First-order approximation for the pressure-flow relationship of spontaneously contracting lymphangions

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Quick CM, Venugopal AM, Dongaonkar RM, Laine GA, Stewart RH. First-order approximation for the pressure-flow relationship of spontaneously contracting lymphangions. Am J Physiol Heart Circ Physiol 294: H2144–H2149, 2008. First published March 7, 2008; doi:10.1152/ajpheart.00781.2007.—To return lymph to the great veins of the neck, it must be actively pumped against a pressure gradient. Mean lymph flow in a portion of a lymphatic network has been characterized by an empirical relationship ($P_{in} - P_{out} = -P_{f} + R_{s}Q_{t}$), where $P_{in} - P_{out}$ is the axial pressure gradient and $Q_{t}$ is mean lymph flow. $R_{s}$ and $P_{f}$ are empirical parameters characterizing the effective lymphatic resistance and pump pressure, respectively. The relation of these global empirical parameters to the properties of lymphangions, the segments of a lymphatic vessel bounded by valves, has been problematic. Lymphangions have a structure like blood vessels but cyclically contract like cardiac ventricles; they are characterized by a contraction frequency ($f$) and the slopes of the end-diastolic pressure-volume relationship [minimum value of resulting elastance ($E_{max}$)] and end-systolic pressure-volume relationship [maximum value of resulting elastance ($E_{min}$)]. Poiseuille’s law provides a first-order approximation relating the pressure-flow relationship to the fundamental properties of a blood vessel. No analogous formula exists for a pumping lymphangion. We therefore derived an algebraic formula predicting lymphangion flow from fundamental physical principles and known lymphangion properties. Quantitative analysis revealed that lymph inertia and resistance to lymph flow are negligible and that lymphangions act like a series of interconnected ventricles. For a single lymphangion, $P_{f} = P_{in} (E_{max} - E_{min})/E_{min} and R_{s} = E_{max}/f$. The formula was tested against a validated, realistic mathematical model of a lymphangion and found to be accurate. Predicted flows were within the range of flows measured in vitro. The present work therefore provides a general solution that makes it possible to relate fundamental lymphangion properties to lymphatic system function.

Lymphangions act as pumps. The function of the lymphatic system is to transport lymph to the great veins of the neck and is necessary for proper interstitial fluid balance (1). Functionally, lymph must be actively pumped against a pressure gradient (18), in contrast with the arterial system where the blood flows from higher pressure arteries to the lower pressure capillaries. Although intestinal motility and skeletal muscle contraction can propel lymph via external compression (19, 29), many lymphangions, the sections of a lymphatic vessel between valves (1, 3, 29), can cyclically contract and actively pump lymph when they are engorged (3). Although they are structured like blood vessels and have a discernable tone, lymphangions function like cardiac ventricles (2, 22, 24).

Although lymphangion contractility was originally characterized in terms of tone, investigators have used the ventricular analogy to describe systolic and diastolic phases of lymphatic contraction (2, 22). This analogy has proved to be particularly appropriate, since lymphangions respond to increased preload by increasing developed pressure and stroke work (both of which correspond in a way that is analogous to the Frank-Starling effect) (2, 23, 27, 34). However, unlike the heart, lymphatic vessels consist of many of these pumps in series, and the afterload of one lymphangion is coupled to the preload of the next (16).

Insight from heart-arterial interaction to mathematically model the lymphatic system. The recurring analogies to both blood vessels and cardiac ventricles were recently leveraged to develop a physics-based mathematical model of a lymphangion (27, 34). With the extension of the transmission line equation description of arteries (26, 35), the resulting lymphangion model included the effects of lymph inertia and viscosity. Similarly, with the extension of the classical time-varying elastance model used to describe cardiac ventricles (31, 32), it also included a description of diastolic tone and contractility. The resulting lymphangion model was more complicated than either arterial or ventricular models, since it included both vessel parameters (radii and length) and ventricular parameters (minimum and maximum elastance). Despite the neglect of non-ideal valve behavior such as lymph backflow through valves, model predictions of flow were validated experimentally (27, 34). The complexity of this detailed model allowed an exploration of the behavior of lymphatic vessels consisting of multiple interacting lymphangions (34) and an illustration that lymphangions act like passive conduits when inlet pressure is raised higher than outlet pressure (27). With the requirement of the numerical solution, however, the model results were only valid for the particular values of assumed parameters. Nonetheless, this approach has allowed lymph flow to be predicted from specific lymphangion properties and fundamental physical principles.

Empirical description of lymph flow in a network. Experiments performed on intact lymphatic networks in vivo indicate that increasing pressure in a particular lymphatic vessel increases flow downstream (9) but inhibits upstream flow (12, 20). This fundamental property has been used to explain the interaction between hepatic and intestinal lymph vessels (30) and the sensitivity of lymph flow measurements to cannula height (20). The measured change in lymph flow with a change in outlet pressure is remarkably linear over a wide range of pressures.
pressures (8–10). To characterize a large number of discrete pressure-flow data points with a simple empirical formula, Drake et al. (9) drew an analogy to an electrical circuit often used to characterize blood flow (Fig. 1A). It consisted of a pressure source [pump pressure (Pp)] and a resistor representing an effective lymphatic resistance (RL). The effective lymph driving pressure acting to propel lymph is thus the sum of the interstitial driving pressure and Pp. This model is empirical in nature in that Pp and RL cannot be predicted from known properties of lymphatic vessels and fundamental physical principles but are found from the linear regression of measured data. In fact, the interpretation of RL and Pp as an actual resistance and generated pressure has been vigorously disputed (1). As of yet, the values of Pp and RL have not been related to lymphangion properties such as contraction frequency, lymphatic vessel tone, lymphangion contractility, or even anatomical structures such as vessel length or radius. Poiseuille’s law provided a simple algebraic formula to relate the blood pressure-flow relationship to fundamental properties of a blood vessel. No analogous formula exists that relates the lymph pressure-flow relationship to fundamental properties of a lymphangion. The purpose of the present work, therefore, is to derive an algebraic formula predicting lymphangion flow from fundamental physical principles and known lymphangion properties, which will be used to interpret the effective resistance (9) of a spontaneously contracting lymphangion.

METHODS

Empirically quantifying lymph flow in a network. To characterize measured changes in mean lymph flow (QL) in a lymphatic network, Drake et al. (9) developed a simple empirical model that became the basis of a number of subsequent studies (8, 10). The pressure gradient from the inlet (Pin) to the outlet (Pout) was related to two factors. The first factor was a pressure source that provides a constant pressure. The second was an effective resistance that yields a pressure drop that is proportional to flow. This simple, first-order linear approximation is equivalent to the slope of the end-diastolic pressure-volume relationship (EDPVR).

\[ Q_L = \frac{P_{in} + P_p - P_{out}}{R_L} \tag{1} \]

Fig. 1. A: empirical model developed by Drake et al. (Ref. 9) to describe the relationship of lymph flow (QL) and both inlet pressure (Pin) and outlet pressure (Pout). It consists of an effective lymphatic resistance (RL) and pump pressure (Pp). Values of Pp and RL are chosen to fit measured data. B: relationship of QL and Pout. Slope of this relationship is 1/RL, and the pressure axis intercept is −Pp. C: the model of a pumping lymphangion was based on the time-varying elastance model first used by Suga and colleagues (31, 32) for cardiac ventricles was applied. First, a measured relationship of instantaneous transmural pressure, P(t), is divided by a measured volume, V(t).

\[ E(t) = \frac{P(t)}{V(t) - V_0} \tag{2} \]

V0 is the dead volume, the theoretical volume at zero pressure. The resulting elastance, E(t), varies as a function of time so that it predicts increases in developed pressure with increased filling. Lymphangion contractility is characterized by the maximum value of E(t), E\text{max}, equivalent to the slope of the end-systolic pressure-volume relationship. Lymphangion tone is characterized by the minimum value of E(t), E\text{min}, equivalent to the slope of the end-diastolic pressure-volume relationship (EDPVR).

Model for lymphangion pumping based on the pressure-volume relationship. A very different approach to modeling lymph flow was taken by Venugopal et al. (34) and Quick et al. (27), who related pulsatile lymph flow to the mechanical properties of lymphangions. With a reliance on the similarity of lymphangion pressure-volume relationships to those of cardiac ventricles, the concept of the time-varying elastance model originally developed by Suga and colleagues (31, 32) for cardiac ventricles was applied. First, a measured relationship of instantaneous transmural pressure, P(t), is divided by a measured volume, V(t).

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Lymphangion contraction (Eq. 2). $Q_l$ in Eq. 3 can be calculated from changes in $V$ in Eq. 2. As described in detail elsewhere (34), the time-varying elastance characterized by Eq. 2 describes the storage of lymph and forms a component that is equivalent to a time-varying capacitance. This mathematical model was evaluated numerically, and its predictions were validated by in vitro experiments on lymphangions (27) and lymphatic vessels (34).

Lymphatic vessel model validation. To test the lymphangion model, data previously reported by Venugopal et al. (34) were plotted. Briefly, segments of postnodal bovine mesenteric vessels were studied with an isobaric preparation. The inlet pressure was maintained at 5.0 mmHg, and the outlet pressure was varied from 5.0 to 7.5 mmHg. Mean flow from each vessel was measured for 1 min after every change in pressure gradient. Data from all vessels ($n = 4$) were pooled, and mean flow was plotted as a function of axial pressure gradient. The results of a linear regression and associated 95% confidence intervals were also plotted.

RESULTS

Approximation of mean lymph flow assuming lymphangions pump against a pressure gradient. Equation 2 can be used to approximate mean lymph flow by following the derivation first developed by Sunagawa et al. (33) to approximate cardiac output. First, end-diastolic volume ($V_{ed}$) can be approximated by end-diastolic pressure ($P_{ed}$) divided by $E_{min}$ plus a dead volume. Second, end-systolic volume ($V_{es}$) can be approximated by end-systolic pressure ($P_{es}$) divided by $E_{max}$ plus a dead volume. Flow is then equal to contraction frequency ($f$) multiplied by the stroke volume (i.e., $V_{ed} - V_{es}$), represented by the width of the pressure-volume loop in Fig. 1C. If lymph inertia and resistance are neglected, $P_{ed}$ can then be approximated by $P_{in}$, and $P_{es}$ can be approximated by $P_{out}$.

$$Q_L = f \left( \frac{P_{in} - P_{out}}{E_{min}} \right)$$

A similar formulation is derived in the appendix (Eq. A1) to describe the pressure-flow relationship in the special case that the inlet pressure is raised above the outlet pressure. Equations 4 and A1 are thus first-order, linear approximations of the lymph pressure-flow relationship in a lymphangion (e.g., Fig. 1D).

Comparison of algebraic approximation and complex numerical solution to quantify the effects of lymph inertia and viscosity. The algebraic approximation for lymph flow in a lymphangion (which notably lacks viscous and inertial effects; Eq. 4) can be compared with numerical simulation results from the model of Venugopal et al. (34) and Quick et al. (27) (which includes viscous and inertial effects; Eq. 3) to quantify the role of lymph resistance and inertia. Figure 2 illustrates the mean flow calculated by assuming that $E_{min} = 106$ mmHg/ml, $E_{max} = 246$ mmHg/ml, inlet pressure = 5 mmHg, and outlet pressure was varied. Figure 2 is completely equivalent to the numerical solution in Venugopal et al. (34), which contains the large numbers of details needed to fully characterize the model. The approximation of Eq. 4 results in <2% error in mean flow. Although the deceleration of the blood entering venticles results in a pressure gradient that tends to close the valve (13), the contribution of inertia is small (29), and for the example given in Fig. 2, the deceleration of lymph causes the pressure gradient across a valve to be very low (0.001% of the total pressure gradient).

Comparison of algebraic solution with data. As outlet pressure was decreased from 7.5 to 5.0 mmHg ($n = 4$), experimental values of mean flow increased, with a linear regression of the pooled data having a slope of 0.040 ml/(min mmHg) (Fig. 2). The results of linear regression with 95% confidence intervals are also indicated. The algebraic model, based on parameters specific to a lymphangion reported by Quick et al. (27), yielded results that fell well within the 95% confidence interval, even though it is expected that each lymphangion had different levels of $E_{max}$ and $E_{min}$.

Reconciliation of first-order approximation with empirical description. The approximation of mean lymph flow in a lymphangion presented in the present work (Eq. 4) is linear, much like the empirical model of Drake et al. (9) (Eq. 1). With $Q_l$ in Eq. 1 set equal to $Q_l$ in Eq. 4, a physical interpretation can be found for $R_L$ and $P_p$.

$$P_p = \frac{E_{max} - E_{min}}{E_{min}} P_{in}$$

$$R_L = \frac{E_{max}}{f}$$

The resulting interpretation for a single lymphangion is illustrated in Fig. 3. An alternate formulation is derived in the appendix (Eqs. A1–A3) for the special case that the inlet pressure is raised higher than the outlet pressure.

Fig. 3. Identification of physiological parameters that affect $R_L$ and $P_p$. The value of $P_p$ is a function of $P_{in}$ and the relative change in elastance ($E_{max} - E_{min}$)/$E_{min}$, which characterize lymphangiome tone ($E_{max}$) and contractility ($E_{min}$). Thus increasing filling pressure or contractility increases the value of $P_p$. The value of $R_L$ is a function of $E_{max}$ and $f$. Increasing $f$ thus decreases the effective $R_L$. 

Fig. 2. Validation of first-order (analytical) approximation of lymph flow in a lymphangion (solid line) (Eq. 4) with a complex hydrodynamic simulation (C) (Eqs. 2 and 3) that includes the effects of lymph resistance and inertia. Complex hydrodynamic model of lymphangion was previously evaluated experimentally and described in detail in both Venugopal et al. (Ref. 34) and Quick et al. (Ref. 27). Experimental data from 4 vessels were used to validate model reproduced from Venugopal et al. (Ref. 34) for comparison purposes (closed symbols). Linear regression of data and 95% confidence intervals are represented by dashed lines. Scatter in data represents variation among vessels.
DISCUSSION

Analogous to Poiseuille’s law, the present work provides a simple algebraic formula relating the mean lymph pressure-flow relationship to mechanical properties of lymphangions. It was possible to derive a first-order approximation because a quantitative analysis revealed that lymph inertia and the resistance to lymph flow are negligible. Lymphangions thus act like a series of interconnected cardiac ventricles. The formula was tested against a validated, realistic mathematical model of a lymphangion and found to be accurate. Not only did the model predict that lymph flow increases as downstream pressure decreases, but the absolute values of flows were within the range of flows measured in vitro. Just as the pressure-flow relationship of an arterial network can be related to the resistances of its component vessels described by Poiseuille’s law, the pressure-flow relationship of a portion of a lymphatic vessel network can be related to the effective lymphatic resistance and pump pressures of its component lymphangions described by Eq. 5. The present work provides the unique insight that lymph inertia and resistance play a negligible role when a lymphangion is pumping against a pressure gradient, and the resulting governing equation is therefore quite unlike Poiseuille’s law. With the development of a first-order approximation for the lymphangion pressure-flow relationship, the present work provides a novel means to relate lymphangion properties to lymphatic network function.

Reinterpreting the pump-conduit duality of lymphangions.

The present work provides insight that has not been available in previous attempts to mathematically model lymphangions (27, 34). The complex mathematical model used in the present work for validation purposes (Fig. 2 and Eqs. 2 and 3) was used previously to illustrate that lymphangions exhibit both pump and conduit behavior (27). However, this complex model assumed that the pressure generated by lymphangion contraction was counteracted internally by both inertia and resistance (Eq. 3). All three components were believed to play a role unless the normal pressure gradient was reversed and the inlet pressure rose above the outlet pressure with interstitial edema, limb elevation, external compression, or constriction of upstream lymphangions (21, 25, 30), as described in detail by Quick et al. (27). With a sufficient pressure gradient to passively propel flow in diastole, the valves are forced open during the entire contraction cycle, and cyclical contraction no longer acts to propel lymph. Vessels in this special case were shown to be solely conduits. The present work, however, expands this insight. When lymphangions are pumping lymph up a pressure gradient, all three components do not contribute equally to lymph flow. In fact, the pressure generated by lymphangion contraction (Eq. 2) is so much larger than lymph inertia and resistance (Eq. 3) that neither plays a significant role. Thus lymphangions act solely as pumps when they transport lymph against a pressure gradient. When the pressure gradient is reversed, lymphangions act solely as conduits, and the resulting resistance is primarily a function of the radius (see Eq. A2). Equations 5 and A2 elucidate which lymphangion properties affect the slope of the pressure-flow relationships when lymphangions are acting as either pumps or conduits. However, neither approximation adequately describes the transition between the two behaviors when the axial pressure gradient is near zero, when contraction in systole and passive flow in diastole both contribute to lymph flow. In this case, lymph resistance and inertia may play an important role in lymph flow.

Sacrificing model accuracy to arrive at an algebraic formulation.

To derive a simple algebraic formula relating lymphangion properties to lymph flow, a number of assumptions were made. First, with the assumption of the time-varying elastance model (Eq. 2), the present model does not include behavior analogous to the Hill effect, where the velocity of contraction limits the force generated by lymphatic muscle (6), or to the Bainbridge effect, where filling increases the frequency of contraction (18, 23). Similarly, the slope of the EDPVR (i.e., $E_{min}$) is assumed to be constant, whereas it is known to be highly nonlinear and sensitive to loading conditions (2, 22). Each effect could be addressed by modifying $E_{max}$ or $E_{min}$ to be a function of pressure, since Eq. 4 would still hold. In contrast, adding complications such as lymphatic backflow through the valves (7) or changes in upstream lymphangion volume due to valve bulging backward may not be worth the cost, since adding the effect would not allow an algebraic solution. More importantly, the simple model derived in the present work neglected both lymph inertia and the effect of resistance to lymph flow, which had very small effects in larger postnodal lymphatic vessels (Fig. 2). Although the resistance to lymph flow is markedly higher in microlymphatic vessels, the flow is also markedly lower. From Eq. 3, the maximum pressure drop in microlymphatic vessels approximated from parameter values reported by Dixon et al. (7) is 0.046 mmHg, suggesting that inertia and resistance effects are negligible even in microlymphatic vessels. To test our simplified model, we relied on a complex realistic mathematical model that was taken as our gold standard, because it is not possible to quantify the influence of lymph inertia and resistance directly from experimental data. The gold standard, however, does not include fluid behavior such as turbulence that may modify lymph flow. Nonetheless, the gold standard we used to test Eq. 4 was itself extensively validated with experimental data by both Venugopal et al. (34) and Quick et al. (27). Adding complexities to the simple, algebraic model (Eq. 4) may not be worth the cost if the resulting equations have to be solved numerically by computer simulation.

Scope of model embodied in analytical approximation.

Mathematical models cannot account for all possible behaviors that can manifest in a physiological system; the process of developing a mathematical model involves critical choices of which behaviors to exclude. Five particular choices limiting the scope of the present work are worthy of note, particularly because there are experimental situations requiring a customization of the model. First, there are no explicit vascular biomechanics. Although lymphangion behavior could be characterized in terms of wall tension (24), this level of detail would not allow the use of simple indexes of lymphangion contractility such as $E_{max}$ and $E_{min}$ (27, 34). Second, there is no collapsible vessel behavior. Although lymphatic vessels can be collapsed when they are faced with a negative transmural pressure (1), the model only embodies dynamics of a cylindrical vessel subjected to positive transmural pressures. Collapsible vessel behavior requires a completely different set of equations and can lead to highly nonlinear behavior (4). Third, there is no stretch-induced contraction. Although the model incorporates increase in stroke volume and work with increased filling, there is no explicit threshold that initiates
spontaneous contraction as pressure rises. Fourth, there are no extrinsic pumping mechanisms. Although extrinsic mechanisms can play a very large role in lymph flow (19), we only addressed lymph flow due to intrinsic pumping. We did not attempt to characterize the expansion of lymphangions by the interstitium or the compression by arterial pulsation, skeletal muscle contraction, loads on skin, or intestinal peristalsis (1, 3). Each mechanism could be addressed by making specific changes to $E_{\text{max}}$ and $E_{\text{min}}$ to reflect changes in the lymphatic pressure-volume relationship. Finally, there are no gravitational effects. The present work focused on the pumping of lymph in horizontal vessels. Although this assumption may be reasonable for the thoracic duct in most animals studied experimentally, it would notably be inappropriate for a standing human. Appropriate modifications could be made to Eq. 3 if thoracic lymph flow in an upright human was to be studied.

Finally, the scope of the present work did not include the reproduction of many excellent experimental studies that manipulated interstitial pressure or lymphatic outlet pressure (8–10, 12, 22, 23). Although it may be conceivable to reproduce such experiments, and also include the simultaneous measurement of all lymphangion pressures, maximum diameters, minimum diameters, and contraction frequencies of all relevant lymphangions, this is beyond the scope of the present work.

Advantages of algebraic approximation. Our simple lymphangion model has a number of advantages over more complicated mathematical models that require simulation by computer. Although complex mathematical models can yield details such as regional endothelial shear stress, they have to be evaluated numerically (7); that is, every parameter has to be assigned a particular value, and the output of the computer simulation is a number or a graphical plot. The simplicity of our algebraic model thus yields five concrete benefits: 1) ease of use: our algebraic model is easy to manipulate without specialized training in solving differential equations; 2) generality of result: although published numerical solutions assume particular parameter values to address a particular research question, our model is a tool that investigators can use by customizing parameter values to answer new questions; 3) conceptual transparency: our model elucidates how three lymphangion properties act synergistically or antagonistically to affect lymph flow (e.g., $E_{\text{max}}$; Eq. 5B), an insight that cannot come from plotting lymph flow as a function of four or more parameters; 4) modeling networks of vessels: our model is amenable to calculating lymph flow in a network of vessels, which is currently not feasible using computational fluid dynamics; and 5) analysis of experimental data: our simple model can be used to infer lymphangion properties from the slopes and intercepts of experimentally measured data. The present work therefore provides a general solution that makes it possible to relate fundamental lymphangion properties to lymphatic system function.

Implications to basic science of interstitial fluid balance and potential to influence clinically relevant research. Studies in intestinal lymphatic vessels have reported that effective resistance ($R_L$) decreases with volume infusion (20) and portal venous hypertension (11). Similar decreases in $R_L$ are observed in the heart, lung, liver, skeletal muscle, and kidney (8, 20) with inferior vena caval pressure elevation. Interventions used in these studies increase not only the lymphatic transmural pressure but also lymph flow. Increased lymphatic transmural pressure increases the lymphangion contraction frequency (1). With the insight provided by the present work, we can now attribute this decrease in $R_L$, in part, to increases in lymphatic contraction frequency (Eq. 5B). Because the reported reductions in $K_L$ are greater than expected for the observed increases in contraction frequency, we can infer that contractility (indicated by $E_{\text{max}}$) may also have declined. This inference is supported by a recent report from in vitro experiments that shows increased luminal flow (and thus presumably endothelial shear stress) inhibits lymphatic contractility (15, 17). Equation 5B provides further insight by suggesting the nonintuitive result that increasing lymphangion contractility (i.e., increasing $E_{\text{max}}$) can increase effective lymphangion resistance, which may not be overcome by the increase in effective pump pressure (Eq. 5A). This suggests that an appropriate goal for the clinical treatment of edema may not necessarily be to stimulate lymphangion contraction but instead to inhibit it. Furthermore, if the inlet pressure rises above the outlet pressure and lymphangions transition from pumps to conduits (27) as described in the Appendix (Eq. A3), increasing contractility could inhibit passive flow. Thus our first-order approximation of the lymphangion pressure-flow relationship not only increases our understanding of the basic science of interstitial fluid balance by relating in vitro studies of lymphangions to in vivo studies of the lymphatic system under edemagenic conditions, but it also suggests a new approach for clinical intervention.

APPENDIX

If the inlet pressure to a lymphangion exceeds its outlet pressure, it is possible to have lymph flow during lymphatic diastole (27). In this case, the valves would remain open, and lymphangions would not be able to generate a pressure by contraction. The total resistance to flow in diastole would therefore be equal to the resistance of the upstream valve, $R_{\text{valve}}$, and the resistance of the lymphangion approximated from Poiseuille’s law (first term of Eq. 3). With the assumption of a cylindrical geometry, the total volume of the lymphangion would equal $\pi r^2 L$. With a substitution into Eq. 2, and with the assumption that chamber pressure is an average of inlet ($P_{\text{in}}$) and outlet ($P_{\text{out}}$) pressures, lymph flow at end diastole ($Q_{\text{ed}}$) would equal

\[
Q_{\text{ed}} = \left(\frac{\pi r_0^2 + (P_{\text{in}} + P_{\text{out}})/2}{8\pi \mu L} + R_{\text{valve}}\right)(P_{\text{in}} - P_{\text{out}}) \quad (A1)
\]

where $r_0$ is the theoretical radius at zero pressure (corresponding to the dead volume $V_0$ in Eq. 2). The effective resistance when a lymphangion is acting like a conduit in diastole ($R_{\text{cd}}$) would be a function of lymphangion tone, characterized by the minimum elastance $E_{\text{min}}$.

\[
R_{\text{cd}} = \frac{8\pi \mu L}{\pi r_0^2 + (P_{\text{in}} - \Delta P)/2} + R_{\text{valve}} \quad (A2)
\]

However, with the assumption that the lymphangion is still contracting, the radius would decrease to a minimum value at end systole. The resulting resistance ($R_{\text{es}}$) therefore would be governed by the maximum elastance $E_{\text{max}}$.

\[
R_{\text{es}} = \frac{8\pi \mu L}{\pi r_0^2 + (P_{\text{in}} - \Delta P)/2} + R_{\text{valve}} \quad (A3)
\]

Increasing contractility (i.e., increasing $E_{\text{max}}$) would therefore decrease lymph flow when $P_{\text{in}} > P_{\text{out}}$. 

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