The structure and function of the normal circulation

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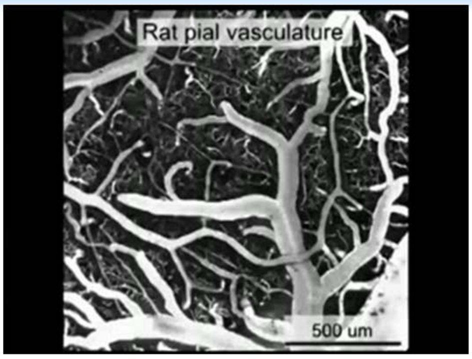
Learning objectives

- Understand the role and design of the normal circulation
- Be able to describe the major physical factors acting on blood vessels and driving flow.
- Know Laplace equation, Poiseuille's equation, 'Ohms law for flow'.
- Know the major classes of blood vessel, their structure and how it relates to function.
- Understand how standing (gravity) affects the circulation

Blood flow

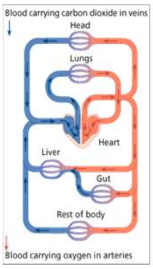


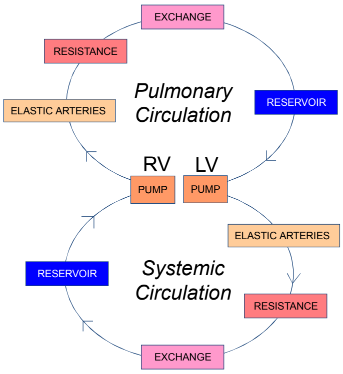
www.youtube.com/watch?v=S54u2hnx5zU

Role and design of the circulation

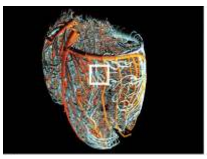
- To transport blood (a fluid containing cells) around the body to allow exchange of gas , nutrients, metabolites, ions, hormones, heat
- Flow is achieved by the action of a muscular pump (heart) propelling blood through a network of tubes (blood vessels).
- The circulation consists of two pumps (left and right heart) which are physically coupled and pump through the systemic and pulmonary circulations respectively.
- Diffusion is crucial for movement of materials through tissues
- Diffusion is only effective over short distances so a capillary needs to be ~10μm from every cell. This necessitates a highly branched structure.

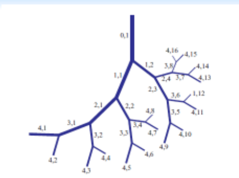
Schematic design of the cardiovascular system





Optimal design of the vascular tree



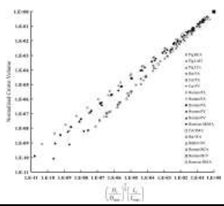


THE PHYSIOLOGICAL PRINCIPLE OF MINIMUM WORK. I. THE VASCULAR SYSTEM AND THE COST OF BLOOD VOLUME

By Cecil D. Murray

Department of Biology, Bryn Mawr College

Communicated January 26, 1926



Zamir The Physics of Coronary Blood Flow. Kaimovitz, B. et al. Am J Physiol Heart Circ Physiol 299: H1064-H1076 2010; doi:10.1152/ajpheart.00151.2010; hou & Kassab Biophys J. 2009; 96(2): 347–353.

Brief physics of flow

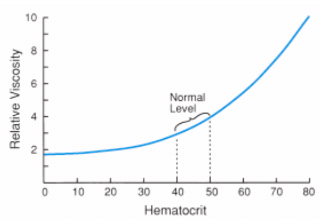
- Viscosity
- Pressure, flow and resistance
- The effects of pressure and flow on blood vessels
  - Transmural pressure & circumferential stress
  - Flow and shear stress

Viscosity - demo

- Dynamic viscosity (μ) is a measure of the resistance of a fluid to deform under shear stress (≡ "thickness of a fluid")
- A Newtonian fluid is defined as one with constant viscosity (i.e. shear rate is directly proportional to the shear stress).

http://groups.physics.umn.edu/demo/fluids/movies

Blood viscosity and haematocrit[1]



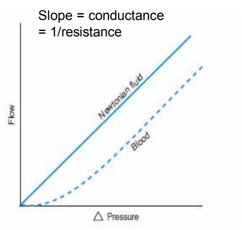
- The viscosity of blood (relative to water) is a function of haematocrit.
- For a normal haematocrit of 45-50% blood viscosity is about 3 time that of water
- The viscosity of plasma (no red cells) is about 1.5 time that of water due to plasma proteins

Essential Medical Physiology – Johnstone

[1]Also sometimes termed packed cell volume (PCV) or erythrocyte volume fraction (EVF)

Blood as a non-Newtonian fluid: anomalous viscosity

Blood flow through a rigid tube



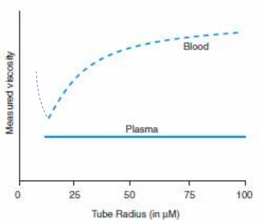
Essential Medical Physiology – LR Johnstone

- Erythrocytes are deformable so can undergo some shear deformation.
- At low shear rates aggregates of erythrocytes (rouleaux) form and increase viscosity contributing to the non-linear relationship between pressure gradient and flow at low flows .

[Bruce Wetzel (photographer). Harry Schaefer (photographer) http://en.wikipedia.org/wiki/Image:SEM_blood_cells.jpg]

Blood as a non-Newtonian fluid (2): Fahreus-Linquist effect

Relationship of blood viscosity to radius of tube



- The viscosity of blood appears to decrease as the diameter of the tube it flows through decreases below ~100μm.
- The Fahreus-Lindquist effect is due to the tendency of red cells to align in the centre of blood flow (axial streaming)
- This results in a low haemotocrit near the wall resulting in a low measured viscosity

Copied from Essential Medical Physiology by LR Johnstone and modified from Fahraeus & Lindquist Am J Physiol 1931; 96: 562.

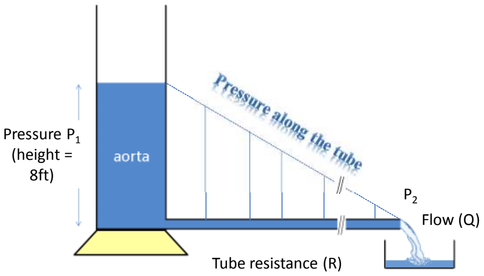
Blood pressure – the force that drives the circulation

Steven Hales, 1733

(Drawing by Cuzzo, 1944. Wellcome Institute Library, London.)

In December I caused a mare to be tied down alive … I inserted a brass pipe whose bore was one-sixth of an inch in diameter [into the crural artery] and to that …I fixed a glass tube …which was nine feet in length. Then, untying the ligature on the artery, the blood rose in the tube to eight feet in length …above the level of the left ventricle of the heart

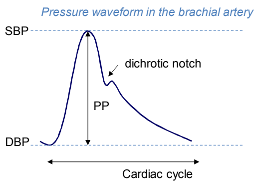
A simplified model of the mare's circulation in Hales experiment



'Blood pressure'

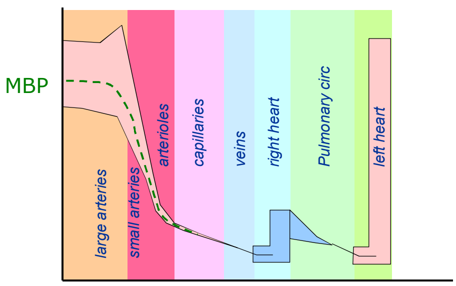
Most commonly measured with a cuff on the upper arm

Image from: http://www.bhsoc.org/default.stm



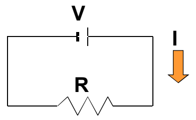
- Systolic blood pressure (SBP)
- Diastolic blood pressure (DBP)
- Pulse pressure (PP) = SBP - DBP
- Mean blood pressure ≈ DBP + 1/3 PP

Pressure throughout the circulation



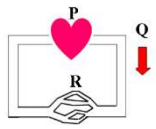
Pressure falls across the circulation due to viscous (frictional) pressure losses. Small arteries and arterioles present most resistance to flow.

Resistance: linking flow and pressure



Electrical Circuit *(Ohm's Law)*

V/R = I



Fluid Circuit (*Darcy's Law*)

P/R = Q

Where
V = voltage difference, I = current flow, R = resistance
P = pressure difference, Q = volumetric flow, R = resistance

The hemodynamic determinants of mean blood pressure (MBP)

ΔP = Q x R

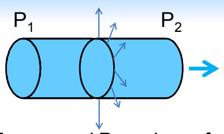
MBP = Cardiac output (CO) x Resistance (PVR)

↓

stroke volume (SV) x heart rate (HR)

(this assumes steady flow and that right atrial pressure is negligible)

Forces acting on blood vessels as a result of pressure



P_1-P_2 = ΔP → flow → shear stress

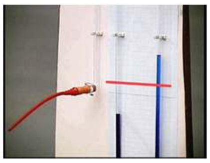
Transmural P → circumferential (hoop) stress

Pressure (P) is a stress i.e. force / unit area.
Two stresses act on blood vessels:

1. Transmural (distending) pressure resulting in a tensile circumferential (hoop) stress in the wall
2. Flow which exerts a shear stress on the vessel wall

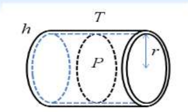
The pressure <u>difference</u> between two location causes flow but the transmural <u>pressure</u> (i.e. intravascular pressure above atmospheric pressure) distends the vessel.

Transmural pressure and distension



http://www.doitpoms.ac.uk/tlplib/bioelasticity/demo.php

Circumferential stress – La Place



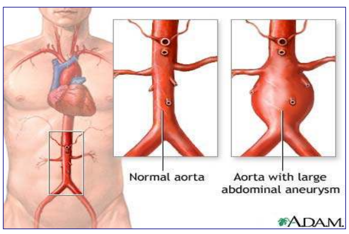
The wall tension *(T)* due to the transmural pressure (*P*) in a cylindrical tube is given by Laplace's relationship:

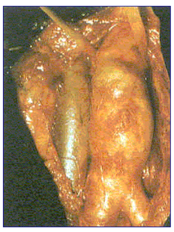
$$T = P.r$$

Circumferential (hoop) stress (σ) = Tension (T)/ wall thickness (h) :

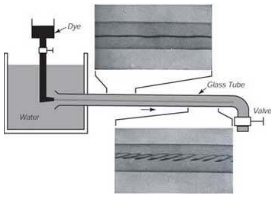
$$\sigma = \frac{P \cdot r}{h}$$

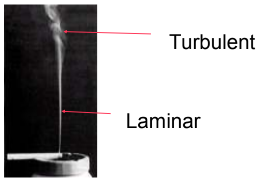
Laplace in action - aneurysms





Laminar and turbulent flow

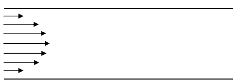




- Turbulent flow is characterized by the irregular movement of fluid particles
- Under physiological conditions blood flow is laminar (i.e. in streamlines) but turbulence can occur in pathological conditions

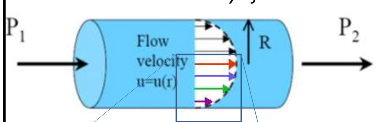
Poiseuille flow and spatial velocity gradients

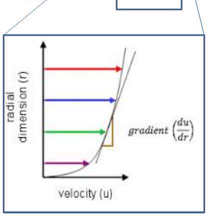
- The instantaneous velocity profile in a long straight tube is parabolic due to the viscous forces opposing fluid motion
- Velocity at wall surface is assumed to be zero (no slip conditions)
- Under these circumstance friction between fluid laminae results in a gradient of laminar velocities across the vessel that adopts a parabolic (Poiseuille) shape.



Flow, shear rate and shear stress

Velocity of streamlines

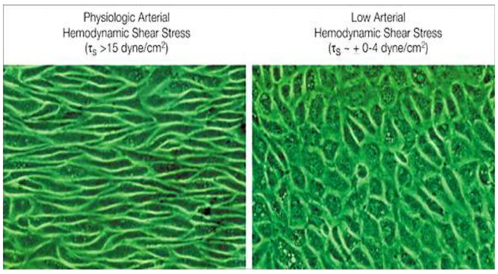




- The shear rate (s) is the velocity gradient at any point s = $\frac{du}{dr}$
- The shear stress (τ) = $\frac{du}{dr}\,\mu$

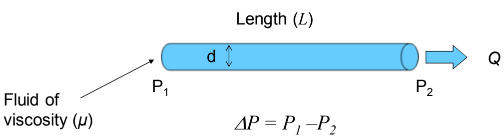
(where *μ = dynamic viscosity)*

Shear stress influences endothelial function



Malek et al JAMA. 1999;282:2035-2042

How do viscosity and shear account for resistance to flow? Poiseuille's law and vessel calibre



$$\Delta P = P_1 - P_2$$

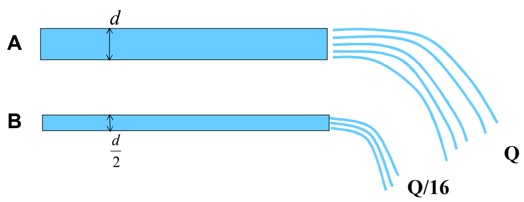
$$R = \frac{\Delta P}{Q} = \frac{8\mu L}{\pi r^4}$$

or

$$R = \frac{\Delta P}{Q} = \frac{128\mu L}{\pi d^4}$$

- Resistance shows a strong dependence on vessel diameter (radius)

Arterial diameter is the major regulator of arterial resistance



Flow ∝ d^4 (Resistance = ΔP/Q ∝ 1/d^4)
So: Flow (Q) through A is 16 times more than B

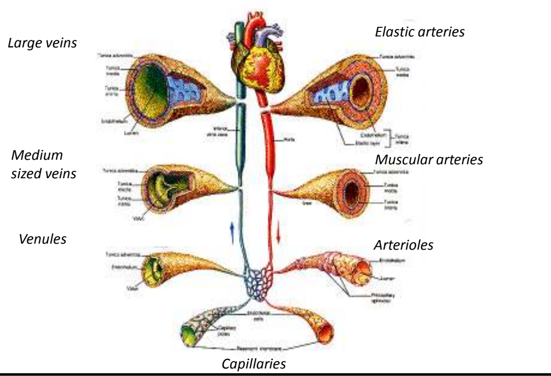
Segmental resistance in the circulation

- You might think that Poiseuille's law implies that capillaries (the smallest calibre vessels) should offer most resistance to flow; however because they are so short and there are so many of them most resistance to flow is due to small arteries and arterioles
- Veins present relatively little resistance to flow

End of part 1

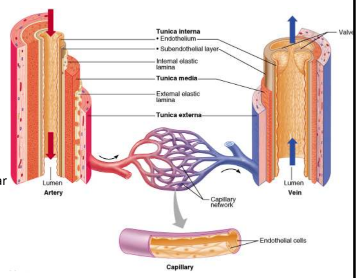
The anatomical design of the circulation

Chapter 19 : The Cardiovascular System: Blood Vessels. G.R. Pitts, J.R. Schiller, and J. F. Thompson

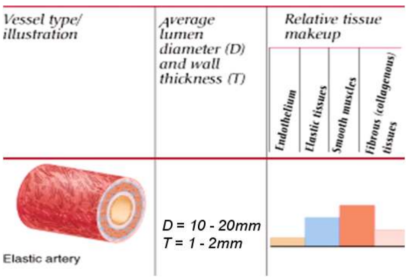


Arterial and Venular Structure

- Arteries and veins have similar structure
  - Tunica adventitia (externa)
    - Collagen
    - Nerves
    - Vasa vasora
  - Tunica media
    - Smooth muscle and extracellular matrix
  - Tunica interna (intima)
    - Endothelium
    - Basement membrane
    - Internal elastic lamina

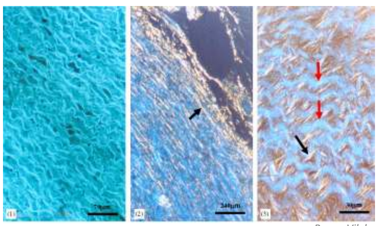


Aorta and elastic arteries



- Large diameter, thick walled arteries rich in elastin
- High compliance (distensibility) damps pressure fluctuation during the cardiac cycle

Elastin and lamellae in the aorta



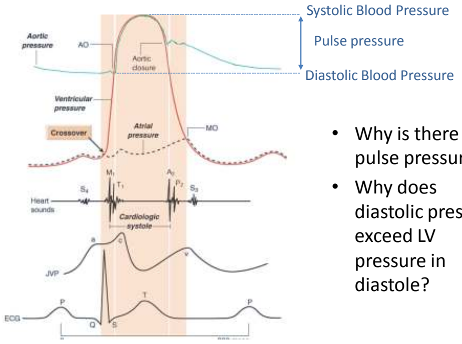
Pig aorta stained with dansyl chloride

Braga-Vilela

1) Fluorescence microscopy - elastic lamellae fluoresce blue
2) Polarized light microscopy. Black arrows indicate birefringent collagen fibrils.
3) Fluorescence and polarized light microscopy. Black arrows show collagen fibrils. Red arrows show elastic fibrils and lamellae.

The aorta and large elastic arteries show a lamellar structure. Lamellae have a thickness of around 15µm in all species

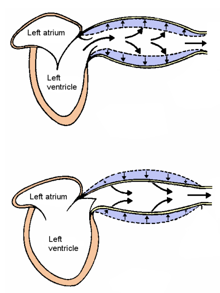
Wiggers' diagram – ventricular and aortic pressure



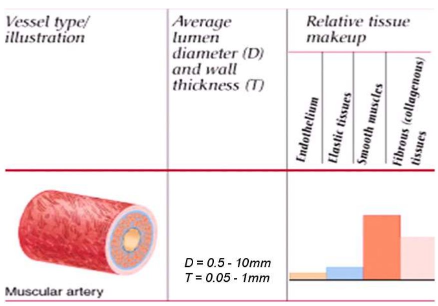
- Why is there a pulse pressure?
- Why does diastolic pressure exceed LV pressure in diastole?

Arterial compliance and pulse pressure

- ~40% of the stroke volume is stored by the aorta and other elastic arteries during systole.
- The stored volume accounts for diastolic flow (there is no ejection by the heart in diastole).
- This is sometimes termed the 'Windkessel' and represents the effect of arterial compliance

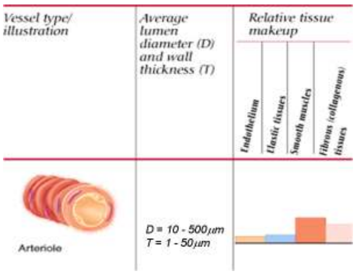


Muscular (conduit/distributing) arteries



- more smooth muscle cells, fewer elastic fibers than elastic arteries

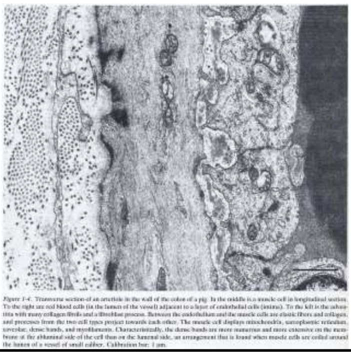
Small arteries and arterioles



- Regulate distribution of blood to and within organs
- regulate resistance and blood pressure by changing vessel diameter

Cells in the arteriolar wall

adventitia media intima lumen



Small arteries and arterioles - contraction

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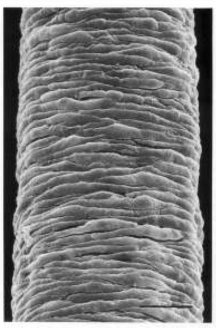

Figure 12-8. Subarachnoidal muscular arteriole of the rat. Muscle fibers are fusiform with tapered ends. They are tightly apposed to each other and are circularly oriented. Bar: 20 μm.

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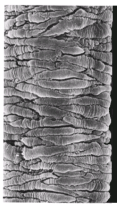
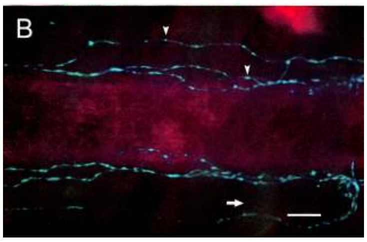


Sympathetic innervation of arterioles



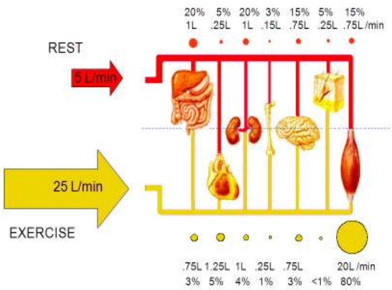
A high magnification view of a rat cremasteric arteriole catecholamine-containing varicosities (arrowheads) are visible (scale bar = 10 µm)

- Arteries and veins receive autonomic innervation (mainly sympathetic NS)
- Capillaries are rarely innervated

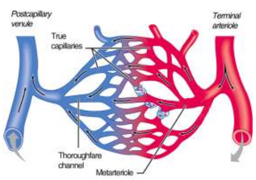
Hungerford et al., FASEB Journal. 2000;14:197-207

Distribution of blood flow to organs

Chapter 19 : The Cardiovascular System: Blood Vessels. G.R. Pitts, J.R. Schiller, and J. F. Thompson



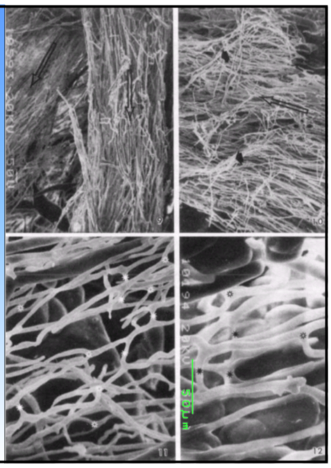
Microcirculation



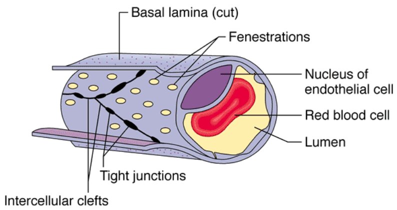
- The microcirculation is located between arteries and veins
- the higher the metabolic activity, the denser the capillaries in a tissue
- Flow is intermittent and governed by vasomotion of terminal arterioles (pre-capillary sphincters probably artifact).
- Pericytes are associated with capillaries and important in their development

The branching structure of capillaries in the dog ventricle

(Anderson Am J Anat 1980; 158:217-227)

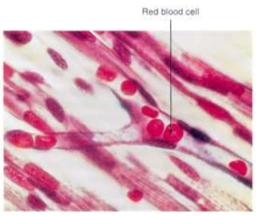


Basic capillary structure



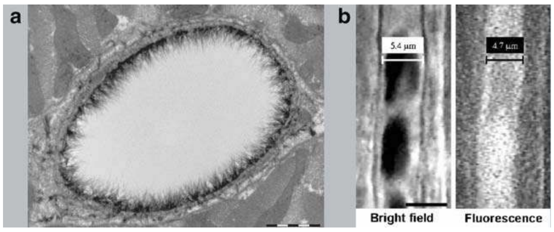
- Basal lamina (connective tissue), endothelial cells
- Details of structure determine specific functions
  - Types: continuous, fenestrated, sinusoid

The microcirculation



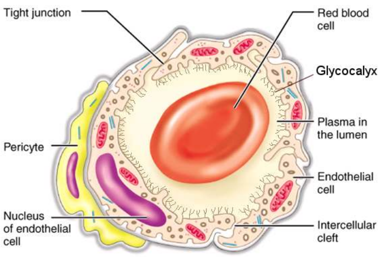
Capillary

Glycocalyx



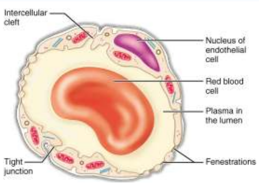
Visualization of the endothelial glycocalyx with different microscopic techniques. a Endothelial glycocalyx of a rat left ventricular myocardial capillary stained with Alcian blue 8GX and visualized using electron microscopy. Bar represents 1 μm. b Intravital microscopic recording of the endothelial glycocalyx of a hamster cremaster muscle capillary. The anatomical diameter of 5.4 μm is larger than the red blood cell column width (left pane) or the plasma column width (right pane) labelled with fluorescent dextran (70 kD). This difference is caused by the presence of the endothelial glycocalyx. Reitsma et al., Pflugers Arch - Eur J Physiol (2007) 454:345–359

Types of capillaries 1: *continuous capillaries*



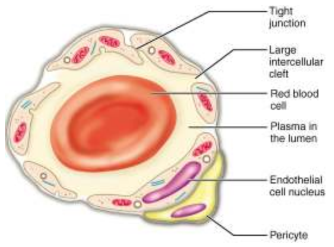
- continuous lining of endothelial cells except for the clefts between cells
- tight junctions between the endothelial cells
- most of the capillaries in the body

Types of capillaries 2: Fenestrated capillaries



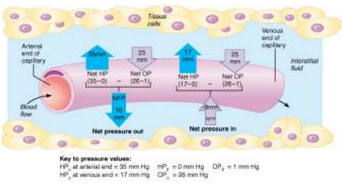
- fenestrations (“windows”) are bridged by a thin membrane (ie not holes)
- More permeable to water and small lipid insoluble molecules
- Fluid exchange tissues
  - Kidney, exocrine glands, intestinal mucosa, joint synovium, chorid plexus, ciliary body of the eye.

Types of capillaries 3: Sinusoidal (discontinuous) capillaries



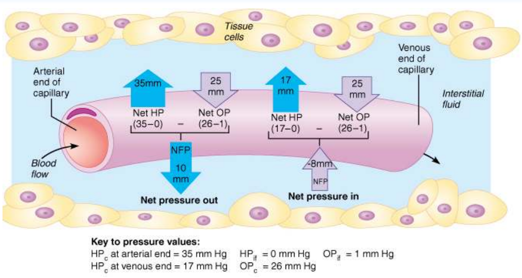
- wider intercellular gaps (>100μm)
- Highly permeable (even to plasma proteins and cells)
- found in tissues where red or white cells need to migrate in/out
  - e.g. liver, bone marrow, spleen, lymphoid tissue

Fluid movement in capillaries – Starling's law



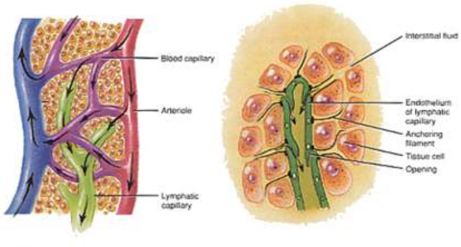
- Forces driving the movement of fluid
  - Hydrostatic pressure capillary (HP_c)
  - Hydrostatic pressure interstitial fluid (HP_{if})
  - Osmotic pressure capillary (OP_c)
  - Osmotic pressure interstitial fluid (OP_{if})
- **Net filtration pressure (NFP) is the net effect of all four forces at any point along the capillary**

Net Filtration Pressure (NFP)



- NFP = (HP_C - HP_{IF}) - (OP_C – OP_{IF}) = Forces out – Forces in
- On average, 85% of fluid entering the tissues on the arteriole side is reabsorbed on venous end

Lymphatics



(a) Relationship of lymphatic capillaries to tissue cells and blood capillaries

(b) Details of a lymphatic capillary

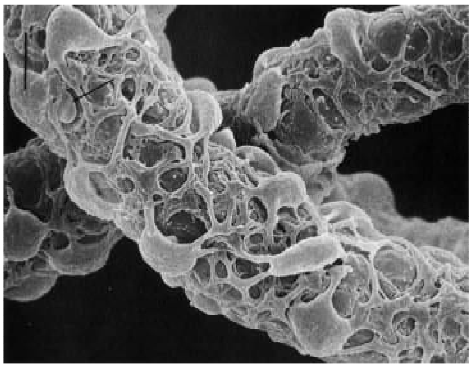
- Blind-ended terminal lymph vessels are ubiquitous in tissues
- Lymphatic endothelial cells overlap to form valve-like structures
- Interstitial fluid drains through lymphatic vessels

Venules

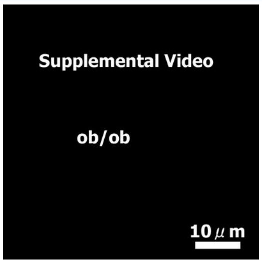
Vessel type/ illustration	*Average lumen diameter (D) and wall thickness (T)*	*Relative tissue makeup* (*Endothelium*, *Elastic tissues*, *Smooth muscles*, *Fibrous (collagenous) tissues*)
 Venule	D: 20.0 µm T: 1.0 µm	

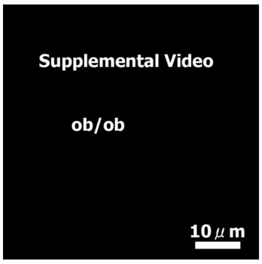
- Major site of emigration of leukocytes (e.g. in inflammation)
- More numerous than corresponding arteries and arterioles – low resistance to flow

Venules



Leukocytes in venules





In vivo imaging in mice reveals local cell dynamics and inflammation in obese adipose tissue J. Clin. Invest. Satoshi Nishimura, et al. 118:710 doi:10.1172/JCI33328

Veins

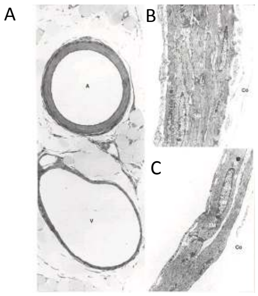
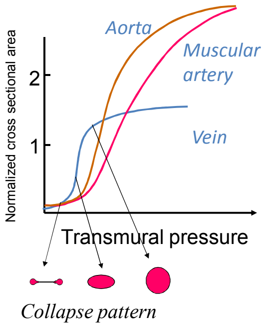


Figure A. Light micrograph of a cross section through a medium-sized artery and vein from the Testis of the squirrel monkey. A, artery; V, vein. 438 X
Figures B and C. Electron micrographs of cross sections taken through the walls of the same artery (Figure B) and vein (Figure C shown in Figure A. Co, Collagen fibrils; E, endothelial cell; EM, Internal Elastic Membrane; F, Fibroblast; N, nerve; SM, smooth muscle; TA, tunica Adventitia; TI, Tunica Intima; TM, Tunica Media.
Figure B, 3,300X; Figure C, 8,900 X

- Vein are less muscular, layers less well defined than arteries
- Limb veins contain semi-lunar valves to prevent backflow (no valves in central veins and veins in the head)

Elastic properties of different vessel types

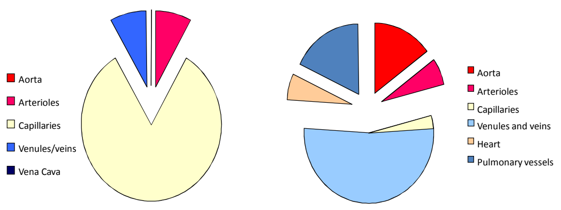


- All vessels show non-linear stress-strain relationships (due to combination of collagen + elastin)
- Veins are highly compliant but over a narrow pressure range
- Elastic arteries are more compliant than muscular arteries

Relative areas and volumes in the circulation

Relative cross-sectional area

Blood Volume (Total = 5L)

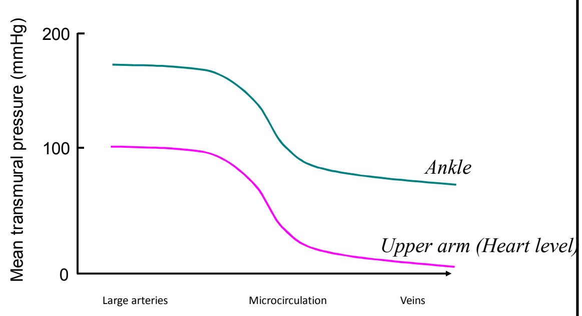


'Exchange' function

'Reservoir' function

Integrating what we have learnt – the effects of standing.

Gravity and blood pressure



Gravity and venous pressure – the problem of standing!

- Standing increases hydrostatic pressure in leg to ~80mmHg as a result of gravity ($h \cdot \rho \cdot g$) .
- Blood 'pools' and reduces the venous volume returning to the heart.
- This would reduce cardiac output and blood pressure if there were no compensatory response.

120cm H_2O ≡ 80mmHg

Why we don't faint on standing

- Standing causes:
  - Activation of the sympathetic nervous system to:
    - constrict venous smooth muscle and 'stiffen' the veins.
    - constrict arteries to increase resistance and maintain blood pressure
    - increase heart rate + force of contraction and maintain cardiac output
  - Myogenic **veno**constriction (in response to elevated venous pressure) to 'stiffen' veins
  - Use of muscle and respiratory 'pumps' to improve venous return
- Nevertheless cerebral blood flow falls on standing
- *Failure of these mechanisms causes fainting (syncope)*

Other problems with standing

- Incompetent valves cause dilated superficial veins in the leg (varicose veins) *[increased circumferential stress due to elevated hydrostatic pressure]*

- Prolonged elevation of venous pressure (even with intact compensatory mechanisms) causes oedema in feet *[increased net filtratin pressure due to elevated hydrostatic pressure]*

References

- Levick JR. An introduction to Cardiovascular Physiology, Hodder Arnold; 2003, ISBN: 0340809213
- Vogel S. Vital Circuits, Oxford University Press, 1991, ISBN 0195082699 (PBK)