min, change in lymphatic microvascular cross-sectional area (} \Delta A_L \text{) = 36%} \] reveals that extrinsic pumping of lymph by venomotion would contribute equally or even more to lymph flow than...
intrinsic pumping \( f_L = 6 \pm 2 \text{ beats/min}, \Delta A_L = 67\% \) (2).  
Third, because the Pallid bats were lightly restrained, did not move during experiments, and have wings devoid of skeletal muscle, the only source of extrinsic compression of lymphangions arose from venomotion. The 58.5 \( \pm \) 15.0% change in lymphangion cross-sectional area suggests that extrinsic propulsion of lymph due to venomotion plays as great a role as intrinsic lymphangion contraction in the normal resting state. 

**Increasing effectiveness of lymph propulsion in the face of an edemagenic challenge.** This is the first work to offer evidence of coordination between intrinsic and extrinsic pumping of lymph. Such coordination may simply increase the efficiency of lymph propulsion. However, such coordination may also increase the effectiveness of lymphangion pumping in the face of an edemagenic challenge. The ability of lymphangions to propel lymph depends on their contractility, diastolic function, preload, and afterload (2). Lymphatic microvascular compression because of venular expansion could enhance lymphatic microvascular contractility, increasing the “effective inotropy.” Similarly, lymphatic microvascular expansion due to venular contraction could facilitate faster lymphatic microvascular filling, increasing the “effective lusitropy.” In addition, venular compression of an upstream lymphangion may increase preload, and venular expansion of a downstream lymphangion may decrease afterload. Because these four behaviors can enhance the intrinsic lymph pump, venomotion may act as an anti-edema mechanism. For instance, locally heating the skin not only leads to greater microvascular filtration but also increased venomotion magnitude, velocity, and frequency (3, 29), and thus possibly enhanced lymphatic function. More importantly, any phenomena that raise capillary pressure, such as arteriolar dilation, increased cardiac output, or change in posture, could simultaneously increase microvascular flux and venomotion (14, 53, 57). The present work thus reveals a mechanism that leads to increased lymphatic pumping that counteracts increases in microvascular flux. Although it has been suggested that arterial vasomotion may enhance lymph flow (25, 26), this is the first report that provides evidence that venomotion in particular can act as an anti-edema mechanism.  

**Broader implications.** Bat wing preparations have been used to make fundamental advancements in the understanding of vascular innervation (54), the myogenic response (4, 15), shear-induced dilation (13, 51), arteriolar and venular vasomotion (3, 47, 53), and capillary recruitment (52). Most vascular responses have been shown to be similar to more common animal models such as the hamster cheek pouch, rat mesentery, and cremaster muscle, although bat wing responses are often more robust (13, 15). Although the rather pronounced venomotion of the bat wing may be unique (47), the coupling of intrinsic and extrinsic pumping may not be. Unlike common animal models, the bat wing model does not require anesthesia, which is known to decrease the magnitude of venomotion (7). Significant venomotion has not only been directly observed in the bat wing, but has been inferred from venous pressure measurements in rabbit ear and dog limbs (21, 55, 56). Arteriolar vasomotion has also been observed in awake animals with implanted skin windows but is inhibited with the administration of anesthesia (8), similar to the inhibition of venomotion (7) with the administration of anesthesia. Recordings of rhythmic pressure oscillations (39) and blood flow velocity (32, 33) in veins of human feet exhibit patterns similar to bat wing venular pressure and blood flow, suggesting a venular origin of the oscillations. It is believed that venomotion, which is typically unpredictable and difficult to measure, becomes prominent under pathological conditions such as reduced perfusion (13, 14, 38). Under these circumstances, venomotion may play a significant role in lymph production and propulsion. Perhaps venomotion in the normal, resting state in other mammals is great enough to produce venomotion-enhanced propulsion of lymph. In fact, we observed in the bat wing that the lymphatic microvessels tend to switch sides (85.7%, \( n = 56, 7/\text{bat} \)) and lie adjacent to parallel arterioles where venomotion is diminished, potentially taking advantage of existing arteriolar vasomotion (41, 44). Lymphatic microvessels in other animal models, including cat mesentery and rabbit omentum (60), have also been reported to be associated with arterioles and venules, suggesting that the lymphatic microvessels may take advantage of preexisting motion due to spontaneous contractions of blood vessels. Furthermore, the present work suggests the possibility that other manifestations of extrinsic pumping, such as that arising from contraction of skeletal muscle, might also trigger, coordinate, and enhance intrinsic lymphangion pumping.  

**REFERENCES**


