

CARDIOVASCULAR / CIRCULATORY SYSTEM

BLOOD:

Plasma (3L), Erythrocytes (2.5L), Leukocytes=====Platelets

Hematocrit: %age by Vol. of RBCs (45%)

PLASMA = BLOOD - CELLULAR COMPONENTS = Plasma Proteins +Inorganics
+ Water

Protein Components: function in the plasma or interstitial fluid.

Serum= Plasma - Clotted Proteins

Bilirubin = Hemoglobin waste product

ERYTHROCYTES essentially Bags of Hemoglobin

Blood Group/Type = F(Plasma Membrane Polysaccharides/Proteins)

Hemoglobin, 15g/dl (Protein)==> 4 [Heme (Fe-O₂)] + Globin (4X
Polypeptide)

1 Erythrocyte ~ 250 X 10E6 Hemoglobin Molecules = 1/3 'cell' mass
~5 X 10E6/mm³

[Recall Cytochromes...Heme containing moleculesformation of
ATP during oxidative phosphorylation via H ion transport across
inner mitochondrial membrane.]

NOTE: RBCs contain on their inner membrane a network of protein fibers that
provide an elastic structural network to maintain their bi-concave shape even
after being distorted in the capillaries.

CONSTITUENTS OF PLASMA-----TABLE 14-1

Erythropoiesis ; Bone Marrow====> (Pluripotent) Stem Cells====>
Myeloid Stem Cell ==>Proerythroblast
hemoglobin production = F(nucleus)====>
reticulocyte==>erythrocyte

IRON; hemoglobin 50%, cytochromes 25%, ferritin 25%
-loss due to excretion===replaced via foods & intestinal
epith.
-Note: Negative feedback mechanism in the gut!
-Fe storage in Liver bound to FERRITIN

Erythrocyte Life Span 120 days [Liver & Spleen recycling plants]
====>10 X E11/day produced
Recycled Fe bound to TRANSFERRIN & sent to Marrow!

[RECALL: Cell division==>DNA replication
purine bases--adenine, guanine
pyrimidine bases--cytosine, uracil, thymine]

Thymine ==> F[Folic acid==>F(B₁₂)]
B₁₂ (Cobalamin)=F[Animal product diet]
B₁₂ absorption=F[intrinsic factor, stomach protein]

Hormonal Erythropoiesis Regulation: Erythropoietin = F[kidney capillaries,
i.e. endothelial cells]

Erythropoietin = F[O₂ & testosterone]

Anemia: too little RBCs, RBCs OK but each too little hemoglobin, or
combo.

Sickle cell anemia: messed up globin, wrong amino acid; at low
O₂ levels in capillaries Hemoglobin tangles==> RBC distortion
==> cap. occlusions==>tissue damage.

Polycythemia: Too many RBCs. Blood μ increases==> capillary sludge!!
P. Vera = Bone Marrow Cancer ?? What is the population
of reticulocytes?

LEUKOCYTES: Polymorphonuclear Granulocytes; Monocytes; Lymphocytes

Function in the interstitial fluid

About 4000 to 11,000/mm³ of blood. They leave the plasma via the process of **DIAPYCNOSIS** i.e. actively squeeze out from between the endothelial cells.

Formed and Stored in the Red Bone Marrow. In the reticular tissue loaded with blood sinusoids.

Too many leukocytes = **LEUKOCYTOSIS**

LEUKEMIA = uncontrolled proliferation of a leukocyte cell line in the bone marrow. Yields non functional cells and too few functional cells are thus produced. e.g. no platelets! What happens??

Pluripotent Stem Cell: ==>

-Lymphoid Stem Cell====> Lymphocyte (25-30%) IMMUNE RESP.

T-Lymphocytes, bind to antigen containing cell and penetrate and kill!!

B-Lymphocytes, multiply & become Plasma Cells that secrete antibodies (proteins that bind to antigens)

-Myeloid Stem Cell====> all other leukocytes & RBCs

==> Myeloblasts==>Neutrophils (>50%) PHAGOCYTIC
many lysosome granules, eat bacteria,
'Kamikaze Cells' ==> puss
Immature neutrophils = band cells
infections are associated with increased
band cells in the blood.

====>Eosinophols (1-3%) Antibody/antigen
Complex Phagocytic, lysosomes killer

====>Basophils (< 1%) histamine granules release
/ mediate inflammation response,
increase capillary permeability ==>
increased WBC population (phagocytic)

[Aside: Antigen = any foreign molecule that induces a response from a lymphocyte. Protein/glycoprotein on a foreign cell plasma membrane or secreted by it.]

====> Monoblast====>Monocytes PHAGOCYTIC (macrophages)

====> Megakaryocytes====> Platelets (Thrombocytes) secrete
thromboplastin, initiates clotting process ==> fibrin
mass created ==> clot!!

Hormonal Regulation: Hemopoietic Growth Factors (HGF > 12 hormones)

e.g. Erythropoietin
Colony-stimulating Factors
Interleukins

Section B
OVERALL DESIGN OF THE CARDIOVASCULAR SYSTEM

BULK FLOW====Concept of PRESSURE Differential

PRESSURE = FORCE/AREA Pascals (Pa) = Newtons/meter sq.
mmHg common unit in med. use

Absolute Pressure, Gage Pressure, Vacuum

Blood borne substances==> diffusion, mediated transport==> interstitial fluid
==> Cells

Arteries==>Arterioles==>Capillaries (5% of the blood)==>Venules==>Veins

WILLIAM HARVEY 17th Cent. English =====Cardiovascular Circuit

HEART==> Functionally Two Pumps:

- Systemic Circulation
- Pulmonary Circulation

Vein=====>Atrium==>AV (Tricuspid Rt, Mitral Lft.) Valve ==> Ventricle ==>
Pulmonary or Aortic Valve==>Artery

FIGURE 14-8

PRESSURE, FLOW & RESISTANCE

Hydrostatic Pressure: Pressure of a stationary fluid.

Flow (L/min) = P/R R = Resistance

$R = (8 \mu L) / (r^4)$

L = Tube Length (m)

r = Tube Radius (m)

μ = fluid viscosity (Ns/m²)

SECTION C THE HEART

Location : Mediastinum of the Thoracic Cavity

Coverings : Pericardium; Fibrous & Serous (Parietal, Visceral) pericardium

Heart Layers : Epicardium (Visceral Pericardium)
Myocardium
Endocardium (endothelial lining)

Valves : A-Vs [Tricuspid, Mitral (bicuspid), Pulmonary & Aortic Semilunar]
Passive Structures activation = F (P)
Papillary Muscles==>Chordae Tendinae, 'eversio limiters'

CARDIAC MUSCLE (see table from Ch 11) branching cells/intercalated disk
containing desmosomes/gap junctions
Conducting System ==> Specialized pacemaker cells

Specialized ATRIAL cells release hormone: ATRIAL NATRIURETIC
FACTOR ==> acts on the kidneys to inhibit the
reabsorption of Na.

Innervation: (Recall Fig. 8-44) Sympathetic post ganglionic, -
adrenergic receptors for norepinephrine. (Note: epinephrine from
adrenal medulla has same cardiac receptors)

Parasympathetic (Vagus Nerve), Muscarinic receptors for
acetylcholine.

Blood Supply: Right & Left coronary arteries; Venous drainage via
coronary sinus into Right Atrium

Heart's 'Skeletal System': Network of connective tissue supports and effectively
electrically isolates atria from ventricles.

COORDINATION OF THE HEARTBEAT

Initial depolarization (action potential): SINOATRIAL (SA) NODE ==> AV NODE
==> Bundle of Hiss ==> RT & LT (SEPTAL) bundles ==> Purkinje fibers
(see Fig 14-18)

Cardiac Action Potential: Resting Potential ~ -90mV about the equilibrium potential of K⁺.

Contrast AP differences between Skeletal & Cardiac

Skeletal: 1-2 ms AP & 100 ms twitch; refractory period ~ 1-2 ms.

Cardiac: 200 ms AP (see Fig 14-16) Note K⁺ and Ca⁺⁺ permeability; 250ms twitch; ~250ms refractory period.

Ca effects result of slow channel opening gated by initial Na depol.
Duration of contraction ~ duration of AP. Thus no tetanic contraction.
See Fig 14-23

Conduction System APs Ca⁺⁺ AP (no Na channels) only slow Ca⁺⁺ channels. Note: non steady resting potential ==> Pacemaker Potential
Discharge rate ~100/min for SA Node. ==> heart rate (also under nervous & hormonal control) ==> reduced K⁺ permeability
See Fig. 14-17

Excitation Sequence: (see Fig 14-18 & 19)

SA Node depolarization ==> Atrial Contractions (~ simultaneous)
==> Atrioventricular Node ==> Ventricular contraction
-slow conduction path thus delay between atrial & ventricular contractions. Takes ~100ms.

AV Conduction Disorders ==> Bundle of Hiss pacemaker cells ~30/sec
Thus atrial & ventricular contractions out of synch.==> electronic implant

MECHANICS OF THE CARDIAC CYCLE

SYSTOLE : Period of ventricular contraction & blood ejection (~.3 sec)

DIASTOLE: Period of ventricular relaxation & blood filling (~.5 sec)

SYSTOLE + DIASTOLE = ONE CARDIAC CYCLE

For terminology see Fig 14- 24,25

Sequence of events :

Systole; isovolumetric ventricular contraction (valves closed) ==> ventricular ejection (stroke volume) semilunar valves open ==> semilunar valves close ==> isovolumetric ventricular relaxation ==> AV valves open ==> ventricular filling ==> Atrial contraction (end diastole).

Stroke Volume = End Diastolic Volume - End Systolic Volume

CARDIAC OUTPUT: CO (L/min)

CO = Heart Rate (beats/min) X Stroke Volume (L/beat)

e.g.

CO = 75 beats/min X .07 L = 4.9 L/min (about equal to total blood volume)

Determinants of CO:

RATE CONTROL:

--Cardiac Nervous input;

Sympathetic Stimulation; increase (norepinephrine)

Parasympathetic Stimulation; decrease (acetylcholine)

via alteration of Na, K, Ca permeabilities.

Note: At rest parasympathetic input drives rate down below the pacemaker rate.

--Hormones:

e.g. epinephrine (adrenal medula)

STROKE VOLUME CONTROL:

- Change End Diastolic Volume
- Alter Sympathetic Input (i.e. contractility)

Starling's law: Increasing the end diastolic volume increases the force of contraction. The stroke volume is increased. (see Fig 14-31)

Observation: The more cardiac muscle is stretched the greater the affinity of troponin for Ca^{++} ==> stronger contraction

Conclusion: Increase the venous return ==> increase cardiac output by increasing stroke volume.

Results in EQUALITY OF RIGHT & LEFT CARDIAC OUTPUTS

Sympathetic input to ventricles: ===> increased contractility at a given end-diastolic-volume. For relation to Starling's law see Fig. 14-32

Contractility can be quantified as:

EJECTION FRACTION EF = Stroke Volume/ End Diastolic Volume

SECTION D

THE VASCULAR SYSTEM

Endothelial Cell lining====> Functions of the endothelial cells Table 14-6

BLOOD VESSELS in general: Tunica Intima
Tunica media ==> parallel arrangement in
heart
Tunica adventitia

Pressure changes from Arteries to capillaries to Veins.

Recall Resistance increases as r^4 ; What about $P = \text{Flow} \times R$
==> F/r^4

ARTERIES: Low Resistance Elastic (Pressure/Blood) Reservoirs
Elasticity ==> Compliance = Vol./ Press.

Systolic Pressure: Peak arterial pressure reached during ventricular
ejection.

Diastolic Pressure: Minimum arterial pressure reached immediately prior
to ventricular ejection.

Pulse Pressure: $PP = \text{Systolic} - \text{Diastolic}$ ==> arterial throb
 $PP = F[\text{stroke vol., compliance}]$

Arterial Pressure = $F[\text{time}]$ == however MEAN ARTERIAL PRESSURE is not
 $MAP \sim DP + 1/3(SP - DP)$ otherwise use calculus!!

MAP is an important METRIC ==> average driving 'force' for the
blood

[Note: Your book makes the point that compliance is important in
determining pulse pressure, but that compliance does not affect
MAP!??]

THE MEASUREMENT OF BP.=====see Fig 14-40

ARTERIOLES:

- 1) Establish the blood flow to a given organ
- 2) Are a major factor in determining MAP

Recall Blood Flow $F = P/R \sim P r^4$ or $MAP r^4$ Vessel RADIUS! is the ultimate determinant of organ F since MAP is about the same through out the body

Arteries = Pressure 'reservoirs' MAP = 90 mmHg

Arterioles.....MAP =35 mmHg & farther downstream PP ==> 0 Blood Flow is no longer pulsatile.

Arteriolar Radius==>Vasodilation..Vasoconstriction= F[Smooth Muscle Contraction]

Arteriolar smooth muscle has an intrinsic / basal tone i.e. a MYOGENIC TONE independent of nerve/hormone/paracrine input ==> spontaneously active. This sets the base line contractile state or vessel radius which can now be affected by the above.

LOCAL CONTROL MECHANISMS: = Arteriolar self-regulation see Fig 14-42

- 1) Active Hyperemia==> active increase of blood F
- 2) Flow autoregulation
- 3) Reactive Hyperemia
- 4) Response to Injury

1) Active Hyperemia = F[metabolic rate] which produces local chemical effects leading to vasodilation.

No Nerves/Hormones are causing the dilation.

Eicosanoids, O₂, CO₂, H⁺, K⁺,etc....increased glandular activity results in production of peptides eg. Bradykinin [from kininogen enzymatically via kallikrein]

2) Flow Autoregulation = The process by which F is kept constant in the face of BP changes either up or down via Radius control.

Control mechanisms: Same as in (1) above ; smooth muscle stretch reflex i.e. Myogenic Responses

3) Reactive Hyperemia = result of complete occlusion ==>extreme dilation

4) Injury Response Vasodilating response to chemical agents released ==> inflammatory response.

EXTRINSIC CONTROLS:

Sympathetic Post ganglionic synaptic activity==> norepinephrine==> -adrenergic receptors ==> vasoconstriction REFLEX CONTROL MECHANISM

Increase inhibitory input into sympathetic spontaneous activity which typically maintains a constrictive steady tone results in dilation

Parasympathetic fibers ==> acetylcholine ==> dilation less important except in external genitals

Hormones ==> Epinephrine ==> constriction ==> -adrenergic receptors
Competition with -adrenergic receptors
Angiotensin II ==> constriction
Vasopressin (post pit)

Endothelial Cells ==> act directly on smooth muscle cells via paracrine agents, eicosanoids, ==> induced by mechanical changes e.g. shear stress, stretch etc...

vasodilation.....prostacyclin; nitric oxide [endothelium derived relaxing factor EDRF]

vasoconstriction.....endothelium I

CAPILLARIES:

Angiogenesis===> angiogenic factors

Basic Anatomy:.....

Substance exchange across capillaries

Diffusion*** vesicle transport bulk flow
[& mediated transport in the brain; recall blood brain barrier]

Diffusion: Concentration gradient
lipid soluble pass through the membrane
polar molecules/ions via H₂O filled pores
intercellular clefts & fused vesicle channels

Protein passage Too big! Never-the-less some leaks! Exocytosis

Capillary leaks lot in liver, marrow.....little in brain

Bulk Flow: ===> i.e. movement of protein free plasma

Blood Plasma about 3L; Interstitial Fluid about 10L

Consider the capillary/interstitial P! favors bulk flow from caps. i.e. a plasma ultrafiltrate
WHY doesn't all the plasma leak out???

Starling Forces Osmosis/ P balance

Plasma ==> permeating solutes (crystalloids)
non permeating solutes==> proteins (colloids)
[Albumins, Globulins, Fibrinogen]

See Fig 14-49

VEINS:

Press. Rt Atrium = ~0mmHg

Venous P = 5 - 10 mmHg

Low Resistance Conduits

determined by ventricular volume = F[venous return, i.e. venous P]

Recall Starling's Law Stroke Volume

Determinants of venous P: Venous Compliance is large compared to arteries

Thus can hold considerable pool (65%) of blood at low P.

1) Sympathetic input (norepinephrine) ==> constriction==> P increases

2) Skeletal muscle pump

3) Respiratory pump

LYMPHATIC SYSTEM: == about 4L excess plasma filtrate/day that must be returned especially the leaked proteins (osmotic P)

[Interstitial fluid = lymph]

Note in CNS excess fluid drains via CSF ==> arachnoid villi==>venous drains

Lymphatic vessels; tissues; organs.==== because of their permeability they are routes for the spread of disease. [Nodes, Spleen, Thymus, Peyer's patches, Tonsils]

Endothelial cell tubes; Lymph capillaries are dead ends!

Highly permeable to all interstitial constituents

Endothelial cell junctions === valve like (one way flow)

Edema ==> swelling; accumulation of interstitial fluid

Lymphatic smooth muscle responds to stretch ==> triggers contractions

Sympathetic input, muscle/respiratory pump helps to drive lymph

SECTION E

REGULATION OF SYSTEMIC ARTERIAL PRESSURE

HOMEOSTATIC CONTROLS:

REFLEX CONTROL MECHANISMS: REVIEW==> FEEDBACK, FEED FORWARD

VARIABLE BEING REGULATED

MEAN ARTERIAL PRESSURE: MAP

$$\text{MAP} = (\text{CO}) \times (\text{TPR}) \quad \text{RECALL:} \quad \text{CO} = (\text{SV}) \times (\text{HEART RATE})$$

SEE FIG 14-57

BARORECEPTORS, PRESSURE REREGULATING FEED FORWARD MECHANISM

SEE FIG 14-61 & 62

NOTE: SHORT TERM EFFECT & RESET POINT.....PHYSICAL EXERCISE TEMP. RESET

LONG TERM EFFECTS =====> BLOOD VOLUME <====> MAP

BYPASS OR INFLUENCE OF MEDULLARY REGULATORY CENTERS BY
CORTICAL/HYPOTHALAMIC INFLUENCES

SECTION F: CARDIOVASCULAR HEALTH & DISEASE

HYPOTENSION SEE FIG 14-65 & 62

BLOOD LOSS

FLUID LOSS

EMOTIONAL RESPONSES

ALLERGIC RESPONSES; RELEASE OF VASODILATORS

SHOCK: A DECREASE IN BLOOD FLOW TO ORGANS RESULTING IN DAMAGE

HYPERTENSION: RENAL HYPERTENSION ==> F(ANGIOTENSION II)

PRIMARY (ESSENTIAL) HYPERTENSION ==> "UNKNOWN CAUSES"

TREATMENTS: DIURETICS

B-BLOCKERS

Ca CHANNEL BLOCKERS

ANGIOTENSIN II BLOCKERS

SYMPATHETIC CNS BLOCKERS

HEART FAILURE: DECREASED CONTRACTILITY

SHIFT OF THE STARLING CURVE TO A LOWER FUNCTION

VENTRICULAR ENGORGEMENT ==> EVENTUALLY LESS CONTRACTILITY

INCREASED PLASMA VOLUME ==> ALTERED KIDNEY FUNCTION

PULMONARY EDEMA ==> LEFT VENTRICLE FAILURE

CORONARY ARTERY DISEASE:

POSTURE; PRONE VS STANDING ==> "HYDROSTATIC" PRESSURE HEAD (80mmHg)

EFFECTIVE BLOOD VOLUME < ACTUAL

INCREASED LOSS OF BLOOD PLASMA FILTRATE

SAME EFFECT AS HEMORRHAGE

EXERCISE;

MAP = CO X TPR

TPR DOWN, CO UP ==> SV UP BECAUSE OF INCREASED SYMP.

ACT

& STARLING'S LAW (DEEP RESPIRATION, LEG MUSCLE

ACTIVITY ==> INCREASED ATRIAL PRESS.)

HR INCREASE VIA SYMP ACT. NOTE. RELN BETWEEN HR & END
DIASTOLIC VOLUME

MAXIMAL OXYGEN CONSUMPTION & TRAINING

LIMITING FACTOR IS O₂ DELIVERY NOT LOCAL METABOLISM

TRAINING EFFECT = INCREASED SV WITH DECREASED HR