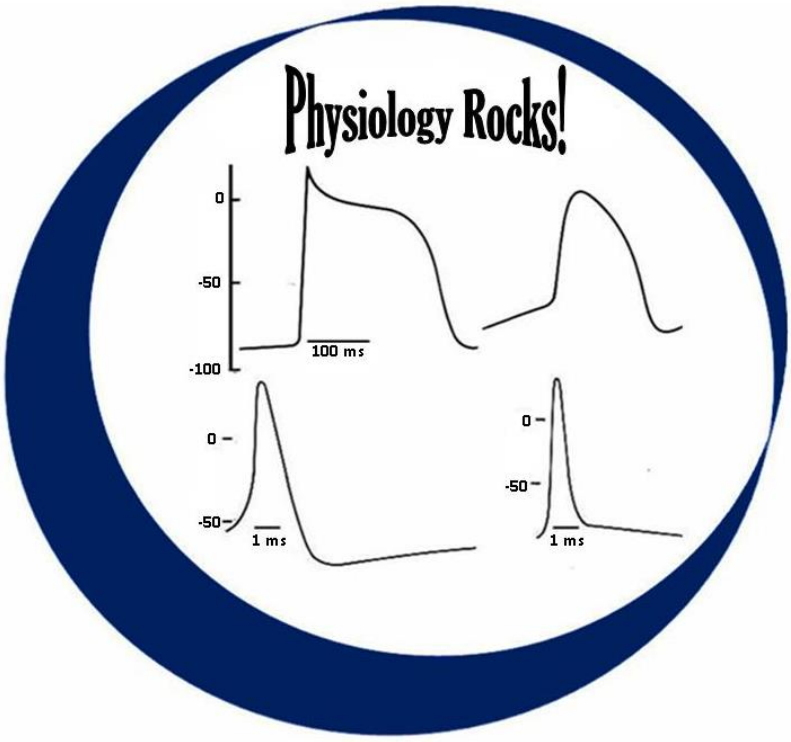
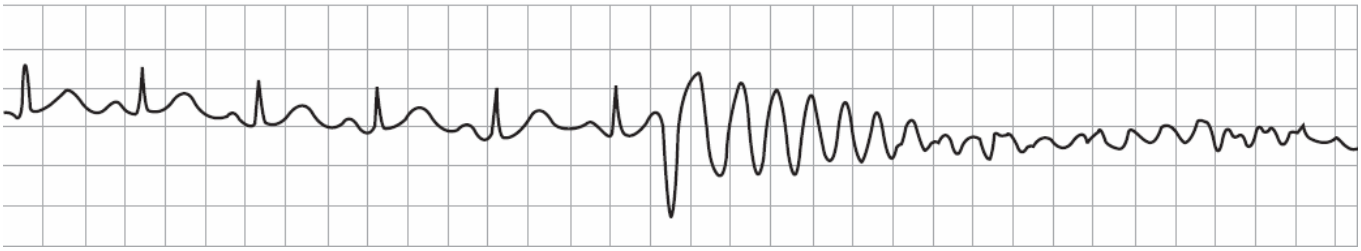
MEDICAL CARDIOVASCULAR PHYSIOLOGY





Medical Cardiovascular Physiology – by Dr. HN Mayrovitz - Table of Contents

CARDIOVASCULAR (CV) PRELIMINARY OVERVIEW AND REVIEW

A. Major Coronary Arteries and Their Distribution Territories TOC

Figures show coronary arteries & regions they supply. Important when discussing regions sensed by EKG leads and arteries that affect those EKG patterns.

SAN = Sino-Atrial Node,

AVN = Atrial-Ventricular Node,

RBB = right bundle branch,

LBB = left bundle branch,

IVC = inferior vena cava,

SVC = superior vena cava,

LCA = left coronary artery

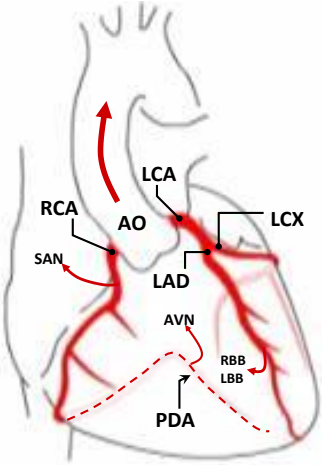
RCA = right coronary a.,

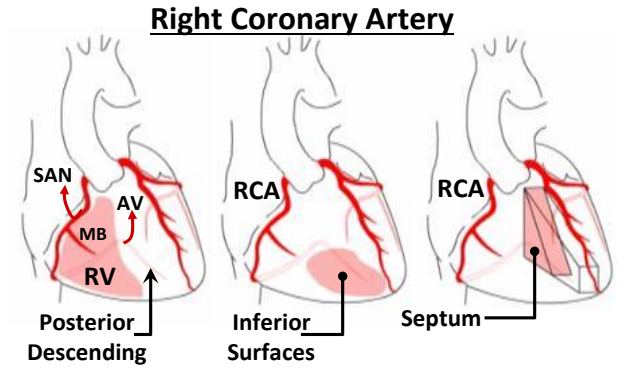
LCX = left circumflex a.,

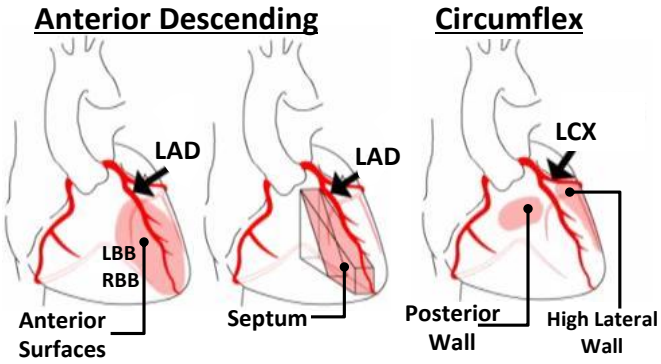
LAD = left anterior descending a.,

PDA = posterior descending a.

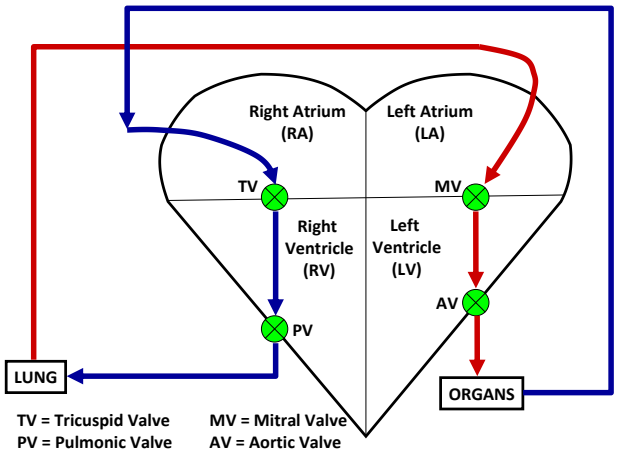
MB = Marginal branch, PA, PV = Pulmonary a & v

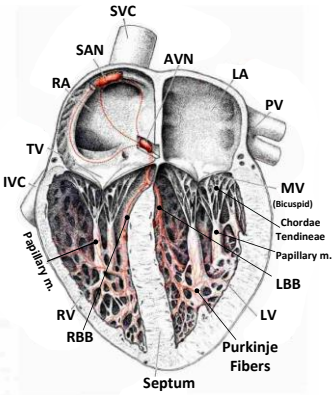


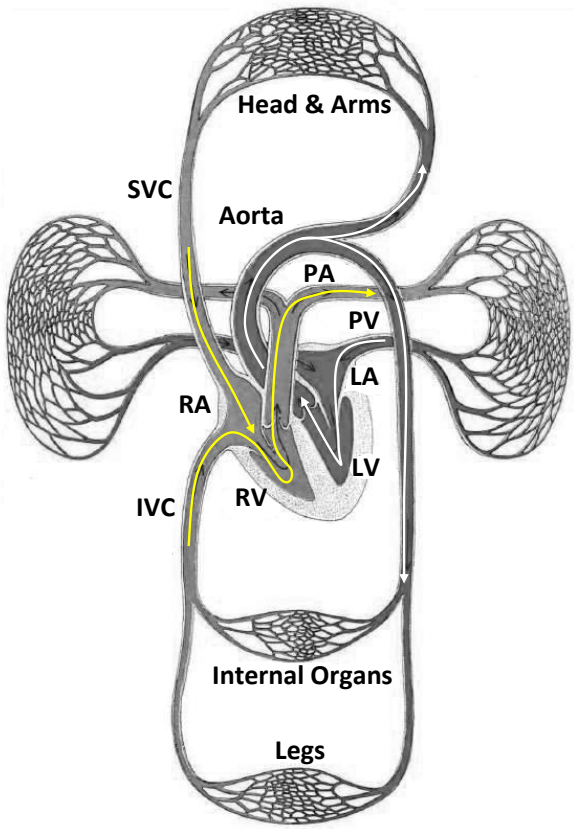




B. General Plan of the CV System



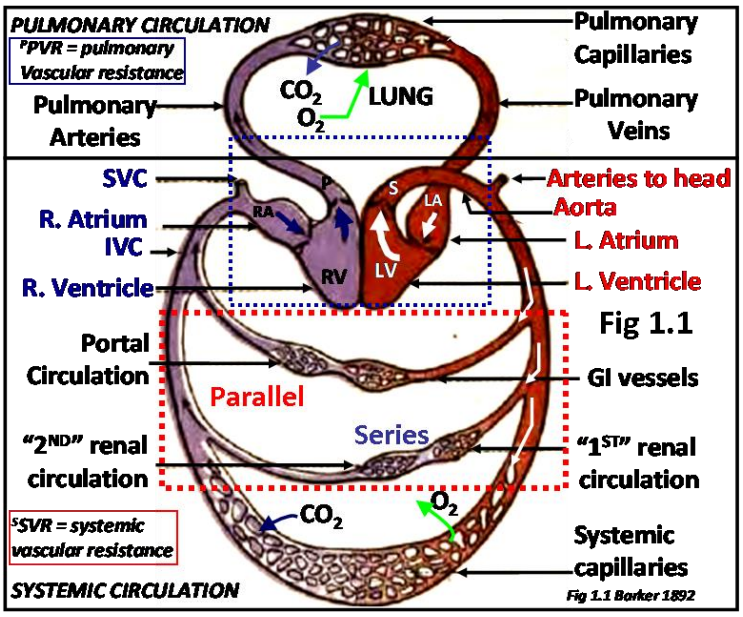




1.0 Introduction & Overview TOC

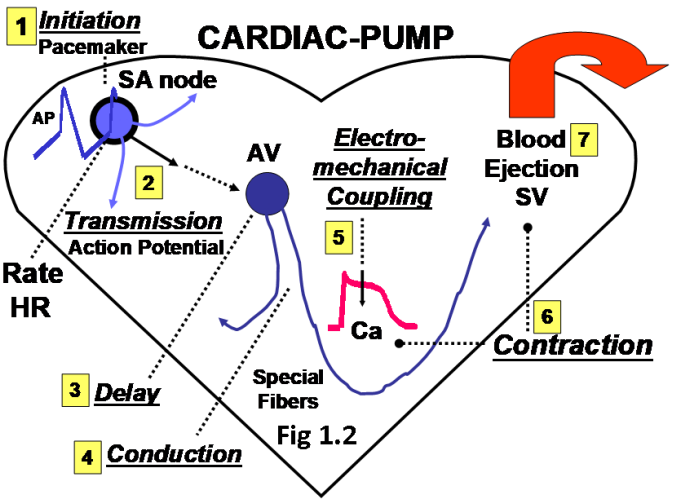
1.1 Main Circulations TOC

Blood leaving the LV each minute (L/min) is the cardiac output (*CO*) that supplies the systemic circulation. *CO* returns to the RV that pumps it through the lungs (pulmonary circulation) to return to the LV (**Fig 1.1**). The lymphatic system (not shown) collects fluids and other materials and transports these to the venous system. The LV and RV are blood pumps that work in series to provide an adequate blood flow to meet overall body needs. Pressure needed to move the blood is achieved by ventricular contraction.



1.2 Excitation and Contraction

are initiated by spontaneous SAN action potentials [AP] that are conducted thru atria to ventricles. The AP arrives at the AV node (**Fig 1.2**) and after a delay is rapidly conducted through special fibers. Atrial APs depolarize atrial myocytes and ventricular APs depolarize ventricular myocytes. During depolarization, Ca^{++} enters myocytes causing contraction that ejects blood (stroke volume, SV) into large vessels through aortic and pulmonic valves.

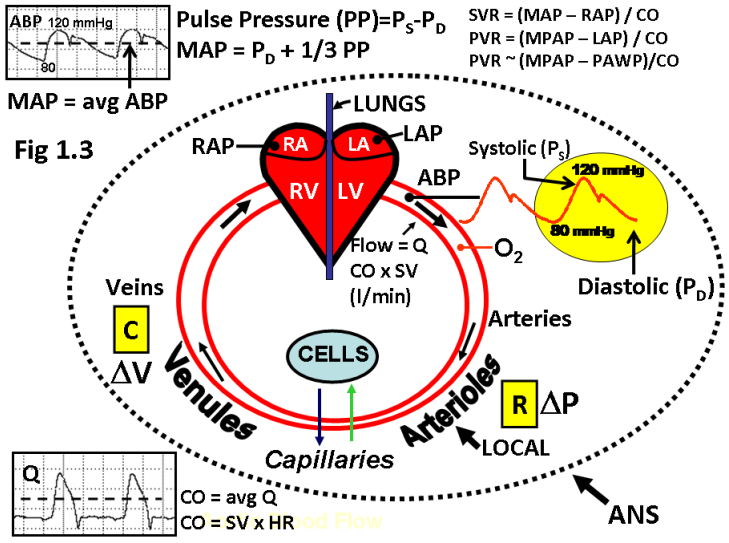


1.3 Stroke Volume (SV)

is blood volume ejected per contraction (~ 60 – 120 ml). As LV contracts and ejects SV into the aorta, there is a rapid rise in the arterial blood pressure (ABP, **Fig 1.3**). As the LV relaxes, ABP falls. Maximum pressure achieved per cycle is called systolic (P_S) and minimum is diastolic (P_D); the difference ($P_S - P_D$) is called pulse pressure. Blood arrives at capillaries where blood-tissue exchange occurs. Blood returns to the RA via veins and is pumped by the RV into the lung to be replenished with O_2 and remove excess CO_2.

1.4 Pressure-Resistance-Compliance

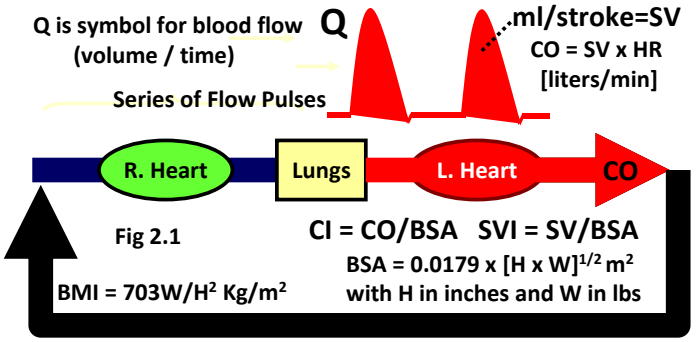
As blood moves it loses energy. A measure of this loss is the pressure difference (ΔP) between two points in the flow-path. The greatest loss is in high resistance (R) arterioles. Vein pressures are low and depend on vein compliance (*C*) and volume changes (ΔV). Compliance relates ΔV to transmural pressure change (δP) in a blood vessel or cardiac chamber and is defined as $C = \Delta V/\delta P$. Expressions for some pressures and vascular resistances are summarized in **Fig 1.3**. SVR is systemic vascular resistance; PVR is pulmonary vascular resistance: MPAP is mean pulmonary artery pressure: PAWP is pulmonary artery wedge pressure. RAP and LAP are Right and Left atria pressures.



2.0 Cardiac & Stroke Volume Index Overview TOC

2.1 Cardiac Index (CI)

CO = SV x HR but to take into account a person's body surface area (BSA) it is normalized to BSA as **CI = CO/BSA (Fig 2.1).** Normal range is 2.5-4.0 l/min/m^2 with average values ~ 3.3 l/min/m^2 with no gender difference but a small age-related decrease.



Organ blood flow through multiple parallel pathways

2.2 Stroke volume index (SVI)

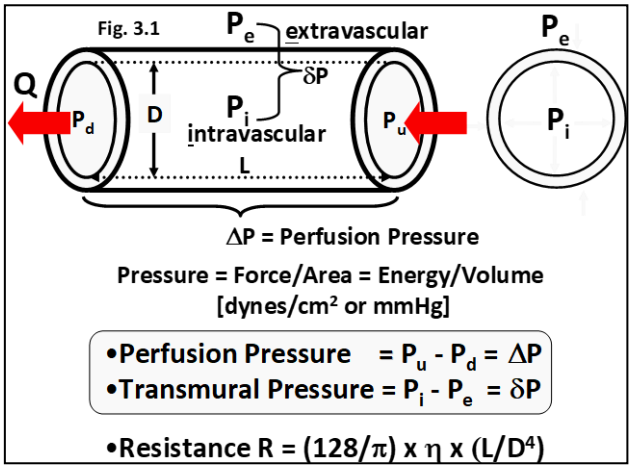
SVI = SV/BSA with normal range of ~ 30-50 ml/m^2. Recall that atrial and ventricular contractions are triggered by excitation initiated by SA node APs. A depolarization wave spreads through atria and into ventricles whereupon ventricular muscle contracts causing SV ejection into systemic and pulmonary circulations; ventricles then relax. Blood flow and pressure are in the form of pulses as illustrated in figures 1.3 and 2.1. The time average of LV outflow is another way to view **CO** and the time average of aortic pressure is mean aortic pressure (MAP).

Example: Bill weighs 160 lbs (W), 69 inches height (H), SV=60 ml and HR =100. What are BSA, BMI, SVI and CI? ANSWERS: BSA=1.88, BMI = 23.6 Kg/m^2, *CO* = 6 l/min, CI = 3.19 l/min/m^2, SVI = 31.9 ml/m^2

3.0 Blood Pressure Overview TOC

3.1 Pressures: Intravascular, Extravascular, Transmural, Perfusion (Fig 3.1)

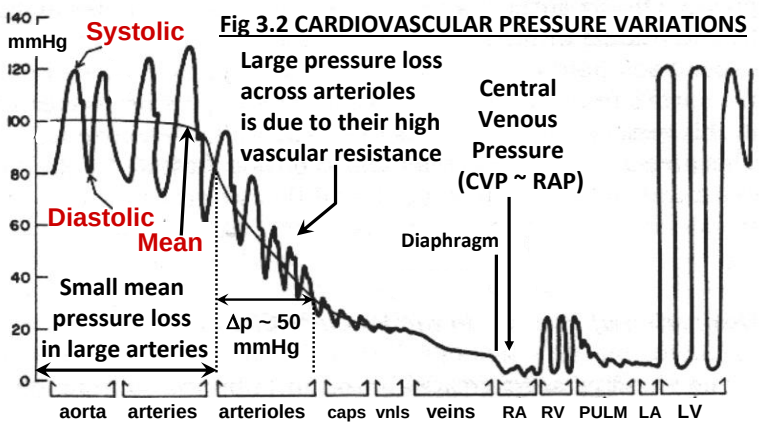
Pressure inside is ***intravascular pressure*** **(P_i).** Pressure outside is ***extravascular pressure*** **(P_e).** A pressure difference δ**P** = **(P_i - P_e)** that acts across the wall is ***transmural pressure***. Whereas δ**P** acts in a radial direction, Δ**P** acts along a vessel's axis and is called ***Perfusion Pressure.*** It is the pressure difference between upstream and downstream shown as **(P_u - P_d)**. This Δ**P** can also be thought of as pressure *loss*. Blood flow along vessels moves according to the relationship **Q = ΔP / R.** Here R is the resistance to blood flow and η is blood's viscosity (see section 4).



Pressure Units: *CGS* units are dynes/cm^2 (1 mmHg =1333 x dynes/cm^2). For SI it is the Pascal: 1 Pa = 1 N/m^2 = 1 Kg/m/s^2 and 1 mmHg = 133 Pa; multiply Pa by 0.0075 to get mmHg. For cm H_2O: 1 mmHg = 1.36 cm H_2O.

3.2 Blood Pressure (BP) Distribution within the Circulation (Fig 3.2) Return Text

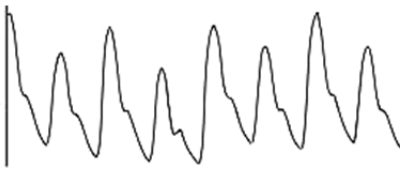
1. Mean BP decreases little in large arteries but decreases greatly in arterioles due to high R.
2. Systemic venous pressure is low and decreases more gradually due to much less resistance.
3. Systolic and pulse pressures increase slightly from aorta to peripheral arteries but pulses then diminish and are much reduced or absent in capillaries and small veins.
4. Venous pressure falls as veins enter the thorax with the lowest pressure near the RA with a CVP of < 5 mmHg. Note the large difference in pulse pressures of the left vs. the right ventricles.



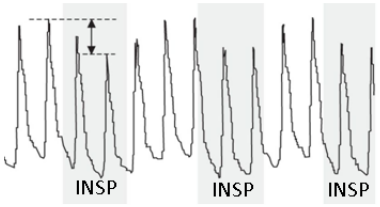
3.3 The PRESSURE PULSE TOC

- Expansion wave travels along arteries caused by expulsion of SV into an already blood-filled arterial system
- Wave travels at high speed ranging between 5-15 m/s depending on vessel properties
- Pulse usually palpated (felt) at the radial artery that is near the surface and supported by the underlying bone
- What is actually felt is a "shock wave" initiated by LV ejection and propagated to the point of palpation.
- Features worth noting when palpating the pulse include the following:
    - FREQUENCY → Heart Rate → # of beats per minute → 1st palpated beat = "0" beat
    - DURATION → Time each pulse-beat occupies
    - REGULARITY → Irregular cardiac action in either FORCE or RHYTHM
        - *pulsus alternans → regular weaker and then stronger pattern*
        - *pulsus paradoxus → weaker during inhalation and stronger during exhalation*
        - *pulsus bigeminus → groups of two rapid with longer space between groups*

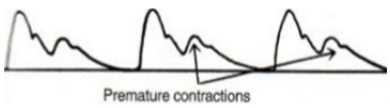
A. Pulsus Alternans
Regular rhythm
systolic high-low
Cause? Alternate cycle changes in Preload? Afterload? *Contractility*?



B. Pulsus Paradoxus
Increase in normal respiratory systolic pressure change



C. Pulsus Bigeminus
Extra systolic due to premature contraction



- TENSION → Force to obliterate → related to BP and state of arterial wall
- STRENGTH → Strong or Feeble → Force of cardiac contraction
    - 0 → can't be felt
    - 1+ → weak – fades in an out
    - 2+ → needs light palpation to detect but stronger than 1+
    - 3+ → NORMAL
    - 4+ → easily palpated – strong- bounding

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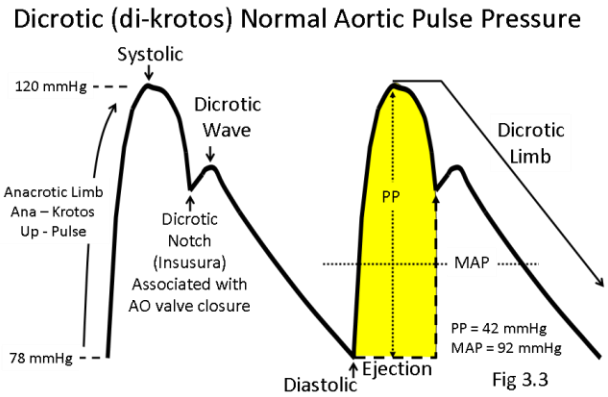
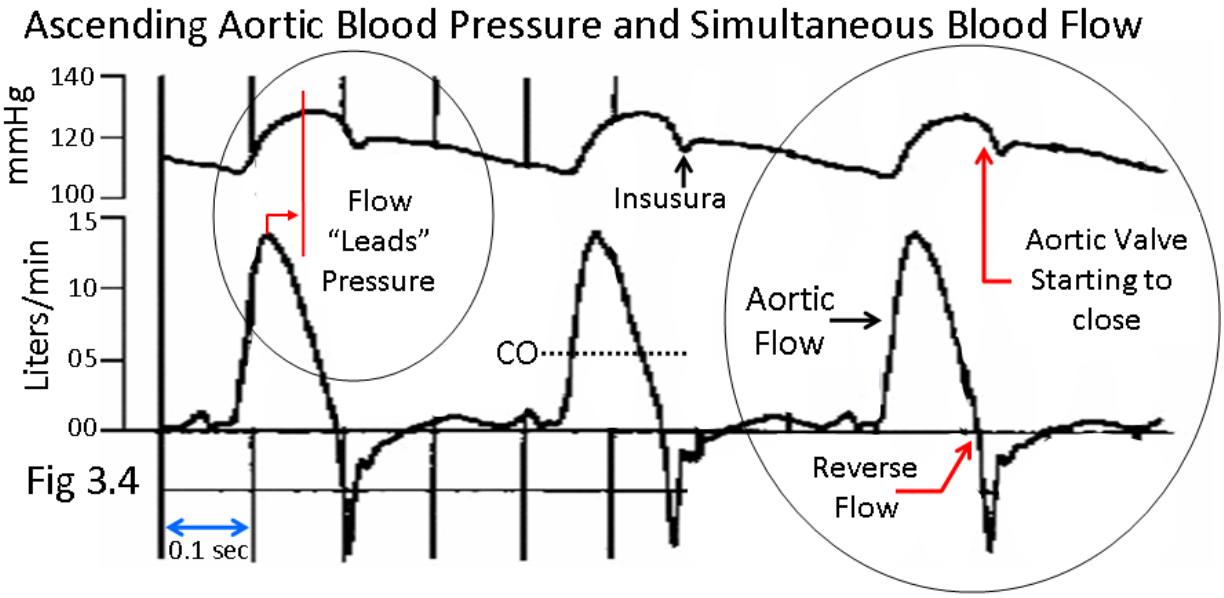


In **Fig 3.3** the location of the dicrotic notch measured in the aorta is normally ~ 1/3 down from the systolic peak. Because it occurs when the LV pressure falls below the aortic pressure it will move further down in cases of low arterial blood pressure. For pressures measured in peripheral arteries (e.g. femoral artery), the location is also further down from the systolic peak. Mean arterial pressure (MAP) can be also calculated as 1/3 Systolic + 2/3 Diastolic.

3.4 The FLOW PULSE TOC

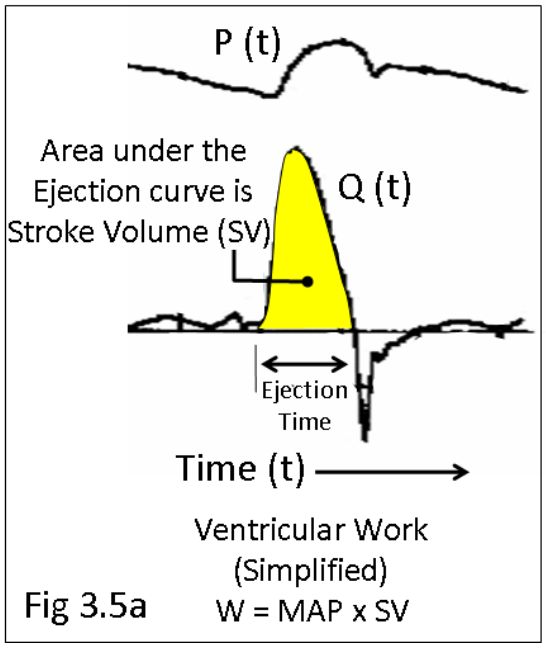
Figure 3.4 below illustrates some features of the arterial flow pulse in relation to the arterial pressure pulse

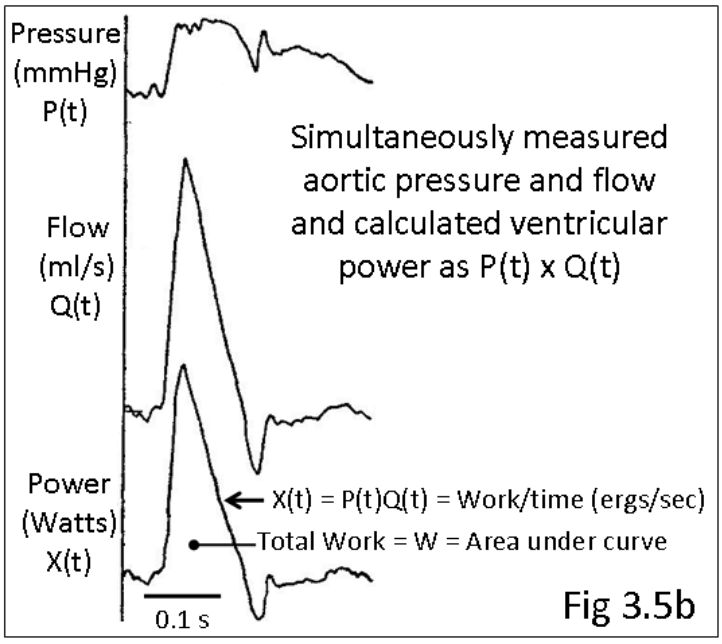
- The flow pulse rises to maximum rapidly with about 2/3 of SV ejected during the 1st 1/3 of the pulse
- The flow pulse "leads" the pressure pulse since the pressure is initiated by the LV ejection
- There is an interval of reverse flow direction close in time with aortic valve closure
- There is an interval of near zero flow that we will learn later is due to reflected wave interactions



3.5 Ventricular External WORK Done

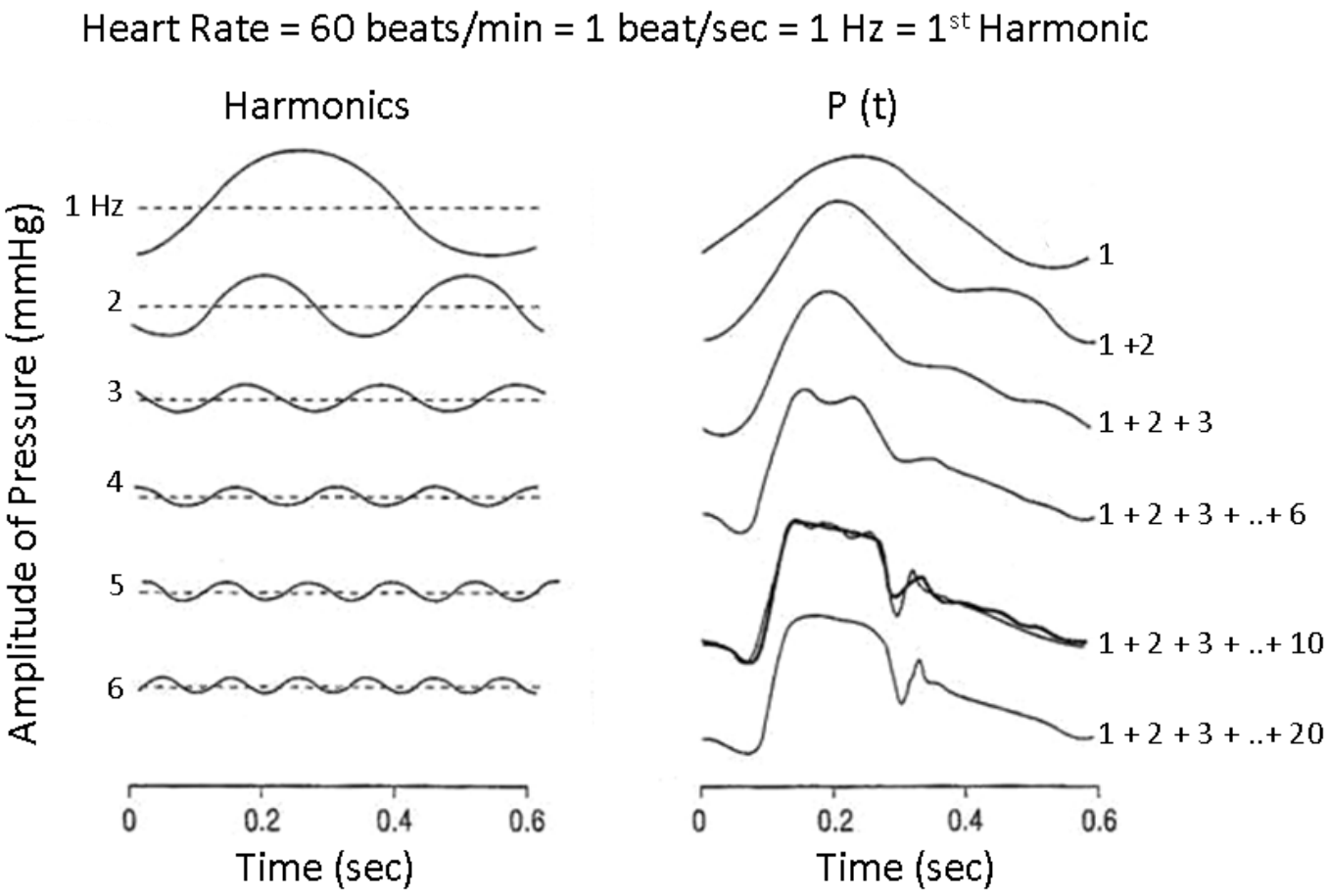
Each ventricular contraction and associated blood volume ejection results in physical work being done by the ventricle. This work can be approximated as the product of the SV x the mean arterial pressure (MAP) or more precisely as the area under the ventricular power curve which itself is determined by the product of the instantaneous flow, Q(t) and pressure, P(t). These concepts are illustrated and summarized in **Fig 3.5**





3.6 SPECTRAL CONTENT of Pressure and Flow Pulses TOC

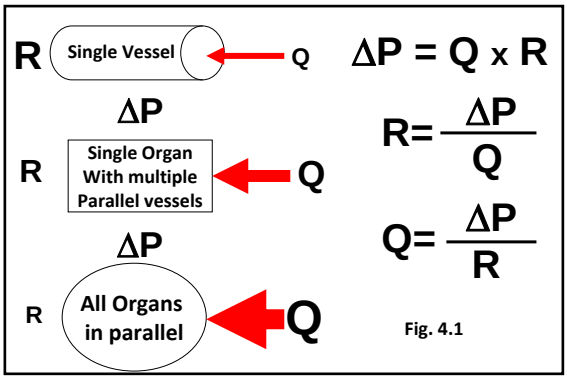
Pressure and Flow pulses as measured show the amplitude of the pulse as a function of time. In **Fig 3.5** this was expressed as P(t) and Q(t). It turns out that these time-domain wave forms have a counter-part in the frequency-domain. What this means practically is that any pressure pulse can considered to be equal to the sum of many superimposed sine waves having different amplitudes and frequencies. This concept is illustrated in 3.6b below an aortic pressure pulse is seen to evolve as the sum of multiple harmonics of a single sine wave as shown in 3.6a. As a consequence of this relationship to spectral or frequency content of P(t), some of its wave progressive and reflective properties may be understood in terms of this frequency content.



As a general rule, rapid changes in the time-domain correspond to higher frequencies. As one example of this note that the visualization of the dicrotic notch in the reconstructed P(t) becomes better seen with the addition of higher and higher harmonics. The opposite of this would also be true. For example, if the pressure wave were subject to a filtering action that removed the high frequencies the dicrotic notch would be less visualized or perhaps not visualized at all! The time varying part of the pressure is sometimes referred to as its "pulsatile component" to distinguish it from the average value of the pressure.

4.0 Vascular Resistance TOC

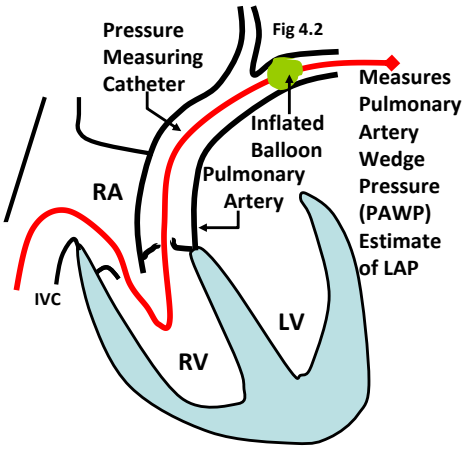
4.1 Vascular Resistance: Concept

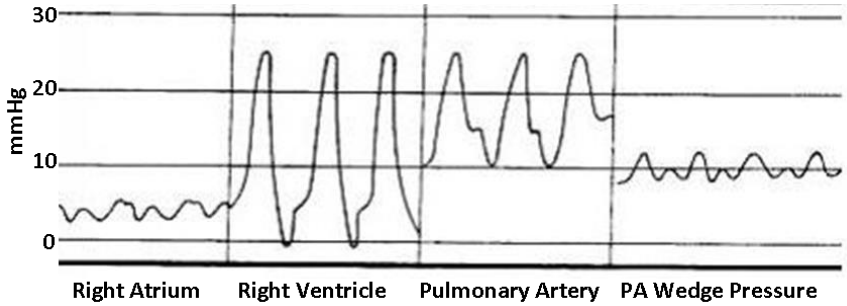


Flowing blood loses energy as heat due to friction. To maintain flow, energy lost must be supplied by pressure. Between two points along a blood vessel the pressure difference ΔP equals energy lost between the two points. The loss depends on volume flow, **Q** and "frictional" resistance, **R** such that **ΔP=QR.** Given two of these, the third is calculated (Fig 4.1). So, Q to an organ depends on **ΔP** across the organ divided by the organ's vascular resistance. Resistance of the entire systemic circulation, called SVR or TPR for total peripheral resistance is calculated as **TPR =(MAP-RAP)/CO**. Since RAP is near CVP another valid relationship is **SVR=(MAP-CVP)/CO.** Further since normal CVP values (1-5 mmHg) are small compared to MAP an approximation is **SVR =TPR = MAP/CO.**

4.2 Pulmonary Vascular Resistance

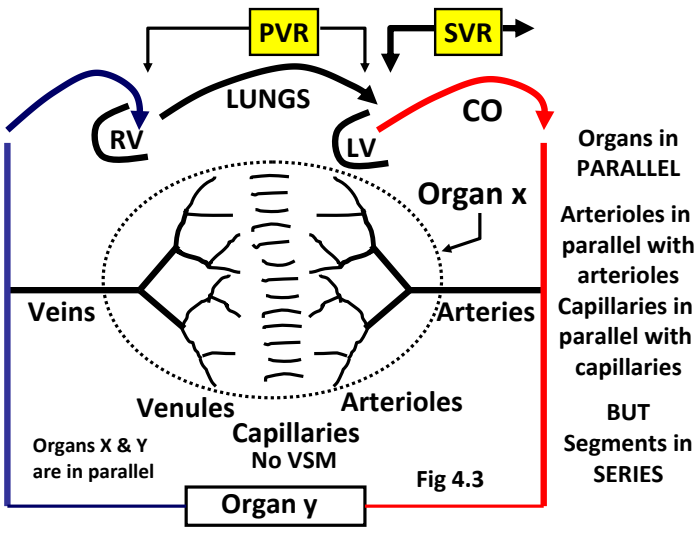
For the pulmonary circulation the pulmonary vascular resistance, **PVR = (MPAP - LAP)/CO.** Since LAP (6-12 mmHg) is hard to measure, pulmonary wedge pressure is used to estimate it; **PVR = (MPAP – PCWP)/CO** (Fig 4.2.)





4.3 Vascular Arrangements and Resistance TOC

Organs are in parallel with each other (Fig 4.3). Pressure differences across organs is **perfusion pressure** = **MAP – CVP.** Organs with greater **R** get a smaller % of CO. An organ's **Q** is changed to meet new conditions by changes in its **R** mainly by arteriole diameter changes. Each organ's vessels have features specific to its needs that may differ with respect to size, number, wall structure, and control, but all have vessels that function to deliver blood, control resistance, facilitate blood-tissue exchange and collect and return blood. The term "vascular bed", conveniently describes the set of vessels within an organ or tissue region. Organs are in parallel with each other but within the organ functionally different vascular beds are in series with each other as in Fig 4.3. Large elastic arteries receive then deliver blood to vessels that supply organ tissues. Arterial vessels diverge, increase in number and get smaller until capillaries are reached. Venous vessels start after capillaries and converge to become larger. Within organs, all arterioles are essentially in parallel with each other and ditto for capillaries, venules. But, groups of same vessel types in the same organ are essentially in series with other types. This series arrangement is why BP decreases from artery to veins.



4.4 Resistance Units and Typical Normal Values TOC

Values are based on **R=ΔP/Q** with several forms of units in use**.** In the *CGS* system pressure is in dynes/cm^2 and flow as cm^3/s. The R unit is (dynes/cm^2)/(cm^3/s) or as dyne s cm^{-5}. Note: 1 mmHg = 1330 dynes/cm^2. ***Examples:*** Sam's data are as follows; *MAP* =110 mmHg, *CVP* = 10 mmHg and *CO* = 6 l/min. What is his TPR? *CALCULATION*: ΔP = 100 mmHg x 1333 dynes/cm^2/mmHg = 133300 dynes/cm^2 and *CO* = 100 cm^3/s so SVR=1333 dyne s/cm^{-5}. In *CGS* units a normal range is ~ 800-1200. If pressure is measured in mmHg and flow in units of l/min then we have TPR in a *Wood unit* with 1 Wood unit = 80 dyne-sec-cm^{-5}; TPR = 1333/80 = 16.7 *Wood Units* with a normal range of ~ 10-15. Another hybrid unit is called *peripheral resistance unit* (*PRU*) and is defined as equal to 1 mmHg/(ml/min) so that 1 PRU = 1 Wood unit/1000.

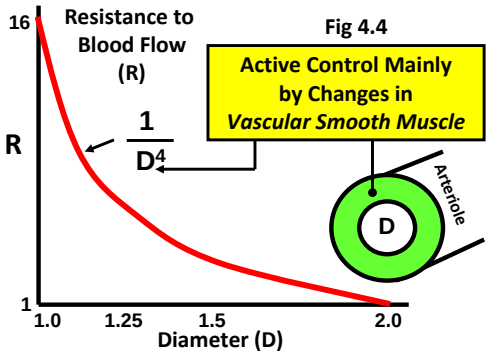
4.5 Resistance (R) of a Single Blood Vessel with Laminar Blood flow

Resistance to blood flowing smoothly (laminar flow) as illustrated in **Fig 3.1** depends on η, the blood's viscosity that is a measure of friction experienced by adjacent blood layers moving along the vessel. **Resistance, R** is given by $\mathbf{R = K\,\eta\,L\,/D^4}$ where K is a constant (128/π). Physiologically, a change in arteriolar diameter is the dominant factor that alters blood vessel resistance. The relationship R=ΔP/Q still applies.

4.6 Factors Affecting Diameter/Resistance

Diameter (D) can change passively or actively (**Fig 4.4**).

*A **passive change*** occurs if transmural pressure δ**P** changes. An increase in δ**P** causes **D** to increase by stretching the wall more. The opposite occurs if δ**P** decreases. These are passive changes. An ***active change*** in **D** occurs if a vessel's own vascular smooth muscle (VSM) in the vessel wall relaxes or contracts. If it relaxes **D** will increase causing a decrease in **R**. The opposite occurs with vasoconstriction.



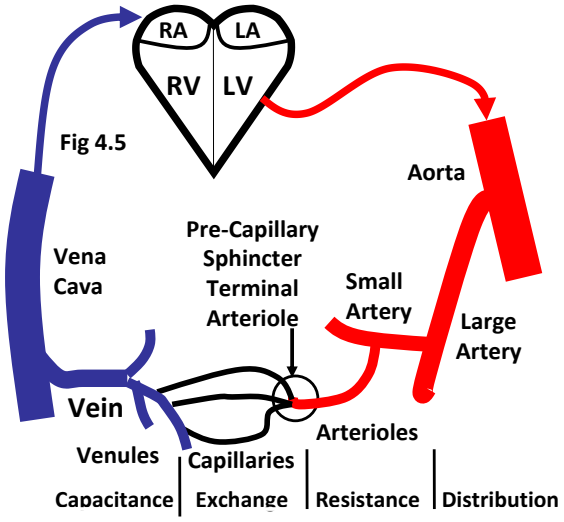
4.7 Summary of Vessel Functional Features (Fig 4.5)

Arteries-Elastic: Aorta and large arteries are conduits with little energy loss and are relatively distensible due to wall elastin content. During LV ejection, they expand and transiently store blood and then recoil during LV relaxation thereby helping maintain flow to smaller peripheral vessels

Arterioles: Resistance vessels; help regulate blood flow and pressure to capillary networks by changing diameter. High resistance is due diameter and number. These arteriolar networks are the major contributor to TPR.

Pre-capillary Sphincters or Terminal Arterioles are distal segments of arterioles that "guard' capillary entrance. "Fine-tune" capillary network pressure, flow and exchange,

Capillaries or exchange vessels exist in networks of interconnected vessels 3-8 μm in diameter and ~ 1 mm long comprising the blood-tissue exchange region. They have no vascular smooth muscle (VSM) and are not innervated and do not actively change diameter. ***Venules/Veins*** are capacitance vessels with blood reservoir and mobilization features. They are thin walled with some VSM and provide return pathways to heart.



All blood vessels are lined with endothelial cells (EC) that release vasoactive substances that help control contribute to controlling vessel diameter via their release of vasoactive substances.

5.0 Basic Aspects of ANS Heart and Vessel Control TOC

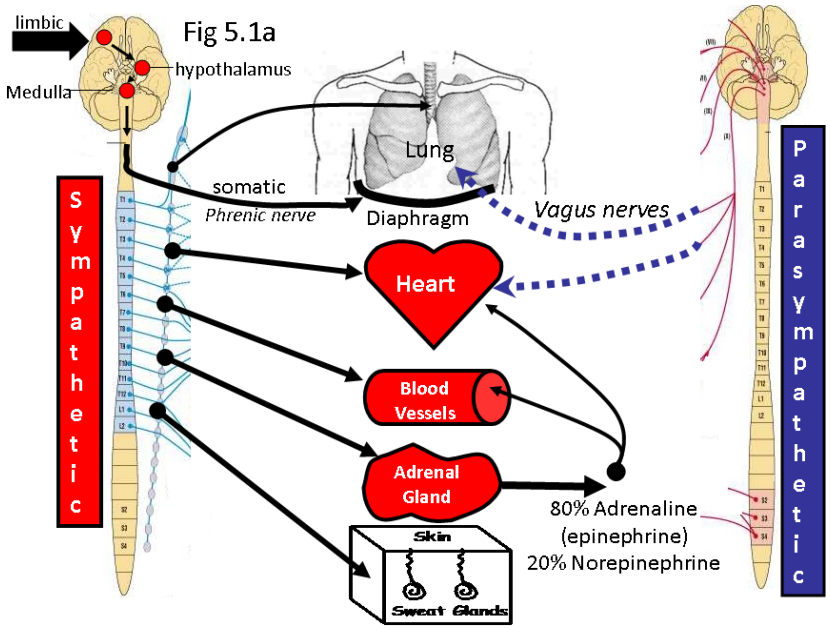
5.1 Overview of Cardiovascular Pathways

Major ANS targets (**Fig 51a**) are heart, blood vessels, adrenal medulla and skin.

If sympathetic nerve impulse traffic increases to heart, HR and SV increase causing CO to increase.

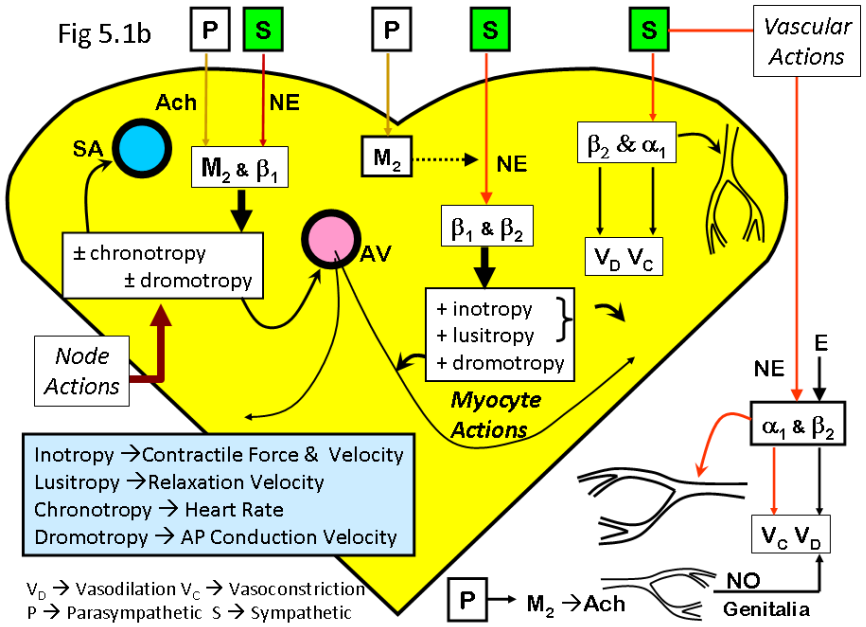
If sympathetic nerve impulses to blood vessels increase, VSM contraction increases causing vasoconstriction.

Increased nerve impulses to the adrenal medulla causes increased release of epinephrine (E) and norepinephrine (NE). NE causes vasoconstriction but E's effect is dose and organ dependent and may cause vasodilation.



ANS activity to heart also affects SAN and AVN and cardiac myocyte actions as shown in **Fig 5.1b.** M_2 is a muscarinic-receptor; β_1 and β_2 are beta-receptors and α is an alpha-receptor. Increases (+) in sympathetic activity (***S***) are associated with *+chronotropy, +inotropy, +dromotropy and +lusitropy* via actions on these receptors.

Contrastingly increases in parasympathetic activity (*+**P***, vagal) or decreases in sympathetic activity (*-S*) cause decreased HR (negative chronotropy) and negative inotropy. Decreases in P-action cause oppositely directed changes. The bottom right of the diagram shows the actions of E and NE and P-activation of M_2 receptors on peripheral vessels and vessels of the genitalia.



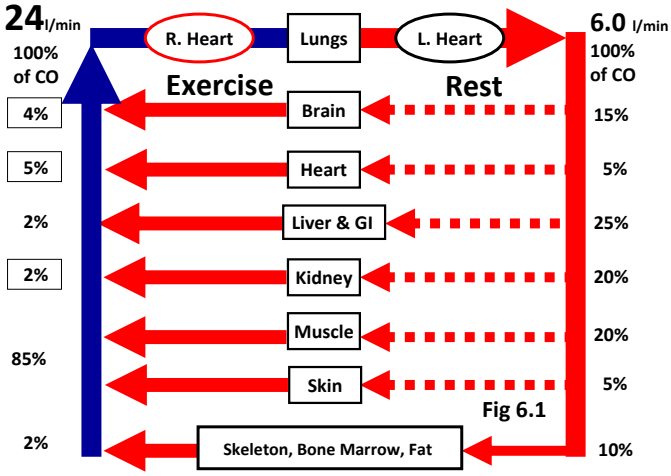
The ANS affects vessels by altering VSM contraction state either directly or indirectly. Effects of *+**S*** depend on the target organ. Except for brain and heart, *+**S*** causes VSM contraction resulting in increased arteriolar resistance and decreased venous compliance.

These actions are mediated by α, β_2 and M_2 receptors that are stimulated by neurotransmitters e.g. norepinephrine (NE), epinephrine (E), Acetylcholine (Ach) and nitric oxide (NO).

6.0 Cardiac Output (CO) and its Distribution: CO = SV x HR TOC

6.1. CO and Venous Return (VR) at rest and in exercise

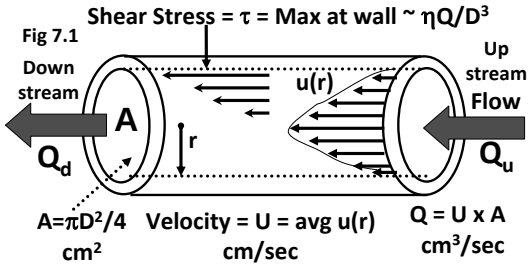
CO is distributed to the systemic circulation from the LV, collected in the venous system and returned to the RA where it is pumped to the pulmonary circulation by the RV. Blood returning to the RA is the **Venous Return (VR)** which on average is equal to **CO**. Changes in SV and HR allow CO to meet variable organ blood flow needs. Each organ receives a percentage of the CO (%CO) in inverse proportion to its **vascular resistance** relative to the other organ's. Fig 6.1 shows the parallel organ arrangement and how CO is distributed at rest and exercise expressed as a %CO. In this example, resting CO is 6.0 L/min and numbers on the right side are approximate %CO taken by each organ. On the left part of Fig 6.1 it is assumed that heavy exercise increases CO to 24 l/min and the numbers listed on the left show %CO now taken by the organs. The %CO taken by active muscle and skin (combined) are greatly increased but %CO taken by kidney, liver and GI is much reduced. Note that during exercise heart %CO is unchanged from rest and brain %CO is reduced.



7.0 Blood Flow and Blood Velocity Features and Determinants TOC

7.1 Blood Flow vs. Velocity

Blood velocity u(r) varies with radial position, r, with arrow lengths proportional to velocity at that radius (Fig 7.1). Velocity is distance per unit time e.g. cm/sec with a average velocity denoted as **U.** Flow (**Q**) is *volume moved per unit of time and* is expressed in units of ml/min, ml/sec, liters/min etc. In a vessel with an area A, and a *given amount* of Q, the relation between Q and U is inverse expressed as **U = Q / A**.



For a given Flow, Velocity is *inverse* to Area $U = \frac{Q}{A}$

shear stress = viscosity x shear Rate = η x du/dr

du/dr = velocity gradient = shear rate

7.2 Blood Viscosity, Shear Stress, Shear Rate

Viscosity (η) is a fluid property that resists relative movement of adjacent "lamina". This friction-like action causes adjacent layers to move at different speeds and is why there is a parabolic like velocity profile (Fig 7.1). If η=0 then u(r) =constant and the velocity profile is flat.

Shear Stress (τ) and Shear Rate (du/dr=γ)

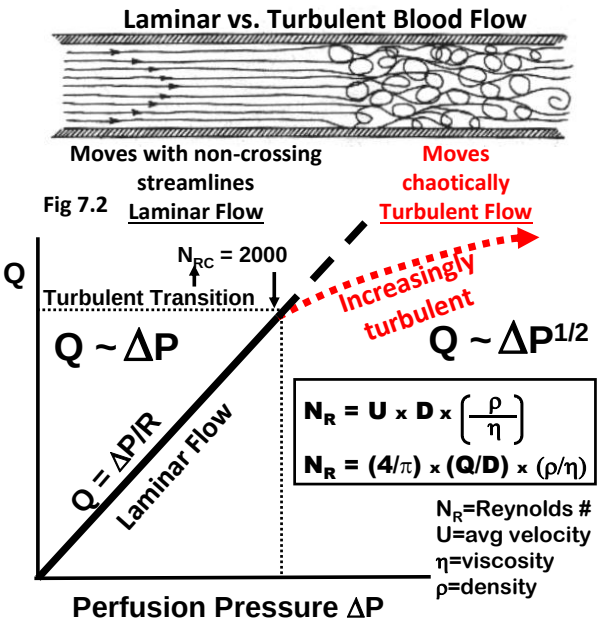
Viscous resistance must be overcome to sustain blood in motion. The force needed per unit surface area is *shear stress* (τ) with units of pressure (e.g. dynes/cm^2). Shear stress is greatest at the wall. Blood velocity differences between adjacent lamina is the *velocity gradient* or *shear rate* ***(γ)*** (units = inverse seconds, s^{-1}). *Shear stress, shear rate and viscosity* are related with η = shear stress/shear rate = τ / γ. Viscosity dominates small vessel flow but has little effect in large arteries. Units for η; 1 Poise =1 dyne-s cm^{-5} and 1 centipoise (cP) = 10^{-2} Poise; η_{H2O} = ~ 1 cP at 20° C and ~0.7cp @37°. Whole blood has a viscosity of ~ 3.5 cP.

Shear stress achieves its maximum at the vessel wall (τ_w)

Its minimum value is at the vessel center (Fig 7.1). Shear stress at the wall, τ_w, causes EC to release vasodilator substances such as nitric oxide (NO). τ_w in N/m^2 is given by τ_w = **(0.32/π) [Q/D^3]** η with Q in ml/sec and D in mm. NO release increases with increasing τ_w causing vasodilation. Injury of EC (atherosclerosis) reduces or eliminates this NO-dependent *vasodilation.*

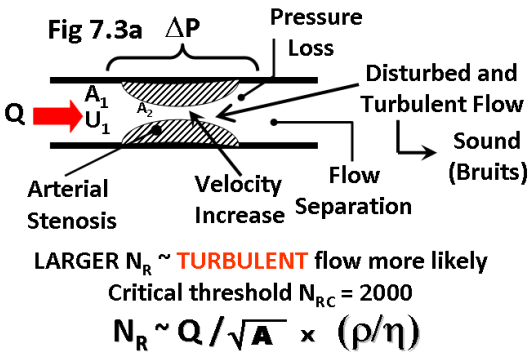
7.3 Turbulent Blood Flow and Reynolds's Number TOC

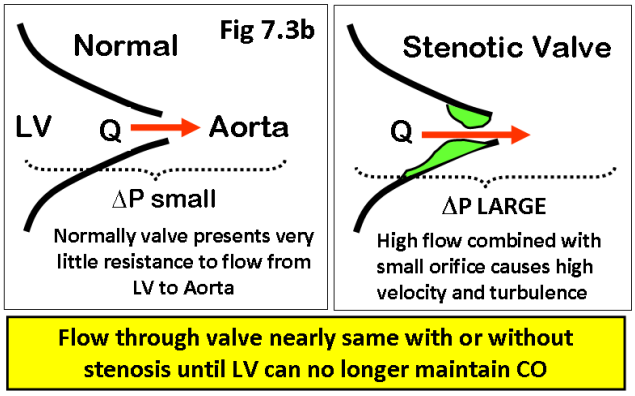
For laminar blood flow, Q varies linearly as **Q = ΔP/R**. Flow tends to be orderly and streamline-like flow as in **Fig 7.2**. But this picture changes to one of chaos if a non-dimensional Reynolds number (**N_R**), exceeds a critical number, **N_{RC}**. The flow regime then becomes turbulent. N_R is actually the ratio of inertial to viscous forces in the flowing blood. This inertial/viscous ratio is $\rho U^2/\eta(U/D)$ which is the ratio of blood's kinetic energy to avg. shear stress.



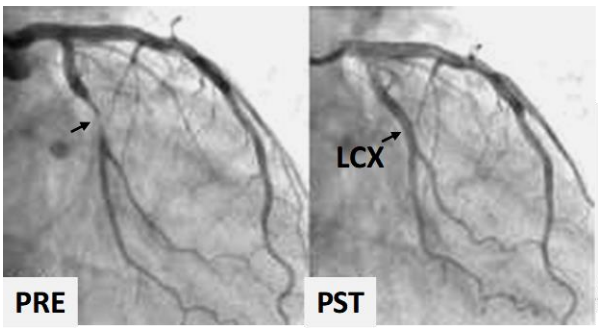
Turbulence ***increases energy loss*** due to added kinetic energy loss by eddies and vortices sometimes heard as murmurs. **N_R** is calculated by either equation in **Fig 7.2**. For a long straight vessel, N_{RC} =~ 2000. If turbulence is present then **Q ~ $\Delta P^{1/2}$**, so if turbulence is present a ***greater ΔP is needed*** to maintain the same flow. Turbulence is not generally an issue in a normal circulation. Contrastingly turbulence is of interest in a ***stenosis*** in arteries or heart valves. A stenosis occurs if an artery or cardiac valve narrows due to accumulation of material or due to an abnormal valve compression. A stenosis in a large artery reduces its local diameter causing velocity in the stenosis to increase. If N_R >=N_{RC}, turbulence ensues. Clinical examples of a vascular and a cardiac valve stenosis are shown in **Fig 7.3 a & b**.

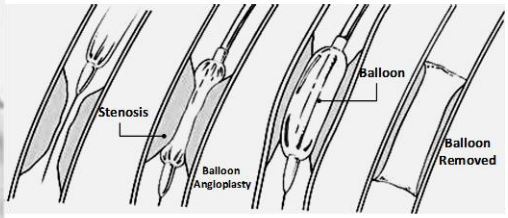
Arterial and Cardiac Valve Stenosis TOC





Opening of a Stenosis via Balloon Angioplasty A stenosis in the LCX is show pre- and post-balloon angioplasty. What was stenosis effect on LCX blood flow and distal pressure prior to treatment? What changes after treatment?

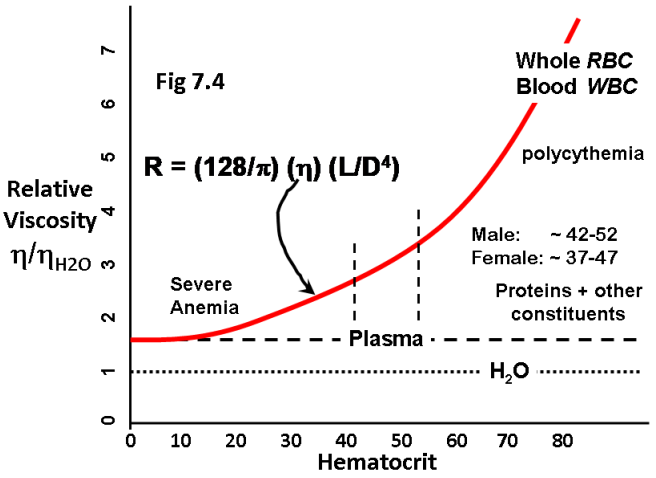




7.4 Factors Affecting Blood Viscosity TOC

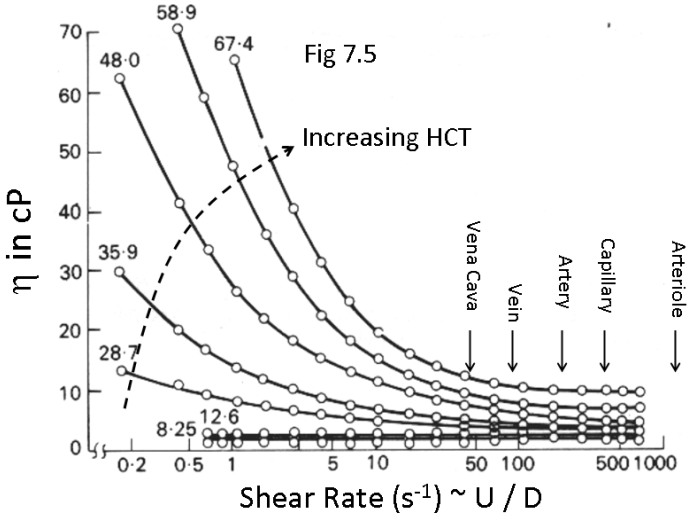
Hematocrit (HCT): Viscosity increases nonlinearly with increased HCT

HCT is the ratio of red blood cell (RBC) volume to whole blood volume; viscosity increases with HCT (Fig 7.4). If η increases more ΔP is needed to maintain flow. Polycythemia is a clinical example in which HCT increases well above the normal range. Reduced HCT, (anemia) decreases η, but the reduced O_2 carrying capacity offsets any advantage due to less resistance. Plasma η is ~1.6 x larger than η_{H2O} due to plasma's protein content. Blood η *increases* ~2% per 1° C *decrease* in blood temperature. This is important in cold temperatures since skin blood flow is abnormally reduced by vasoconstriction in persons with Reynaud's phenomenon. Among other conditions associated with increased HCT are erythrocytosis and chronic low oxygen (hypoxemia) as in COPD. Conditions showing reduced HCT include bleeding, leukemia and chronic kidney disease (insufficient erythropoietin). What is the effect of dehydration on blood viscosity?



7.5 Shear rate effects on viscosity TOC

Average shear rate in a vessel is **U/D** and is normally large enough to prevent an increase in blood viscosity. But, if there is a substantially reduced blood velocity and/or increase in venous diameters, a large rise in effective viscosity may be observed as shown in Fig 7.5. Note that η increases with decreasing shear rate and the effect increases with increasing HCT. Note also that average shear rate is lowest in large veins and does not progressively decrease from artery to vein as it depends on U/D.



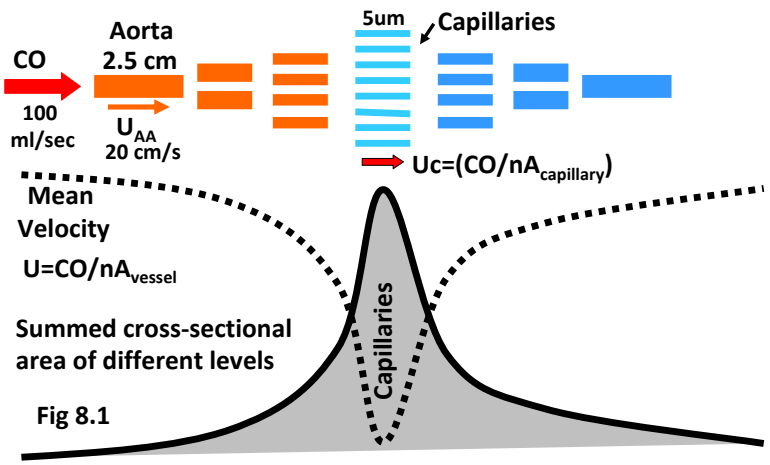
Low shear rate effects depend partly on RBC rouleaux formation, a form of reversible RBC aggregation that tends to occur at low shear rates and is facilitated by plasma fibrinogen and globulins that increase RBC-RBC attraction.

Viscosity is also higher if RBC are hardened, as in sickle cell anemia. Cell hardening (also called cell sphering) renders RBC less capable of being sheared. White blood cells (WBC) also contribute to increased blood viscosity at low shear rates. In venules and capillaries, low shear rates inhibit passage of WBC, which are larger and less deformable than RBC. Low shear rates promote adherence of WBC to endothelium, further increasing viscosity.

ESR Test The dependence of RBC aggregation on fibrinogen concentration is in part the basis for the erythrocyte sedimentation rate (ESR) test. In response to acute stresses (e.g. trauma, infection, inflammation) liver synthesizes increased levels of proteins, one being fibrinogen. Larger RBC clusters thus form that fall at a greater rate than normal blood in a test tube.

8.0 Average Blood Velocity and Blood Volume Variations TOC

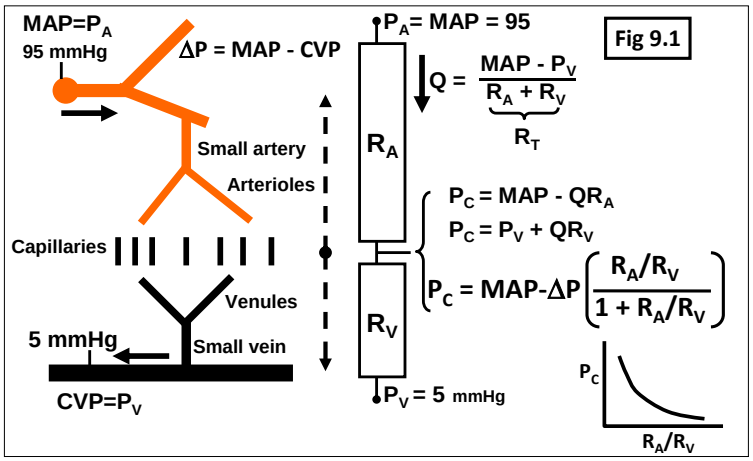
8.1 Blood velocity varies throughout the vasculature as shown in Fig 8.1, **U** is the average blood velocity at any segment of the vasculature. It decreases toward capillaries, achieves a minimum and increases on the venous side. Low capillary velocity occurs despite capillaries having the smallest diameter because the large number of capillaries results in a large total cross-sectional area for the entire capillary network. **U** in the ascending aorta (U_{AA}) is ~20 cm/sec but in capillaries (U_C) it is about ~0.05 cm/sec; a 400:1 range! If the length of a capillary were 1 mm, how long would a red cell stay in that capillary?



8.2 Blood Volume: Total vascular blood volume varies by individual. Typical values: men: 6 L (80 ml/kg); women 5 L (70 ml/kg). The venous side holds ~ 2/3 of systemic blood volume. Plasma volume (~3.5 L) is small compared to interstitial fluid (~ 12 L) and cellular fluid volume (~35 L).

9.0 Resistance Partitioning Concept – Pressure and Flow TOC

A useful approach to handle vascular complexity is to partition vascular resistance into two parts (Fig 9.1) All resistance "upstream" from mid-capillary is viewed as **pre-capillary resistance (R_A)** and all resistance "downstream" from mid-capillary is **post-capillary resistance (R_V)**. This approach applies to the entire vasculature or any individual organ or vascular region. For the systemic vasculature ~80% of TPR at rest resides in the pre-capillary part and ~ 20% in the post-capillary part. Proportions may be different in individual organs. Changes in arteriole diameter due to VSM relaxation or contraction will change these proportions and alter pressure and flow to, and within a vascular region. When partitioned as described above, the two parts (pre- and post-capillary) are in series (**R_A and R_V**). Flow through the combination is simply **$\Delta P/R_T$** where **$R_T = R_A + R_V$** and **ΔP is (P_A-P_V)** which is **MAP-CVP** for the systemic vasculature**.** Mid-capillary pressure (**P_C**) can be determined by subtracting the pressure loss across R_A from P_A (**MAP – QR_A**) or by adding P_V to the pressure loss across R_V (**$P_V + QR_V$**). For a given MAP and ΔP, **P_C** depends on upstream to downstream resistance ratio (**R_A/R_V**). Pc decreases if the ratio increases and increases if the ratio decreases.

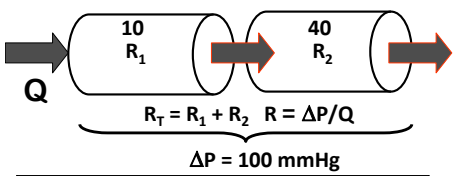


Examples

1. If R_A = 8 pru and R_V = 2 pru. What is blood flow (Q) and capillary pressure? A. Q = 9 ml/min, Pc = 23 mmHg

2. A drug decreases R_A from 8 to 6 pru and simultaneously increases R_V to 4 pru. Does total Q change and if so in which direction? Which way does Pc change, up or down? What is the new value of Pc? Answer Pc = 41 mmHg

3. For the series and parallel arrangements below what is R_T and Q if R_1 = 10 & R_2=40 pru & ΔP = 100 mmHg.



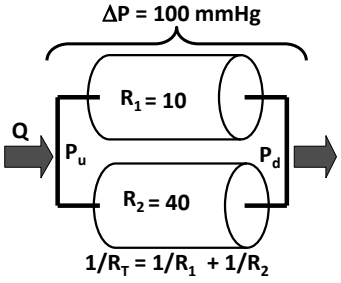
- Flow same in series-coupled parts
- Resistances sum directly
- Total R greater than individual R

$R_T = 10 + 40 = 50$

$Q = 100/50 = 2$

$q_1 = q_2 = q = 2$

$\delta p_1 = q r_1 = 2 \times 10 = 20$



$1/R_t = 0.1 + 0.025$

$R_T = 1/0.125 = 8.0$

$q = 100/8 = 12.5$

$q_1 = (r_t/r_1)q$

$= (8/10) \times 12.5$

$= 10.0$

$q_2 = (r_t/r_2)q$

$= (8/40) \times 12.5$

$= 2.5$

- Perfusion Pressures are the same
- Resistances sum reciprocally
- Total R is LESS than any individual R

10.0 Compliance and Vessel Wall Structure-Function TOC

10.1 Wall Components

All blood vessel walls contain elastin and collagen and most (except capillaries) have VSM (Fig 10.1).

Elastin is rubber band-like but is ~ 6X easier to stretch than most rubber. It is almost purely elastic – energy needed to stretch is stored and is recoverable.

Collagen is elastic but much stiffer. Elastin/Collagen ratio varies by vessel type and organ. Relative proportions of each in part determine wall stiffness; the greater the ratio of collagen/elastin the stiffer is the vessel.

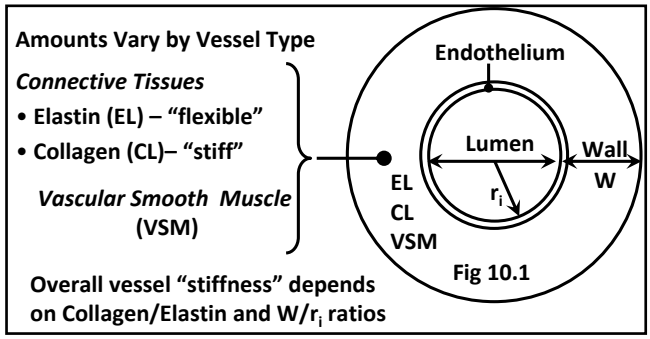


Fig 10.1

VSM: The % of VSM in walls varies greatly; arterioles generally having the greatest %. When VSM contracts it makes vessels stiffer; when VSM relaxes it makes vessels less stiff. The ascending aorta is the largest artery (~ 25 mm in diameter). The wall components and dimensions affect vessel function via effects on vessel compliance stiffer vessels ~ less compliance.

10.2 Compliance Concept

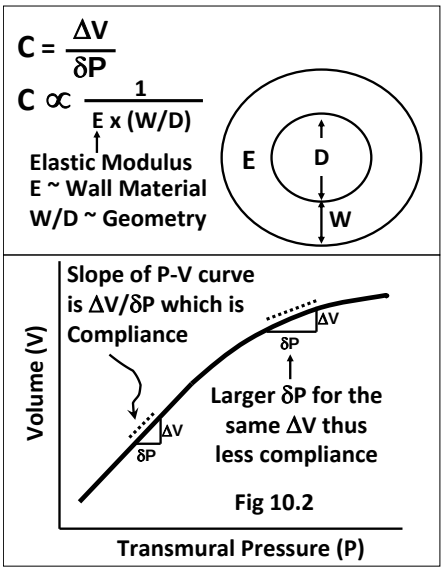


Fig 10.2

The term compliance (**C**) has a special meaning in physiology (Fig 10.2). Broadly it describes the ease with which a vessel or chamber can expand when transmural pressure (δ**P**) is increased. For equal δ**P** changes a high compliance vessel expands more than a lower compliance one. Alternately, compliance is a measure of the δ**P** increase when a vessel or cardiac chamber has its volume increased (Δ**V**). The definition of compliance is **C = Δ V / δP.** Recall that the pressure difference δ**P** is the transmural pressure. If external pressure is much less than intravascular pressure, using intravascular pressure in this relationship instead of transmural pressure may be ok. Compliance depends inversely on wall stiffness (**E**) and the thickness ratio (**W/D**); so, all else the same, anything that makes the wall stiffer or thicker decreases compliance. Wall stiffness depends on wall constituents and physical properties and relative amounts of these constituents as previously noted.

Elastic Modulus (E): Wall ratios (elastin/collagen) and (thickness/diameter) are determinants of compliance. A way to describe composite wall properties is to express its mechanical property by its *elastic modulus* defined as the ratio of wall stress to wall strain. **E** is a measure of the force required to increase the wall length. **E** values; steel → very large, soft rubbers → low. Vessel compliance: **C ∝ 1 / [(E x (W/D)]**.

Significance of Compliance (C) and its Change

Compliance can change due to physiological as well pathophysiological causes. If *C* decreases, it is less easy for a vessel to expand to accommodate a blood volume increase. So, a greater pressure change in the vessel must occur. This fact is summarized by rearrangement of the defining compliance relationship as **δP = ΔV/C**. Thus, the resultant change in transmural pressure for a given volume change is inversely proportional to *C*. This concept is important to understand how changes in aortic compliance affect aortic systolic and pulse pressures; Decreased *C* results in a greater pressure change leading to increased systolic blood pressure.

10.3 Pressure-Volume Relationships

As blood volume (V) is added to a vessel or cardiac chamber the internal pressure (P) rises. The P-V curve shows how P varies with V (Fig 10.3). Over a certain volume range, it is near-linear. At any point on these curves, compliance is the inverse of the slope. It is the inverse since its slope is dp/dV but compliance is defined as dV/dp. Fig 10.3 shows a linear relationship between transmural pressure and intravascular blood volume. This is an approximation since with increasing volume pressure tends to rise nonlinearly.

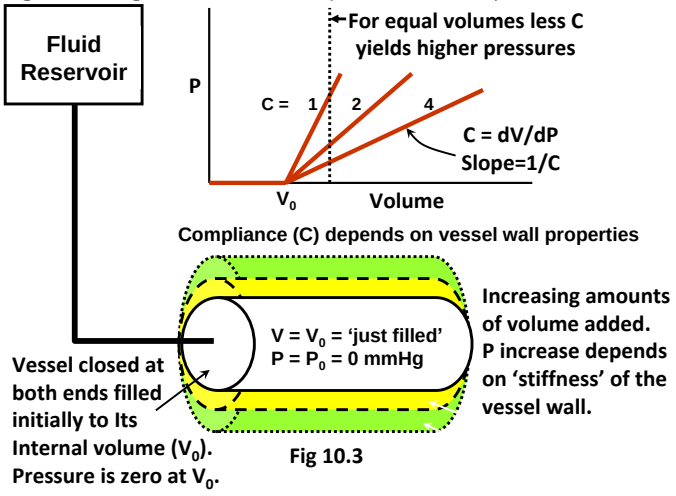


Fig 10.3

10.4 Resistance-Compliance Interaction as Determinants of MAP TOC Return Text

MAP depends on arterial blood volume relative to arterial compliance **and** on pressure due to cardiac output. To clarify, consider first a case in which Q=*CO* is zero (10.4a). Blood volume (**V**) distributes itself such that within each vessel the pressure (**P**) in all connecting vessels are equal and determined by the volume held (**V**) divided by the compliance (**C**). If *C* is low, equal volumes cause a higher pressure (P_2) than if *C* were high (P_1). If the heart is then started (**Fig 10.4b**), Q increases starting at P_1 or P_2. Assuming P represents **MAP** then the amount **MAP** changes with changing Q is **CO x TPR.** The slopes of the **P-Q** curves in 10.4b are thus determined by this product (*CO* x TPR).

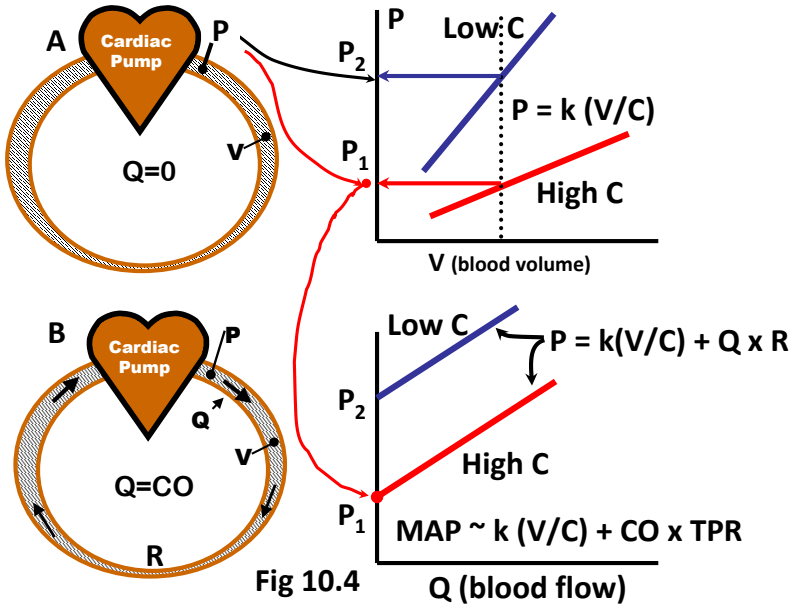


Fig 10.4

The take home is that for any CO, MAP is determined by both TPR and blood volume relative to compliance!

10.5 Kidney as a Determinant of Arterial Blood Pressure TOC

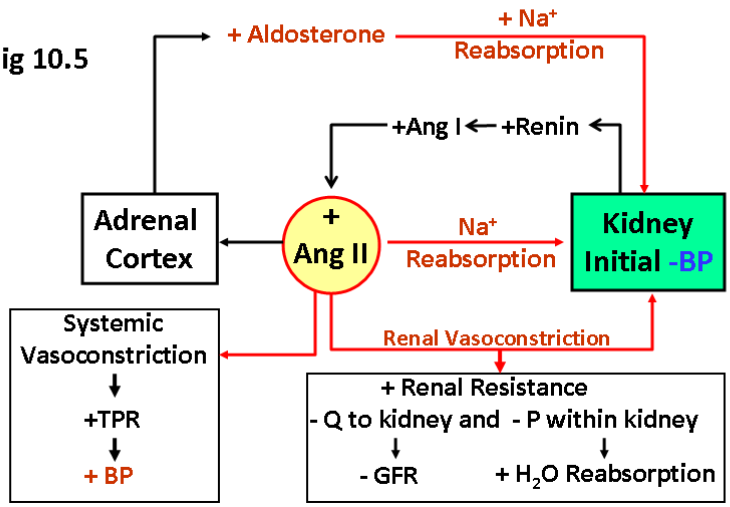
Salt: A normal kidney outputs water and Na^+ to match intake via urination. Output depends on a renal function curve that links Na^+ and blood pressure (BP). If Na^+ intake increases a transient BP elevation causes a *pressure diuresis* and a *pressure naturesis that tends to restore the balance (negative feedback).*

1) Pressure Diuresis: -BP → -Q and - Filtration → -Urine output → +Volume → +BP

2) Pressure Naturesis: -BP → - Na^+ excretion → - H_2O excretion → +Volume → +BP

3) Renin – Angiotensin – Aldosterone System

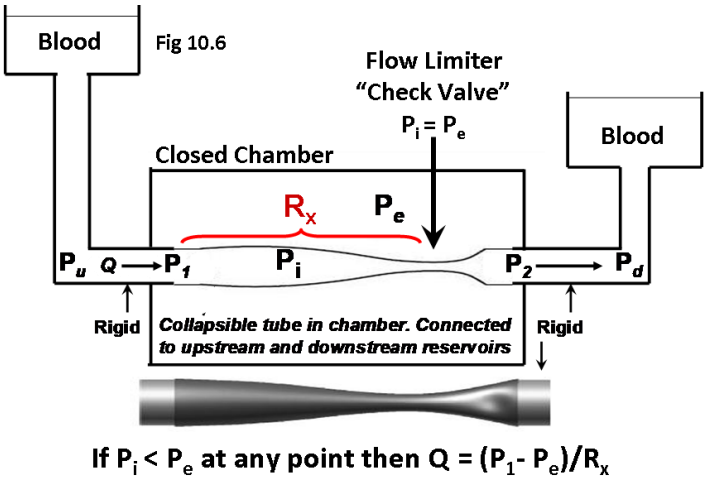
Fig 10.5



Pressure: The kidney helps maintain pressure by controlling blood volume with mechanisms in **Fig 10.5** that shows responses to decreased BP. Ang II = angiotensin II, a potent vasoconstricting hormone with other actions as shown. GFR is glomerular filtration rate which is an index of the amount of blood filtered through the kidney and is directly related to kidney blood flow (Q). The + and – signs refer to increases and decreases respectively. H_2O reabsorption occurs if intra-renal pressure falls. These directional changes act to increase vascular volume. Promotion of Na+ reabsorption or inhibition of urination tends to raise blood volume and thereby maintain BP. More details on the renin-angiotensin-aldosterone system are in section 46.1

10.6 Blood Flow in Collapsible Vessels TOC Return Text

A collapsible vessel (e.g. large vein) buckles if its intravascular pressure is less than its surround pressure. In such vessels, the normal relationship between Q and ΔP breaks down. So, if transmural P is sufficiently low at any point, wall buckling and collapse can occur. If so, Q now depends on the difference between upstream and external pressure **($Q \sim P_1 - P_e$)** as shown in Fig 10.6. Q now depends on the resistance (Rx) upstream from the collapse point. This causes a "vascular waterfall" effect; **$Q = (P_1 - P_e) / R_x$** in which Rx is the total resistance proximal to the collapse point.

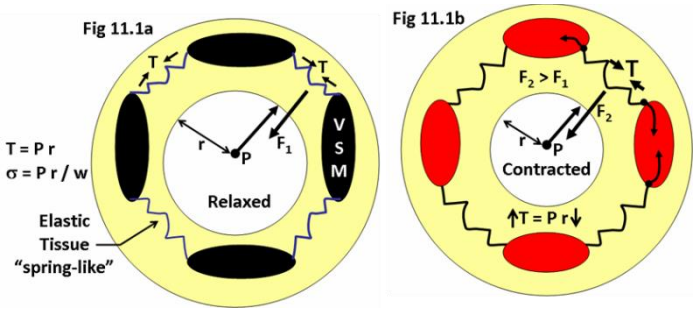


11. Blood Vessel and Cardiac Wall Mechanics TOC

Wall Tension, Stress, and Laplace's Law

What follows is a simplified but highly useable explanation of the way in which changes in muscle state within the walls of blood vessels or walls of cardiac chambers affect vessel lumen and chamber size. For a more detailed and rigorous approach to blood vessel mechanics please review the material in appendix 1.

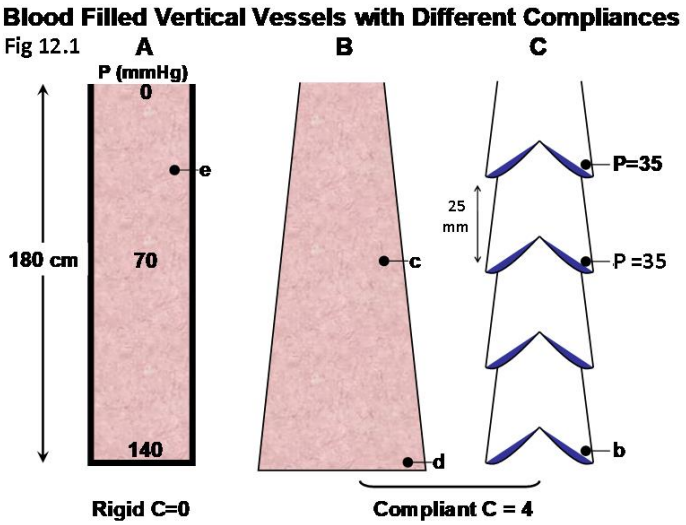
Figure 11.1 represents an arteriole with wall thickness (w) in which the vascular smooth muscle (vsm) is relatively relaxed (11.1a) and then relatively contracted (11.1b). The squiggly lines represent connective tissue (some combination of elastin and collagen), that for our purpose can viewed to function as springs. When the "springs" are stretched due to actions of transmural pressure (P) and force exerted by the muscle (11.1a), they resist with a circumferential tension, T. This tension gives rise to a radial component (F_1) that balances the distending pressure and the vessel achieves an equilibrium radius r. At equilibrium, if the wall is very thin relative to the radius (w/r small) then the thin-walled version of Laplace's Law applies, namely T = Pr. A modified version is needed for vessels to account for their finite wall thickness. The modified form is given as σ = Pr/w. Here the term σ is the stress in the wall and has the same units as pressure (Force/area).



If the muscle in the wall contracts (11.1b), the "spring" tends to be stretched due to the increase in the muscle force acting on it. This causes the tension, T to rise resulting in an increase in the radial directed force F_2. This action causes the radius to become smaller and achieve a new equilibrium compatible with the now elevated tension. That is, assuming P remains unchanged, then if T rises, then r decreases to become the now reduced equilibrium radius. The opposite occurs if the muscle in the wall relaxes instead of contracting. Laplace's Law applied to the heart needs consider the shape being closer to spherical then cylindrical as in blood vessels. The Laplace law applied to the heart has the form T = Pr/2. This means that for a spherical-like shape the wall tension is ½ of that in a cylindrical shaped vessel exposed to the same transmural pressure.

12. Gravity Affects Pressure, Flow and Volume TOC

12.1 Vertical Vessels

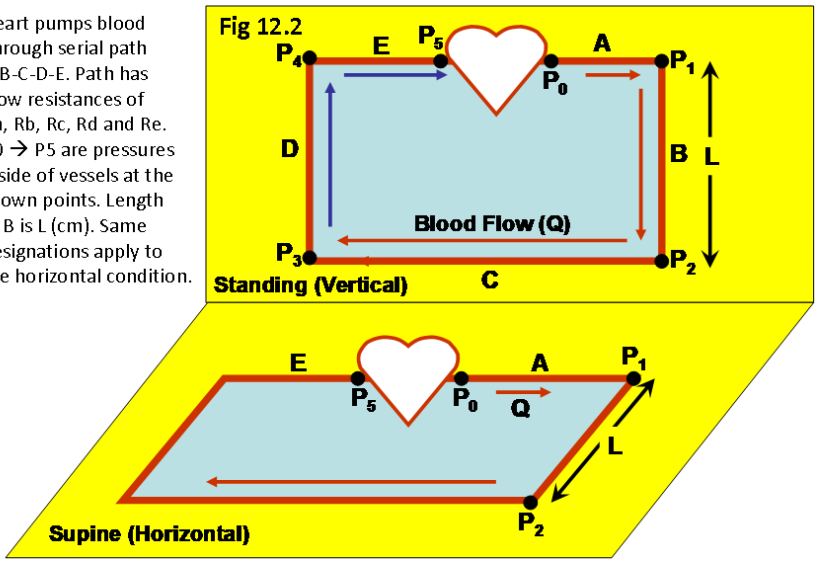


Consider the three vertical vessels in Fig 12.1. In **A**, pressure increases with depth = ρgL with ρ=whole blood density (~1060 Kg/m^3), L = height below the top surface and g = gravity acceleration (9.8 ms^{-2}). A height of 1.8m yields a value of 18,698 Kg/m/s^2 (N/m^2); Multiplying by 0.0075 yields 140 mmHg. Since the vessel is rigid (E→∞) then pressure differences (top to bottom) do not cause diameters to be different. Contrastingly, in vessel **B** that has a nonzero compliance, the vertical pressure differential causes more volume to be held towards the bottom. Valves in vessel **C** segment the vertical weight load every 25 cm thus limiting the maximum transmural pressure to about 35 mmHg. Venous valves in legs help prevent large volume accumulations.

12.2 Posture Effects on Blood Flow (excluding reflexes)

If a person is supine, gravity minimally affects circulation. If standing, foot arterial pressure P_2 (Fig 12.2) is increased by an amount = ρgL above that when supine. This increase is with respect to P_1 at heart level. So why does blood move from P_1 to P_2 if P_2 is greater than P_1? The explanation relies on the fact that flow is in a closed system from P_0 to P_5 and back to P_0. The driving force for Q is perfusion pressure (ΔP) of the system which is $P_0 - P_5$. Since these points are at the same level, the gravitational component that may be added to or subtracted from each of these pressures is the same at P_0 as it is at P_5. So, ΔP is unchanged by gravity. Flow magnitude depends on ΔP divided by the summed resistances of paths A→E. Gravity affects these resistances by affecting vessel diameters. So, for a given perfusion pressure, Q can be different standing vs. supine. Also, if g-forces increase, blood's weight also increases and more energy is needed to move blood up from heart level to brain. Physiological reflexes due to posture changes are not considered here. Test your proficiency with the following two examples

Heart pumps blood Through serial path A-B-C-D-E. Path has Flow resistances of Ra, Rb, Rc, Rd and Re. P0 → P5 are pressures inside of vessels at the shown points. Length of B is L (cm). Same designations apply to the horizontal condition.



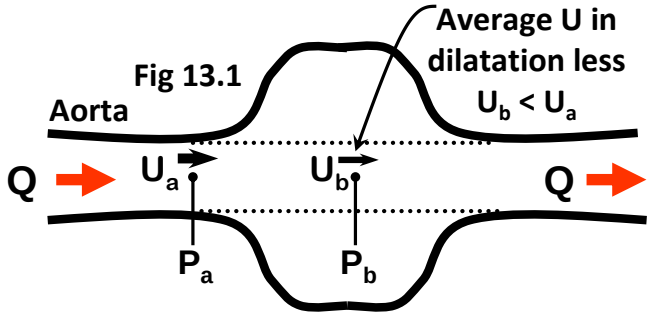
Resistances of A-E are respectively 1,2,3,2,1. If P0=100 and P5=10 What is P2 if supine?
A. 60
B. 70
C. 80
D. 90
E. 100

L=1.8 m, Resistances of A-E are 1,2,3,2,1. P0=100, P5=10 and all vessels are rigid. What is P2 in mmHg if standing upright?
A. 70
B. 170
C. 210
D. 240
E. 290

13. Energy Considerations in Blood Flow TOC

13.1 Aorta with a Local Dilatation Distal to a Stenosis

Total fluid energy is conserved if energy loss → zero as for ideal fluids in which viscosity → 0. Under certain conditions blood with a non-zero viscosity can exhibit such properties; e.g. in large arteries resistance is very small so blood flow can approach "lossless" or so-called inviscid flow. This condition occurs if viscous forces are << inertial forces so N_R is >> 1 but is still < 2000. For this condition, Bernoulli's equation applies approximately. It states that total energy per unit volume (**E**) along a streamline is a constant (**K**) and equals the sum of kinetic (**$1/2\rho u^2$**), potential (**P**) and gravitational (**ρgh**) energy all per unit volume. One practical application of this relates to an abnormal vessel dilatation that sometimes occurs distal to a stenosis in a large artery (Fig 13.1). In the dilatation, blood velocity (U) is reduced and the moving blood's kinetic energy is converted to potential energy causing pressure in the dilatation (P_b) to be greater than upstream pressure (P_a). So, in this case blood moves from lower to higher pressure! This occurs because of the assumed negligible viscosity affect. But, blood can't move from a lower to a higher energy because there is a monotonic decrease in energy in the direction of blood flow.



If "lossless" total E conserved

$$E = P + 1/2\rho u^2 + \rho gh = K$$

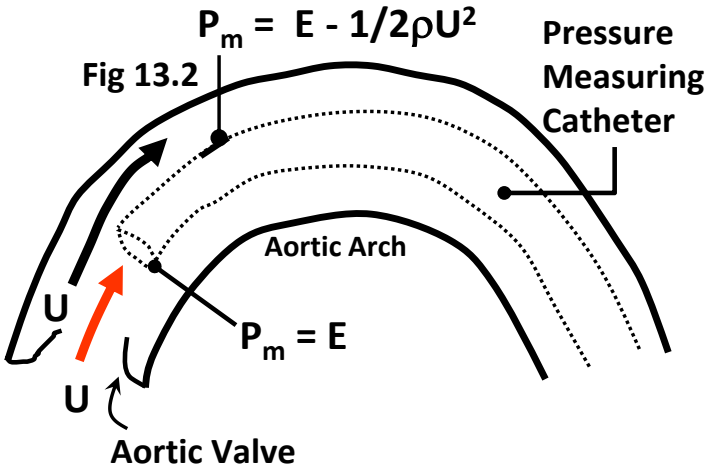
$$P_b = P_a + 1/2\rho(u_a^2 - u_b^2)$$

$$P_b > P_a$$

So - P within expansion is greater than upstream
A case where flow is not from higher to lower pressure

13.2 Measuring Aortic Blood Pressure

Because of energy conversion, pressure measured in large arteries on the location of the pressure sensing device. If it is on the end of a catheter (Fig 13.2) all kinetic energy is converted to pressure energy since the blood's velocity becomes zero on impact. So, the pressure recorded (end pressure) is greater than "true" pressure. Contrastingly, if the sensor is on the catheter's side the sensor measures a lateral pressure that is the same as the vessel wall experiences and is the pressure of interest. The amount that these two pressure readings differ depends on the blood velocity, so this becomes an issue in regions with high blood velocity most frequently in the aorta.

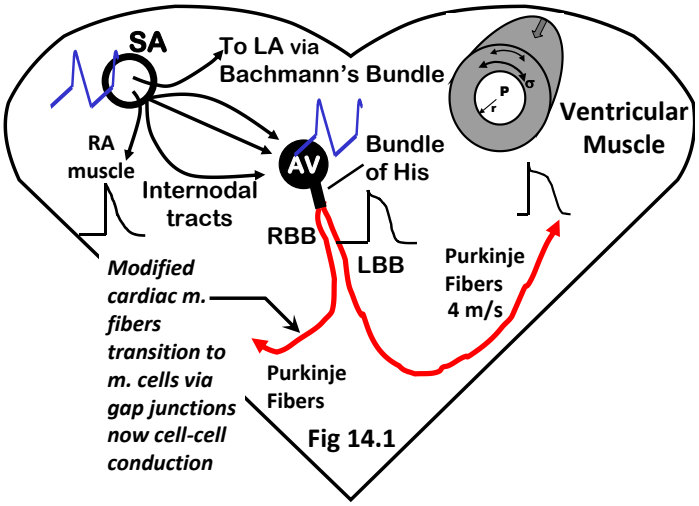


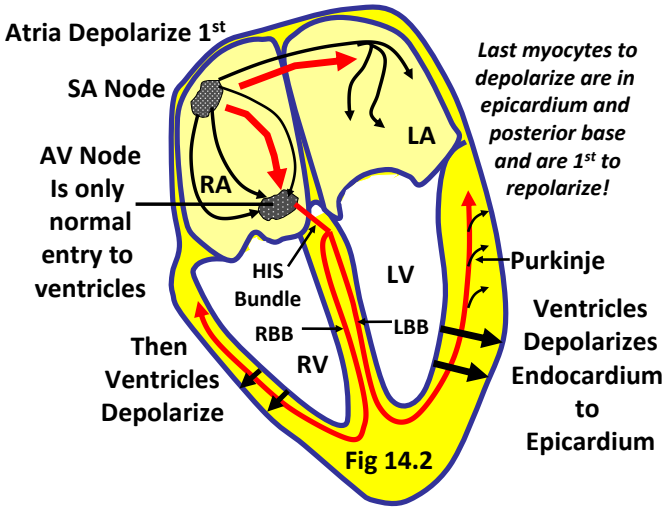
Measuring "end" pressure gives a pressure value that is higher than aortic wall truly experiences

14.0 Cardiac Electrical Activity Overview TOC

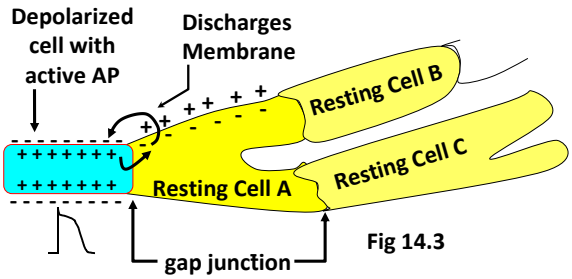
14.1 Pathways and Excitation Sequence Overview

SA node: In posterior part of RA near junction of superior vena cava (**Fig 14.1 & 14.2**). Specialized cells spontaneously depolarize and act as normal pacemaker. SA node APs are transmitted in an orderly and coordinated way causing muscle contraction in atria and then ventricles.





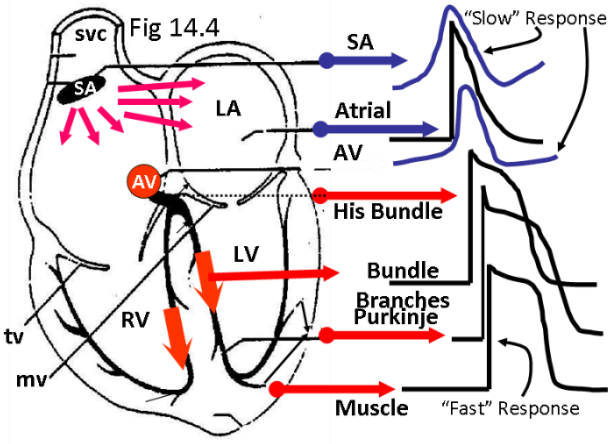
Conduction Mechanism and Speed: Conduction through atrial and ventricular muscle is facilitated by tight gap junctions that provide low resistance pathways from one cell to the next (**Fig 14.3**). The resting cell membrane (RCM) potential is negative inside relative to the outside. When the RCM depolarizes sufficiently, an action potential (AP) is generated that causes a forward ion movement (current) that passes through resting cell gap junctions. This current, discharges the RCM of cell A and brings it to threshold, which then generates an AP that is conducted through the interconnected cardiac network. Conduction speed is faster for larger cell diameters, for faster rising rates of AP and for greater AP amplitude. Fast rising and larger APs cause larger currents that project further distances from the active region and cause faster conduction speeds.



When Cell A membrane reaches threshold it generates an AP that serves to discharge cells B & C bringing them To threshold and thereby conducting the AP throughout

Bachmann's bundle: Specialized inter-atrial tract that provides a conduction pathway from RA to LA.

Internodal tracts are bands of specialized cells for conduction from SA->AV at ~ 1 m/sec. APs are also transmitted through atrial myocytes via cell-to-cell conduction at ~ 0.4 m/sec



AV node: Located in inferior-posterior part of the inter-atria septum. It is the only normal place for passing APs to ventricles. Conduction speed in AV is slow (0.05 m/sec) that causes a transmission delay of ~0.1 s that allows atria contraction to occur before ventricular contraction starts. The slow conduction speed also limits the transmission of pathologically high rates being transmitted to ventricles.

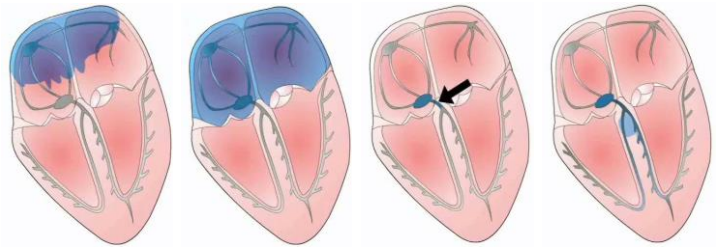
Bundle of His: conducting pathway leading from AV; inserts into interventricular septum; gives rise to left/right bundle branches (LBB and RBB) with conduction speed of ~ 2 m/s.

Bundle Branches: Travel down septum on right (RBB) and left (LBB); Left divides into 2 separate main pathways; the anterior and posterior fascicles. There is a third minor branching called the septal branch.

Purkinje Fibers: Conduction pathways that connect to myocytes which become final cell-to-cell conduction pathways. Purkinje have fastest conduction speed (4 m/s) speed allowing fast spread throughout myocardium causing near synchronous contraction. Apex contracts slightly earlier causing upward directed "squeeze".

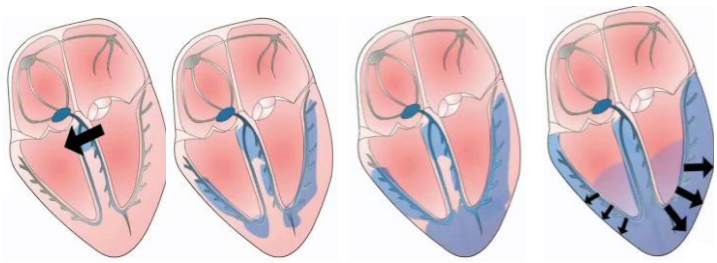
14.2 Pictorial Representation of Cardiac Depolarization and Repolarization TOC

Atrial depolarization begins in the RA triggered by the SAN impulse. The impulse spreads through the RA and into the LA as shown in blue in the figure. Arrival of the depolarization wave at the AV node, which is the only normal conduction pathway from atria to ventricle, allows the depolarization wave (DW) to progress into the His bundle, down the septum and to spread through the right and left ventricle.



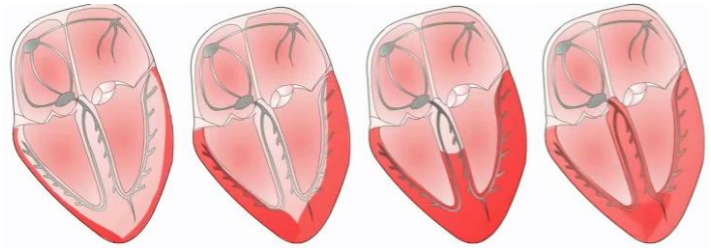
Atrial Depolarization Thru AV → His → Septum

The initial septum depolarization is from left to right as shown by the arrow and then the DW spreads as illustrated by the blue regions in the figure. Wall depolarization is from endocardium to epicardium with the more muscular LV dominating.



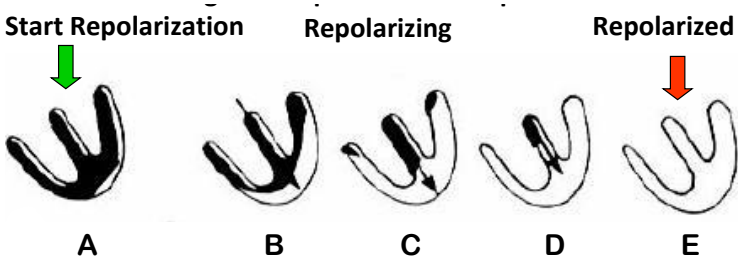
Ventricular Depolarization

Repolarization normally starts at the regions most recently depolarized because those regions have the shortest recovery times. The repolarization sequence is shown in red. The repolarization wave moves more slowly than does the DW and it proceeds starting from the epicardium and the posterior base.



Ventricular Repolarization

Later we will learn that the wave of ventricular depolarization is responsible for the QRS complex of the EKG and the wave of repolarization is responsible for the T-wave of the EKG. It will be shown that the direction of movement of the depolarization and repolarization waves relative to the positions of the sensing electrodes determine the direction and pattern of the deflections as recorded by the electrocardiogram. The DW can be thought of as a moving dipole (section 23.1).



Repolarization begins at site most recently depolarized

- ***Repolarization ~ in reverse order to which myocytes depolarized***
- ***Myocytes in epicardium and posterior base have shorter APD than AP in endocardium and apex BECAUSE of : Different K channel features → determinant of AP duration***

15.0 Cardiac Action Potentials

15.1 Ion channels and currents: Basis of Cardiac APs TOC

Ion channels are macromolecular pores that span the cell membrane lipid bilayer. Conformational transitions change (gate) a single ion channel from closed to open. This allows selected ions to flow passively down their electrochemical activity gradient. Ion channels are often named after the strongest permeant ion (Na^+ Ca^{++}, K^+ etc). Channels are also named after neurotransmitters, e.g. acetylcholine-sensitive K^+ channels, $I_{K.Ach}$. Some channels are not selective (e.g. gap junction channels). Ion channels may be gated by ligands, transmembrane voltage changes, and mechanical stress. These events are the basis of various cardiac APs

15.2 General Principles of Ion Current Flow: Ion current flow through specific ion channels depends on membrane potential (V_m), ion concentration gradient across the membrane, and the probability of the open-state of ion channels. For a fixed ion concentration gradient and fixed membrane potential, whole cell ion current depends on the product of the number of functional ion channels in the membrane (N) x the probability of the open-state of these channels x the single open channel current I_S. N is relatively constant for a given cell and ion channel type, but both I_S and probability change with V_m. A depolarizing stimulus initiates an action potential if the open-state probability of a sufficient number of Na^+ channels is increased.

15.3 Action Potential Types and Phases: Fast and Slow Responses

Fast response APs (FRAP) have 5 phases as shown in Fig 15.1. Φ_0 = upstroke (rapid depolarization), Φ_1=early rapid repolarization; Φ_2=plateau; Φ_3=repolarization; and Φ_4=resting membrane potential. Phases result from passive ion fluxes moving down electrochemical gradients established by active ion pumps and exchange mechanisms. Each ion moves through its own ion-specific channel that is open or closed depending on membrane potential (voltage-gated).

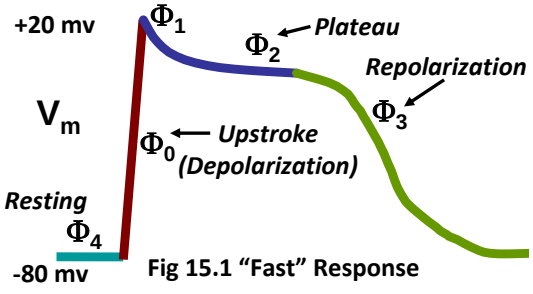
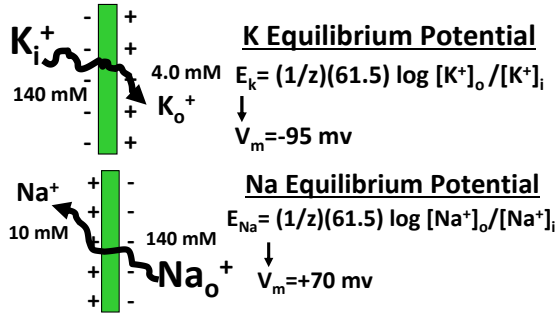
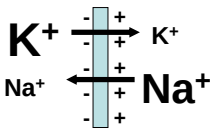


Fig 15.1 "Fast" Response



Approximate Resting Membrane Potential



$$V_m = \frac{E_k + E_{na}\,(g_{na}/g_k)}{1 + (g_{na}/g_k)}$$

V_m~-79mv

At rest: g_k ~ 10 x g_{na}

$V_m = (-95 + 70 \times 0.1) / 1.1$

g_{na}/g_k ~ 0.1

A slow response AP (SRAP) is visualized in Fig 15.2. APs in SA and AV nodes have slower upstrokes and are classified as *slow response*. These SRAP have prolonged activation/inactivation times and excitability recovery times longer than for FRAP. The SA node SRAP is the natural pacemaker that is conducted to atria myocytes where it brings them to threshold resulting in an atrial FRAP. The FRAP is triggered when a myocyte's membrane potential becomes sufficiently less negative to cause voltage dependent Na^+ gates to rapidly open generating a rapid inrush of Na^+ (I_{NA}) thereby initiating the FRAP Φ_0. Contrastingly, Φ_0 of SRAP is dominated by an inward Ca^{++} current (I_{CA}).

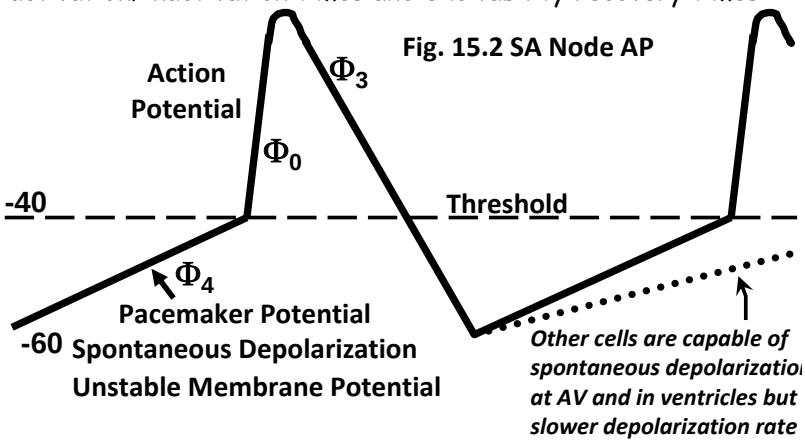


Fig. 15.2 SA Node AP

The details of these ion currents are presented in sections 15.4-15.6.

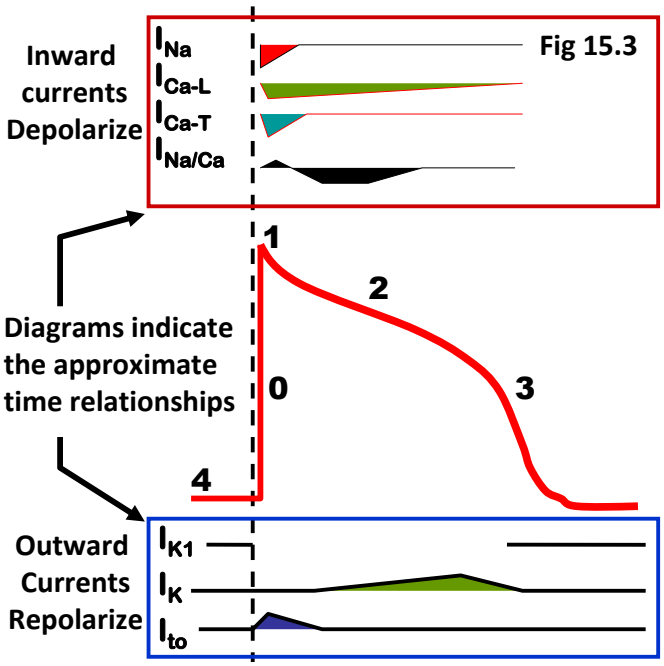
15.4 Main Cardiac Channels/Currents Synopsis (Fig 15.3) TOC

I_{NA}: A fast Na current during FRAP Φ_0. Na channels rapidly open and then rapidly inactivate causing an inward Na current spike

I_{K_1}: A K^+ current that helps maintain the FRAP Φ_4. Its channel activity is a function of both V_m and external potassium concentration $[K^+]_0$. This channel is fully open during Φ_4 in which I_{K_1} has a net component directed outward from the cell. Also called the *anamolus inward rectifying current*.

I_K: A K^+ current through voltage-gated K^+ channels. Consists of rapid (I_{K_r}) and slow (I_{K_s}) components that collectively equal I_K; also called the *delayed rectifier current*. I_K channels are closed during Φ_4; I_K starts during ϕ_0 and increases in magnitude during Φ_2 causing repolarization (Φ_3).

$I_{K_{Ach}}$: Activated by vagal stimulation, hyperpolarizes membrane and decreases rate of rise of spontaneous depolarization phase (Φ_4) of *slow response* action potentials.



$I_{CA,L}$: L-type (*L*ong *L*asting) inward Ca^{++} current through voltage-gated channels. Activated on upstroke ~-35 mv; Contributes to Φ_2 by balancing against I_K. Triggers Ca^{++} release from sarcoplasmic reticulum (Ca^{++}- induced - Ca^{++} release) and is involved in Φ_0 depolarization in SA and AV nodal tissue

$I_{CA,T}$: T-type *T*ransient inward Ca^{++} current via voltage-gated channels. Activated during fast response Φ_0 ~-30mv. Contributes an inward current to late spontaneous depolarization phase of SA and AV cell APs

I_f: Hyperpolarization-activated (funny current) carried mainly by Na^+ (some K^+) through hyperpolarization-activated cyclic nucleotide-gated (HCN) channels in SA and AV nodal cells; major involvement in initiating Φ_4 spontaneous (diastolic) depolarization in pacemaker cells as they open at about -50 mv during repolarization.

Main Cardiac Channels and Currents

Na^+	K^+	Ca^{++}
• Fast • *Funny*	• K_1 • K • K, Ach	• L (Long lasting) • T (Transient)

Inward current → Depolarize
Outward current → Repolarize

$I_{Na/Ca}$ represents the Na^+-Ca^{++} exchanger current (**NCX**) that also affects Φ_2 duration and shape.

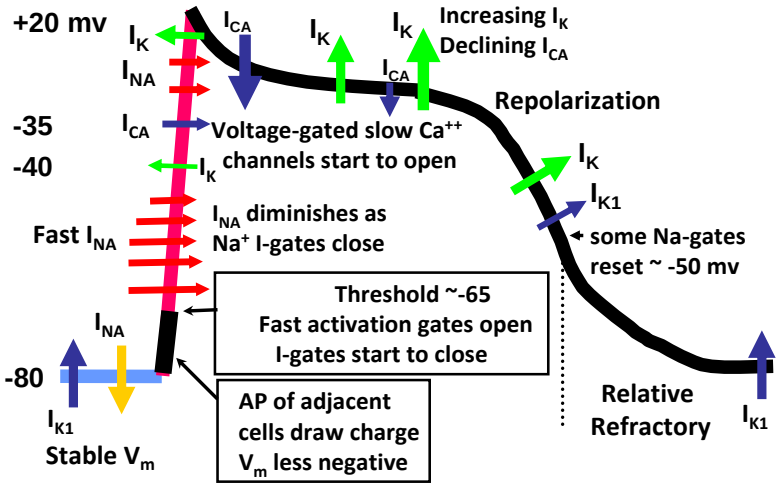
Very small ion concentration changes accompany the cardiac AP

A myocyte (assumed ta have an ellipsoid shape) at rest contains ~$2.5x10^{11}$ Na^+ ions with ~ 6×10^7 enter during ??this is only ~ 0.025% increase! Although ion shifts during the cardiac action potential produce moderate changes in membrane potential (V_m) of about 100 mv (0.1 volts) say from -80 to +20 mv, there is a very small number of ions that are shifted. During the opening of the fast Na channels there is an inrush of Na ions to generate the upstroke but the change in the internal concentration is less than 0.1% as will be shown by the following illustrative calculation. Assume a myocyte is an ellipsoid with radius b=c=10^{-3} cm and length a=10^{-2} cm. It has a volume of $4.19x10^{-8}$ cm^3 and surface area = 9.84×10^{-5} cm^2 and a cell membrane capacitance (C) of $1x10^{-6}$ F/cm^2. To change V_m by 0.1 volts requires a charge transfer Q = CV = (10^{-6} F/cm^2) x (0.1V) x $9.84x10^{-5}$ cm^2 = 9.84×10^{-12} Coulombs (CL). Since one mole of Na^+ has a total charge = $9.65x10^4$ CL (Faraday's constant), the number of moles of Na^+ needed to be transferred = ($9.84x10^{-12}$ CL)/($9.65x10^4$ moles/CL) = 1.02×10^{-16} moles. Using Avogadro's number (6.02×10^{23}/mole) the number of Na ions transferred = $1.02x10^{-6}$ moles x 6.02×10^{23} ions/mole = **$6.14x10^7$**. The # of Na ions in the cell assuming 10 mM/L is $6.02x10^{23}$ x 10^{-2} x $4.19x10^{-8}cm^3$ x 10^{-3} L/cm^3 = **$2.5x10^{11}$** ions. So, the change in intracellular concentration is only $6.14x10^7/2.5x10^{11}$ = 2.45×10^{-4} = 0.025%. Similar calculations can be done for K^+ and Ca^{++} with similar results.

15.5 Fast Response Action Potential: Ion Currents and Forces Further Details TOC

During Φ_0, the membrane rapidly depolarizes as fast, voltage-gated Na^+ channels open causing an inward inrush of Na^+ (I_{NA} in **Fig 15.4**). I_{NA} is turned off by inactivation gates that start closing during Φ_0. Also, during Φ_0 a Ca^{++} current ($I_{CA\text{-}L}$) and a K^+ channel current (I_K) start but another K^+ current (I_{K1}) turns off. I_K is outward and I_{CA} is inward so these +ion fluxes tend to balance each other for a while, resulting in the Φ_2 plateau (~ zero net current). The NCX current (**Fig 15.3**) also plays a role in Φ_2 duration. As I_{CA} declines, the gradually opening I_k (delayed rectifier) current dominates; this imbalance initiates repolarization Φ_3. As it progresses I_{K1} channels reactivate and repolarization accelerates. The Φ_2 duration depends on relative amounts of I_K and I_{CA} and on Na^+-Ca^{++} exchanger activity.

Fig 15.4 Fast Response Ionic Currents



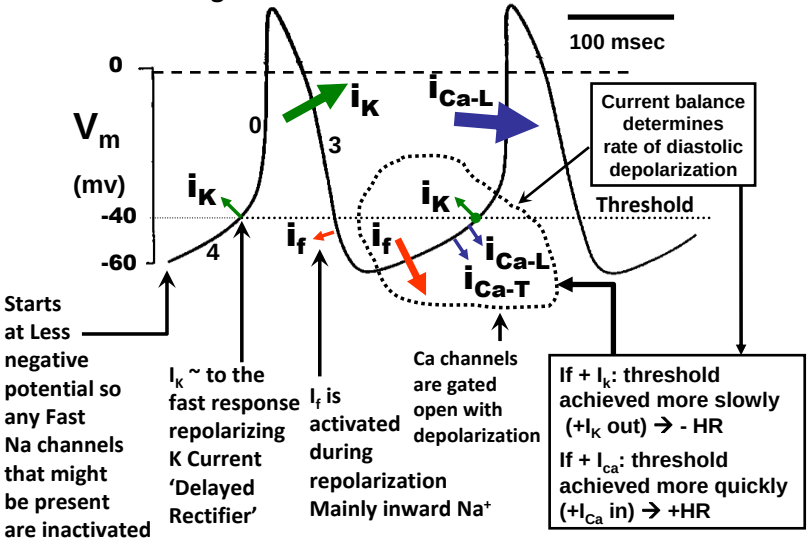
15.6 Slow Response Currents TOC

Spontaneous Φ_4 depolarization (slow diastolic depolarization) is due to interactions between repolarizing current I_k and depolarizing currents I_f, $I_{CA\text{-}L}$ & $I_{CA\text{-}T}$ (**Fig 15.5**).

I_K: In SA & AV node tissue, I_K is activated at a more negative potential than for fast response AP so any Na^+ channels present are inactivated. I_K is the current responsible for repolarization. I_{K1} is absent in SA and AV nodal tissue

I_f: Near the end of repolarization a "funny" [mostly Na^+ current (I_f)] is activated at ~ -50 mv; Funny = strange, since an inward Na^+ current was not expected during repolarization. The depolarizing effect of increasing I_f causes V_m to "turn-the-corner" for slow diastolic depolarization.

Fig. 15.5 Pacemaker Ionic Currents

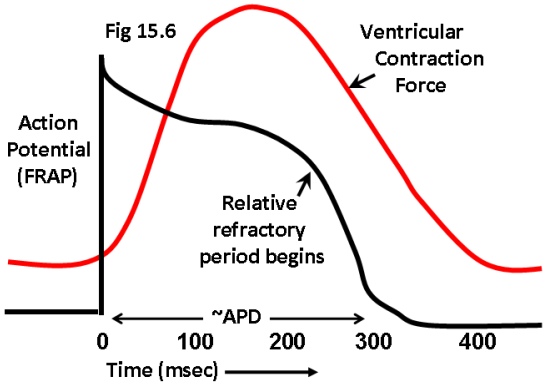


I_{CA}: At a V_m of ~ -55 mv, inward calcium currents ($I_{Ca\text{-}T}$ & $I_{Ca\text{-}L}$) are activated (gated open) causing acceleration of diastolic depolarization. At threshold, Ica-L channels fully open causing AP upstroke.

15.7 Electrical-Mechanical Relation for FRAP

The total amount of Ca^{++} entry during Φ_2 depends in part on the action potential duration (APD, **Fig 15.6**) and the contraction force depends on the amount calcium available at contraction start. So, LV contraction force and pressure are related to the APD; a greater APD normally causes more contraction force!

Fig 15.6



16.0 Automaticity, Rhythm and ANS Effects TOC

16.1 Overview: Some cardiac cells can automatically depolarize and repolarize to act as pacemakers. The SAN spontaneous depolarization rate normally exceeds that of all other potential pacemakers and it maintains dominance of cardiac rate and rhythm as the natural pacemaker. The SAN depolarization rate is also more sensitive to NE and Ach than are other cells. But, abnormal automaticity can render other cells to have a spontaneous depolarization rate that is faster than the SAN and take over the cardiac rate and rhythm.

16.2 Natural Pacemaker: SAN cells have an unstable Φ4 that spontaneously depolarizes (diastolic depolarization). An AP upstroke results when threshold is reached. The time to reach threshold depends on the rate of Φ4 depolarization (dV_m/dt), the threshold potential and the maximum negative diastolic potential.

Fig 16.1a HR Changes: Vagal Activity

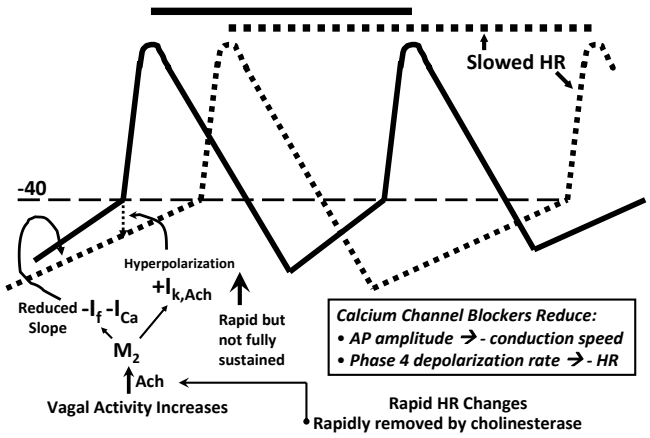
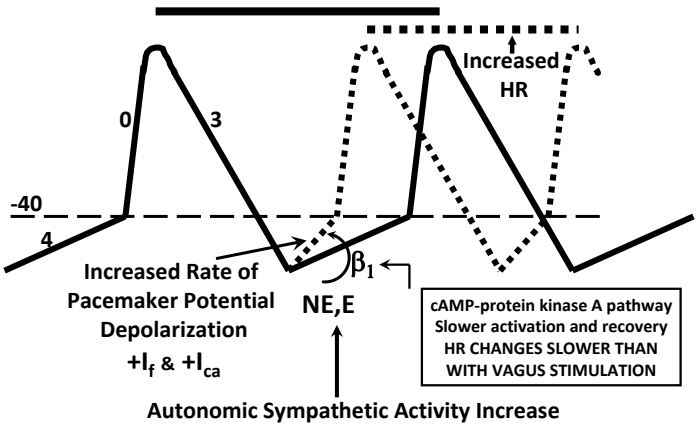


Fig 16.1b HR Changes: Sympathetic Activity



16.3 ANS Effects on SAN and AVN

ANS activity modulates node channel currents and affects HR as in **Fig 16.1**. A steeper Φ_4 slope results if either or both I_{Ca} and I_f increase relative to I_k. Increased temperature raises HR by about 10 beats/min/°C. Sympathetic and vagus effects tend to be reciprocal with an increase in one occurring together with a decrease in the other. Increased sympathetic activity is also associated with a +dromotropic effect.

SAN Vagal stimulation (Ach) increases K^+ conductance (g_K) by activating specific Ach K^+ channels. It also reduces both I_{CA} and I_f. Result = decreased slope and hyperpolarization = *Decreased HR.*

SAN Sympathetic effects are via NE and E release that increases the rate of Φ_4 depolarization by increasing I_{Ca} and I_f; threshold is thus reached sooner resulting in an *Increased HR*

AVN Effects Increased vagal activity to the AV node causes a decrease in conduction speed (- dromotropic) and thereby a greater conduction delay to match a slowed HR. Increased sympathetic effects are opposite.

16.4 Mechanisms Summarized

The processes embodied in **Fig 16.1** depend on activation or inhibition of membrane bound receptors as in **Fig 16.2**. Activation of β_1 receptors by NE released from nerve terminals or via circulating E causes a sequence of ionic current changes producing +chronotropic, +lusitropic, +inotropic and +dromotropic effects via stimulating g-protein (Gs) – cAMP related effects. Opposite effects are triggered by Ach activation of M_2 receptors that activate the inhibitory G-protein (Gi).

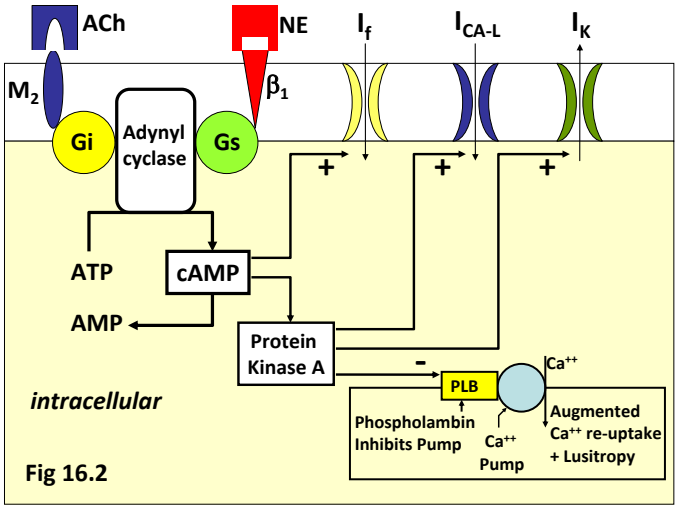
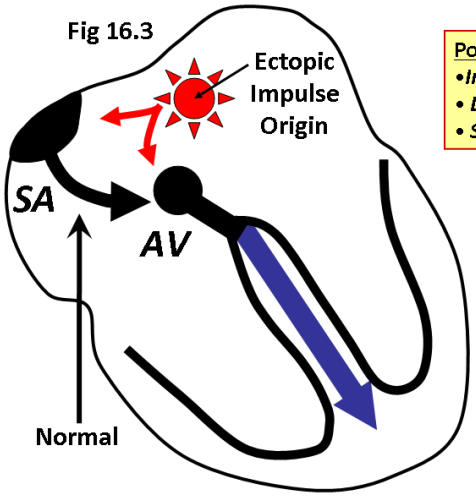


Fig 16.2

16.5 Ectopic pacemakers or foci TOC

Regions, *other than SA node*, may initiate impulses that may become pacemakers. These may occur if "ectopic" cell excitability is enhanced, SA pacemaker activity is depressed, or if all conduction pathways between SA and potential ectopic foci are blocked thereby eliminating the normal suppression of ectopic firing. Effects of an ectopic or premature impulse on cardiac activity importantly depend on the timing of the event in relation to the electrical status of target cells on which the ectopic impulse acts. Target cell action potential duration and refractory period are important factors. These aree discussed in subsequent sections.



Possible Causes of Ectopic Activity
- *Increased Excitability*
- *Depressed pacemaker*
- *SA-to-Ectopic pathway blocked*

Possible Effects
Effects depend on type, location and timing of arrival of Ectopic Impulse

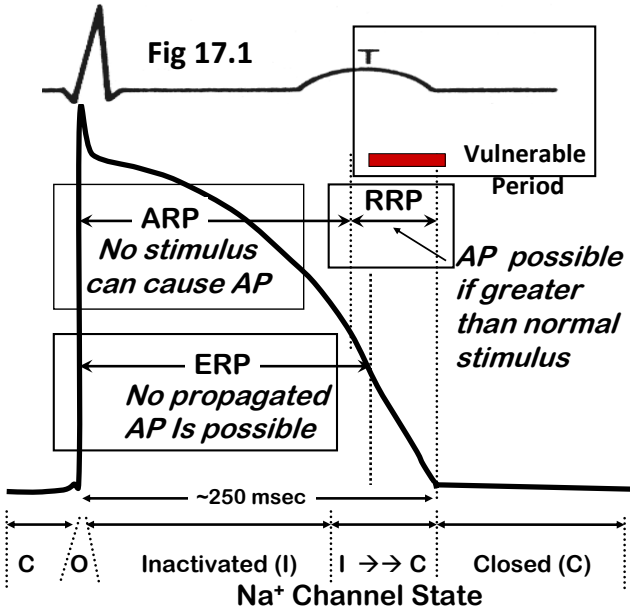
17.0 Refractory Periods (RP) - Na^+ Channel States - Ectopic Effects TOC

Absolute (ARP): No stimulus can evoke an action potential (AP) as shown in **Fig 17.1**.

Effective (ERP): No stimulus can evoke an AP that propagates.

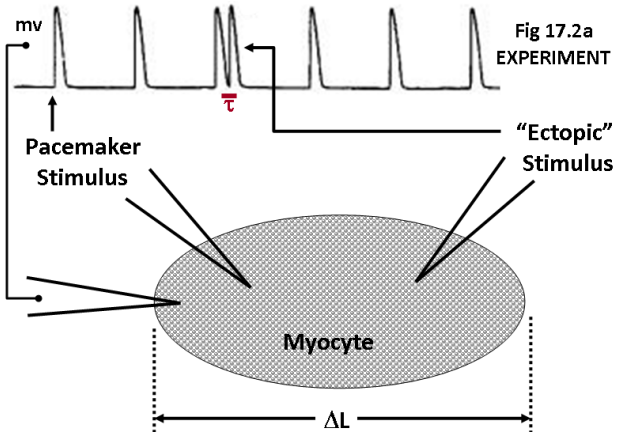
Relative (RRP): A larger than normal stimulus can cause a *propagated* AP. The RRP starts when a sufficient number of Na channels have recovered. But, since cells recover at different rates the recovery is not uniformly complete among cells so the resultant AP has a reduced amplitude and slower rate of rise. These AP features increase the chance that an ectopic impulse will trigger a disorganized multiple reentrant arrhythmia (section 21.2). This may occur in the so-called vulnerable period that approximately coincides with the 2nd half of the EKG T-wave.

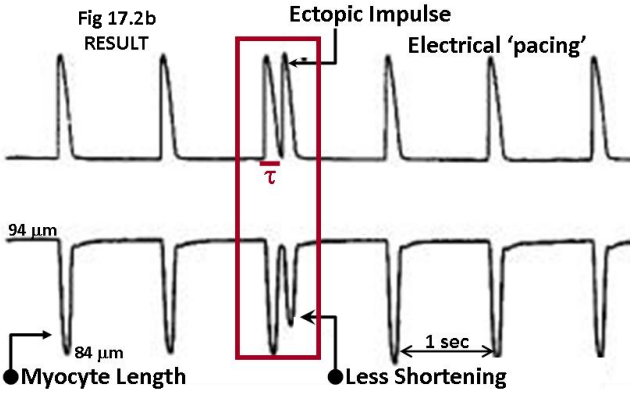
Recovery Variability: Recovery of cellular excitability is temporally and spatially non-uniform so recovering cells have varying states of excitability. The effect of an arriving ectopic impulse depends on the distribution of excitability/refractory states encountered by the stimulus. If the impulse encounters cells that in all directions are fully excitable or fully refractory then the impulse triggers APs that respectively propagate normally or not at all. If the stimulus arrives when cells in one direction are in ARP, while those in other directions are either in RRP or are fully excitable, then the impulse is blocked from triggering a propagating AP in the ARP direction but free to travel in the others. The vulnerable period is a time period in which this latter condition is more likely to occur. Its probability of occurrence is greatest during the 2ND half of the EKG T-wave and is a period in which susceptibility to reentry arrhythmias is greatest.



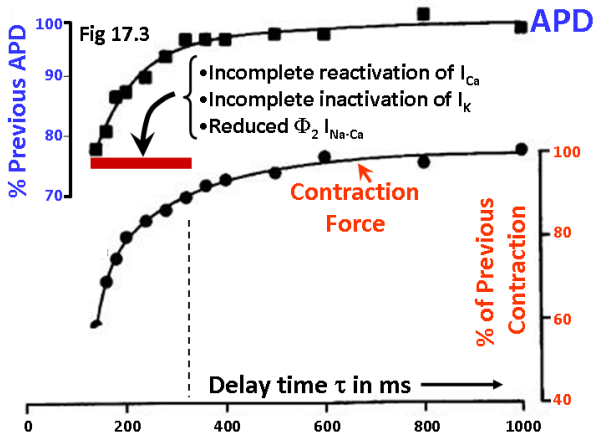
17.2 Action Potential Durations (APD) and role of Na^+- Ca^{++} Pump TOC

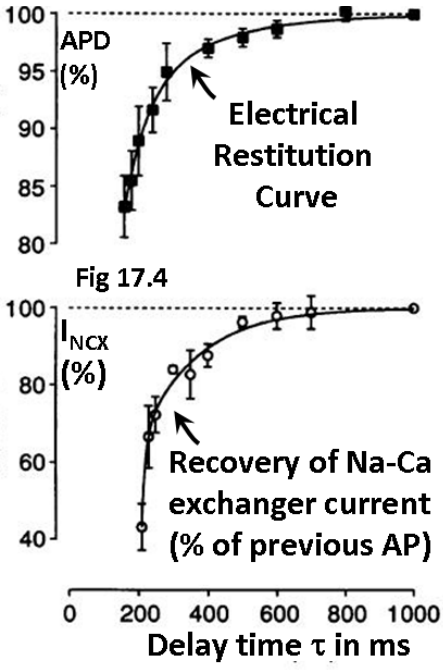
The APD of an AP that is triggered by ectopic impulse depends on when the ectopic impulse arrives. Experiments on isolated cardiac myocytes (**Fig 17.2a**) in which simulated ectopic impulses are inserted at various time delays (τ) reveal that contraction force decrease as τ decreases (**Fig 17.2b**).

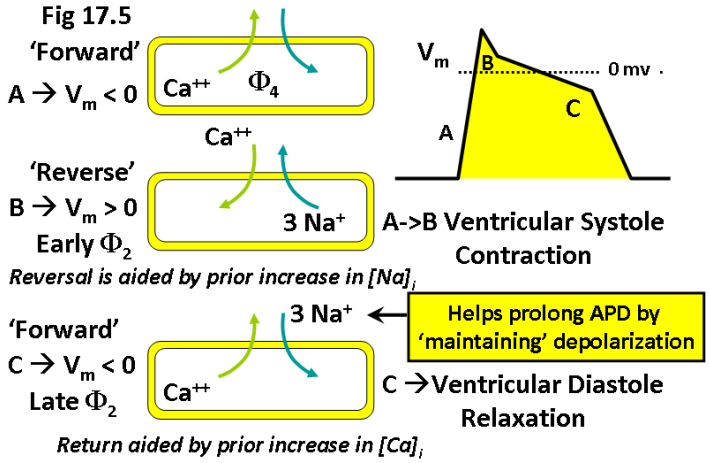




Further work indicates that the APD decreases with decreasing τ and that this is associated with a decrease in contraction force (**Fig 17.3**). These effects are mainly due to Φ_2 duration changes. Although electrical restitution depends on each Φ_2 current (e.g. I_{Ca} and I_K) the APD effect appears to best correlate with changes in the Na-Ca exchanger current (I_{NCX}, **Fig 17.4**). The exchanger net current direction depends on the cell membrane potential (V_m) and the ion concentration gradient across the membrane. **Fig 17.5** shows the forward direction of the pump and its reversal due to the change in membrane potential and Na^+ accumulation



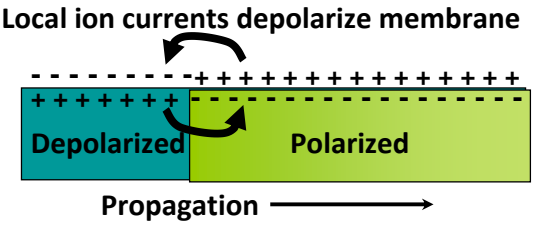




The shift to the reverse direction occurs during ventricular systole with a return to the forward direction during late Φ_2. The added Na^+ helps to further extend the APD. As an aside it should be noted that APD shortening also normally occurs with increasing HR.

18.0 Conduction Speed Determinants & Decremental Conduction TOC

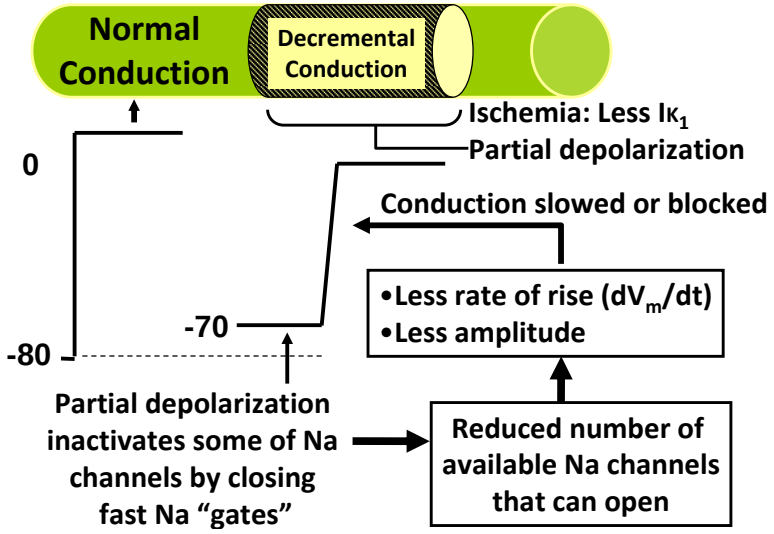
The adjacent figure shows a wave of depolarization moving from left to right. The local ion currents (arrows) arise due to the voltage gradient that is present between the depolarized and as yet to be depolarized region. In order for the action potential to propagate, the membrane of the polarized region needs to be discharged. The time it takes for this to occur depends on the magnitude of the voltage gradient and its rate of change. As a consequence, the conduction speed down the fiber (or a depolarization wave in the heart) is decreased if the AP amplitude or rate of rise is decreased. Also, since it takes longer for higher AP thresholds to be reached, increased thresholds would also decrease conduction speed.



2. When threshold reached (~-65 mv) for fast and (~-40 mv) for slow, AP (Phase 0) results

3. Impulse conduction speed depends on:
AP amplitude: If Less = Slower speed
Rate of rise: If Less = Slower speed
Threshold: If More = Slower speed

Regions of decremental conduction are often associated with partially depolarized membranes. The AP in such a region has a reduced amplitude and rate of rise as shown in the adjacent figure. So, if a normal AP approaches this region, and if in this region a sufficient number of channels have recovered at the time of its arrival, then a conducted (propagated) AP is generated, but it propagates at a slowed speed for the reasons already given. If a region is not recovered then conduction through the region is blocked.

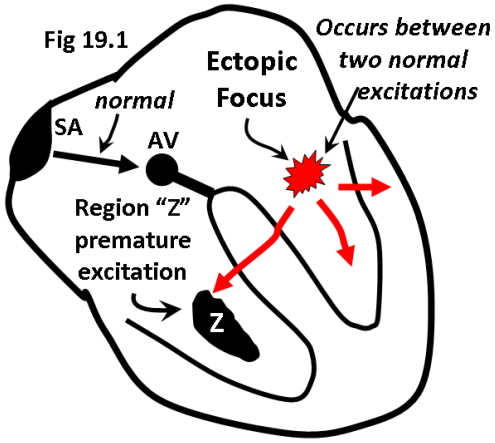


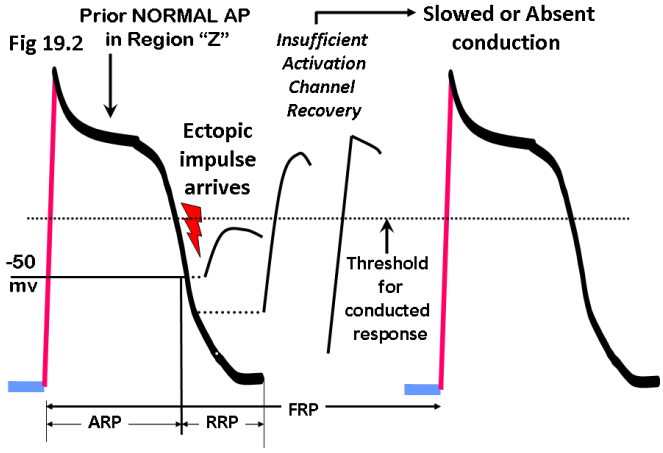
Slow conduction is normal in SA and AV nodes but can be abnormal. One example is cardiac tissue that has suffered a significant blood flow reduction. In this *ischemic* tissue, the Φ_4 membrane potential (V_m) is partially depolarized due to a fall in the ratio $[K^+]_i$ / $[K^+]_o$. The ratio decreases because the ischemia causes a leak of intracellular K^+ into the interstitium thereby causing $[K^+]_o$ to increase. This V_m change *inactivates some Na^+ channels* because the probability of channel "openness" is Vm dependent. As a result, if this tissue region was excited, the AP upstroke would be less steep with reduced amplitude. Some cardiac glycosides also can cause a partial depolarization resulting in similar effects.

In summary, if a normal AP encounters a decremental region its conduction through it is ***slowed***, or if the evoked potential within the region does not reach threshold, its conduction through the region is ***blocked***. Slowed conduction speed and 'unilateral' blockage, increases the likelihood for *reentrant arrhythmias*.

19.0 Ectopic Excitation prior to Full Recovery TOC

An ectopic impulse triggering a region "Z" is shown in Fig 19.1. If cells are stimulated early, prior to their full recovery, evoked response features depend on the timing of the ectopic impulse's arrival. The earlier it arrives in the RRP the slower is the upstroke and the smaller is the triggered AP amplitude (Fig 19.2).





20.0 Clinical Correlation: Hyperkalemia → High K^+ in blood or ECF TOC

Possible Causes

- Low renal output of K^+;
- RBC hemolysis releasing internal K^+
- Cellular ischemia causing K^+ leak

Normal range

- Serum K^+ → 3.5 to 5.0 mM/l

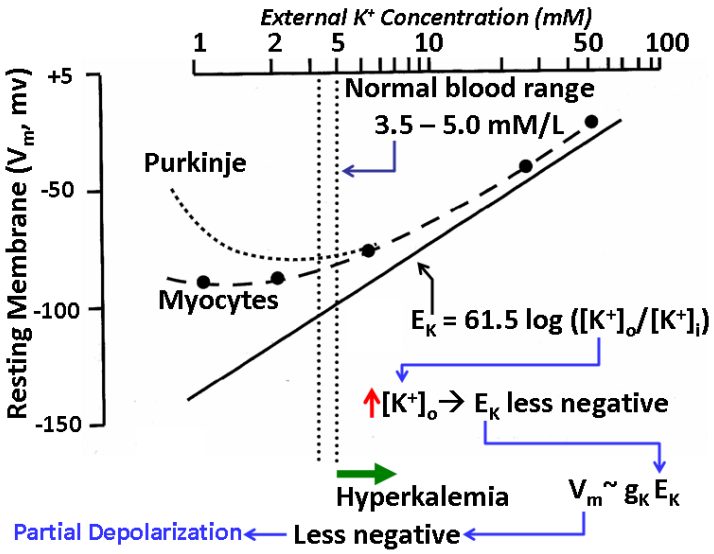
Hyperkalemia Levels

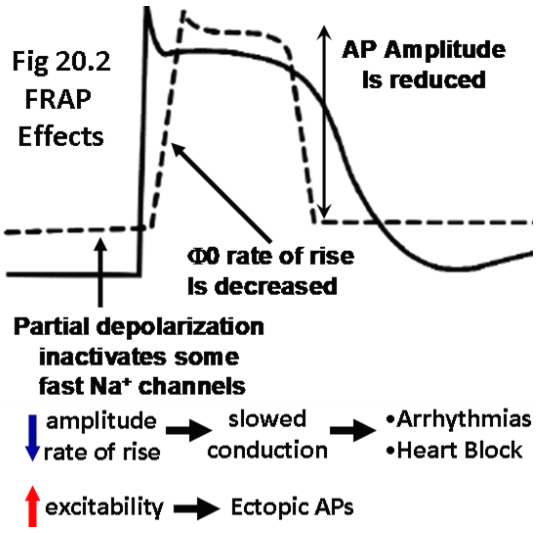
MILD 5.1-6, MODERATE 6.1-7, SEVERE >7 mM/l

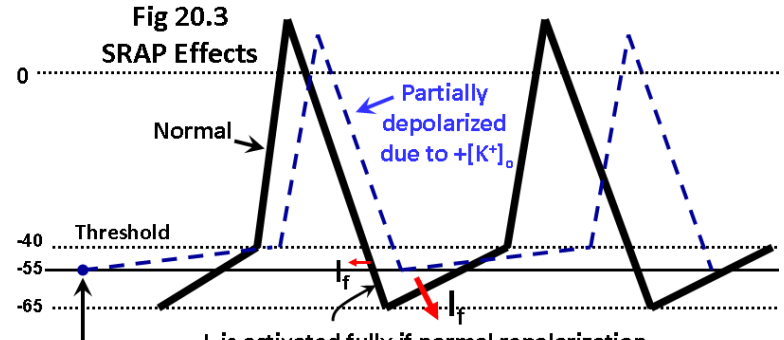
K^+ effects are greater as hyperkalemia increases;

- to ~5.5 mMl/l -> EKG T-wave peaking
- to 6.5 mM/l → lengthened P-R interval;
- to >7.0 mM/l →bradycardia/AV block;
- to > 9.0 mM/l → cardiac arrest Vfib

Fig 20.1 Partial Membrane Depolarization with Increasing $[K^+]_o$







If membrane partially depolarized due to hyperkalemia, full I_f activation does not occur! Rate of spontaneous depolarization less = reduced HR!

If membrane doesn't repolarize to at least -50 mv then No I_f and no action potential! No pacemaker action!

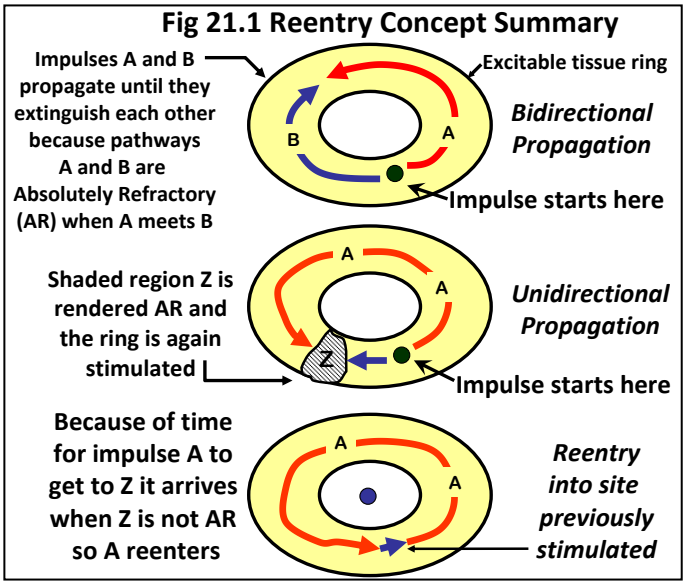
21.0 Reentrant Arrhythmias *"a reentrant mechanism underlies ventricular fibrillation in the setting of acute myocardial ischemia. The occurrence of the arrhythmia is facilitated by heterogeneities in excitability and refractoriness and is initiated by a premature beat resulting from a 'current of injury' "Coronel 2010.* TOC

21.1 Reentry Excitation

Reentry occurs if an impulse reenters a site previously excited (Fig 21.1). Requisites for reentry are:

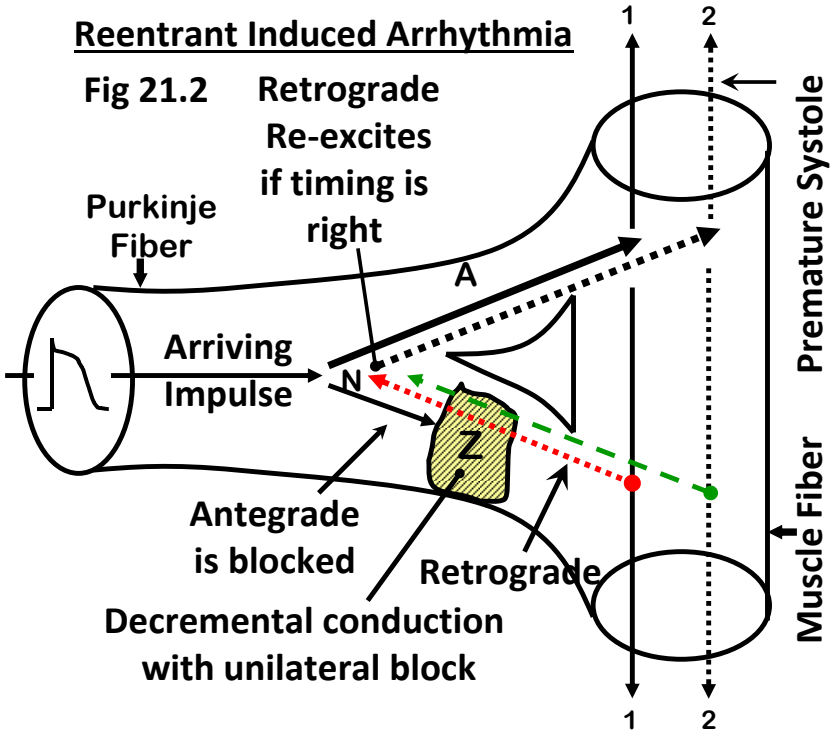
1. A circuitous pathway (ring of excitable tissue).
2. Impulse must initially encounter a *unidirectional block (region "Z")* e.g. tissue is absolutely refractory (AR) when B impulse arrives, so B can't pass through Z.
3. The travel time for impulse A to get to Z must be such that when it arrives at Z, Z is no longer AR. *Slowed conduction velocity favors this aspect!*

If the above conditions are present, a continuous circus movement of excitation **may occur** causing a **reentrant tachyarrhythmia**. Formalization of risk factors for this to occur is in section 28 in conjunction with atrial fibrillation and other aspects.



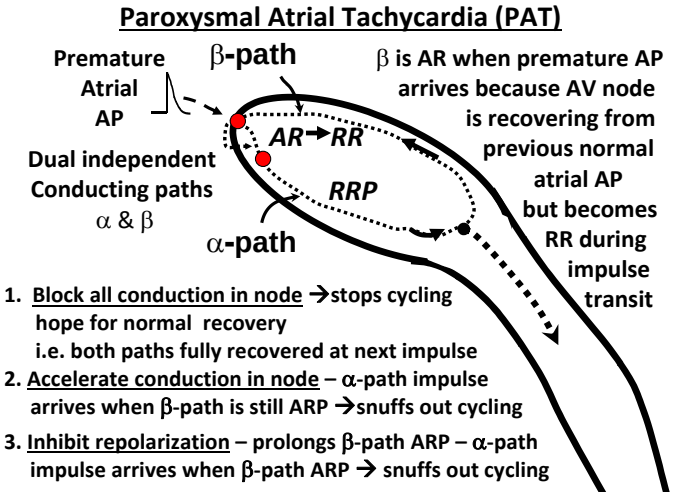
21.2 Reentrant Arrhythmias

Prior concepts can be combined to describe basic aspects of how reentrant arrhythmias lead to serious effects. The hatched area (**Z**) in Fig 21.2 is a region that is absolutely refractory (AR) when a normal forward (***antegrade***) impulse arrives. Because it is AR the impulse is blocked and can't pass through Z. Because of the alternate pathway ***A***, this impulse is conducted to the muscle fiber (impulse 1) through ***A*** causing a normal systole (contraction). But, a ***retrograde*** impulse may pass through Z if it arrives at Z when Z has partially recovered to its RRP. If the retrograde impulse arrives at the normal proximal region **N** when N has recovered from its prior excitation, it will re-excite N, and cause a ***premature systole*** (impulse 2). Process may continue causing a reentrant ***tachyarrhythmia***.

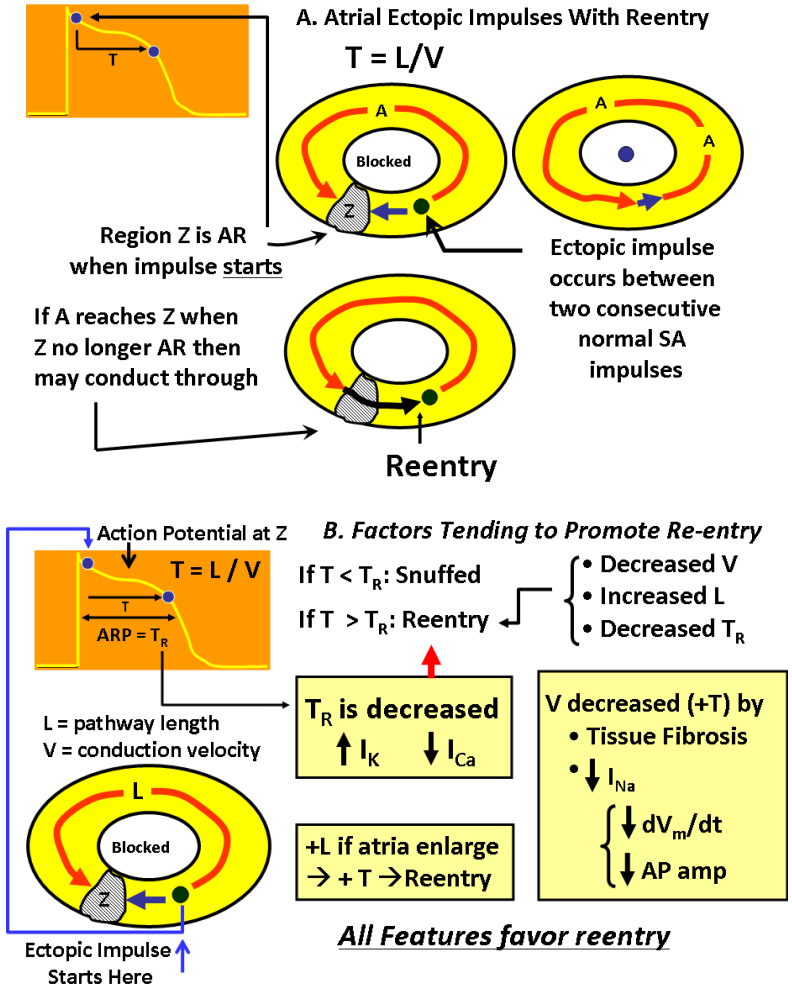


21.3 Paroxysmal Atrial Tachycardia (PAT)

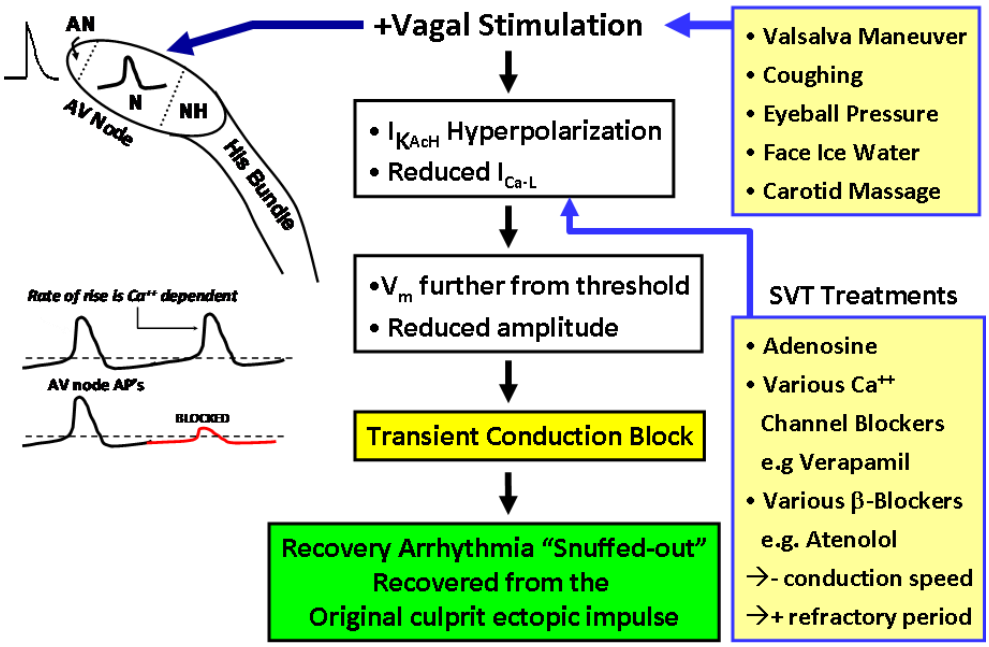
A specific example of a reentrant arrhythmia is paroxysmal atrial tachycardia or PAT that is form of Supraventricular tachycardia (SVT). These have bursts of tachycardia with abrupt start and stop and are often initiated in atria or AV node which is called a junctional origin. Either origin (atrium or AV) are often called PAT. An example of a junctional PAT is illustrated in the adjacent figure along with three general ways to potentially break or snuff out the arrhythmia. Further details are in section 21.5.



21.4 Clinical Correlation- Atrial Ectopic Impulse with Reentry TOC



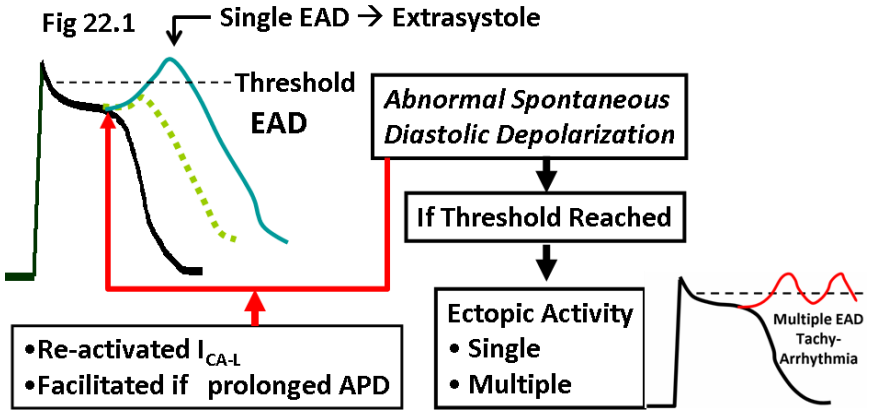
21.5 Clinical Correlation- Supraventricular Tachycardia (SVT) Treatments TOC



22.0 Afterdepolarizations: Early (EAD) and Delayed (DAD) TOC

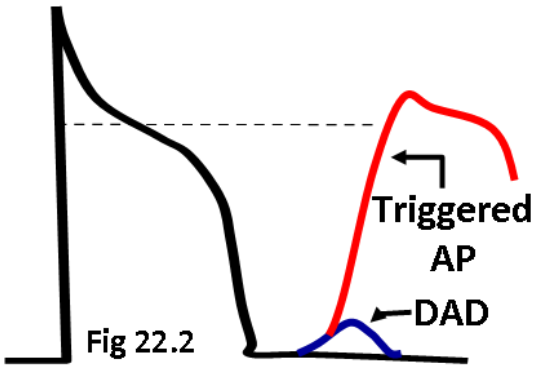
Not all arrhythmias are reentrant. Two examples are triggered by EAD or DAD.

22.1 EAD: Towards the end of Φ_2 or during Φ_3 there may be a reversal of the repolarization process brought about by the reactivation of previously inactivated I_{CA-L} channels or by an abnormal reduction in repolarizing I_K. This is facilitated by AP duration prolongation. It may cause no effect if the depolarization is below threshold or may produce a single extra-systole as shown in Fig 22.1 or may lead to multiple systoles causing a significant ventricular tachyarrhythmia.



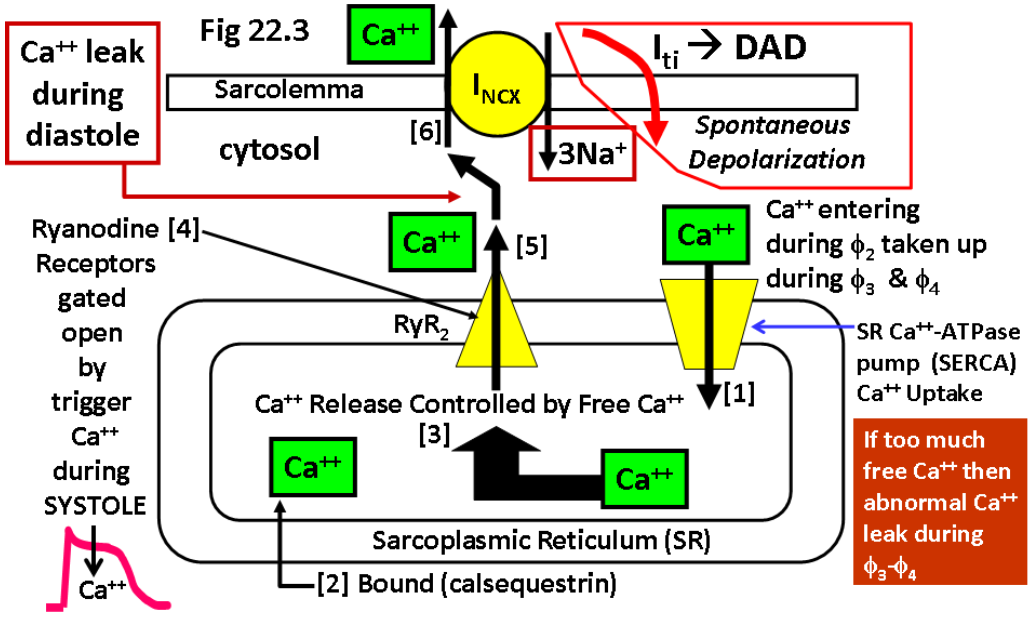
2.2 DAD: These occur in late Φ_3 or early Φ_4 and are associated with deficits in Ca^{++} handling (Figs 22.2,22.3). Too much Ca^{++} entry or too little Ca^{++} binding leads to an abnormal Ca^{++} leak from the SR during diastole. The result is an increase in cytosol Ca^{++} that is pumped out into extracellular space at the cost of entry of $3Na^+$. This causes a transient inward Na current (I_{ti}) and membrane depolarization. If depolarization reaches threshold an abnormal AP occurs. Inherited or acquired abnormalities in SR Ca-release channels or SR Ca^{++}-binding proteins may be involved. DAD occurrence is linked to Ca overload.

DAD due to transient Na^+ inward current due to abnormal Ca^{++} handling processes



22.3 Calcium Handling in relation to DAD Initiation (Fig 22.3)

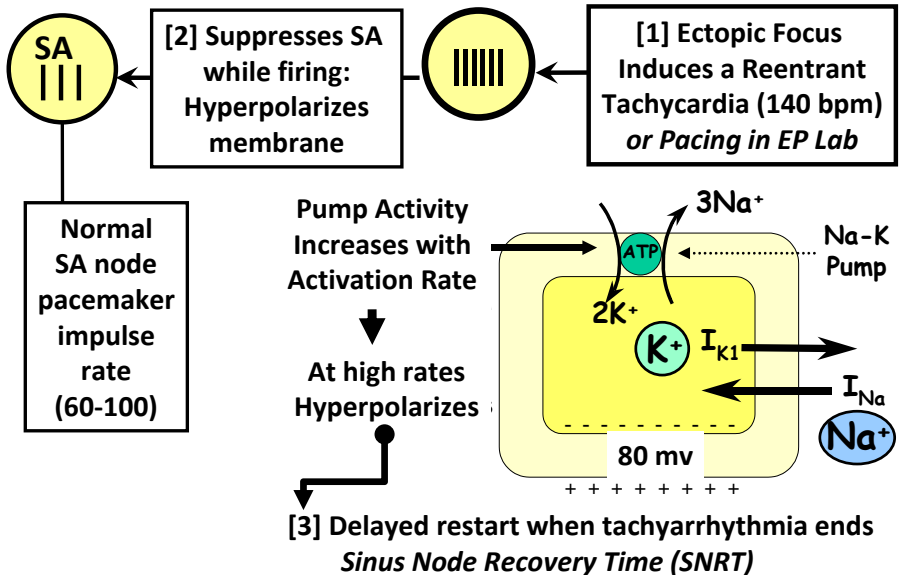
Ca entering myocyte cytosol during Φ_2 is taken up and stored in the sarcoplasmic reticulum (SR) during Φ_3 and Φ_4 to be available for release during the next systole. Uptake [1] is via a SERCA pump. Ca^{++} is bound by the protein calsequestrin [2] and some as free Ca^{++} in SR lumen [3].
During systole, a normal AP causes entry of trigger Ca^{++} that acts on ryanodine receptors [4] to facilitate release of bound Ca^{++} into cytosol [5] for use by contractile machinery.
Cytosol Ca^{++} removal is by the Ca^{++}-Na^+ exchanger [6] and SR re-uptake.



If too much Ca^{++} enters the SR or too little that enters becomes bound, then free Ca^{++} increases. This causes abnormal Ca^{++} leak to the cytosol during diastole (Φ_3-Φ_4). Processing this increased Ca^{++} by the Ca^{++}-Na^+ exchanger causes inward Na current (I_{ti}) that likely causes the DAD.

22.4 Overdrive SA Node Suppression

If an ectopic impulse induces a tachycardia, the SAN is bombarded by impulses that hyperpolarize the membrane. This because Na^+-K^+ pump activity increases with activation rate causing more Na^+ leaving than K^+ entering. This hyperpolarization suppresses SAN activity and may delay its recovery when arrhythmia ends.



23.0 EKG Genesis and Relation to Cardiac Electrical Activity TOC

23.1 Moving Waves of Changing Electrical Activity are Source of the EKG text return

Ion currents & voltages

Ion currents and AP *changes* produce "remote" voltages sensed by skin electrodes. The voltages reflect all electrical changes in heart, surrounding tissues and fluids. Voltages depend on: (a) magnitudes of "source" membrane current and voltage changes, (b) volume conductor electrical properties and (c) electrode position relative to the depolarization wave (DW). Electrodes record voltages these DW produce resulting in the electrocardiogram (EKG) deflections (Fig 23.1).

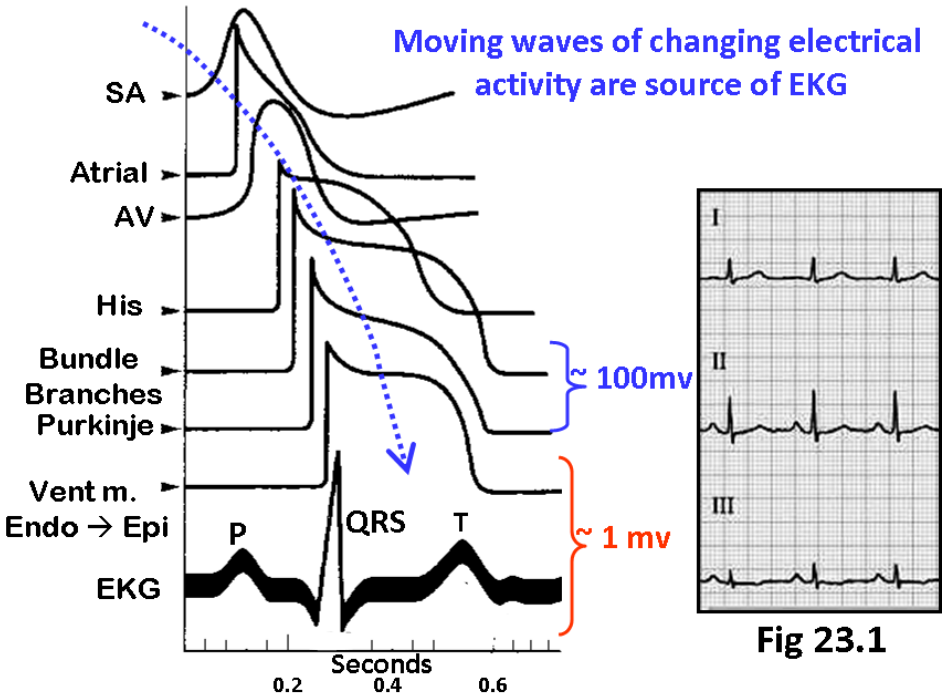
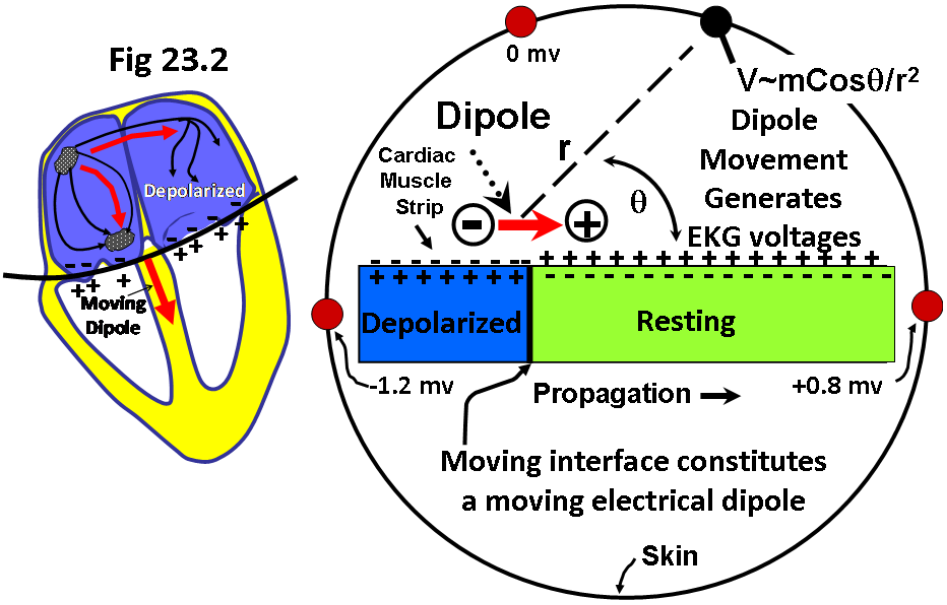


Fig 23.1

23.2 Moving Dipoles as Source of EKG Voltages TOC

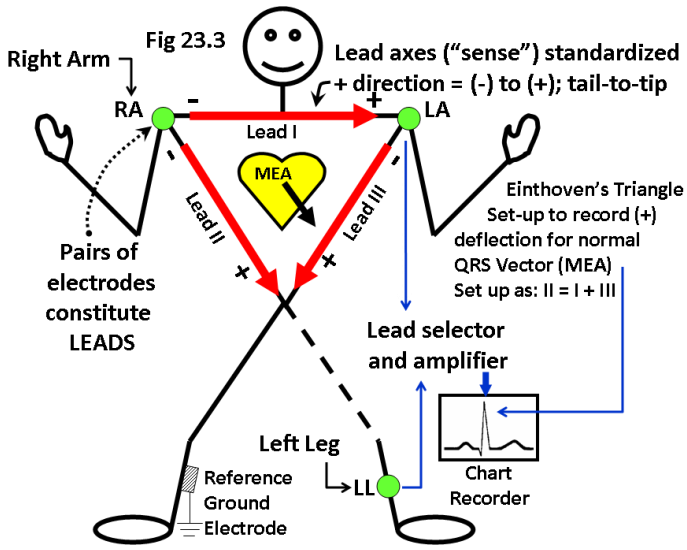
A moving dipole concept to explain EKG voltage deflections is summarized in Fig 23.2. According to this concept, the waves of depolarization that sweep through the heart starting with the normal SA node depolarization can be represented as the movement of the interface between myocardial cells that are depolarized and the resting cells that have yet to be depolarized. Because external charges surrounding cells in the depolarized region are negative with respect to resting cells, movement of the interface corresponds to movement of an electrical dipole - equal but opposite charges separated by a small distance. As these dipoles move, they cause voltage changes that are recorded as the EKG.

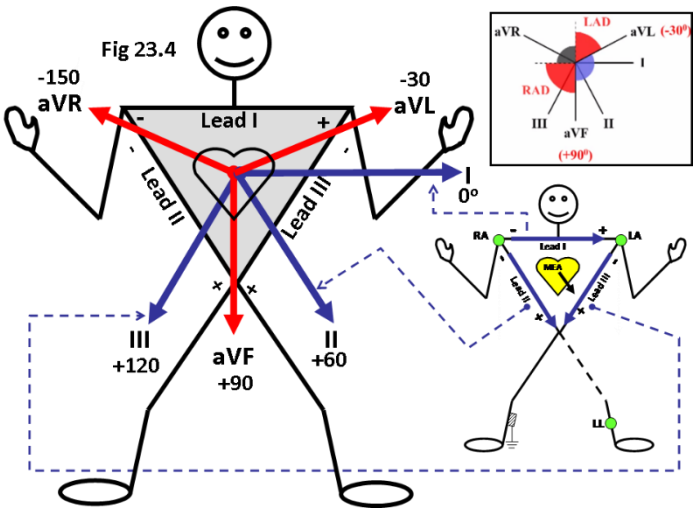
Fig 23.2



23.3 Standard Lead Arrangement Synopsis TOC

The standard 12 lead EKG (section 25.2) has 3 frontal limb lead voltages (Leads I, II, III, **Fig 23.3**), 3 augmented leads (aVL, aVR, aVF, **Fig 23.4**) and 6 chest (precordial) electrodes (section 23.5).

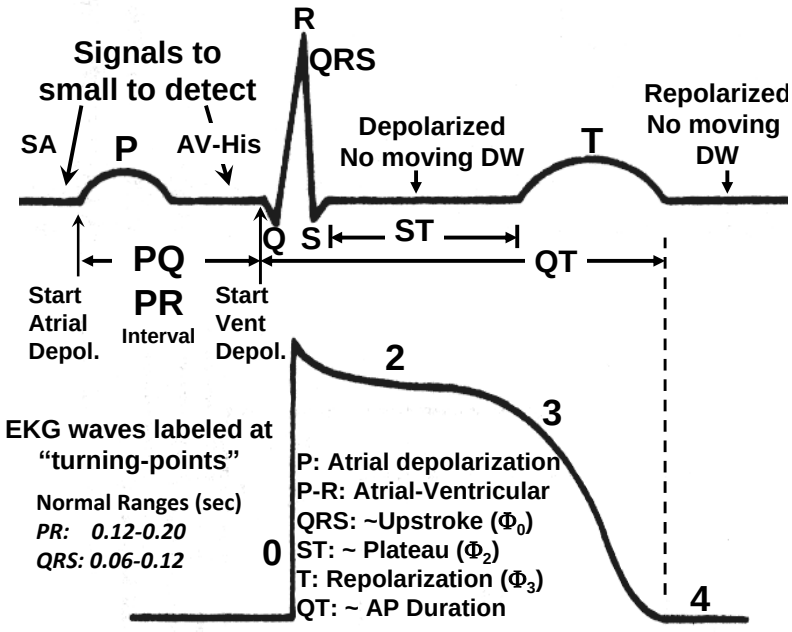




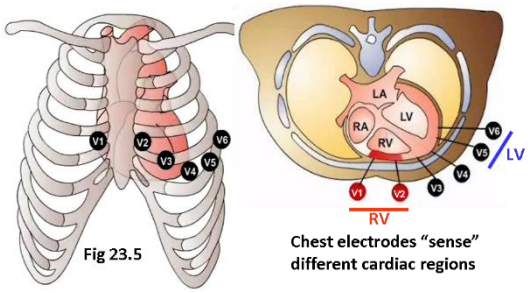
Each lead axis has a standardized direction that is set up so that a normal EKG pattern will register as positive deflections in standard leads I and II and the sum of lead I and III = lead II voltage. The average direction of the DW during ventricular depolarization is normally between + 90° and -30° (**Fig 23.4** inset in blue). Right or left deviations are called right and left axis deviations with causes discussed subsequently.

23.4 EKG Components and Relationship to Cardiac Action Potential TOC

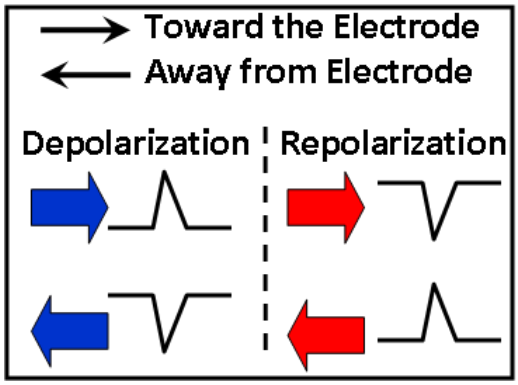
The DW sweeps through the heart starting with SAN depolarization. The 1st EKG deflection is the P-wave caused by atria depolarization. DW spread through atria to and through the AVN and into the His bundle with no EKG deflection because signals are too small. The P-R interval is the time for the DW to pass from atria to ventricles. The QRS complex is due to DW rapidly sweeping down the septum and depolarizing the ventricles. The *ST-segment is isoelectric* since all ventricular regions are depolarized during this time interval. It corresponds closely to Φ_2. Repolarization causes the T-wave representing the end of Φ_2 and start of Φ_3. The T-wave is wider than the QRS since the repolarization wave does not spread as rapidly as the DW. Normally the EKG R and T waves are directionally concordant. The Q-T interval approximates the APD. The P-wave is really the summation of RA and LA depolarizations with the RA preceding the LA. RA or LA enlargement extends the p-wave duration as illustrated in appendix A1.



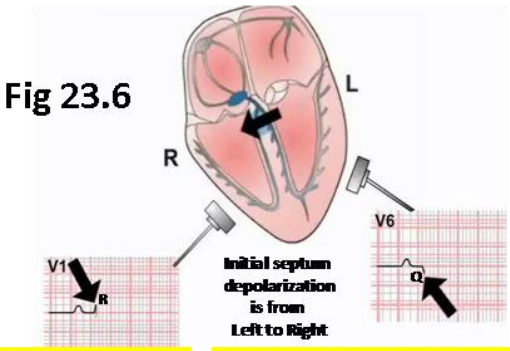
23.5 Chest (Precordial) Lead Placement and EKG Sensing TOC text return

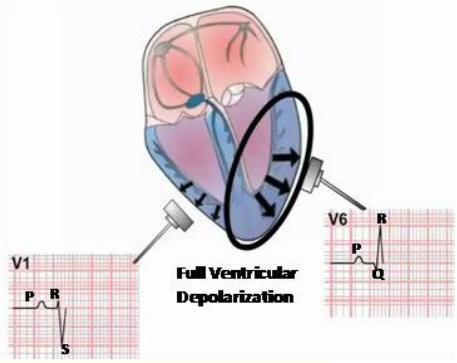


A DW moving toward an electrode and a repolarizing wave (RW) moving away cause upward (positive) EKG deflections and negative deflections if DW or RW are away and toward the electrode respectively.



23.6 Chest (Precordial) Leads Deflections and Naming





The 1st + deflection is called the R-wave

If the 1st deflection is negative it is called Q

A negative deflection following R-wave is S

23.7 Chest and Limb Lead Sensed Territories

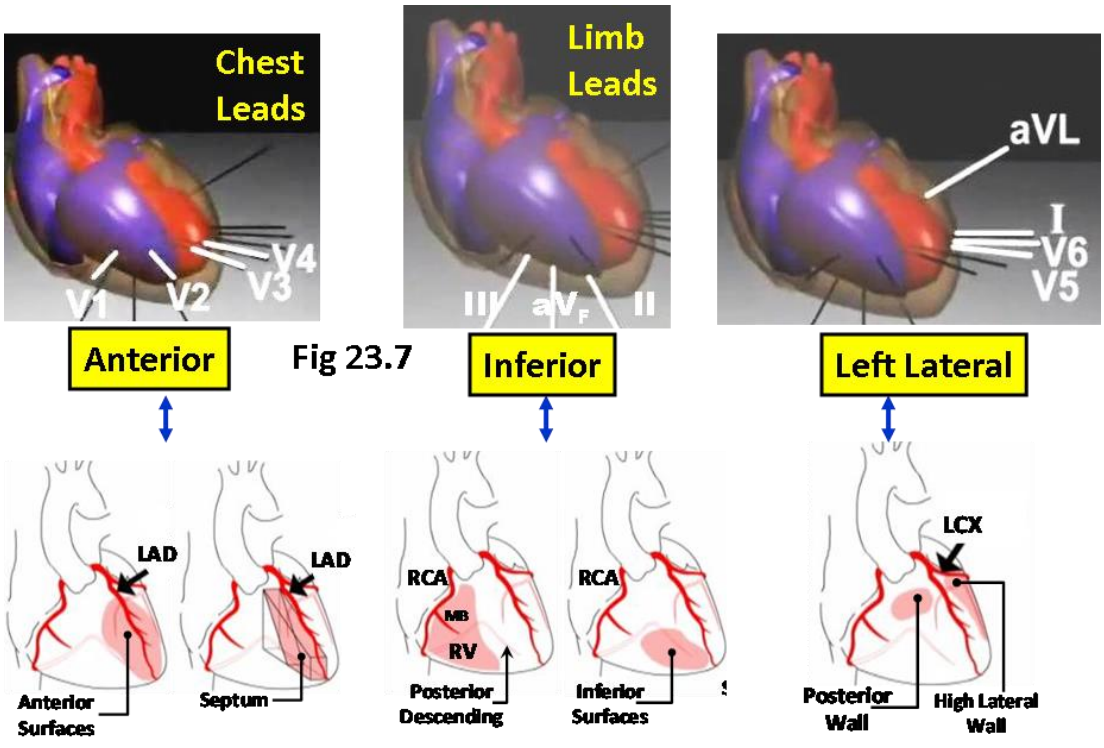
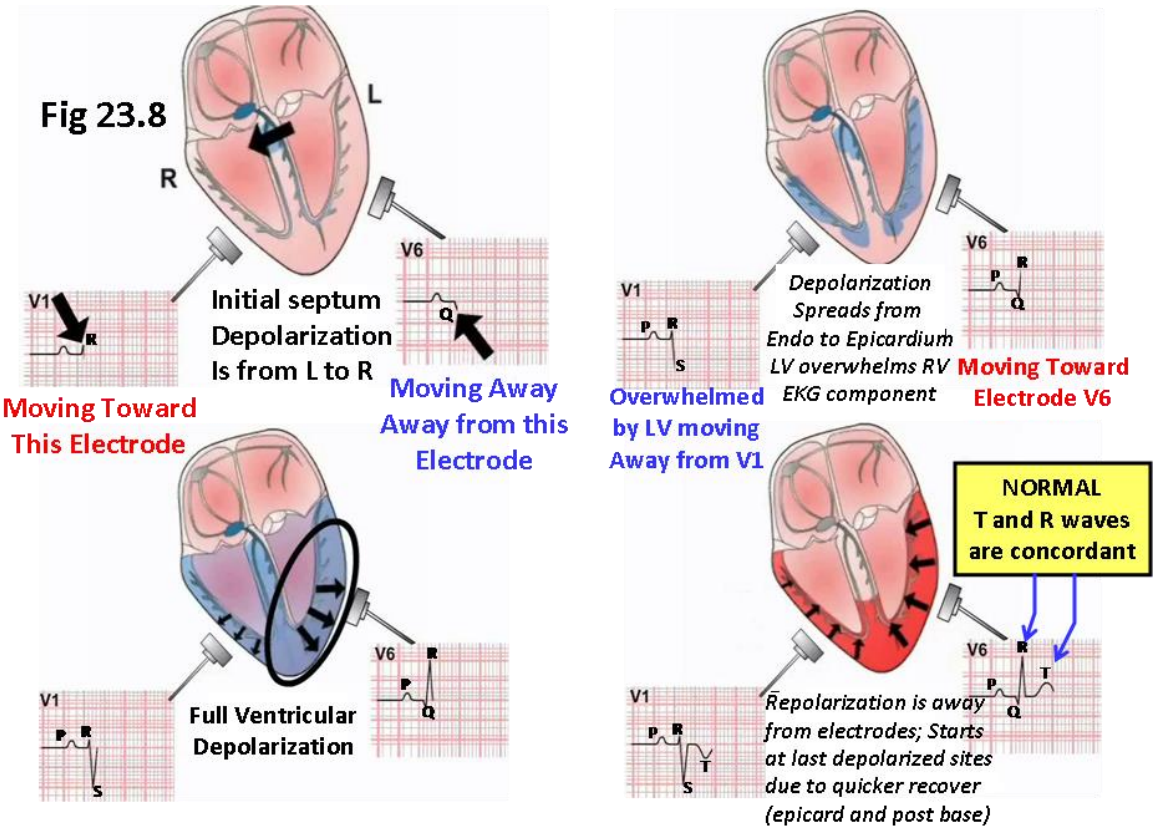


Fig 23.7

23.8 Chest EKG Sensing Sequence Features TOC



24.0 Cardiac Vectors TOC

24.1 Mean Instantaneous Vector

As shown in Fig 24.1, at any instant the depolarization wave sweeping through the heart consists of a multitude of individual dipoles that are pointing and moving in various directions. The average of all these *instantaneous* propagating dipoles at a fixed instant is viewed as a single cardiac dipole called the ***mean instantaneous vector***.

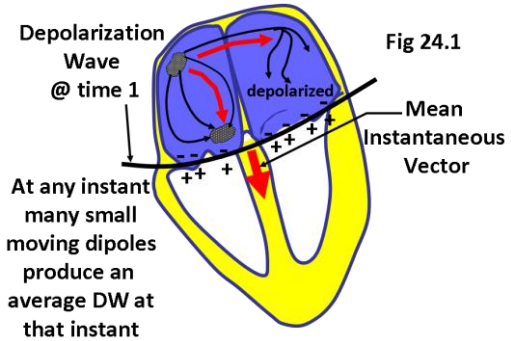


Fig 24.1

24.2 Mean QRS Vector

The DW direction and magnitude changes as it sweeps through the heart. The mean QRS vector during the approximately 0.10 sec it takes to inscribe the QRS complex is called the ***Mean Electrical Axis (MEA)***. In Fig 24.2 instantaneous vectors (Q, R & S) that occur during ventricular depolarization (QRS) added vectorially to yield one vector that is an average direction over that time interval. This vector is the **MEA**. Mean vectors can also be determined corresponding to the p-wave or the T-wave.

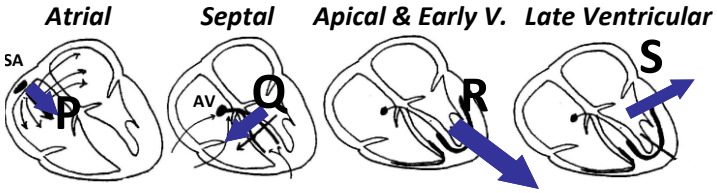
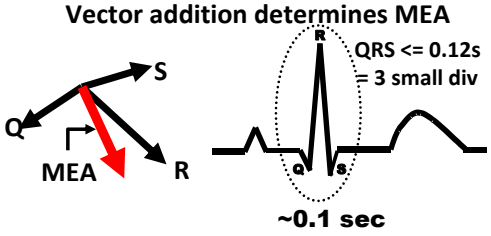


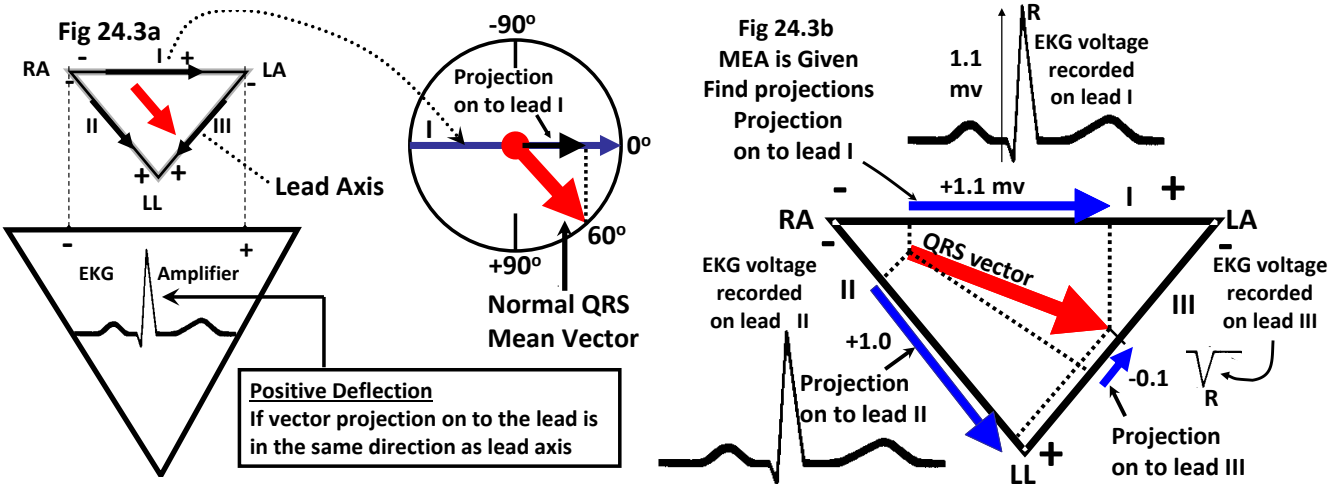
Fig 24.2

Vector addition determines MEA



24.3 LEAD Vector Projections TOC

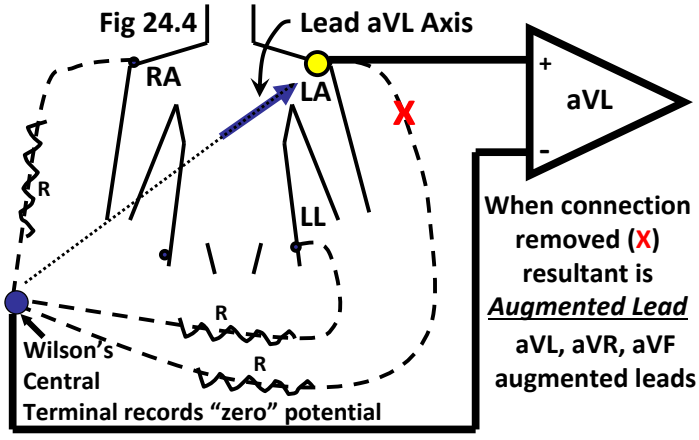
Recall from **Fig 23.3** that electrode pairs are *leads* that record voltage ***differences***. Each lead (I, II & III) has a defined axis direction shown by an arrow pointing from negative (-) to positive (+). A positive EKG deflection (upward) is produced if the projection of the MEA onto a lead is in the lead +axis direction. In **Figs 24.3a** and **24.3b** an MEA is inscribed in Einthoven's triangle. Its projection onto a lead is found by dropping a perpendicular to the lead from the MEA tip & tail. If the projection direction is in the positive sense of the lead (- to +), an upward deflection on the EKG occurs. In this example lead III projection is opposite to the lead axis so a small negative R-wave is seen. In this example, an MEA is given but often you want to determine the MEA from an observation and analysis of the EKG itself.



Because the MEA direction relative to a lead's direction determines the magnitude and direction of the projection onto the lead and so determines magnitude and deflection direction of the EKG voltage in that lead. So, the following statements about the DW are true. (1) directed toward the + of a lead causes a + (upward) EKG deflection; (2) directed perpendicular causes zero deflection; (3) directed away from the + of a lead causes a - (downward) EKG deflection; (4) Deflection magnitude (+ or -) is greater if electrical activity is more parallel (or anti-parallel) to the lead

24.4 Augmented Limb Leads TOC

If instead of measuring voltage differences between electrode pairs, voltage at one electrode is measured in relation to an "indifferent" electrode formed by connecting the (-) pole of the other leads together, an augmented lead is defined (**Fig 24.4**). Since augmented leads have different axes than the three standard leads they provide additional information for the MEA direction. Augmented leads are aVR, aVL and aVF corresponding to voltages at the RA, LA and LL (Foot).



24.5 Frontal Plane Lead Axis Summary and Axis Deviations TOC

In the 12-lead system, voltages are acquired from 3 bipolar limb leads I, II & III, 3 augmented leads aVR, aVL and aVF (Fig 24.5a) and six precordial leads, V1-V6 (Fig 24.5b). The magnitude and direction of EKG QRS complex deflections depend on the relation between lead axes and MEA direction. If an MEA projects onto a lead in the direction of the lead's axis a positive deflection is recorded by that lead. Positive angles are measured clockwise from a 0° reference (Fig 24.5b). A QRS axis is ~ 60° with a normal range from +90 to -30°. Depolarization waves directed inferiorly cause a + deflection on leads II, III and aVF so these leads are called "inferior" leads. Leads having a +deflection when depolarization waves move superiorly are sometimes called "superior" leads.

Fig 24.5a

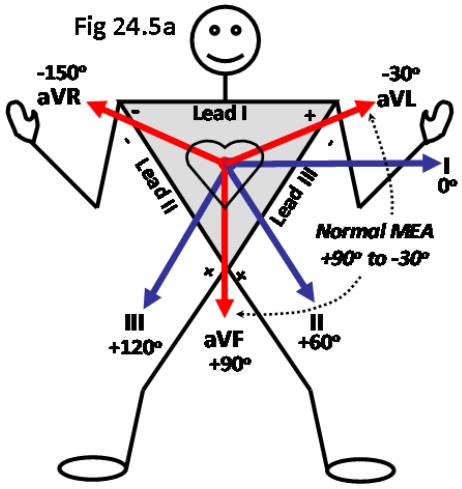
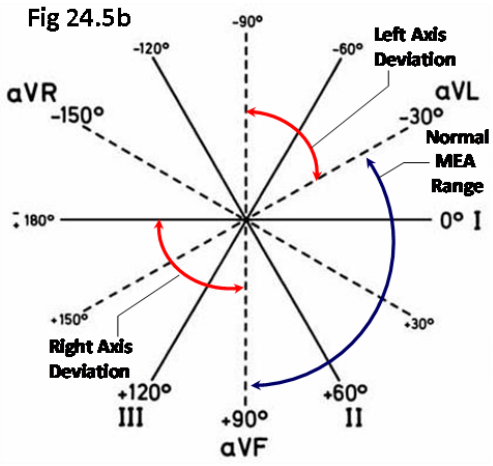


Fig 24.5b



24.6 Axis Deviations

If an MEA exceeds normal limits there is an axis deviation that is either right or left axis deviation. Conduction speed reductions or blocks are a frequent cause of axis deviations. For example, a complete BBB shifts the axis toward the block. (Fig 24.6). Left or right shifts may also be due to large LV or RV mass respectively. Also, anatomical differences or changes in heart angular position due to sitting vs. standing, tall and lean vs. short and fat, during pregnancy, and gastric distension shift the axis but are usually not large enough to move the MEA out of normal range.

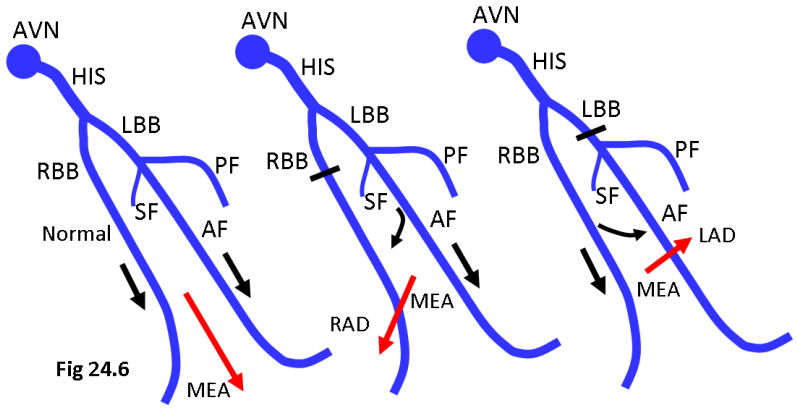
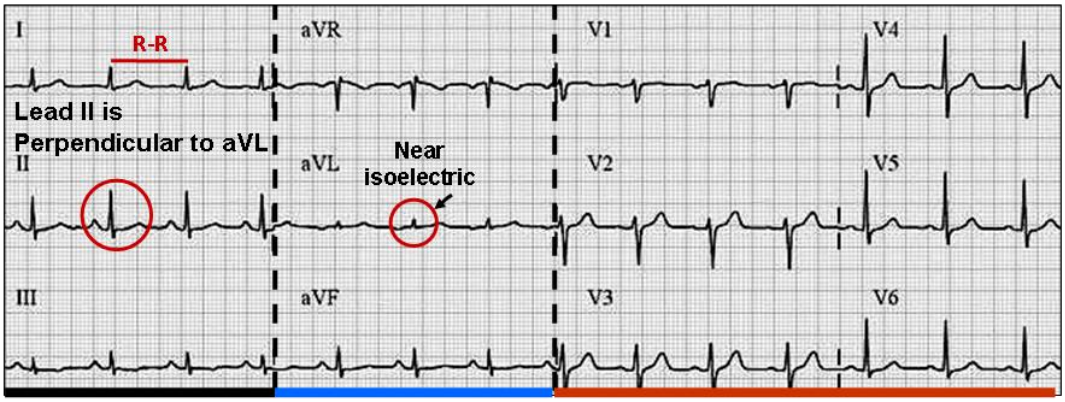


Fig 24.6

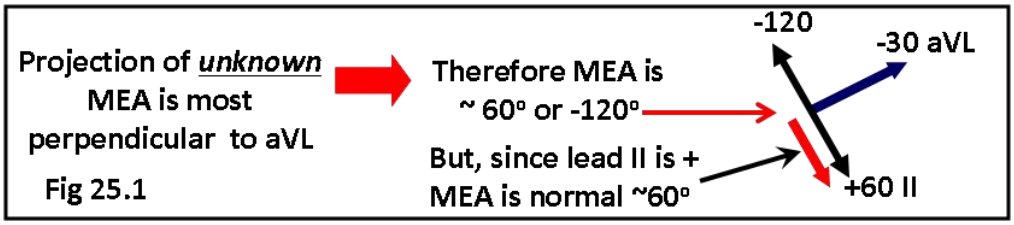
24.7 Effects of Partial LBB Block on MEA TOC

As shown in Fig 24.6, the left bundle branch (LBB) divides early into a left anterior fascicle (AF), a posterior fascicle (PF) and septal fascicle. Rich anastamosing (interconnecting) between AF and PF distal terminals allows retrograde conduction if one pathway is blocked. As a result of the conduction direction shift, a normal MEA may become left or right axis deviation depending on which fascicle is blocked. The normal MEA is down at an angle of about 60°. When one considers the modified directions of conduction associated with these partial LBB blocks, the net MEA shifts toward a left axis deviation (LAD) for an AF block and toward a right axis deviation (RAD) for a PF block. This is a consequence of the anastamosing between the AF & PF, if one is blocked, conduction is through the other at a slowed speed.

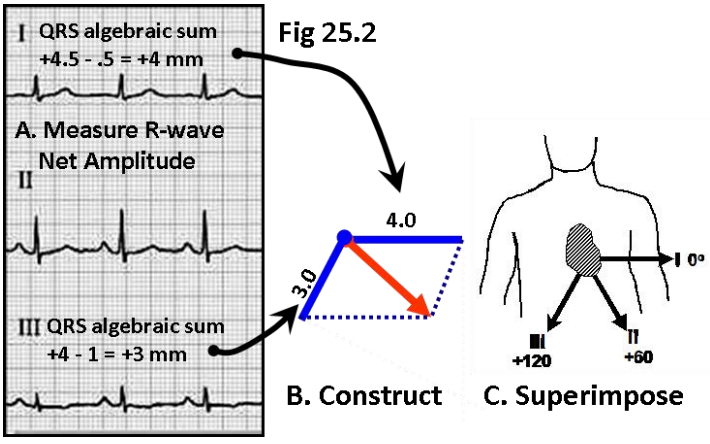
25.0 Estimating MEA from 12-Lead EKG TOC text return



1 mm = 0.1 mv @ 25 mm/sec → 1 mm = 0.04 s or 5 mm = 0.20 s



The above is a standard normal 12 lead EKG with calibration scales (know these). Note that @ 25 mm/sec HR (bpm) = 1500/(R-R interval in mm). To estimate the MEA, first locate the limb lead that has the most isoelectric QRS-complex (near zero average deflection or small ± deflections of near equal amounts). In this example lead aVL seems to fit. So the MEA must be most perpendicular to aVL and is thus near to either +60° or -120°. To determine which is correct, first locate the limb lead that is most perpendicular to the "isoelectric" QRS-complex; in this case it is lead II. Since the R-wave of lead II is predominantly + (upright), the MEA is most parallel to lead II and points toward the (+) pole of that lead. So, the MEA is normal at about 60°.



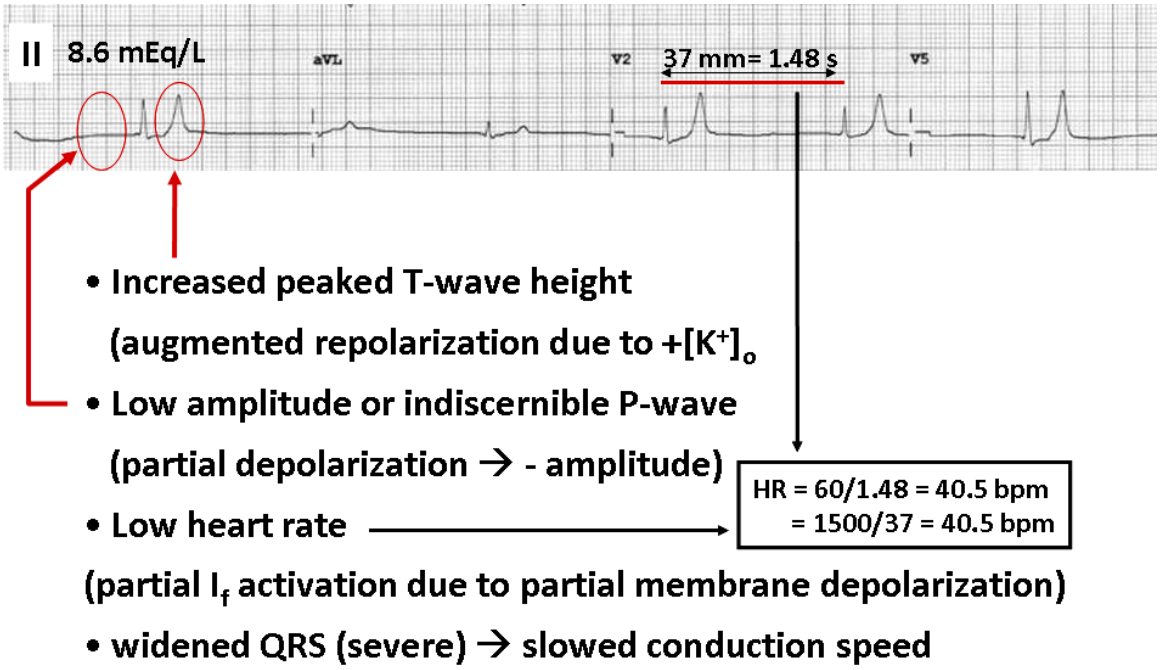
Another method is shown in Fig 25.2. The QRS algebraic sum is determined in mm for two frontal plane leads by measring the R-wave net amplitude [**A**]. These "lengths" are laid out along their respective axes with scaled lines as in [**B**]. Perpendiculars from each are dropped to their point of intersection (dotted lines in [**B**]. A line drawn from center to point is the MEA.

Some Factoids Regarding EKG QRS Complex Amplitude of Standard Limb Leads

- Normal amplitude range 0.5 to 2.0 mv
- If sum of leads I, II and III greater than 4 mv then considered HIGH VOLTAGE EKG
- High voltage due to Left or right ventricle hypertrophy (LVH or RVH) → +mass = greater amplitude
- Low voltage due to reduced muscle mass → prior MI that has destroyed some muscle mass
- Low voltage due to increased pericardial fluid → high conductivity → "shorts out" EKG transmission
- Low voltage due to excess air in the lung (emphysema) → low conductivity → diminishes currents

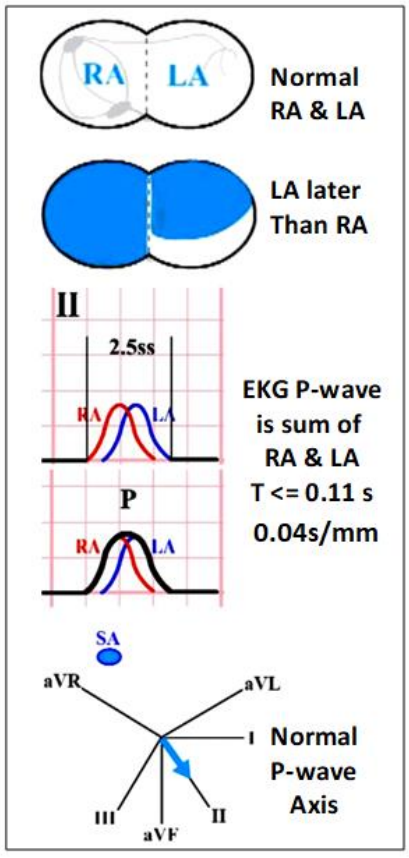
25.1 CLINICAL CORRELATION

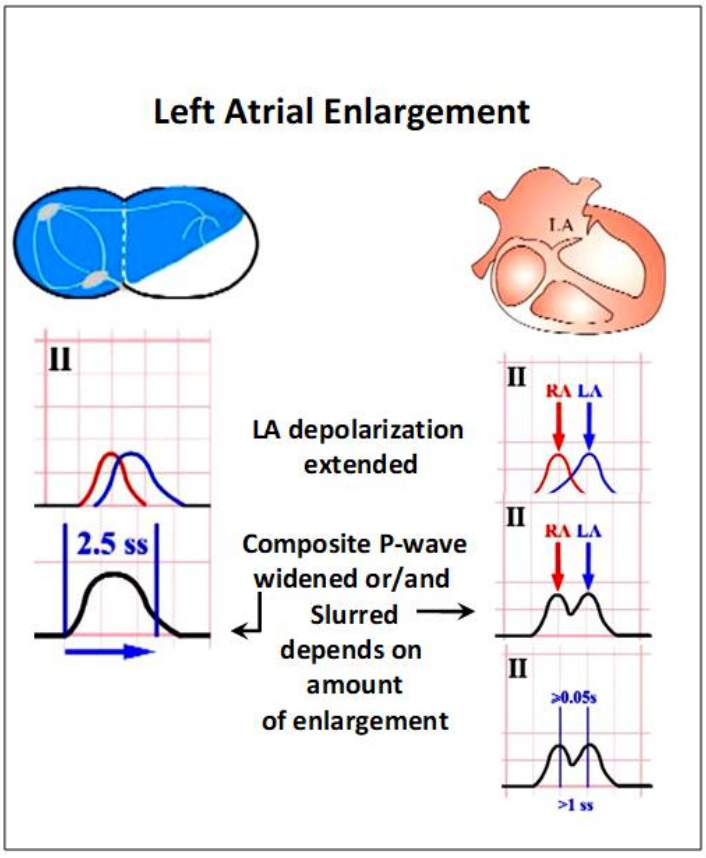
82 YR OLD MAN WITH HYPERKALEMIA DUE TO ACUTE RENAL FAILURE



25.2 CLINICAL CORRELATION

ATRIAL ENLARGEMENT AND P-WAVE CHANGES

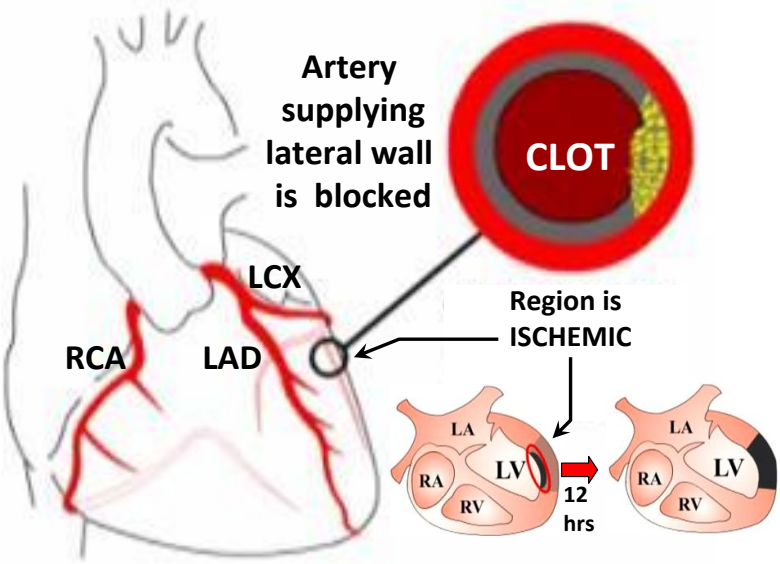


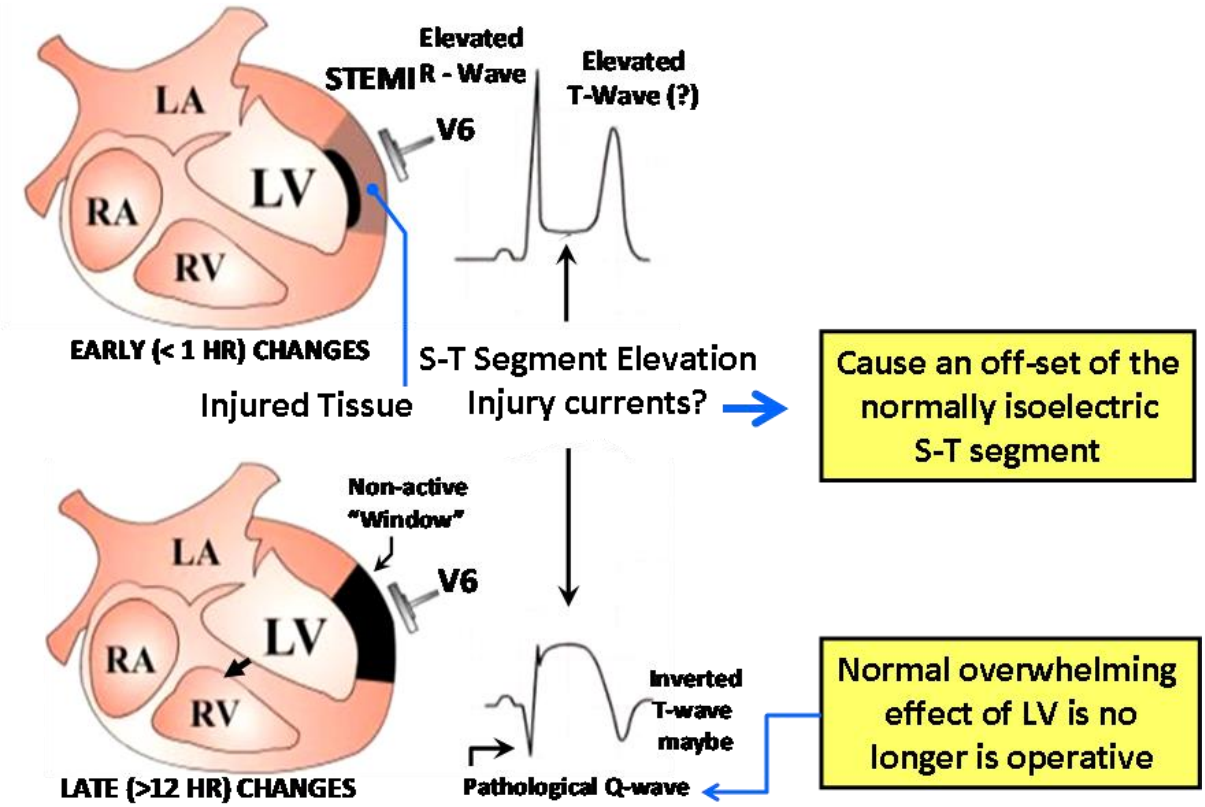


26.0 EKG Manifestations of Coronary Artery Blockage

26.1 ACUTE CORONARY SYNDROME (ACS – STEMI) TOC

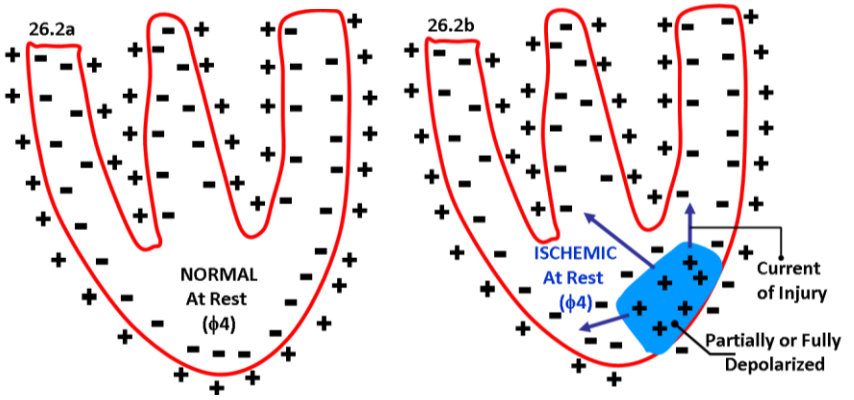
A coronary artery becomes blocked. If block is complete or nearly complete then myocardial region supplied by that artery becomes ischemic (inadequate blood flow to match demand) and tissue begins to become injured and then die (myocardial infarction). The pictorial representation below is for such a case in which the lateral wall tissue is compromised by the blockage and the EKG changes shown are those recorded by precordial lead V6. STEMI stands for **ST** Segment **E**levation **M**yocardial **I**nfarction.

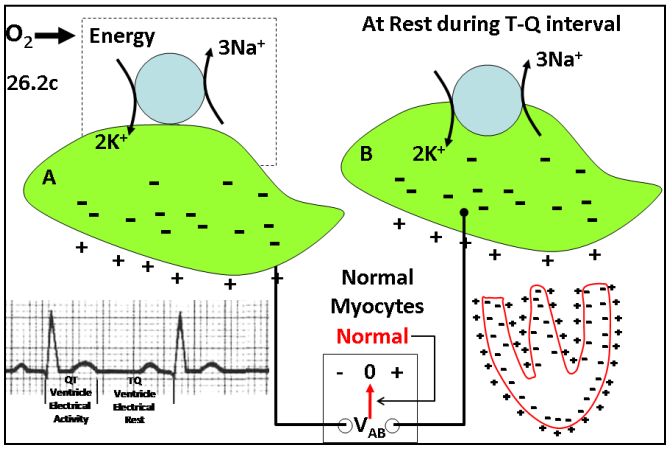


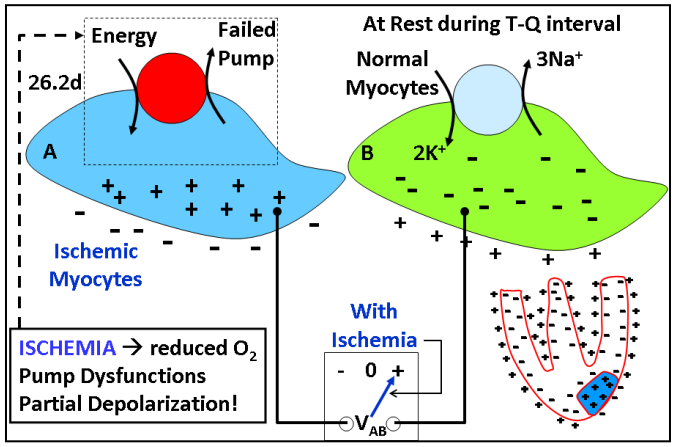


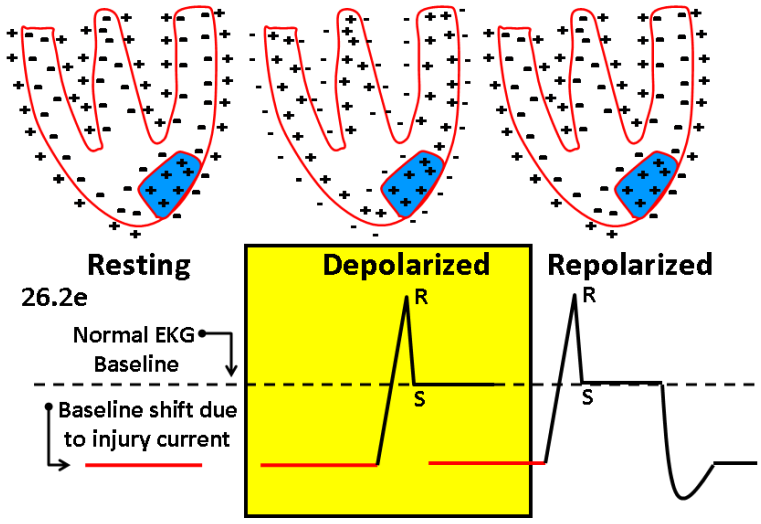
26.2 Myocardial Ischemia and Injury Current TOC Text Return

The normal resting charge distribution (**Fig 26.2a**) changes if a region of myocardial tissue becomes depolarized at rest due to ischemia (**Fig 26.2b**). The resultant voltage gradient from ischemic to normal tissue now has injury currents present at rest (**Fig 26.2b**). The dynamics are clarified by considering the role of the Na-K-ATPase pump to help maintain resting membrane potentials (**Fig 26.2c**). The pump needs energy that is supplied by the O_2 delivered to cell groups A and B. If normally functioning there is a zero-voltage gradient between A & B cells and no injury current is present. Reduced O_2 delivery (**Fig 26.2d**) causes the pump to fail so the normal 3 Na^+ out for 2 K^+ schematized in **Fig 26.2c** is stopped or reduced causing partial cell depolarization During intervals in which other cells are repolarized (T-Q interval) this ischemic region remains depolarized with associated injury currents. This process causes an apparent elevation of the EKG baseline (**Fig 26.2e**) during the ST segment causing ST-segment elevation (or depression).



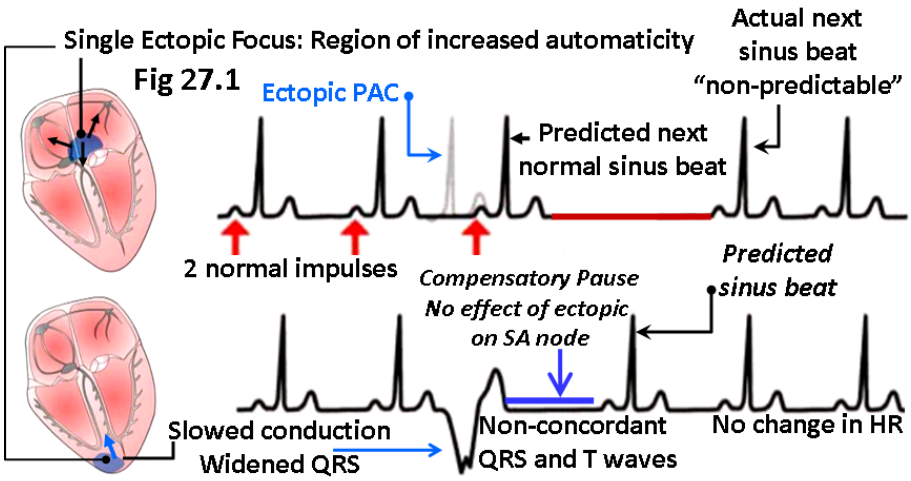




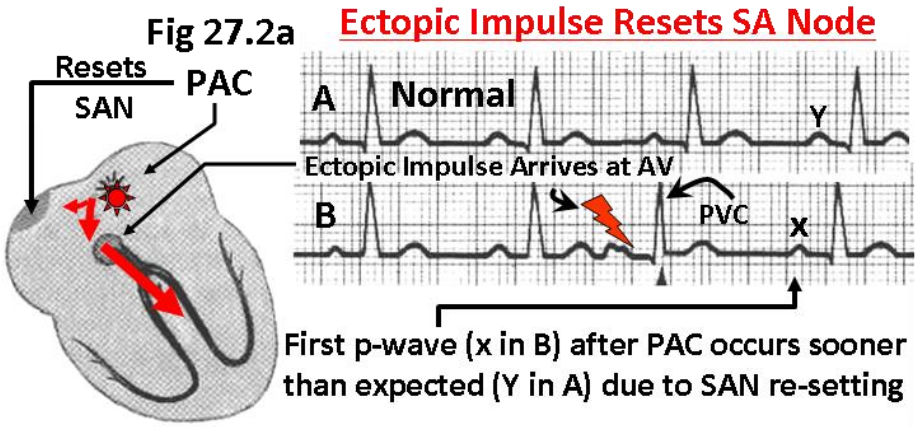


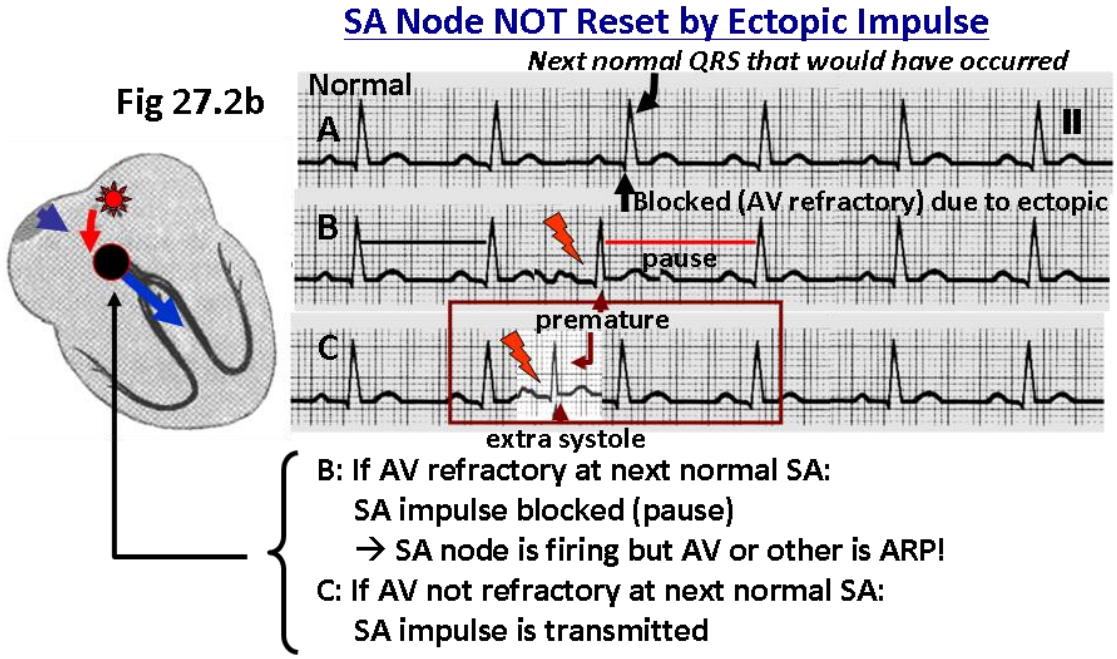
27.0 Abnormal Impulses and Impulse Conduction Features TOC

27.1 EKG manifestations of Atrial vs. Ventricular Premature Ectopic Triggers



27.2 Atrial Ectopic Effect: Depends on Timing and if the SAN is Reset or Not





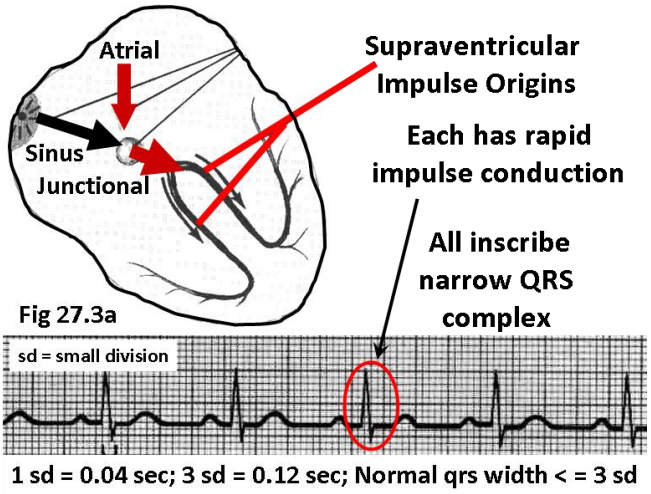
27.3 Supraventricular Arrhythmias TOC

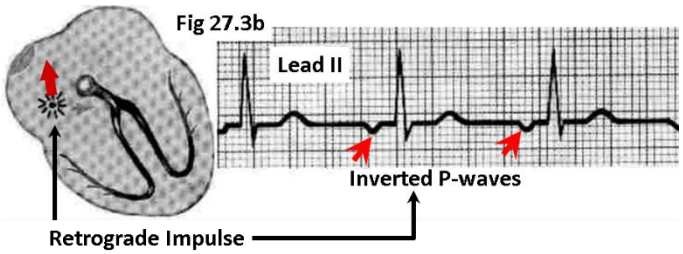
Arrhythmias reflect abnormalities of impulse initiation or conduction that impact rate or rhythm. They can be classified by type or cardiac structure in which it starts.

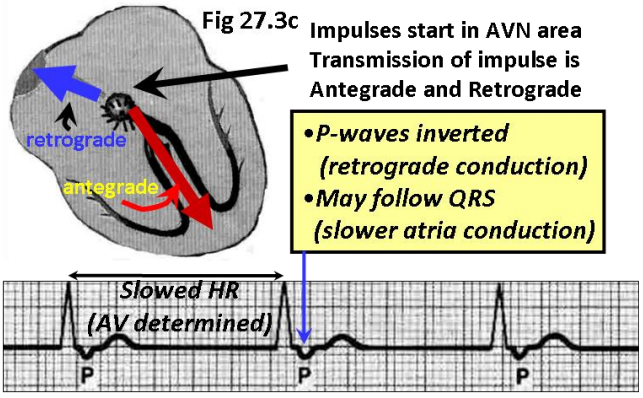
Tachyarrhythmia: Arrhythmias with HR >100 bpm

Bradyarrhythmia: Arrhythmias with HR <60 bpm.

Supraventricular arrhythmias start in or above the AV node. EKG has near normal QRS duration since impulse conducts rapidly through His-Purkinje system (**Fig 27.3a**). SA arrhythmias are common in children and young but in elderly sinus irregularities, bradycardia, or sinus pauses may indicate degenerative SA changes. If the impulse originates in the atria EKG effects depend on its location. **Fig 27.3b** shows an atrial retrograde ectopic pacemaker causing inverted p-waves. **Fig 27.3c** shows a junctional rhythm, i.e. ectopic impulses that start in or near the AV node. Impulse transmissions from the node are antegrade (normal) and also retrograde back into the atria. Junctional rhythms usually have *inverted p-waves* that may *follow* the QRS complex as shown or may occur before the QRS or simultaneously with it but be unseen.

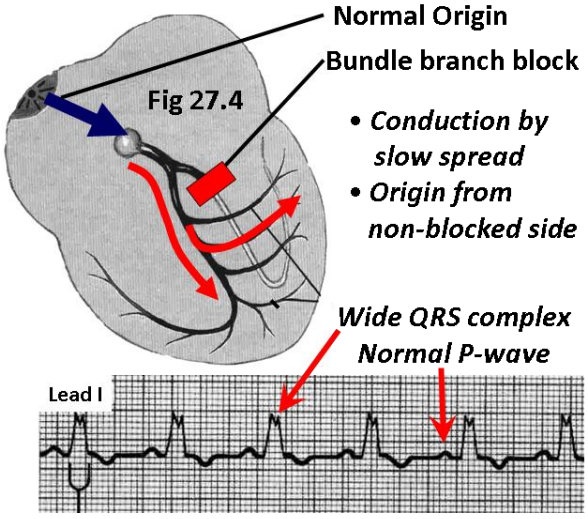






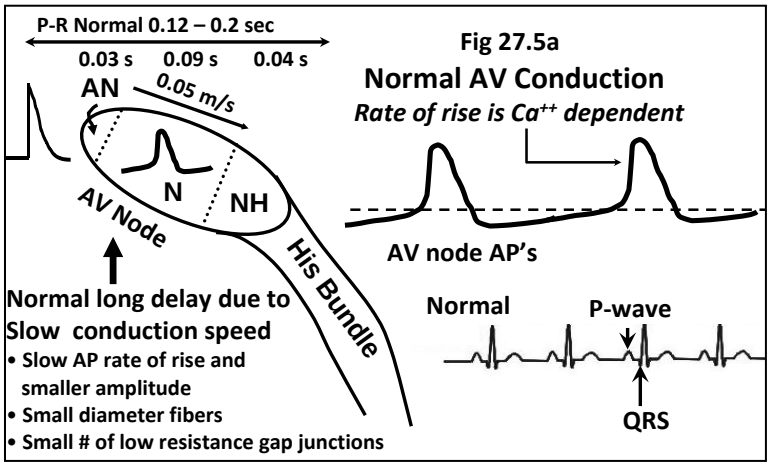
27.4 Bundle Branch Blocks (BBB)

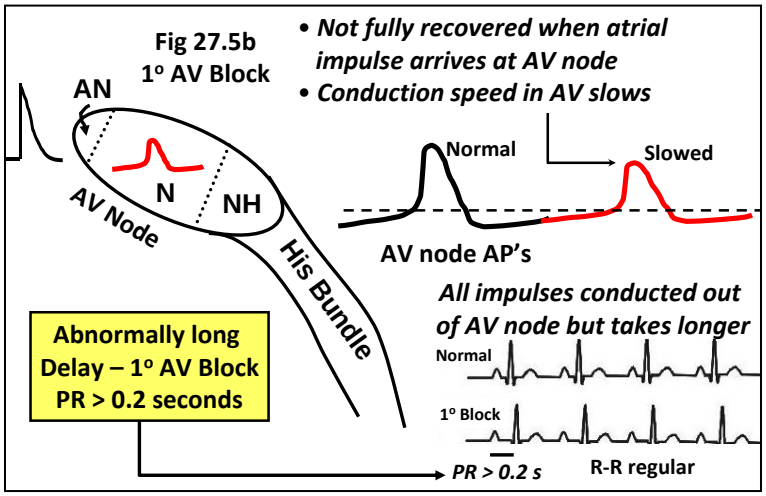
Functional or organic changes causing delay or block through left (**LBBB**) or right (**RBBB**) bundle branches. **LBBB:** Septum is activated from R-L not normal L-R. Delay in LV activation causes *QRS widening* as shown in **Fig 27.4**. Late LV base activation is associated with left axis deviation; late activation also accounts for notch in the R-wave. An inverted QRS deflection seen in V1-V4 is due to the late LV depolarization wave that is moving away from these chest leads. **RBBB:** RV is depolarized by impulses that cross over from LBB via myocardium. This delays RV depolarization causing *QRS widening, and* emergence of normally masked RV electrical activity in EKG. Right axis deviation may be due to late activation of RV base directed to the right.

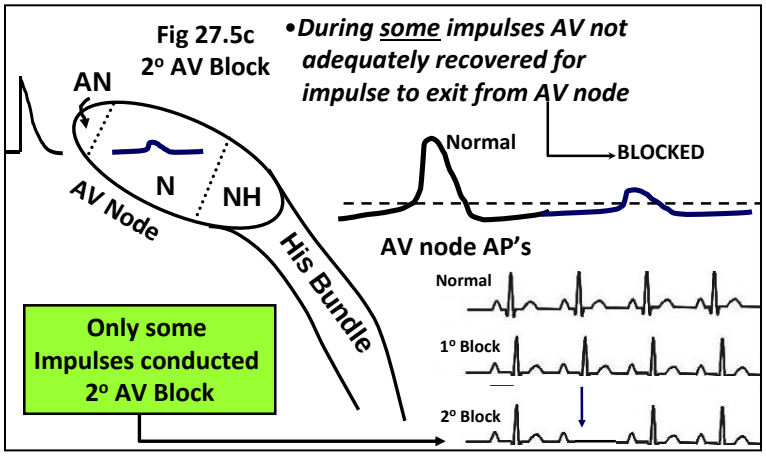


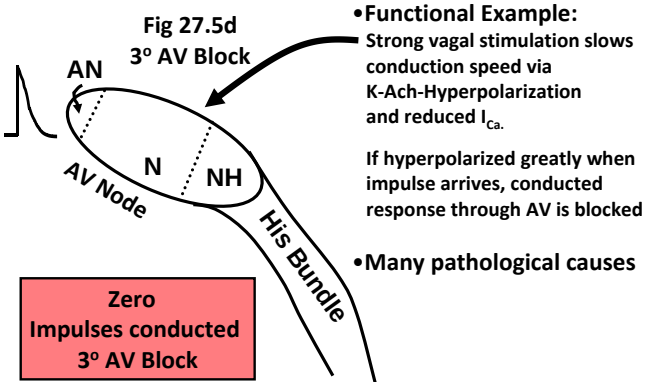
27.5 AV Blocks: Features and Examples TOC

The normal PR interval is 0.12-0.20 sec. AV conduction block is classified as 1st, 2nd and 3rd degree as summarized in **Fig 27.5a-d**. Functionally, *any AV process that inhibits calcium channel opening can cause AV block.* Although I_{CA} and I_f both affect depolarization, it is $I_{CA\text{-}L}$ that is the main determinant of the AP upstroke. Restricting I_{CA} by any means causes a slower and smaller AP upstroke causing reduced conduction speed in the node. AV block also occurs if a normal SAN AP arrives at the AV node when the node is refractory. This can happen if there were a prior ectopic impulse that rendered it refractory. As noted the AV blocks are 1st degree, 2nd degree or 3rd degree. These correspond respectively to 1) an abnormally long delay (long PR interval) 2) some impulses not passing through the AVN and 3) no impulses passing through the AVN. **Fig 27.5d** is indicating a 3rd degree block and also suggests some ways in which this might occur. For example, strong vagal stimulation could cause a block by hyperpolarizing the AVN membrane and reducing the depolarizing calcium current. This could simply slow conduction or if hyperpolarization were great enough cause a complete block. There are many pathological based reasons that might account for a block including reduced blood flow to the region (ischemia).

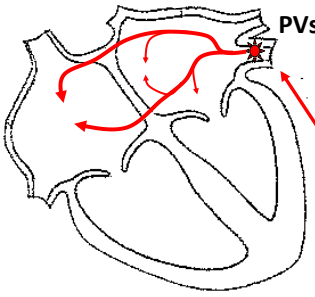








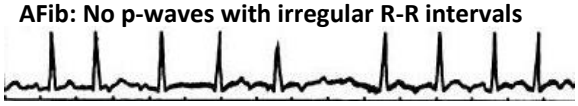
28.0 Atrial Fibrillation and Atrial Flutter (Reentry Arrhythmias) TOC



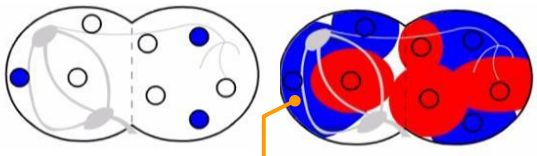
- *Ostia embryonic origins similar to SA and AV node tissue*
- *Aging or disease may "re-ignite" spontaneous depolarizations*

- + Automaticity
- DAD/EAD

AFib: No p-waves with irregular R-R intervals



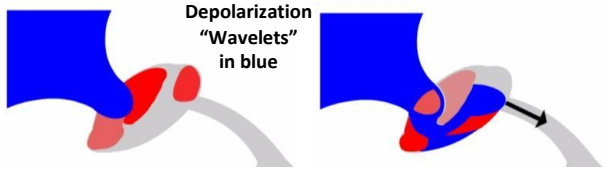
- Single or multiple atrial ectopic foci firing randomly
- Variable and erratic transmission through the AV node
- No organized atrial contraction
- Depolarization rates ~300-500 (400-700) per/min
- Heart disease (rheumatic, ischemic, hypertensive, CHF)



Multiple atrial sites that are randomly depolarizing

Depolarizations are local as blocked by refractory

Depolarization "Wavelets" in blue



Atrial wavelet arriving at AV node That is refractory to conduction

Atrial wavelet arriving at AV node That is permissive to conduction

Resulting EKG is "irregularly" irregular

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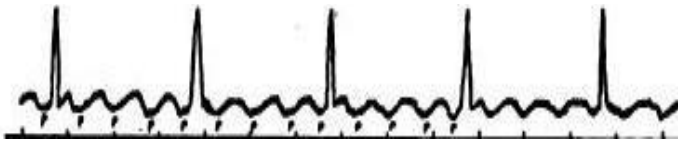
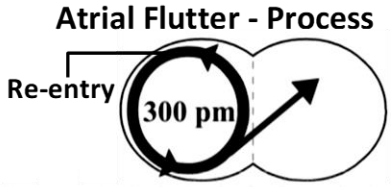
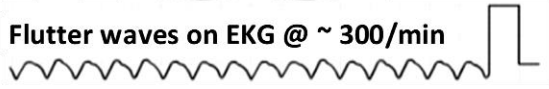
28.1 Atrial Flutter

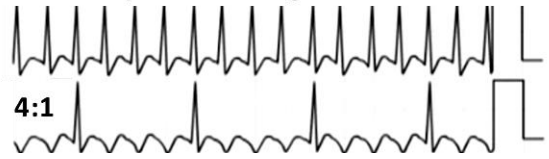


- Atrial ectopic focus firing repetitively with variable transmission through the AV node.
- Atrial depolarization/contraction coordinated
- Typical rates ~200-300 bpm
- Here – AV node responds to ¼ impulses





If all waves passed through A-V – no time to fill!



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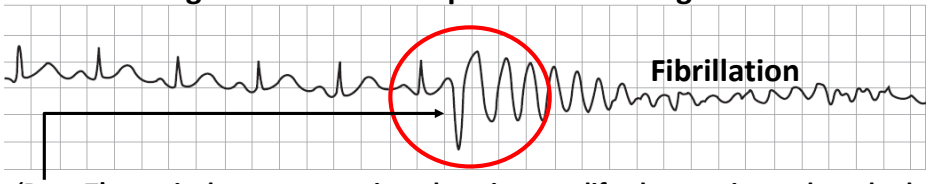
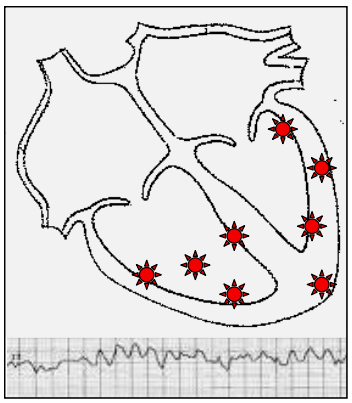
28.2 Ventricular Fibrillation TOC

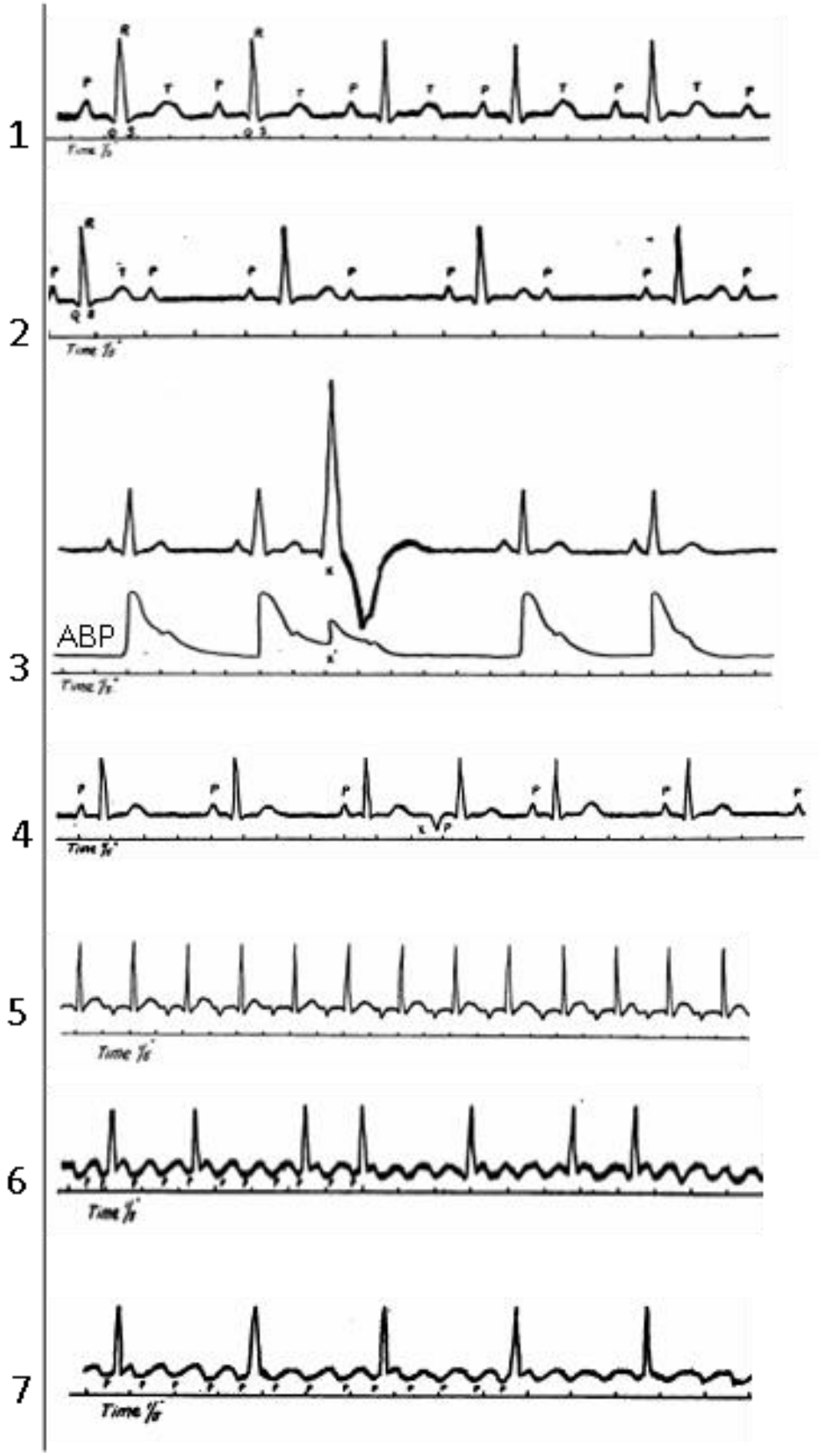
vFib: Heart depolarizes in the midst of its repolarization
e.g. Chest trauma impact at the wrong time!



An 'R-on-T' ventricular premature impulse triggers a life-threatening tachyarrhythmia



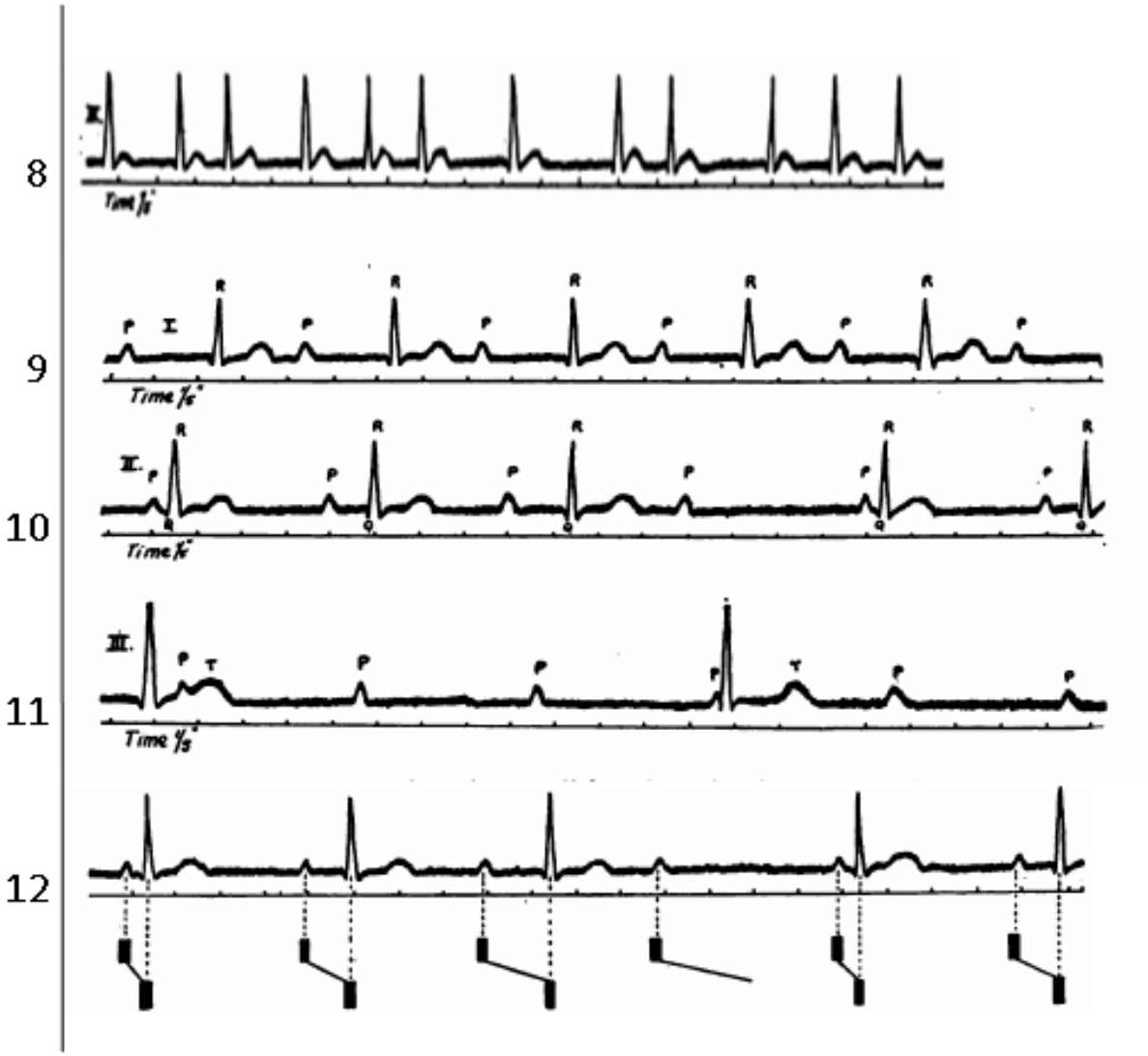
28.3 Describe the Feature (time marks 0.2 sec - see appendix A1 for descriptions) TOC



#1 is a

NORMAL pattern

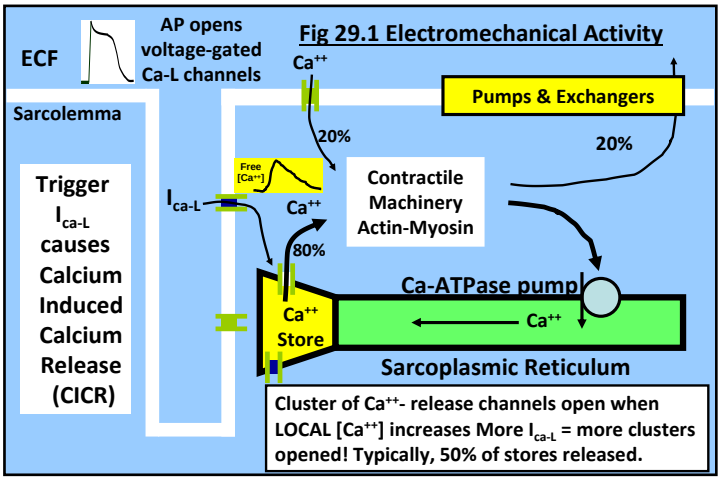
28.3 Describe Feature (see appendix A1 for descriptions) TOC (continued)



29.0 Cardiac Muscle Electromechanical Activity TOC

29.1 Contraction Initiation due to Ca^{++} entry during the AP plateau phase

1. Propagated electrical activity, initiated at the SA node is transmitted to the ventricles via specialized electrical pathways. The arriving AP causes depolarization of cardiac contractile myocytes (Fig 29.1).
2. The AP causes sarcoplasmic [Ca^{+}] to rise in about 10 msec. This is sufficient to activate some of the available cross bridges.
3. Free cytosolic [Ca^{++}] increase with more; (1) sympathetic activation, (2) circulating adrenaline, and (3) inotropic drugs. More free [Ca^{++}] increases contraction force and its rate of development.
4. Ca^{++} comes from 2 main sources; (1) **SR stores** (internal, 80%) and (2) **Ca^{++} Current** during Φ_2 (external 20%). SR membrane has Ca-release channels that open if local cytoplasmic [Ca^{++}] increases.
5. SR Ca^{++} release triggered by Ca^{++} entry.
6. Trigger Ca^{++} raises $[Ca^{++}]_i$ causing opening of Ca-release channels (calcium-induced calcium release). Ca^{++} diffuses rapidly to nearby (<1μm) sarcomeres causing contraction.

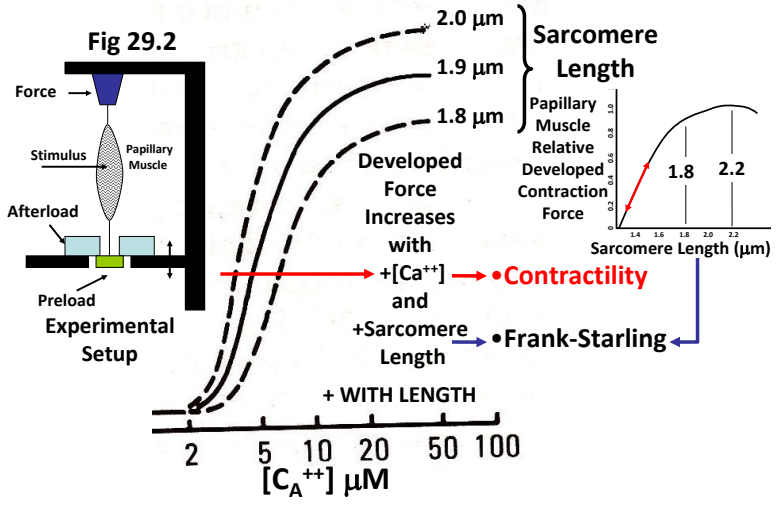


29.2 Contraction Termination via reuptake and expulsion of calcium

Elevated sarcoplasm [Ca^{++}] increases Ca^{++} pump and ion transporter activity that reduces cytosolic [Ca^{++}] via Ca^{++} re-uptake by the SR (80%) and via Ca^{++} expulsion by sarcolemmal transporters (20%). SR re-uptake via the Ca-ATPase pump is controlled by the re-uptake inhibitory protein phospholamban. Reducing phospholamban's inhibition enhances Ca^{++} re-uptake and facilitates relaxation. Time is needed to restore SR [Ca^{++}] to pre-systolic levels, so early excitation (ectopic) causes reduced contraction force.

29.3 Contraction force depends on Preload, Contractility and Afterload

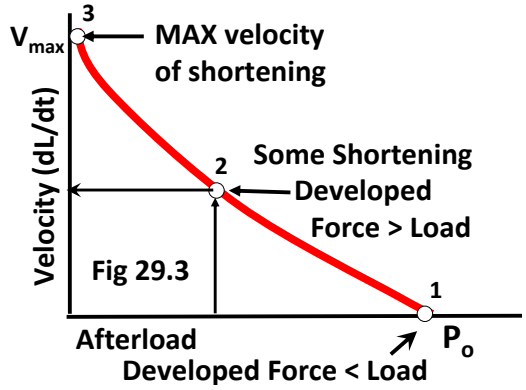
Preload is the amount of stretch on muscle as it starts to contract. For intact hearts, preload is the ventricular volume at the instant the ventricle starts to contract called end diastolic volume (EDV). As shown in Fig 29.2 force developed by contraction depends directly on preload. This relationship is the basis of the Frank-Starling "Law of the Heart".

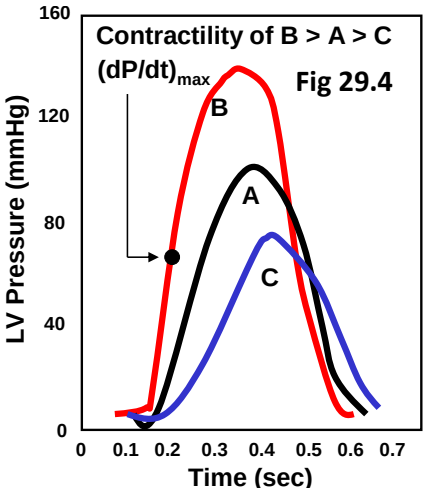


Contractility describes myocardial force-generating and length shortening potential at a given preload. *Inotropic state* is also used as a term for contractility. It depends on factors that affect a myocyte's contractile machinery. **Ca^{++}** is a major factor as shown in Fig 29.2. Changes in contractility may be positive or negative. A +inotropic effect denotes increased force and rate, a +lusitropic effect describes more rapid

relaxation. Contractility depends on the stored Ca^{++} pool at the start of systole. This Ca^{++} pool in turn depends on the amount of Ca^{++} influx and release during Φ_2 and on the amount of Ca^{++} expelled during the previous diastole. So, the intracellular calcium pool depends on (1) the amount of I_{Ca}, (2) relative Ca^{++} influx (systole) and efflux (diastole) and (3) extracellular $[Ca^{++}]$.

Afterload is the load that contracting muscle works against. All else the same, an increase in afterload causes a decrease in shortening rate (V = dL/dt) as shown in **Fig 29.3** for a fixed preload. If preload were to increase, points 1 and 2 would shift to the right but there would be very little change in the Vmax point. V_{max} is the maximum shortening velocity at zero load and is increased if contractility increases.



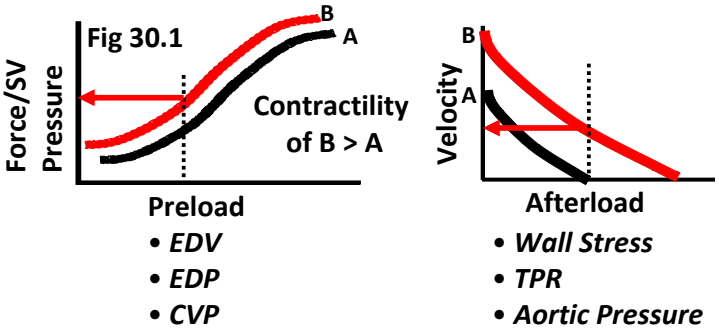


Ventricular Pressure and Contractility

Sympathetic stimulation of myocardium increases the calcium pool and thus increases contractility. Changes in contractility caused by any mechanism affect the ventricular pressure. At any preload, the maximum of dP/dt = $(dp/dt)_{max}$ is an index of cardiac muscle V_{max} (**Fig 29.4**) and is a clinically useful indicator of cardiac contractility and systolic pump function . The $(dp/dt)_{max}$ point usually is located on the ascending limb of the pressure pulse contour about midway between the base and the peak pressure.

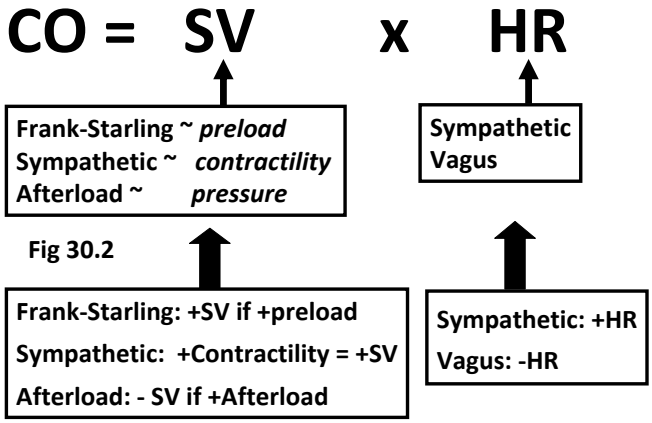
30.0 Cardiac Pump Function - Intact Heart Features TOC

30.1 Overview: Stroke volume depends on the force and rate of cardiac muscle contraction which in turn depends on preload, afterload and contractility as discussed above and summarized in **Fig 30.1**. Increased **contractility** increases muscle force and shortening velocity at all levels of preload and afterload. Increased **preload** also increases contraction force but works through a different mechanism (Frank-Starling). End diastolic volume (**EDV**) is the best index of preload since EDV is ventricle volume at the onset of ventricular systole and is the best index of myocardial fiber stretch. End diastolic pressure (**EDP**) and central venous pressure (**CVP**) are less good estimators but are easier to measure and are thus used as indices of ventricle filling. The problem with EDP as an index is that it depends on ventricular compliance. The best index of **afterload** is the ventricle wall stress that needs to be overcome by cardiac muscle to shorten. Although TPR is the next best indicator, the clinical parameter most often used is aortic pressure. In the figure above note that at any preload, curve B has a larger SV than for curve A, and that increased afterload decreases shortening velocity. Decreased SV (due to decreased preload) may be offset by increased contractility.



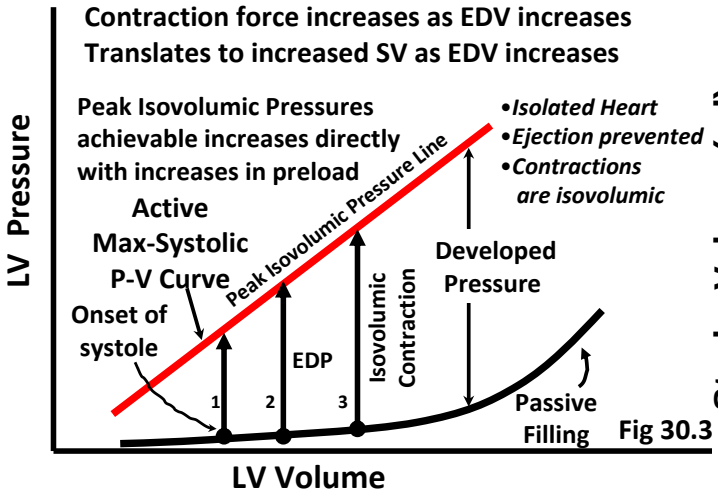
30.2 Major Determinants of Pump Function

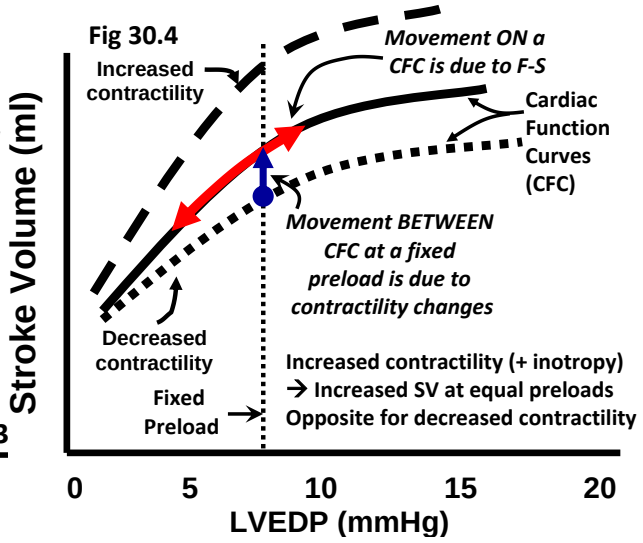
The major physiological determinants of cardiac pump function are summarized in Fig 30.2. These are related to factors that determine cardiac output. Stroke volume (SV) depends on preload, afterload and on contractility. Contractility in turn strongly depends on sympathetic excitation of myocardium. The other component is heart rate (HR), which depends strongly on the relative balance between sympathetic and vagus nerve activation of the SA node. Each factor is discussed starting with the Frank-Starling "Law of the Heart" in Fig 30.3.



30.3 Frank-Starling "Law of the Heart" TOC

If the ascending aorta is clamped and the LV stimulated to contract at increasing levels of **EDV**, developed *peak isovolumic pressure* (**PIP**) increases nearly linearly as shown in Fig 30.3. The PIP increase is due to the *Frank-Starling (F-S) mechanism* → developed force increases as muscle fibers are stretched. If outflow from the LV is permitted, an increase in **EDV** causes increased **SV** as shown in Fig 30.4 in which the ***Cardiac Function Curve*** (CFC) refers to the relationship between SV and either EDV or EDP.





Frank-Starling (F-S) Mechanisms

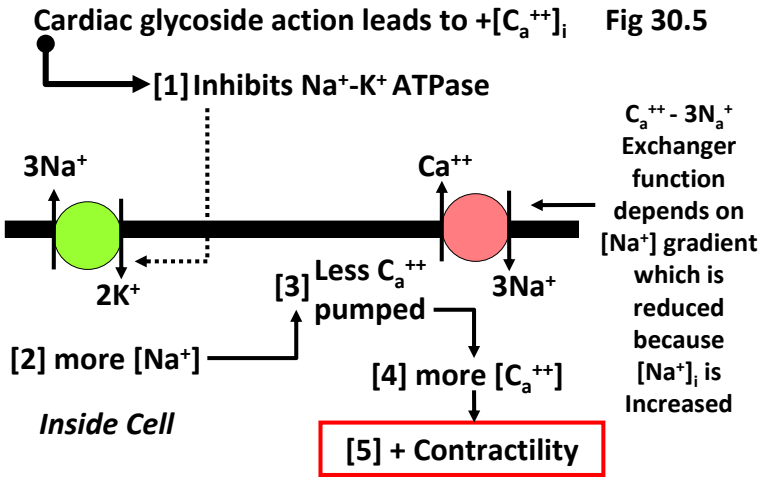
Two mechanisms likely explain the F-S property. With stretching, myocardial sarcomere overlap becomes more efficient resulting in greater contraction force. Also with stretching, some additional Ca^{++} channels may open or those open, open wider, causing greater Ca^{++} availability or increased sensitivity to Ca^{++}. The latter seems to mimic increased contractility, but don't confuse increased SV due to F-S with increased SV caused by increased myocardial contractility. The difference is shown in Fig 30.4. The near straight-line portion of the curves (between ~2-8 mmHg) corresponds to the PIP line in Fig 30.3.

Beat-by-Beat Balance of Left and Right Outputs

Increased afterload or decreased contractility can cause an initial increase in preload due to reduced SV. As described, F-S tends to normalize SV. Such F-S compensation also occurs if there is an imbalance in left and right ventricle outputs. For example, a sudden increase in RV output would transiently increase LV preload by increasing its EDV. In turn, F-S would increase LV output. Thus F-S helps maintain a balance between left and right outputs on a beat-to-beat basis and accommodates transient differences in volume returning to the right and left heart as occurs with respiration, postural changes and other conditions.

30.4 Effects of Contractility on Cardiac Function Curve and Cardiac Output TOC

Contractility's effect on the **CFC** is shown in Fig 30.4. An increase in contractility increases the slope of the **PIP line** with a slight upward shift. The result is a greater SV. Decreased contractility has the opposite effect. Physiological contractility increases are mostly due to cardiac directed sympathetic activity. Drugs used to increase contractility are called ***positive inotropic agents***. Recall that changes in Ca^{++} entry and storage in ventricular myocytes cause physiological changes in contractility. These Ca^{++} changes may be due to sympathetic activity to the heart and/or changes in circulating catecholamine (epinephrine and norepinephrine). Drugs to increase pathologically depressed contractility often achieve this effect by acting to increase Ca^{++} availability to myocyte contractile machinery. Cardiac glycosides achieve this by increasing $[Ca^{++}]_i$ as shown in Fig 30.5.

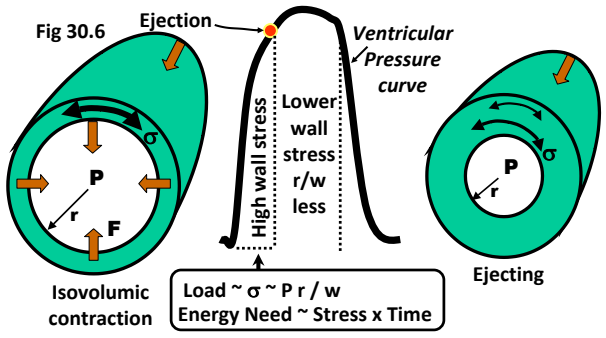


30.5 Afterload and Frank-Starling (F-S) Interaction TOC

The true ventricular afterload is proportional to wall stress (σ) within the myocardium during its contraction. This stress must be overcome for muscle fibers to shorten and eject blood from the ventricle. These aspects are discussed in the next section (30.6) In practice, afterload is taken as the arterial pressure against which the heart must contract; the greater the afterload, the greater the required ventricular force. Afterload effects stroke volume in a complex way. But it may be thought of in the following manner. Because ventricles must develop a greater pressure if afterload is increased, more of the contraction energy goes into raising pressure than into ejecting blood. This results in a reduced SV unless compensated. In a normal heart, the F-S mechanism can somewhat compensate because the increased EDV caused by the reduced SV moves the ventricle's operating point further along the F-S curve. So, SV may be maintained at or near its value before the increased afterload, but at the cost of greater EDV and EDP.

30.6 Pressure Load and Energy Considerations of Ventricular Myocardium TOC

Raising ventricular chamber pressure from its low value (EDP) prior to onset of systole to that needed to initiate ejection causes a large increase in wall stress (σ) experienced by the contracting myocardial muscle; $\sigma \sim Pr/w$. It is during isovolumic contraction, the interval when the ventricle contracts with all valves closed, that (r/w) is greatest because r is at its maximum and w is at its minimum as illustrated in Fig 30.6. So, average myocardial wall stress is greatest during this interval. This is true even though the maximum chamber pressure during isovolumic contraction is less than the maximum during ejection. The amount of internal energy that the myocardium needs depends on the wall stress and on the time over which this stress is acting.



30.7 Measures of Ventricular Energy Demand TOC

During ventricular systole, contracting myocardial fibers work against the wall stress (σ) which is the load that must be overcome to allow and then maintain ejection. Wall stress is thus the best index of ventricular *afterload*. But, in clinical practice afterload is generally viewed as the arterial blood pressure. Since pressure varies with time, one approach is to consider as a reasonable estimate of cardiac energy demand the ***area under the aortic pressure-time curve*** as in *Fig 30.7*. Increased area is an increased afterload. But, alone, does not consider changing myocardial wall thickness and radius that also occurs. So, another clinically relevant index, that does consider energy demand of wall stress, is the ***Tension-Time Integral*** (TTI). TTI is the time-integral of the time varying wall stress during the cardiac cycle. Myocardial O_2 consumption is directly proportional to TTI. Another clinical estimate of energy demand is the so called "***double-product***" defined as **MAP x HR**. This also correlates with myocardial O_2 consumption.

Fig 30.7 Estimates of Load Energy Demand

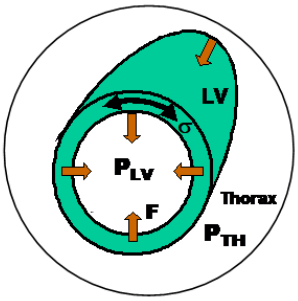
- **Area under the P – T curve**
- **Tension Time Integral (TTI)**
- **Double product (MAP X HR)**

30.8 Respiratory-Cardiovascular Interactions TOC

Intrathoracic Pressure → Effect 'Afterload' and Blood Pressure

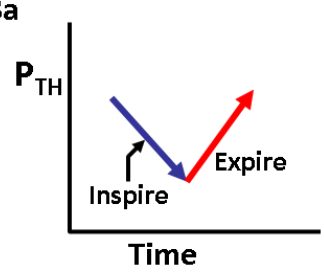
The heart is in the thoracic cavity so its 'surround' pressure is thoracic pressure (P_{TH}). LV contraction force must overcome the LV's transmural pressure ($P_{LV} - P_{TH}$) to achieve muscle shortening and ejection during systole (**Fig 30.8a**). P_{TH} varies from ~3.5 to 5.5 mmHg less than atmospheric. This small surround pressure normally has little effect on ejection.

Decrease in Intra-thoracic Pressure → + 'Afterload' Effect



$P_{TM} = P_{LV} - P_{TH}$

Fig 30.8a



But, during a deep inspiration against a closed glottis, P_{TH} can achieve larger sub-atmospheric values. The larger LV transmural pressure is an effective increase in afterload that can reduce SV. Normally, during inspiration there is a small decrease in systolic blood pressure (SBP) via processes summarized in **Fig 30.8b**. If the reduction is greater than 12 mmHg as illustrated in **Figs 30.8c/d** on the next page it is abnormal (pulsus paradoxus).

Summary of Some Inspiration-related Changes

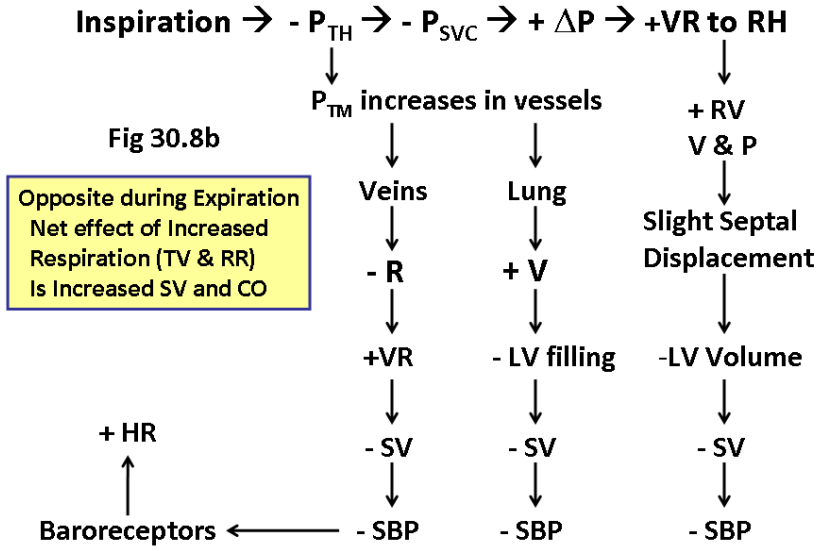
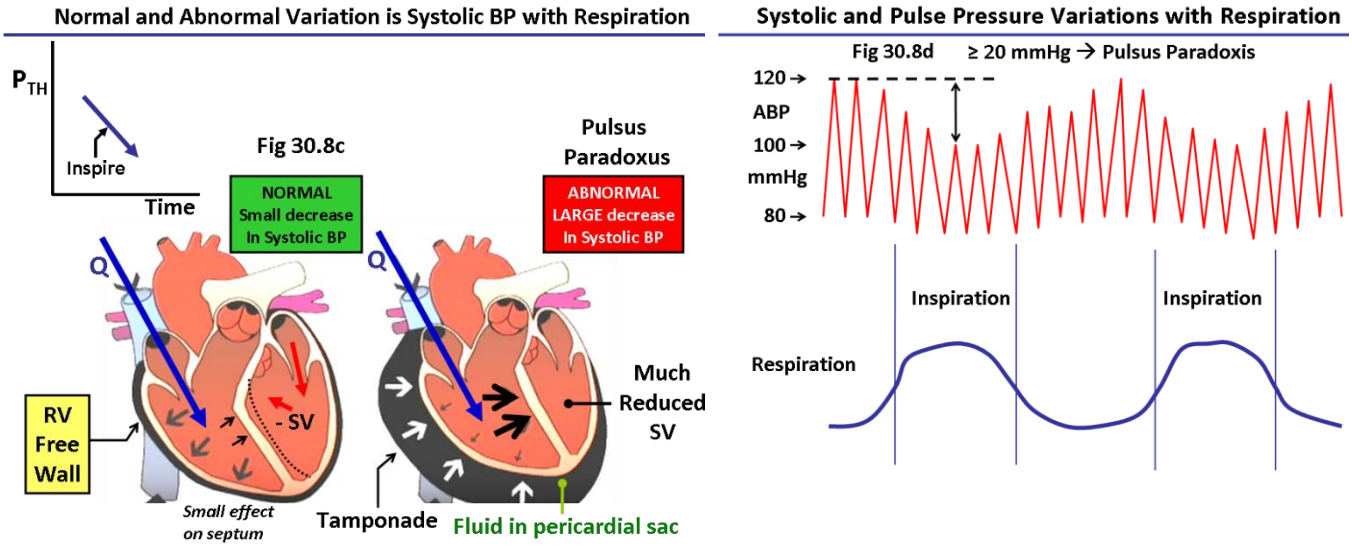


Fig 30.8b

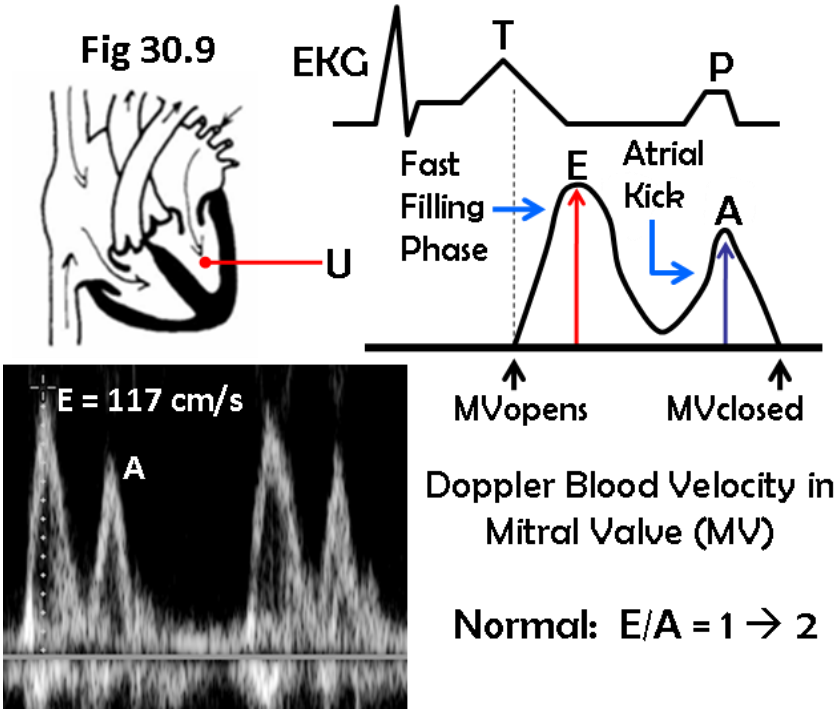
Opposite during Expiration
Net effect of Increased Respiration (TV & RR) Is Increased SV and CO

Fig 30.8c shows a slight septum displacement during normal inspiration that causes a slight decrease in LV volume that contributes to a slight systolic blood pressure (SBP) decrease. But if there is increased effective stiffness of the RV, as occurs with cardiac tamponade, or other conditions, this effect is amplified causing a greater SBP decrease (**Fig 30.8d**).



30.9 Clinical Correlation: LV Diastolic Filling via Ultrasound Blood Velocity TOC

Fig 30.9 depicts a Doppler ultrasound measurement of the blood velocity (U) passing through the mitral valve and shows the relationship between the measured velocity and the EKG timing. The E-wave corresponds to the rapid inflow when the mitral valve opens and the A-wave corresponds to the contraction of the atrium also called the atrial kick. Normally the ratio A/E would be greater than 1 and between 1 and 2. If the ratio is low, then it could be due to a stiff ventricle causing a low entering velocity (small A-wave) and/or a large A-wave as the atrial volume is forcefully ejected into a stiff, low compliance ventricle.

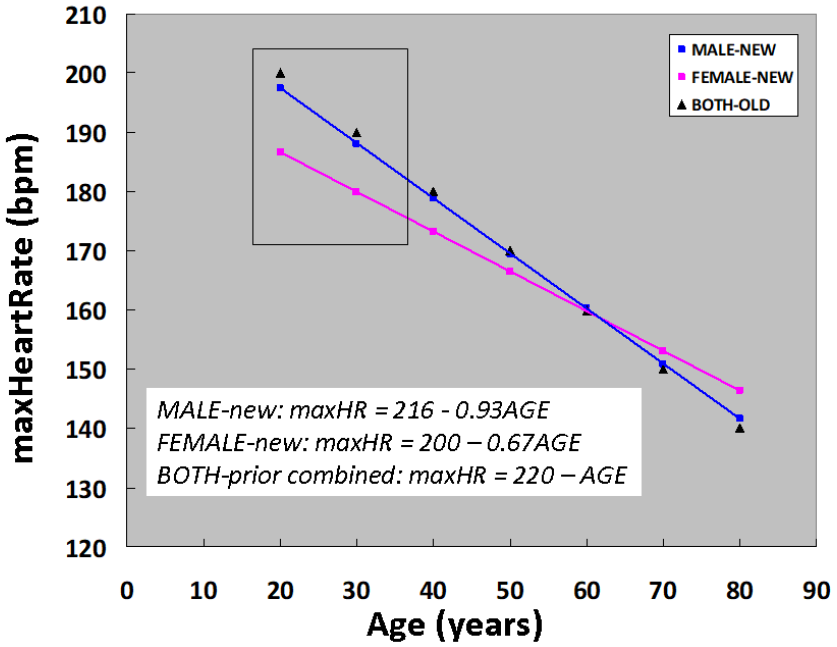


30.10 Clinical Correlation: Hemodynamic Changes - Age & Posture

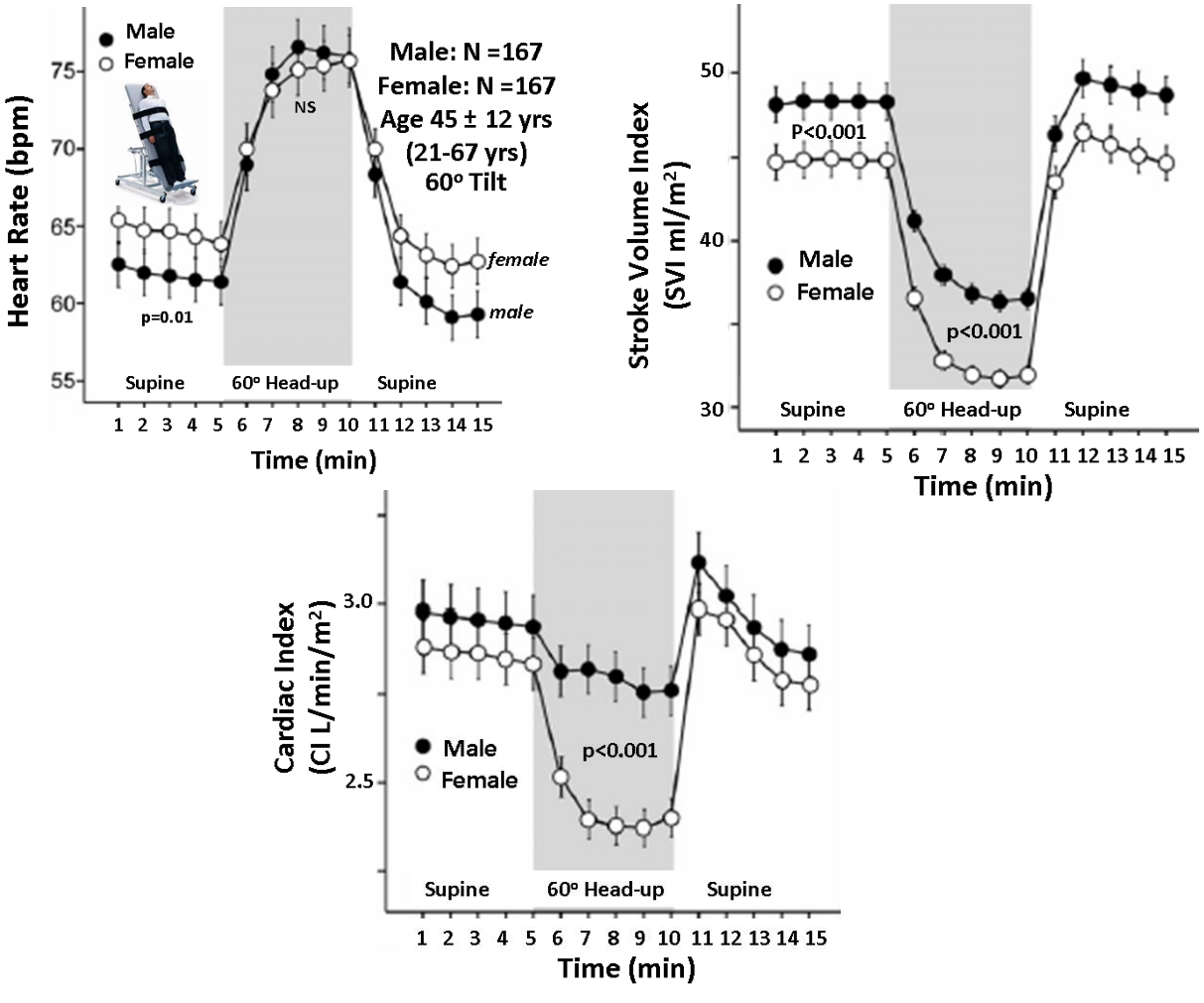
HR: Age & Gender

One rule of thumb is that maximum heart rate (HR) could be calculated via the equation 220-AGE. Some more recent data may indicate a gender difference in the maximum HR that is calculated based on two different equations as shown in **Fig 20.10a.** The gender difference in predicted HR becomes less with increasing age until about age 60-70. The difference is greatest for ages boxed in in the figure.

Fig 30.10a Maximum Theoretical Heart Rate



Posture Effects on HR SVI and CI (Data after Kangas_2016, J Am Heart Assoc)



31.0 The Cardiac Cycle TOC

The cardiac cycle (Fig 31.1 & 31.2) is the series of mechanical, electrical and hemodynamic events that describe changes in chamber volumes, pressures and flow of heart pumping action during each heartbeat.

31.1 Overview (described below for the Left Ventricle)

Filling: LV is relaxed & LVP is low, Mitral valve is open and aortic valve is closed.

(1) Rapid filling occurs; increased pressure with filling slows filling (diastasis).

(2) atrial contraction (atrial systole) expels volume into ventricles **"atrial kick"**

(3) *Ventricular Systole* starts with the initial contraction. LVP increases and the mitral valve closes. With all valves closed the chamber volume is constant so ***isovolumic contraction***.

(4) *Ejection* starts when LV pressure exceeds aortic pressure and aortic valve opens.

(5) *Isovolumic relaxation* starts if LVP falls below aortic pressure. The aortic valve closes and the chamber is isovolumic. When LVP falls below LAP the mitral valve opens; filling starts

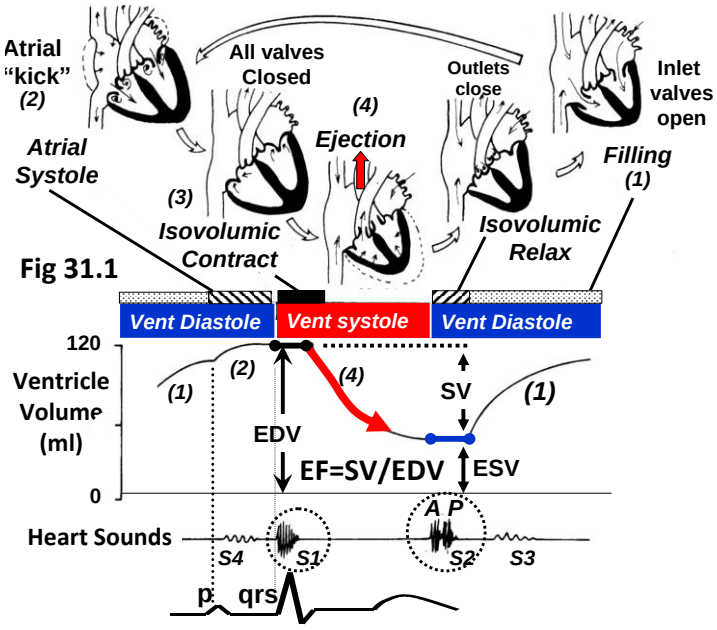


Fig 31.1

Volumes: Ventricular volume at start of systole (end of diastole) is end diastolic volume (**EDV**) that is reduced by the end of systole to end systolic volume (**ESV**). The difference between these volumes EDV-ESV = stroke volume (SV). The fraction of EDV ejected is called the ***ejection fraction*** **(EF = SV/EDV)** and is one of the best indicators of pump function.

31.2 The Wiggers Diagram is the classical depiction of the cardiac cycle TOC

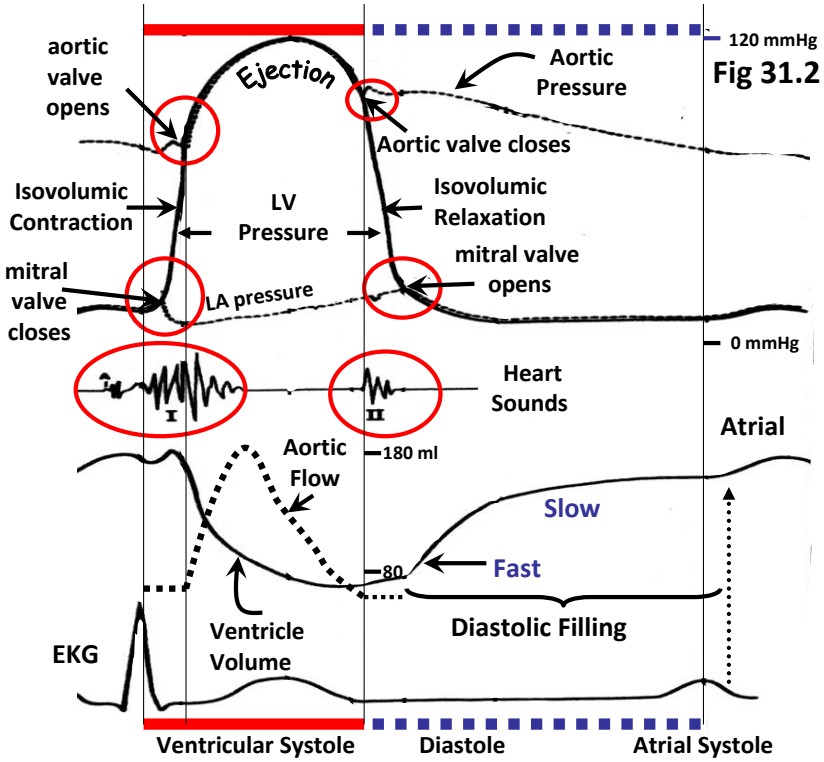
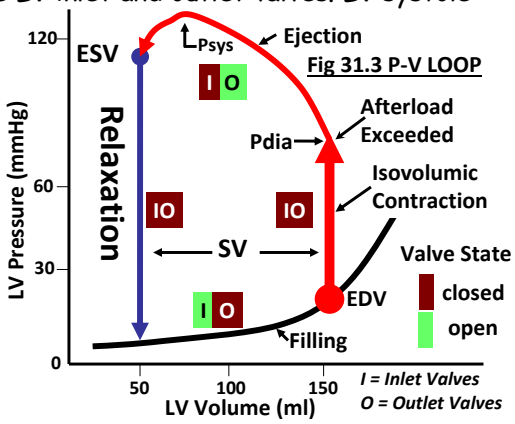


Fig 31.2

31.3 Pressure-Volume (P-V) Loop Representation of the Cardiac Cycle TOC

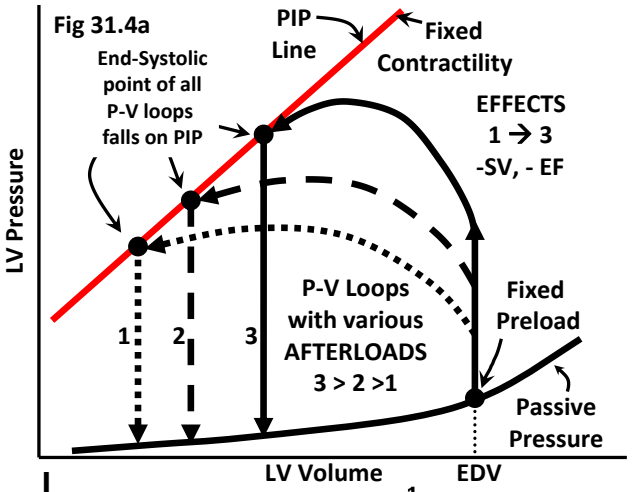
Basic Loop Properties: For the P-V loop in **Fig 31.3** I and O are LV inlet and outlet valves. LV systole starts at EDV causing LV pressure (LVP) to rise and close the mitral valve (MV). LV contracts and LVP increases at a constant chamber volume (isovolumic). When LVP exceeds, afterload (aortic pressure), aortic valve opens, ejection begins and LV volume decreases. After ejection, volume remaining is end systolic volume (ESV). As LV relaxes, LVP falls below aortic pressure and aortic valve closes and LVP falls at constant chamber volume. When LVP falls below atrial pressure, the MV opens, filling starts and the cycle repeats.

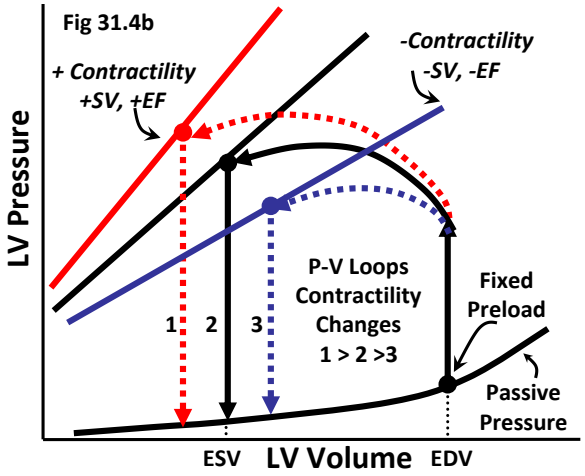


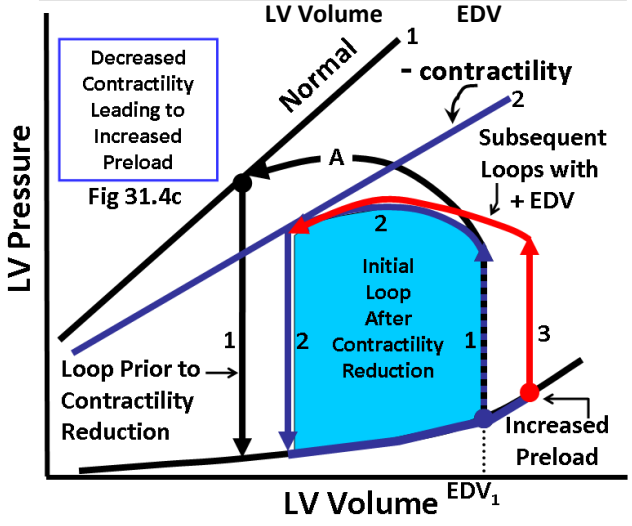
Stroke Work: Loop width is SV = EDV-ESV and work done by the heart per beat is *stroke work*, (**SW**). SW is the P-V loop area *approximated* as **SW = SV x MAP**.

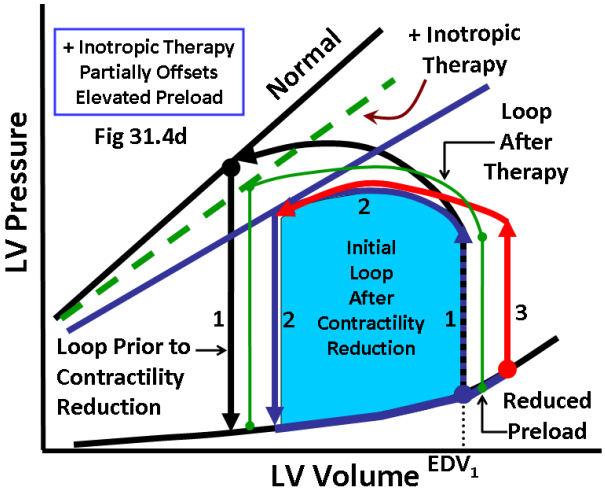
31.4 Pump Function Assessed Using P-V Loops

Experiments show that the *end systolic point of any P-V loop falls on or near the PIP line*. This allows PIP line placement and estimation of function with changes in *afterload*, *contractility* and *preload as* in 31.4a-d.





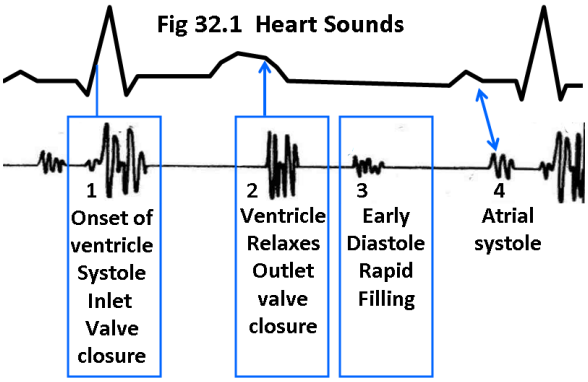


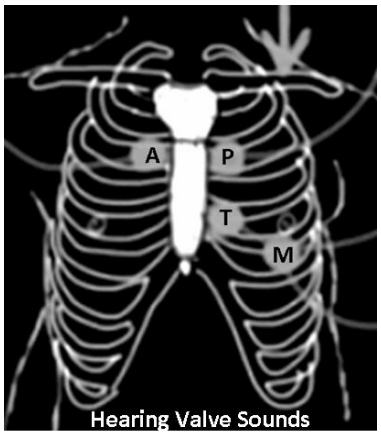


*Effects of afterload (AL) on p-v loop is in **31.4a** and of contractility (CT) is in **31.4b**. Increased (+) AL causes + myocardial energy demand and -SV and -EF. Increased CT increases loop width and SV and EF. Effects of + an - CT on PIP lines are shown in comparison to control (solid line). For +CT, the end systolic point occurs at a reduced ESV resulting in a +SV and +EF with the heart a more efficient pump; -CT effects SV & EF oppositely. Reduced CT (**31.4c**) causes preload (EDV) and ESV to increase. Initial 'compensation' is via F-S as SV is returned toward normal at the cost of the EDV and EDP elevation. **Fig 31.4d** shows CT reduction followed by inotropic support. The PIP line and PV loop now lie between the two prior conditions, slightly reducing elevated EDV and ESV.*

32.0 Sounds and Murmurs TOC

32.1 Heart sounds (Fig 32.1) arise from vibrations induced in blood, heart muscle and tissues. Vibrations are initiated by acceleration or deceleration of blood and tissues caused by mechanical actions of the contracting heart and blood and valve movements.





(1) S1, S2, & sometimes **S3 and S4** heard.
(2) S1 is due to onset of ventricular systole and inlet valve closure. Sound intensity greater if flow toward atria greater during contraction; e.g. if AV leaflets are initially further apart or contraction is stronger
(3) S2 is associated with the onset of diastole and the closing of the outlet valves. Sound intensity is greater if valves close more rapidly. This occurs in hypertension where elevated aortic pressure is present
(4) S3 is due to rapid filling during early diastole and associated with the transition from rapid to slowed filling (rapid deceleration causes vibrations); *Normal in young persons* **S4** is due to the atrial kick

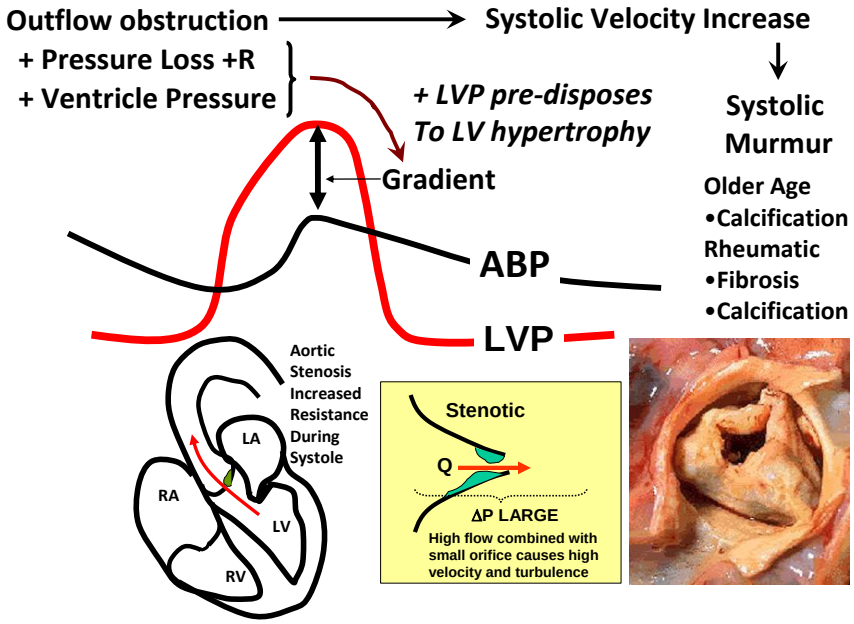
MURMURS
- **Sound produced by turbulent flow**
- **Occur if local critical N_R exceeded**
- **In/distal to organic/structural obstruction (stenosis - valve or vascular)**
- **High cardiac output (functional) e.g severe anemia, hyperthyroid, fever etc.**
- **High regional flow**

32.2 Murmurs are sounds due to disturbed or turbulent flow. Turbulent- sound producing processes are most often due to increased blood velocity through stenotic ***vascular*** or ***valvular*** areas. Murmurs can occur critical Reynolds's number is exceeded.

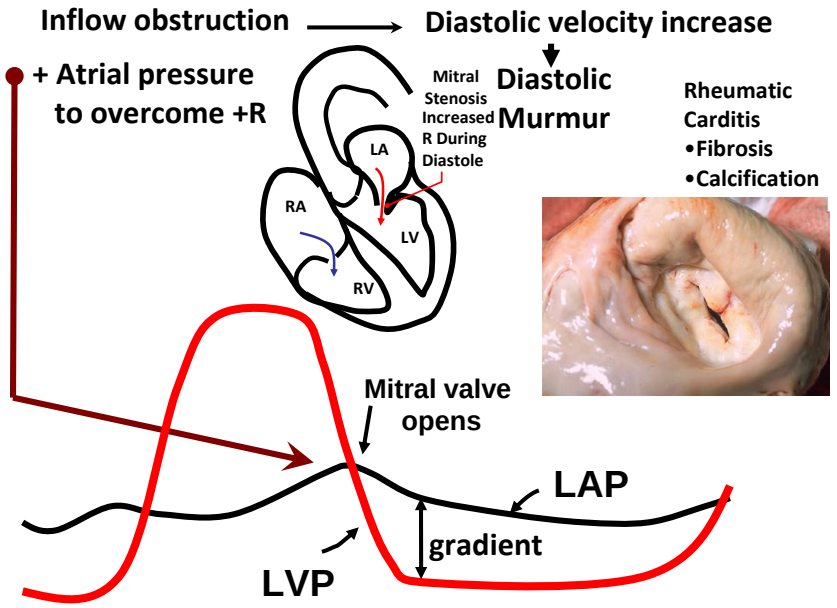
Mitral insufficiency (MR) - incompetent valve → backflow (**regurgitation**) → SYSTOLIC MURMUR → + systolic LAP
Mitral stenosis (MS) – reduced valve area → **+ diastolic velocity** → DIASTOLIC MURMUR → + diastolic LAP
Aortic insufficiency (AR) - incompetent valve - **regurgitation** during **diastole** – DIASTOLIC MURMUR
Aortic stenosis (AS) - obstruction to flow → reduced area →- increased **systolic** velocity → SYSTOLIC MURMUR→+LVP

32.3 Some Major Features Associated with Cardiac Valve Dysfunction TOC

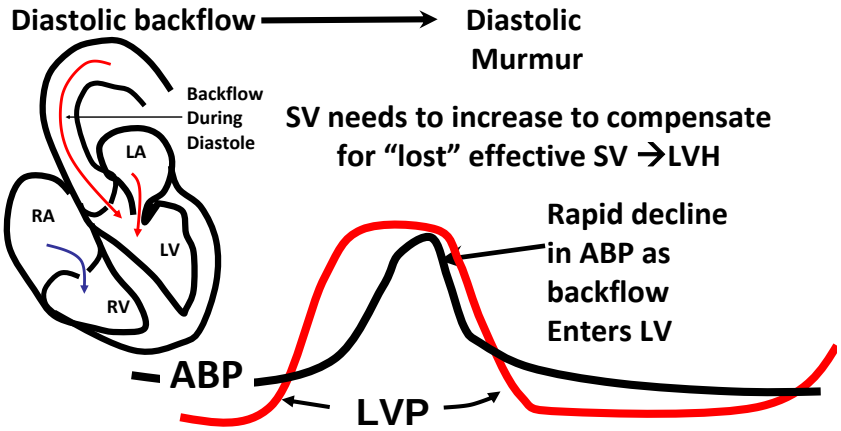
32.3a Aortic Stenosis



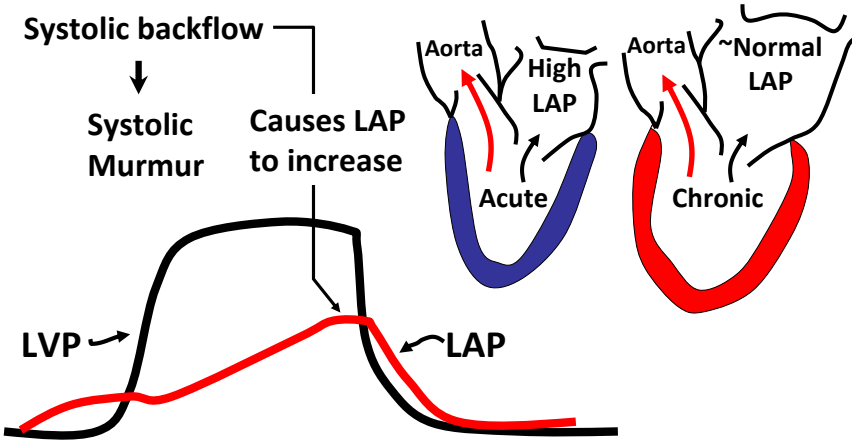
32.3b Mitral Stenosis



32.3c Aortic Insufficiency - Regurgitation



32.3d Mitral Insufficiency - Regurgitation



Note the difference in effect of mitral regurgitation (**Fig 32.3d**) depending on whether it occurs acutely or abruptly compared to when it develops over a considerable amount of time – the chronic version. In the chronic version that develops over time the left atrium adapts (dilates) to accommodate the additional volume injected during systole so that the left atria pressure (LAP) tends to normalize. However, in the acute case, for example a sudden rupture of the chordae tendinae, systolic volume entering the LA significantly elevates LAP since the LA has not yet adapted. The acute abnormal elevation of LAP is a precursor for pulmonary congestion and edema. Corresponding P-V loop is in **Fig 32.5a**.

In the case of mitral stenosis (**Fig 32.3b**) there is a rise in LAP during LV filling that causes increased pressure gradient between the LA and the LV. The elevated LAP is a potential cause of pulmonary edema due to its causing an increase in pulmonary capillary pressure. PV loops for mitral stenosis is shown in **Fig 32.5b**.

Additional examples of the hemodynamic and murmur effects of aortic stenosis and regurgitation and mitral stenosis and regurgitation and their corresponding pressure-volume loops are shown in section 32.4 and also importantly in **appendix 5** And should be reviewed!

32.4 Aortic Stenosis and Regurgitation: Clinical Correlation TOC

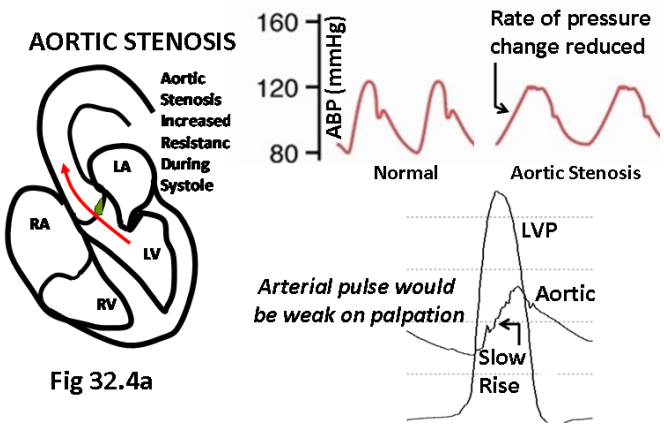


Fig 32.4a

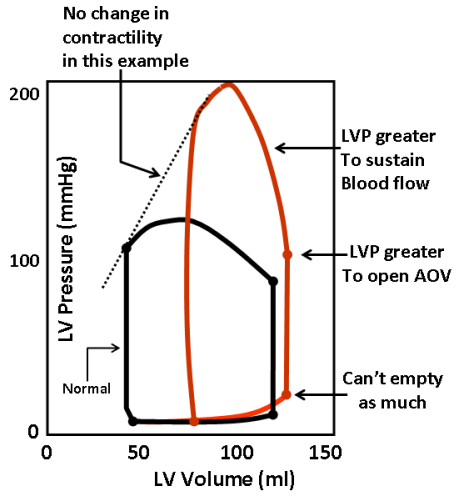
AORTIC STENOSIS

Increased outflow R causes increase in effective afterload

SV & EF are reduced

LV pressures are elevated and don't represent aortic pressure as they normally would

Fig 32.4b



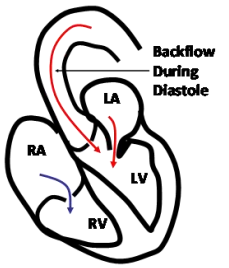


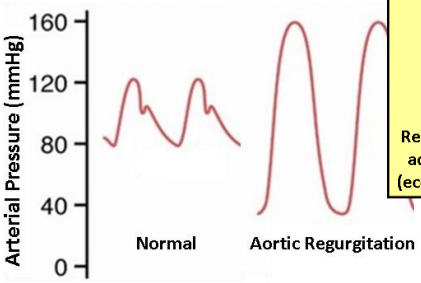
Fig 32.4c

AORTIC REGURGITATION

+ EDV → + SV → + Systolic Pressure

Low R pathway → - Diastolic Pressure

Combination → + Pulse Pressure

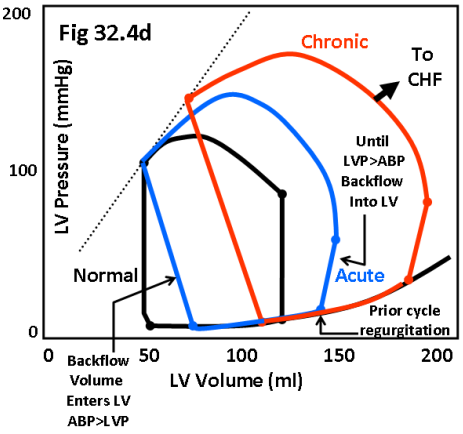


AORTIC REGURGITATION

Regurge during systole increases ESV and EDV

Relaxation not isovolumic NOR is There an "Isovolumic" contraction

Remodeling over time adds to EDV increase (eccentric hypertrophy)



32.5 Mitral Stenosis and Regurgitation: Clinical Correlation TOC

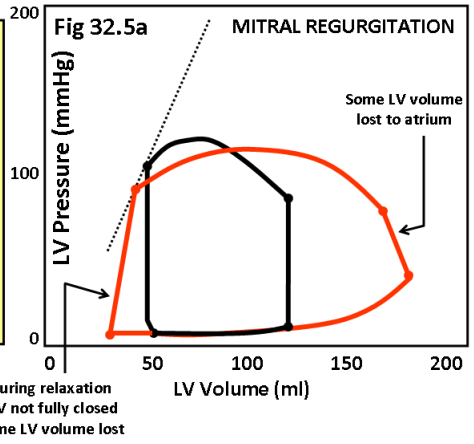
Systolic backflow into Left Atrium (LA)

Elevated LAP transmitted to LV during filling

EDV is increased

Adaptation over time to compensate for lost SV further increases EDV

No isovolumic contraction or relaxation



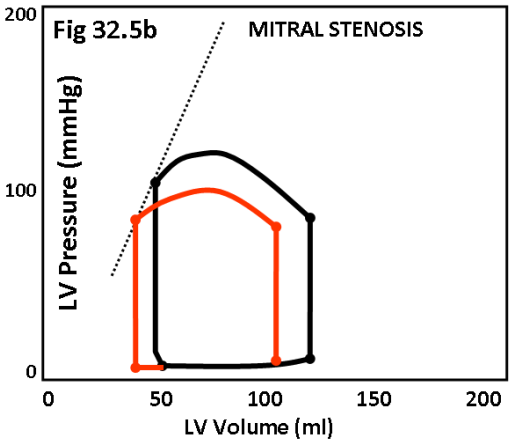
Reduced LV filling due to increased R

↓

Decreased EDV

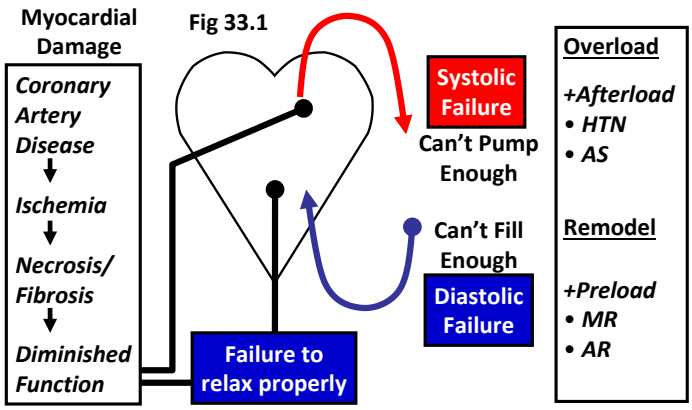
↓

Decreased ESV
But reduced SV
and reduced EF

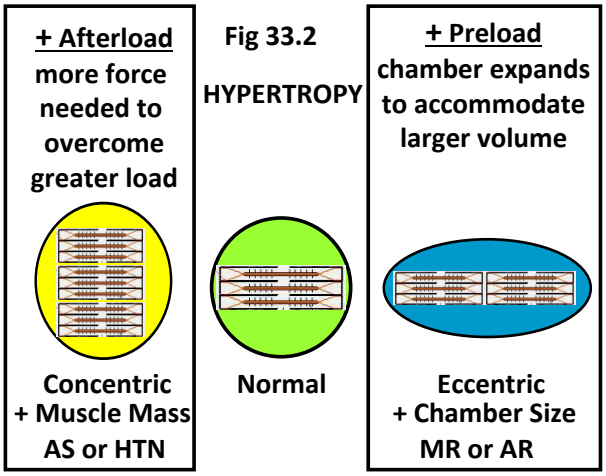


33.0 Heart Failure and Cardiac Adaptations TOC

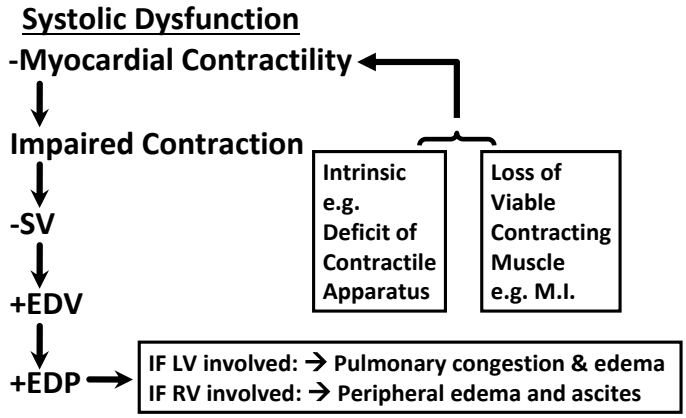
Heart Failure = Pump Failure
Develops Rapidly ('Acute') • M.I. • Infection • Post bypass surgery
Over Time ('Chronic') • Pressure / Volume Overload HTN/AS / AR/AS • Adaptive Remodeling • Functional Decline

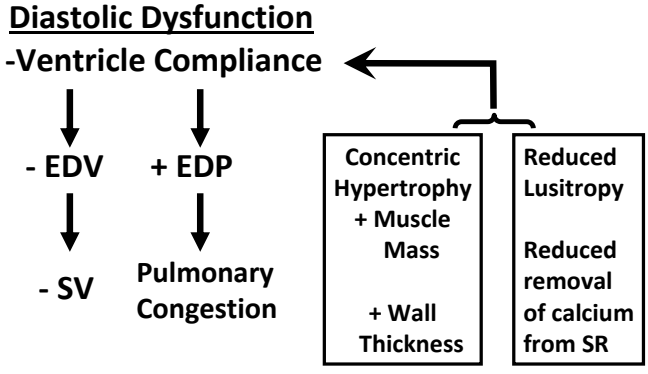


Hypertrophy and remodeling are compensatory, time dependent processes in response to pressure and volume burdens. LV and RV hypertrophy are triggered by excess wall stress. ***Chronic pressure-overload*** (HTN or AS) may cause *concentric hypertrophy* in which new sarcomeres are formed in parallel with the old causing wall thickening. This adaptive wall mass increase tends to counteract elevated wall σ (since r/w decreases) and maintains normal systolic function but diastolic compliance decreases. ***Chronic V-overload*** (preload) as in MR, AR or systolic dysfunction, triggers synthesis of new sarcomeres in series with old. Chamber size increases as does r/w (*eccentric hypertrophy*).



Summary of Systolic and Diastolic Dysfunction TOC





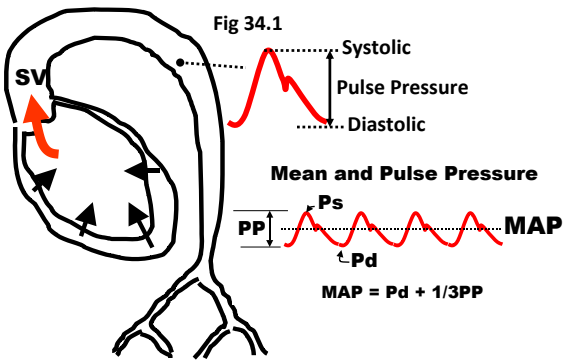
Brief Bullet Summary of some points associated with Cardiac Pump Function TOC

01. Contraction initiation is mainly due to Ca^{++} entry during the action potential plateau phase
02. Calcium entry triggers release of more Ca^{++} that diffuses to nearby sarcomeres causing contraction
03. More Ca^{++} entry associated with more packets/clusters of Ca^{++} release causing greater contraction
04. Contraction end and relaxation onset depends on Ca^{++} re-uptake by SR and Ca^{++} expulsion via transporters
05. Early ectopic stimuli prior to full re-uptake results in reduced contraction force.
06. Contraction force and SV increase with increases in preload and contractility and with reduced afterload.
07. Muscle fiber preload is the fiber stretch at the instant of the fiber's active contraction
08. Ventricular preload depends on stretch but is defined as the volume at systole onset or at end of diastole.
09. The volume within the ventricular chamber at this point is defined as the end diastolic volume or EDV
10. Contractility is an index of the myocardial force-generating/length-shortening potential at a given preload
11. Increased contractility causes increased peak force, rate of force and myocardial relaxation rate.
12. V_{max} is an index of contractility that increases with increases in positive inotropic interventions.
13. One clinical estimate of V_{max} or contractility is based on the maximum change rate of ventricular pressure
14. The dependence of SV on EDV is governed by the Frank-Starling "law of the heart"
15. One feature of this dependence is that the ventricular peak isovolumic pressure (PIP) increases with EDV
16. A 2^{nd} feature is that PIP values that occur for varying values of EDV will fall along a line – the PIP line
17. It turns out that the PIP line will always intersect a ventricular P-V loop at the loops end systolic point
18. The EDV-SV relationship determined by Frank-Starling is also called the Cardiac Function Curve (CFC)
19. The CFC shifts upwards with a greater initial slope if contractility increases; = greater SV at same preload
20. Contractility Is increased via positive inotropic stimuli, agents or drugs; most cause increases in Ca^{++} entry
21. Afterload (AL) is a general concept that reflects the load against which the contracting ventricle must work
22. The truest (but not clinically useful) index of AL is the stress on myocytes they must overcome to shorten
23. Ventricle or arterial BP is an AL surrogate since wall stress depends on ventricular transmural pressure
24. Myocardial energy and O_2 need depend directly on both the myocardial wall stress and the time it acts
25. The cardiac cycle (CC) describes the electrical, mechanical and hemodynamic events of heart function.
26. The CC can be shown with time implicit via a Wiggers diagram or by a time explicit pressure-volume loop
27. The width of the P-V loop defines SV and the ratio of SV/EDV defines the ejection fraction (EF)
28. Contractility, preload and afterload changes alter P-V loops in predictable ways; used for analyzing effects
29. Left and right ventricles function (pump) in series and both obey the Frank-Starling "law of the heart"
30. Consequently, beat-to-beat changes in output of each are largely regulated by this mechanism
31. Identifiable characteristic heart sounds are heard mainly related to closure of the inlet and outlet valves
32. S1: inlet valve closure, S2: outlet valve closure, S3 sometimes during early diastole, S4: atrial contraction
33. Murmurs are sounds heard mainly due to cardiac valve problems or the presence of vascular stenosis.
34. Cardiac murmurs: aortic stenosis (AS), mitral stenosis (MS), aortic regurgitation (AR), mitral regurg. (MR)
35. Systolic murmurs: AS/MR; Diastolic murmurs: MS/AR each with various patterns/hemodynamic features
36. Sustained ventricular pressure or volume overloads results in remodeling classically called hypertrophy
37. Pressure overloads occur with systemic hypertension and AS that cause increases in ventricular wall stress
38. Volume overloads occur with conditions that tend to cause abnormal increases in EDV such as MR or AR
39. Type of (initial) ventricular remodeling depends on type and duration of overload
40. Adaptation to pressure overload: myocyte hypertrophy & increased wall mass with hyperplasia (parallel)
41. Adaptation to volume overload: myocytes lengthen with serial hyperplasia; chamber dilatation
43. Hypertrophy functional changes: decreased compliance-increased EDP-increased O_2 demand
44. Dilatation functional changes: increased compliance-decreased EDP-decreased SV

34.0 Arterial Blood Pressure (BP in Aorta and Large Arteries) TOC

34.1 REVIEW of Arterial blood pressure (ABP) [See also section 3.2 & section 10.4]

ABP has a mean value (**MAP**) and a pulse component; **MAP** (Fig 34.1) depends on:
[1] Blood volume in arteries in relation to their compliance, [2] the product of CO x TPR and [3] Gravity. Regarding [1], even if the heart were not pumping, some pressure is measurable due to blood volume in the vessels. Regarding [3] there is a pressure due to blood's weight. In a vertical vessel, pressure at the bottom is greater than at the top.



Pulse components also depend on three factors;
[1] **Ventricular ejection** rate and amount
[2] **Compliance** of the arteries receiving the SV and
[3] **Pulse-wave reflection** effects

LV contraction causes SV to enter the aorta and distend it causing a rise in ABP from a ***diastolic*** to a ***systolic*** peak. During early rapid ventricle ejection, volume enters the aorta rapidly causing the systolic pressure peak. As entering volume declines, the aortic wall recoils and helps propel blood distally. On a beat-by-beat basis, aortic volume at any instant depends on LV inflow relative to outflow to the periphery. Since ABP depends on volume it also depends on aortic inflow vs. outflow. The pressure difference (systolic – diastolic) is ***pulse pressure*** (PP) and area under aortic flow pulse vs. time is the SV.

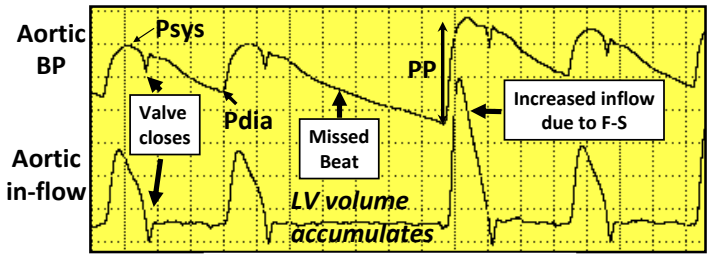
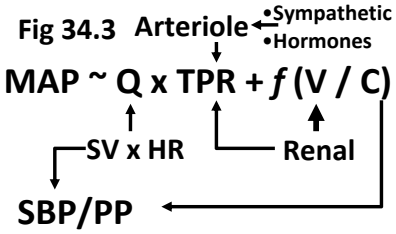


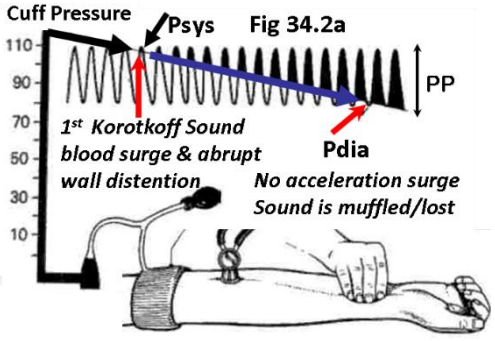
Fig 34.2 + PP ∝ + dV/dt, + SV, - C
- Increased rate of LV ejection
- Increased stroke volume
- Decreased aortic compliance

The effect of a missed beat (Fig 34.2) shows that if aortic volume is not replenished continuously, peripheral 'runoff' causes a progressive decrease in ABP. The missed beat allows LV volume to accumulate since the LV fills for 2 cycles without an intervening ejection. At the next beat SV is greater due to F-S and causes a larger PP; if all other factors are fixed, ***PP ∝ SV***. But, for any SV, PP is greater if ejection rate is greater since ~75% of SV occurs during early ventricular ejection. PP also depends on aortic compliance. Lower compliance causes greater systolic and pulse pressures since to accommodate SV, a less compliant artery has a greater pressure increase. So, systolic and pulse pressure are increased if LV ejection rate and SV are increased or if aortic compliance is decreased.

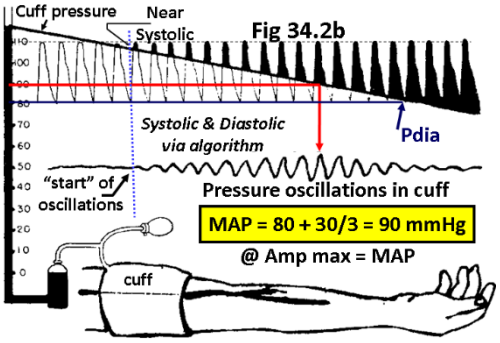
MAP is the time-average ABP approximately equal to Pdia + 1/3 PP. MAP is not a simple arithmetic average of Psys and Pdia, so an increase in Pdia has a greater relative effect on MAP than Psys. The full relationship is **TPR = (MAP – CVP) / CO.** MAP (Fig 34.3) can be expressed approximately as shown in Fig 34.3 with V = blood volume that is largely regulated by kidney via excreting or conserving water and sodium. Increased V tends to increase MAP. Since MAP-CVP is systemic perfusion pressure, MAP must be sufficient for adequate flow yet not be too large, since a large MAP increases heart workload.

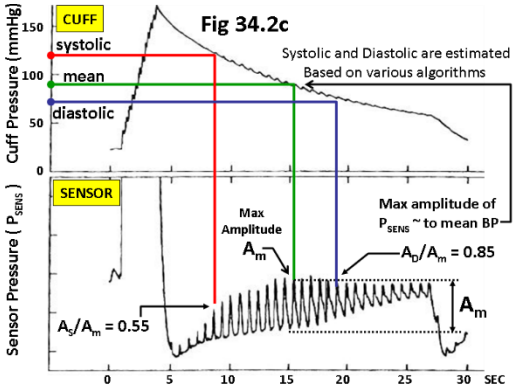


34.2 Noninvasive BP: Sphygmomanometer and Oscillographic Methods TOC



A cuff, acting as a transducer, is placed snugly around an arm and inflated to compress underlying arteries so no pulse is palpated at a distal artery. Cuff pressure (Pc) is slowly released until peak pressure slightly exceeds tissue pressure around the artery; Pulse becomes palpable and manometer pressure is systolic (Psys). A spurt of blood through the artery causes audible 1st Korotkoff sound heard by a stethoscope over the artery (**Fig 34.24a**). A tapping sound is heard due to acceleration transients that cause abrupt arterial wall distention as a blood jet surges under the cuff into a distal artery. As Pc is further reduced, the (Pc – Psys) difference increases and the artery stays open longer during each pulse. More blood surges through and sound intensity increases. When Pc becomes less than the lowest artery pressure, the artery remains open and sounds become muffled since the acceleration surge is lost. Manometer pressure at the start of this phase is Pdia and MAP is estimated from Psys and Pdia. Abnormally high blood pressure may occur with increases in Psys alone, Pdia alone or elevations in both. Arm blood pressure measurement *must be made* with the arm supported at the *level of the right atria*. If the arm hangs down, a hydrostatic pressure is added to the transducer. This is true even if a catheter is inserted in an artery for pressure measurement. If the transducer is at heart level there will be no added hydrostatic pressure. Automated BP devices are now routine and work on different principles. One common method is the **oscillographic method** (**Fig 34.4b**) and used in most home automated devices. It estimates Psys and Pdia from the mean that is detected from the amplitude of vibrations sensed during the BP measurement as shown in **Fig 34.2c**.



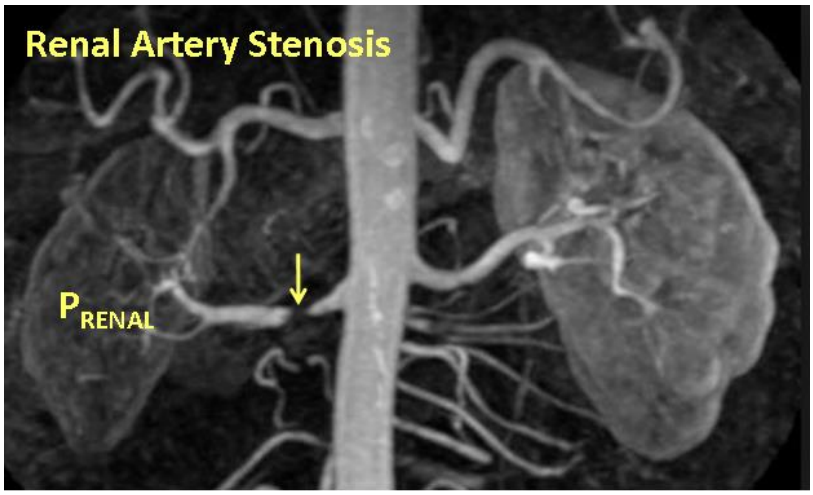


34.3 Hypertension (HTN) TOC

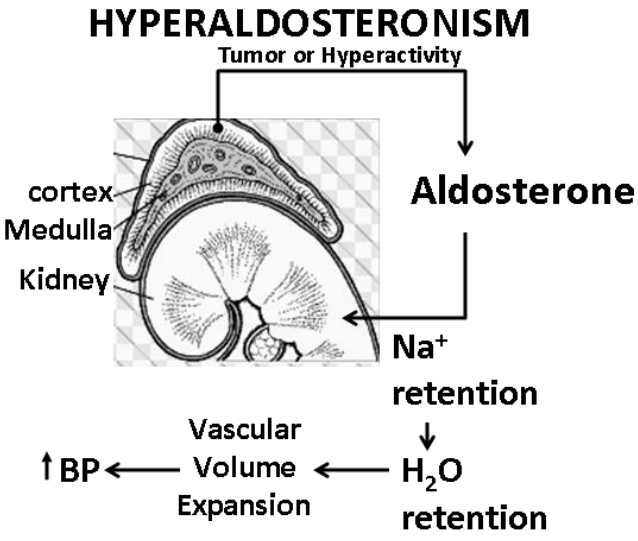
About 50 million Americans have HTN. In 5-10% HTN is secondary due to conditions such as renal stenosis, chronic renal disease, hyperthyroidism and etc. In the rest, it is called primary or essential hypertension with the main sustaining event increased TPR caused mainly by increased arteriole resistance. Both active constriction and endothelial structural hypertrophy contribute to the increased TPR. Resistance is also increased by microvessel rarefaction - a decrease in the number of parallel arterioles. Decreased arterial compliance causes systolic pressure to selectively increase resulting in Isolated Systolic Hypertension (ISH). Some antihypertensive drugs target TPR reduction while attempting to maintain normal cardiac function. Other drugs affect blood volume and SV. Modes of action depend on the drug's target. Risk of cardiovascular disease (CVD), starting at 115/75 mmHg, doubles with each increment of 20/10 mmHg; persons who are normotensive at age 55 have a 90 percent lifetime risk for developing hypertension. "The relationship between BP and risk of CVD events is continuous, consistent, and independent of other risk factors. The higher the BP, the greater is the chance of heart attack, heart failure, stroke, and kidney disease". BP classifications are based on average of two or more properly measured seated BP readings on two or more office visits.

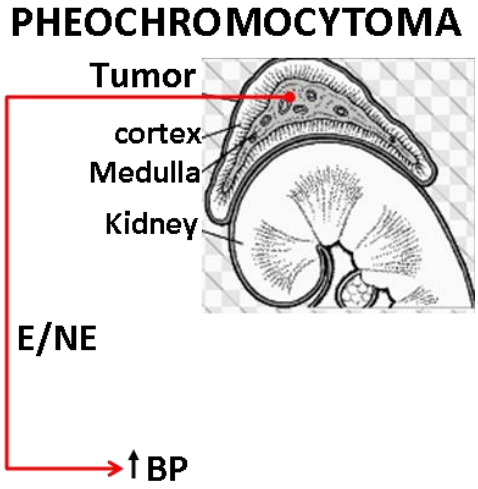
BP CLASSIFICATION	SBP (mmHg)	DBP (mmHg)
Normal	< 120	AND <80
Prehypertension	120-139	OR 80-89
Stage 1 Hypertension	140-159	OR 90-99
Stage 2 Hypertension	>= 160	OR >= 100

34.4 Clinical Correlation: Secondary Hypertension Examples



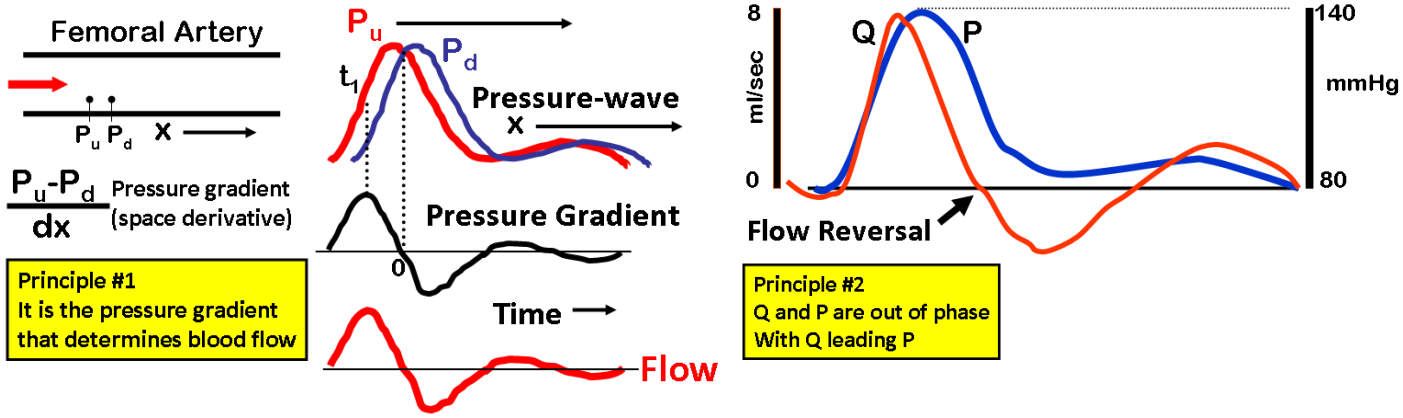
$\downarrow P_{RENAL} \rightarrow \uparrow$ Renin $\rightarrow \uparrow$ Angiotensin II $\rightarrow \uparrow$ TPR



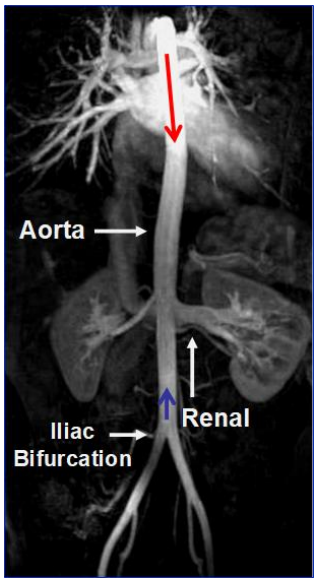


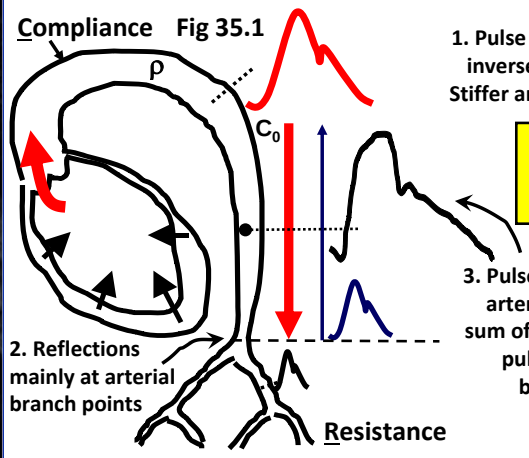
35.0 Arterial Pulse Propagation and Reflection TOC

General Principles of Pulsatile Arterial Blood Pressure and Flow



35.1 Pulse-Waves in Arteries

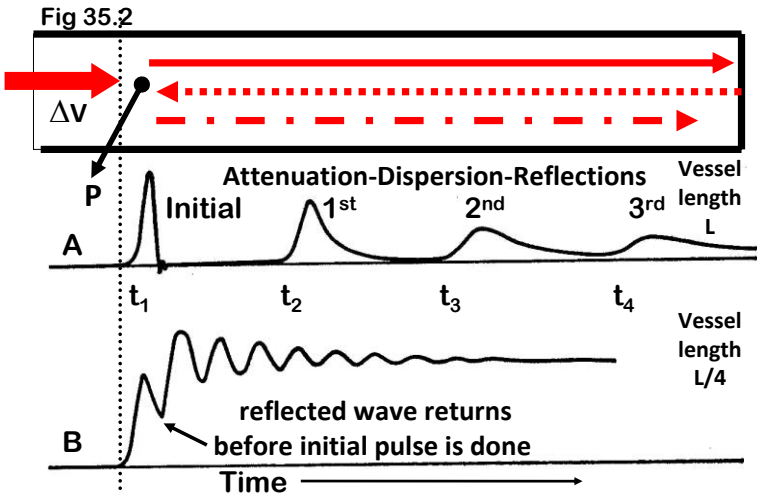




Pressure and flow pulses caused by ventricular ejection are **transmitted** peripherally as forward-moving waves. A portion of the forward **pulse-wave** is **reflected** back toward the heart. Reflections occur at artery branches and other sites. The **wave speed, C_0** that pulses move varies from ~6 m/sec in aorta to ~12 m/sec in femoral artery. C_0 is inverse to an artery's compliance (C) → **$C_0 \sim 1/\text{sqrt}(\rho C)$**. C_0 is frequency dependent so it depends on pulse shape.

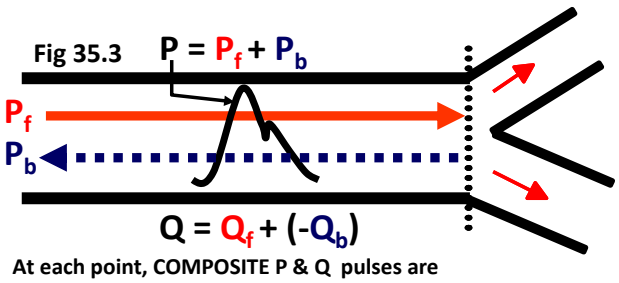
35.2 Pulse-Wave Features

Pulse transit time from ascending to distal aorta (~0.6 m) is ~0.1 sec for C_0 = 6 m/sec. So, pulse-waves reflect from this site and return to the heart in ~0.2 sec. So, the pulse returns to its source during the ascending aortic pressure pulse that caused it! **Fig 35.2** shows the basic factors involved as a volume (ΔV) is injected into a fluid filled compliant vessel. In **A,** pressure pulses at the origin are shown after they are transmitted and then reflected having experienced attenuation and dispersion. In **B,** the reflections return so quickly that they add to the impulse at the origin that generated the initial pulse. Conditions in B simulate that in the aorta.



35.3 Reflection Properties: Pressure Waves Add but Flow Waves Subtract TOC

When a forward ***pressure wave*** (**P_f**) arrives at a branch site (Fig 35.3), reflected pressures (**P_b**) are "in-phase" with P_f. So, as P_b travels back toward the heart it ***adds*** to the forward wave, creating a composite pressure-pulse that is greater than the forward wave alone. The opposite is true for the ***flow wave***. The reflected flow wave (**Q_b**) is "180° out-of-phase" with the forward wave and ***subtracts*** from the forward wave (**Q_f**). The closer the "match" between certain properties of the parent artery and its combined daughter branches, the smaller is the reflection.



At each point, COMPOSITE P & Q pulses are the algebraic sum of forward (f) & backward (b) pulses. The reflected P wave ADDS to the forward P wave and the reflected Q wave SUBTRACTS from the forward Q wave

35.4 Less Reflection if Lower Resistance

If the resistance (R) of the pathway into which the wave is moving is less, the reflection is less (Fig 35.4). If R is increased, reflections are increased. So, if R is decreased, reflected components that would *add* to the pulse-pressure amplitude and reflected components that would *subtract* from the flow-pulse will both be less and the composite pressure pulse peak is reduced and the negative contribution to flow pulses is less.

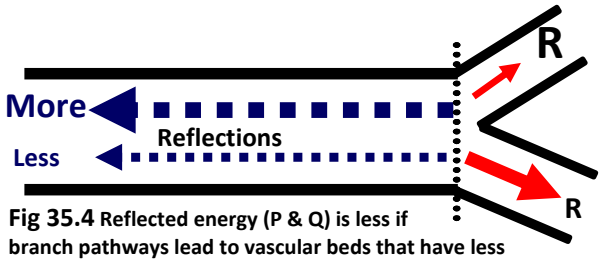
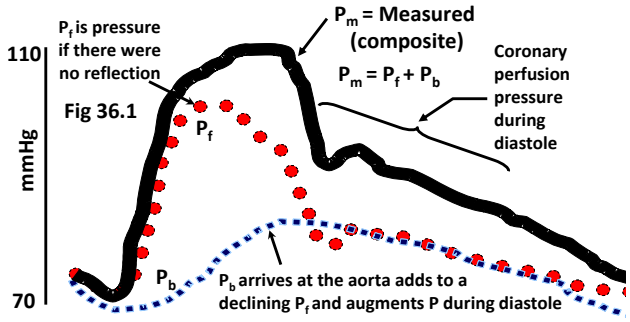


Fig 35.4 Reflected energy (P & Q) is less if branch pathways lead to vascular beds that have less Resistance, R). Reflection is greater if these have greater R.

36.0 Physiological and Clinical Manifestations of Pulses TOC

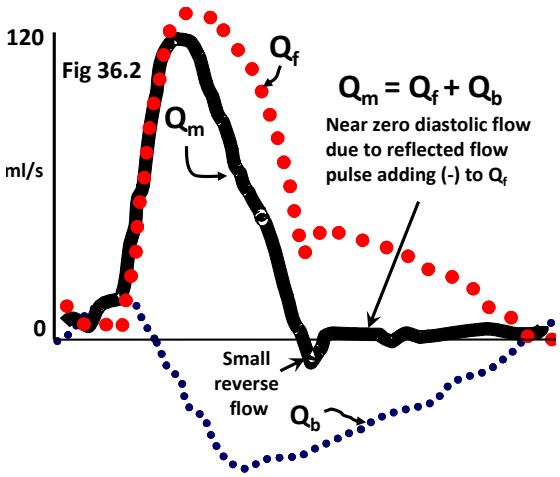
36.1 Aortic Pressure Pulse

Pulse-wave reflections affect the shape and functional attributes of aortic pressure (Fig 36.1). Pressure measured in the ascending aorta (**P_m**) is the sum of **P_f** and **P_b**. P_b causes an increase in pressure during diastole. Since myocardial blood flow occurs mainly during diastole this aids flow. During rapid ejection, P_m and P_f are similar since a reflection has not yet returned. Reflections generally broaden the systolic pressure contour.



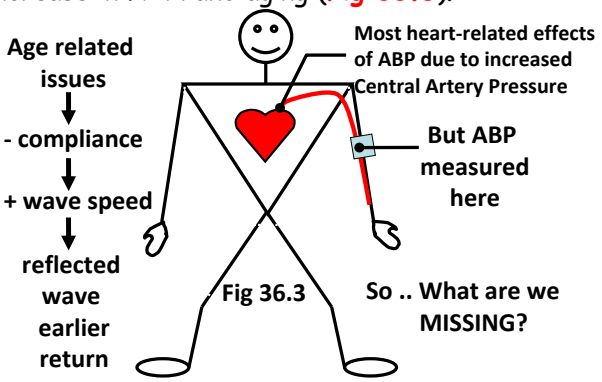
36.2 Aortic Flow Pulse

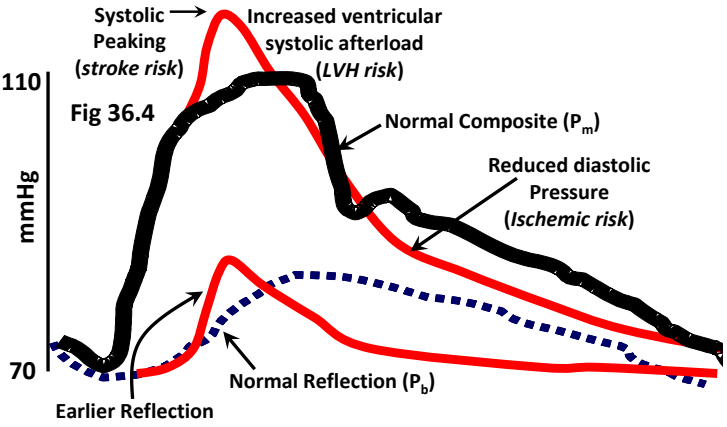
The flow pulse (Fig 36.2) is affected by ventricular ejection rate, SV and reflected waves. The reflected flow wave (**Q_b**) is out-of-phase with the forward wave and when it arrives back at the ascending aorta it subtracts from the forward wave yielding the measured flow pulse **Q_m**. It is this interaction that results in the measured pulse having a zero or near zero value for most of the diastolic interval. Importantly note however that the forward blood flow (**Q_f**) continues to provide flow to the periphery although it declines during the diastolic runoff interval. So, measured pulse flow would look like the pictured Q_m but actual blood flow to the periphery continues throughout the cardiac cycle.



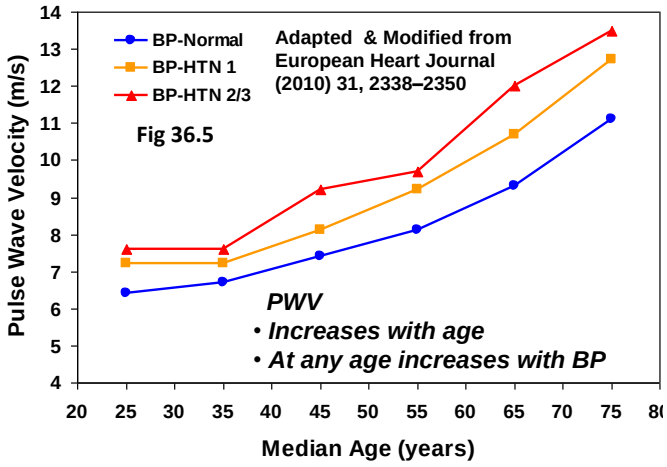
36.3 Reflection-Related Central Pressure Augmentation TOC

Standard arm BP may miss stuff that affects heart (Fig 36.3). Reasons are related to pressure wave interactions that are influenced by pulse wave speed and reflection amplitudes (Fig 36.4). These both increase in HTN and aging (Fig 36.5).



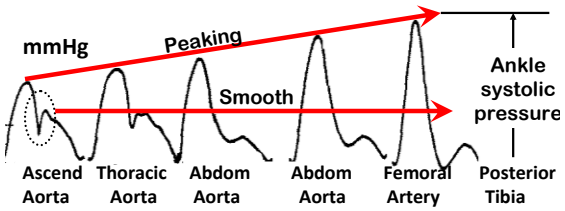


Pulse wave velocity (PWV) increases with age mainly due to decreased arterial compliance (Fig 36.5). At any age, the PWV tends to be greater for higher blood pressure. The effect of this increase in PWV is to cause the reflected wave to arrive at the aortic root earlier than normal causing the pressures seen by the heart during systole to be greater and the perfusion pressure during diastole to be less as shown in Fig 36.4 having the various negative effects as summarized in that figure.



36.4 Peripheral P and Q Pulses TOC

Frequency dependent wave speeds, frequency selective filtering and reflections affect the shape of P & Q pulses. Higher frequency wave-components travel with higher speeds. Because P and Q pulses are composed of a mixture of frequencies higher frequency components tend to "overtake" lower frequency components. This causes a more rapidly raising contour and pulse peaking to occur distally. This peaking effect is counter balanced by selective frequency filtering. As a pulse moves peripherally higher frequency energy is selectively absorbed by the actions of blood viscosity and density and vessel wall compliance. This selective frequency filtering causes dispersion and tends to counter the effect of the higher wave speed of the higher frequencies. The resulting precise pressure waveform contour depends in part on the relative balance between these two factors and also on the effects of wave reflection already

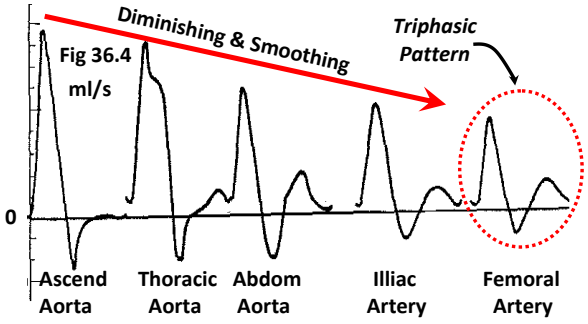


SHAPE CHANGES:
- *Wave-Speed differences*
- *Frequency Filtering*
- *Reflections*

Fig 36.4

ABI = (Ankle/Brachial) Systolic Pressure

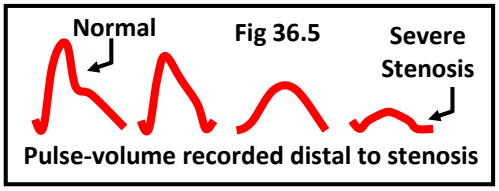
Normal ~ 1.00 – 1.40, Abnormal <0.90

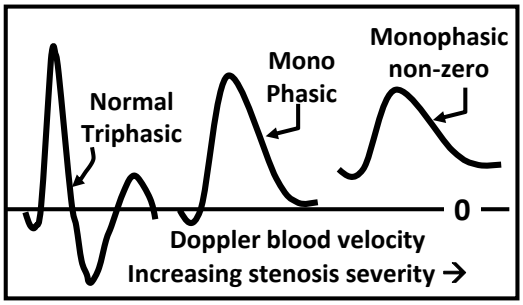


discussed. It's a complex story! But, what we can definitely say is that for a pressure pulse, the systolic peak increases from the aorta → peripherally in arteries and its rapidly changing parts (high frequencies) are "filtered" during its forward journey so it becomes "smoothed". The pressure increase is seen in peripheral arteries but *as* pulses pass through arterioles the amplitude decreases due to resistive losses. Contrastingly, the flow pulse peak decreases in a peripheral direction due to flow supplied to branches. A "triphasic" flow pattern develops due to normal flow-pulse reflections and the pressure gradient that is prominent in lower extremities. Deviations from a triphasic pattern occur in peripheral arterial disease.

36.5 Pathological Changes: TOC

Patients with lower extremity arterial disease (LEAD) also called peripheral arterial disease (PAD) have compensatory arteriolar vasodilation distal to sites of chronic stenoses. This vasodilation reduces flow pulse reflections and thus causes a loss of the normal triphasic flow pattern, which becomes biphasic or monophasic as shown in the Doppler blood velocity (**Fig 36.5**). Also, pressure pulses near and distal to a stenosis are changed with typical pulse changes as illustrated in the pulse volume recording (PVR). PVR changes may include *reduced systolic pressure, reduced rate of rise and fall*, and a broadened and smoother contour (**Fig 36.5**).





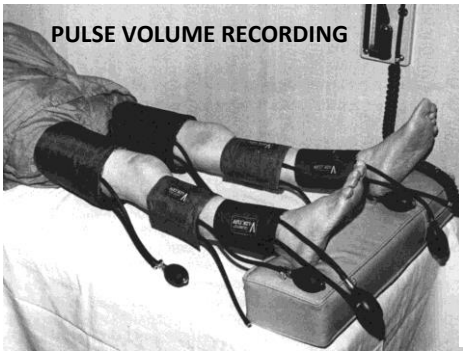
36.6 Ankle-Brachial Pressure Index (ABI) TOC

Normal → 1.00 – 1.40
Borderline → 0.90 – 0.99
< 0.90 → Abnormal

	0.80 – 0.89 Mild Blockage
Claudication →	0.50 – 0.79 Moderate Block
Rest Pain →	< 0.50 Severe Block

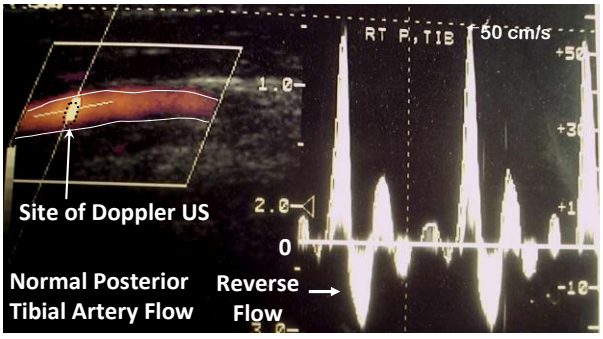
Early detection of PAD is vital since there is a strong correlation between it and the presence of coronary and cerebral artery disease. A simple ABI (ankle-brachial systolic pressure ratio) is a useful screening method with values and criteria as shown in the adjacent table.

36.7 Pulse volume recording (PVR) and Doppler Ultrasound (US) Methods



Cuffs are inflated to pressures sufficient to sense the volume of the blood entering the artery segments under the cuffs.

Resultant signals define the PVR used for diagnosis and stenosis location



36.8 Brief bullet points of some main items about the Arterial System Pressure/Flow TOC

01. LV ejects SV; raises aortic pressure to systolic pressure (SP) value; systolic-diastolic = pulse pressure (PP)

02. SP and PP are increased with increased rate of LV ejection, increased SV and decreased aortic compliance

03. Mean pressure (MAP) depends on both cardiac function and the blood volume (BV) to compliance (C) ratio

04. MAP ≈ CO x TPR + *ƒ* (BV/C) and when measured via standard cuff MAP is given as MAP ≈ DP + 1/3PP

05. Hypertension (HTN) IS due to organ specific causes (e.g. kidney) or what is called "essential" hypertension

06. Hypertensive levels can occur with an isolated increase in SP (>139) or DP (>89) or both.

07. Isolated HTN is usually due to decreased aortic compliance that accompanies calcification and/or aging

08. Isolated HTN can occur with exaggerated systolic ejection into normal arterial blood vessels

09. Hypertensive levels of DP are usually associated with increased total peripheral resistance (TPR)

10. Ejection of SV into the aorta produces a BP pulse that is propagated distally at a finite wave speed (C_0)

11. The propagation speed depends inversely on the compliance of the vessels in which the wave propagates

12. Initially propagated waves consist of both a pressure and flow waves referred to as "forward" waves

13. Each wave experiences attenuation and dispersion but are reflected back toward the source (aortic root)

14. Pressure waves reflect in phase with forward waves; Flow waves reflect 180^o out of phase

15. The magnitude of reflected energy is directly related to the effective distal resistance at the reflection site

16. Reflected waves interact with the initially propagated waves by adding or subtracting

17. Pressure waves add and flow waves subtract resulting in a "composite" wave that exists at all points

18. At the aortic root these cause changes in the pre-reflected pressure and flow that may be "good or bad"

19. If wave speed is abnormally high early pressure reflections cause a peaking in the central aortic pressure

20. Such peaking effects would not be detected by standard arm-cuff sphygmomanometer measurements

21. The arterial pulsatile flow pattern depends on the local pressure gradient not on the measured pressure

22. Patterns and magnitudes also depend on pulse reflection, attenuation, dispersion and frequency filtering

23. The ratio of ankle to brachial systolic pressures defines a so-called ankle-brachial pressure index (ABI)

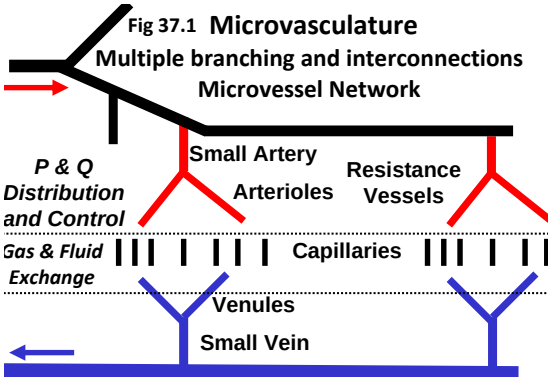
24. The ABI is a useful index to ascertain the possible presence of peripheral arterial disease (PAD)

25. Other methods with diagnostic criteria include pulse volume recordings (PVR) and Doppler ultrasound

37.0 Microcirculation TOC

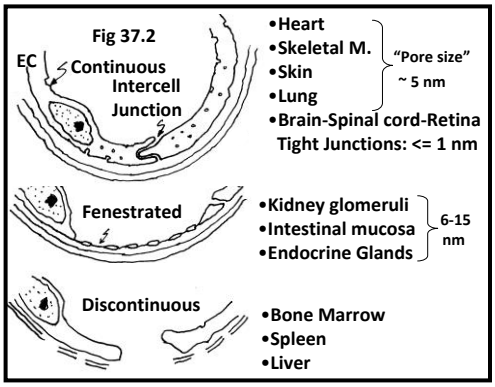
37.1 Main Vessel Types (Fig. 37.1)

Arterioles are multifunctional: Diameter changes caused by neural or local mechanisms alter vascular resistance via changes in VSM; this affects both arterial and capillary BP. Arterioles also control flow to and within organs. ***Venules*** function as blood collection and return vessels and exchange sites. Post-capillary venules are immediately distal to capillaries. They have little VSM. A confluence of increasing size venules merges to form larger venules and then larger veins. ***Capillaries***: Vascular-tissue exchange; Smallest vessels (3-8 μm); endothelial cell (EC) lined tubes; no VSM. EC arrangement depends on organ function. Gas exchange (O_2 and CO_2) is by diffusion through wall governed by Fick's law. Fluid exchange is via convection (small and large pores) via aquaporin channels. Protein passes through large pores.



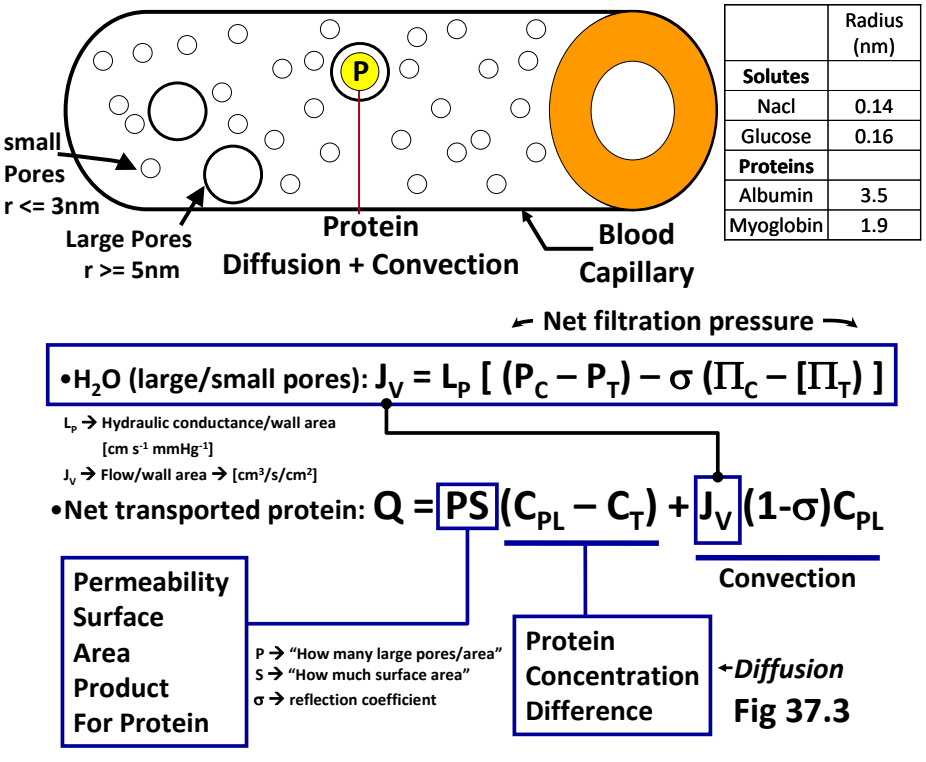
37.2 Capillaries: Variability Among Organs (Fig 37.2)

Flow is via single file RBC movement; RBC's fold/deform with their membrane near wall. Capillary resistance is high due to small D but capillary network resistance is low due many parallel capillaries. RBC speed ~0.5-1.0 mm/s varies with time and conditions; some capillaries may have no flow while others have flow. A non-rhythmic change in arteriole diameter is called vasomotion.



37.3 Transport Processes (Phenomenological Model)

Fig 37.3 represents various processes that determine the transcapillary movement of fluids and proteins from the capillary to interstitium and from interstitium back into the capillaries. Water flux (J_V) is flow/wall area determined by hydrostatic and oncotic gradients and the hydraulic conductance (Lp). Protein transport depends large pore number density (P) and the surface area (S) these occupy and on concentration gradient and the convective flow that carries some protein.



	Radius (nm)
Solutes	
Nacl	0.14
Glucose	0.16
Proteins	
Albumin	3.5
Myoglobin	1.9

37.4 Capillary Filtration TOC

The direction and amount of fluid movement across capillary walls depends on net filtration pressure ΔP_{FILT} and resistance to fluid flow through the wall (Fig 37.4a). Driving force, ΔP_{FILT} is the difference between fluid and oncotic transmural pressures and σ is the osmotic reflection coefficient. Filtration flow in ml/min/100g tissue is $Q_F = K_T \times \Delta P_{FILT}$. K_T is tissue dependent and depends on capillary permeability and exchange surface area. and has units of conductance. Fig 37.4b shows protein dynamics.

What is filtration rate for this data?

Plasma colloid osmotic pressure = 25 mmHg
Capillary hydrostatic pressure = 25 mmHg
Interstitial fluid hydrostatic pressure = - 5 mmHg
Interstitial colloid osmotic pressure = 10 mmHg
Capillary filtration coefficient = 10 ml/min/mmHg

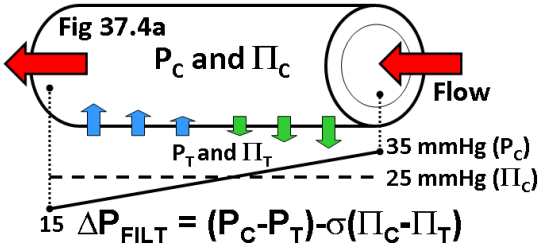
$Q_F = K \Delta P_{eff}$

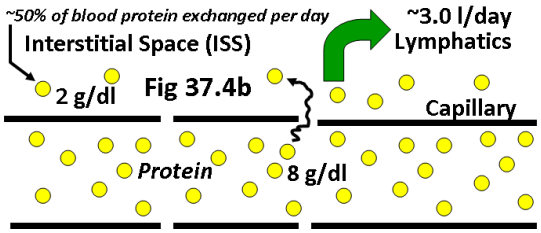
$\Delta P_H = P_{TM} = [25 - (-5)] = 30$ mmHg

$\Delta P_{\Pi} = [25 - 10] = 15$ mmHg

$\Delta P_{eff} = 30 - 15 = 15$ mmHg

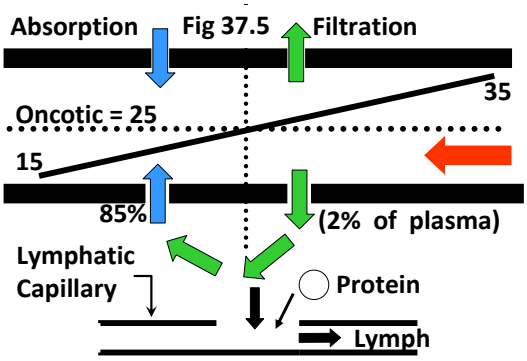
SO .....$Q_F = 10 \times 15 = 150$ ml/min





37.5 Classic Fluid Exchange Model

This view of capillary exchange (Fig 37.5) is filtration at the arteriolar end and absorption toward the venous end. The crossover between filtration and absorption is when forces tending to absorb balance forces tending to filter. This occurs if the transmural pressure equals the osmotic pressure difference. The crossover occurs when average pressure is about (35+15)/2 = 25 mmHg = capillary oncotic pressure.



37.6 Vasomotion Fluid Exchange Model

Some information suggests that fluid exchange is dynamic and in part controlled by spontaneous diameter changes of terminal arterioles (Fig 37.6). This causes capillary pressure to be above or below oncotic pressure depending on the state of contraction or dilation of arterioles that are proximal to the capillaries. For example, a strong vasoconstriction of the arterioles can reduce intravascular capillary pressure below oncotic pressure so that no filtration occurs along the capillaries entire length. Contrastingly, an intense vasodilation will raise capillary pressure and possibly allow for outward filtration along the entire capillary length. Thus, prolonging or shortening these contraction/dilation phases has a strong impact on the transcapillary exchange process.

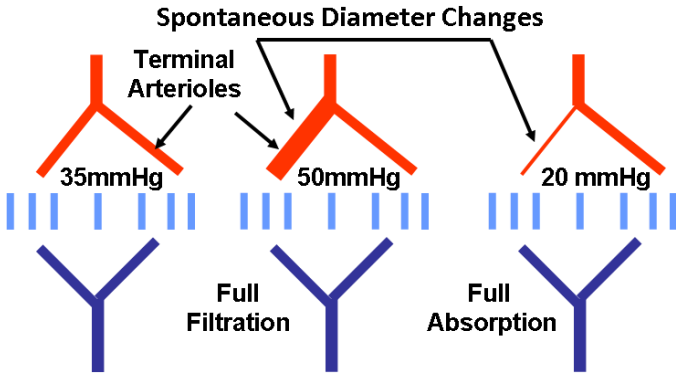


Fig 37.6 *Prolonging or shortening contraction or dilation phases affects filtration*

38.0 Lymphatic System TOC

38.1 Pictorial Overview of Main Lymphatic Arrangements and Flows

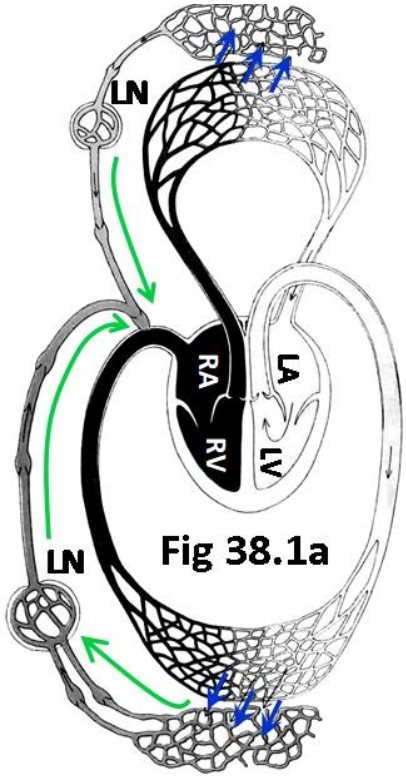


Fig 38.1a

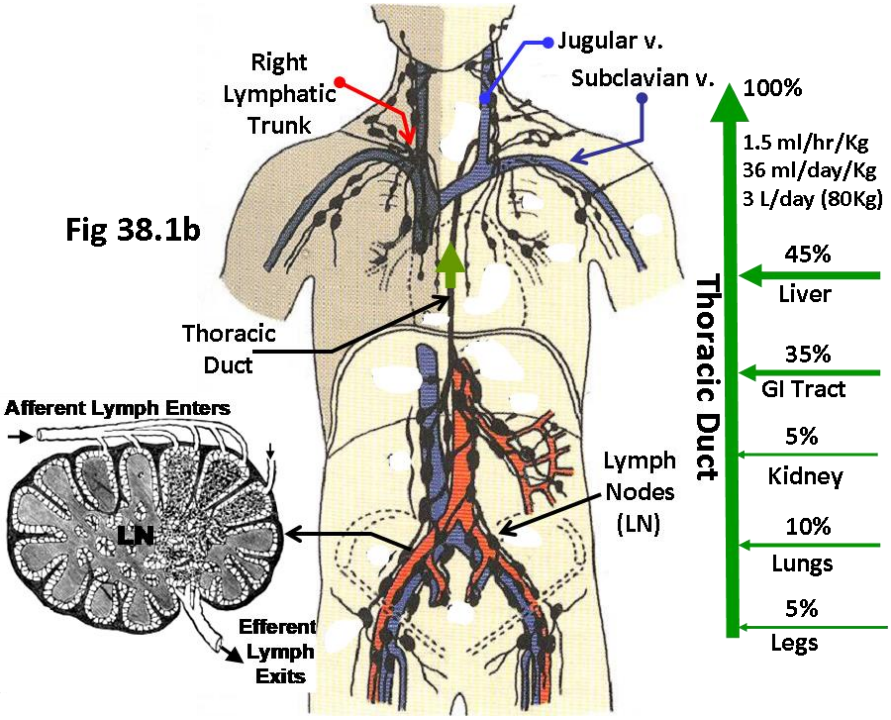


Fig 38.1b

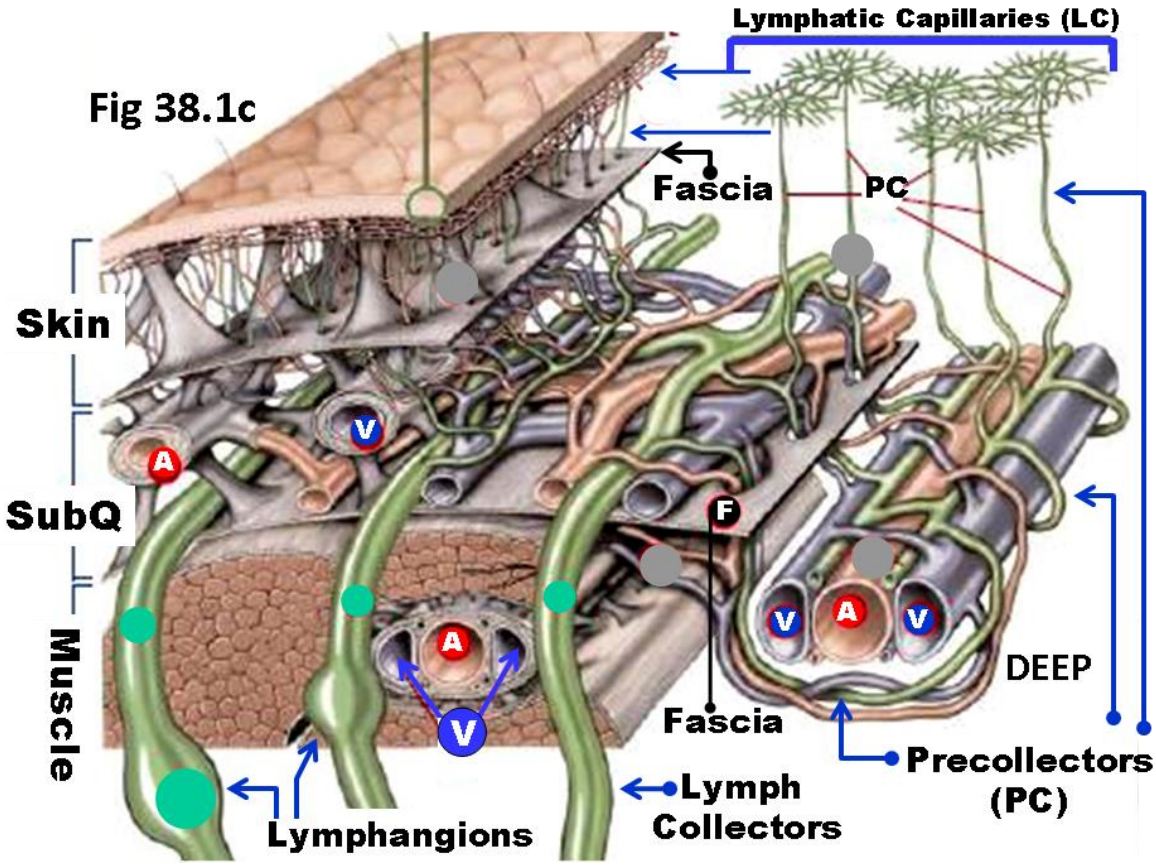


Fig 38.1c

38.2 Initial Lymphatic Vessels

Lymphatic capillaries (terminal lymphatics) are endothelial cell (EC)-lined blind-sac structures in which adjacent EC ends overlap with the other end tethered via anchoring filaments to surrounding tissue (**Fig 38.2**). Fluid and protein entry into lymph capillaries occurs if these overlap sections open due to increased tissue pressure (P_T) that exceeds pressure inside the lymphatic capillaries (P_L). It acts like a gate.

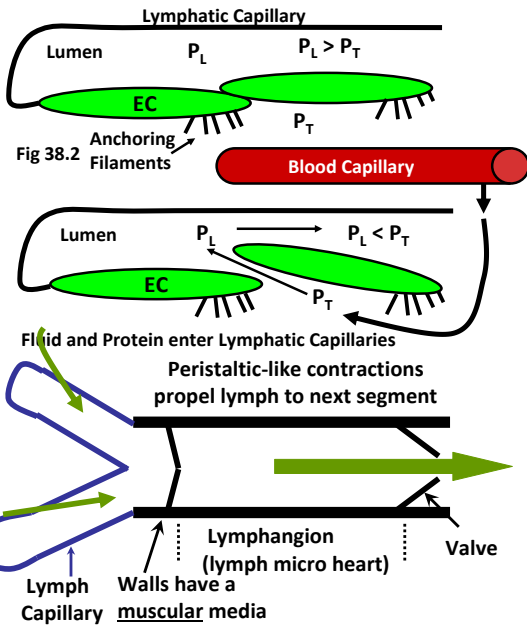


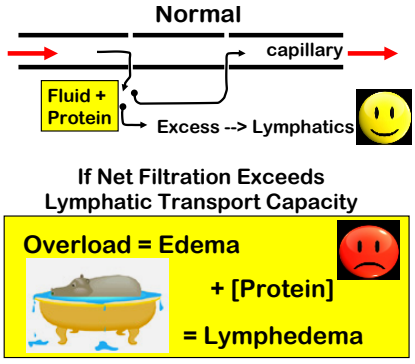
Fig 38.2

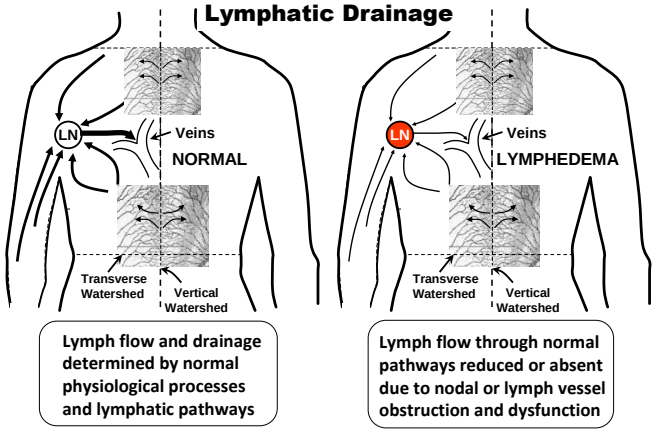
Fig 38.3 Contraction force (& frequency) is preload & afterload dependent - analogous to heart

38.3 Lymphangions

Lymphatic capillaries join and enter collecting vessels that have smooth muscle in their walls and valves spaced at varying distances. Segments between valves are lymphangions (**Fig 38.3**). When they contract, a peristaltic-like pattern expels lymph content to the next lymphangion. They function as "microhearts" since contraction force and frequency are preload and afterload dependent. Dysfunction of lymphatic microvessels, lymphangions or larger collecting lymphatics may cause lymphedema.

38.4 Lymphedema = Edema + Protein





38.5 Conditions tending to cause edema

Increased capillary pressure (P_C) tends to cause excess fluid filtration into tissue spaces. If fluid accumulates we have edema. Predicting increases in Pc is done with the partition model. Factors involved in edema formation include changes or derangements related to venous, arterial, lymphatic, osmotic and permeability components.

Capillary pressure increases if:
- Venous Pressure Increases
- Arteriole Resistance Decreases
- Venous Resistance Increases
- R_V/R_A increases

In addition any condition that decreases the osmotic pressure gradient between capillary and tissue will tend to increase filtration and promote edema

(1) Venous events that increase Pc: Increased venous volume (e.g. venous insufficiency); compression (e.g. pelvic vein in pregnancy); obstruction (e.g. venous thrombosis), congestive heart failure

(2) Arterial events that increase Pc: Arteriole vasodilation (e.g. heat, inflammation, trauma, allergic reactions, drugs)

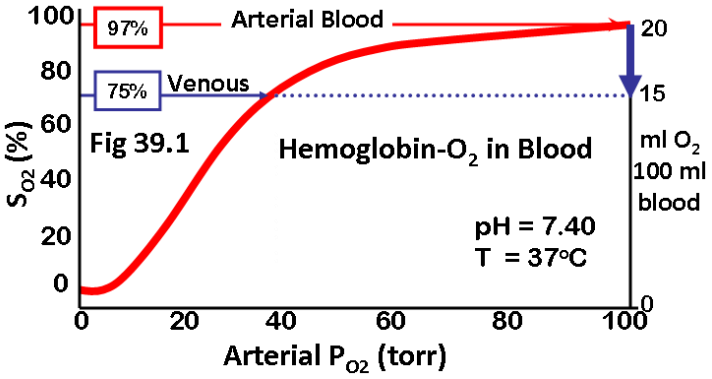
(3) Lymphatic events that diminish lymphatic function: Obstruction (e.g. lymph node removal), Insufficiency (e.g. fluid overload), Lymphangitis (e.g. inflammation)

(4) Osmotic events that increase fluid filtration from capillary to interstitium: Decreased capillary osmotic pressure as in hemodilution (e.g. water retention) or hypoproteinemia (e.g. starvation); increased tissue osmotic pressure (e.g. protein leak in inflammation)

(5) Permeability increase of capillary or post-capillary venule walls (e.g. due to histamine or allergy)

39.0 Oxygen Exchange TOC

Oxygen (O_2) in RBC's is carried to capillaries after O_2 loading in lungs. O_2 in arterial blood bound to hemoglobin is expressed as oxygen saturation (S_{O2}). At approximately 100% saturation (S_{O2}=100) there is approximately 20 ml of O_2 per 100 ml of blood (**Fig 39.1**). After blood passes through the systemic circulation, O_2 saturation is reduced to ~ 75% which represents ~ 15 ml O_2 per 100 ml of blood. In other words, about 5 ml O_2 per 100 ml of blood is utilized.



39.1 Oxygen Delivery and Uptake

If 20 ml of O_2 /100 ml of blood, then a person with a CO of 6 L/min has 1.2 liters of O_2 delivered per minute (**Fig 39.2**). The whole body at rest uses ~300 ml/min. The amount used (whole body or any organ) is called O_2 extraction or utilization. For a specific organ, e.g. heart, maximum O_2 extraction depends on blood flow and the arterial-venous O_2 concentration difference aO_2-vO_2 for that organ. If more O_2 is needed because of physiological demands (e.g. exercise) this increased demand is met by an increase in blood flow and in some tissues by an increase in extraction.

BLOOD FLOW

O_2 Used = 5 mlO_2/100 ml blood x 60 [100 ml blood units/min]

$\dot{V}_{O2}$ = 300 ml/O_2/min $\dot{V}_{O2}$ = O_2 uptake = O_2 utilization

General Relationship → $\dot{V}_{O2}$ = CO x (aO_2 - vO_2)

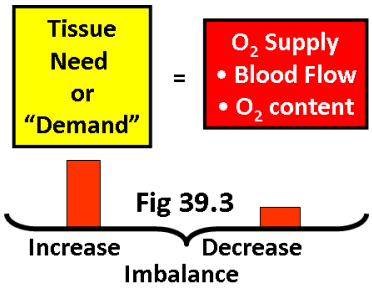
= 6000 x (20 - 15)/100

= 6000 x 0.05 = 300

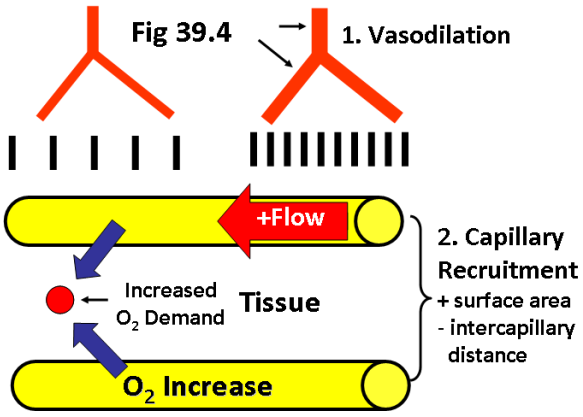
Applies to an organ and whole body calculations

39.2 Increased Tissue O_2 Demand

Increased O_2 need accompanies increased cellular metabolism and work since O_2 is consumed at a higher rate (e.g. heart and skeletal muscle during exercise). An imbalance between demand and supply may also occur at a fixed metabolic need if O_2 delivery is reduced (e.g. when blood flow or O_2 content is reduced, **Fig 39.3**).

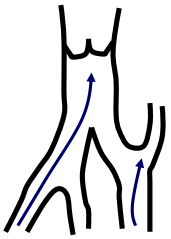


Two main *compensatory mechanisms* are available to help correct an imbalance in O_2 supply vs. demand at the tissue level - *vasodilation and capillary recruitment* (**Fig 39.4**). Local or regional vasodilation increases flow and, with increased flow, comes greater O_2 supply. Capillary recruitment draws upon anatomically present, but previously nonperfused capillaries, to increase surface area for O_2 exchange and to reduce intercapillary distance. So, more capillaries are now available to provide more O_2 to tissue areas, previously low in O_2.



40.0 Venous System TOC

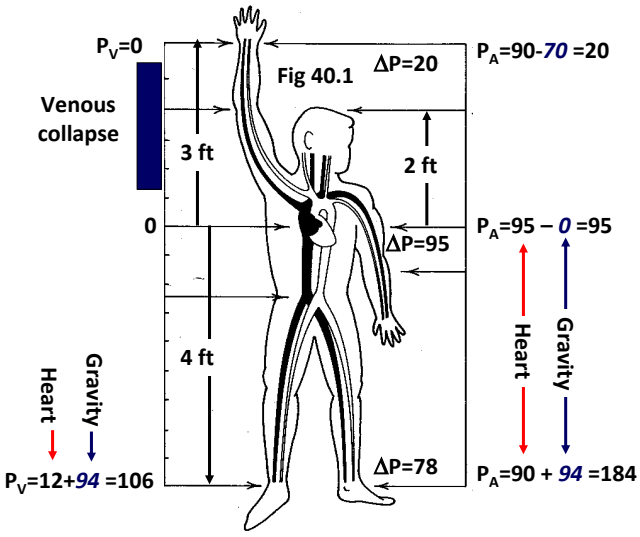
40.1 Gravity Effects



Veins have low pressure, large volume, and are thin walled. They are thus susceptible to effects of small internal/external pressure changes. Positive transmural pressure is needed to keep most veins fully open. Normal supine average pressures are: RA and CVP ~3-5 mmHg, peripheral veins/venules ~12 mmHg. Because the arterial system is rigid as compared to the venous system, its vessels are much less influenced by gravity effects. Veins above heart tend to collapse and veins below heart increase in diameter.

Below heart: Blood shifts to dependent veins. Volume increase causes pressure increase of ~0.77 mmHg for each cm below the right atrium. Results in venous distension and reduction in central venous volume.

Above heart: Vein blood drains toward central veins and pressure in veins above heart decreases. If transmural pressure is reduced to about 0 mmHg then veins collapse. Neck veins will thus normally not be fully distended. Dural sinuses are not collapsible, so their pressure is sub-atmospheric by an amount that is directly related to the distance above the top of the collapsed neck vein (which is at ~ 0 mmHg). Opening of the dural sinus would suck air in (air embolis).



Changes due to gravity: These affect perfusion pressure as shown in Fig 40.1. Since veins collapse if transmural pressure is less than atmospheric, their internal pressure can't be less than zero. Arteries have much higher internal pressure and more rigid walls, so above heart level they experience the full gravity related reduction in pressure and perfusion pressure significantly falls.

40.2 Blood Flow in Collapsible Vessels

In collapsible vessels, such as veins, the normal relationship between Q and ΔP breaks down if a vessel is subject to a P_{TM} sufficiently low. For this condition, Q is ~ to the difference between upstream and external pressure; Q ~ Pu – Pe (See section 10.6).

40.3 Respiratory Pump TOC

Changes in intrathoracic (P_{TH}) and intraabdominal (P_{ABD}) pressures alter venous pressures (Fig 40.2). During inspiration P_{TH} falls and during expiration it increases. These changes effect venous pressure and flow: (1) decreased P_{TH} increases transmural pressure that expands veins and reduces resistance; (2) some of the P_{TH} decrease is transmitted to veins causing venous perfusion pressure to increase. In addition, during inspiration, P_{ABD} increases ("squeezes blood centrally). Combined effect is increased blood flow (increased venous return, VR). Opposite occurs during expiration. Net effect however is a gain in venous return due to inspiration

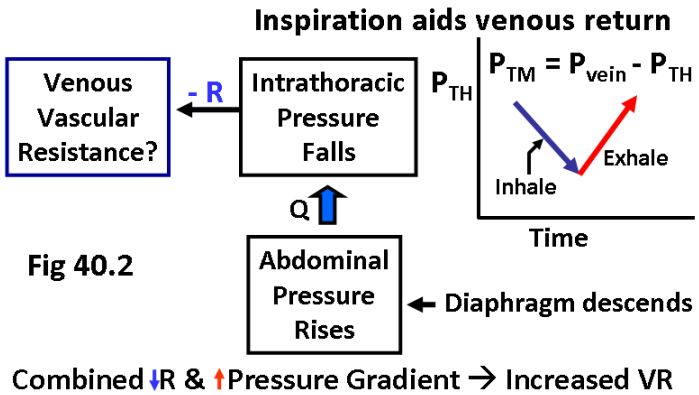
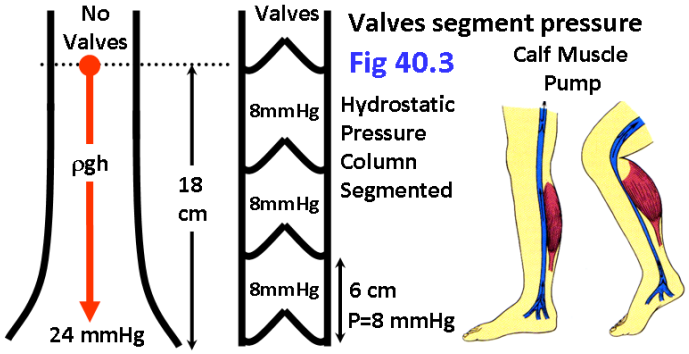
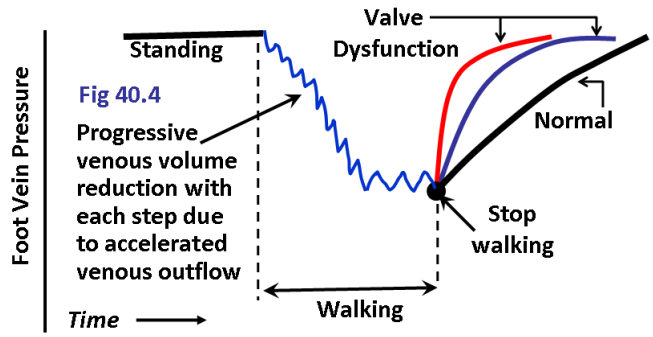


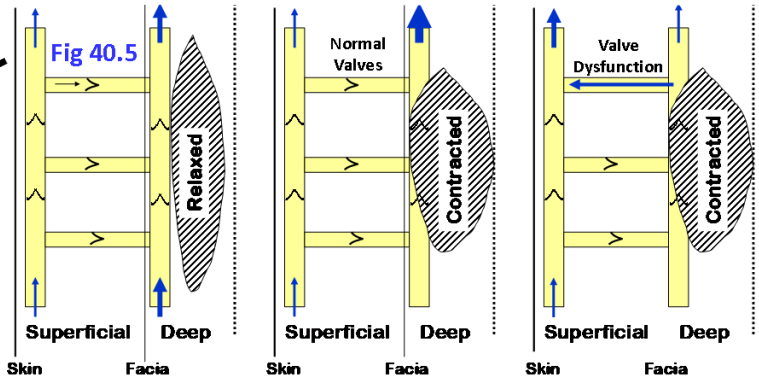
Fig 40.2

40.4 Venous Valves TOC

With legs in a gravity dependent and relaxed position, valves segment the hydrostatic pressure column thereby reducing gravity dependent pressure (Fig 40.3). Calf contraction acts as a pump by compressing veins; flow is directed centrally via valve presence. Walking vs. standing *reduces dependent vein* pressure by displacing volume centrally (Fig 40.4). Adequate function depends on normal valves, so valve incompetence (Fig 40.5) causes altered patterns of venous flow exposing superficial veins to high impulse pressures and an elevation in average venous ambulatory pressure, and a more rapid refilling after calf exercise. The venous hypertension may lead to the development of edema and/or venous ulcers.

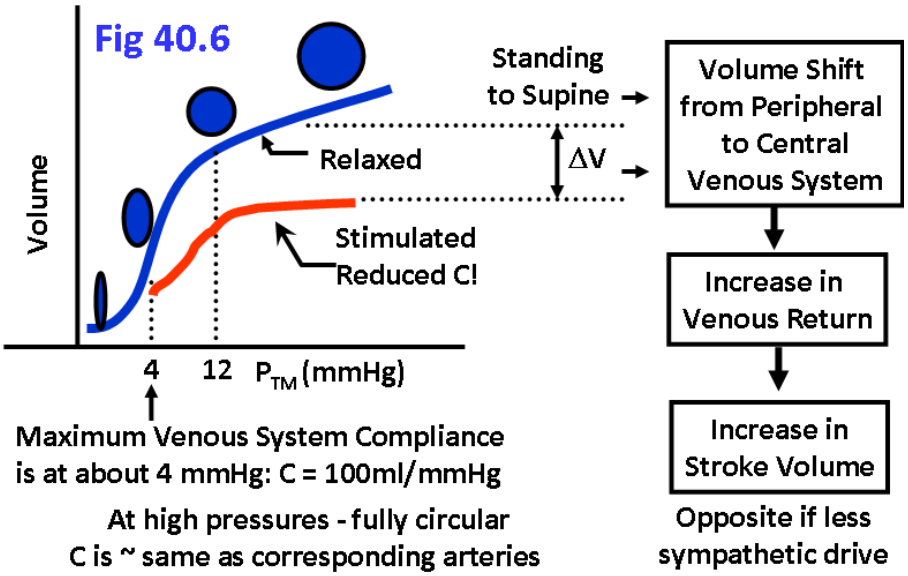




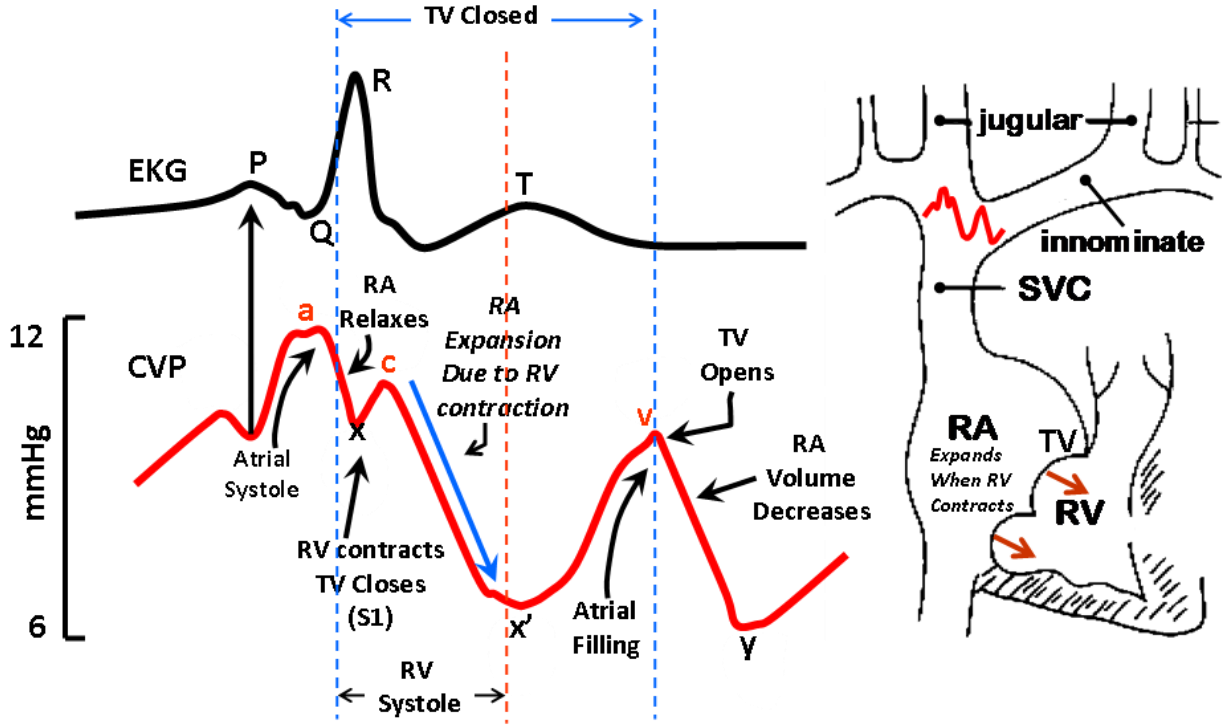


40.5 Venous System Reservoir Role

Blood volume held by the venous system depends on venous compliance, transmural pressure and the contractile state of venous VSM. When VSM is stimulated by sympathetic nerves (Fig 40.6) venous "tone" is increased and vein volume holding capacity is decreased. Some volume is translocated from peripheral veins to central veins increasing CVP; the increased venous return promotes increased SV. The volume reservoir role is facilitated by the large compliance of the venous system, which is ~100 ml/mmHg at 4 mmHg. This means that if 10 ml of blood were added, pressure would raise only 0.1 mmHg. In contrast, the compliance of the arterial system is ~2 ml/mmHg! The large venous compliance is due to the fact that at low pressures veins are partially collapsed and little pressure is needed to expand them. They become circular at ~12 mmHg.

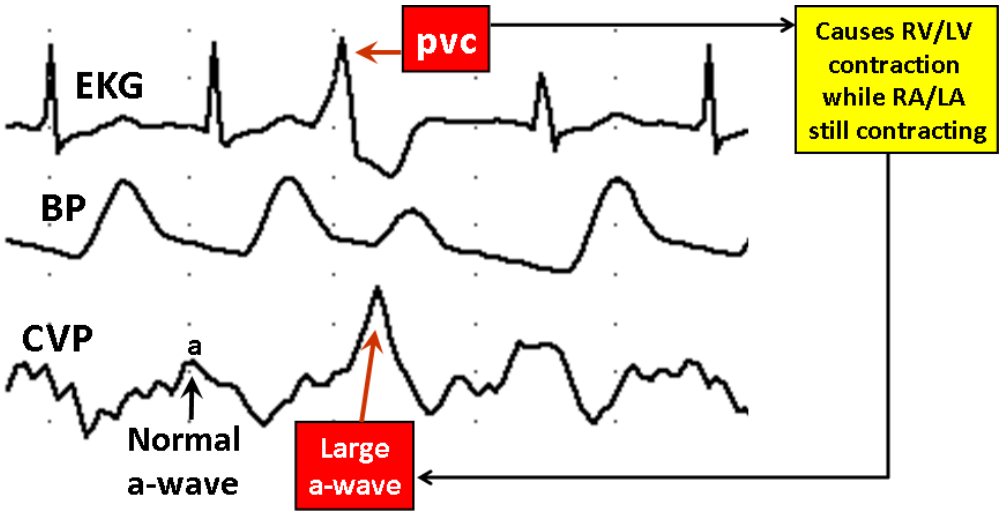


40.6 Central Venous Pressure Pulse (Jugular Pressure Pulse) TOC



a-wave: Venous distension and backward pressure wave during right atrial (RA) systole
x-decent: RA relaxes
c-wave: RV contraction closes TV that bulges into RA (interrupts decent)→ RAP transient increase
x': continuation of x-decent (RV contraction continues "expands" atrium – RAP falls)
v-wave: Rise in RAP with atria filling (Relaxing RV → RA expansion reversed)
y-decent: Decline in RAP when tricuspid valve reopens

40.7 Some Factors Affecting the A-Wave



- *a-waves increased if RA contracts while RV contracting*
- *a-waves increased if tricuspid valve stenosis*
- *a-waves increased if atrium contracts with TV closed*
- *a-waves disappear in atrial fibrillation*
- *a-waves increased if low RV compliance*

40.7 Bullet Summary of some points about Micro/Lymph/Venous Systems TOC

01. Microvasculature is characterized by interconnecting vessel networks; arterioles-capillaries-venules
02. Arterioles serve both blood pressure control and also local perfusion flow and capillary pressure
03. Arteriole vasoconstriction tends to increase local vascular resistance and decrease capillary pressure
04. Blood flow in capillaries is single file with red blood cell (rbc) size similar to the capillary lumen
05. Capillary structure is variable and generally designed to the needs of the organ or tissue in which it resides
06. Transcapillary exchange involves movement of substances across the capillary wall to and/or from tissue
07. Gas and material exchange processes can be described via Fick's law and/or via the PS product concept
08. Water exchange processes are determined by trans-capillary hydrostatic and oncotic pressure differences
09. Normally the hydrostatic pressure difference (δP) tends to move fluid from intravascular to extravascular
10. Normally the oncotic pressure difference ($\delta\pi$) tends to move fluid from extravascular to intravascular
11. Fluid will either filter or absorb depending on the net effective driving pressure ($\Delta P_{FILT} = \delta p - \delta\pi$)
12. The amount of transcapillary flow also depends on the wall resistance to flow as set by its permeability
13. Excess fluid not reabsorbed, leaked protein and interstitial debris are normally removed via lymph vessels
14. Entry is 1st into lymphatic capillaries (terminal lymphatics) and then into lymphangions & lymph collectors
15. Ultimately, collected lymph moves through lymph nodes on its way to returning to the venous circulation
16. Lymphatic system dysfunction may cause abnormal interstitial fluid & protein accumulations-lymphedema
17. Tendency for fluid accumulation (edema) enhanced with an increase in δp and/or a decrease in $\delta\pi$
18. O_2 delivery to tissues depends on blood flow (Q) to tissue and blood's O_2 content and release to tissue
19. Increased O_2 demand is normally met by vasodilation resulting in increased Q and capillary recruitment
20. In some organs there is additionally an increase in the amount oxygen that is extracted
21. In upright human, gravity forces affect arterial-venous pressure gradients and thereby blood flow aspects
22. Below heart, gravity adds to pressures; above heart it subtracts but differentially in arteries and veins
23. Above heart perfusion pressure falls due to venous vessel collapse at transmural pressures less than zero
24. Blood flow in "collapsible" vessels (thin walled veins) may not be determined by perfusion pressure
25. If intravascular pressure (Pi) is < external pressure (Pe) then Q ~ Pu – Pe where Pu is upstream pressure
26. Effects of gravity on lower extremity veins are mitigated by valves that segmentized the pressure load
27. Valve presence also aids venous return associated with the action of the calf muscle pump
28. Dysfunction or failure of venous valves for any reason predispose to venous hypertension/insufficiency
29. Chronic venous insufficiency (CVI) is associated with development of skin disorders and venous ulcers
30. Peripheral veins serve a blood reservoir function since blood can be sympathetically translocated centrally

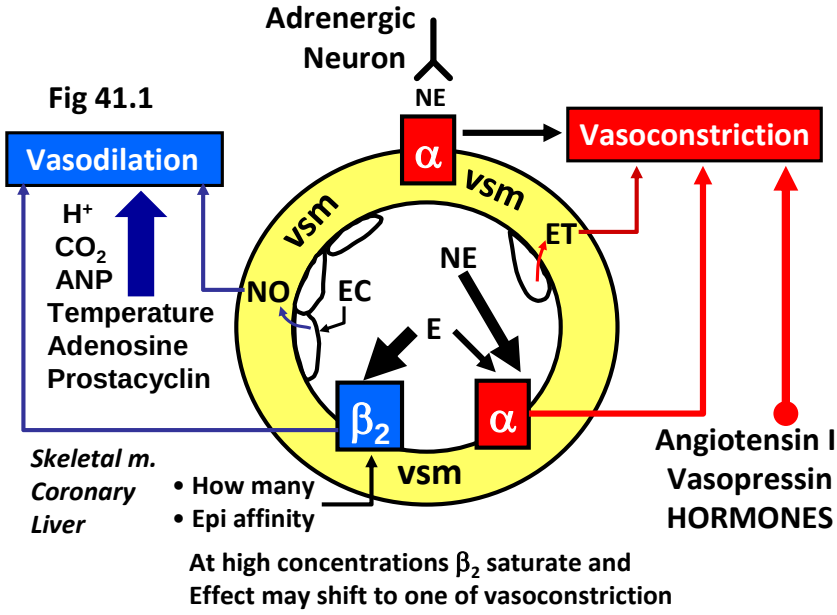
41.0 Peripheral Vascular Control TOC

Neural, chemical and physical processes cause changes in VSM contractile state to alter diameter and wall properties. In the systemic circulation, arterioles are the major player. Events/conditions cause changes in tissue and vessel environment requiring more or less blood flow. Vascular resistance (R) changes in response to these changing needs. In addition to chemical mediators, mechanical factors influence arteriolar diameter and thus affect R. Examples include the myogenic response and wall shear stress due to blood moving adjacent to endothelial cells (EC). Increased shear stress causes EC to release more nitric oxide (NO) that causes VSM to relax (vasodilation). Since increased blood flow causes vasodilation, this is called *flow-induced* arterial vasodilation. Another EC released substance is Endothelin (ET) that is a powerful vasoconstrictor. A vascular receptor mini-review is in **appendix 3** and should be reviewed.

41.1 Sympathetic: Neural and Hormonal (Fig 41.1)

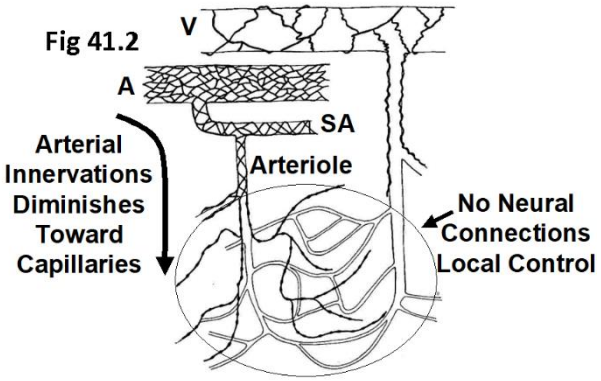
Norepinephrine (NE) acts on α–receptors → vasoconstriction'; Increased sympathetic impulses → more vasoconstriction; less impulses → less constrict = vasodilation ("withdrawal of sympathetic tone"). Epinephrine (E) from adrenal medulla → acts on α and β_2 receptors. Response depends on E concentration and relative number of receptors (α vs β_2). At Low E concentrations in vessels with both α and β receptors cause vasodilation since the generally smaller number of β-receptors are proportionally more activated. At higher concentrations, β-receptors are saturated and there is increasing activation of α-receptors causing vasoconstriction. This is exploited when a high E concentration is included in locally injected anesthetic to to keep the anesthetic localized.

- >Skin arterioles: only α receptors therefore vasoconstriction
- >Skeletal muscle arterioles: both α and β_2 – predominate response to epinephrine is vasodilation
- >Myocardial muscle arterioles: Mostly β_2 receptors - response to epinephrine is vasodilation



41.2 Neural Distribution

Sympathetic vasoconstrictor fibers innervate vessels down to arterioles with similar innervations on the venous side, *but do not innervate vessels in the terminal microvasculature.* Innervations diminish toward capillaries and at terminal arteriole and capillary levels, vessels are *devoid of central neural control.* Changes to meet local tissue demands are *controlled by local vasoactive mechanisms.*



41.3 Vascular "Tone"

"Tone" is a term used to describe VSM activation. More activation implies greater tone. Often the term is used to describe sympathetic activity experienced by the vessels; more impulses → more tone.

41.4 Noncholinergic - Nonadrenergic Neurons (NCNA)

Some autonomic postganglionic neurons don't release NE or Ach but do release NO and other substances (e.g. vasoactive intestinal peptide, VIP and calcitonin gene-related peptide, CGRP) that vasodilate some arterioles. NCNA effects are prominent in the enteric nervous system (GI vasculature) and in the penis where activation of these neurons helps mediate penile erection.

41.5 Important Hormones with Vascular Actions (details later)

- Angiotensin II → constricts most arterioles; part of the renin-angiotensin system
- Vasopressin → constricts arterioles; released from posterior pituitary gland
- Atrial natriuretic peptide (ANP) → dilates renal arterioles; released from atria via stretch

41.6 Endothelial Cells in Vascular Control: (details later)

- Nitric oxide (NO) release from EC is continuous but release is increased by a variety of stimuli including local shear stress and chemical mediators
- Prostacyclin (PGI_2) released in low amounts but secretion can be significantly increased
- Endothelin-1 (ET-1) is a very potent vasoconstrictor

41.7 Mechanisms of Contraction - *Major Role of Calcium*

Contraction of VSM is initiated by a rise in free Ca^{++} in cytoplasm from about 10^{-7} M in the relaxed state, to about 6 x 10^{-7} M in the fully contracted state. Sources of free Ca^{++} are via internal stores and external calcium entry via membrane Ca^{++} channels. Both internal and external sources are required for adequate contraction. Ca^{++} induces contraction by actin-myosin interactions as in cardiac muscle, with differences.

(1) Unlike cardiac or skeletal muscle myosin, VSM-myosin only interacts with actin after ATP has phosphorylated the light chains of cross-bridge heads.

(2) A rise in cytoplasmic Ca^{++} causes a Ca-calmodulin complex to form that activates phosphorylating myosin light-chain kinase leading to cross-bridging and contraction.

(3) Compared to skeletal muscle cross-bridge cycling, VSM cross-bridges are maintained (latch-bridges) at sustained tension with lower energy.

41.8 Calcium's central role in VSM contraction is from these main processes

1. Ca^{++} *entry* into VSM via *Receptor Operated Channels* (ROC)
2. Ca^{++} *entry* into VSM via *Voltage Operated Channels* (VOC)
3. Ca^{++} *release* from SR stores
4. Ca^{++} *removal* via SR and membrane "pumps"
5. Ca^{++} *sensitivity* of VSM

42.0 Vascular Smooth Muscle Contraction Processes TOC

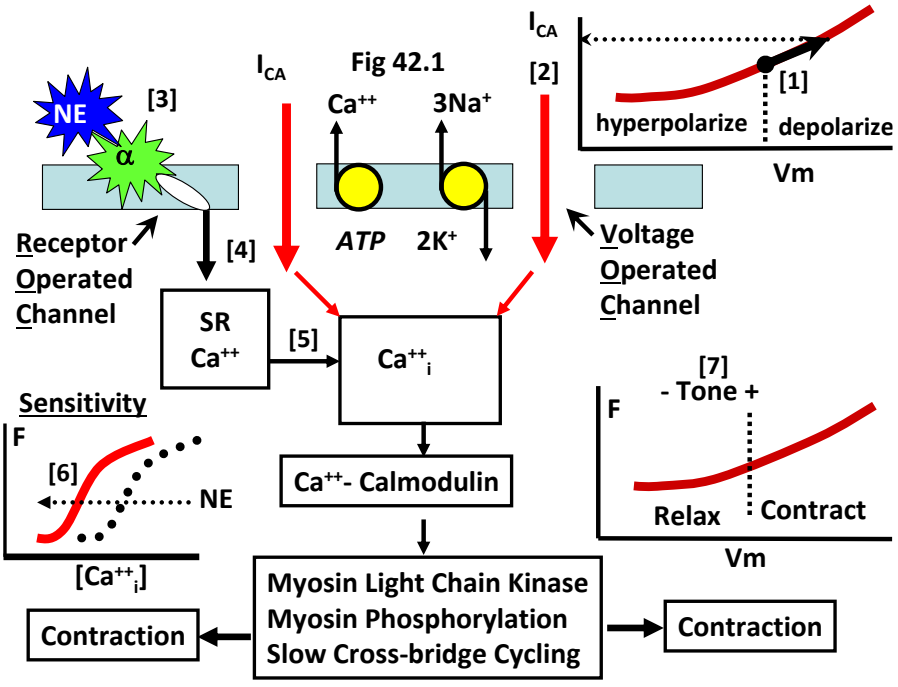
Overview

VSM Resting membrane potential (Vm ~-50 – 70 mv) is mainly determined by high K^+ permeability and outward K^+ current. Internal [K^+] is maintained by active 3Na^+-2K^+-ATPase pump. Entry of Ca^{++} via Voltage Operated Channels (VOC) is an *electromechanical coupling* event that causes vasoconstriction by membrane depolarization. Receptor Operated Channel (ROC) activation-initiated Ca^{++} entry and release is a *pharmacological coupling* event that can result in vasoconstriction. Ca^{++} release from SR stores makes more Ca^{++} available and promotes vasoconstriction whereas Ca^{++} removal by the SR and membrane pumps reduces Ca^{++} availability promoting less vasoconstriction (vasodilation). Sensitivity of VSM contractile machinery to [Ca^{++}] increases with increased [NE] enhancing VSM contraction.

42.1 Voltage Controlled (VOC) and Receptor Operated (ROC) Channels (Fig 42.1)

VOC are controlled by Vm changes. Depolarization [1] opens more VOC and increases [2] I_{CA}. AP's are not needed for VSM contraction! Small changes in Vm affect contractile state; relative depolarization → vasoconstriction (more I_{CA}) and relative hyperpolarization (less I_{CA}) → vasodilation.

ROC are activated by membrane receptor interactions with chemical agents (agonists) e.g. NE, vasopressin, angiotensin, serotonin, histamine, and etc. These agents change VSM contractile state in a depolarization-independent way.



Activation [3] (channel opening or more opening) causes Ca^{++} entry [4] and release of Ca^{++} from sarcoplasmic reticulum (SR) [5]; Result→+cytosol $[Ca^{++}_i]$.

Sensitivity of VSM contractile apparatus to cytoplasmic $[Ca^{++}]$ is controllable by chemical factors. Sigmoidal relation between VSM contractile force, **F** and $[Ca^{++}]$ is shifted left [6] by NE (increased sensitivity). Right shift (decreased sensitivity) may occur via different substances.

Blood Vessel Tone: Changes in vessel "tone" [7] effects the vessel's compliance, generally making it less compliant with increased VSM activation. When VSM of venous vessels is further activated (e.g. by sympathetic impulses) the resultant tone increase affects the volume holding capacity of the involved veins. Thus, a vein with a greater tone can hold less volume at the same pressure than one with less tone. One effect is that blood volume is shifted out of a vein in which the tone has been increased.

Receptor activation and cAMP-related Mechanisms

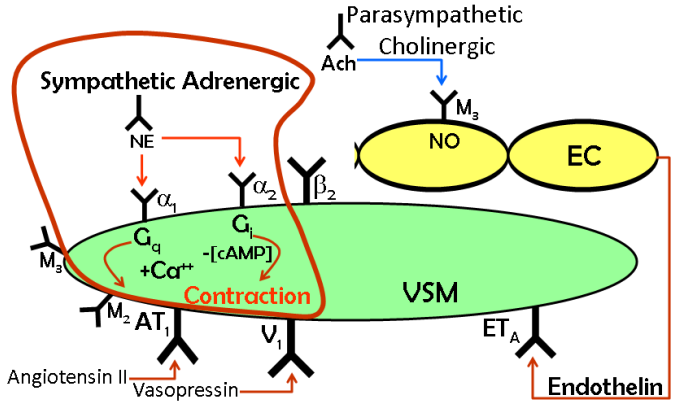


Fig 42.2 VSM CONTRACTION MECHANISMS

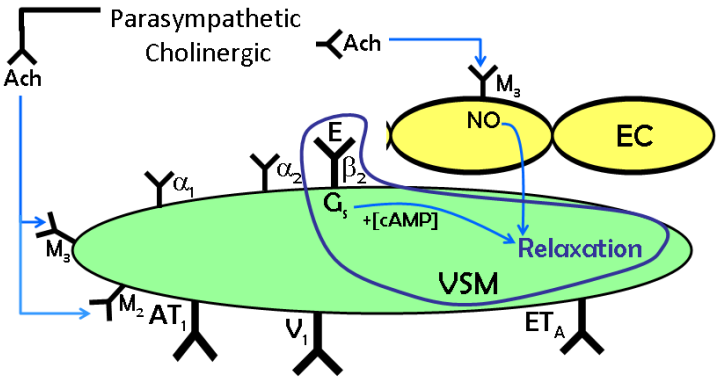


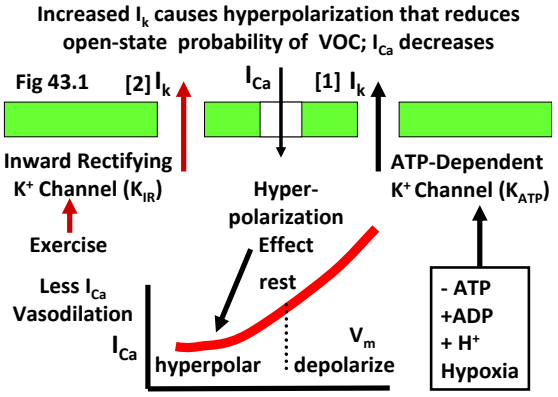
Fig 42.3 cAMP-MEDIATED VASODILATION

Fig 42.2 shows sympathetic activation & release of NE that acts on α-receptors to release Ca^{++} via a g_q mechanism (α_1) and reduction in cAMP via Gi action (α_2) with both effects leading to vasoconstriction. Fig 42.3 shows E acting on β_2 receptor causing increased cAMP via Gi inhibition leading to vasodilation. Also shown is the Ach effect on M2 receptors causing the release of nitric oxide aiding in the vasodilation process.

43.0 Vasodilation Mechanisms TOC

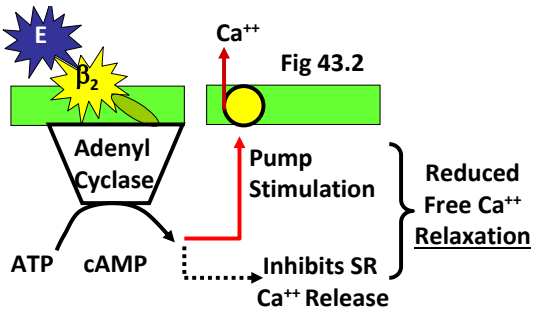
43.1 Hyperpolarization-mediated vasodilation

Hyperpolarization reduces the number of open VOC which in turn reduces I_{Ca} and thereby reduces intracellular Ca^{++} causing VSM relaxation. Hyperpolarization occurs via increased outward I_K through several VSM K^+ channels (**Fig 43.1**). ATP-dependent channels (K_{ATP}) open due to reduced (-) intracellular ATP, increased (+) ADP or increased [H^+] that accompany increased metabolic demand or ischemia; Causes increased I_K through K_{ATP} channels [1]. Vasodilation can also result from hyperpolarizing effects of increased outwardly directed I_K through *inward rectifying K^+ channels* [2]



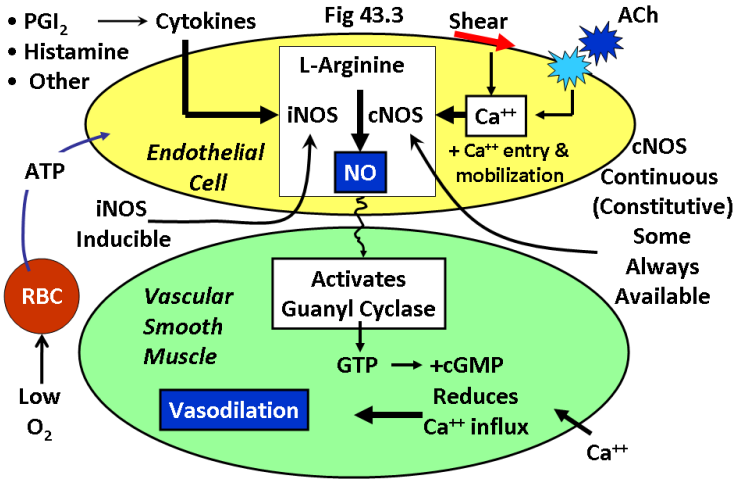
43.2 Cyclic AMP-mediated Vasodilation

β_2-receptors are abundant in some arterioles (**Fig 43.2**) and are linked to a membrane bound G-protein that activates membrane adenylate cyclase (AC). AC catalyzes ATP to cAMP that lowers cytoplasmic Ca^{++} by inhibiting Ca^{++} release and by stimulating pump removal of Ca^{++}. *Result = vasodilation.* E, VIP and histamine acting on H_2 receptors cause vasodilation by this G-protein-adenylate cyclase-cAMP mechanism.



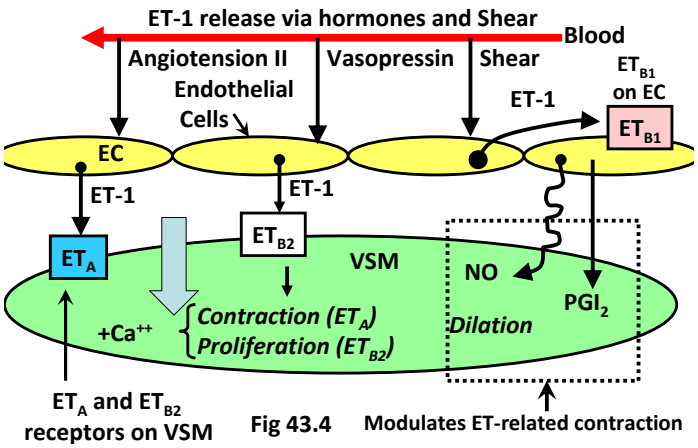
43.3 Endothelial Cell (EC) - cGMP-mediated-Nitric Oxide (NO)

EC affects depend on EC synthesis and release of vasoactive substances such as nitric oxide (NO). NO release is induced by chemical and physical stimuli including Ach, ATP, bradykinin, serotonin, substance-P, histamine and shear stress. NO, synthesized from L-arginine in the presence of iNOS or cNOS, diffuses to VSM (**Fig 43.3**) where it activates cytoplasmic guanosine tripohsphate (GTP) that then increases cyclic guanosine monophosphate [cGMP], causing a decrease in cytosolic free Ca^{++} in VSM causing relaxation. Stripping of, or injury to, EC, eliminates or severely blunts this response; thus, coronary artery *constriction* may occur to Ach challenge if EC are dysfunctional. Nitrates, clinically used as vasodilators, produce their dilator action via NO production. In **Fig 43.3** *cNOS=constitutive NO synthase (continuous and Ca^{++} dependent) and iNOS=inducible NO synthase*



43.4 Less ET = Vasodilation

ET-1 released from EC acts on ET_A & ET_{B2} receptors on nearby VSM & on ET_{B1} receptors on EC. Main ET effect on VSM is contraction but activation of ET_{B2} leads to VSM cell proliferation. Activation of EC ET_{B1} receptors by ET-1 causes NO and prostaglandin I_2 (PGI_2) release. This vasodilation tendency helps mediate constriction of VSM ET_A receptor activation. If ET_A is blocked, ET-1 causes vasodilation. Release of ET-1 is facilitated by shear stress and circulating hormones e.g. angiotension II and vasopressin that help control blood pressure.



44.0 Local Controls TOC

Events/conditions cause changes in tissue and blood vessel environment requiring either more blood flow or sometimes less flow. The mechanisms and mediators discussed are available to cause blood flow adjustments to meet flow and other demands. Three important local responses are:

- **Autoregulation** (blood flow maintenance despite changes in organ perfusion pressure)
- **Active hyperemia** (blood flow changes to meet current or changing metabolic demands)
- **Reactive hyperemia** (blood flow increases to meet prior blood flow deficits).

In addition to the variety of chemical mediators, certain mechanical factors influence arteriolar diameter and thus affect resistance and blood flow.

- **Myogenic Response** (increased stretch of the vessel wall due to changes in transmural pressure causes a reflex constriction and decreased stretch causes a reflex dilation).
- **Shear Stress** due to blood moving adjacent to endothelial cells causes these cells to increase or decrease the release of vasoactive substances. Nitric oxide (NO) causes VSM to relax (vasodilation). Since an increase in flow causes a vasodilation this is called ***flow-induced arterial vasodilation***.

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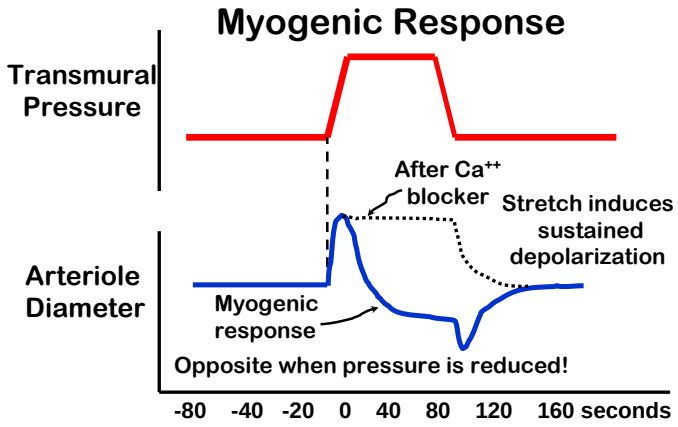
44.1 Myogenic Control TOC

This is a process in which changes in transmural pressure (TMP) are countered by changes in VSM activation causing vasoconstriction if TMP is increased and vasodilation if TMP is reduced. The adjacent figure shows the response to a sudden increase in TMP before and after blocking VSM calcium channels. The initial response to increased transmural pressure is an increase in arteriole diameter. This initial response is purely mechanical due to pressure-induced distension of the wall. But, in many arterioles this initial wall stretch evokes a ***vasoconstriction response*** with a diameter decrease below its pre-stretched diameter. This ***myogenic response*** increases the arteriole's resistance. If TMP is decreased an opposite response occurs.



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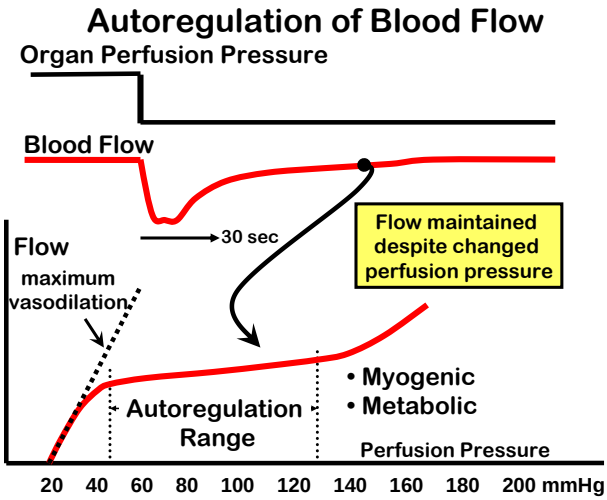
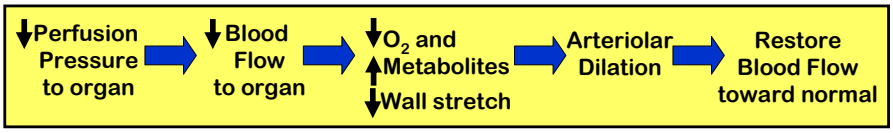
44.2 Autoregulation TOC

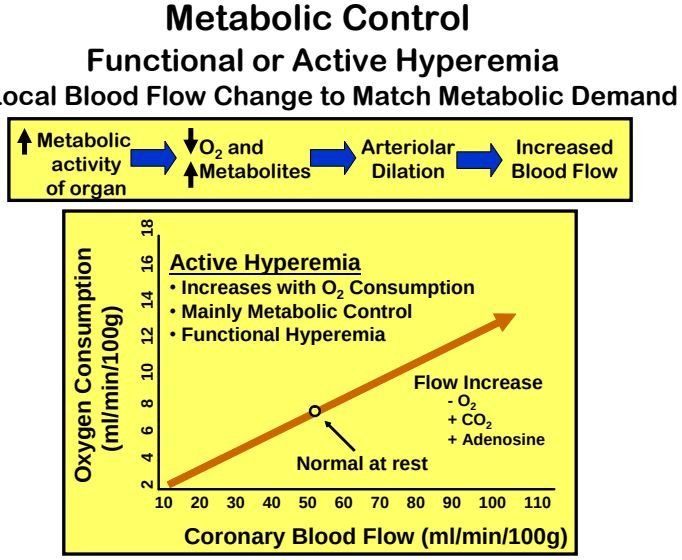
The term autoregulation refers to a process whereby blood flow to an organ is maintained within narrow limits in spite of *changes in perfusion pressure to that organ.* Autoregulation is present in skeletal and cardiac muscle, kidney, brain and other tissues (not the lung). It is partly explained by the *myogenic response* but *vasodilator metabolites are also involved.* The pressure range over which autoregulation is effective is limited. This useful range is called he *autoregulation range.* At pressures above or below this range this control is not useful.

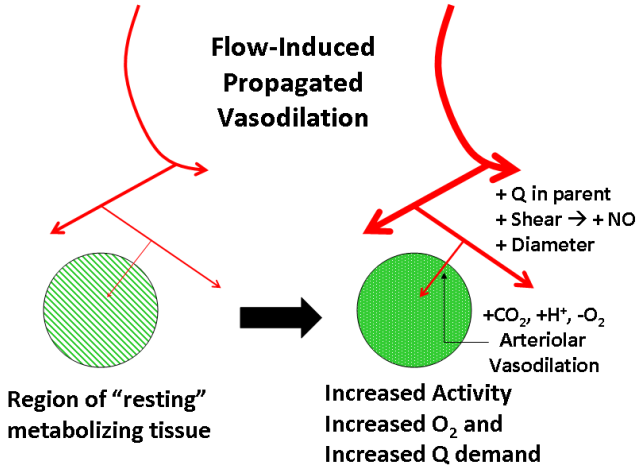




44.3 Local Metabolic Control - Functional Hyperemia TOC

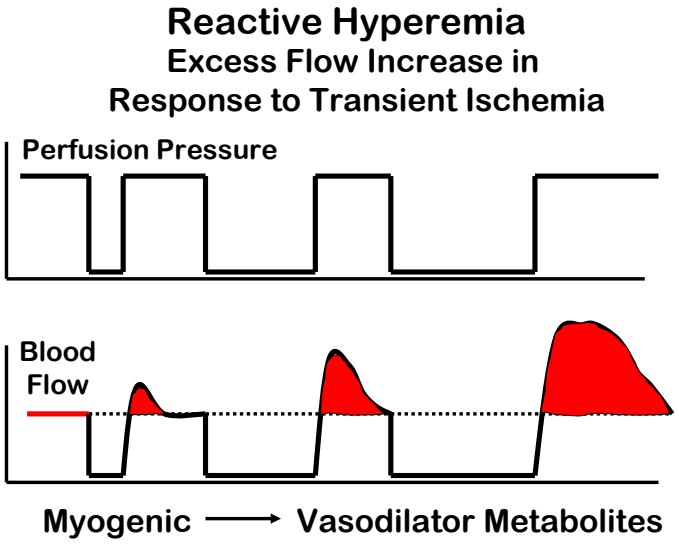
Most metabolic by-products cause vasodilation and facilitate local blood flow adjustments to meet increased blood flow demand. This process, variously called ***functional hyperemia***, ***metabolic vasodilation*** and ***active hyperemia***, should not be confused with the autoregulatory process. Functional hyperemia is increased blood flow associated with **increased *demand*** stemming from increased metabolic activity. For example, an increase in heart rate will increase myocardial metabolic activity that will then requires more blood flow to meet the increased demand. The blood flow increase is caused mainly by metabolic vasodilation in direct proportion to metabolic rate as measured by oxygen consumption. The functional hyperemia is thus caused by arteriolar vasodilation secondary to release of vasodilator substances from active tissue. There are many such vasodilator substances (K^+, H^+, adenosine and etc.). An important aspect of functional hyperemia is the upward spread of vasodilation from arterioles in which metabolic substances caused the initial dilation. This is achieved in part from ***flow-induced vasodilation*** in medium and larger arteries supplying blood to increased metabolically active tissue as illustrated in the adjacent figure.





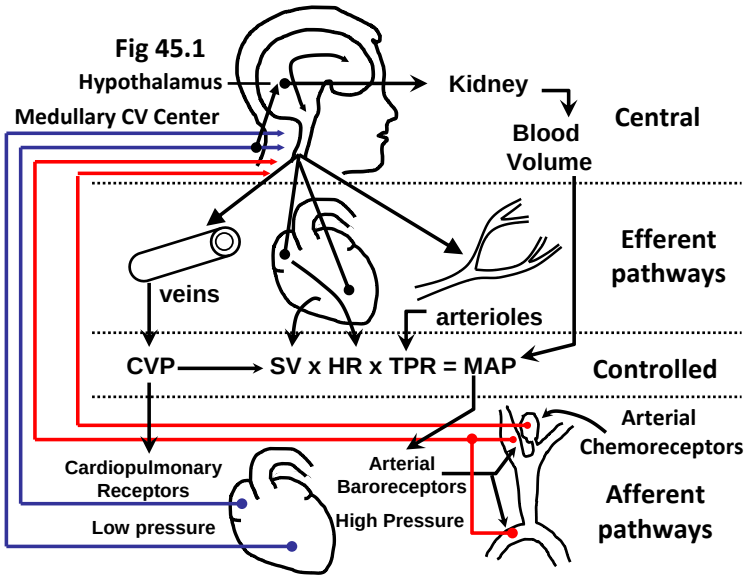
44.4 Reactive Hyperemia TOC

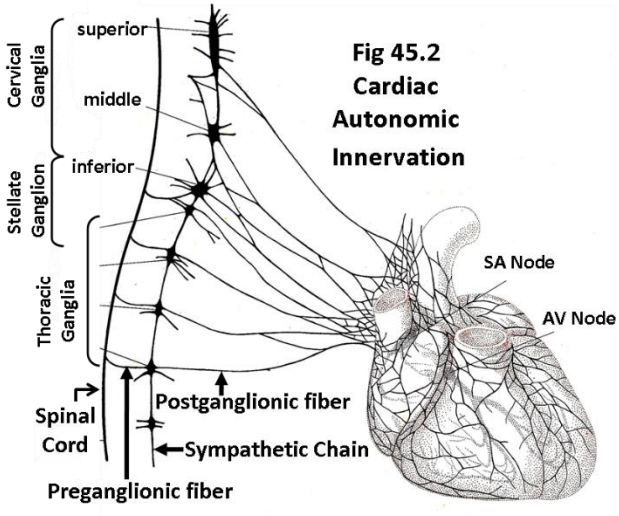
If blood flow is reduced below that needed to supply dependent tissue needs (**ischemia**) via vascular blockage or compression, and then the blockage is removed, the returning blood flow will transiently exceed the pre-blocked blood flow. This response is called ***reactive hyperemia***. The hyperemic flow peak and duration depend on the *amount of flow deprivation*. Myogenic response partially accounts for short duration flow reduction (~ 1-3 min). Longer duration occlusion responses are dominated by vasodilator metabolite build-up within tissue. After ~ 15 minutes of flow stoppage, hyperemic response is near maximal. If flow deprivation is extended (as may occur during surgical procedures), the hyperemic response ***may not occur*** and blood flow may actually fall to levels below normal after occlusion is removed. This impairment is related to ***ischemia-reperfusion injury*** that is in part due to damage caused by oxygen-derived free radicals during ischemia and the effects mediated by returning blood flow.



45.0 Cardiovascular Controls, Reflexes and Regulation TOC

45.1 Overview: Combined neural, local and humoral mechanisms act on heart and blood vessels to help maintain cellular environmental parameters within ranges adequate for function via feedback (**FB**) (Fig 45.1 & 45.2).



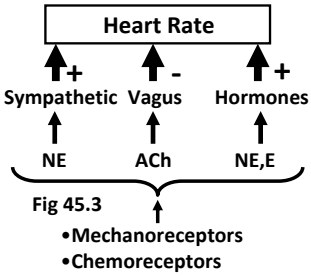


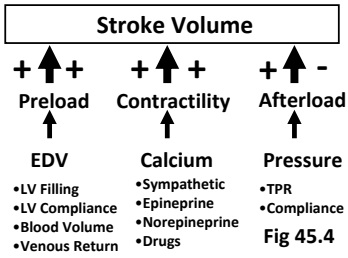
Since conditions change due to altered functional demands, age or pathology, the system monitors key parameters, and, if these are too low or too high, **FB** to the control center cause actions that try to return values toward needed functional levels. For example, to restore blood pressure from a sudden drop due to blood loss, the system needs a way to detect that pressure has dropped and a way to use this information to counteract the change. ***Sensing*** is by strategically placed ***receptors*** that respond to pressure changes with altered *afferent FB neural activity* to the *medullary cardiovascular control centers* (***vasomotor center***). In turn, the vasomotor center processes this information and issues control commands in the form of altered levels of *efferent nerve impulse* rates directed toward heart and blood vessels. Fig 45.1 shows the main parts of cardiovascular reflex control. The sensors/receptors provide afferent feedback to the central processor, which alters efferent neural commands to heart and vessels to cause variables (e.g. BP & CO) to change in appropriate directions.

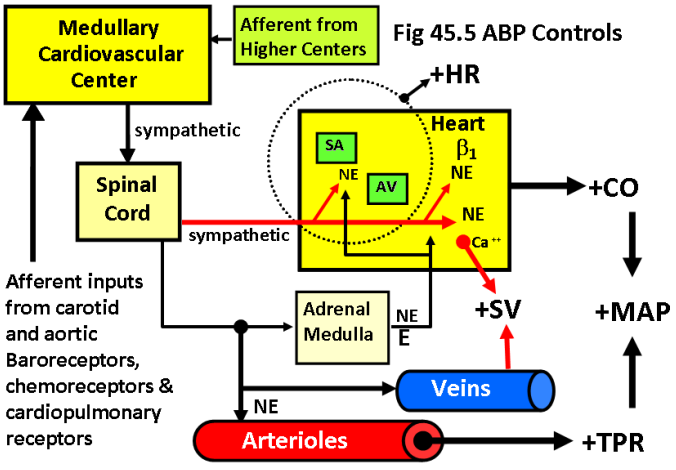
45.2 Review of Heart Rate, Stroke Volume and Blood Pressure Regulation

Heart Rate: Mainly determined by interplay of sympathetic and vagal activity. Medullary efferent signals are modulated by feedback from receptors (Fig 45.3).

Stroke Volume: Depends on sympathetic components that alters Ca^{++} availability and changes in cardiac contractility. SV also depends on pre- and afterloads (Fig 45.4)





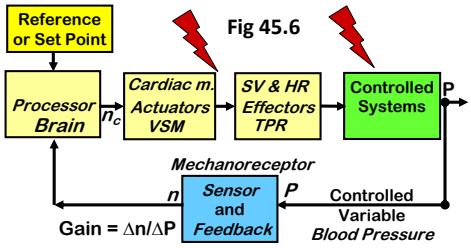


MAP =~ CO x TPR for a fixed blood volume.

TPR depends mainly on sympathetic activity acting on arterioles. Since **CO = SV x HR** its control depends on changes in **SV** and **HR**. So, maintaining or adjusting MAP depends on control of SV, HR and TPR. Cardiac and peripheral factors interact as a system and depend on ***negative feedback*** for cardiovascular control. Aspects of ABP control are shown in Fig 45.5.

45.3 Negative Feedback and its Relationship to Cardiovascular Control TOC

Negative feedback (Fig 45.6) limits the amount of change in a controlled variable such as ABP. It works because small changes are sensed by receptors that feed this information back to a processor that takes actions to counteract the initial change. A key feature is the feedback gain. Since some change must occur for the process to be activated, a larger gain results in a smaller net change in the controlled variable. For example, if without feedback, pressure would change by 10 mmHg, then for a feedback gain of 10 it will change by 1 mmHg. So, negative feedback stabilizes controlled physiological variables. The high-pressure baroreceptors (HPB) located in the carotid sinus (CS) and aortic arch. They respond BP changes by altering neural afferent discharge rate (n) to the vasomotor center (processor), which in turn alters its efferent nerve traffic rate (n_c) to heart and vessels. The reflex effect alters SV, HR and TPR, so as to oppose the initial BP change.



(P) only

- Change in P if there were no feedback = δP
- Change in P with feedback = δP/Gain

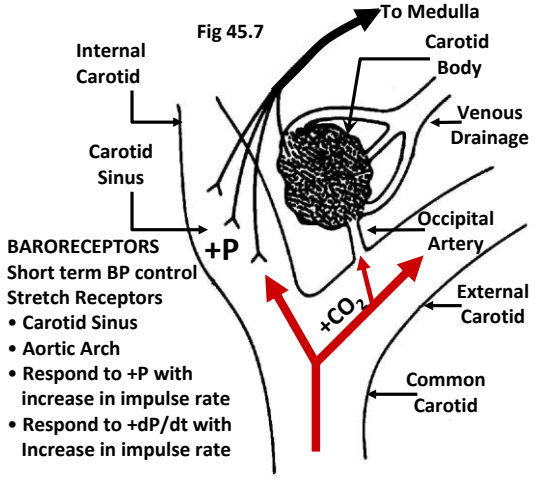
A perturbation occurs that, in the absence of feedback would cause a δP of 10 mmHg. For feedback gains of 2 and 20 how much will the actual pressure change?

δP = 10 mmHg/2 = 5 mmHg
δp = 10 mmHg/20 = 0.5 mmHg

are to

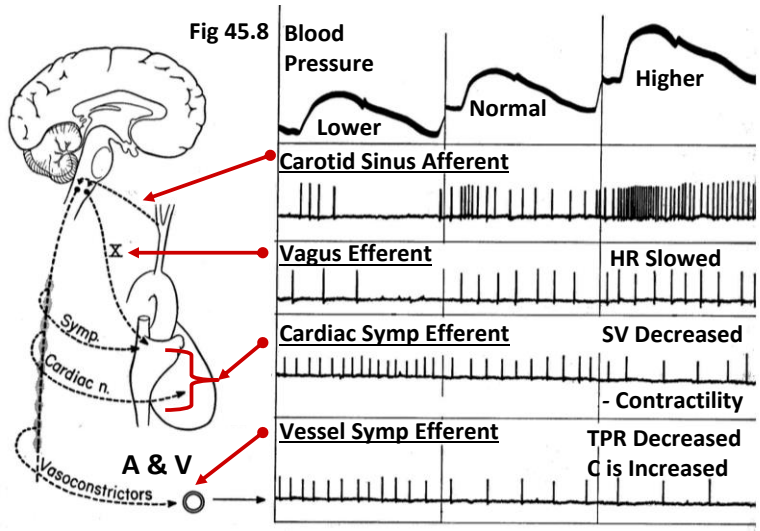
45.4 Arterial Baroreceptor Reflex TOC

The HPB have richly innervated sensory nerve endings in the (Fig 45.7) and aortic arch wall. Receptors are sensitive to stretch and rate of change of stretch. Changes in ABP and dp/dt cause afferent and efferent impulse rate changes as shown in Fig 45.8. This control is concerned with short-term regulation and is bidirectional. A BP increase in the CS causes nerve ending distortion that triggers more afferent nerve traffic to the medullary control center resulting in reduced sympathetic efferent nerve traffic to heart and vessels and increased vagal nerve traffic to heart. Since the reflex is sensitive to rate of change of BP, baroreceptors are also important in conditions in which MAP is near normal, but cardiac ejection rate is low which is sensed as a need to increase sympathetic activity; with the reflex effect causing increased cardiac contractility and TPR. If pressure initially decreases, the reflex attempts to restore Baroreceptor reflex gain is maximum near normal BP values and is reduced if BP is too or too high.



CS

BP



BP.

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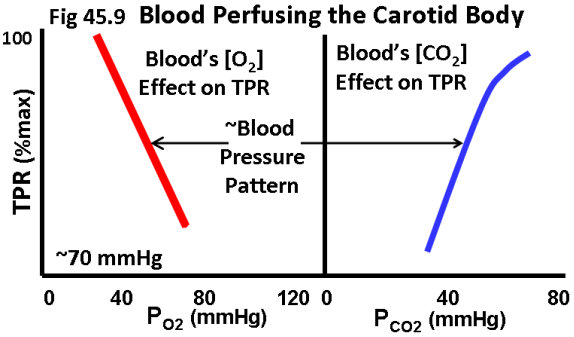
Other ABP Controls: Fibers in descending tracts from the cerebral cortex that relay the hypothalamus initiate BP and HR increases associated with *emotions* (sexual excitement, anger and etc.) in a way similar the baroreceptor reflex response to *hypotension*. Afferent impulses originating in the reticular formation that converge on the vasomotor center cause BP changes induced by *pain*. Pain usually causes BP to increase, but if pain is prolonged and severe BP may decrease and fainting may occur.

45.5 Peripheral Chemoreceptors TOC

Carotid and aortic bodies have a large blood flow/g of tissue and respond to **hypoxemia** (low blood O_2), **hypercapnia** (high CO_2) and **acidosis** (low pH). These chemoreceptors help regulate breathing but also affect cardiovascular function. Hypercapnia and hypoxia cause increased afferent impulses to the medullary CV center. This reflexively increases TPR thereby raising BP. Small increases in arterial CO_2 trigger the response, but the response to reduced O_2 occurs only if P_{O2} falls to ~65-70 mmHg from a normal value of ~95 mmHg (Fig 45.9). The reflex BP rise increases brain and coronary blood flow to offset O_2 fall. The chemoreceptor-driven vasoconstriction (other than brain and heart) helps support BP during *hypotension* (e.g. severe hemorrhage). Since the low-end threshold for baroreceptor activation is ~60 mmHg, a BP fall to less than this strongly depends on chemoreceptor responses to help maintain BP.

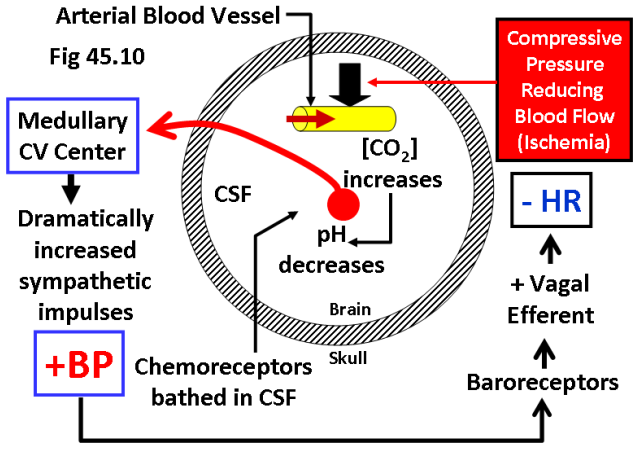
Fig 45.9 **Blood Perfusing the Carotid Body**



45.6 Central chemoreceptors TOC

Similar directional changes in TPR and BP occur if *central* chemoreceptors (Fig 45.10), located in the medulla, experience pH changes. A decreased pH of the cerebral spinal fluid can occur if arterial CO_2 content increases or via various renal-related changes. They are insensitive to reduced levels of arterial PO_2. If blood flow to the vasomotor center is severely depressed, for example due to a high intracranial pressure, the fall in brain oxygen is large and central chemo-responses cause a large increase in blood pressure that is accompanied by a baroreceptor induced *reflex bradycardia;* called the **Cushing reflex**.

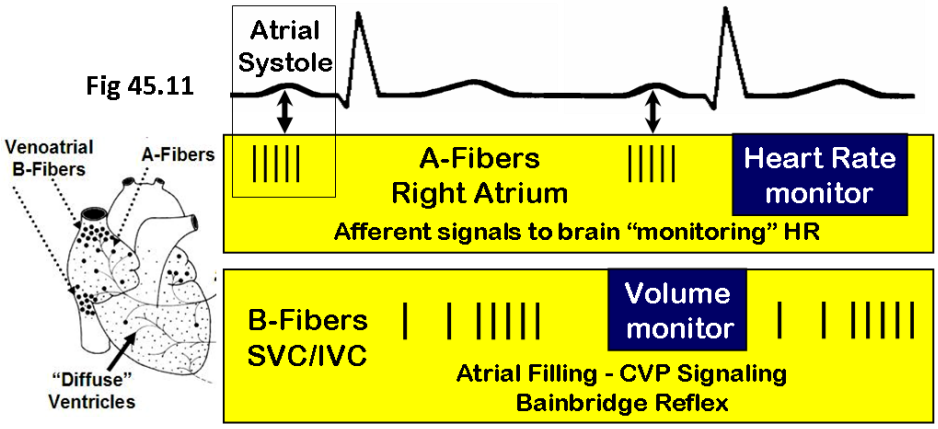
Fig 45.10



45.7 Cardiopulmonary Receptors (low pressure receptors) TOC

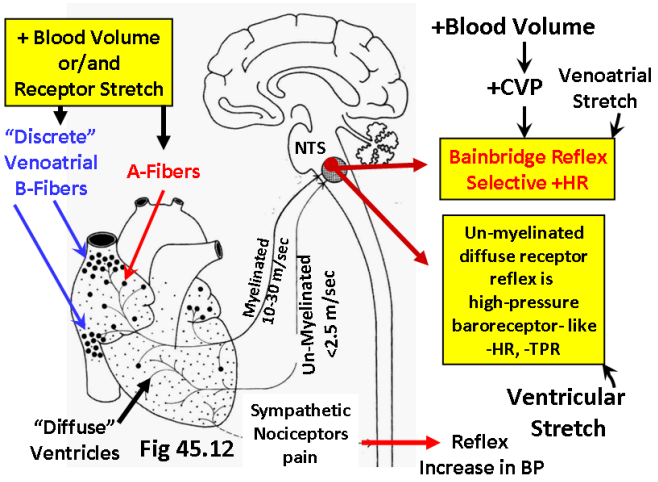
Discrete mechanoreceptors are located near venoatrial junctions (myelinated A and B fibers) and others are diffusely scattered (non-myelinated) in atria and right ventricle (Fig 45.11). Electrical activity from the A and B fibers differ in timing during the cardiac cycle. The fiber firing rate increases with atrial filling and is viewed as a volume monitor sensitive to the value of central venous pressure and thus sensitive to venous return. Contrastingly, A-fiber firing seems to be HR dependent and is viewed as a 'heart rate monitor'. It is mainly the B-fibers that are responsible for the Bainbridge Reflex (section 45.8). Firing rate of B-fibers increases if circulating blood volume is increased above normal but the firing rate does not generally decrease if volume is reduced.

Fig 45.11



45.8 Bainbridge Reflex TOC

Afferent impulses from discrete receptors increase in response to their **stretch**. This occurs if CVP increases due to increased blood volume. Increased afferent traffic from B-fibers (Fig 45.12) results in a **selective increase** in efferent nerve impulses to the SA node causing an increase in heart rate (Bainbridge Reflex). This reflex tends to reduce central blood volume. Sympathetic drive to heart *muscle* is **not** increased nor is TPR changed.



45.9 Diffuse receptors

These are connected to the vasomotor center via vagal unmyelinated fibers. They have a low resting impulse rate that *increases if RV pressure/stretch becomes large.* If this occurs they initiate a reflex **systemic vasodilation and bradycardia**. In addition, sympathetic nociceptive chemoreceptors send afferents via the spinal cord (sympathetic afferents) that are involved in signaling cardiac pain. Triggers include adenosine, prostaglandins and lactic acid. Mixing with somatic fibers may explain arm/chest wall referred pain. Reflex response to these sympathetic afferents is usually increased BP.

46.0 Low Pressure Receptor (LPR) Involvement in Blood Volume Control TOC

LPR are involved in regulating circulating blood volume in several ways (Fig 46.1). Each depends on LPR stretch and reflexes that are elicited. One main feature is the effect on kidney; increased volume promotes increased urine that reduces the volume. Other LPR reflexes change TPR to move BP in a direction opposite to that caused by volume changes.

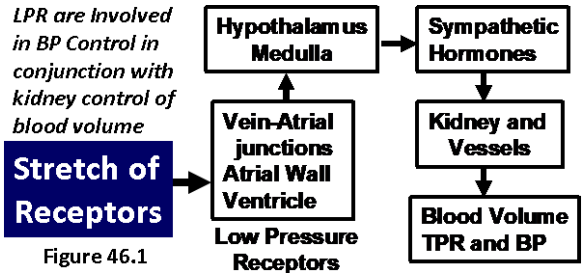


Figure 46.1

46.1 Renin-Angiotensin-Aldosterone System (RAAS) TOC

The RAAS and kidney are involved in blood volume regulation and BP regulation. General aspects are in Fig 46.2 with more details later. Increased renin is released in response to 1) sympathetic impulses to β_1-receptors in and around walls of renal arterioles; 2) if kidney baroreceptors sense that kidney BP is too low and 3) feedback from macula densa cells in walls of distal tubules. They sense salt content and tubule fluid volume that depends on GFR (glomerular filtration rate). If salt content is high, or fluid volume is low, feedback to granular cells increases renin release and dilates afferent arterioles causing increased renal flow and GFR. The increased renin interacts with angiotensin I that in the presence of angiotensin converting enzyme (ACE) yields angiotensin II (ANG II) which is a potent vasoconstrictor. ANG II also promotes renal Na retention and stimulates aldosterone release from the adrenal cortex causing further Na retention and urine reduction helping to increase BP.

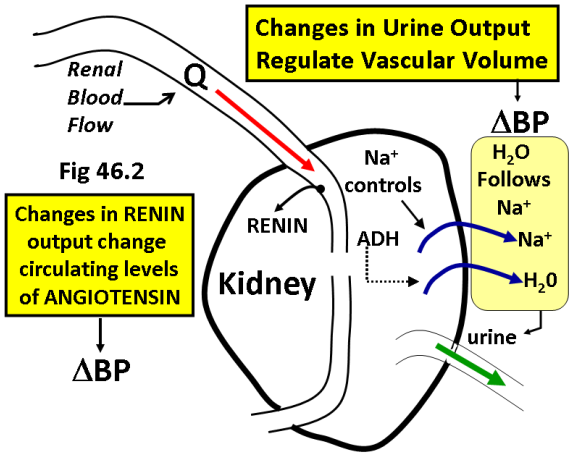


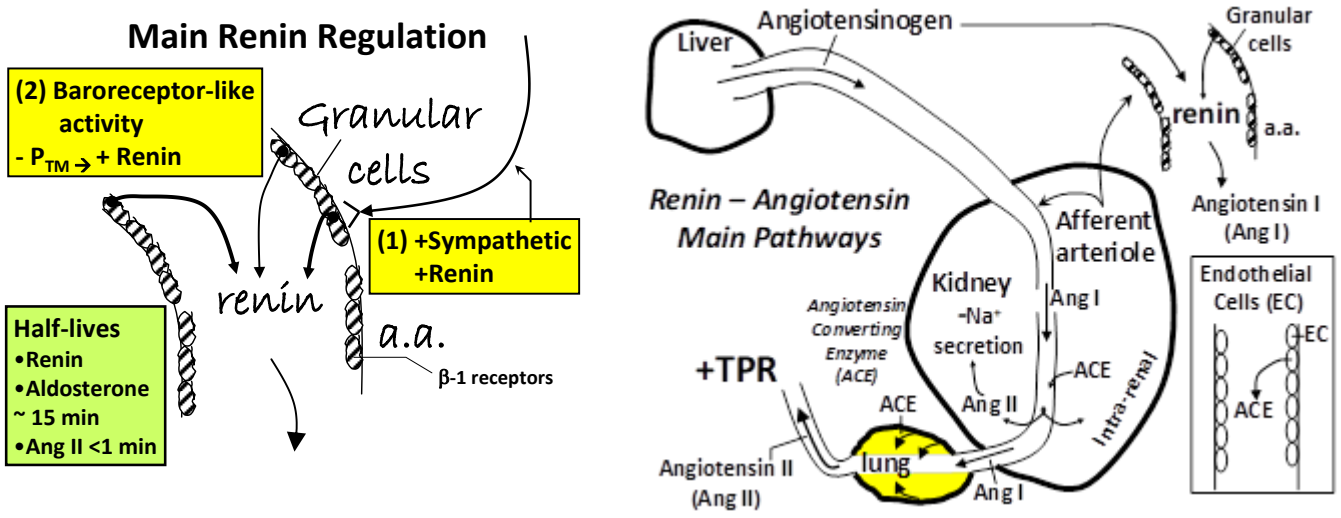
Fig 46.2

Renin-Angiotensin-Aldosterone System: Role in blood pressure control

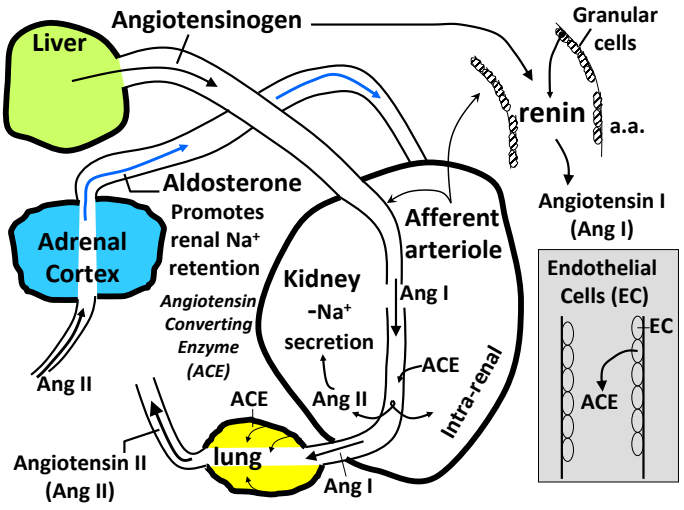
The "Players"

- **1. Angiotensinogen → Protein mfg and released from liver**
- **2. Renin → Proteolytic Enzyme → Kidney**
- **3. Angiotensin I → (Ang I) → Formed by 2 on 1 in kidney**
- **4. Angiotensin Converting Enzyme (ACE)**
- **5. Angiotensin II → (Ang II) → ACE on Ang 1 → Constrictive Peptide**
- **6. Antiduretic Hormone (ADH) also called Vasopressin (Pituitary)**
  - **→ Vasoconstrictive**
  - **→ Water reabsorption**
- **7. Aldosterone → steroid hormone → adrenal cortex**
  - **→ Promotes Na^+ reabsorption (and H_2O)**
  - **→ Promotes K^+ excretion in kidney**
  - **→ Increased by Angiotensin II**

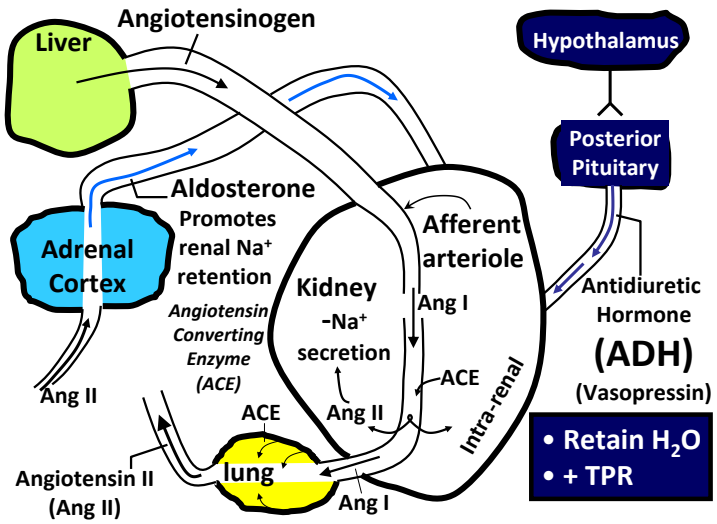
46.2. Renin – Angiotensin Main Pathways *(granular cells = juxtaglomerular cells)* TOC



46.3 Include Aldosterone as a Modulator of Na Retention and Urine Output



46.4 Include Effects of ADH (Vasopressin) as a Modulator of H_2O Excretion



46.5 Summary of 2 Neural and One Direct Response to Increased Atrial Stretch

Neural Response #1 to Increased Atrial Stretch

+ Heart Rate → "Bainbridge Reflex"

- Sympathetic Only to kidney

↓

Renal Vasodilation & Reflex tachycardia

↓

+ Renal Blood Flow
+ Urine Output (Diuresis)

Volume Reduction!

Neural Response #2 to Increased Atrial Stretch

Hypothalamus → - Antidiuretic Hormone (ADH=Vasopressin)

ADH also has strong vasoconstrictive actions so if less ADH → TPR Reduction!

Inhibits ADH release

Increased Atrial Stretch

Axon transport → Posterior Pituitary → Blood transport → Kidney (Less ADH) Conserves less H_2O Volume reduction!

Reduced TPR and BV → Reduced BP

***Non-Neural* Response to Atrial Stretch**

Atrial Myocytes → +Atrial Natriuritic Peptide (ANP)

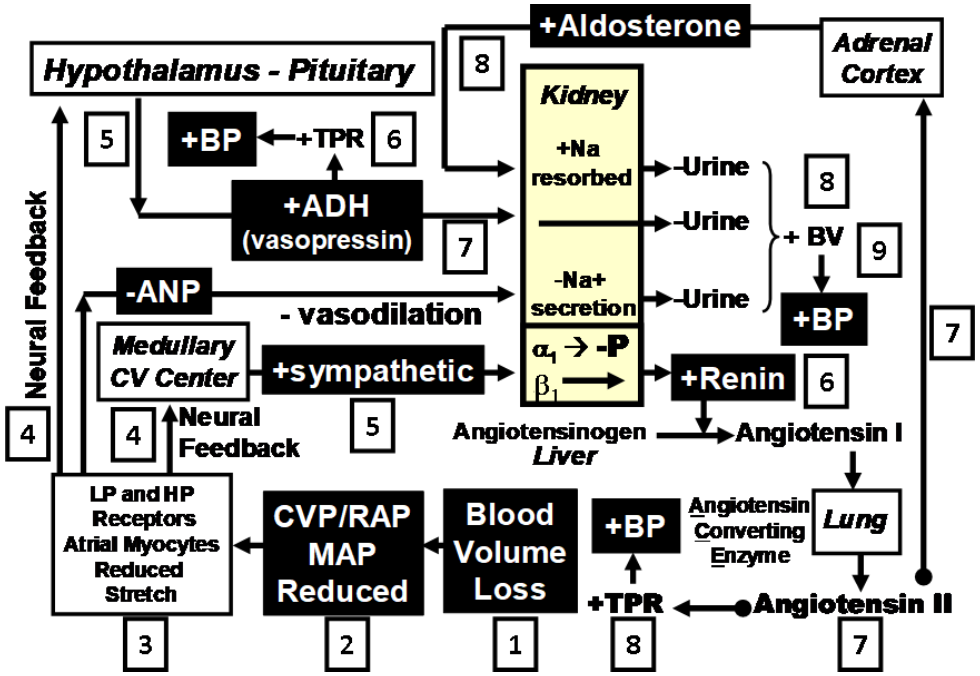
Increased Stretch

• Renal Vasodilator
• Renal Natriuresis (+Na^+ excretion)

↓

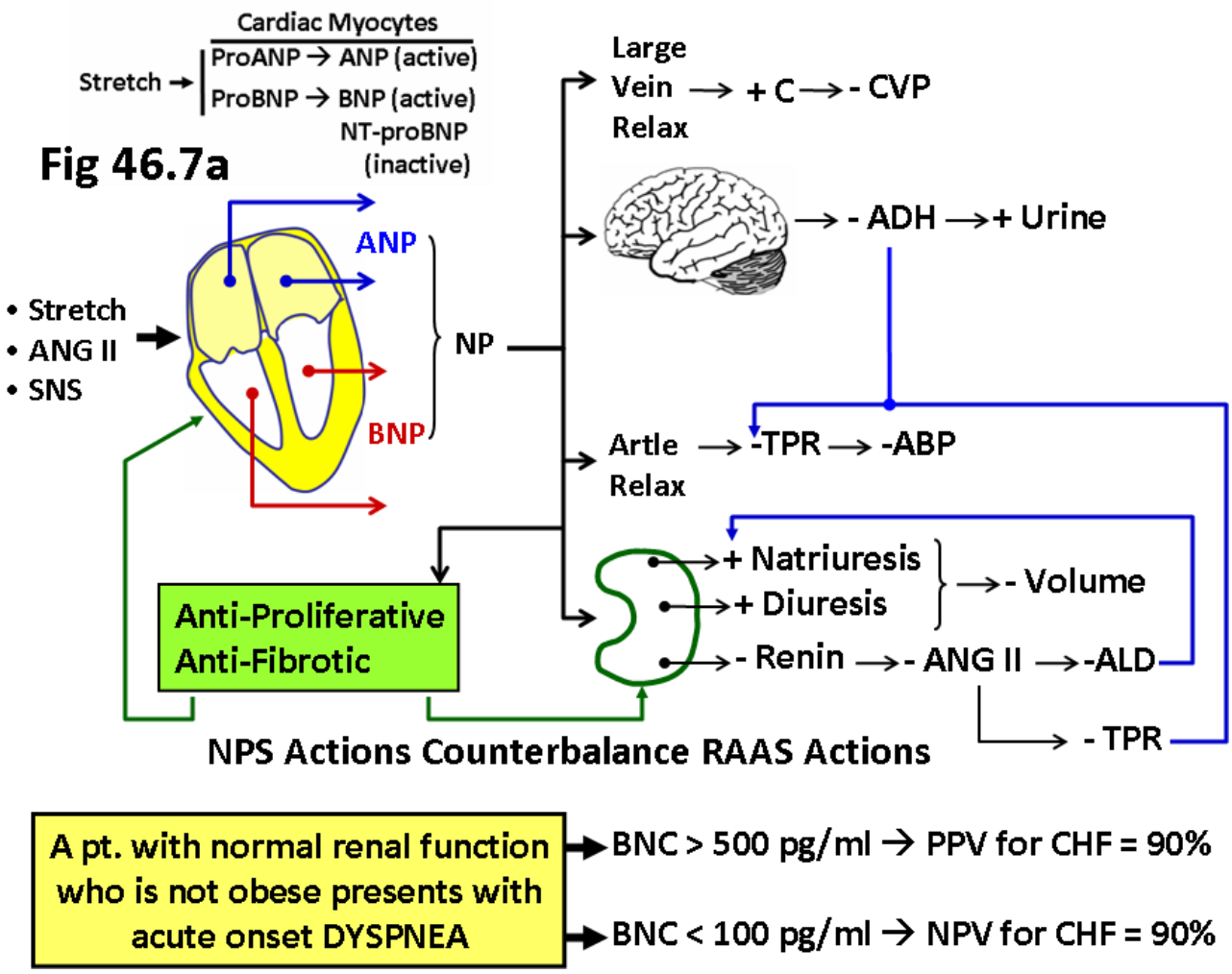
+ Urine Output
- Volume

46.6 Clinical Correlation: Significant Blood Loss → RAAS Controls TOC



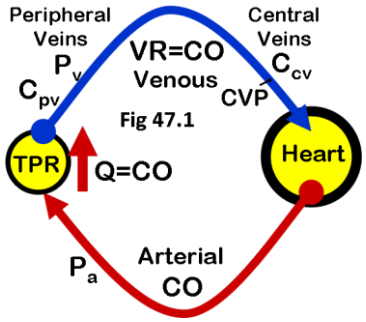
46.7 Clinical Correlation: Natriuretic Peptide System (NPS) and CHF TOC

There are three main peptides involved in the NPS; (1) Atrial Natriuretic Peptide (ANP), (2) B-type (or Brain) Natriuretic Peptide (BNP) and (3) C-type Natriuretic Peptide (CNP). Cardiac ANP is released from atrial myocytes and BNP from ventricular myocytes (Fig 46.7). BNP is stored as a long-chain polypeptide (ProBNP). CNP is released from endothelial cells in response to increases in shear stress and exerts its vasodilatory effect locally. ANP and BNP release are stimulated in response to stretch, ANG II and increases in sympathetic nerve stimulation (SNS). The NPS produces its effects by actions on Natriuretic Peptide Receptors (NPR). ANP and BNP both selectively bind to receptor NPR-A and cause similar physiological responses as described in Fig 46.7. CNP binds to receptor NPR-B. Both receptor types utilize cGMP as a 2nd messenger. Each peptide is cleared by either the enzymatic action of neutral endopeptidase (NEP) or by binding to a third widely distributed receptor (NPR-C) that internally degrades the peptides. The half life of BNP is ~ 20 minutes and that of NT-proBNP is about 120 minutes. As a general principle NPS actions tend to counterbalance RAAS actions. A current major use of BNP or the inactive NT-proBNP is as a marker for CHF and Acute Coronary Syndrome severity and progression. Recent studies indicate positive and negative predictive values for acute onset of CHF as indicated in Fig 46.7a. Other uses of these peptides as markers are being evaluated.

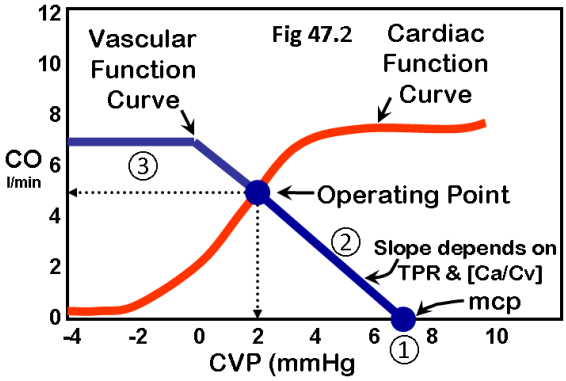


47.0 Cardiac-Vascular Coupling and Interactions TOC

47.1 Overview: The heart pumps blood and the vasculature receives, distributes and then returns blood to the RV. At a fixed HR, the cardiac output of the pump depends on specific *heart* features (e.g. contractility) that affect SV and thus CO. But, it is not just heart properties that are involved. The pump's output also depends on the blood volume(BV) returning to the heart (venous return = VR) as determined by the Frank-Starling mechanism. Although in steady state VR = CO (Fig 47.1), CO and VR also depend on vasculature properties including vessel compliance and TPR. So, *both heart and vasculature* operate together to determine CO. See **appendix A4** for the interaction model development.



47.2 Conceptual Approach: A way to account for heart – vascular function interdependencies is to represent CO as a function of the heart's input "filling" pressure. Central venous pressure (CVP) is such an index, and is useful to represent this 'input' pressure to graphically analyze how various changes in cardiac function and vascular properties interact to determine CO. To use this approach, two function curves are defined (Fig 47.2); one for CO changes with CVP considering only cardiac changes and the other CO changes with CVP considering only vascular changes.

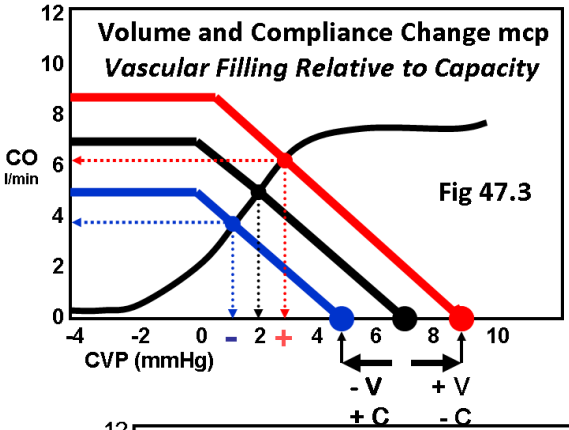


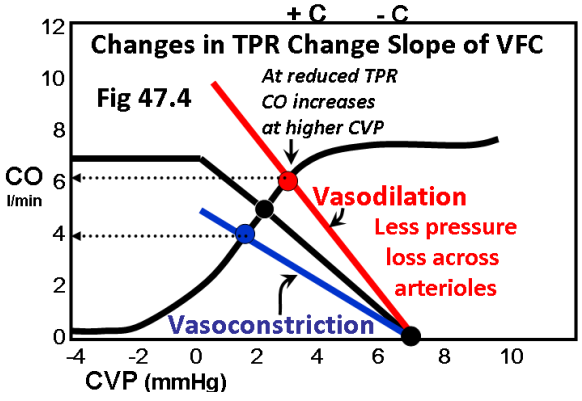
Cardiac Function Curve (CFC): depicts CO dependence on Frank-Starling. In this depiction, the F-S dependency on EDV is replaced by its dependency on CVP with HR fixed.

Vascular Function Curve (VFC): depicts the relationship between CO and CVP determined by vascular properties. Since the closed cardiovascular system can, at any instant, have only one CO and one CVP, it operates at a point that satisfies both cardiac and vascular conditions. This is the ***Operating Point*** (Fig 47.2) where the two function curves intersect.

47.3 Vascular Function Curve TOC

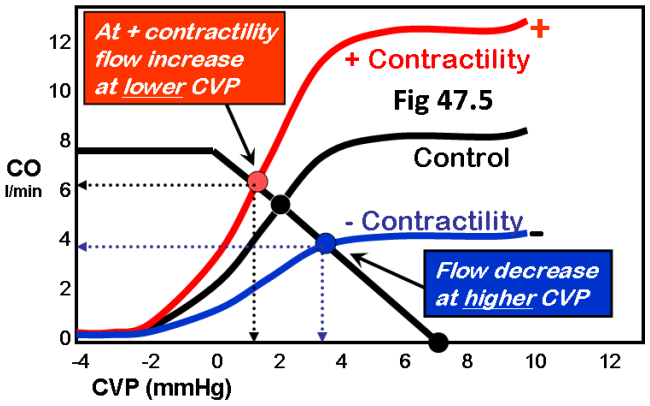
Three aspects of the VFC (Fig 47.2) are; (1) the value of CVP if CO is zero, (2) its slope and (3) the flattened portion. Point (1) is called the mean circulatory pressure (mcp) and is the value of pressure in the vascular system if the heart were stopped and CO were zero; it is determined strictly from vascular blood volume relative to vascular volume handling capacity (compliance). A larger blood volume and/or a lesser compliance yields a greater mcp, i.e. point (1) would shift to the right (Fig 47.3). A lesser volume or greater compliance decreases mcp. The slope is determined mainly by TPR (Fig 47.4) with some dependence on compliance ratios. If TPR is greater, the slope is less so the VFC would intersect the CFC at a lower value of CVP. This effect could be thought of as due to a larger pressure drop across a larger TPR that reduces CVP. The flat portion is explained by low values of CVP that are associated with "collapse" of central veins, which limits CO from increasing further in a way described for collapsible vessels.





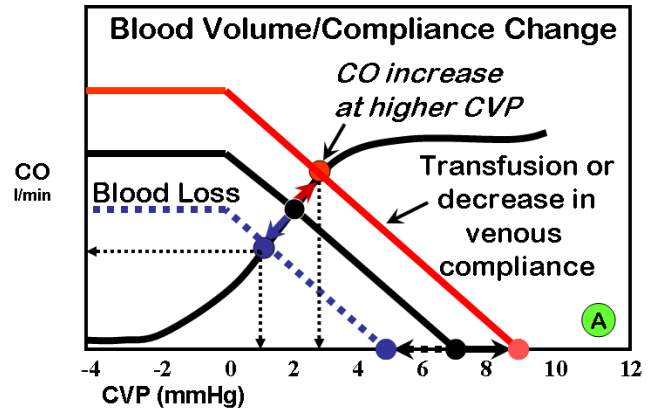
47.5 Cardiac Function Curve (CFC) TOC

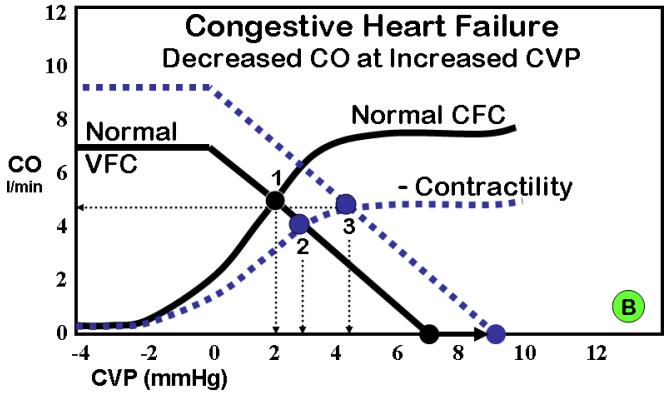
The CFC depends on the F-S mechanism and cardiac contractility. Increases in contractility raise the CFC and increase its slope (Fig 47.5); decreased contractility shifts it down and decreases its slope. Such changes occur since for the same preload (CVP as an index of EDV), increased contractility increases SV. Note that *the CFC, the VFC and their intersection represent the cardiovascular status at a particular equilibrium condition. Reflex changes may alter either or both CFC and VFC and hence their intersection. Time as a factor is not included in these representations*

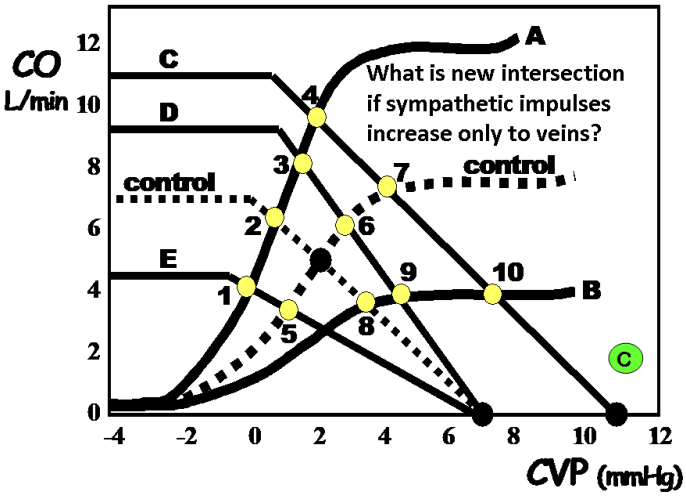


47.6 Summary TOC

Overall cardiovascular system function depends on the interaction between the cardiac pump and the vasculature; changes in one-part affect function of the other. Although interactions are complex, many aspects can be modeled in a simplified, but useful fashion that takes into account simultaneous constraints of cardiac and vascular function. Graphically this means that cardiac function, represented by CFC, and vascular function, represented by VFC, can intersect at only one point - the operating point of the system. Shifts in the operating point depend on the type, amount, and direction of changes in cardiac, arterial and venous parameters. For the heart, these changes are related to changes in contractility and its filling pressure represented by CVP. For the arterial side, TPR changes are of most interest. For the venous system, the main factor is volume filling with respect to capacity. Volume capacity depends on peripheral and central vein compliances (C_{PV} and C_{CV}). Graphical/model representations do not intrinsically include or account for reflex responses but do provide a way to interpret interactive effects. An increased contractility shifts CFC up; if no other change → increased CO and decreased CVP. *Increased peripheral venous compliance and/or decreased blood volume* shifts VFC to the left; if no other changes → decreases both CVP and CO. *Increased TPR* decreases slope of VFC; if no other changes both CO and CVP decreases. Examples of using and interpreting such changes are shown in Fig A, B & C.

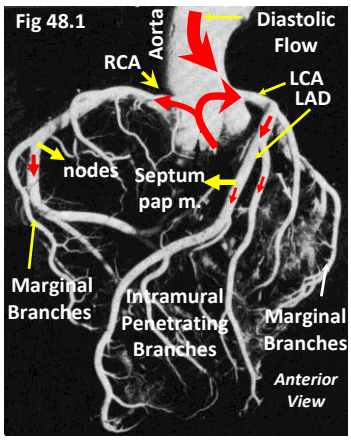






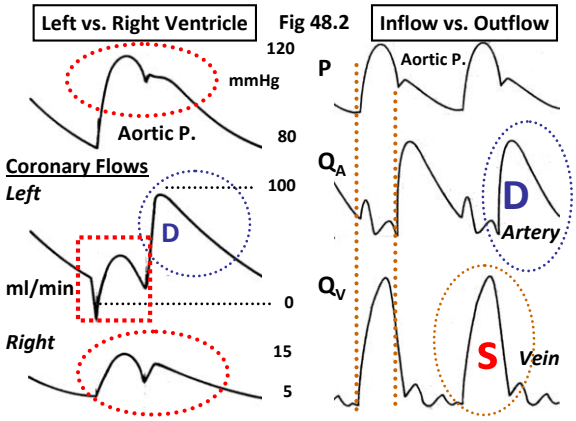
48.0 Coronary Circulation TOC

48.1 Structure-Function



Blood flow (Fig 48.1) is via left and right (main) coronary arteries (LCA & RCA). These arise in the sinus of Valsalva at the root behind the aortic valve cusps. RCA mainly supplies RV and RA; LCA mainly supplies LV and LA but there is considerable overlap between the two territories. Branches of large epicardial arteries penetrate into myocardium and divide into smaller arteries, arterioles, capillaries and venous vessels. Blood drains mainly to RA via the coronary sinus (95%); ~5% returns via anterior cardiac and thebesian veins. Thebesian drainage is directly into left chambers. Blood entering LV via thebesian vein has low O_2 and slightly "dilutes" O_2 tension in systemic circulation. Resting CBF is ~ 75 ml/min/100g. A 5X increase may occur at maximum cardiac work. At rest O_2 consumption is ~8 mlO_2 /100 g which is ~ 20x that of resting skeletal m.

48.2 Phasic Aspects of Coronary Flow



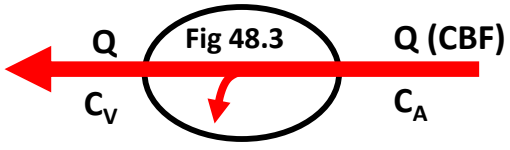
Blood flow to RCA and LCA is phasic (Fig 48.2), some during systole but *most during diastole*. Flow pattern, in LCA, is due to systolic compression of vessels within contracting myocardium. Blood flow into (coronary arteries) and out (coronary sinus) differ significantly in phasing since during systole blood is "squeezed" out of veins. So, *arterial inflow peaks during diastole as the ventricle relaxes and venous outflow occurs during systole as intramyocardial forces compress veins.*

48.3 Myocardial Microcirculation

Capillary density is high (3000-5000 / mm^2), with ~ one capillary/muscle fiber and an inter-capillary distance of ~ 10 μm. Skeletal muscle, also has a capillary-to-fiber ratio of about one, but has a capillary density ~ 1/10 of the myocardium. Not all myocardial capillaries are "open" or functional at all times. Changes in metabolism and O_2 demand serve to "recruit" some of the "reserve" capillaries although not nearly to the extent of recruiting capillaries in exercising skeletal muscle.

48.4 Myocardial Oxygen Extraction and Blood Flow Determinants

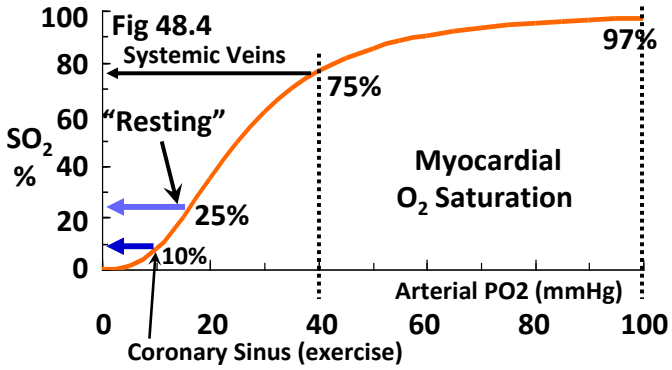
O_2 demand is the most important factor determining coronary blood flow (CBF), so CBF control is mainly metabolic. Myocardial O_2 extraction is high, ~ 75% but may rise to 90% during exercise. Increased demand is met mainly by increased blood flow. O_2 consumed is determined from blood flow and amount of O_2 extracted from blood by tissue [Fig 48.3]. Compared to O_2 saturation of systemic veins (~75%), O_2 saturation of venous blood draining cardiac tissue (25%) is low [Fig 48.4]. Because of high myocardial O_2 demand and high O_2 extraction, there is little O_2 reserve. So, increased O_2 demand is adequately met only by *blood flow increase.*



O_2 consumption=Q (C_A - C_V) [ml/O_2/min]

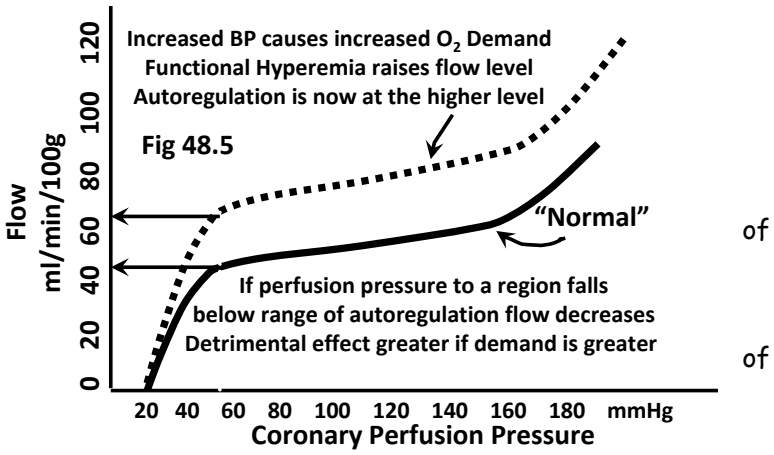
C_A & C_V = [O_2] Extraction [mlO_2/100ml]

75-90% → Flow-Dependent



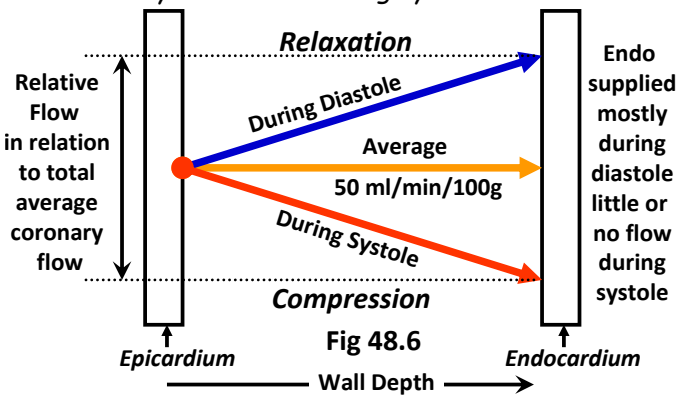
48.5 Autoregulation of Coronary Blood Flow (CBF)

CBF shows autoregulation with a low end of the range at ~ 50-60 mmHg (Fig 48.5). Below this, further vasodilation is not present. So, if perfusion pressure falls further, flow will continue to decrease since vasodilatory reserve is exhausted. The amount of autoregulated flow (vertical position of "plateau") shifts upward with increased metabolic demand. The low end the range remains about the same. But, since flow demand is elevated, a decreased perfusion pressure now has a more severe effect because that elevated blood flow demand. Persons with hypertension or LVH, where basal O_2 demand is elevated and who also have a coronary artery stenosis are particularly vulnerable to these effects due to their resting blood flow demand.

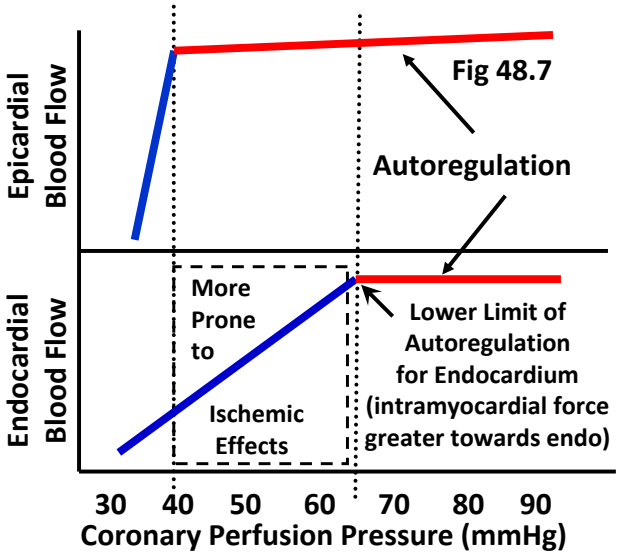


48.6 Systolic Compression and Myocardial Regional Blood Flow

Compression of intramural vessels results in a *reduction in total coronary blood flow during systole*. Effects are greatest *in vessels near the inner wall*. Compression of epicardium is least during systole, so its flow is fairly uniform over the cycle. But, endocardium experiences large compressive stresses and its flow occurs mostly during diastole. This is due to the stress distribution within the myocardium that causes a higher tissue pressure in deeper layers of the heart. So, in systole, flow toward the endocardium is reduced (Fig 48.6) and is much more *dependent on diastolic perfusion to meet metabolic demands* than are regions closer to epicardium. This is one reason why endocardium is more vulnerable to coronary artery disease that restricts diastolic blood flow.



A second reason for increased vulnerability of the endocardium and subendocardium is due to differences in regional autoregulatory capacity. The endocardial region *has much less autoregulatory reserve*. As shown in Fig 48.7, the lower end of the autoregulatory range for endocardium is ~70 mmHg as compared to ~40 mmHg for epicardium. Once these thresholds are reached, further reductions in perfusion pressure will cause flow to decrease (unregulated). So, if a stenosis develops in a coronary artery, the *critical pressure level will be reached first* at the endocardium, rendering it more vulnerable since ischemia develops at a higher perfusion pressure.



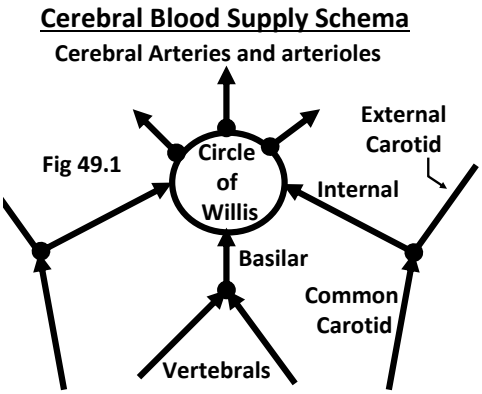
49.0 Cerebral Circulation TOC

49.1 Maintains Oxygen and Glucose to Hypoxia-Intolerant Grey Matter

Main Features

1. Circle of Willis - Anatomical guard against ischemia
2. High capillary density - Small O_2 diffusion distance
3. Blood brain barrier - Stable neuronal environment
4. High Basal Blood Flow ~ 50 ml/min/100g
5. Brain controls own flow by changing *CO* and TPR
6. Highly developed blood flow autoregulation
7. Mainly metabolic control
8. Physiological vasodilators: CO_2, K^+, adenosine, low O_2

Structure-Function: Brain blood flow (BBF) is by internal carotid and vertebral arteries (**Fig 49.1**). Vertebrals join to form the basilar artery that joins with branches of the internal carotids to form the *circle of Willis*. Branches of this arterial circle (anterior, middle and posterior cerebral arteries) supply tissues. The circular pattern and multi-vessel anastomosing provides blood flow margin against blockages.



Artery Branches: Divisions of main cerebral arteries give rise to arteries then arterioles that penetrate into brain matter. Because cerebral arterioles are short, small arteries penetrating the brain account for a larger proportion of cerebral vascular resistance than in most organs.

Capillary density is high; large exchange area; small capillary-tissue diffusion distances.

Blood-Brain Barrier (BBB) is due to tight capillary junctions. BBB permits easy lipid soluble exchange (O_2, CO_2) and easy exchange of some H_2O soluble substances (e.g. glucose/ amino acids) but *restricts passage* of most other substances (mannitol, sucrose, and most ions and NE and E).

Rigid Enclosure: Circulation lies within enclosed rigid structure (cranium); increases in blood or tissue volume cause increases in extravascular pressures reducing BBF due to vessel compression.

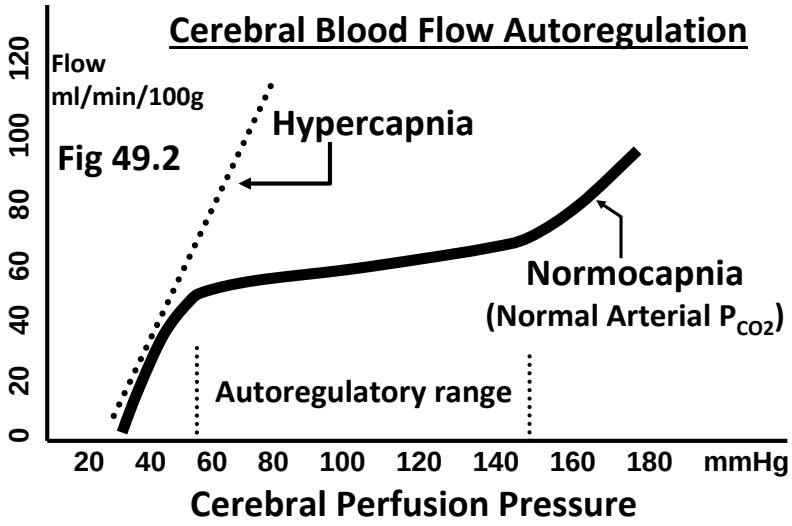
Blood Flow: Average BBF is ~15% of resting *CO* (50ml/min/100g) and is distributed *mostly to grey matter* (100 ml/min/100g, 40% of brain mass). O_2 extraction is about 35%. Grey matter has a very high O_2 consumption, (7 ml/min/100g - about 20% of whole body O_2 consumption at rest).

Blood Flow Margin: Hypoxia of a few seconds results in unconsciousness; irreversible cell damage occurs within a few minutes. *Main task of cerebral circulation is to maintain continuous and adequate O_2 delivery to brain cells.* O_2 demands of specific brain regions vary with brain activity; regional BBF adjusts.

49.2 Determinants of Cerebral Blood Flow TOC

1. Reflex control of blood pressure: The brain can uniquely *control its own blood flow by changing its perfusion pressure* by changing vascular resistance of other organs via autonomic outflow. This allows the brain to help preserve its own blood flow as needed. Systemic hypotension, hemorrhage and other conditions leading to a compromise in BBF will elicit such reflexes.

2. Autoregulation is highly developed; operates over range of ~ 60 to 150 mmHg (**Fig 49.2**); Pressures below lower limit cause reduced flow and possible syncope (light-headedness/fainting); BP above upper limit may cause increased permeability of cerebral capillaries causing partial *breakdown of blood-brain barrier and cerebral edema*. Autoregulation is reduced or lost if significant hypercapnia is present (increased CO_2 in arterial blood).



3. Carbon Dioxide: Increased CO_2 → *Vasodilation.*

4. Hydrogen and Potassium Ions:

Arterial blood H^+ changes can't pass the BBB, but increased H^+ in cerebral spinal fluid causes vasodilation. K^+ increase during hypoxia → vasodilation and +BBF.

5. Adenosine Vasodilation in Response to Increased O_2 Demand

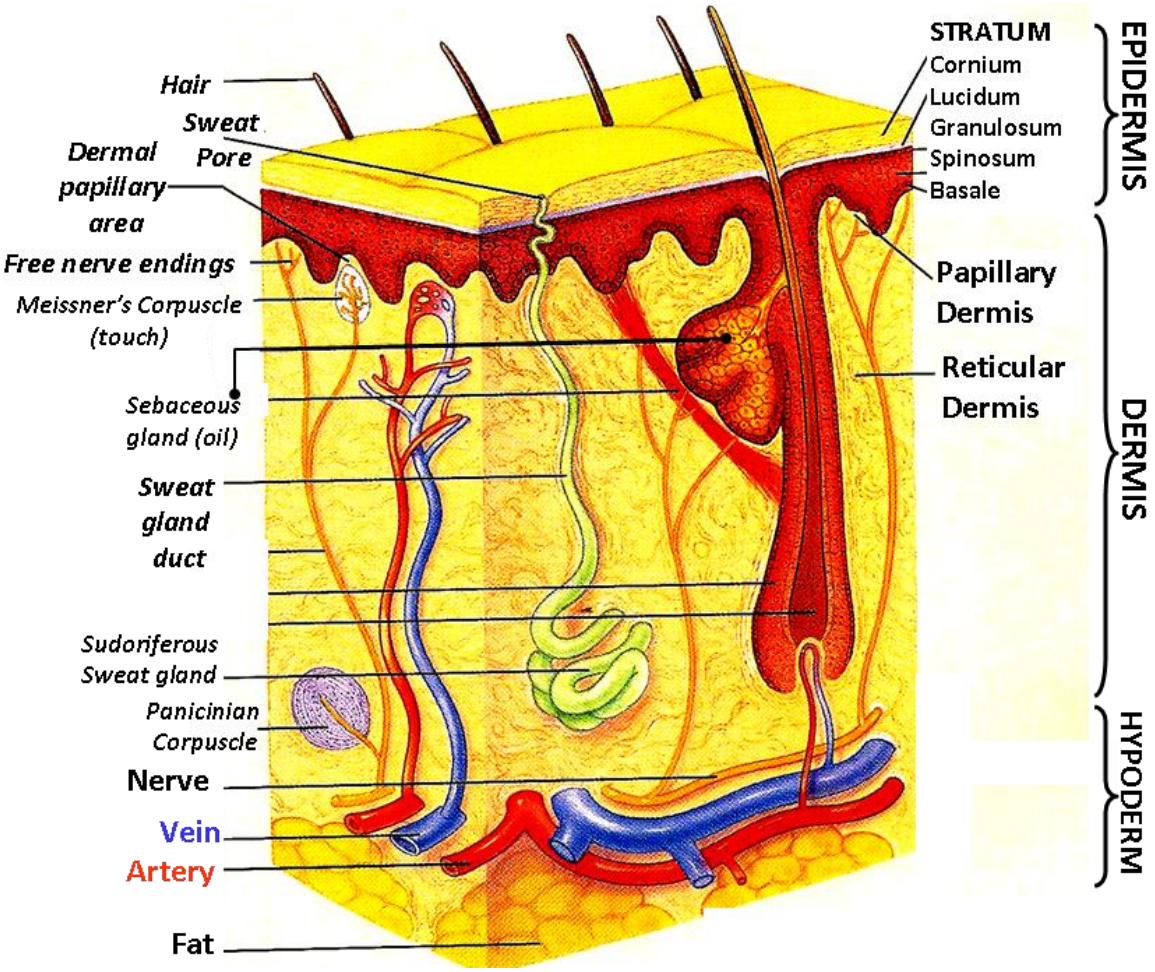
Decreased O_2 availability vs. O_2 need (ischemia, hypoxemia, hypotension) increases adenosine causing cerebral vasodilation. Adenosine is a primary mediator of vasodilation under conditions of *inadequate O_2 supply-demand balance.*

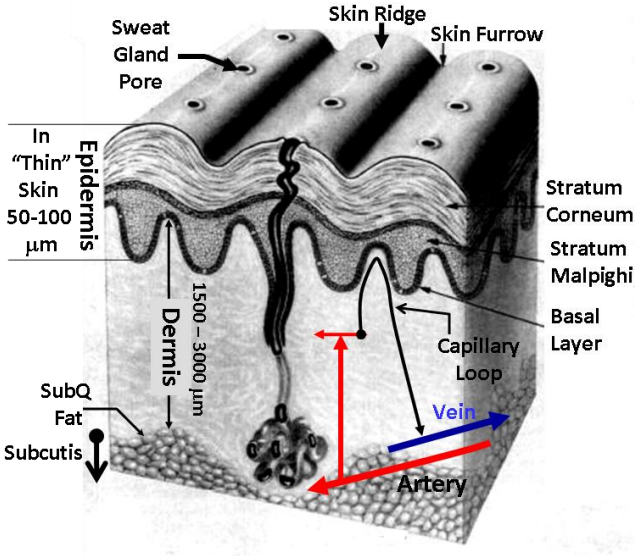
6. Intracranial Pressure A space-occupying material (e.g. tumor or cerebral hemorrhage) increases intracranial pressure, which compresses vessels and tissues. Compression transmitted to brainstem causes a rise in generalized sympathetic drive casing the *Cushing's reflex or phenomenon*. Resulting HTN helps maintain perfusion by increasing transmural pressure in compressed cerebral vessels and by increasing perfusion pressure. The HTN induces a reflex

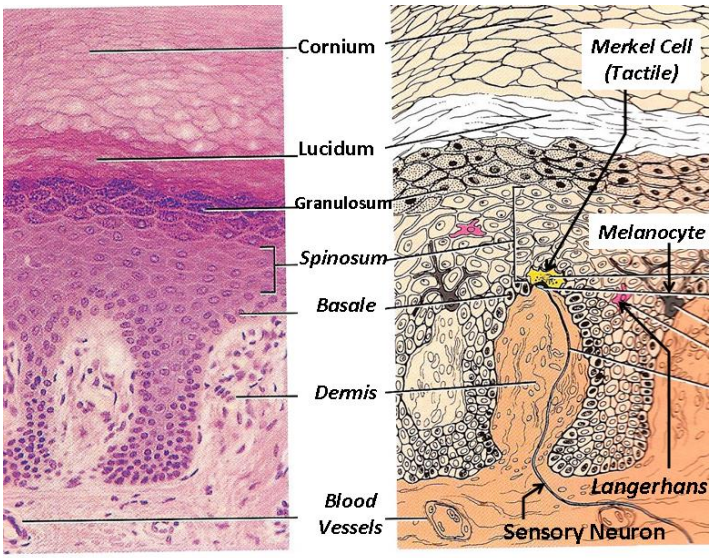
(baroreceptor-mediated) bradycardia. Outcome is significant HTN and bradycardia.

50.0 Cutaneous Circulation TOC

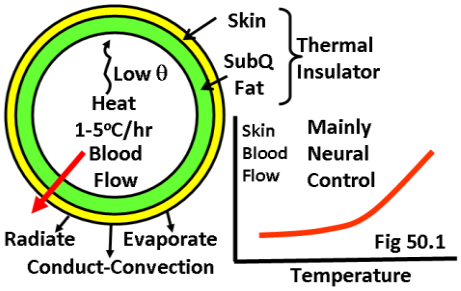
ANATOMY REVIEW







50.1 Heat Elimination: Skin & fat are thermal insulators. Since internal metabolic activity causes continuous heat generation, mechanisms to remove it (or conserve if temp falls) are needed. Core temp rises 1-5°C/hr. (Fig 50.1) if no heat removal! Heat exchange is by heat transfer to skin by blood flow to, and through, skin. Heat loss rate from skin to environment is determined by 3 processes:

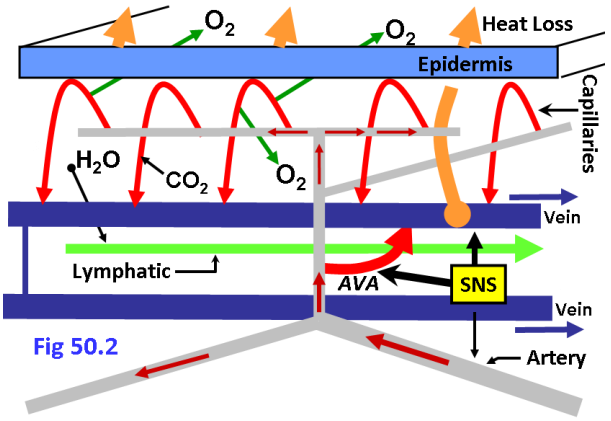


(1) *Radiation:* ~ to difference between skin and air temperature **(2) *Conduction-Convection*:** air next to skin is heated by heat *conduction* from skin and is removed by *convection* via air currents.

(3) *Evaporation*: one gm of H_2O evaporated → 27 kJ heat loss.

50.2 Thermal Blood Flow Control

Skin blood flow (**SBF**) is controlled (Fig 50.2) by sympathetic nerves (**SNS**) acting on arteriovenous anastomoses (**AVAs**) in acral skin (digits, hand & feet palmer & plantar surfaces, ears, nose and lips). In a thermo-neutral environment (~27-28°C) with skin at ~33°C, *AVAs are constricted via high sympathetic tone.* If core temperature rises, SNS drive decreases, AVAs dilate, and SBF and *heat loss increase.*



Local heating causes vasodilation of skin arterioles, venules and small veins. Heat decreases VSM response to sympathetic stimuli; if heated to ~45°C vessels are unresponsive to sympathetic drive.

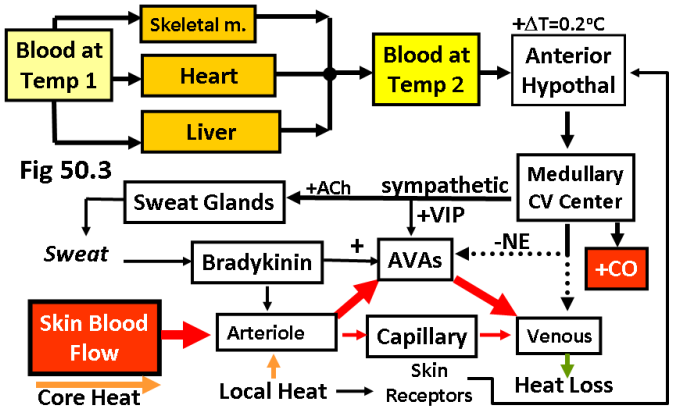
Local cooling, to, but not below ~ 12°C causes *vasoconstriction and venoconstriction* due to *increased VSM sensitivity* to sympathetic nerve stimulation and to circulating catecholamines.

Venoconstriction of *surface veins* diverts flow to deeper veins so more insulation. Cool venous blood diversion also causes a slight counter-current heat exchange between vein & artery conserving more heat.

Vasoconstriction to cold depends on α_2-receptors in skin vessels. NE affinity of α_2-receptors increases with decreasing temperature; but, cooling below ~12°C, results in cold-induced vasodilation (constriction suppression). This "paradoxical" cold vasodilation is why red noses and fingers are seen on cold days.

Receptors: Temperature induced SBF changes in one limb affect SBF in the other limb in the same direction by sympathetic spinal reflexes initiated by skin receptors

Regulation: Blood warmed by 0.2°C (Fig 50.3) causes increased impulses to the medullary CV center. Adrenergic outflow to AVA's is reduced & SBF increases. Sympathetic cholinergic excitation of sweat glands causes sweating and promotes bradykinin release and dilation. VIP release also causes vasodilation. For high heat loads, %CO to skin increases. Local skin heating causes vasodilation due to direct effects on VSM and local neurochemical actions. Skin receptors sense skin temp and alter afferent impulse rate to the anterior hypothalamus reinforcing SBF control.



Heat Stroke: At high ambient temperatures, heat can't be removed, even at maximum SBF. Dilated vessels *take up heat* and core temperature rises. If brain temperature rises to ~42°C, heat stroke!

Heat-Induced Fainting: Hypotension due to heat-induced vasodilation/venodilation.

Blood Pressure Maintenance via Skin Vessel Constriction: Hypotension (e.g. blood loss) causes intense vasoconstriction of skin arterioles and venules. Increased resistance helps support BP and venoconstriction helps redistribute blood centrally to support central venous pressure.

51.0 Skeletal Muscle Circulation TOC

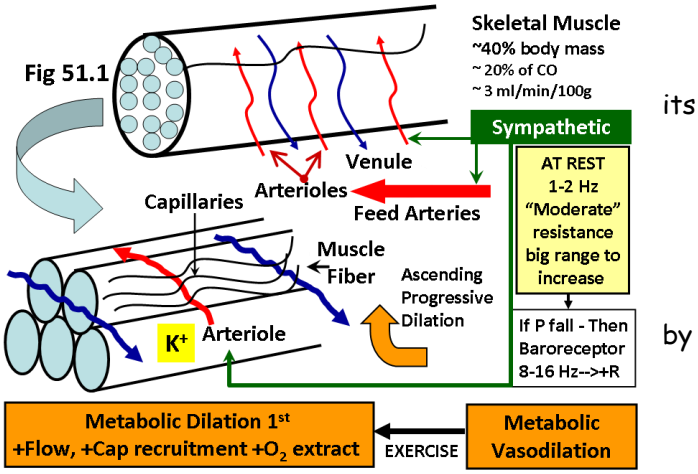
High degree of Neurogenic Tone

High Tone maintained in vessels to provide reserve capacity for large increase in muscle blood flow (**MBF**).

Dual Blood Flow Control

Extrinsic (neural) predominates during ***rest***. Muscle is a target of cardiovascular regulation and its vascular resistance is important in BP regulation. Sympathetic denervation increases MBF 2x-3x.

Intrinsic (local) predominates during ***exercise***. Mainly via vasoactive metabolites produced in proportion to metabolic activity. MBF may increase 20x (functional hyperemia) by



Neurogenic vasodilation

(a) Less sympathetic drive → reduces tone → dilate
(b) Activate sympathetic Cholinergic fibers → dilate

Reflex Vascular Responses

(a) Baroreceptor and Chemoreceptor
(b) Emotion may trigger vasodilation via increased cholinergic activation

Exercise related changes in skeletal muscle Blood Flow

1. Blood flow increases almost linearly with *metabolic rate*
2. In exercising muscle, interstitial K^+ is increased; promotes vasodilation via hyperpolarization
3. Tissue clearance of K^+ into circulation increases arterial blood K^+ from resting level of ~4 mM to as high as 7 mM; this increases blood *osmolarity* and contributes to overall vasodilation
4. *Inorganic phosphate* released from exercising muscle also contributes to hyperemia
5. *Local hypoxia* when occurring, contributes to the metabolic vasodilation
6. *Capillary recruitment*: At rest ~1/3 are perfused; arteriole dilation recruits remaining 2/3
7. *O_2 extraction* increases from rest level of ~30% up to ~90%. Partly due to muscle myoglobin.

Oxygen Debt

1. In strenuous exercise, cellular P_{O2} falls and anaerobic glycolysis ensues; lactic acid is formed
2. Lactate formed is an index of "oxygen debt"; can reach levels as high as 2-3 liters
3. Lactic acidosis and K^+ accumulation stimulate nociceptive *C* fibers causing pain
4. After cessation of exercise oxygen debt is "repaid" during a period of post-exercise reactive hyperemia during which O_2 is re-supplied and lactate and other metabolites are "washed-out".

Mechanical Factors

Muscle pumping assists limb perfusion particularly in calf. But, very strong contractions (~50% of max voluntary force) compress intramuscular vessels and impair blood flow. In rhythmic exercise (jogging) flow alternates between max/min levels. But, isometric contractions (carrying a heavy suitcase) sustain compression and flow impairment. Since myoglobin O_2 stores last only about 5-10 seconds, sustained contraction beyond this leads to hypoxia, lactate accumulation and pain!

52.0 Splanchnic Circulation TOC

Combined Blood flow through *Liver, Stomach, Spleen, Pancreas, Large Intestines and Small Intestines*

Highly interconnected vascular supply (Fig 52.1) with systemic and portal blood flows
In each GI region blood flow (Q) ~ metabolic activity ~ digestive and absorptive activity in that region
Q increases sequentially from stomach to more distal segments in accord with segmental activity

Liver receives outflow of gut organs via the portal vein (Fig 52.1,2) and an arterial input via the hepatic artery. Total splanchnic Q is ~25% of CO with ~25% of this supplied via the hepatic artery (Fig 52.2), which is main source of liver O_2. All vascular beds are in parallel with each other and their combination is in series with the gut and liver. Pressure in portal vein and hepatic veins. the liver sinusoids (capillaries) is low and slightly greater than in

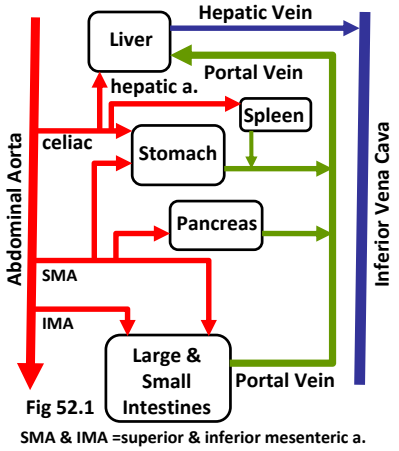


Fig 52.1
SMA & IMA =superior & inferior mesenteric a.

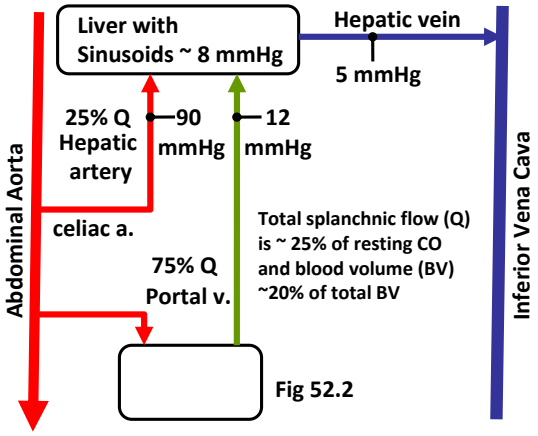
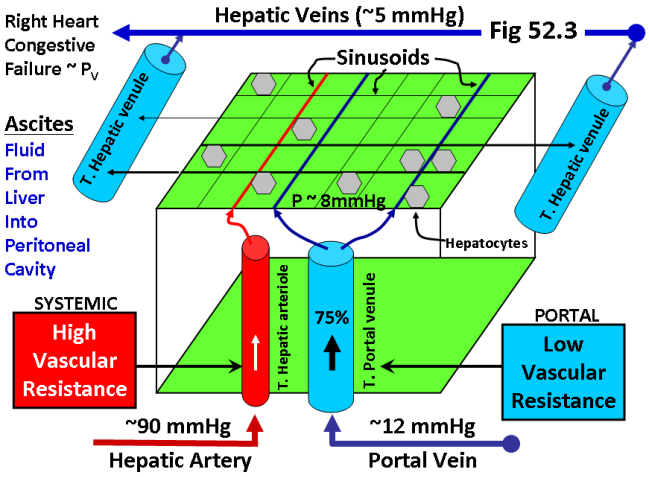


Fig 52.2

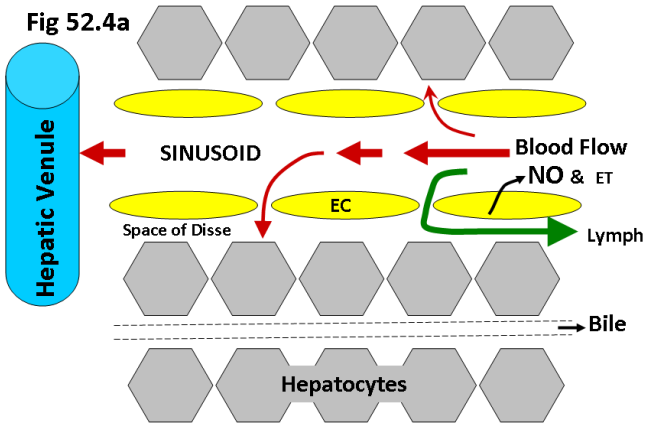
Hepatic precapillary resistance (R) must be high to reduce 90 mmHg to the level of ~ 8 mmHg (Fig 52.3).

All splanchnic vessels except capillaries have sympathetic innervation. Increased sympathetic activity causes vasoconstriction via actions mediated by VSM α-adrenoreceptors that decrease blood flow and shift some blood volume into the systemic circulation. Parasympathetic activity produces vasodilation indirectly (active hyperemia) in response to increased metabolic activity associated with parasympathetic-induced increase in motility and secretion. Connections between portal and systemic veins are present in the esophagus, stomach, small intestine and rectum. Normally, no back flow from portal to systemic circulation.

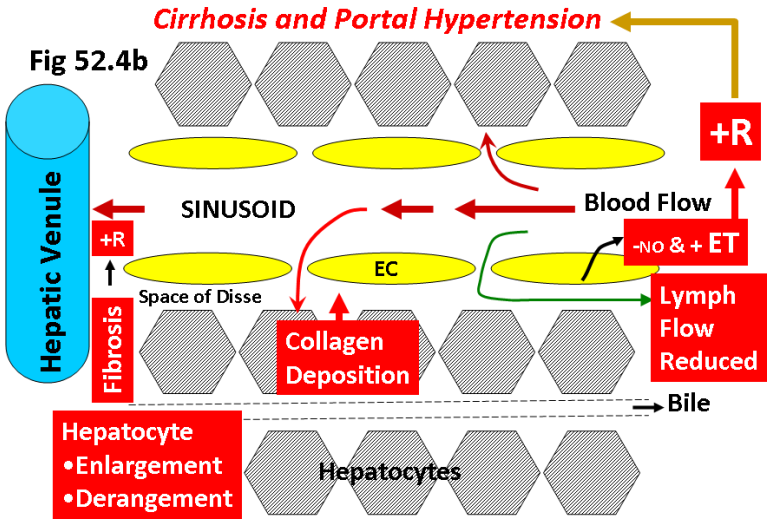


Liver Sinusoids: Fenestrated capillaries or sinusoids (Fig 52.4a) supply liver hepatocytes.

Cirrhosis of the liver, caused by liver damage, is characterized by replacement of normal hepatocytes with fibrosis and nodules and an altered liver architecture render the liver "stiffer". These changes (Fig 52.4b), which include collagen deposition in the Space of Disse, fibrosis, enlargement and derangement of the hepatocytes, lead to an increase in liver vascular resistance in part due to compression of some blood channels and in part due to a degrading of normal vasodilatory controls. In particular there is a reduction in NO release and an increase in ET-1 from the endothelial cells of the sinusoids. As a result of an increase in liver resistance (of any cause) there is an increase

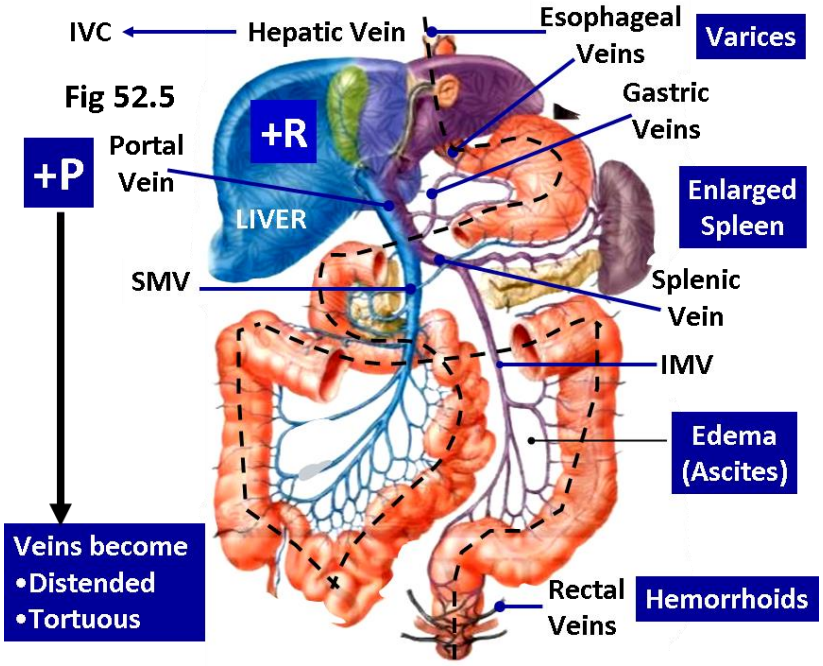


in portal pressure (portal hypertension) that causes some blood to flow retrograde into the systemic veins instead of into the liver. Exposure of these veins to the elevated pressure (and possibly to the contents of the portal blood) causes them to become distended and tortuous a condition called *varices* when it occurs in esophageal or gastric veins (e.g. esophageal varices) and *hemorrhoids* when present in rectal veins (**Fig 52.5**). Esophageal veins are thin walled and not designed for the higher pressures so they are at particular risk of rupturing. In addition to this serious danger, the redirection of flow away from the liver causes blood, not been processed by the liver, to enter the systemic circulation. This can lead to serious consequences. Also, the portal hypertension causes increased liver sinusoid filtration, leading to fluid accumulation in the abdomen (ascites) and peripheral edema if systemic venous pressure is large enough. Right heart congestive failure resulting in elevated venous pressure can cause ascites with subsequent fluid from the liver entering into the peritoneal cavity.

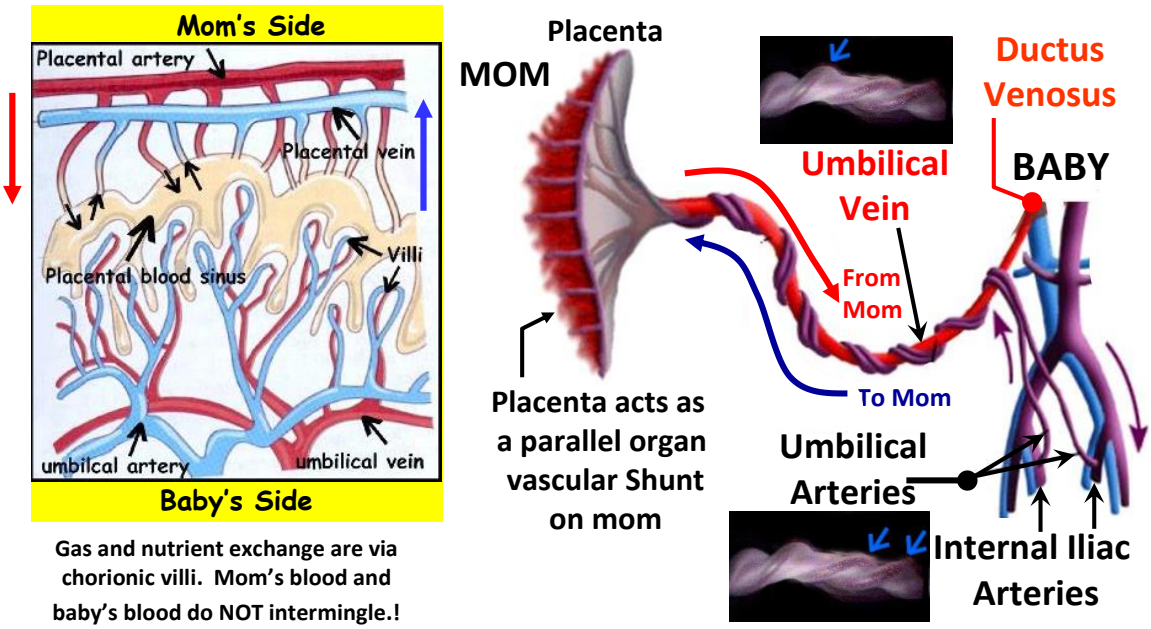


Gastrointestinal Circulation

During and after a meal splanchnic blood flow increases sequentially along the GI tract. A blood flow increase in the stomach is followed by flow increases in more distal parts of the tract as digestion proceeds. Stomach and intestine vasculatures are similar in several aspects. In small intestines, there are three different functional regions supplied by branches of a common parallel vasculature located in submucosa, 1) submucosa itself, 2) muscle and 3) the mucosa and villi. During the absorption process, mucosal metabolic rate increases causing mucosal vasodilator metabolites to form (e.g. adenosine and CO_2) cause mucosal blood flow to increase. Nutrient absorption also results in a localized blood hyperosmolarity that stimulates vasodilation. More vasodilation is attributable to release of vasodilators such as *bradykinin* and *kallidin* from intestinal epithelium. Blood flow is also affected by vasodilator hormones released throughout the GI tract during digestion. These include *cholecystokinin* and *neurotensin*.



53.0 Fetal Circulation TOC



Gas and nutrient exchange are via chorionic villi. Mom's blood and baby's blood do NOT intermingle.!

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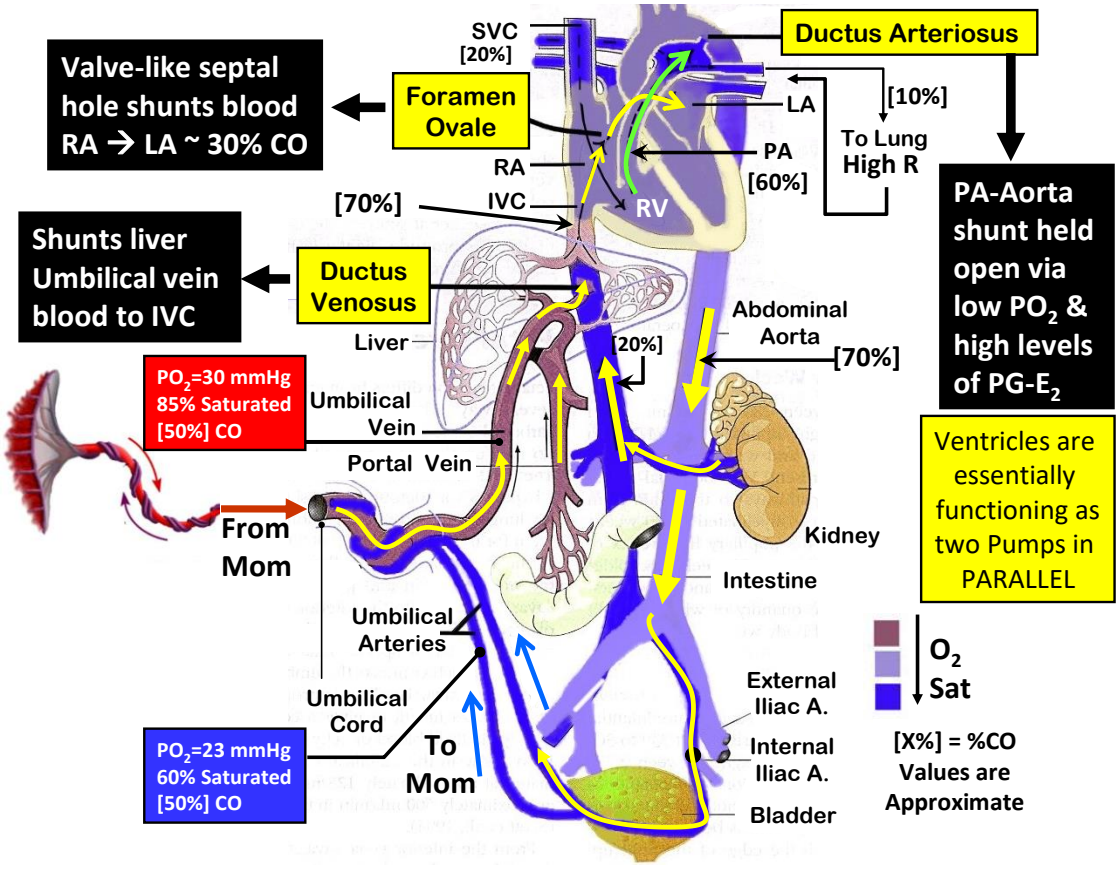
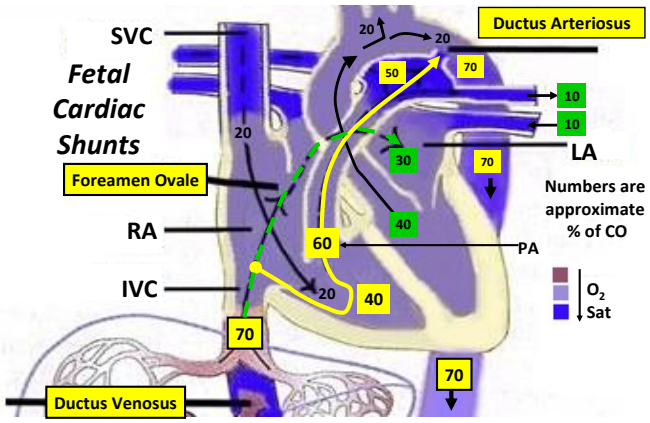
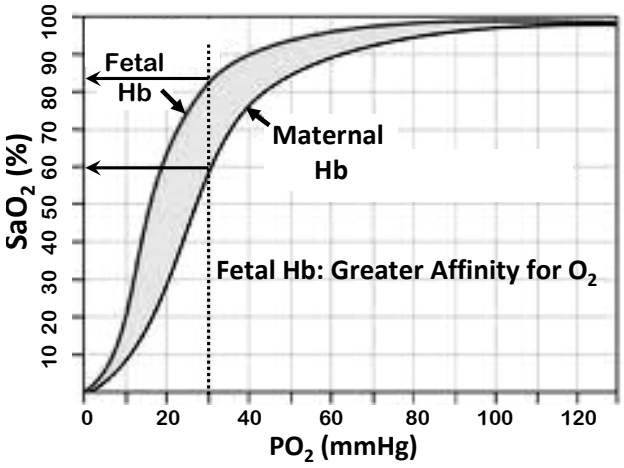
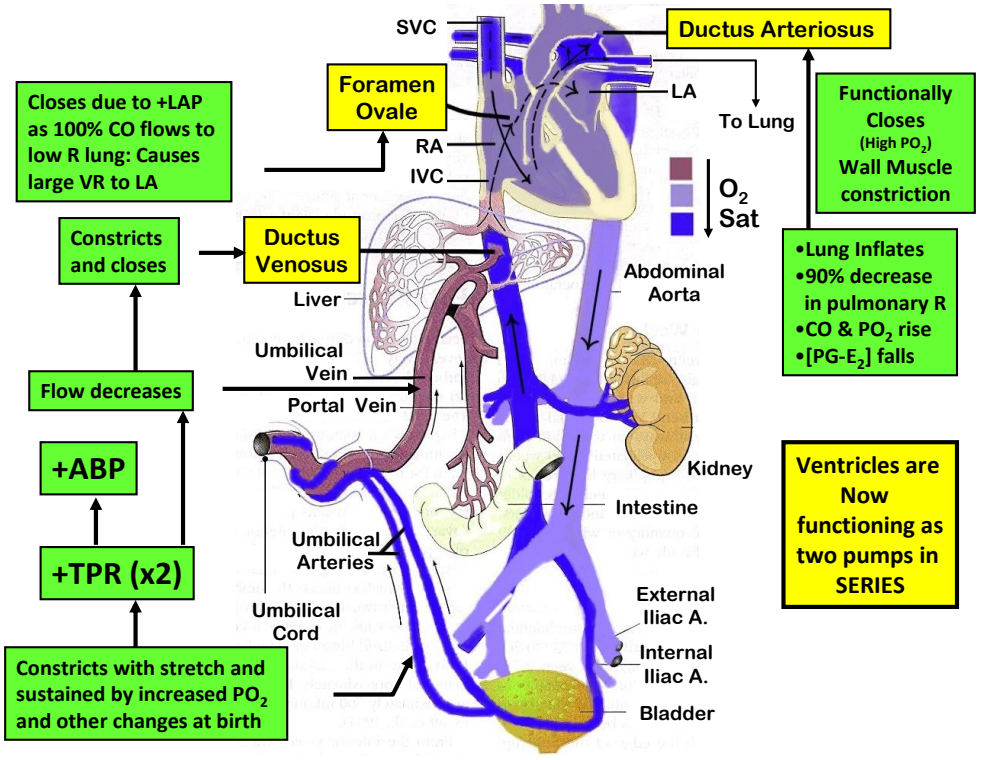






After Birth Vascular Events TOC

Smooth muscles in the umbilical arteries constrict in response to trauma, P_{O2} changes and a variety of chemical stimuli unleashed at birth. Stretching the umbilical arteries during birth is one of the triggers for constriction. The constriction increases vascular resistance of the placenta which, because it is a parallel vascular shunt, causes the TPR of the infant to increase (~double) causing the infant's BP to rise. Subsequent to flow reduction in the umbilical vein the **Ductus Venosus** constricts and closes (mechanism unknown). This removes it as a shunt to the portal circulation (liver); portal BP rises and liver blood flow increases. With the first breath (triggered by the placental functional disconnect and the associated asphyxia) the lung inflates and the very high vascular resistance of the fetal lung now becomes about 1/10 of what it was. The lungs start to function and they now receive a substantial portion of the cardiac output (CO) causing the arterial blood P_{O2} to rise. The **Ductus Arteriosus** gradually (1-2 days) closes due to constriction of its muscular walls thought to be triggered by the now high P_{O2} of the blood passing through it. The **Foramen Ovale** initially closes due to a reversal of the pressure gradient across the atrium that accompanies the increased TPR and the dramatic decrease in the pulmonary vascular resistance. This reversed pressure difference closes a valve over the foramen ovale and eventually the hole becomes permanently sealed (several days) as the septal leaflets fuse together.

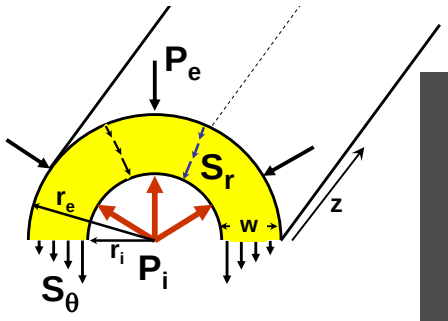


APPENDICIES

A1. Blood Vessel and Cardiac Wall Mechanics (Rigorous treatment) TOC RTT

Wall Stress and Tension

A vessel with internal (P_i) and external (P_e) pressures (Fig 11.1) experiences stresses acting in radial (S_r), circumferential (S_θ), and longitudinal (S_z) directions. For static equilibrium, these internal stresses must balance net forces due to applied pressures. This force balance requires a determination of the product of stress x the area on which each stress is exerted. Since stress varies with radial position in the wall, a spatial average stress $\langle S_\theta \rangle$ is used. For a wall segment of length ℓ in the z direction, the area upon which S_θ acts is ℓ x w.



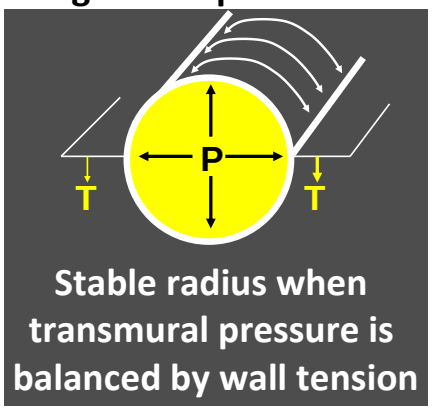
S_θ = circumferential stress
$\langle S_\theta \rangle$ = average wall stress
S_r = radial stress
P_i = internal pressure
P_e = external pressure
T = average wall tension

$$P_i r_i - P_e r_e = \langle S_\theta \rangle w = T$$

Force Balance / unit length

$r_i \rightarrow r_e \rightarrow r$

Fig 11.1 Laplace's Law



$T = (\delta P)r$ = "Pr"

The force due to the radial stress, expressed per unit longitudinal length, is $\langle S_\theta \rangle w$. This term is the average wall tension (**T**) with units of F/ℓ. The radial F/ℓ due to applied pressures is given by $(P_i r_i - P_e r_e)$ and a relation between applied pressures and resultant stress is given as **[1]** $T = \langle S_\theta \rangle w = (P_i r_i - P_e r_e)$. If T is positive the wall is in tension and if it is negative it is in compression. A similar analysis for a sphere, possibly representing a cardiac ventricle yields a similar relationship given as **[2]** $T = \langle S_\theta \rangle w = (P_i r_i^2 - P_e r_e^2) / (r_i + r_e)$.

Relationship to Laplace's Law

For an infinitely thin walled vessel, $r_i \rightarrow r_e \rightarrow r$ which using [1] yields **[3]** $T = (P_i - P_e)r$; this is Laplace's Law! The transmural pressure P_i-P_e is shown in Fig 11.1 simply as **P** so the basic Laplace law becomes **T=Pr**. It states that an equilibrium radius (**r**) occurs if tension (**T**) in a wall just balances the distending tendencies of **P**. The equilibrium radius is **r = T/P**. Physically this equilibrium means that wall tension (wall force/ longitudinal length) resisting expansion is equal and opposite to the force due to P tending to cause expansion. Looking at it another way, it states that to change the radius to a new equilibrium value (say to increase it), requires a greater **P** with a value $P = T_{new}/r_{new}$. Looking at it a final way, it states that to hold a vessel at a given equilibrium radius, r_o, the required wall tension must be $T = Pr_o$. Each way of viewing Laplace's Law is helpful in different situations.

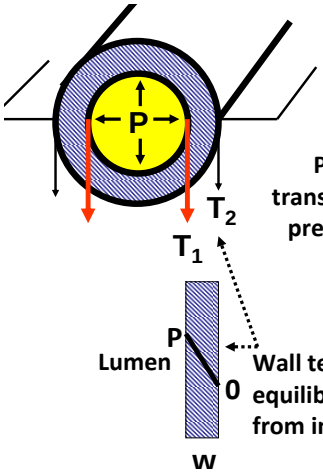
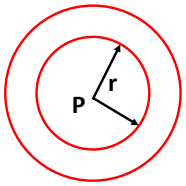


Fig 11.2 Modified Laplace's Law
$\sigma = Pr/w = \langle S_\theta \rangle$="avg Tension"

P is transmural pressure

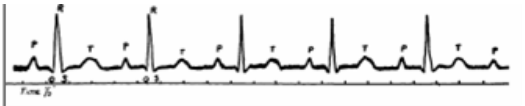


Need to use wall stress (σ)

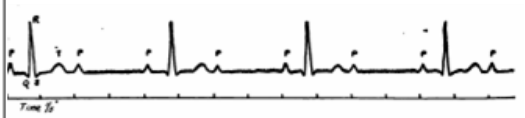
Wall tension needed for equilibrium decreases from inner to outer wall

But, most vessels and certainly walls of ventricles do not have "thin" walls, so the basic "Law" needs modification. To consider **W**, average wall stress $\langle S_\theta \rangle$ is used. So, a 'modified' Laplace's Law is used **[4]** $\langle S_\theta \rangle = Pr/w$.

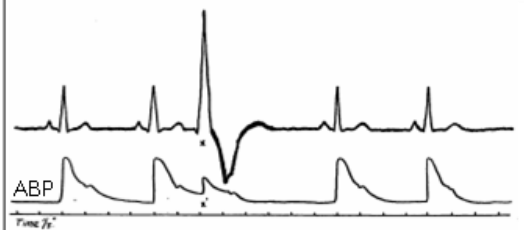
A2. EKG Rate and Rhythm Example Descriptions TOC Return to Text

1 

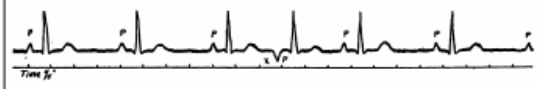
Normal pattern

2 

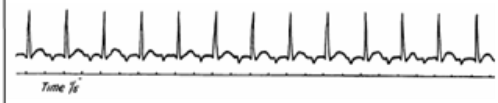
Two p-waves/qrs 2° block?

3 

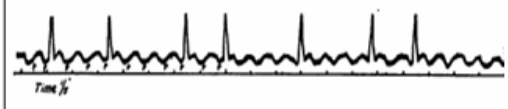
Ventricular ectopic beat causing small
Impact on peripheral Arterial pulse (ABP)

4 

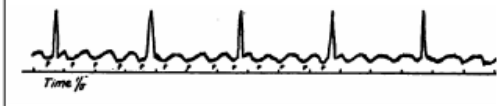
Premature atrial ectopic inverted p-wave
Causing early (extra) qrs complex and beat

5 

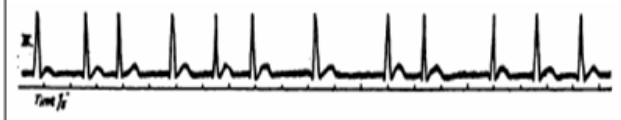
Tachycardia – inverted atrial p-waves – regular
Ectopic atrial pacemaker – paroxysmal tachycardia

6 

Multiple p-waves with IRREGULAR qrs occurrence
Atrial flutter -Atrial ectopic excitation

7 

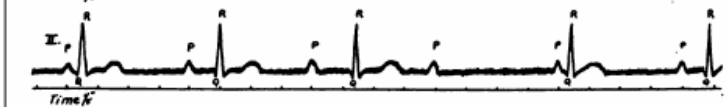
Multiple p-waves with REGULAR qrs occurrence → 1 in 4
Atrial flutter - Atrial ectopic excitation

8 

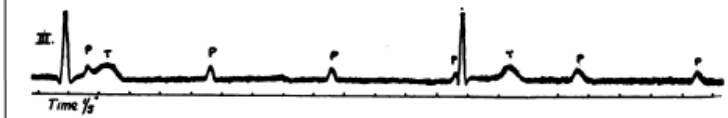
Tachycardia with "regularly-irregular"
qrs complexes and no indication
of p-waves → AFib

9 

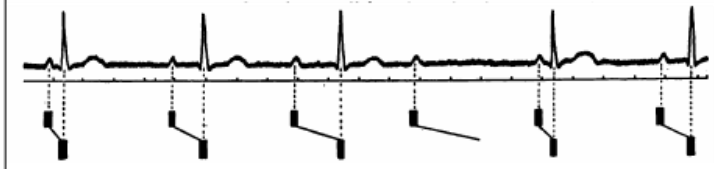
1° AV Block

10 

2° AV Block

11 

3° AV Block

12 

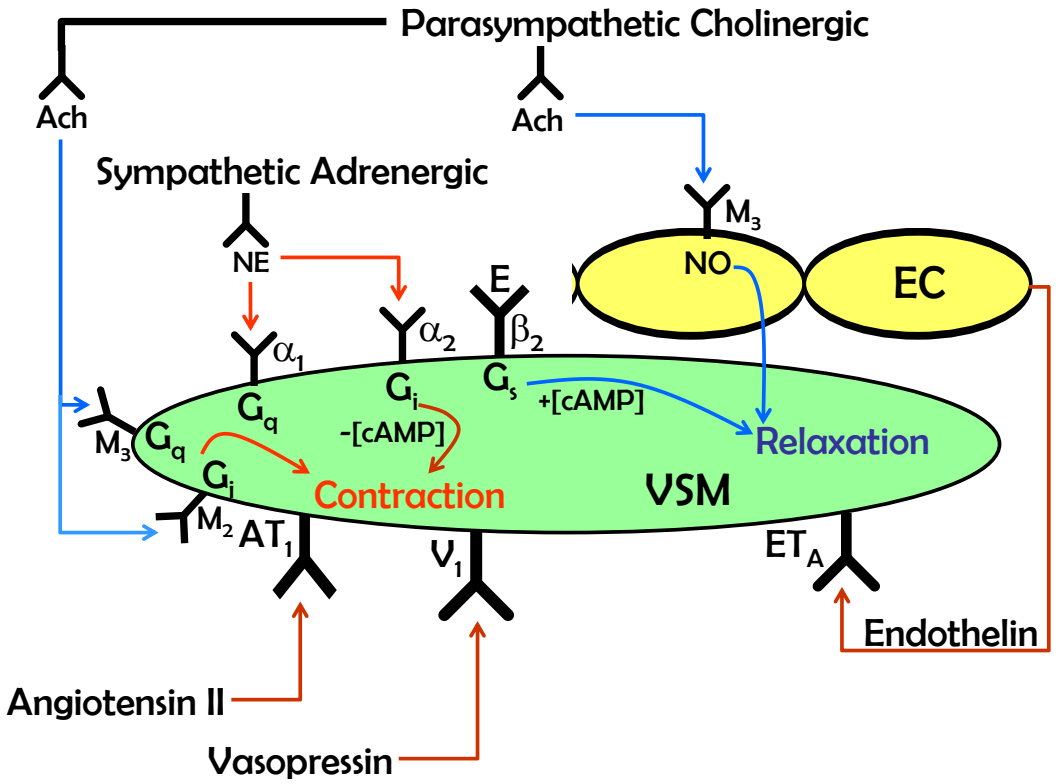
2° AV Block

A3. Vascular Receptor Mini-Overview TOC TEXT RETURN

G-Proteins for Kindergarten

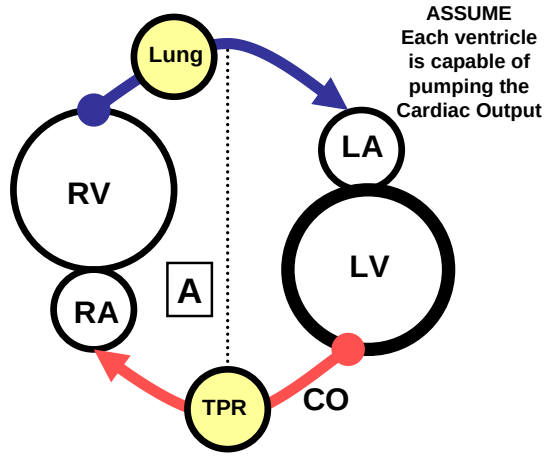
Activate	2ND messenger	Receptor	Agonist
G_s	ATP → cAMP (+ Intracellular Concentration)	β_2	E
G_i	ATP ⇢ cAMP (- Intracellular Concentration)	α_2	NE/E
G_q	IP_3 (Inositol Triphosphate) + $[Ca^{++}]$	α_1 ET_A → Endothelin AT_1 → Angiotensin II V_1 → Vasopressin	NE/E

Receptors in a Nutshell

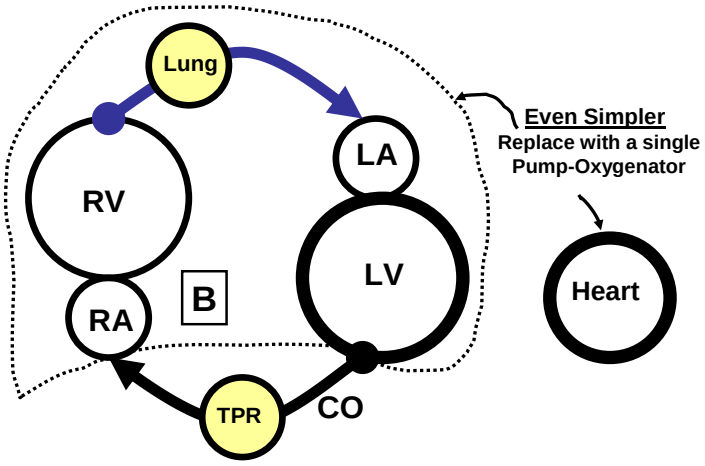


A4. Major Steps to Develop Cardiac-Vascular Interaction Curves TOC Text Return

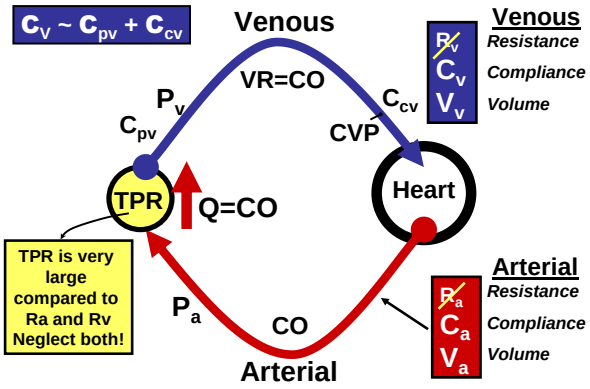
1st Model of C-V Coupling



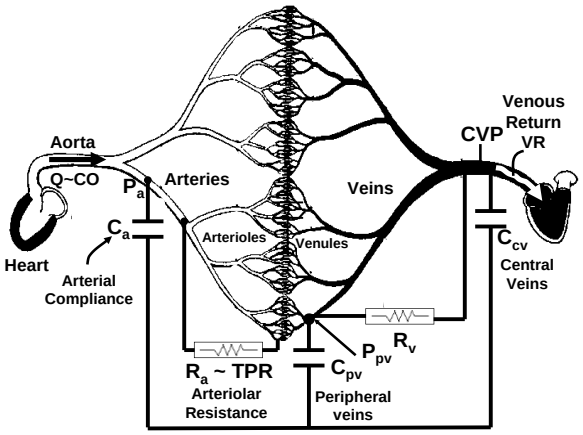
2nd Model of C-V Coupling



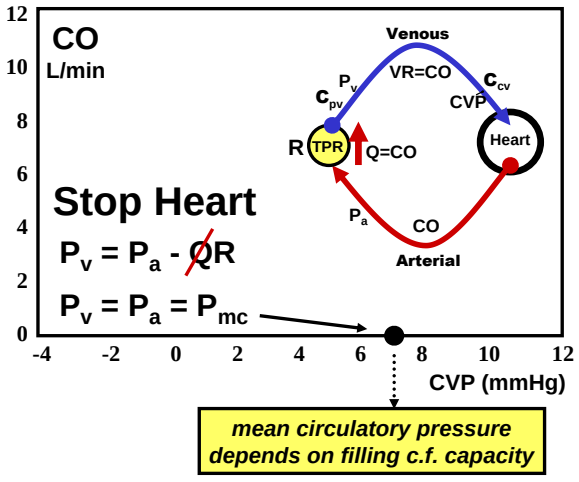
Single Pump - Oxygenator = Heart



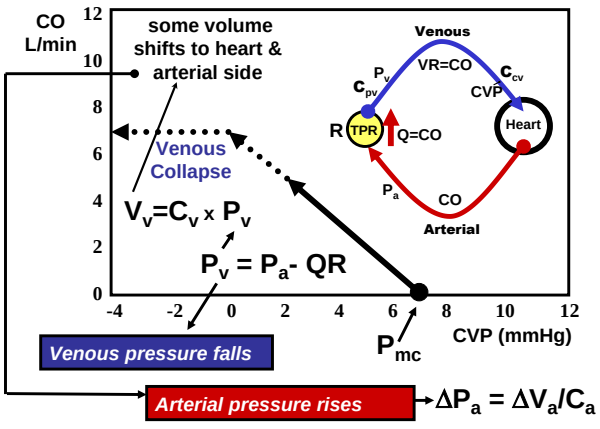
Model Representation in Context



Vascular Function Curve

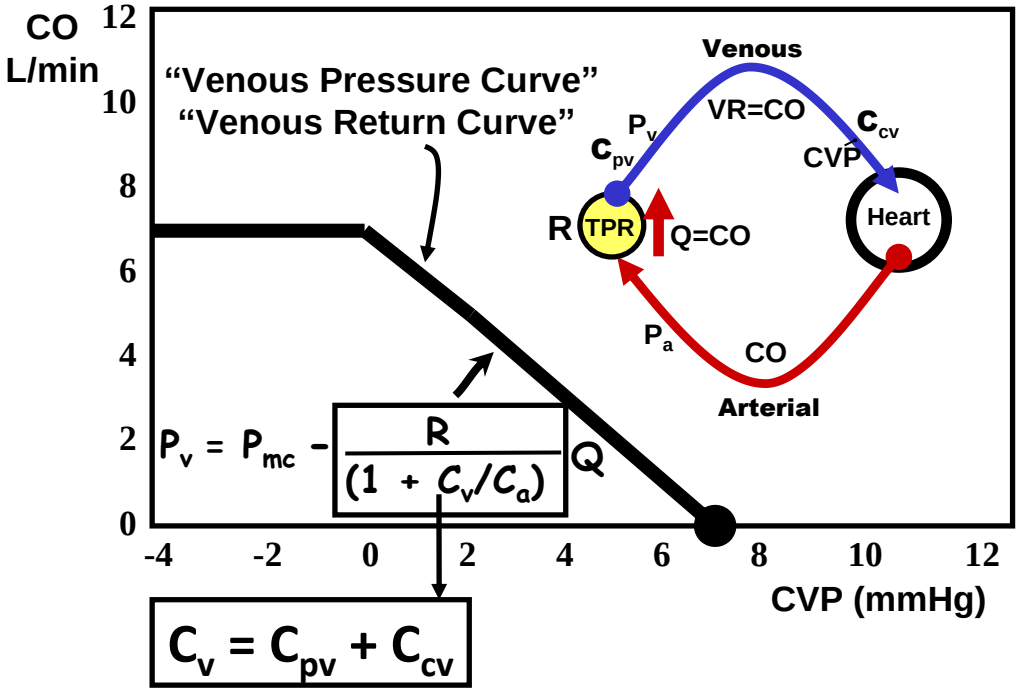


Restart Heart -Begin Pumping

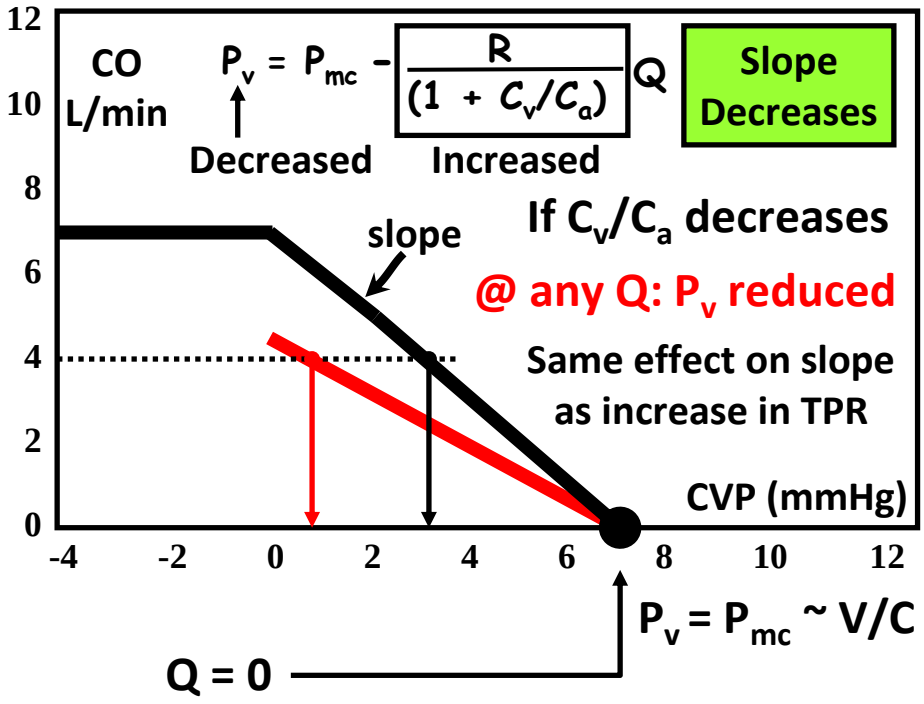


A4. Continued

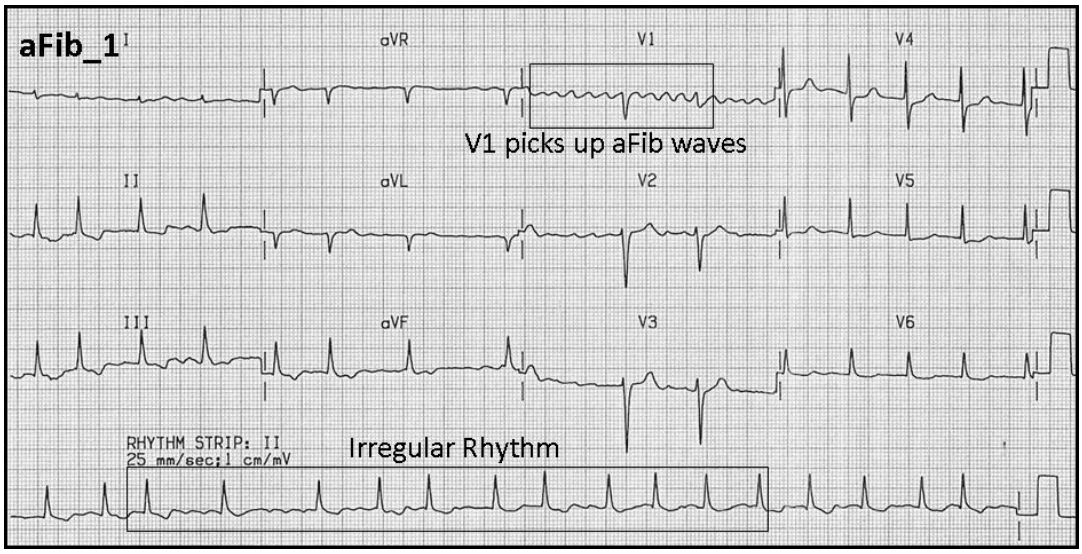
Vascular Function Curve

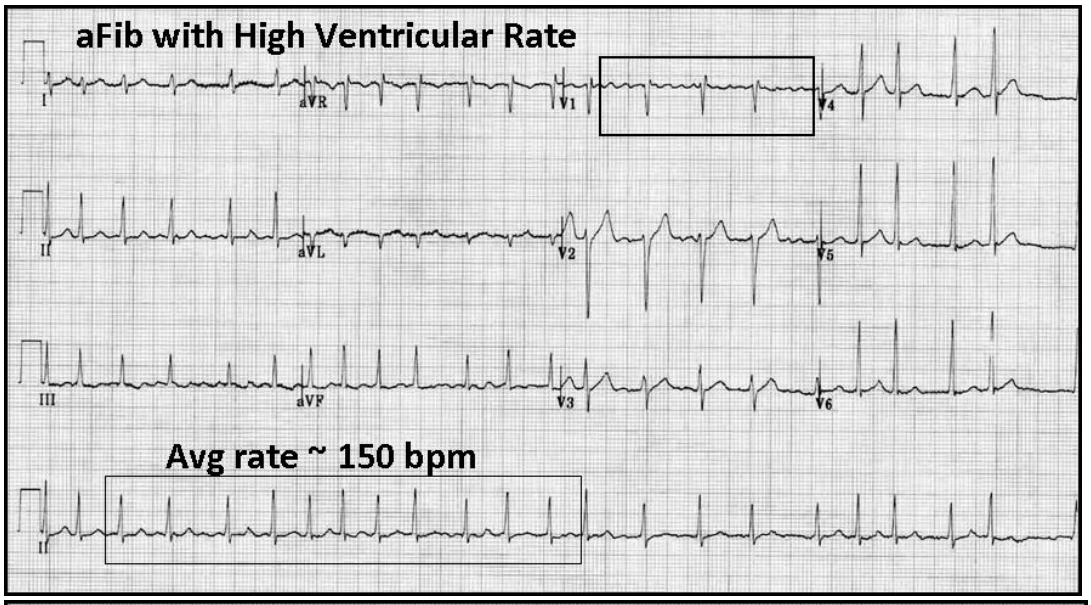


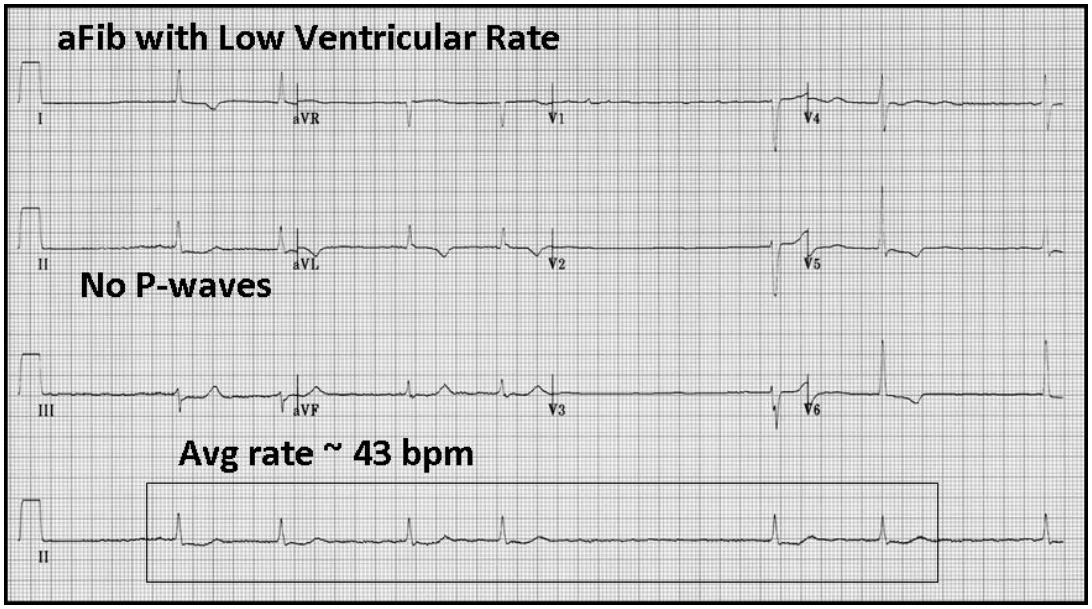
Examine Slope More Closely



A5. Atrial Fibrillation Instructive EKG Examples TOC





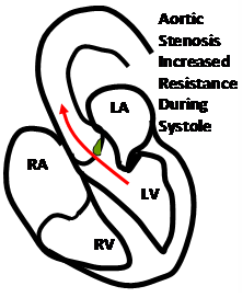


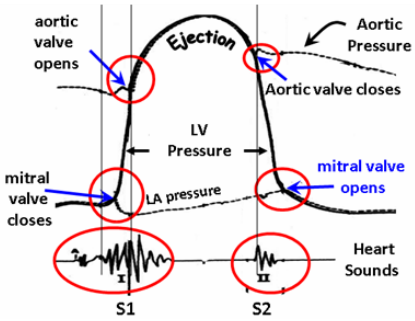
A6. Cardiac Valve Dysfunction Examples: Hemodynamics & Murmurs TOC text return

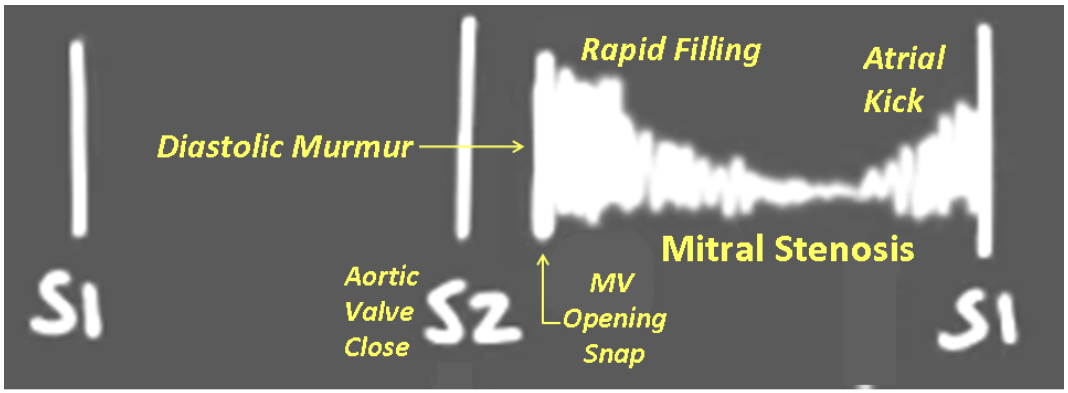
Aortic Stenosis

MV
Closes

Aortic blood flow
Increases then
Decreases
(Crescendo- Decrescendo)

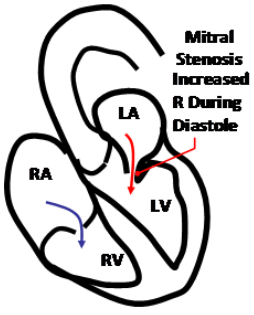


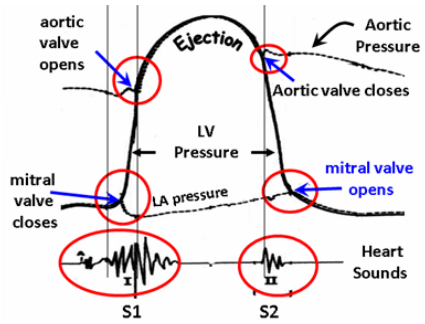


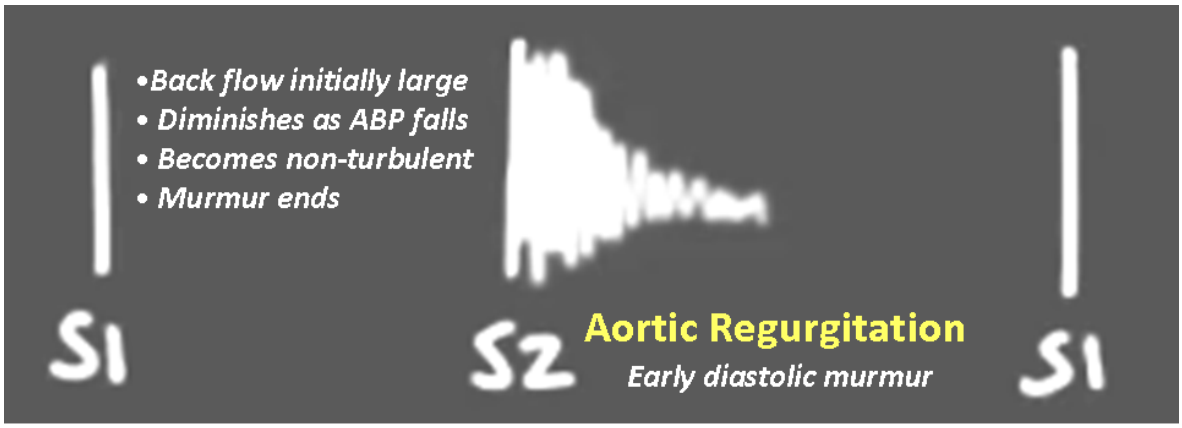


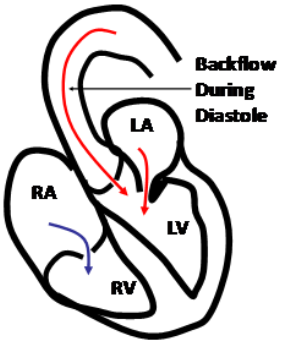
Mitral Stenosis

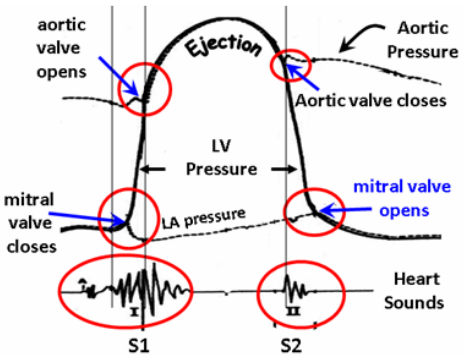
Atria-to-Ventricle
Blood Flow
Increases then
Decreases



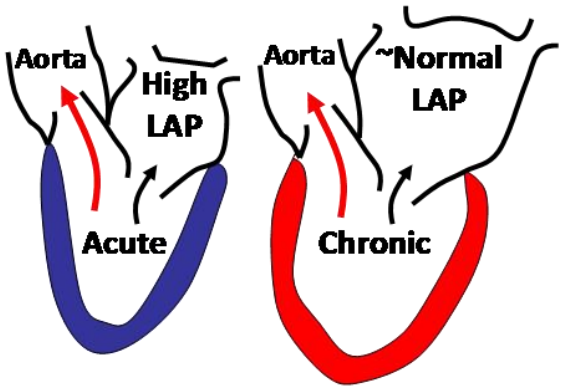


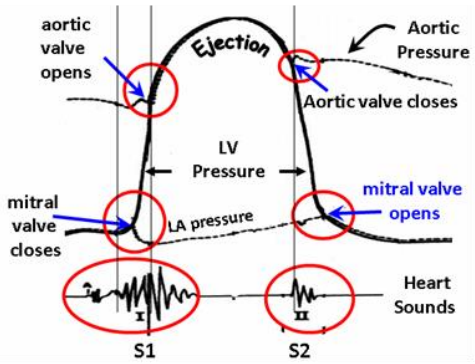

•Back flow initially large
• Diminishes as ABP falls
• Becomes non-turbulent
• Murmur ends
S1
S2
Aortic Regurgitation
Early diastolic murmur
S1


Backflow
During
Diastole
LA
RA
LV
RV

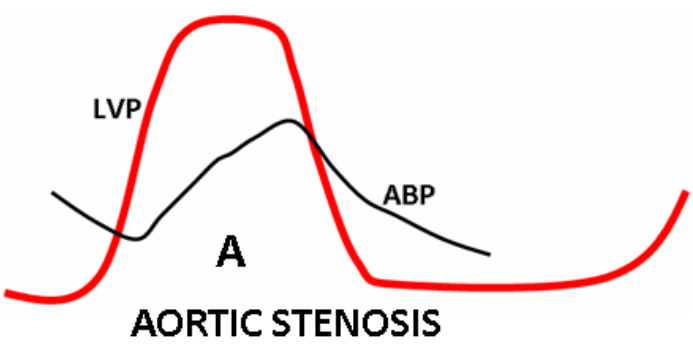

aortic
valve
opens
Ejection
Aortic
Pressure
Aortic valve closes
LV
Pressure
mitral valve
opens
mitral
valve
closes
LA pressure
Heart
Sounds
S1
S2


Mitral Regurgitation
S1
Pan Systolic
Holo Systolic
S2
S1

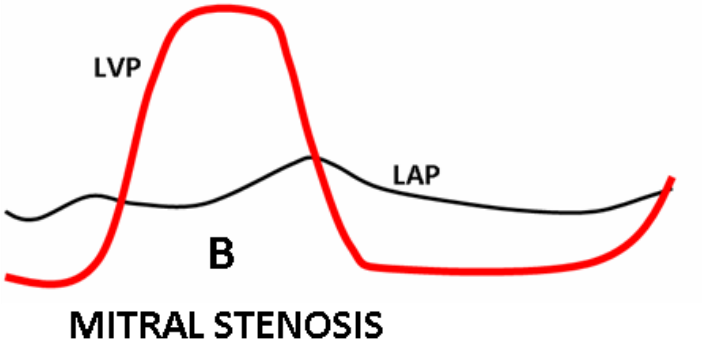

Aorta
High
LAP
Acute
Aorta
~Normal
LAP
Chronic


aortic
valve
opens
Ejection
Aortic
Pressure
Aortic valve closes
LV
Pressure
mitral valve
opens
mitral
valve
closes
LA pressure
Heart
Sounds
S1
S2

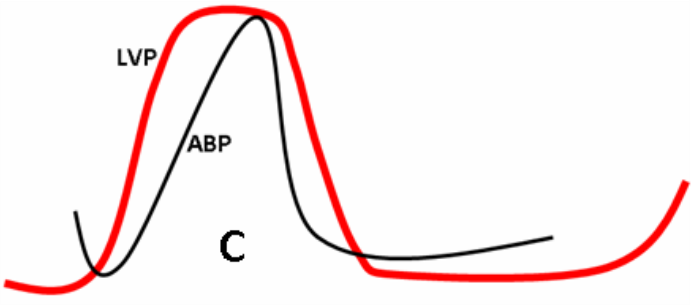
EXAMPLES OF BASIC HEMODYNAMICS ASSOCIATED WITH VALVE CONDITIONS TOC



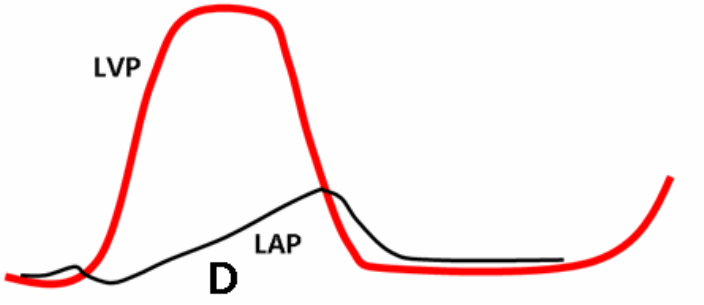
AORTIC STENOSIS



MITRAL STENOSIS

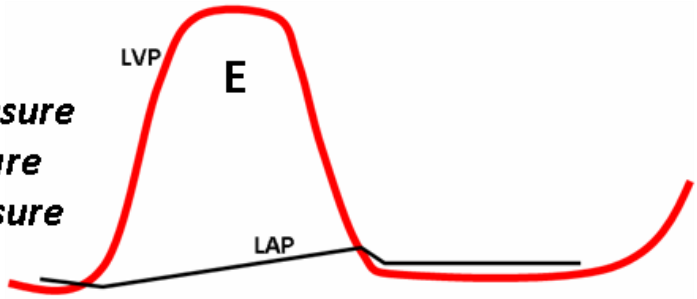


AORTIC REGURGITATION



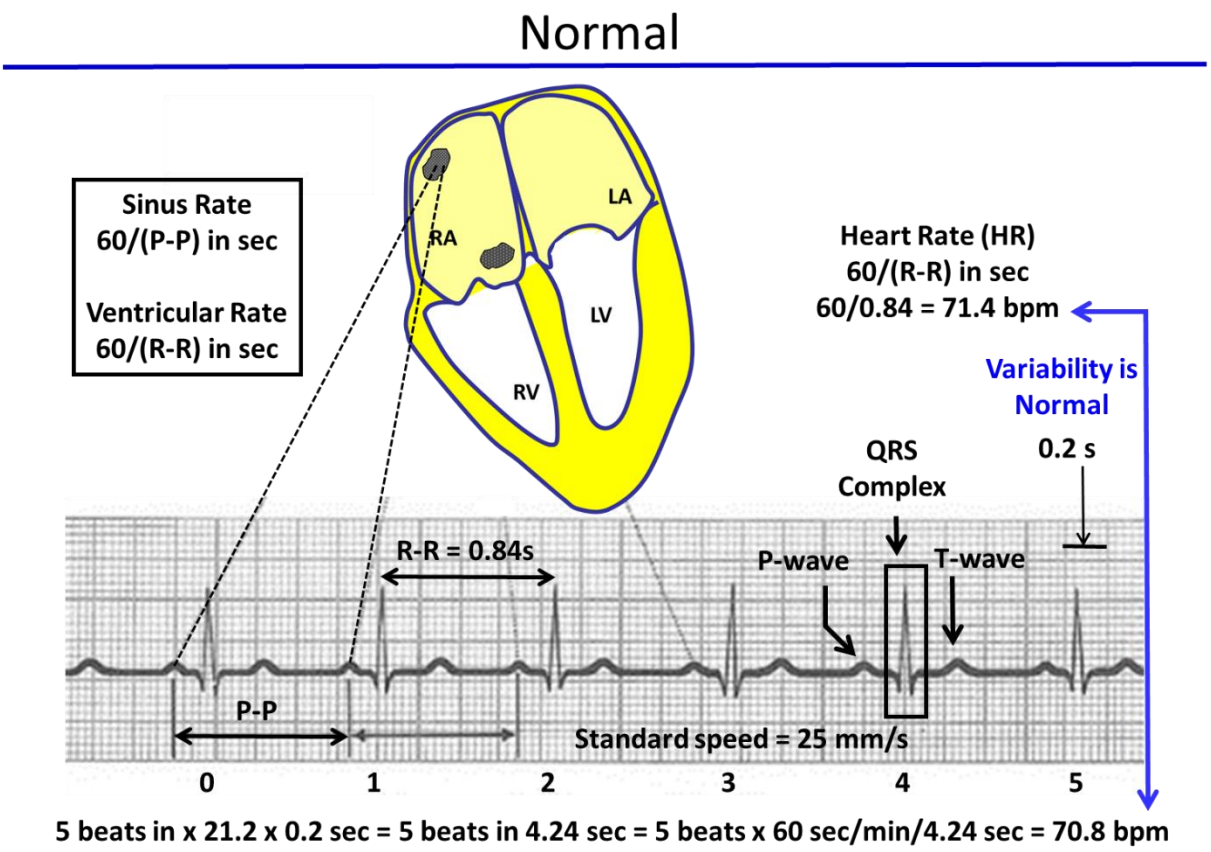
MITRAL REGURGITATION

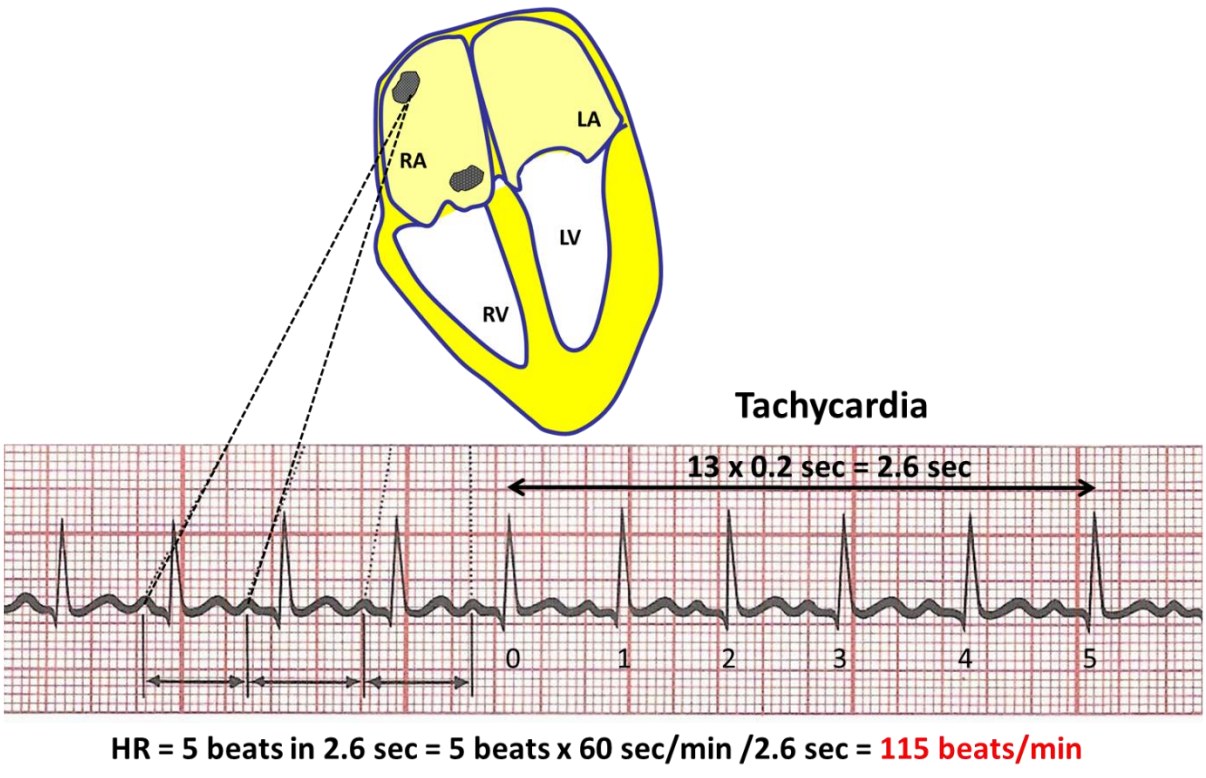
LVP = Left Ventricle Pressure
LAP = Left Atrium Pressure
ABP = Aortic Blood Pressure



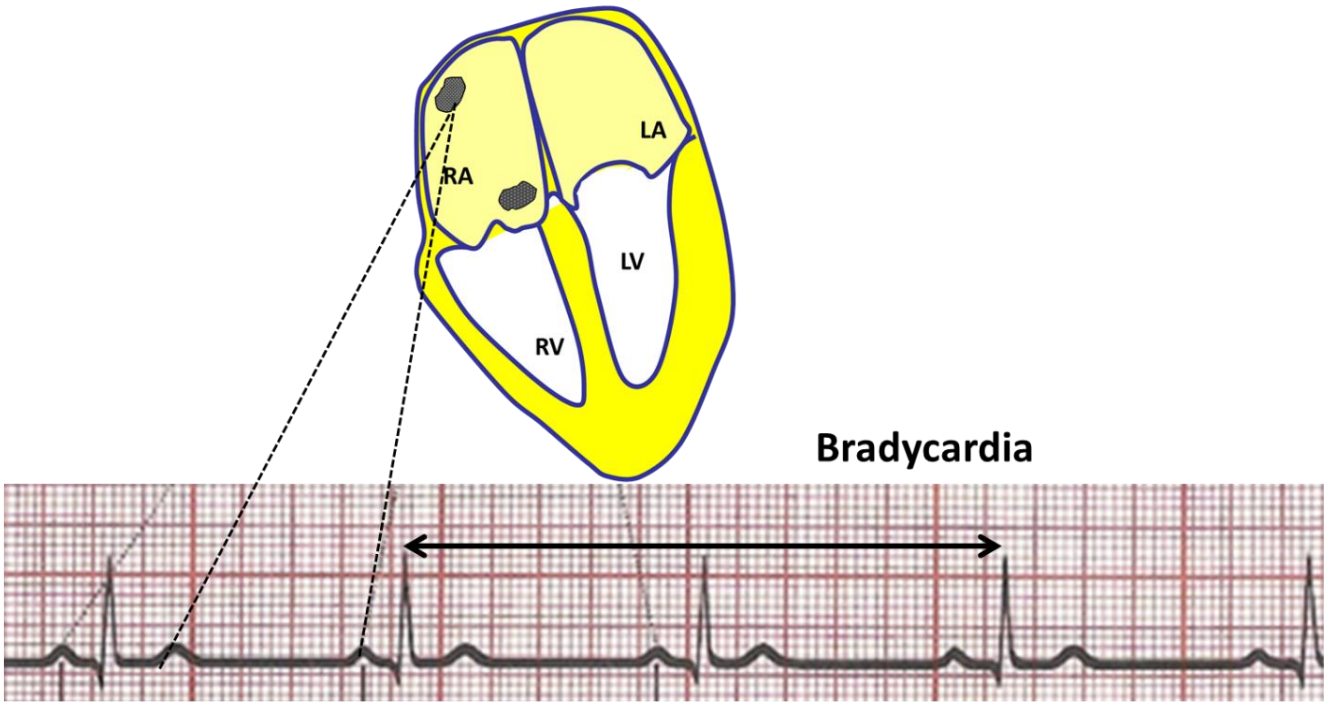
NORMAL

A7. Some EKG Patterns: Normal and Not So Normal TOC



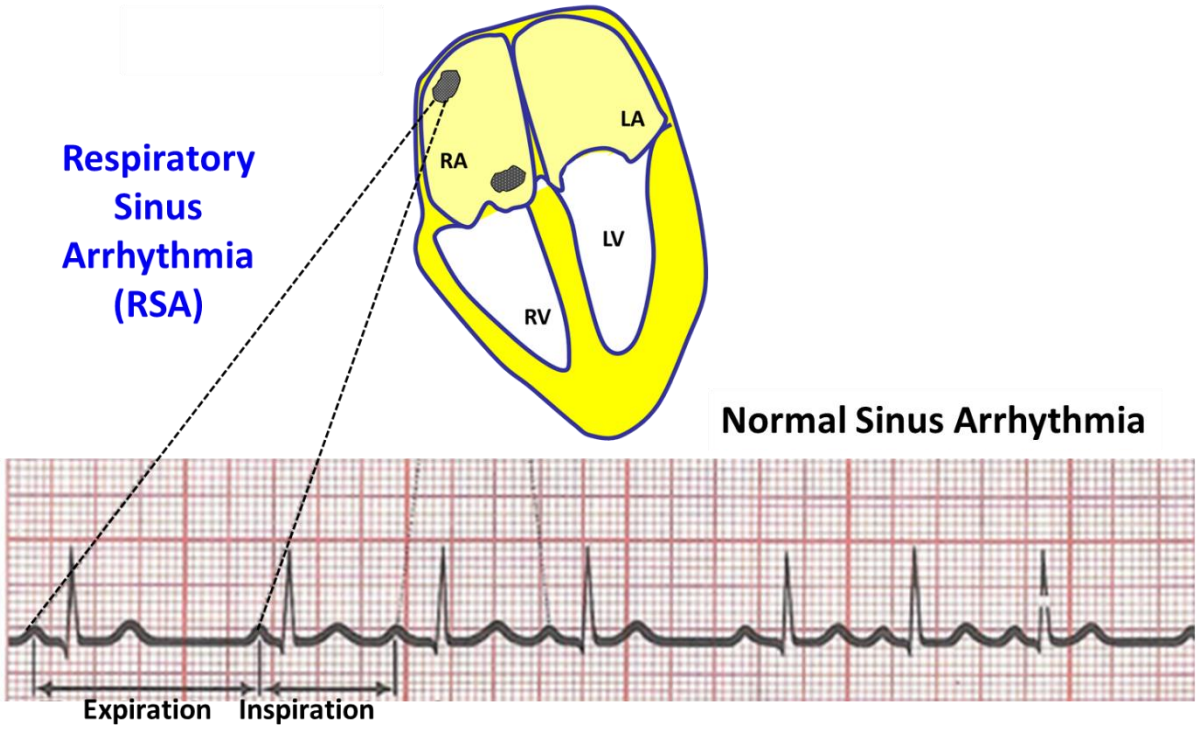


Sinus Rhythm - Bradycardia

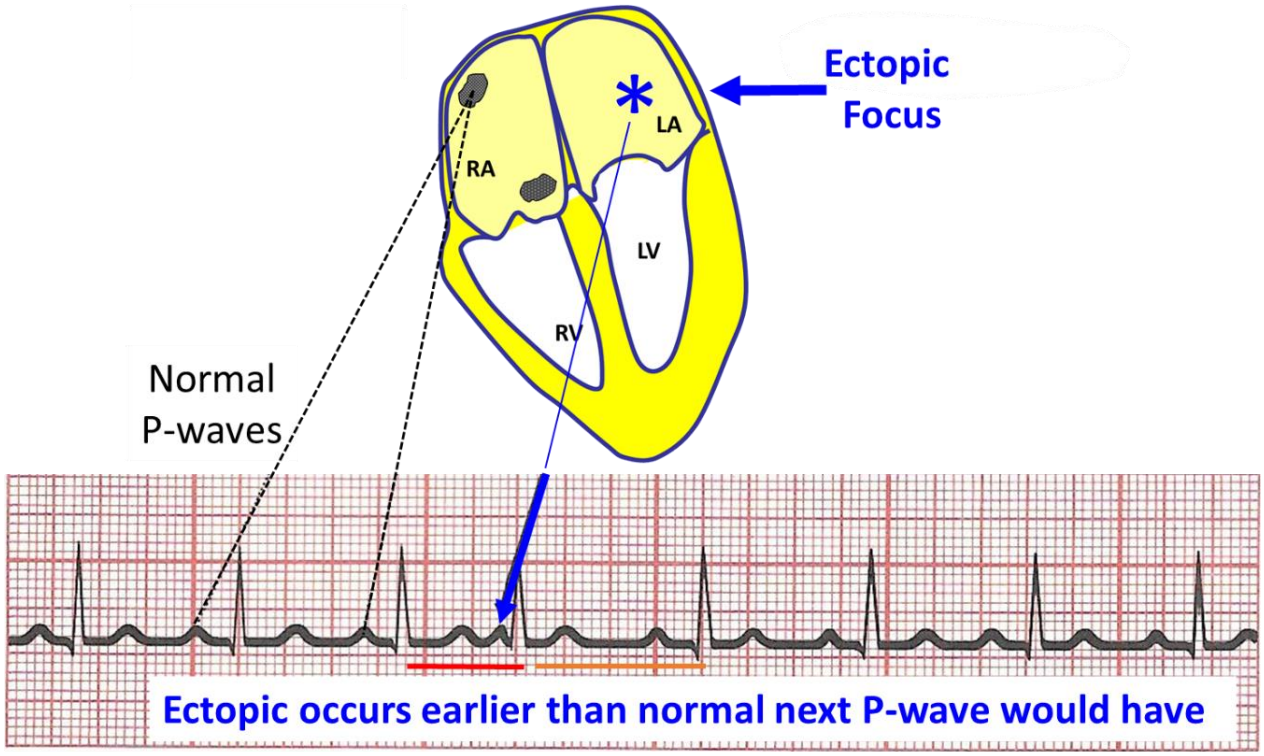


2 beats in ~ 2.4 s; HR = (2 beats x 60s/min)/2.4s = 50 bpm

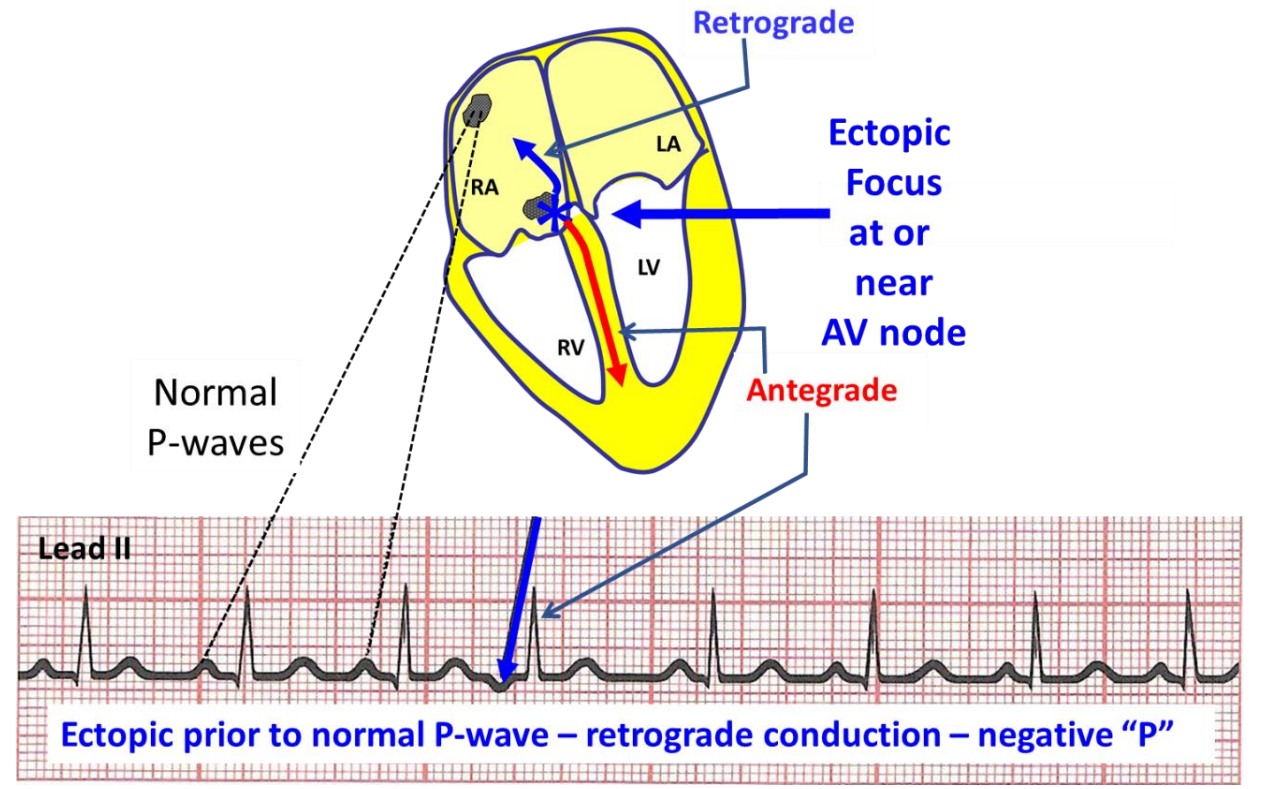
Respiratory Sinus Arrhythmia (RSA)



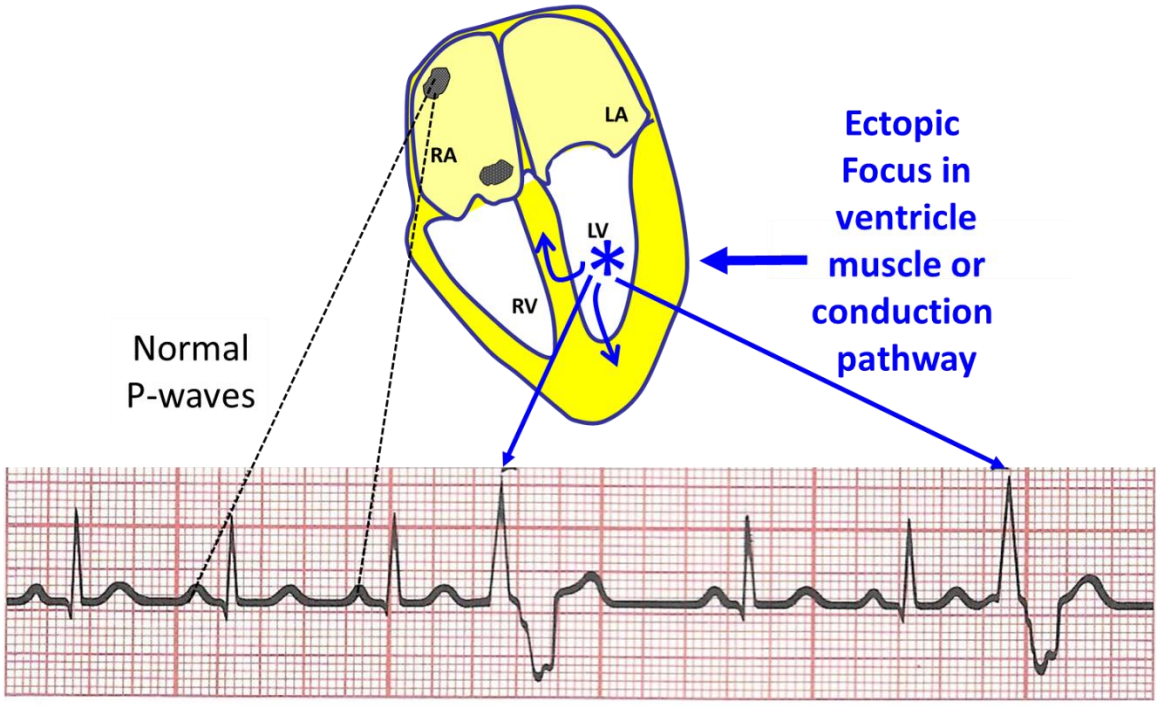
Atrial Ectopic Impulse – Early



Ectopic Impulse – Negative P-Wave

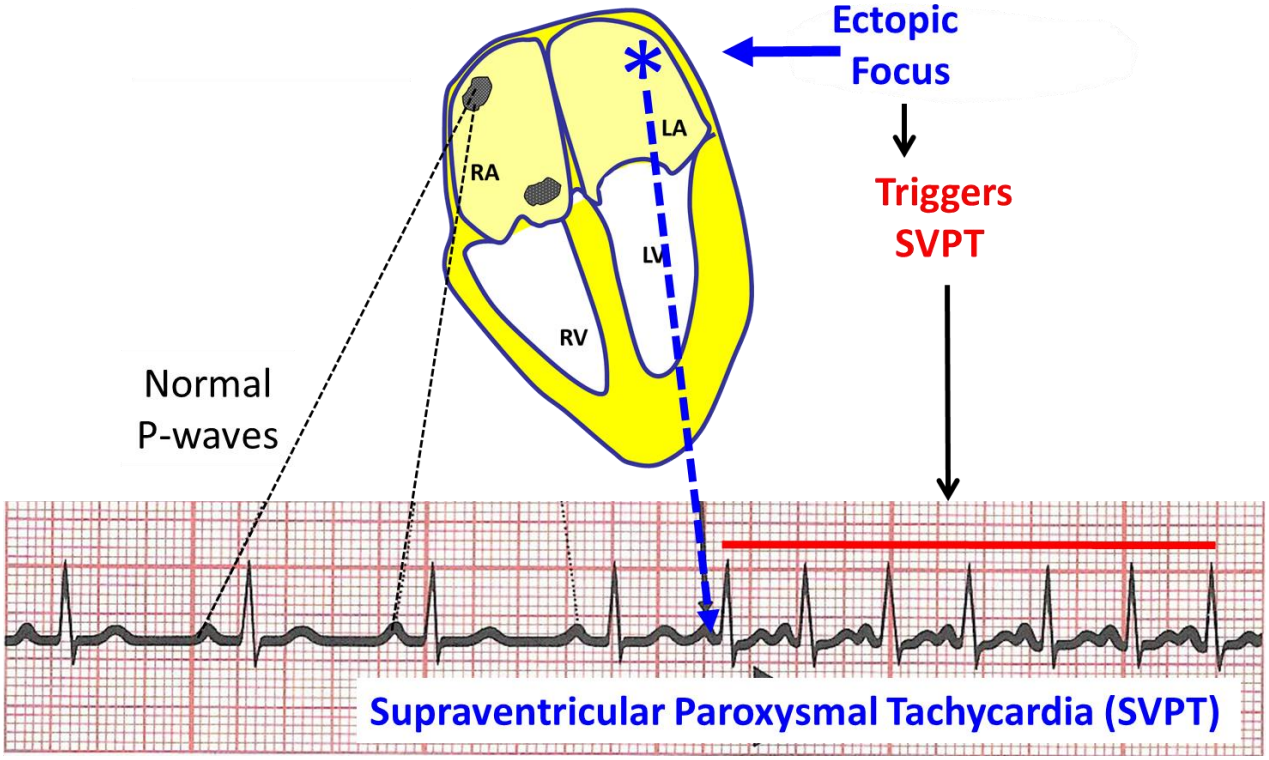


Ectopic Impulse – Ventricular

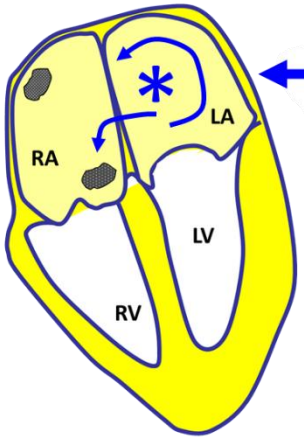


Ectopic prior to normal P-wave – retrograde and antegrade conduction

Supraventricular Paroxysmal Tachycardia

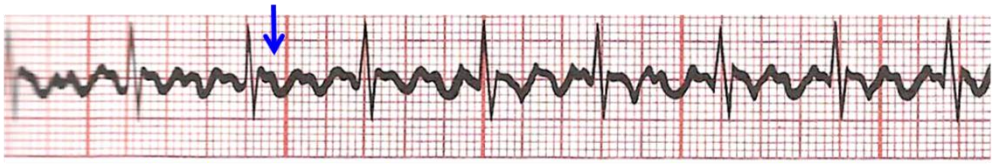


Flutter Waves



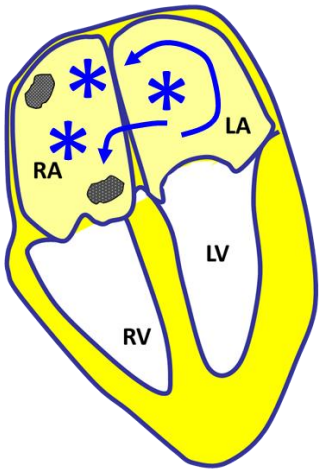
Ectopic Focus With Reentry and Re-excitation

"Flutter Waves" 0.6 s HR = 60/0.6 =100

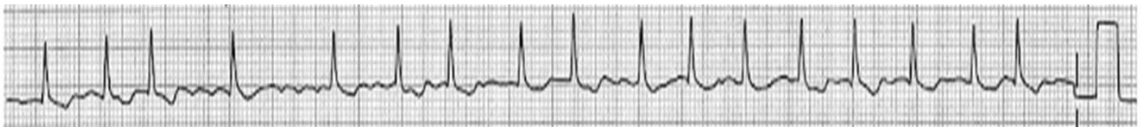


Atrial depolarizations not passing through AV

Atrial Fibrillation

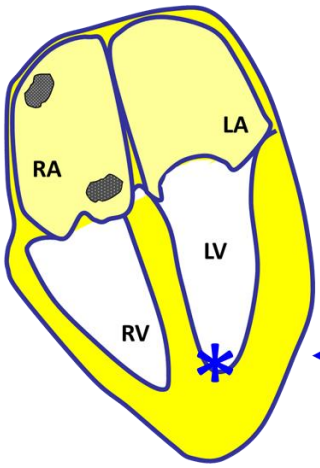


MULTIPLE Ectopic Foci causing uncoordinated impulse transmission through AVN



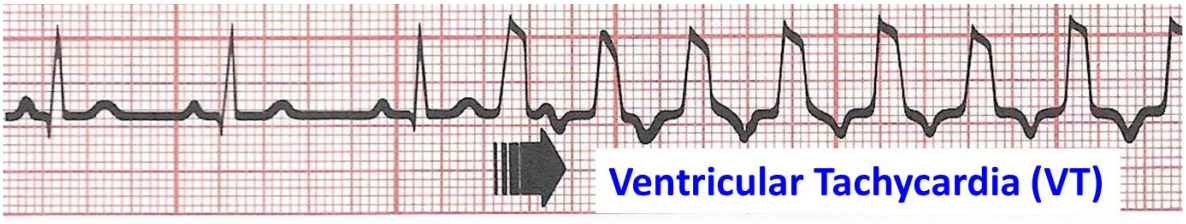
Atrial Fibrillation (aFib) → Rhythm is irregularly irregular

Ventricular Tachycardia



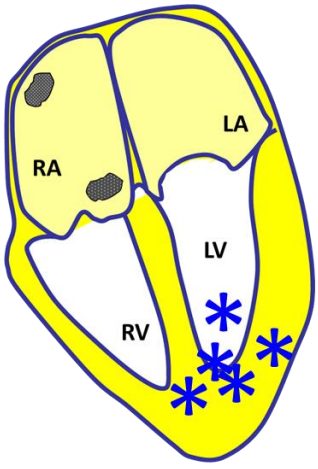
Ectopic Focus Ventricle Triggers VT

HR ~ 60/0.4 = 150 bpm



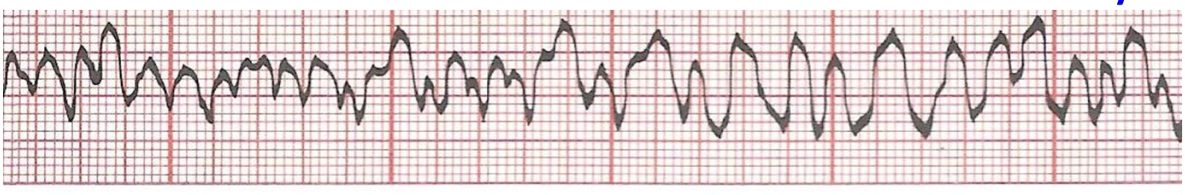
Ventricular Tachycardia (VT)

Ventricular Fibrillation

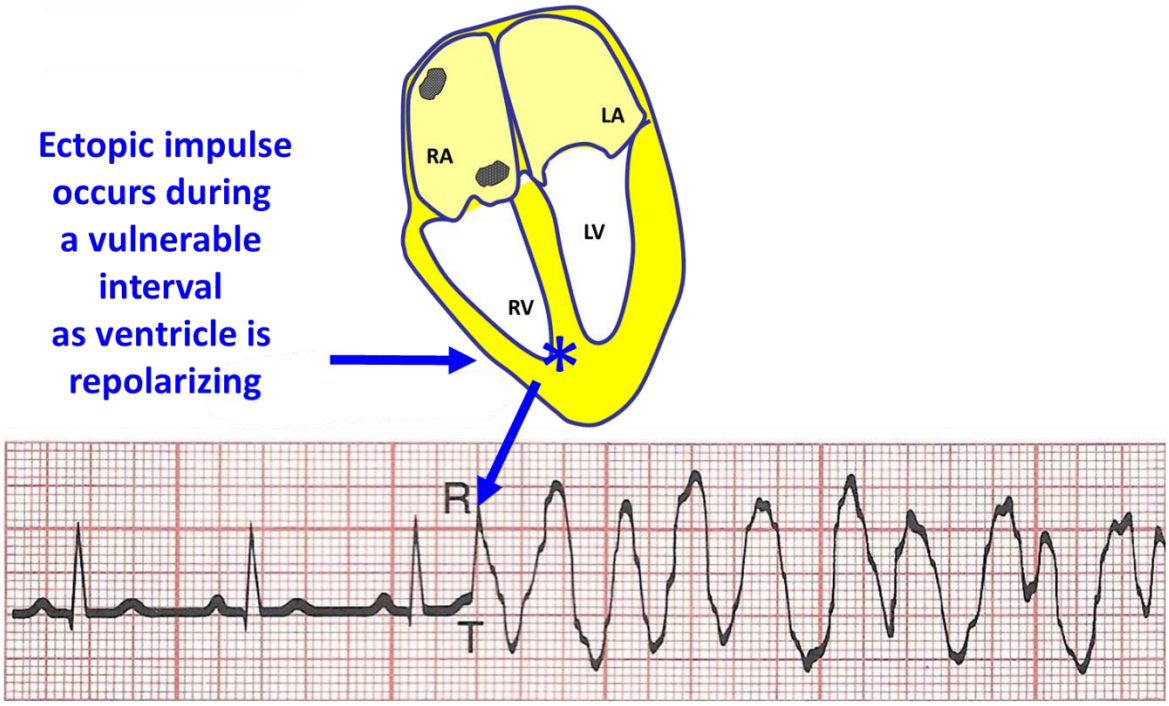


MULTIPLE Ectopic Foci

Erratic uncoordinated electrical and mechanical activity



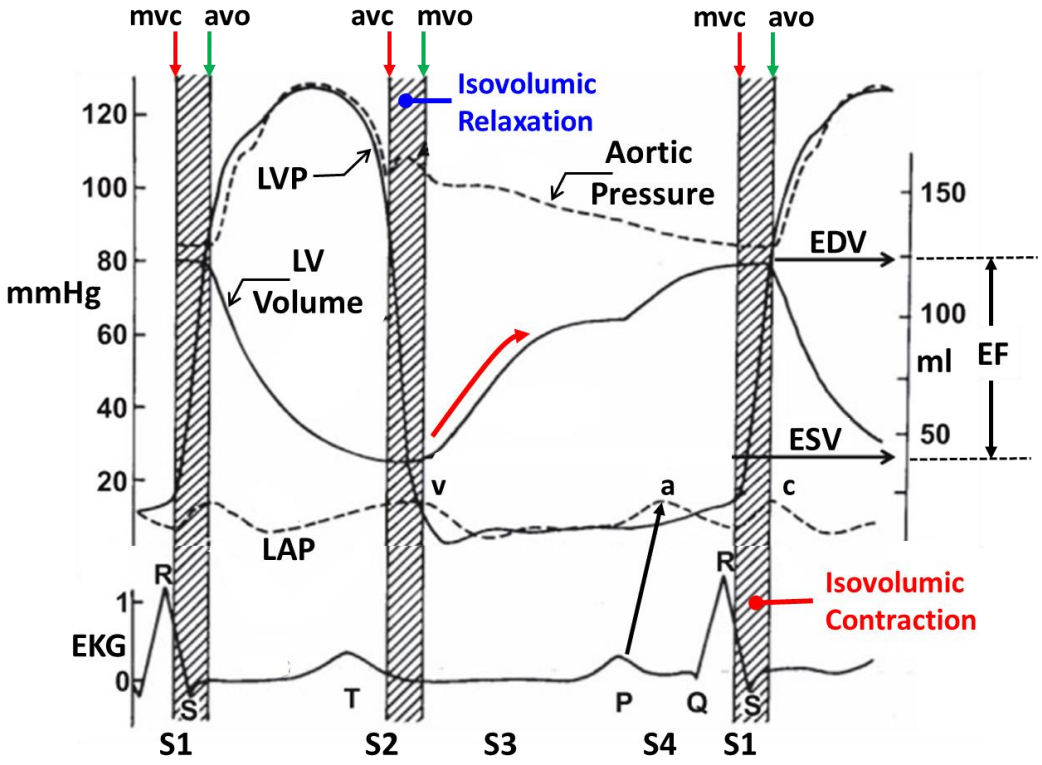
R on T: Ventricular Fibrillation



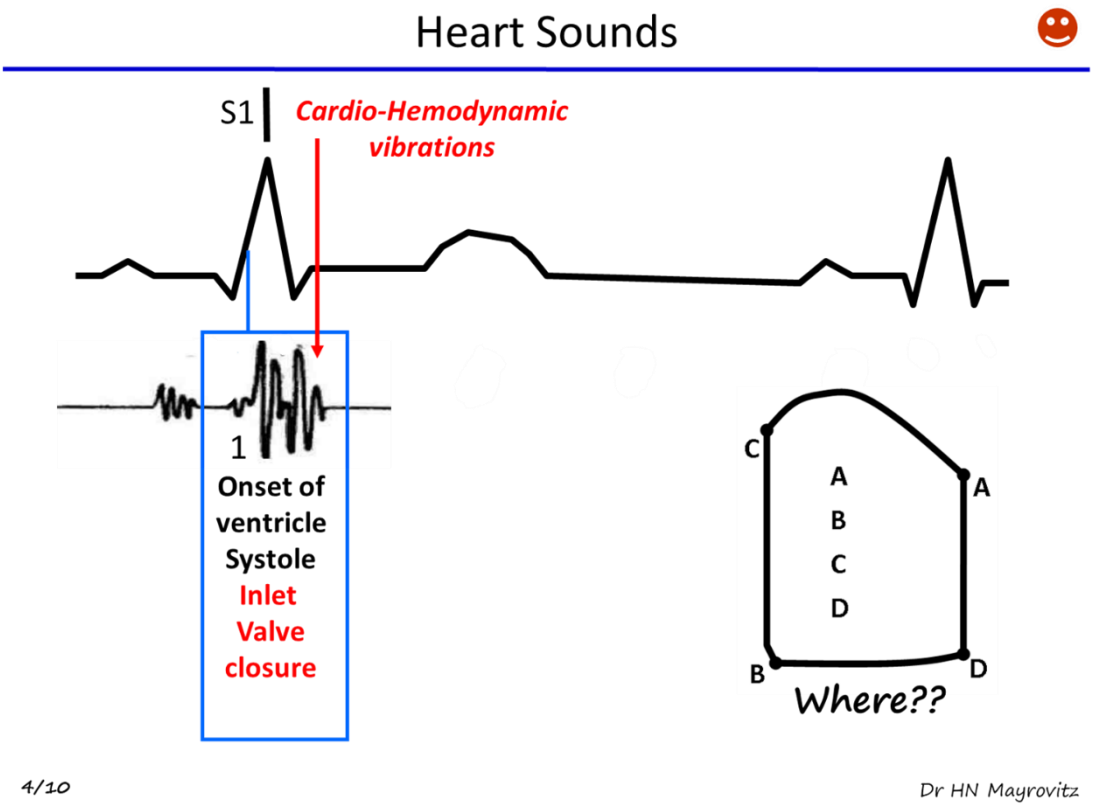
So called R on T triggers vFib

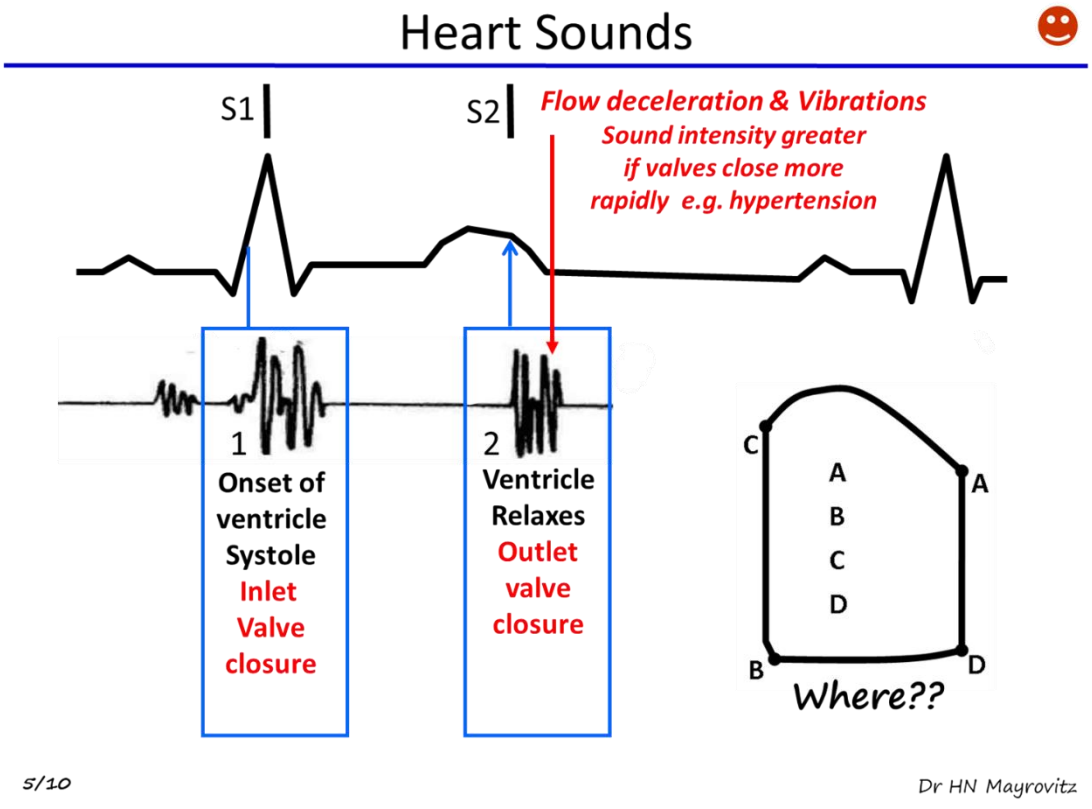
A8. Cardiac Cycle Essentials via Wiggers's Diagram TOC

Cardiac Cycle Essentials via Wiggers's Diagram

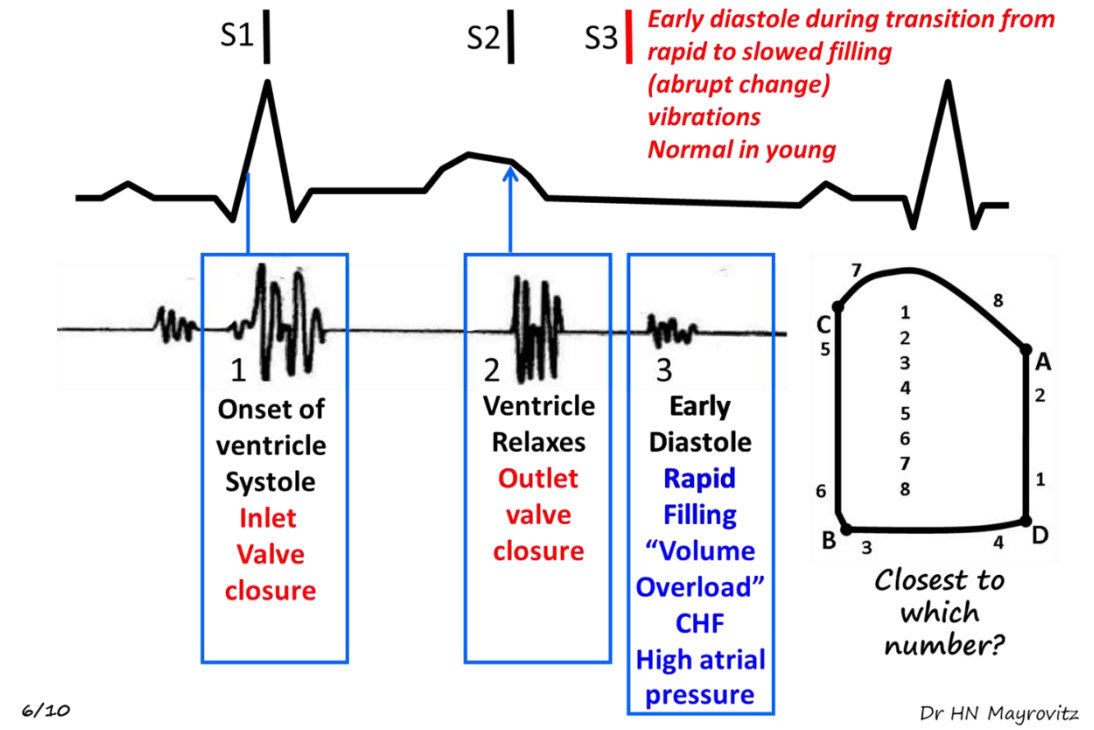


A9. Heart Sounds in Relation to the Cardiac Pressure-Volume Loop TOC





Heart Sounds



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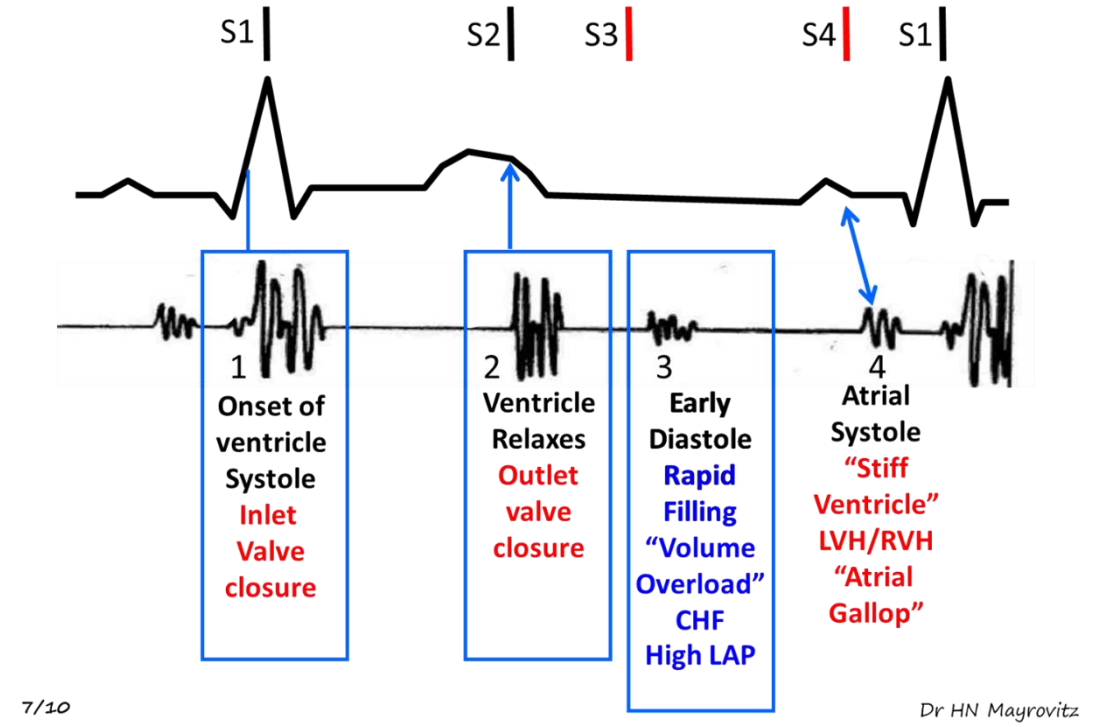
Heart Sounds



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A10. One-Liner Study Questions TOC

1. What are the major cardiovascular components and their general arrangements?
2. What is the general pattern of blood circulation through heart and blood vessels?
3. What are the main functions of the various major blood vessel types?
4. What is meant by the terms cardiac output (CO), stroke volume (SV) and heart rate (HR)
5. What is the quantitative relationship between CO, SV and HR?
6. What is meant by the terms "vascular bed" and vascular resistance?
7. How are most vascular beds arranged with respect to each other?
8. What is meant by the terms "perfusion pressure" and mean aortic pressure (MAP)?
9. What is the relationship between vascular resistance, perfusion pressure and blood flow?
10. What is meant by the specific term "total peripheral resistance" (TPR)?
11. What is the conceptual difference between the term vascular resistance and TPR?
12. What is meant by the term "central venous pressure" (CVP)?
13. How does the magnitude of CVP compare with the magnitude of right atrial pressure (RAP)?
14. How does the magnitude of MAP compare with CVP?
15. What formula would you use to calculate TPR?
16. What are the blood and geometric factors that affect resistance to blood flow of a single vessel?
17. What is the main way in which resistance of individual vessels is physiologically changed?
18. How do vascular resistance changes effect CO distribution?
19. In which vascular segment is most blood volume held?
20. What happens to central venous volume when you stand up?
21. In which part of the arterial system is the mean blood pressure the greatest?
22. If arterioles constrict what happens to capillary pressure and to MAP?
23. If arterioles in only one vascular bed dilate, what happens to its vascular resistance and flow?
24. What is your concept of the physical meaning of the term vascular or cardiac compliance?
25. What is the quantitative relationship between pressure, volume and compliance?
26. What is significant about the slope of the volume-pressure curve?
27. If a blood vessel has a fixed volume but its compliance decreases, what happens to its pressure?
28. In what tissue does the cardiac impulse normally start?
29. In what regions would you find slow response AP's? fast response AP's?
30. In which region is AP conduction the slowest? The fastest?
31. For each phase of fast response APs describe the actions of the relevant ion channels and currents
32. Same as #31 but for the pacemaker AP
33. What is the effect of sympathetic and vagal activity on HR?
34. What are the mechanisms that account for #33?
35. During which AP interval would a less than normal stimulus produce a response?
36. During which AP interval would a stimulus, however large not produce a response?
37. During which AP interval would a larger than normal stimulus produce a less than normal response?
38. What is meant by the vulnerable region?
39. What is a latent pacemaker?
40. What is an ectopic pacemaker?
41. What is the cardiac excitation sequence?
42. What are the necessary conditions for reentrant arrhythmia?
43. What is the source of the voltages measured by ekg electrodes on the skin?
44. What are the approximate temporal relationships between each of the main ekg waves (P, QRS and T) and the cardiac action potential phases?
45. Which ekg interval is an approximate estimate of the duration of the action potential?
46. What are examples of the units of blood flow, blood velocity and shear rate?
47. Which of the those in #46 would increase in a vessel with a local reduction in its cross-sectional area?

48. If flow is maintained constant in a vessel, what is the effect of area changes on mean blood velocity?
49. What is meant by perfusion pressure and transmural pressure in a vessel?
50. Which of #49 would increase if only the upstream intravascular pressure increased?
51. Which of #49 mainly effects the diameter of the vessel?
52. What is meant by the term velocity gradient in a blood vessel?
53. If blood viscosity increases is it easier or harder for blood to flow?
54. If each of the following, what is the effect on blood's effective viscosity?
    - Hematocrit increases
    - Shear rate decreases
    - Fibrinogen concentration increases
    - Blood velocity increases
    - Blood temperature increases
55. In which part of a blood vessel is the shear stress produced by flowing blood the greatest?
56. What are some differences between laminar vs. turbulent blood flow?
57. What is Reynold's Number, what is its significance and what are its determinants?
58. What is a stenosis?
59. If a stenosis were present in a large artery what is its effect on the following?
    - Likelihood of turbulence
    - Blood velocity within the stenosis
    - Energy or pressure loss across the stenosis
60. In physical terms, what is blood pressure?
61. What equations relate blood flow (Q) and pressure difference (DP) in laminar vs. turbulent blood flow?
62. In an individual vessel how do its length, diameter and the blood's viscosity effect resistance to flow?
63. In #62 which is normally having the greatest effect?
64. How is total resistance determined when blood vessels are in series and when the are in parallel?
65. Considering either vessels in series or in parallel, in which do the following apply?
    - Perfusion pressures are equal
    - Blood flows are equal
    - Total resistance is less than any individual vessel's resistance
66. What is meant by pre-capillary and post-capillary resistance?
67. If pre-capillary resistance increases, what happens to capillary pressure?
68. If pre-capillary resistance decreases, what happens to blood flow in a vascular bed?
69. What is the Law of Laplace and how does it relate to blood vessels?
70. How do each of the following vary within the consecutive segments of the systemic vasculature?
    - Mean Blood Velocity
    - Mean Blood Pressure
    - Mean Blood Flow
    - Blood Volume
    - Resistance
71. What is meant by isovolumic contraction?
72. What is meant by the term preload and what quantity best represents it in the intact heart?
73. What is the Frank-Starling mechanism and what role does it play in cardiac pumping?
74. What is cardiac contractility and what role does it play in cardiac pumping?
75. What are the sequential mechanical events of the cardiac cycle?
76. What are the states of the valves during the cardiac cycle?
77. What is the temporal relationship between the EKG and the events of the cardiac cycle?
78. What is meant by the term ejection fraction and how is it calculated?
79. During which part of the cardiac cycle is the load on cardiac muscle the greatest?
80. Which part of the pressure-volume loop represents useful mechanical work?
81. What is meant by the term Tension-Time Integral (TTI) and why is it important?

82. What factors would increase the TTI?
83. What is meant by the term "double product" and what is its significance?
84. What is the relationship if any between the Frank-Starling mechanism and contractility?
85. What is the effect of a decrease in contractility on peak isovolumic pressure (PIP)?
86. What cardiac mechanical events are associated with the heart sounds?
87. What mechanical events are associated with heart sounds S3 and S4?
88. What role does trigger-Ca++ play in the excitation-contraction process?
89. If you knew the EDV of a patient what would need to know to determine ejection fraction?
90. What is a main difference between left and right ventricular features as a blood pump?
91. Assuming arterial diastolic pressure is constant, what factors would affect the aortic pulse pressure?
92. During which part of ventricle ejection does the largest fraction of SV enter the aorta?
93. What is the effect of a decreased aortic compliance on aortic systolic pressure and pulse pressure?
94. How would you determine MAP from standard cuff measurement of brachial artery pressures?
95. What is essential hypertension? What is isolated systolic hypertension?
96. What is meant by pulse-wave speed?
97. If aortic compliance decreased what would happen to pulse-wave speed?
98. What is the difference between pulse-wave speed (wave-velocity) and blood-velocity.
99. Which of #98 is faster? Which are you sensing when you palpate the radial artery?
100. What accounts for the presence of forward and backward waves in the arterial system?
101. What accounts for a larger systolic pressure in the femoral artery than in aorta?
102. What are the diastolic and systolic pressure limits above which are considered as hypertensive?
103. Which vessels mainly control local blood flow to and pressure within the capillary network?
104. What is the main function of the capillary circulation?
105. If arterioles dilate what happens to blood flow in the capillary network?
106. If arterioles constrict, what happens to the capillary pressure?
107. If, arterioles dilate causing capillary recruitment, what happens to available capillary surface area?
108. If capillary network permeability to water doubles due to injury what happens to transcapillary flux?
109. What factors determine the amount and direction of transcapillary fluid exchange?
110. For an increase in each of the following conditions state if edema tendency is increased or decreased.
    venous pressure
    precapillary resistance
    post capillary resistance
    pre/post capillary resistance
111. For each of the following conditions state whether capillary pressure is increased or decreased.
    compression of the pelvic vein
    compression of the femoral artery
    an arterial blood clot
    a venous thrombosis
112. For each of the following conditions state if edema tendency is increased or decreased and why.
    Dehydration
    fluid retention
    lymph node removal
    right heart failure
    hypoproteinemia
113. What cardiovascular mechanisms are available to increase oxygen supply to systemic microcirculation?
114. In what way does the venous system function as a variable blood reservoir?
115. What is the effect of decreasing the compliance of the venous system?
116. What are the effects of venous valve dysfunction?
117. In what way does respiration effect venous blood flow?
118. In what way do the effects in #117 effect cardiac output?

119. When going from a supine to an upright position what are the effects on the following and why?
pressure in the dural sinuses
pressure in foot arteries
pressure in foot veins
perfusion pressure for the foot circulation
120. What events and reflexes are initiated by going from a supine to an upright position?
121. After standing at attention for 15 minutes what effect will walking have on foot vein pressure?
For questions 122-136, what is the effect on the indicated parameters (e.g. HR, SV, CO, TPR or MAP) if each indicated change acts initially alone? Increase = (+) and Decrease = (-).
122. + sympathetic impulses to SA node on HR
123. + sympathetic impulses to myocardium on SV
124. + sympathetic impulses to arterioles on TPR
125. + sympathetic impulses to peripheral veins on Venous Return
126. + EDV on SV
127. + afferent impulses from carotid sinus (CS) to medullary vasomotor center (VMC) on TPR
128. - blood pressure within the carotid sinus on HR
129. + blood concentration of epinephrine on SV
130. + arterial blood levels of H+ on CO
131. + arterial blood levels of CO2 on TPR
132. + vagus impulses to SA node on HR
133. administering a cardiac specific positive inotropic drug on SV and CO
134. administering a cardiac specific calcium channel blocker on SV
135. administering an arterial specific calcium channel blocker on TPR
136. administering a drug with a norepinephrine-like action on TPR
137. What role does sympathetic adrenergic stimulation play in the direct control of the diameter of terminal arterioles and capillaries?
138. Activation of arteriole a-receptors by epinephrine causes what to happen?
139. Activation of arteriole a-receptors by norepinephrine cause what to happen?
140. Activation of arteriole b2-receptors causes what to happen?
141. What is the role of the endothelium in controlling VSM contractile state?
142. What is myogenic control?
143. What is autoregulation?
144. What is functional hyperemia?
145. What is reactive hyperemia?
146. If an arteriole that was capable of a myogenic response experienced a sudden decrease in its transmural pressure, what would be the effect on the diameter of this arteriole?
147. If arterioles have both a and b receptors, what determines if changes in circulating levels of co-present epinephrine and norepinephrine will cause vasodilation or vasoconstriction?
148. What is the calf muscle pump and how does it affect blood flow?
149. According to the new hypertensive guidelines, what is meant by "prehypertensive"?
150. What types of murmurs (systolic or diastolic) would occur in the following conditions?
Mitral valve stenosis
Mitral valve regurgitation
Aortic valve stenosis
Aortic valve regurgitation
151. Explain the reason for the pressure-dependence of vascular compliance.
152. Under what conditions would veins not have lower compliance than corresponding arteries?
153. Explain the difference between vessel compliance and vessel distensibility.
154. Explain how both TPR and Compliance combine to determine arterial pressure.
155. What is meant by electromechanical coupling?

156. In what tissue does this coupling occur?
157. Which ion is most involved in this coupling?
158. What is meant by the term rectification?
159. What is meant by the term delayed rectification? What cardiac current has this property?
160. What is meant by the term inward rectification? What cardiac current has this property?
161. What is meant by reentry and how does it arise?
162. What is meant by unidirectional block?
163. What is meant by bi-directional block?
164. What are the differences between 1o, 2o and 3o AV blocks?
165. In what way does the recovery state of a cardiac fiber affect AP conduction velocity through that fiber?
166. What are the necessary conditions for reentrant arrhythmia?
167. Suppose ventricle myocytes experienced a partial depolarization of their normal resting membrane potential. What would be the likely effect of this on the steady-state availability of fast sodium channels?
168. For #167, what effect would this have on the magnitude of the peak INa during phase 0?
169. For #168, What effect might this then have on conduction properties of the AP?
170. The puffer fish poison tetrodotoxin (TTX) will very selectively block fast sodium channels. Would this directly and significantly affect SA nodal slow response diastolic depolarization rate?
171. Diltiazem is a drug that inhibits calcium entry through slow channels (ICa-L). What is the effect of this drug on the rate of diastolic depolarization and on heart rate?
172. What is meant by the terms early and delayed afterdepolarization and how do they differ?
173. Digitalis is a cardiac b-adrenergic stimulating agent that increases myocyte internal calcium. What type of arrhythmia induction might be associated with this induced calcium "overload".
174. What is meant by decremental conduction and describe one scenario in which it may occur in the heart.
175. Explain why the measured ekg voltage only about 1 mv whereas cardiac AP's are about 100 times larger?
176. What is the difference between an ekg electrode and an ekg lead?
177. What is the difference between a unipolar and bipolar lead?
178. What is meant by the axis of a lead and how is it defined for standard limb leads?
179. What is meant by the term mean cardiac vector and the specific term mean QRS vector?
180. What is meant by the concept of cardiac vector projection onto lead axis?
181. What are the axes angles/directions for the six frontal plane leads?
182. If the projection of a cardiac vector onto a lead is in the direction of lead axis what can you say about the ekg voltage measured by that lead?
183. If a cardiac wave of depolarization is approaching the positive pole of a lead, what can you say about the ekg voltage measured by that lead?
184. What accounts for the fact that the ST segment is normally isoelectric?
185. Which ekg interval is an approximate estimate of the duration of the action potential?
186. What is a normal range for the mean QRS vector (also called mean electrical axis or MEA)?
187. If a MEA is at -120o is this right or left axis deviation?
188. Sustained significant hypertension may lead to left ventricular hypertrophy (LVH). What type of MEA deviation would be most likely if it were to occur?
189. To which direction would you expect the MEA to shift in the case of complete right bundle branch block?
190. To which direction would you expect the MEA to shift in the case of left anterior fasicular hemiblock?
191. If the R-waves of leads I and II are predominantly positive, what is true regarding the MEA?
192. What is meant by the terms bradycardia and tachycardia?
193. What is the difference between heart rate and heart rhythm? Can one be abnormal the other normal?
194. By what procedure can the ekg be used to estimate the MEA?
195. If the only irregularity detected on an ekg was an inverted P-wave, what might account for this observation?
196. If a wide (and bizarre looking) QRS complex were seen on the ekg together with a left axis deviation, what conduction abnormality might account for this observation?
197. What are the main ekg differences between 1o, 2o and 3o AV block?

198. What is the genesis and effect of Paroxysmal Atrial Tachycardia?
199. What are the basic ekg patterns associated with impulses originating soley in the left ventricular?
200. What are basic differences in ekg patterns among ectopic foci arising in the atria, AV node and ventricle?
201. If only blood flow in a vessel increases, what happens to the shear stress experienced by endothelial cells?
202. Increased wall shear stress will release what vasoactive substance from endothelial cells?
203. Explain the difference between wall tension and wall stress as experienced by blood vessel and heart walls?
204. What is the modified form of Laplace's Law and why is it needed?
205. What is meant by the term "positive inotropic intervention"?
206. How, if at all, does #205 differ from "an increase in contractility"?
207. Based on energy considerations, is it more efficient to increase CO by increasing HR or by increasing SV?
208. What would be the immediate effect on ventricular preload of a rapid increase in ventricular afterload?
209. In what way is the P-V representation of the cardiac cycle changed if the following occur:
    Increased sympathetic impulses to heart
    Increased contractility
    Increased afterload
    Increased preload
210. Describe the relationship/correspondence between cardiac cycle events as depicted on the P-V loop with those on the Wiggers diagram showing temporal features.
211. What mechanism helps balance transient, beat-by-beat differences in SV of the right and left ventricles?
212. What changes in ventricular pressure features would occur if myocardial contractility decreased?
    Peak pressure
    Rate of pressure increase (dP/dt)
    Rate of pressure decrease
213. What changes in ventricular outflow features would occur if myocardial contractility increased?
    Peak flow
    Rate of early ejection (dQ/dt)
214. What cardiac mechanical events are associated with heart sounds S1 and S2?
215. What cardiac mechanical events are associated with heart sounds S3 and S4?
216. What is the reason that mitral and aortic insufficiency may lead to ventricular hypertrophy?
217. In which cardiac valve condition would you expect an abnormally large atrial-ventricular pressure gradient?
218. In which cardiac valve condition would you expect an abnormally large ventricular-aortic pressure gradient?
219. In which cardiac valve condition would you expect an abnormally elevated atrial pressure & systolic murmur?
220. In which cardiac valve condition would you expect to see an abnormally rapid fall-off in aortic pressure?
221. What is the main difference between left and right ventricular features as a blood pump?
222. As applied to the left ventricle, what is meant by the terms hypertrophy and dilatation?
223. Which of #222 is associated with a greater ventricular wall stress?
224. In the heart, what is meant by the term postextrasystolic potentiation?
225. If cardiac contractility increases, what will happen to the forward wave speed of the aortic pressure pulse?
226. How do forward and backward pulse-waves interact to effect pulsatile pressure and flow?
227. What is the general effect of peripheral vasodilation and vasoconstriction on pulse-wave reflection?
228. What physiological effects do reflections have on the pressure pulse shape in the ascending aorta?
229. What physiological effects do reflections have on the shape of flow pulses in the lower extremities?
230. What accounts for a larger systolic pressure in the femoral artery than in aorta?
231. What accounts for blood flow reversal in lower extremity arteries?
232. How is the ankle-brachial pressure index (ABI) determined and why is it clinically important?
233. Does the pulse volume diagnostic procedure measure pressure?
234. Does the pulsed Doppler diagnostic method measure blood flow?
235. What are the diastolic and systolic pressure limits that are considered as hypertensive?
236. What is the approximate speed of rbc's in systemic capillaries?

237. If, by the vasodilation of terminal arterioles, capillary recruitment occurs, what happens to total surface area available for exchange?
238. If the permeability of the capillary network to a substance doubles due to injury, but the injury results in only half the number of capillaries being available, what happens to the transcapillary flux?
239. What is the effect of raising your hand above your head on the venous system of the hand and arm?
240. Approximately how much oxygen is carried by fully saturated blood expressed in ml/100 ml of blood?
241. What is the initial direct effect of a transient increase in afterload on EDV?
242. If CVP increased due an over-transfusion, what reflex-related change in HR would occur?
243. If sympathetic impulses to peripheral veins were significantly reduced, what would happen to CVP?
244. What is meant by the terms negative feedback and feedback gain in the context of CV control?
245. Describe the roles of voltage operated and receptor operated channels as they affect the state of vascular smooth muscle with respect to vasoconstriction or vasodilation.
246. What is meant by the following statement?
The intersection of the cardiac and vascular function curves determines the system operating point.
247. Describe how the operating point changes for any single or combined change in sympathetic activity, total peripheral resistance, vascular compliance or blood volume and cardiac contractility
248. What is meant by the term mean circulatory pressure (mcp) and what factors affect its value?
249. For the following single changes, what are the effects (increase or decrease) on CVP and CO?
    Increased venous compliance?
    Significant blood loss?
    Left ventricular failure?
    Increased TPR?
    Increased myocardial contractility?
    Less sympathetic impulses to veins?
    Less sympathetic impulses to myocardium?
250. For the following combined changes, state the effect on CO (increase or decrease).
    Increased mcp and decreased TPR
    Increased volume and contractility
    Decreased volume and decreased TPR
251. Is it possible for CO and CVP to change in opposite directions? If so what might cause this effect?
252. A patient, while seated is noted to have a visibly distended external jugular vein. Offer a reason!
253. A patient's CVP is close to normal. Can you conclude that his CO and blood volume are both normal?
254. On average how many capillaries supply one myocardial myocyte?
255. What is the effect of blood drainage via the thebesian vein on arterial O2?
256. During which part of the cardiac cycle is LCA blood flow the greatest?
257. During which part of the cardiac cycle is Left ventricular outflow the greatest?
258. During which part of the cardiac cycle is Coronary outflow the greatest?
259. Which region of the LV is most affected by the compression effects of contraction and why?
260. Which ventricle is more effected by compression effects and why?
261. What is the effect of increased metabolic activity on coronary sinus SO2?
262. To what extent does an increase in O2 extraction help meet increased O2 demand?
263. What is the main way in which the coronary circulation responds to an increased O2 need?
264. What mechanisms are involved in #263?
265. Does coronary autoregulation function during sustained increases in cardiac O2 demand?
266. What factors increase the risk of regional myocardial ischemia?
267. What feature of the cerebral arterial vasculature "guards against vascular blockage" ?
268. Which brain tissue receives most flow?
269. What are the blood flow implications of the fact that the cerebral circulation is encased?
270. What effect might significant hypertension have on the blood brain barrier?
271. What effect might hypotension below the limit of cerebral autoregulation have?

272. What is hypercapnia and how does it affect cerebral blood flow and its autoregulation?
273. What is the Cushing reflex?
274. What is the effect of increased levels of perivascular K+ and H+ on cerebral blood flow?
275. What is the main function of skin blood flow?
276. What are AVAs and how are they controlled?
277. In what regions are AVA density largest?
278. How do central and local responses interact to control skin blood flow to elimiate heat?
279. What neural pathways are involved in #277?
280. What is the triple response and what neurotransmitters are involved?
281. What is meant by the statement "skeletal muscle has dual control"?
282. Why is a high degree of resting (neural) tone in skeletal muscle a useful feature?
283. What is meant by the term autoregulation?
284. What is meant by the term reactive hyperemia?
285. What is meat by the term active hyperemia?
286. What is meant by the term "myogenic control"?
287. What is the effect of increased amounts of renin on the following?
    Angiotensin I
    Angiotensin II
    Kidney sodium excretion
    Urine output
288. What is the effect of increased amounts of aldosterone on the following?
    Kidney sodium retention
    Urine output
289. What is the effect of increased amounts of ADH on the following?
    Kidney water retention
    Total peripheral resistance
    Arterial blood pressure
290. What is the effect (direct or indirect) of a slarge increase in stretch of the right atria on the following?
    Heart rate
    Urine output
    Kidney blood flow
    Vasopressin
    ADH
    TPR
    ANP
291. Blood flow entering the liver comes from which two blood vessels?
292. Of the two vessels in #291 which has the greater blood flow?
293. Of the two vessels in #291 which has the greater blood pressure?
294. What vascular active substance is released in greater quantities in liver cirrhosis?
295. What vascular active substance is released in lesser quantities in liver cirrhosis?
296. What is the effect of a significant increase in liver vascular resistance on esophageal veins?
297. During and soon after a meal in which direction do the following change (decrease or increase)?
    gastrointestinal blood flow
    bradykinin release
    cholecystokinin release
    adenosine
298. With respect to the fetal circulation, what is the ductus arteriosus?
299. With respect to fetal and maternal blood, at the same PO2 which holds more oxygen?
300. What mechanism is thought to cause the ductus arteriosus to normalize in the afterbirth?
301. Name one factor that would increase the amplitude of the QRS complex

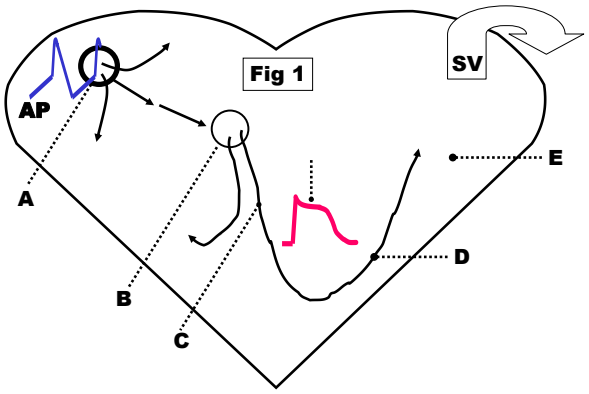
302. Name one factor that would decrease the amplitude of the QRS complex
303. Name one factor that would cause a bizarre looking QRS complex
304. Name one factor that would cause a widened QRS complex
305. Myocardial cells undergoing blood flow deprivation (ischemia) show what type of membrane potential change?
306. Regarding 306 what is the mechanism causing the membrane change?
307. What is meant by the term "pressure diuresis"?
308. What is meant by the term "pressure naturesis"?
309. What is the effect of an increase in angiotensin II on aldosterone?
310. What is the effect of aldosterone on the kidney?
311. What is the effect of angiotensin II on GFR?
312. From which organ is aldosterone released?
313. What is the upper limit of normal for the ankle brachial index (ABI)?
314. What classification would you give for a measured ABI of 0.88?
315. What classification would you use for a person with a resting heart rate of 57?

A11. Multiple Choice Question Set #1 TOC

Please note that these questions are not necessarily new, do not cover all aspects of the material covered, do not necessarily represent in form or fashion what might be seen on an exam. They are given strictly as an aid to study and review. No answer sheets are provided but consultation with Dr. Mayrovitz is always a possibility. Further note that some of the questions are on material that Dr. Mayrovitz may not be lecturing on this year.

For the next 2 questions refer to Fig 1.

Fig 1 represents normal cardiac action potential (AP) conduction, pathways, myocardium and stroke volume (SV).



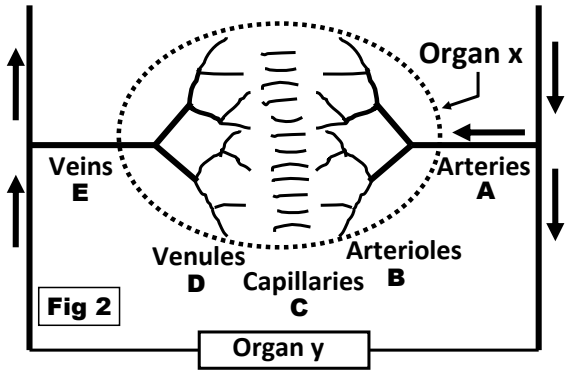
1. At which site in Fig 1 is the AP conduction speed the least?
A. A
B. B
C. C
D. D
E. E

2. A full conduction block at which site in Fig 1 would most likely result in the AV node becoming the cardiac pacemaker?
A. A
B. B
C. C
D. D
E. E

3. An increase in sympathetic nerve activity to which site in Fig 1 would most likely increase stroke volume?
A. A
B. B
C. C
D. D
E. E

For the next 2 questions use Fig 2. It shows two identical organs between the aorta and the inferior vena cava.

4. In Fig 2, If perfusion pressure to organs X and Y remains constant which of the following statements is true?
A. Arteriolar constriction of X increases flow to Y
B. Arteriolar vasodilation of Y increases flow to X
C. Arteriolar vasodilation of X decreases capillary pressure in X
D. Venous dilation of Y increases flow to Y
E. Venous dilation of X decrease flow to Y



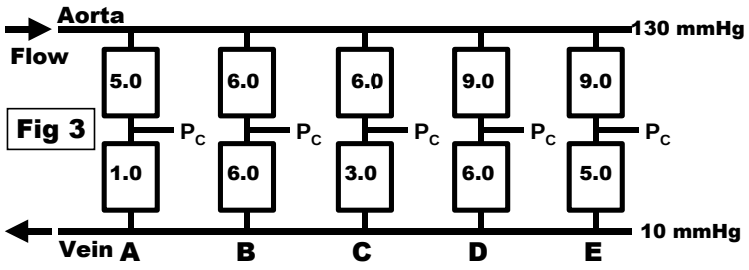
5. Assume sympathetic activity to all innervated vessels of organ X in Fig 2 is increased. Which segment's vascular resistance will not directly change?

A. A
B. B
C. C
D. D
E. E

For the next 2 questions use Fig 3 that shows 5 parallel vascular pathways (A→E). Numbers are resistance in pru.

6. Which pathway in Fig 3 has the greatest capillary pressure?

A. A
B. B
C. C
D. D
E. E



7. In Fig 3, If all pathway arterioles have the same diameter which pathway has the least arteriole average velocity?

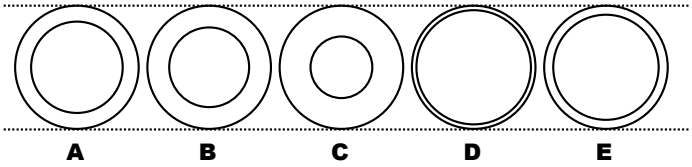
A. A
B. B
C. C
D. D
E. E

For the next 5 questions refer to Fig 4. Wall elastic modulus and blood flow are the same for all vessels.

8. Which vessel in Fig 4 has the least compliance?

A. A
B. B
C. C
D. D
E. E

Fig 4. Five vessels of equal length shown in cross-section



9. In which vessel of Fig 4 would the un-modified Laplace's Law be most applicable?

A. A
B. B
C. C
D. D
E. E

10. Which vessel in Fig has the greatest Reynold's number?

A. A
B. B
C. C
D. D
E. E

11. Which vessel in Fig 4 has the lowest wall shear stress?
A. A
B. B
C. C
D. D
E. E

12. Which vessel in Fig 4 has highest average shear rate?
A. A
B. B
C. C
D. D
E. E

For the next question refer to Fig 6 that shows a blood vessel with various obstructions.

13. At which location in Fig 6 would you measure the least transmural pressure?
A. A
B. B
C. C
D. D
E. E

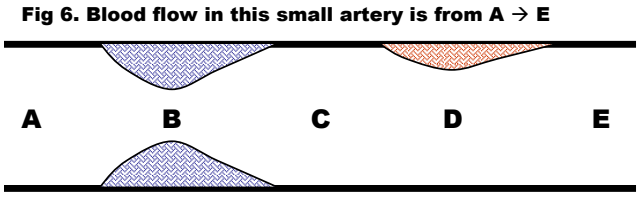
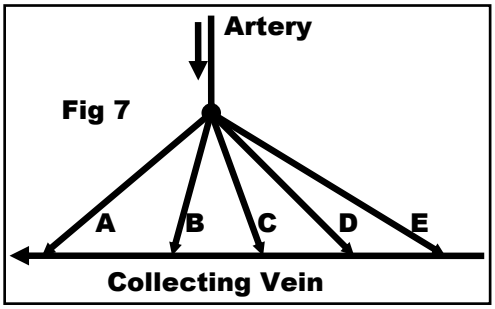


Fig 6. Blood flow in this small artery is from A → E

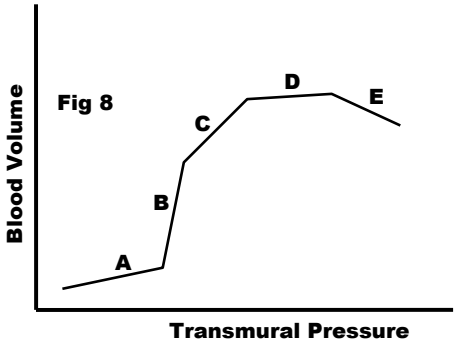
For the next question refer to Fig 7. It shows an artery with 5 arteriole branches A through E. Blood is flowing into a collecting vein. All vessels have resistance and flow directions are indicated by the arrows.

14. Which branch in Fig 7 has the greatest perfusion pressure?
A. A
B. B
C. C
D. D
E. E



For the next question refer to Fig 8 that shows a theoretical pressure-volume curve for a cardiac chamber.

15. Which segment in Fig 8 shows the greatest chamber compliance?
A. A
B. B
C. C
D. D
E. E



16. A vascular bed (Fig 9A) has a perfusion pressure of 100 mmHg and pre- and post- capillary resistances of 1.50 and 0.50 pru. A vasoactive drug is then given causing the conditions shown in Fig 9B. **If** perfusion pressure does not change, which statement best describes the drug's action?

A. It increases blood flow
B. It causes venous smooth muscle to relax
C. It decreases blood flow
D. It causes arteriolar smooth muscle to relax
E. It decreases capillary pressure

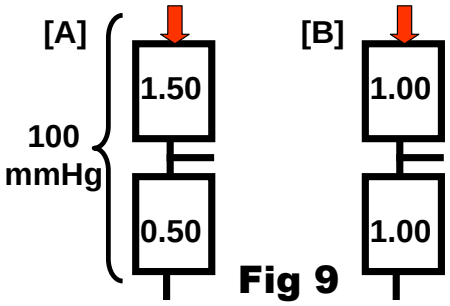
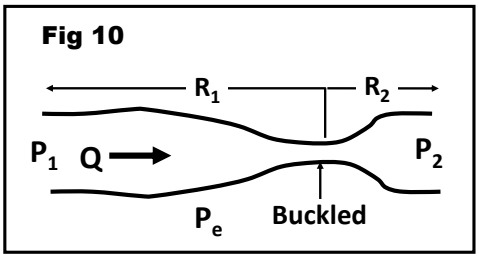


Fig 9

17. The collapsed vein segment shown in Fig 10 is contained within a closed box with external pressure Pe. The following are the pertinent parameter values.
P_1 = 90 mmHg, P_2 = 10 mmHg, Pe = 15 mmHg, R_1 = 15 pru and R_2 = 5pru.
Which of the following is closest to the value of Q in ml/min?

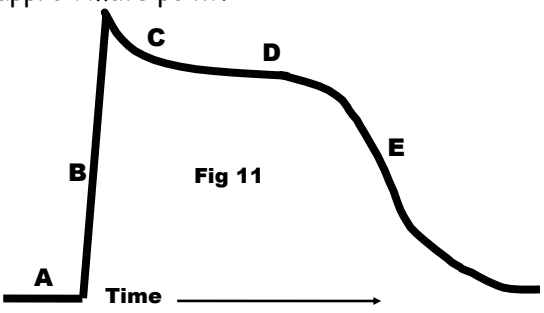


A. 4.0
B. 4.5
C. 5.0
D. 6.0
E. 16.0

<u>For the next 3 questions refer to Fig 11 that shows a fast response cardiac action potential.</u>

18. In Fig 11, inward Ca^{++} current exceeds outward K^+ current at which approximate point?

A. A
B. B
C. C
D. D
E. E



19. In Fig 11, Na+ channels start to reset at which approximate point?

A. A
B. B
C. C
D. D
E. E

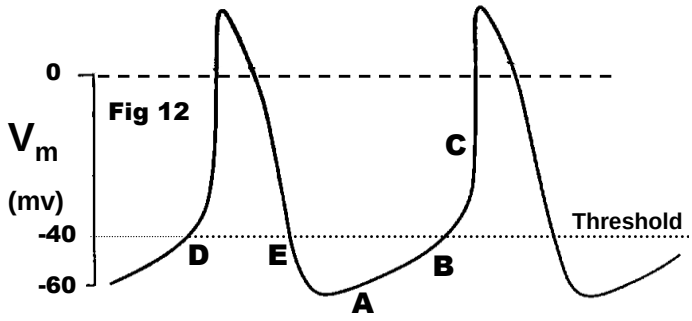
20. In Fig 11, At which approximate point does the T-wave of the EKG start?

A. A
B. B
C. C
D. D
E. E

For the next 3 questions refer to Fig 12 that shows a slow response action potential

21. At which approximate point does inward funny current become activated?

A. A
B. B
C. C
D. D
E. E



22. At which approximate point is $I_{Ca\text{-}L}$ value the greatest?

A. A
B. B
C. C
D. D
E. E

23. At which approximate point is I_K initiated?

A. A
B. B
C. C
D. D
E. E

24. A drug partially blocks fast Na^+ channels. What is the drug's effect on the His bundle action potential (AP)?
   A. AP duration decreases
   B. AP amplitude increases
   C. AP phase 0 rate of rise increases
   D. AP conduction speed decreases
   E. P-R interval of the EKG is reduced

25. Which one of the following is the most likely cause of ventricular delayed afterdepolarizations?
   A. increased Na^+ current during phase 0 of ventricular action potentials
   B. excess Ca^{++} binding of the sarcoplasmic reticulum (SR)
   C. increased cytosol Ca^{++} during ventricular diastole
   D. reduced inward Na^+ current late in the phase 2
   E. increased SR uptake of Ca^{++} during ventricular diastole

26. Ischemic injury that causes partial depolarization of myocardial fibers results in which of the following?
   A. Increased AP conduction speed in this region
   B. Decreased AP phase 0 rate of rise in this region
   C. Decreased AP duration in this region
   D. Reduced delay in conducting the AP through this region
   E. Increased AP amplitude in this region

27. Which best describes the distinguishing feature associated with a second-degree AV block?
   A. A PR interval less than 0.2 seconds
   B. An abnormally widened QRS complex
   C. Conduction of every third impulse through the AV node
   D. Absence of conduction of some impulses through the AV node
   E. An increase in the AP conduction speed in the AV node

28. Which of the following best describes a cardiac result of hyperkalemia?
    A. Increased fast response action potential amplitude
    B. Partial depolarization of cardiac myocyte membranes
    C. Increased duration of the fast response action potential
    D. Decreased EKG T-wave amplitude
    E. Increase in heart rate due to effects on SA node

29. Which of the following would be most likely to result in a 3rd degree AV block?
    A. A hyperpolarization of the AV node membrane
    B. A large increase in sympathetic stimulation of the AV node
    C. A drug that increases AV node calcium currents
    D. A drug that increases AP conduction speed within the AV node
    E. A large decrease in vagus nerve stimulation of the AV node

30. Which of the following is most likely to cause an inverted p-wave on the EKG?
    A. A right bundle branch block
    B. A 1st degree AV block
    C. Atrial Fibrillation
    D. An atrial ectopic impulse
    E. A supraventricular tachycardia

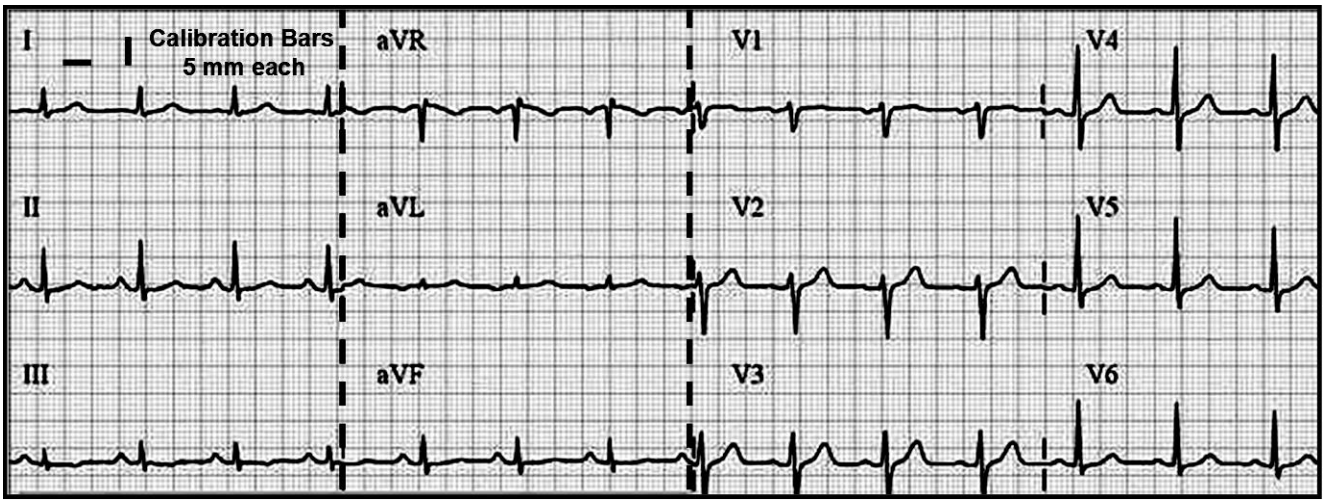
31. Bill has a mean electrical axis (MEA) of -60°. Which of the following statements is most likely true?
    A. He has a right axis deviation
    B. He has significant right ventricular hypertrophy
    C. He has a complete right bundle branch block
    D. He has a negative R-wave in lead aVL
    E. He has a positive R-wave in lead I

32. A patient has an MEA of exactly -90°. Which lead records the largest negative going R-wave?
    A. I
    B. II
    C. III
    D. aVF
    E. aVR

33. An EKG at standard conditions has a regular, uniform R-R interval of 30 mm and a PR interval of 6 mm. This EKG data is most consistent with the presence of which of the following?
    A. A 2nd degree AV block
    B. A 3rd degree AV block
    C. Bradycardia
    D. Tachycardia
    E. Wandering pacemaker

34. Which of the following is a true statement?
    A. The algebraic sum of EKG lead voltages I and II equals the voltage measured by lead III
    B. A calcium channel blocking drug will increase the conduction speed through the AV node
    C. HR changes occur more rapidly with vagal changes to the SA node then with sympathetic nerve changes
    D. A complete left bundle branch block tends to produce a right axis deviation of the MEA
    E. A necessary condition for occurrence of reentrant arrhythmias is decremental conduction

35. Mary went for her yearly physical. Her EKG is shown below.
Based on this EKG which of the following is the most likely to be a true statement?
A. The axis of her mean QRS vector is almost parallel to that of lead aVL
B. The axis of her mean QRS vector is almost perpendicular to lead II
C. She does not have a 1st degree AV block
D. Lead V_1 R-wave is inverted from normal
E. She does have a bradycardia



36. Which of the following directly contributes to the ST segment shift observed in myocardial ischemia?
A. The presence of a hyperpolarized ischemic region
B. The presence of a current of injury
C. The presence of increased activity of the Na^+-K^+ pump
D. The presence of a region of unidirectional propagation
E. The presence of a region of decremental conduction

37. Which one of the following is true regarding atrial fibrillation (aFib)?
A. It may occur due to a rapidly discharging ectopic focus in the pulmonary vein
B. It is associated with a very rapid but regular ventricular heart rate
C. It is generally associated with normal to enlarged p-wave amplitudes
D. It differs from atrial flutter in that it is more likely to occur in atria of small volume
E. It is unlikely to be precipitated by a delayed afterdepolarization

38. Which two pressures should be used in the determination of pulmonary vascular resistance?
A. Mean arterial pressure and pulmonary artery wedge pressure
B. Mean arterial pressure and left atrial pressure
C. Mean arterial pressure and right atrial pressure
D. Mean pulmonary artery pressure and pulmonary artery wedge pressure
E. Mean pulmonary artery pressure and central venous pressure

39. Which of the following is most likely to occur in response to a significant systemic blood pressure reduction?
A. Increased renal pressure diuresis
B. Increased renal pressure naturesis
C. Increased urination
D. Increased aldosterone release
E. Increased renal blood flow

40. Which of the following best explains the normally negative EKG R-wave in precordial lead V_1?
    A. Right ventricle slower depolarization as compared to the left ventricle
    B. Right ventricle faster depolarization as compared to the right ventricle
    C. Right ventricle depolarization wave moving toward the V_1 electrode
    D. Left ventricle depolarization wave moving toward the V_1 electrode
    E. Left ventricle depolarization wave moving away from the V_1 electrode

41. Which of the following tends to make the amplitude of the EKG R-wave abnormally large?
    A. Reduced functional cardiac muscle mass subsequent to a myocardial infarction
    B. Increased pericardial fluid
    C. Right ventricular hypertrophy
    D. Excess air in the lungs causing low conductivity pathways
    E. A left shit in the mean electrical axis (MEA) beyond -30 degrees

42. A drug reduces cardiac AP conduction speed AND reduces HR. The drug's action is best described as:
    A. Negative inotropic and negative chronotropic
    B. Negative dromotropic and negative lusitropic
    C. Negative chronotropic and negative dromotropic
    D. Negative inotropic and positive lusitropic
    E. Negative lusitropic and negative inotropic

A12. Multiple Choice Question Set #2 TOC

Please note that these questions are not necessarily new, do not cover all aspects of the material covered, do not necessarily represent in form or fashion what might be seen on an exam. They are given strictly as an aid to study and review. No answer sheets are provided but consultation with Dr. Mayrovitz is always a possibility. Further note that some of the questions are on material that Dr. Mayrovitz may not be lecturing on this year.

For questions 1 and 2 use one of the following descriptors

1. Aortic compliance
2. Stroke volume (SV)
3. Heart rate (HR)
4. Left ventricular ejection rate
5. Total peripheral resistance (TPR)

1. Which of the above, if decreased, would tend to <u>increase</u> aortic systolic pressure?
    a) 1
    b) 2
    c) 3
    d) 4
    e) 5

2. Which of the above is most likely to <u>decrease</u> if sympathetic activity increases?
    a) 1
    b) 2
    c) 3
    d) 4
    e) 5

3. If precapillary sphincters constrict what happens in the capillaries?
   a) Blood pressure and flow both increase
   b) Blood flow and pressure both decrease
   c) Fluid filtration and pressure increase
   d) Fluid filtration increases and flow decreases
   e) Fluid filtration decreases and flow increases

4. Which changes are caused by passive movement from an upright to a supine position?
   a) Blood volume increases in veins of the lower part of the body
   b) Venous return transiently decreases
   c) Ventricular preload increases
   d) Central venous pressure decreases
   e) Stroke volume decreases

5. Left ventricle (LV) compliance is reduced by a decrease in the:
   a) rate of calcium re-uptake by sarcoplasmic reticulum (SR)
   b) amount of trigger calcium
   c) release of calcium SR stores
   d) ventricle wall thickness
   e) LV end diastolic volume (EDV).

6. A rapid decrease in pressure in an arteriole that has a myogenic response causes:
   a) the arteriole's diameter to first get bigger and then to vasoconstrict
   b) the arteriole's diameter to first get smaller and then to vasodilate
   c) blood flow in capillaries supplied by the arteriole to initially increase
   d) the arteriole's resistance to first decrease and then myogenically increase
   e) the filtration in capillaries it supplies to initially increase

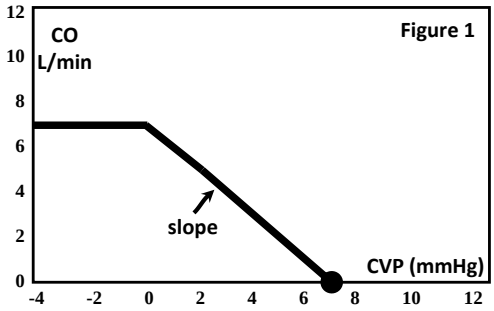
7. Which of the following is the best clinical index of Vmax in the left ventricle (LV)?
   a) Maximum aortic pressure
   b) Maximum LV pressure
   c) Maximum rate of change of aortic pressure
   d) Maximum rate of change of LV pressure
   e) Maximum systolic afterload

8. Sarah has isolated systolic hypertension. She is prescribed a hypothetical drug that normalizes her systolic pressure with no change in her diastolic pressure.
Which of the following best describes the drug's action?
   a) It increased her pulse pressure
   b) It decreased her aortic compliance
   c) It increased her ventricular ejection rate
   d) It decreased her myocardial contractility
   e) It increased the width of her ventricular p-v loop

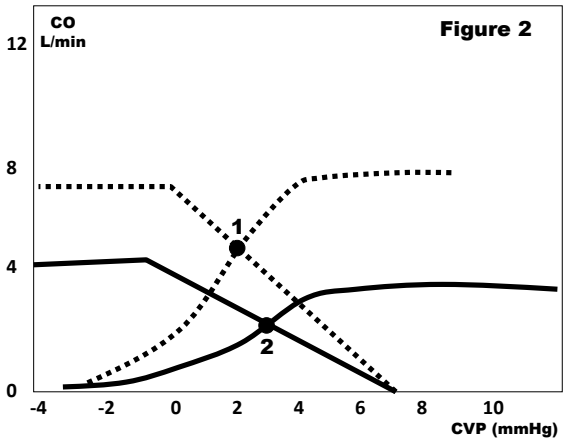
9. Cerebral ischemia caused by brain compression that elicits a Cushing reflex causes a reflex:
   a) increase in heart rate
   b) decrease in blood pressure
   c) increase in blood pressure and heart rate
   d) increase in blood pressure and decrease in heart rate
   e) decrease in blood pressure and increase in heart rate
   f)

10. Which of the following cardiac valve conditions would cause diastolic murmurs?
    a) Aortic and Mitral stenosis
    b) Aortic and Mitral insufficiency
    c) Aortic insufficiency and Mitral stenosis
    d) Aortic stenosis and Aortic regurgitation
    e) Aortic stenosis and Mitral insufficiency

11. Which is true according to Sam's vascular function curve (VFC) shown in Figure 1?
    a) His central venous pressure (CVP) is about 7 mmHg.
    b) At a CVP of 2 mmHg his cardiac output (CO) is greater than 6 L/min
    c) His mean circulatory pressure is less than 10 mmHg
    d) His VFC slope would increase if TPR increased
    e) His VFC pressure intercept at zero CO would increase if vascular compliance increased



12. In Figure 2 a shift in operating point from 1 to 2 is best explained by:
    a) Reduced sympathetic drive to heart combined with increased venous compliance
    b) Reduced myocardial contractility combined with increased TPR
    c) Reduced myocardial contractility combined with increased venous compliance
    d) Reduced sympathetic drive to heart combined with a blood volume loss
    e) Increased sympathetic drive to the heart combined with an increased TPR



13. Which of the following is most likely to cause the normal difference between brachial artery and central aortic systolic pressure to increase?
    a) Increased aortic compliance
    b) Decreased TPR
    c) Decreased pulse wave reflections
    d) Increased pulse wave speed
    e) Decreased cardiac contractility

14. Bill has a long present stenosis that has reduced the lumen of his <u>left femoral artery</u> by 90%. His right leg vasculature is normal and he is not receiving any medications.
For Bill, which of the following statements is the one most likely to be true?
    a) Vascular resistance of his left foot is less than his right foot
    b) Systolic pressure at his right ankle is less than at his brachial artery
    c) His left ankle brachial systolic index (ABI) is likely between 0.80 and 0.89
    d) A left ankle pulse volume recording shows a more rapid upstroke than normal.
    e) His left posterior tibial artery shows a greater than normal reflected flow pulse

15. P-V loops for Bill and Sam are shown in Figure 3.
Bill and Sam have the same age and weight. Bill's aortic systolic/diastolic pressure is 145/92 mmHg. The value of P_3 in the figure is 165 mmHg. Which best describes Bill?

a) He has isolated systolic hypertension
b) He has an aortic stenosis
c) His stroke volume is less than Sam's
d) His ejection fraction is greater than Sam"s
e) His end systolic volume is less than Sam's

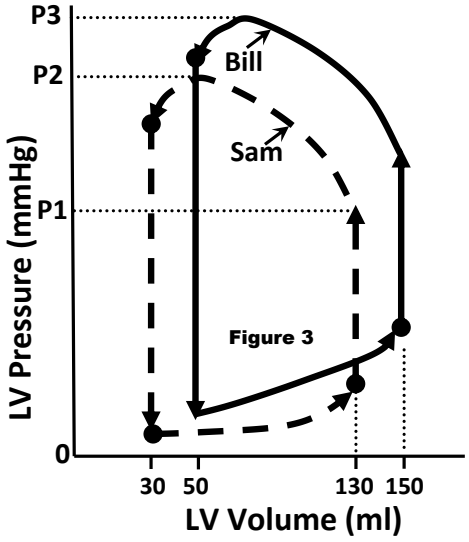


Figure 3

For the next 2 questions refer to Figure 4 below that shows P-V loops for 3 different cardiac cycles; beat #1, beat #2 and beat #3. Beat #1 has solid lines. All cardiac valves are normal.

16. In Fig 4, which best describes the relationship among beats?

a) Beat #2 has a greater ejection fraction than beat #1
b) Beat #1 produces the most stroke work
c) Beat #3 has a greater contractility than beat #2
d) Beat #3 has a greater end systolic volume than beat #1
e) Beat #2 has the greatest preload of any beat

17. In Fig 4, which is true during segment A of beat #1?

a) Myocardial oxygen demand is less than during segment C
b) Coronary blood flow is less than during segment D
c) The T-wave of the EKG is initiated
d) The second heart sound occurs
e) Ventricular volume decreases

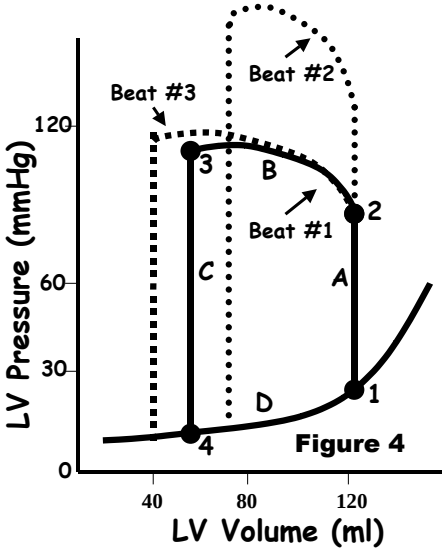


Figure 4

18. Charles experiences an intense vasoconstriction of the arterioles supplied by the femoral artery. What is the likely direct effect on his femoral artery circulation?

a) Pressure pulse reflections are decreased
b) Flow pulse reflections are increased
c) Femoral vascular bed resistance decreases
d) Femoral artery systolic pressure decreases
e) Pressure and Flow pulse reflections are both decreased

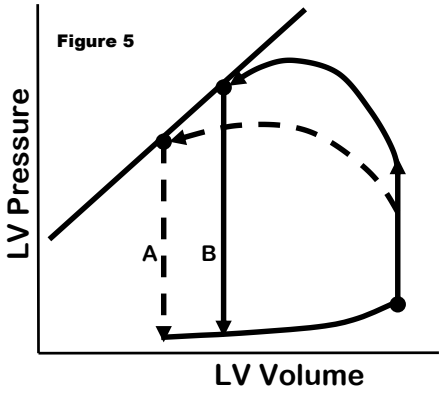
19. Laura has major multiple leg vein valve incompetence. Which best describes Laura?

a) During walking her foot vein pressure is less than normal
b) After walking, her foot venous volume returns to resting levels slower than normal
c) Due to calf muscle compression, her foot venous volume increases during walking
d) During walking, the pressure in her superficial leg veins is greater than normal
e) While standing still, her foot vein pressures are abnormally low

20. Which statement about normal arterial pulse waves is true?
   a) Their speed is usually the same in the aorta and the large artery branches
   b) Their speed decreases with increases in calcium deposition in artery walls
   c) Their reflected energy is less from vasodilated vs. vasoconstricted vascular beds
   d) Their low frequency components are selectively filtered during transmission
   e) Their reflected energy arrives at the aorta early in systole of the next beat

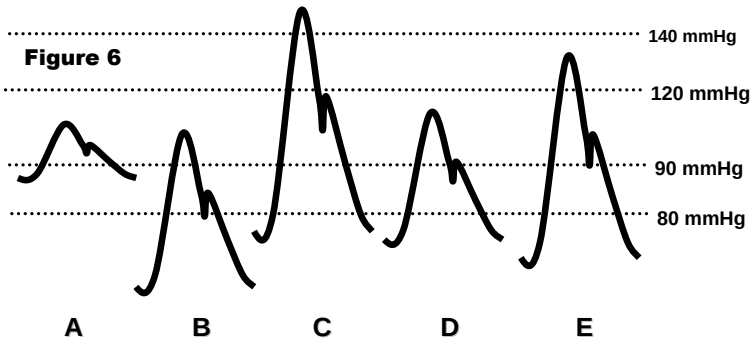
21. Which of the following is **LEAST** likely to occur due to incompetent leg venous valves?
   a) Lower extremity venous hypertension
   b) Lower rates of venous refilling
   c) Greater ambulatory venous pressure
   d) Greater incidence of venous ulcers
   e) Lower effectiveness of the calf muscle pump

22. Figure 5 shows a P-V loop for patients A and B. Both A and B have normal cardiac valves. Which is greater for patient B compared to patient A?
   a) Afterload and stroke volume
   b) Afterload and ejection fraction
   c) Aortic systolic pressure and contractility
   d) Aortic diastolic pressure and preload
   e) End systolic volume and afterload



For the next 2 questions use figure 6 showing arterial blood pressure (ABP) in 5 patients.

23. For patients in Fig 6 who have an ABP classed as normal, which one has the greatest pulse pressure?
   a) A
   b) B
   c) C
   d) D
   e) E



24. If all patients in Fig 6 have the same cardiac output, which one has the least TPR?
   a) A
   b) B
   c) C
   d) D
   e) E

25. Listed below are data for an organ's vascular bed.

Mean capillary hydrostatic pressure = 26 mmHg
Plasma protein osmotic pressure = 25 mmHg
Tissue hydrostatic pressure = -4 mmHg
Tissue colloid osmotic pressure = 5 mmHg
Plasma protein reflection coefficient = 1.0
Mean artery pressure = 95 mmHg
Mean venous pressure = 5 mmHg
Capillary filtration coefficient = 20 ml/min/mmHg

What is the rate of net fluid movement across the capillary wall?

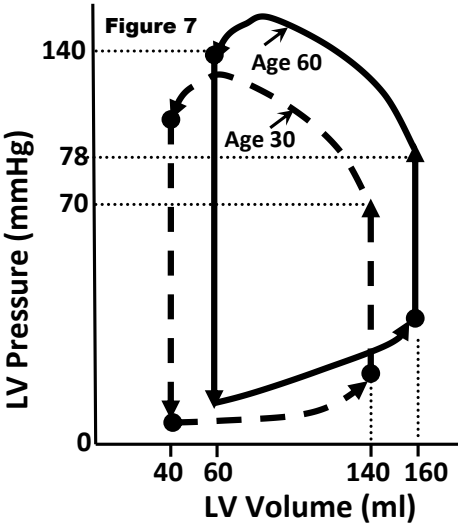
a) 50 ml/min
b) 100 ml/min
c) 150 ml/min
d) 200 ml/min
e) 250 ml/min

26. Which of the following is least likely to cause peripheral edema?

a) Blockage or compression of the terminal lymphatics
b) Blockage or compression of the veins
c) Arteriole vasoconstriction induced by low temperature
d) Arteriole vasodilation due to local inflammation
e) Decreased lymphangion function due to lymphangitis

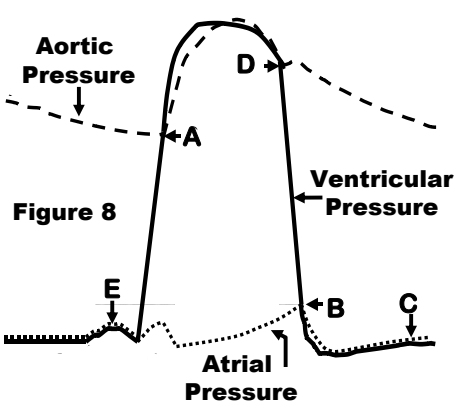
27. Barbara had cardiac evaluations at age 30 and 60. Echocardiography showed her to have normal cardiac valves at both evaluations. Her P-V loops are shown in figure 7.
Which of the following most likely is true of Barbara?

a) She developed isolated systolic hypertension
b) She has become pre-hypertensive
c) Her stroke volume decreased with age
d) Her ejection fraction increased with age
e) Her end systolic volume decreased with age



28. Figure 8 shows LV chamber and aortic pressures vs. time. If a heart sound were to be present it would be heard closest to which point?

a) A
b) B
c) C
d) D
e) E



29. Which reflex response is caused by a decrease in carotid sinus pressure?
    a) increased carotid sinus afferent impulse rate
    b) increased vagus efferent impulse rate to heart
    c) decreased sympathetic efferent impulse rate to heart
    d) increased sympathetic efferent impulse rate to veins
    e) decreased sympathetic efferent impulse rate to arterioles

30. In the absence of high-pressure baroreceptor (BR) feedback, a certain perturbation would cause an increase of 10 mmHg in mean arterial blood pressure (MAP). Considering this fact and your knowledge of physiology which of the following is most likely true?
    a) A feedback gain of 100 is needed to reduce the MAP excursion to 1 mmHg
    b) The feedback gain has its least effectiveness near an MAP of 95 mmHg
    c) An MAP level of 100 mmHg is out of the range of the normal BR reflex
    d) A feedback gain of less than 100 could reduce the excursion to 1 mmHg
    e) A decrease of 10 mmHg would cause an increase in BR afferent impulse rate

31. Which arterial change causes the carotid body to trigger a reflex increase in TPR?
    a) Increased P_{O2}
    b) Increased pH
    c) Increased P_{CO2}
    d) Increased mean arterial blood pressure
    e) Increased cardiac output

32. Which of the following normally causes most peripheral arterioles to dilate?
    a) A drug that causes a more negative vascular smooth muscle membrane potential
    b) A drug that facilitates activation of vascular smooth muscle β-receptors
    c) A drug that increases arteriole tone
    d) A drug that increases the sensitivity of vascular smooth muscle to Ca^{++}
    e) A drug that increases Ca^{++} into vascular smooth muscle cells

33. Which of the following would cause most peripheral arterioles to actively constrict?
    a) A decrease in transmural pressure
    b) An increase in the shear stress acting on endothelial cells
    c) A decrease in vascular smooth muscle membrane potassium current
    d) An increase in local pH
    e) A relative hyperpolarization of the vascular smooth muscle membrane

34. Which one of the following is true about the coronary circulation?
    a) Oxygen extraction is usually low under resting conditions
    b) Blood flow to endocardium depends mainly on perfusion pressure during systole
    c) Autoregulation's lower limit is at a lower pressure for endocardium vs. epicardium
    d) Intramyocardial forces during systole are greater in endocardium vs. epicardium
    e) Matching of blood flow to changing O_2 demands is defined as autoregulation

For question 35, consider five statements about the arterial pressure pulse-wave.
1) Its wave-speed is much greater than the blood flow velocity in the ascending aortic
2) Its wave-speed is directly proportional to the vessel compliance in which it travels
3) Its wave-speed tends to increase in aging due to stiffening of the aorta
4) Its reflection is greater from branches feeding a region of lower vascular resistance
5) Its reflection is in-phase with the forward wave

35. Which combination of the above best describes pressure pulse-wave features?
    a) 1 and 4
    b) 1 and 3
    c) 1, 2 and 3
    d) 1, 3 and 4
    e) 1, 3 and 5

36. Which of the following is **NOT** a property of the cerebral circulation?
    a) High capillary density
    b) High degree of metabolic control
    c) High degree of autoregulation
    d) High resting blood flow per gram
    e) High degree of sympathetic control

37. Vasomotion of terminal arterioles supplying a capillary network is most likely to cause:
    a) absorption over the entire capillary length during the dilation phase
    b) capillary pressure decreases over the entire length during the dilation phase
    c) filtration over the entire capillary length during the constriction phase
    d) absorption over the entire capillary length during the constriction phase
    e) capillary blood flow to decrease during the arteriole dilation phase

38. Which may cause edema mainly because of a decrease in capillary osmotic pressure?
    a) Venous compression due to a tumor
    b) Venous obstruction due to a venous thrombosis
    c) Arteriolar vasodilation due to localized inflammation
    d) Vascular hemodilution due to water intoxication
    e) Lymphatic obstruction

39. In response to a large loss of blood volume, which does **NOT** reflexively increase?
    a) Vasopressin release
    b) Aldosterone release
    c) Sympathetic drive to renal α_1 arteriole receptors
    d) Atrial natriuretic peptide release
    e) Sympathetic drive to renal β_1 receptors

40. Figure 9 below shows venous reflux test results for 3 patients named A, B and C.

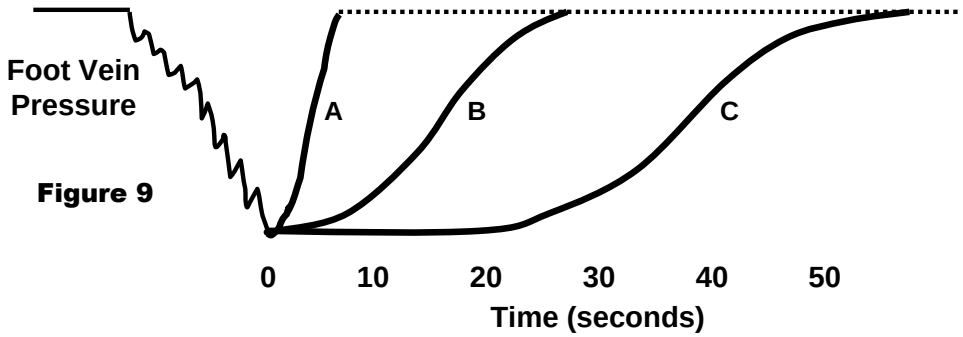


Figure 9

Based on your knowledge and figure 9, which statement is most likely true?

a) Patient A shows the most normal test response
b) Patient B shows the most normal test response
c) Patient C shows the most normal test response
d) Patient B is less likely to develop a venous ulcer than patient C
e) Patient A is the least likely to develop a venous ulcer

For question 41 please use the following hypothetical data for an organ.
Total blood flow =3000 ml/min
Arterial O_2 concentration = 19 ml/100 ml of blood
Venous O_2 concentration = 10 ml/100 ml of blood

41. How much oxygen (ml) is being utilized by the organ each minute?

a) 70
b) 140
c) 210
d) 270
e) 300

42. Ann has sudden complete blockages of right and left internal carotid arteries due to emboli as shown in figure 10. Which best describes a <u>*baroreceptor reflex*</u> result?

a) Mean aortic pressure (MAP) decreases
b) Cerebral perfusion pressure decreases
c) MAP and heart rate (HR) increase
d) Total peripheral resistance and HR decrease
e) MAP and cerebral perfusion decrease

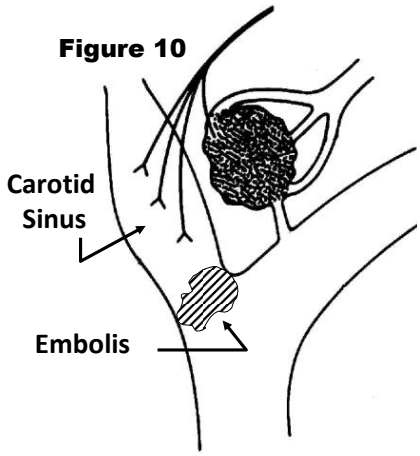
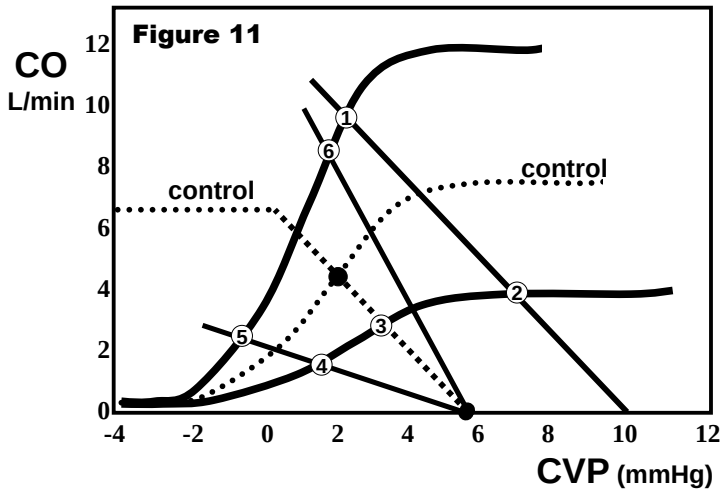


Figure 10

For questions 43 and 44 please refer to figure 11

43. In fig 11, starting from the control intersection point, what is the new intersection point if sympathetic activity increases to ventricular myocardium and decreases to all peripheral arterioles? Don't consider reflexes in selecting an answer.

a) 1
b) 2
c) 3
d) 5
e) 6



44. In fig 11, what is represented by point 4 with respect to the control curve intersection point?

a) Increased myocardial contractility
b) Increased central venous pressure
c) Increased peripheral resistance
d) Increased vascular compliance
e) Decreased vascular compliance

45. The heart is experimentally stopped and blood is allowed to distribute and equilibrate in the cardiovascular system. Which of the following now best describes the aortic blood pressure?

a) It is called the mean arterial pressure
b) It is significantly greater than central venous pressure
c) It is less than the mean circulatory pressure
d) It is less if system compliance is greater
e) It is less if total peripheral resistance is less

46. Which of the following would decrease as a consequence of a large blood loss?

a) Antidiuretic Hormone
b) Angiotensin II
c) Atrial Natriuretic Hormone
d) Aldosterone
e) Amount of sodium reabsorbed in the kidney

47. Which of the following is true concerning skeletal muscle circulation?

a) During aerobic exercise, vascular control is mainly due to sympathetic nerve activity
b) During aerobic exercise, interstitial potassium concentrations tend to decrease
c) Most capillaries experience active blood flow during rest
d) During intense sustained aerobic exercise oxygen extraction rises to about 60%
e) During intense sustained isometric exercise oxygen delivery is reduced

48. Which of the following is true of the splanchnic circulation?

a) Blood flow is inversely related to the digestive activities in a given gut region
b) Intravascular pressure in liver sinusoids is about midway between arterial and venous
c) The portal circulation may be characterized as having low vascular resistance
d) The hepatic circulation may be characterized as a low pressure system
e) Portal hypertension is strangely associated with decreased endothelin release

49. Which of the following is **NOT** true of the maternal-fetal circulation?
    a) Mom and baby blood mix in the placenta to provide baby with oxygen
    b) The ductus venosus shunts umbilical vein blood away from baby's liver
    c) The foramen ovale shunts blood from the right atrium to the left atrium
    d) The ductus arteriosus shunts blood from the pulmonary artery to the aorta
    e) Fetal blood has a greater affinity for oxygen than does maternal blood

50. Which of the following is true of early after birth changes?
    a) The umbilical artery dilates causing an increase in blood flow
    b) Reduced flow in the umbilical vein triggers closure of the ductus venosus
    c) The ductus arteriosus closes within about 15 minutes of birth due to the low PO_2
    d) The foramen ovale closes within about 15 minutes of birth due to increased blood flow
    e) The Baby's pulmonary vascular resistance increases slightly