Journal of Biomechanics 48 (2015) 3584–3590

Contents lists available at ScienceDirect

Journal of Biomechanics

journal homepage: www.elsevier.com/locate/jbiomech
www.JBiomech.com

Determining the combined effect of the lymphatic valve leaflets and sinus on resistance to forward flow

John T. Wilson [a], Raoul van Loon [b], Wei Wang [c], David C. Zawieja [c], James E. Moore Jr.[a,*]

[a] Department of Bioengineering, Imperial College London, South Kensington Campus, London SW7 2AZ, UK
[b] College of Engineering, Swansea University, Singleton Park, Swansea SA2 8PP, UK
[c] Department of Medical Physiology, Texas A&M Health Science Center, 702 Southwest H.K. Dodgen Loop, Temple, TX 76504, USA

ARTICLE INFO

Article history:
Accepted 30 July 2015

Keywords:
Finite element analysis
Computational fluid dynamics
Lymphatic valves
Flow resistance

ABSTRACT

The lymphatic system is vital to a proper maintenance of fluid and solute homeostasis. Collecting lymphatics are composed of actively contracting tubular vessels segmented by bulbous sinus regions that encapsulate bi-leaflet check valves. Valve resistance to forward flow strongly influences pumping performance. However, because of the sub-millimeter size of the vessels with flow rates typically <1 ml/h and pressures of a few cmH_2O, resistance is difficult to measure experimentally. Using a newly defined idealized geometry, we employed an uncoupled approach where the solid leaflet deflections of the open valve were computed and lymph flow calculations were subsequently performed. We sought to understand: 1) the effect of sinus and leaflet size on the resulting deflections experienced by the valve leaflets and 2) the effects on valve resistance to forward flow of the fully open valve. For geometries with sinus-to-root diameter ratios >1.39, the average resistance to forward flow was 0.95×10^6 [g/(cm^4 s)]. Compared to the viscous pressure drop that would occur in a straight tube the same diameter as the upstream lymphangion, valve leaflets alone increase the pressure drop up to 35%. However, the presence of the sinus reduces viscous losses, with the net effect that when combined with leaflets the overall resistance is less than that of the equivalent continuing straight tube. Accurately quantifying resistance to forward flow will add to the knowledge used to develop therapeutics for treating lymphatic disorders and may eventually lead to understanding some forms of primary lymphedema.

1. Introduction

The lymphatic system plays vital roles in physiologic fluid and solute homeostasis as well as immune cell transport. It is responsible for the uptake of fluid and solutes from the interstitial spaces and their subsequent return to the venous system. Its dysfunction could result in a number of pathologies, including lymphedema, e.g. build-up of interstitial fluid (IF) that, if left untreated, could lead to chronic inflammation and/or tissue fibrosis (Avraham et al., 2013). Two types of valves are present within the lymphatic vasculature (primary and secondary) and both play a crucial role in maintaining effective net forward lymphatic fluid (lymph) flow. Valve defects have been shown to underlie the pathogenesis of lymphatic distichiasis, a dominantly inherited form of primary lymphedema (Mellor et al., 2007; Petrova et al., 2004). Additionally, physical injury to valves occurs in lymphatic filariasis (Case et al., 1991), which is the most common cause of lymphedema in the world (Pfarr et al., 2009). The initial lymphatics eventually give rise to collecting vessels which are tubular in structure and segmented into discrete units called lymphangions (Mislin and Schipp, 1966) by bulbous sinus regions that encapsulate bi-leaflet check valves.

Non-linear optical microscopy imaging of rat mesenteric lymphatic vessels has shown the valve leaflet matrix to be primarily composed of elastin but anchored to the wall of the lymphatic vessel by thick axially oriented bands of collagen (Rahbar et al., 2012). The region of the lymphatic wall containing these secondary valves is surrounded by a bulbous sinus. The sinus represents an increase in the radial dimension of the lymphatic starting near the upstream site where the leaflets radially insert into the lymphatic wall that continues axially past the trailing edge of the valve leaflets. This suggests that the regional differentiation of composition provides structural support for the lymphatic valves. The valve leaflets of rat mesenteric lymphatics are covered by lymphatic endothelium on the inner and outer surfaces. The endothelium on the valve leaflets and sinus region has been shown to have a high expression of endothelial nitric oxide synthase, the

* Corresponding author. Tel.: +44 20 75 945179; fax: +44 20 75 94 9817.
E-mail address: james.moore.jr@imperial.ac.uk (J.E. Moore Jr.).

http://dx.doi.org/10.1016/j.jbiomech.2015.07.045
0021-9290/

enzyme responsible for shear-dependent production of nitric oxide (NO) in the lymphatics (Bohlen et al., 2009) and serves as a critical regulator of lymphatic pumping function (Bohlen et al., 2011). It has also been shown through experiments with isolated and pressurized rat mesenteric lymphatic vessel segments with multiple valves that gradual increases in outlet pressure result in decreases in opening times. The closing pressure difference (across pipettes and vessel segments) required for one valve segment varied more than 20-fold (0.1–2.2 cmH_2O) with increasing transmural pressure. The pressure difference required to open the valve varied as well, but not to the same degree (Davis et al., 2011). The results further demonstrated the valve is biased in the open position. However, given that the valve closing pressure experiment begins with flow in the vessel, it is necessary to account for pipette resistance in estimating the true pressure difference required for closing (Bertram et al., 2014b). Both closing pressure and opening pressure differences are certainly dependent on transmural pressure, but experimental evaluation is confounded not only by issues such as pipette resistance, but also by the sizes of the vessels (approximately 100 μm in diameter).

Lumped parameter modeling of lymphatic pumping has shown the valve resistance to forward flow to be one of the most important parameters in determining pumping efficiency (Jamalian et al., 2013), particularly at lower values of imposed pressure difference. In particular, that model demonstrated an order-of-magnitude increase in flow rate results when the minimum valve resistance is decreased from 8×10^6 to 1×10^6 [g/(cm^4 s)] for an imposed adverse pressure difference of 0.10 cmH_2O. As a follow-up study to the above-mentioned valve opening and closing experiments, Bertram et al. estimated the open valve resistance and found it to be 0.6×10^6 [g/(cm^4 s)] (Bertram et al., 2014b). This estimation involved experiments where lymphatic vessels were cannulated and pressurized, whilst a constant flow rate was applied through each segment. There were considerable technical challenges involved, including the fact that the majority of the resistance in the flow system is determined by the cannulating pipettes. The resulting pressure-flow data were quite noisy as a result, and since resistance is estimated by the slope of that relationship, there was considerable uncertainty in the result.

Unlike valves in blood vessels, lymphatic valves have not been studied extensively, in part because of the experimental difficulties listed above. The only modeling study we are aware of is our previous work analyzing flow patterns in a stationary valve geometry based on a three-dimensional (3D) confocal image of a lymphatic valve (Wilson et al., 2013). We found that flow stagnation occurred in regions adjacent to the valve leaflets, resulting in a build-up of lymphatic endothelial cell-derived NO that matched the NO data we have previously measured using NO sensitive electrodes in rat mesenteric lymphatics *in situ* (Bohlen et al., 2009). However, the valve and wall geometries in this computational model were completely static, failing to account for leaflet movement as well as the fact that lymphatic vessels expand and contract dramatically, often more than 50% of the original diameter (Dixon et al., 2006). Capturing fully dynamic images of valve movement is experimentally complicated by the fact that these large deflections occur over small time-scales of less than 0.5 s.

The study reported herein seeks to investigate: 1) the effect of sinus and leaflet size on the resulting deflections experienced by the valve leaflets and 2) the resulting effects on valve resistance to forward flow. In particular, we seek to calculate the valve resistance to forward flow using a combination of finite element (FE) analysis of the structural deflections of the valve leaflet and computational fluid dynamics (CFD) to determine the local flow patterns based upon the leaflet configurations resulting from these deflections. Because we are most interested in the minimum resistance to flow, we employ an uncoupled approach in which the deflection of the fully open valve is first calculated, and then the flow is calculated.

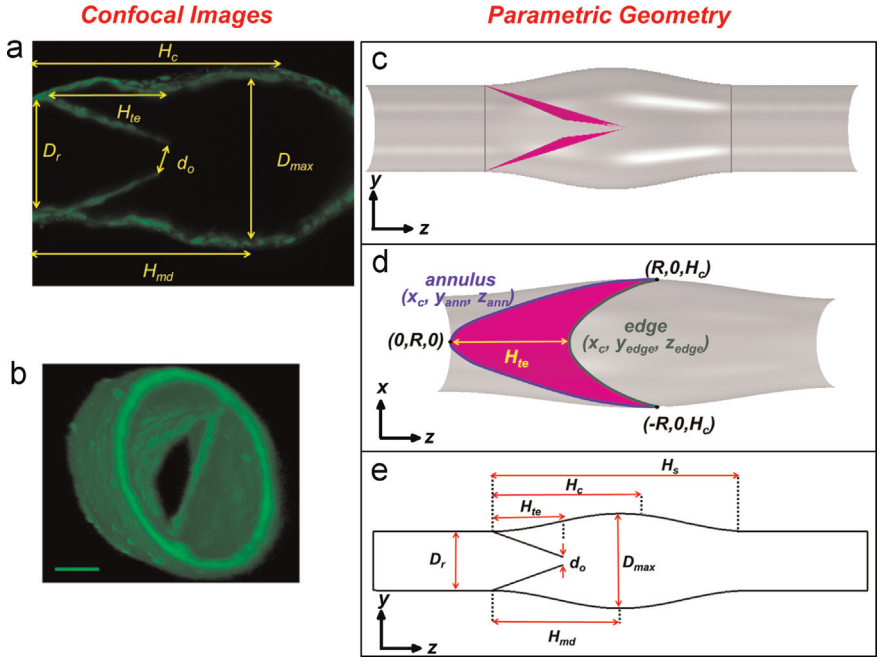

Fig. 1. Example of confocal images (a) and 3D reconstruction (b) analyzed to construct the parametric geometry (c–e). (a) In-plane confocal image from a 3D stack of a rat mesenteric lymphatic vessel. (b) 3D confocal reconstruction to illustrate the geometry of the valve. Calibration bar=40 μm (Davis et al., 2011). (c) Side-view of the lymphatic geometry with leaflets in a barely open position. Vertical gray lines at the root of the valve near the leaflet insertions and at the end of the sinus indicate cross-sectional locations of pressure sampling planes used during Step III. (d) View of the lymphatic valve leaflets where trailing edge and commissural incissura are clearly visible. Note coordinates of the annulus (x_c, y_{ann}, z_{ann}) and leaflet edge (x_c, y_{edge}, z_{edge}) are indicated in blue and green text, respectively. (e) Schematic of the lymphatic valve geometry with key dimensions (dimension values are noted in Table 2). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)