Vessels

Introduction: the blood vessel as a grand stage

- Where many critical processes of life go forward – necessary for tissue and organ function
- Consists of vascular wall – endothelial cells and smooth muscle cells
- Liquid and cellular elements of the blood interact here (e.g. clot formation)
    - Platelet activation – platelets are attaching to denuted surface of vessel to make a clot, they then release many chemicals into the bloodstream which affect vascular wall and circulating blood cells
- Cells of the vascular wall (endothelial and smooth muscle cells) are active participants – modify caliber of vessel, quality and characteristics of flow, many other important functions
    - Sense shear force as blood flows through lumen
    - Sense cyclic stress from pulsatile flow through arterial circulation
    - Actively participate in inflammation and coagulation
    - Initiate outgrowth of new vessel elements into areas of tumor formation or wound healing through angiogenesis

Tissue Layers of Blood vessels

- "Tunica" – a layered garment or coat (Greek), like skin of an onion
- Intima – innermost layer, covered with endothelial cells
    - Provides surface over which blood may flow without obstruction
    - Anticoagulant surface
    - Actively interacts with cells of the bloodstream

"Tunic"	**Content**
Intima	Endothelial cells, pericytes
Internal Elastic Lamina	Elastin
Media	Smooth muscle cells
External Elastic Lamina (*muscular arteries only)	Elastin
Adventitia (externa)	Collagen, fat, fibroblasts, vaso vasorum*

Vessel	**Intima**	**Media**	**Adventitia**
Artery	Yes	3-4+	1-2+
Vein	Yes	1+	3-4+
Capillary	Yes (pericytes)	No	No
Lymphatics	Yes	No	1+
Heart (analogous)	Endocardium	Myocardium	Epicardium

Vessels tour as the blood flows: arteries, capillaries, veins, lymphatics, and back to the heart

- How to look at blood vessel sections
    - First orient oneself as to where the lumen is
        - Look for debris, red blood cells, and clot in the lumen
- Muscular artery
    - Intima – monolayer of endothelial cells with prominent nuclei (outpouch into lumen of vessel), very thin strip on inner surface of the vessel
    - Internal elastic lamina – beneath intima
        - Lamina closest to intima
        - Elastic laminae features general to internal and external
            - Laminae appear as wavy pale lines in H&E
            - Smooth muscles cells found in between laminae
            - In EM, elastic laminae appear with many holes like a Rubbermaid mat in the bottom of one's sink
            - Individual fibers are elastic, but mesh structure adds another element of stretchability
    - Media – very thick, about 6 layers of irregularly arrayed smooth muscles cells that may contract and impact blood flow through vessel, little paler nuclei
    - External elastic lamina – outer coat of media
        - Lamina closest to adventitia

    - Adventitia (tunica externa) – composed of collagen fibers and fibroblasts; appears as whispy, fibular material in outer coat of vessel
        - Again you see more prominent, darker nuclei; fibroblasts
- Elastic arteries (e.g. aorta and common carotid artery) have multiple elastic laminae that separate smooth multiple muscle lamella units, each containing many layers of smooth muscle cells
    - Elastic content of these arteries in an important adaptive mechanism that allows the very large arteries to react to the pulsatile flow and high pressure differences between systolic and diastolic pressures
    - As age progresses, elastic elements deteriorate and arteries become more like a stiff pipe which changes the flow characteristics of blood flow and is responsible for some of the pathology of hypertension and how it affects downstream organs (e.g. kidney)
    - As one moves from common carotid to internal carotid, there is a simplification of the elastic components of the media with a much more prominent smooth muscle component and a much simpler elastic component
    - As one continues to move toward the brain and away from the heart in the internal carotid, there is more of a transition from an elastic to a muscular artery topography
    - As the transition is completed, the only elastic elements are the internal and external elastic lamina
- Arteriole
    - Much shorter vessels (1-2 mm)
    - Can be open or completely closed depending on contraction of smooth muscle cells of the tunica media
    - In EM, can see the close opposition of the endothelial cell layer and the smooth muscle cells separated only by a little ECM basal lamina from endothelial cell
        - In fact, there are direct junctions between endothelial cells and smooth muscle cells of the tunica media in arterioles.
        - Gap junctions exist, or myo-endothelial junctions, where endothelial cells directly contact smooth muscle cells. Thus, we see direct regulation of smooth muscle tone by endothelial cells and their products
    - Smooth muscle contraction – slow, tonic, strong contraction
        - Rho kinase and myosin light chain kinase (MLCK) phosphorylate the myosin light chain (MLC). Cells progress from relatively relaxed to a contracted state
        - Regulated by several vasoreactive products of endothelial cells
            - Endothelin – causes vasoconstriction and also proliferation of vascular smooth muscle cells
                - Inhibitors used during illnesses like pulmonary hypertension to control contraction
            - Nitric Oxide – very potent vasodilator, relaxes smooth muscle cells and decreases proliferation
                - Used in very acute situations (e.g. pulmonary vasoconstriction), delivered exogenously through airway
            - Prostacyclin – vasodilator and antiproliferative agent; also delivered by inhalation in intensive care setting with patients with severe pulmonary arteriolar hypertension
        - Also regulated by neuronal input – axons end on smooth muscle cells shown in EM
            - Fluorescence labeling shows catecholamine synapse at smooth muscle portions of arterioles
            - Some arterioles have many nerve endings and are highly regulated neuronally
            - There are also parasympathetic, cholinergic pathways (vasodilation) that oppose adrenergic effect (vasoconstriction)
- Capillaries – endothelial cells form a monolayer that creates a tube through which red blood cells go, often single file, sometimes decorated by pericytes on the abluminal (outside) surface
    - Pericytes are contractile cells, myofibroblast relatives, that can decrease lumen size and regulate flow
        - Foot processes extend from the pericytes onto the surface of the capillary
        - When they contract, they circumferentially constrict the capillary lumen
    - Three types of capillaries
        - Continuous – seen in muscle and connective tissue, variant seen in the brain
            - Tight junctions between endothelial cells are maintained for permeability seal
            - At cell-cell junction, probably tight junction medicated by ZO1 protein making an occlusive zonular occludens that prevents leakage (e.g. blood-brain barrier)
        - Fenestrated – serve a filtration function (e.g. glomerulus), fenestration is an area where capillary lumen is separated from the outside world only by a thin basal lamina
            - Plasma and filtrate can move into the tissue through the fenestrae (windows allowing filtration of blood content)
            - Caveolae – transport vesicles
        - Discontinuous – (e.g. bone marrow)
            - Megakaryocyte has long tentacle-like projections that go through the openings in the wall of the discontinuous capillary and come out into the capillary lumen and buds off platelets
- Veins
    - Small veins
        - The wall of the small vein has very little tunica media and smooth muscle cell content

        - In SEM, the veinous wall is much thinner than the arterial wall; the tunical media is much thinner in the vein
    - Large vein s
        - You can see invaginations of the wall
        - Adventitial layer is much more prominent than the tunica media
- Post-capillary venule – very small venous vessels on the other side of the capillary network from the arterioles
    - A place of much action – fluid leakage, white cell emigration from circulation (diapedesis)
    - Looser organization of endothelial cell junctions
    - Diapedesis – white blood cell squeezes its way between two pairs endothelial cells and escapes from circulation
        - Rolling - P-selectin and L-seletin involved in rolling; low affinity between WBC and the wall of the small vessel
        - Sticking – higher affinity interaction mediated by integrins (CD 11/18)
        - Emigration – crossing of endothelial barrier involves unzipping of endothelial cell junctions, proteases, and several adhesion molecules (including PCAM)
        - WBC invades the tissue and leaves bloodstream, and is now available for inflammatory reaction, response to infection, or initiation of lymphoma
- Lymphatic vessels – another mechanism by which fluid is returned to the heart, via the thoracic duct which returns blood to the central veins
    - Structures
        - Intima – a monolayer of endothelial cells
        - Adventitia – a little bit in some cases
        - Not much else
    - TEM can show direct connection between interstitium and open-ended lymphatic vessel, which feeds into larger and larger lymphatics that ultimately lead to the lymphatic duct and the venous circulation
    - Lymphatics are underappreciated but critically important
        - Infants born with pulmonary lymphangiectasia – the lymphatic system in the lung is improperly formed, fluid builds up in interstices of the lung and interferes with normal gas exchange and lung function. Can be fatal.

Endothelial cells – do many interesting things

- Not all endothelial cells do the same things
- There is active, dynamic rearrangement of endothelial cells in the vessel wall
- Much responsiveness to flow patterns and shear force inside of a vessel (different at branching points)
- At high power, endothelial cells are not completely smooth, but have a lot of projections
    - Projections serve as mechanosensors and change the growth behavior and gene expression of endothelial cells depending on blood flow.
    - Also provide more surface area for interaction with platelets and WBCs that attach to the endothelial wall
- Have well-developed cell-cell junctions easily seen with silver stain
- Have active transport systems to bring their products into capillary lumen – active transport across endothelial cell barrier through a series of plasmalemmal vesicles (caveolae)
    - Caveolar membrane system – well-developed and well-studied thanks to GFP-caveolin chimera
        - Flask-shaped caveolae communicate with membrane and luminal surface of capillary and post-capillary venules. Caveolae can bud off and bring elements into the cell toward cell center in cavicles that travel along microtubules and join a very large network of fused caveolae near the microtubule-organizing center.
        - There is shuttling of proteins and metabolites across endothelium via plasmalemmal vesicle shuttle transport in some capillary endothelium (e.g. liver). Move from abluminal surface (outside) to the lumen
        - Not as prominent in places of restrictive transport (e.g. brain)
- Hemostasis
    - Platelet aggregation
        - Weibel-Palade Bodies – contain von Willebrand factor made by endothelial cells, stored in these bodies, and released under conditions when platelet activation is required
            - In ICU, administration of Desmopressin releases von Willebrand factor from Weibel-Palade bodies to the endothelial surface and favors the activation of platelets in their interaction with the endothelial cell surface and hemostasis and bloodclotting
            - Very prominent in endothelial cells, but finite. A process of tachyphalaxis occurs in which subsequent doses don't work as well because the supply of von Willibrand factor becomes exhausted
            - Only part of the coagulation process
    - Blood vessel constriction – Endothelial cells also regulate
    - Coagulation Cascade – also occurs on endothelial cell surface

        - Activated platelets become spider-like in their morphology, interacting with fibrin (white dots that result from activation of coagulation cascade) forming a hemostatic plug and preventing loss of blood
        - Very complicated cascade
            - Thrombin (from prothrombin) serves as an enzyme that cleaves fibrinogen and make fibrin (the final endpoint of the cascade which participates with platelets in making the blood clot)
        - Coagulation has positive and negative aspects
            - Positive
                - Prevent exsanguinations after accidental or surgical trauma, or indwelling devices
                - Wound healing
            - Negative
                - Disseminated intravascular coagulation
                - Pulmonary microthrombi – develops in sepsis and trauma
                - Local tissue hypoxia, vital tissue death (e.g. heart or brain)
                - Vascular graft, shunt (placed surgically), and limb loss

Heart – wall can be divided into layers analogous to tunica intima, media, and externa (adventitia)

- Endocardium – innermost surface of the heart, lined with endothelial cell surface
    - More complex than tunica intima – contains some smooth muscle cell elements, matrix and elastic elements
- Myocardium – analogous to the tunica media, can see septations between bundles of cardiac myocytes
- Epicardium – also has blood vessel elements and connective tissue
- Cardiac myocytes
    - Intercalated discs – look like hyphens that connect sarcomeres within the myocardium
        - Includes insertions of actin filaments and desmosomes
        - Communication mechanisms by which myocardial contraction is coordinated
        - Make coordinated contraction more likely to occur
    - Sarcomere
        - Transverse tubule – structure which enables rapid changes in calcium concentration to contact many cardiac muscle cells in a short time frame and enhance coordination of contraction
        - When Ca^{2+} comes in sarcomere, tropomyosin has a conformational change allowing myosin to interact with actin, the Ca^{2+} makes impact on tropomyosin through interactions with troponin (I, T, C)
            - Troponin C in the blood is a very specific and sensitive measure of myocardial injury
    - Purkinje fibers – propagates electrical impulses throughout the heart allowing for coordinated contraction of the myocardium and efficient cardiac function

<u>Microlectures</u>

- Cardiac muscle, H&E
    - Heart structurally related to the vessels
        - Endocardium → t. intima, myocardium → t. media, epicardium → t. adventicia
    - Endocardium – lined by endothelial cells just like blood vessels
    - Myocardium – a very thick layer of cardiac muscle cells
    - Epicardium – fibrous and adipose connective tissue, autonomic nerves, vaso vasorum
    - Cardiac muscle cells differ from smooth muscle cells
        - Much larger, branched, striated (orderly arranged actin and myosin), connected via intercalated discs which allow communication between cells, large central nucleus with pale area around it (where glycogen accumulates)
- Myocardium and arteries, Azan
    - Impulse-generating cells of the heart are modified – larger, paler
        - SA node (pacemaker), AV node, bundle of His (AV bundle branches), Purkinje fibers (modified cardiac muscles cells responsible for rapid conduction of electrical signals to the apex of the heart)
        - Purkinje cells – located near the endocardium; larger, paler, fewer fibrils, large store of glycogen
    - Two types of arteries – elastic and muscular
        - Muscular arteries are for more numerous than the larger elastic arteries
        - Elastic arteries – closer to the heart (e.g. aorta, pulmonary trunk), greater diameter, thicker multilayered tunica media which consists of alternate layers of smooth muscle cells intermixed with elastic laminae
            - Act as pressure reservoirs stretching in response to blood ejected from the heart

        - Aorta has ≈50 elastic laminae in tunica media – stretche in response to blood ejected from ventricles, passively contracts as ventricle relaxes between contractions
        - Walls are so thick they need their own supply of nutrients – vaso vasorum
    - Collagen fibers and elastin are made by the smooth muscle cells
    - Atherosclerosis – disease of large and medium-sized elastic and muscular arteries; results in progressive accumulation of *inflammatory cells*, *smooth muscle cells*, *lipid*, and *connective tissue*
        - This fibroinflammatory lipid plaque in intima is called the atheroma, develops over several decades
        - Encroaches on other layers of the vessel wall, narrows the lumen, and eventually leads to reduced or blocked blood flow
  - Aortic semilunar valve – has three cusps, has collagen bundles and elastic fibers, base near the heart is a thick collagenous valve ring
- Pulmonary Artery, Elastic
  - Parts of the pulmonary valve contain elastic fibers
  - Many elastic laminae in pulmonary artery
  - Vaso vasorum seen in adventitia – supply O_2 and nutrients to the outer parts of the thick wall
- Common carotid, Elastic
  - Supply oxygenated blood to head and neck, divides into internal and external carotids which become muscular arteries
  - T. intima is thickened – due to early atherochlerosis
  - Black radiating lines are just artifacts
  - Vein below is a tributary of brachiocephalic vein with no elastic fibers
  - Autonomic ganglion seen – has large neurons (cell bodies) inside as well as axons
- Common carotid, H&E
  - Elastic fibers stain a brighter pink than surrounding structures
- Abdominal aorta and IVC, H&E
  - Abdominal aorta still very much an elastic artery
  - Inferior vena cava has smooth muscle cells in extensive longitudinal bundles rather than in layers between elastic fibers
- Mesentary vessels, H&E
  - Muscular arteries from mesentery (fold of peritoneum that suspends intestines from dorsal abdominal wall and conducts blood vessels, nerves, and lymphatics to the intestines)
  - Both the muscular artery and the vein have the three tunica layers
    - Artery is thicker, rounder
- Mesentery, Toluidine blue
  - Artery has internal elastic lamina, external elastic lamina
  - Vein has a thin internal elastic lamina but no external
  - Can see small capillaries – just a few RBC's in the lumen
  - Lymphatic has a valve, no RBCs
    - Collect fluid, or lymph, that is oozed into tissue spaces from the capillaries which is returned to the blood by the larger lymphatic trunks
    - Lymphatic capillaries are blind-ended, and have thin walls made of a single layer of endothelial cells
    - Often have valves – composed of single layer of endothelial cells that lead off from endothelium of vessel itself
- Mesentery, H&E
  - Sometimes lymphatics in mesentery have thicker walls with some smooth muscle to help pump lymph toward the large veins near the heart
  - Capillaries lined by simple squamous epithelium, structure varies in different tissues and organs but cannot tell in light microscope (only in EM)
    - Continuous – might find in brain (blood-brain barrier); composed of just one endothelial cell holding hands with itself via a tight junction (very little exchange of fluid between lumen and outside)
    - Fenestrated – found in endocrine glands, allow secretions to enter the blood
    - Discontinuous – sinusoidal (liver, bone marrow, spleen), have huge spaces