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Pump function curve shape for a model lymphatic vessel

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ABSTRACT

The transport capacity of a contractile segment of lymphatic vessel is defined by its pump function curve relating mean flow-rate and adverse pressure difference. Numerous system characteristics affect curve shape and the magnitude of the generated flow-rates and pressures. Some cannot be varied experimentally, but their separate and interacting effects can be systematically revealed numerically. This paper explores variations in the rate of change of active tension and the form of the relation between active tension and muscle length, factors not known from experiment to functional precision. Whether the pump function curve bends toward or away from the origin depends partly on the curvature of the passive pressure–diameter relation near zero transmural pressure, but rather more on the form of the relation between active tension and muscle length. A pump function curve bending away from the origin defines a well-performing pump by maximum steady output power. This behaviour is favoured by a length/active-tension relationship which sustains tension at smaller lengths. Such a relationship also favours high peak mechanical efficiency, defined as output power divided by the input power obtained from the lymphangion diameter changes and active-tension time-course. The results highlight the need to pin down experimentally the form of the length/active-tension relationship.

1. Introduction

The lymphatic system scavenges water and protein from the body's interstitial spaces, returning them to the circulation at the subclavian veins. In the process it also collects foreign matter (particles, bacteria, viruses) which is brought into intimate contact with immune cells in lymph nodes. The lymphatic vessels of the gut have a specialised role in nutrient uptake.

The lymphatic vascular system consists of nonmuscular initial lymphatics where lymph is admitted via endothelial primary valves, and muscular collecting lymphatics. Collecting vessels consist of a series of lymphangions, contractile segments of vessel bounded by one-way valves. Thus each lymphangion is a pump. Analysis of intrinsic[1] lymphatic pumping begins by examining individual lymphangions, proceeding from there to networked structures. The clinical importance of achieving better understanding of lymphatic pumping rests primarily with the role of impaired pumping in lymphœdema. Impairment can arise from surgical interruption of the lymphatic conduit network or from radiation-induced lymphatic muscle dysfunction, but measurements of maximal pumping pressure show that there is also a wide range of pumping ability in normal volunteers [1].

The steady-state performance of any type of pump can be characterised by a single curve relating the mean flow-rate $\overline{Q}$ through the pump to the adverse pressure difference ΔP which the pump is overcoming. Generally, $\overline{Q}$ depends inversely on ΔP; thus, considering only positive flow-rates and outlet pressures higher than inlet, the pump function is expressed by a curve of negative slope intersecting the $\overline{Q}$ and ΔP axes. One intersection describes the adverse pressure difference which is just sufficient to stop the mean flow; the other describes the maximum possible flow-rate which would be achieved in the absence of all load on the pump, i.e. equal inlet and outlet pressures. Possible shapes corresponding to qualitatively different pumping abilities are shown in Fig. 1.

Drake et al. [2] attributed a curve which bent inward toward the origin of $\overline{Q}$–ΔP coordinates to the onset at high vessel distension of active pumping, in a bed which had previously yielded lymph by extrinsic mechanisms alone (intermittent passive compression of lymphatic vessels from lung inflation and deflation). They attributed one which bent outward, away from the origin, to a Starling-resistor effect, i.e. the collapse of lymphatic vessels at low transmural pressure (Δp_{tm} = internal pressure p_{m} minus external pressure p_{e}). They also showed theoretically [3] that the parallel combination of two systems of lymph vessels would yield a curve bending inward toward the origin.

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[1] There is also extrinsic pumping, whereby lymph transport occurs through the passive squeezing of lymphangions by adjacent tissue.

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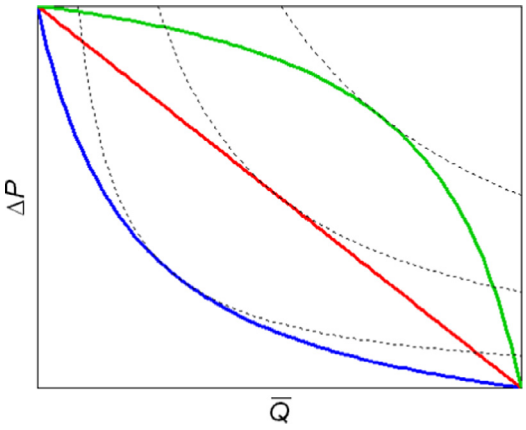

Fig. 1. Three theoretically possible shapes for a pump-function curve, each describing a different pump with the same limiting maximum $\overline{Q}$ and maximum ΔP. Also shown are curves of constant power (the product of $\overline{Q}$ and ΔP) which are tangent to the three pump-function curves at their respective points of maximum power. The maximum power increases from blue to red to green, although all three pumps work within the same limits of $\overline{Q}$ and ΔP. (For interpretation of the references to colour in this figure caption, the reader is referred to the web version of this article.)

Table 1
Default parameter values, and the typical ranges of ΔP and $\overline{Q}$ which result. The middle column gives values in the units which are commonly used in lymphatic vascular research; for those quantities which have units, the right-hand column gives their SI equivalents.

Number of valves	2	
Lymphangion length, L (cm)	0.3	3×10^{-3}
Normalising diameter, c_9 (cm)	0.02598	2.60×10^{-4}
Diameter at $\Delta p_{tm} = 0$, D_d (cm)	0.0084534	8.45×10^{-5}
P-scale in Δp_{tm}–D relation, P_d (dyn/cm^2)	732	73.2
Peak active tension, M_0 (dyn/cm)	150	0.15
Contraction waveform frequency, f (Hz)	0.5	0.5
$M_t(t)$ rise/fall-rate multiplier, m	1 or 2	
Refractory period, t_r (s)	1	1
Valve state-change offset from $\Delta p_v = 0$	$= f$(valve state, Δp_{tm})	
Valve-closure slope const., s_o (cm^2/dyn)	0.4	4
Min. valve resistance, R_{Vn} (dyn/cm^5 s)	6×10^5	6×10^{10}
Δ(valve resistance), R_{Vx} (dyn/cm^5 s)*	$10^{10} - R_{Vn}$	$10^{15} - R_{Vn}$
Valve-closure threshold factor, c_{fact} [8]	0.221	
Lymph viscosity, μ (Poise)	0.01	10^{-3}
Default $\Delta p_{ae} = p_a - p_e$ (dyn/cm^2)	3924 (4 cm H_2O)	392.4
Typical maximum $\Delta P = p_b - p_a$ (dyn/cm^2)	9810 (10 cm H_2O)	981
Typical maximum $\overline{Q}$ (cm^3/s)	2.78×10^{-5} (0.1 ml/h)	2.78×10^{-11}

* Maximum valve resistance $R_{Vn} + R_{Vx}$ is thus 10^{10} dyn/cm^5 s (10^{15} in SI units)

However there are many other possible influences. Given biological variability and the difficulty of the experiments, the subject of what and how many factors affect the shape of pump function curves is not readily explored empirically, but additional light can be shed through analysis of theoretical models [4–5]. The numerical model of two lymphangions in series by Venugopal et al. [4] displayed a perfectly linear relation between $\overline{Q}$ and ΔP. Bertram et al. [5] introduced an asymmetrically sigmoidal dependence of lymphangion diameter D on transmural pressure Δp_{tm}, which led to pump function curves which almost everywhere bent away from the origin, i.e. were concave as viewed from the origin. The $\overline{Q}$–ΔP relation was shown to depend on the lymphangion transmural pressure, the offset from zero of the trans-valvular pressure difference at which valves changed state, the sharpness of the valve resistance-change function, and the two scale parameters of the passive pressure–diameter relation. The $\overline{Q}$–ΔP relation rose to higher values of ΔP when the number of lymphangions (and valves) increased, and higher values of both ΔP and $\overline{Q}$ when the magnitude of the peak active tension increased.

Our model has since been developed to include (1) valves with switching hysteresis and Δp_{tm}-dependent bias to the open state [6], (2) a refractory period between contractions, (3) non-sinusoidal waveforms of activation, (4) the length-dependence[2] of active tension developed during contractions, and (5) parameter values tailored more closely to those measured in experiments on isolated lymphatic vessels of 100–250 μm diameter from rat mesentery. We therefore revisit the concept of the pump function curve and report on how some of these changes affect the curves, with particular reference to the question of whether the curves bend toward or away from the origin. As shown in Fig. 1, this has consequences for the maximum power which can be developed by a pump working within limits on maximum $\overline{Q}$ and ΔP which are likely to be set by fixed physiological properties. In pathological situations, these properties may change so as to diminish maximum $\overline{Q}$ and ΔP, or may combine with other facets of pumping so as to depress maximum power while preserving maximum $\overline{Q}$ and ΔP. Maximum power relates directly to the lymphatic intrinsic pumping reserve which is the mechanism of last resort to prevent interstitial swelling [7].

[2] Length here means circumference. With lymphangions assumed to remain circular, circumference is proportional to diameter. If collapse occurs, 'diameter' then has the sense of hydraulic diameter and retains the same relation to circumference. Thus a single relation between active tension and instantaneous diameter is added.

2. Methods

2.1. Description of the model

The equations of the single-lymphangion model are unchanged from Bertram et al. [8]; in brief,

$$\frac{dD}{dt} = \frac{2(Q_1 - Q_2)}{\pi L D}; \quad p_1 - p_m = \frac{64}{\pi}\frac{\mu L Q_1}{D^4}; \quad p_m - p_2 = \frac{64}{\pi}\frac{\mu L Q_2}{D^4} \tag{1}$$

$$p_{i-1,2} - p_{i1} = R_{Vi} Q_i, \; i = 1, 2; \quad R_{Vi} = R_{Vn} + \frac{R_{Vx}}{1 + \exp\left(-s_o(\Delta p_{Vi} - \Delta p_{oi})\right)}; \quad \Delta p_{Vi} = p_{i-1,2} - p_{i1} \tag{2}$$

$$p_m - p_e = f_p(D) + f_a(D, t) \tag{3}$$

where i is valve number, $D(t)$ is diameter, t is time, $Q(t)$ is flow-rate (through a valve), L is lymphangion length, $p_1(t)/p_m(t)/p_2(t)$ is the pressure at the upstream end/midpoint/downstream end of the lymphangion, μ is lymph viscosity, $R_V(\Delta p_V)$ is the function describing valve resistance, Δp_V is the trans-valvular pressure drop, R_{Vn} is minimum valve resistance, $R_{Vn} + R_{Vx}$ is maximum valve resistance, $\Delta p_o(\Delta p_{tmv})$ is the pressure drop threshold for switching, Δp_{tmv} is valve transmural pressure[3], s_o is a constant determining the slope of $R_V(\Delta p_V)$ at $\Delta p_V = \Delta p_o$, p_e is external pressure, p_a ($= p_{02}$) is inlet reservoir pressure, p_b ($= p_{21}$) is outlet reservoir pressure, f_p(D) is the curvilinear passive relation between p_m–p_e and D, and $f_a(D, t)$ is the time-varying curve describing the contribution of active tension to the relation between p_m–p_e and D. See Table 1 for the default values of constants in Eqs. (1)–(3).

The passive and active Δp_{tm}–D relationships, and the valve-switching arrangements, are described in Sections 2.2 to 2.4.

[3] Δp_{tm} has a specialised definition in the valvular context; see [9].