Lymphatic pump failure and valve dysfunction in response to modest gravitational loads: a contributing mechanism to peripheral lymphedema

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Contrast imaging of the lymphatic system in patients with lymphedema often reveals an uninterrupted, static column of lymph, implying impaired contractile function of the collecting lymphatics and/or dysfunction of lymphatic valves. The prevailing view is that valves become inflamed and degenerate following chronic distention of the collecting vessels; however, this hypothesis has not been experimentally verified. We investigated the sequence of events leading to dysfunction of the lymphatic pump and valve system in rat mesenteric lymphatic vessels. Single lymphangions containing two valves were isolated from anesthetized rats (Nembutal, 60 mg/kg, i.p.), cannulated for *in vitro* study and connected to a servo system to independently control input (P_{in}) and output (P_{out}) pressures. Intraluminal pressure (P_L) was measured between the valves using a servo-null micropipette while tracking vessel diameter and monitoring valve leaflet position using video methods. Under normal conditions, with the vessel working against a physiological pressure gradient ($P_{out} > P_{in}$), the output valve opened transiently during each spontaneous contraction when peak systolic P_L transiently exceeded P_{out}, so that the lymphangion ejected a portion of its contents. Most vessels could pump against an adverse pressure gradient ≥12 cmH_2O when P_{in} (preload) was held at 1 cmH_2O. However, if P_{out} and P_{in} were slowly raised in parallel, with $P_{out} - P_{in} = 4$ cmH_2O, to simulate pressure conditions in a dependent extremity during acute development of edema, the vessel progressively distended and the output valve would, at a relatively low diastolic pressure ($P_L = 8.9 \pm 0.5$ cmH_2O), appear to stick or "lock" into the open position. We hypothesized that this behavior results from a combination of three processes: 1) progressive or sudden pump failure preceded by an increasing component of negative stroke work; 2) an increasing adverse pressure gradient required for normal valve closure as vessel diameter increased; 3) subtle changes in the coordination of contraction on the two sides of the valve. If the output valve hesitated to close in the transition from systole to diastole, P_L could equilibrate with P_{out}, preventing closure and giving the appearance of being "locked open", despite continued contractions of the vessel. The valve was not damaged nor did it prolapse because, in separate tests of passive vessels, valve back-leak did not occur until P_{out} exceeded 97 ± 17 cmH_2O. Active, myogenic tone of the lymphatic muscle served to resist pressure-induced expansion of the lymphangion, thereby retarding valve-lock, perhaps by reducing tension at the base and/or buttress of the leaflets. Valve-lock occurred more often in fatigued vessels that lost tone, but was reversible if P_{out} was lowered to reduce diameter below a critical point, or if tone was enhanced using a contractile agonist while P_{out} remained elevated. Testing the same protocol on vessels containing 4-5 valves, we found that once valve-lock occurred in one lymphangion, it progressed to neighboring lymphangions as their pressure rose. We propose that tone, pump strength, and valve leaflet stiffness normally interact to minimize the likelihood of valve-lock, which reflects an inherent, but previously unidentified, susceptibility of the intraluminal valves. Thus, acute valve dysfunction can be triggered by modest pressure/volume overload and lead to subsequent exacerbation of edema by creating an uninterrupted, standing lymph column that would be transmitted back to the lymphatic capillaries in the form of elevated hydrostatic pressure.