Cardiovascular Physiology

Lecture Outline

- **Cardiovascular System Function**
- Functional Anatomy of the Heart
- Myocardial Physiology
- Cardiac Cycle
- Cardiac Output Controls & Blood Pressure

Cardiovascular System Function

- Functional components of the cardiovascular system:
  - Heart
  - Blood Vessels
  - Blood
- General functions these provide
  - Transportation
    - Everything transported by the blood
  - Regulation
    - Of the cardiovascular system
      - Intrinsic v extrinsic
  - Protection
    - Against blood loss
  - Production/Synthesis

Cardiovascular System Function

- To create the “pump” we have to examine the Functional Anatomy
  - Cardiac muscle
  - Chambers
  - Valves
  - Intrinsic Conduction System

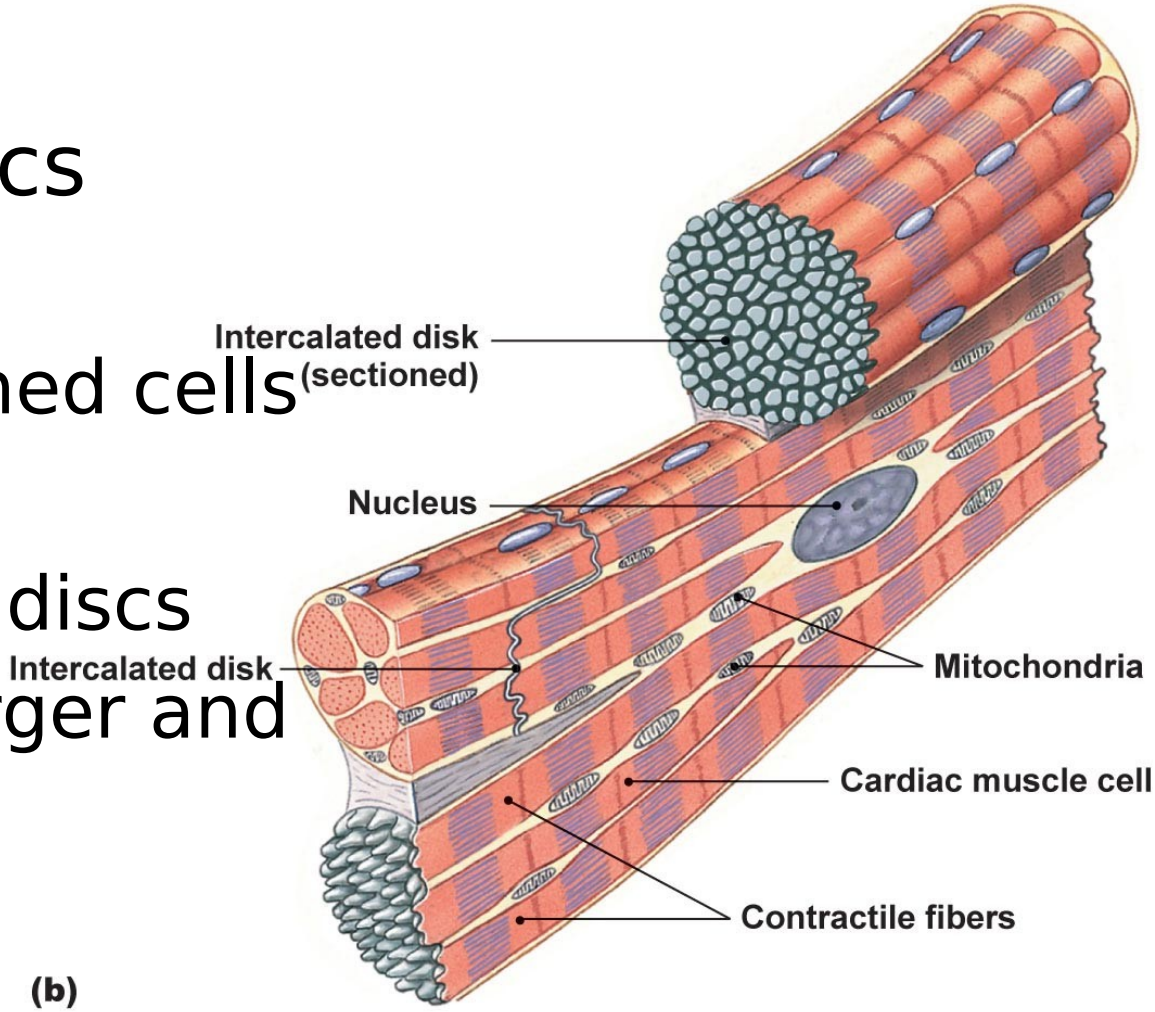
Lecture Outline

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- **Functional Anatomy of the Heart**
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- Cardiac Output Controls & Blood Pressure

Functional Anatomy of the Heart

Cardiac Muscle

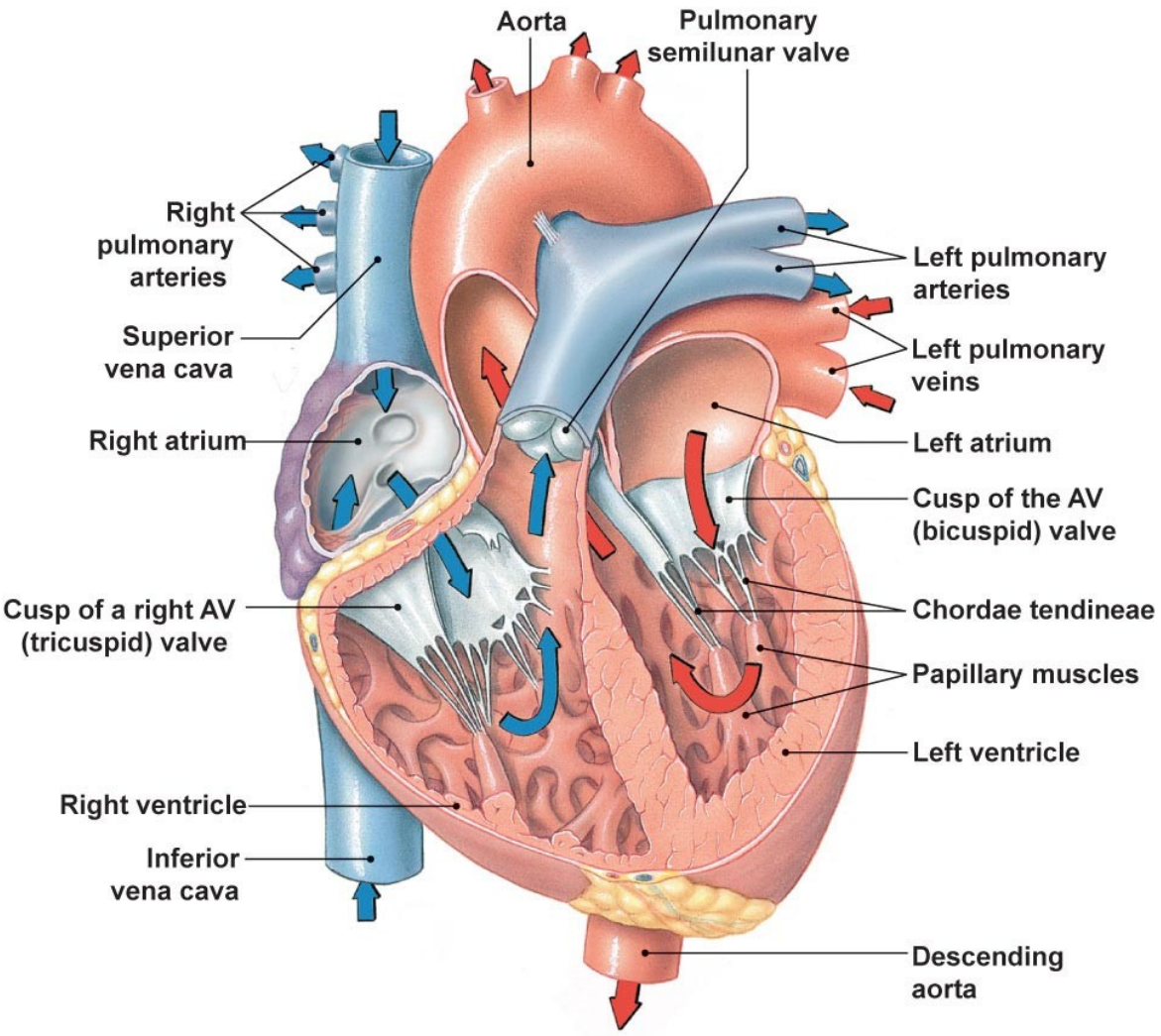
- Characteristics
  - Striated
  - Short branched cells
  - Uninucleate
  - Intercalated discs
  - T-tubules larger and over z-discs



Functional Anatomy of the Heart

Chambers

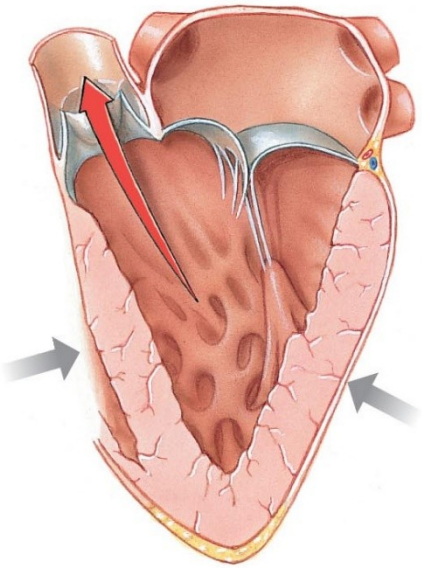
- 4 chambers
  - 2 Atria
  - 2 Ventricles
- 2 systems
  - Pulmonary
  - Systemic

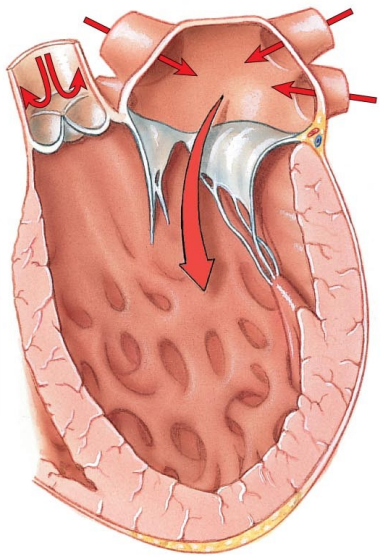


Functional Anatomy of the Heart

Valves

- Function is to prevent backflow
  - Atrioventricular Valves
    - Prevent backflow to the atria
    - Prolapse is prevented by the chordae tendinae
      - Tensioned by the papillary muscles
  - Semilunar Valves
    - Prevent backflow into ventricles

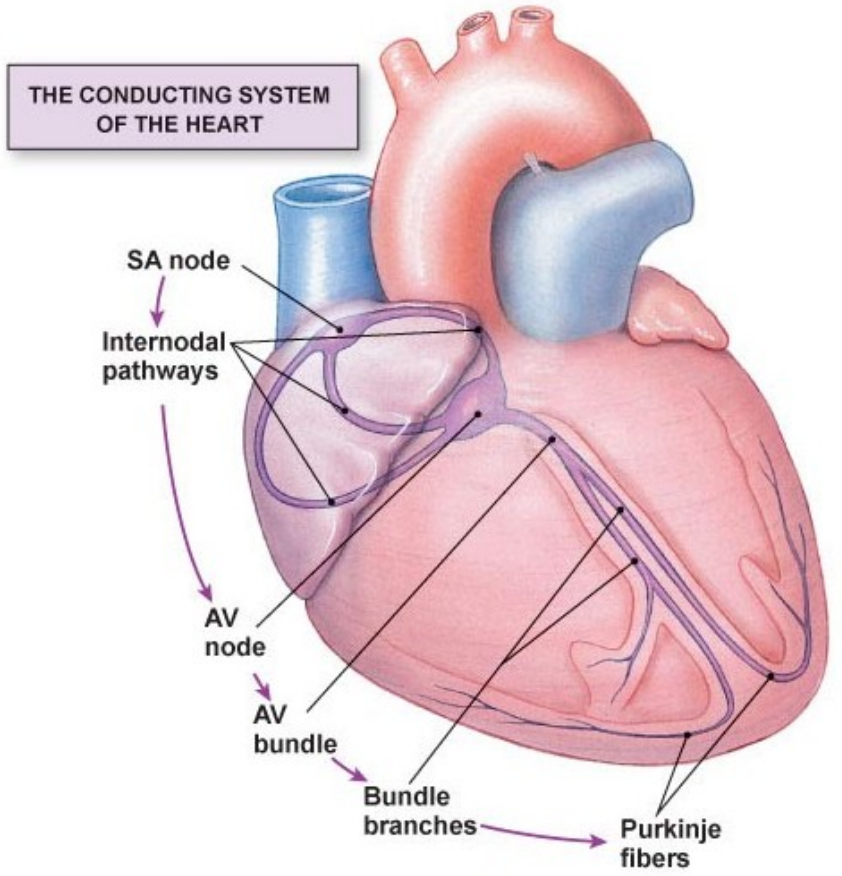




Functional Anatomy of the Heart

Intrinsic Conduction System

- Consists of "pacemaker" cells and conduction pathways
  - Coordinate the contraction of the atria and ventricles

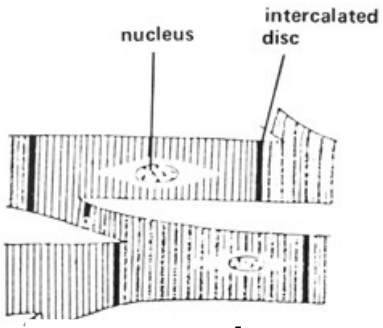


Lecture Outline

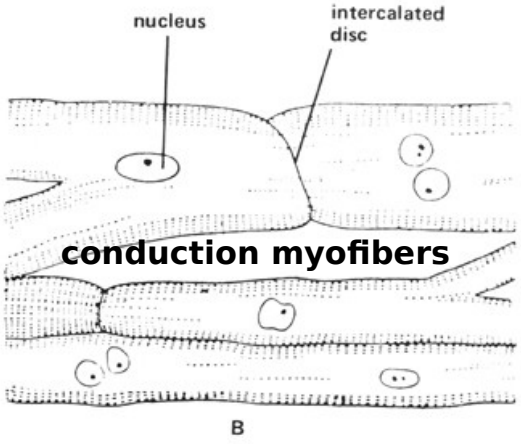
- Cardiovascular System Function
- Functional Anatomy of the Heart
- **Myocardial Physiology**
  - **Autorhythmic Cells (Pacemaker cells)**
  - **Contractile cells**
- Cardiac Cycle
- Cardiac Output Controls & Blood Pressure

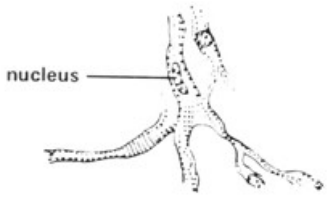
Myocardial Physiology
Autorhythmic Cells (Pacemaker Cells)

- Characteristics of Pacemaker Cells
  - Smaller than contractile cells
  - Don’t contain many myofibrils
  - No organized sarcomere structure
    - do not contribute to the contractile force of the heart

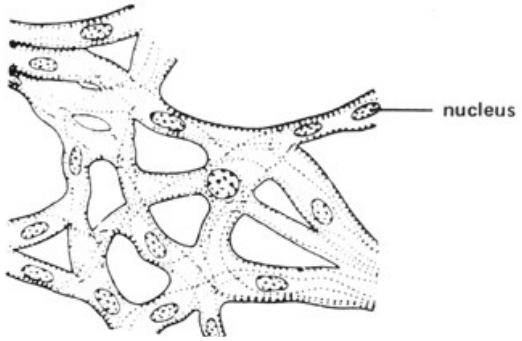


normal contractile myocardial cell





SA node cell



AV node cells

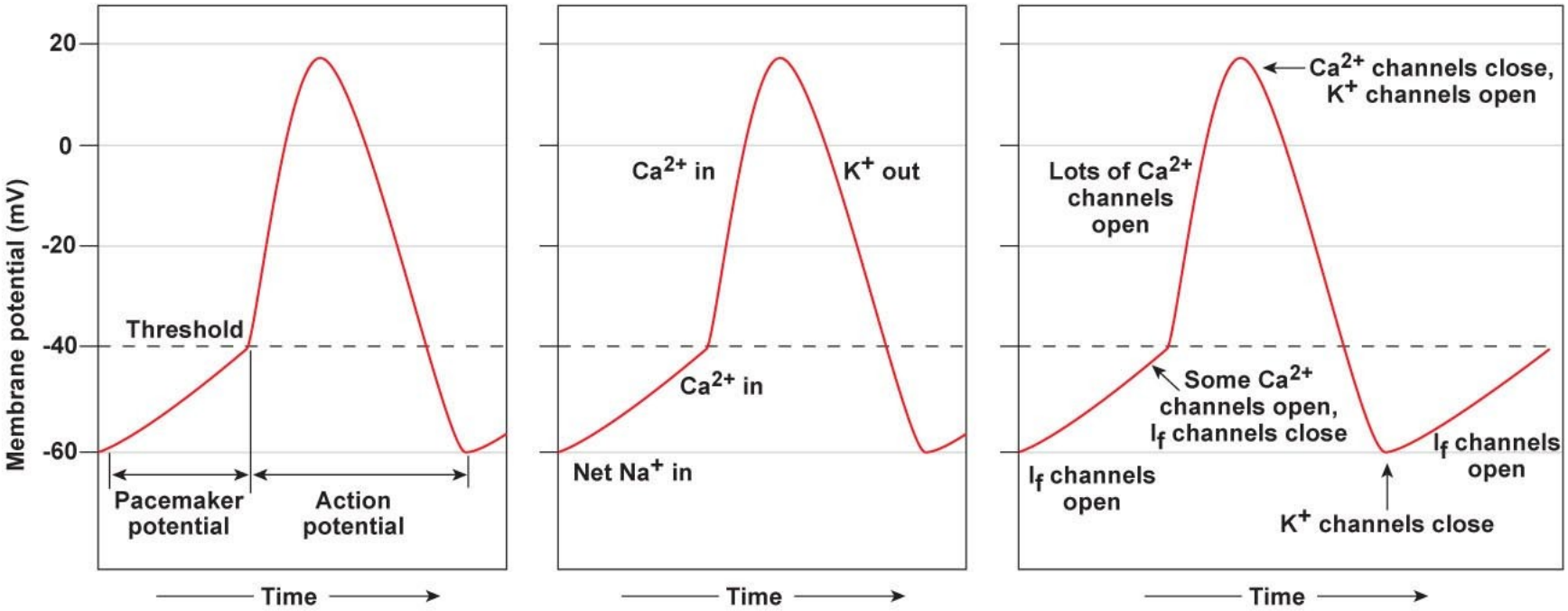
Myocardial Physiology

Autorhythmic Cells (Pacemaker Cells)

- Characteristics of Pacemaker Cells
  - Unstable membrane potential
    - "bottoms out" at -60mV
    - "drifts upward" to -40mV, forming a pacemaker potential
  - Myogenic
    - The upward "drift" allows the membrane to reach threshold potential (-40mV) by itself
    - This is due to
      1. Slow leakage of K^+ out & faster leakage Na^+ in
         - » Causes slow depolarization
         - » Occurs through I_f channels (f=funny) that open at negative membrane potentials and start closing as membrane approaches threshold potential
      2. Ca^{2+} channels opening as membrane approaches threshold
         - » At threshold additional Ca^{2+} ion channels open causing more rapid depolarization
         - » These deactivate shortly after and
      3. Slow K^+ channels open as membrane depolarizes causing an efflux of K^+ and a repolarization of membrane

Myocardial Physiology
Autorhythmic Cells (Pacemaker Cells)

- Characteristics of Pacemaker Cells



(a) The pacemaker potential gradually becomes less negative until it reaches threshold, triggering an action potential.

(b) Ion movements during an action and pacemaker potential

(c) State of various ion channels

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Myocardial Physiology
Autorhythmic Cells (Pacemaker Cells)

- Altering Activity of Pacemaker Cells
  - Sympathetic activity
    - NE and E increase I_f channel activity
      - Binds to β_1 adrenergic receptors which activate cAMP and increase I_f channel open time
      - Causes more rapid pacemaker potential and faster rate of action potentials

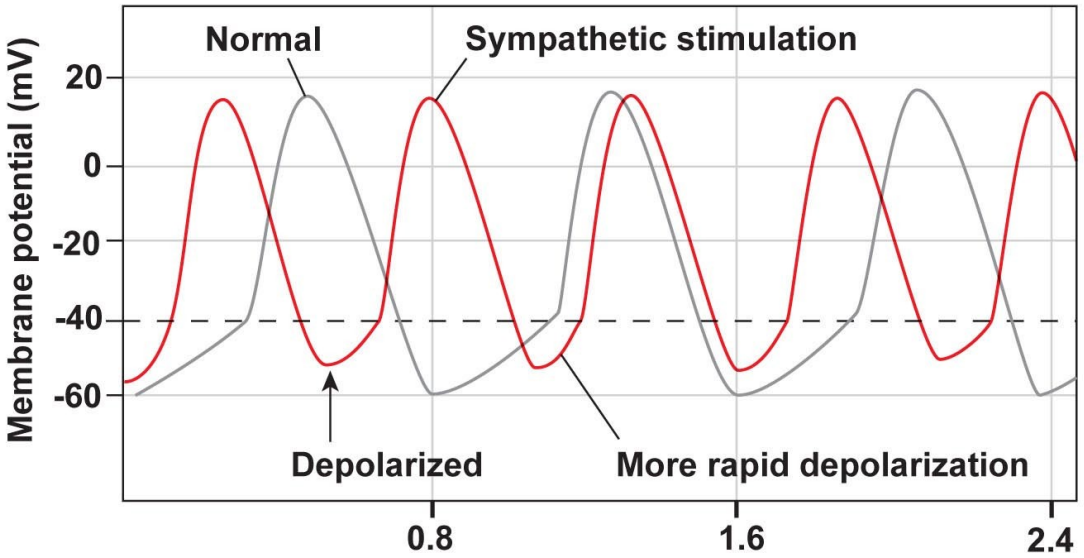
<u>Sympathetic Activity Summary:</u>

increased chronotropic effects

↑heart rate

increased dromotropic effects

↑conduction of APs



Myocardial Physiology
Autorhythmic Cells (Pacemaker Cells)

- Altering Activity of Pacemaker Cells
  - Parasympathetic activity
    - ACh binds to muscarinic receptors
      - Increases K^+ permeability and decreases Ca^{2+} permeability = hyperpolarizing the membrane
        - » Longer time to threshold = slower rate of action potentials

<u>Parasympathetic Activity Summary:</u>

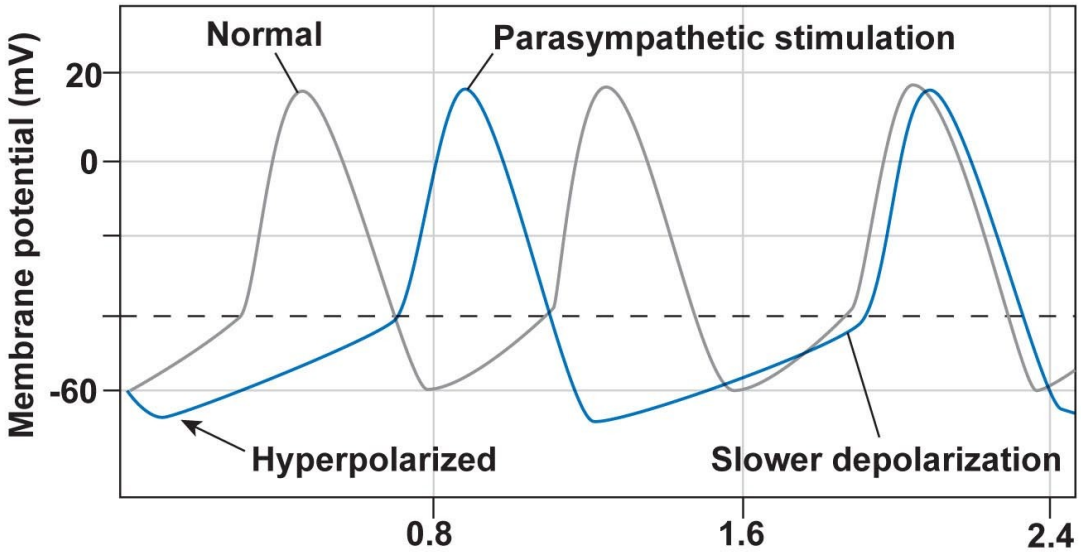
decreased chronotropic effects

↓heart rate

decreased dromotropic effects

↓ conduction of APs

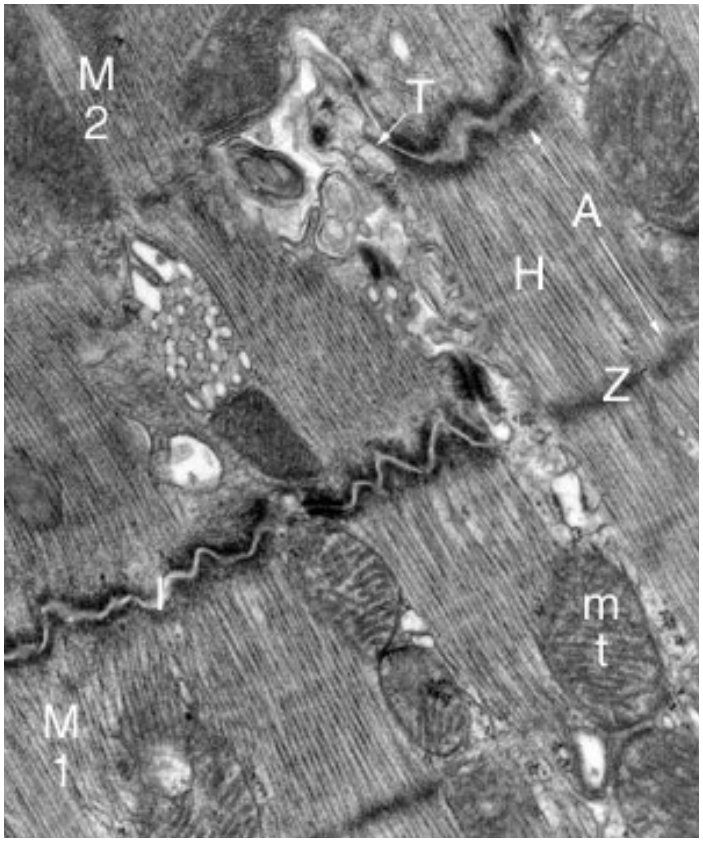
decreased inotropic effects



Myocardial Physiology

Contractile Cells

- Special aspects
  - Intercalated discs
    - Highly convoluted and interdigitated junctions
      - Joint adjacent cells with
        - » Desmosomes & fascia adherens
      - Allow for synticial activity
        - » With gap junctions
  - More mitochondria than skeletal muscle
  - Less sarcoplasmic reticulum
    - Ca^{2+} also influxes from ECF reducing storage need
  - Larger t-tubules
    - Internally branching
  - Myocardial contractions are graded!



Myocardial Physiology

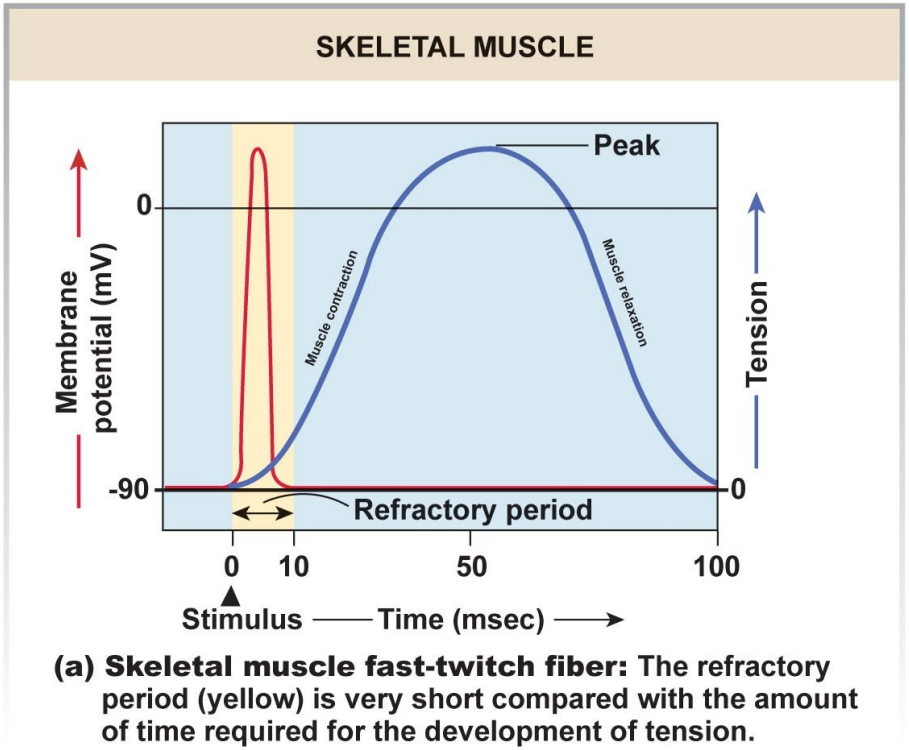
Contractile Cells

- Special aspects
  - The action potential of a contractile cell
    - Ca^{2+} plays a major role again
    - Action potential is longer in duration than a “normal” action potential due to Ca^{2+} entry
    - Phases
      - 4 – resting membrane potential @ -90mV
      - 0 – depolarization
        - » Due to gap junctions or conduction fiber action
        - » Voltage gated Na^{+} channels open… close at 20mV
      - 1 – temporary repolarization
        - » Open K^{+} channels allow some K^{+} to leave the cell
      - 2 – plateau phase
        - » Voltage gated Ca^{2+} channels are fully open (started during initial depolarization)
      - 3 – repolarization
        - » Ca2+ channels close and K+ permeability increases as slower activated K+ channels open, causing a quick repolarization
  - What is the significance of the plateau phase?

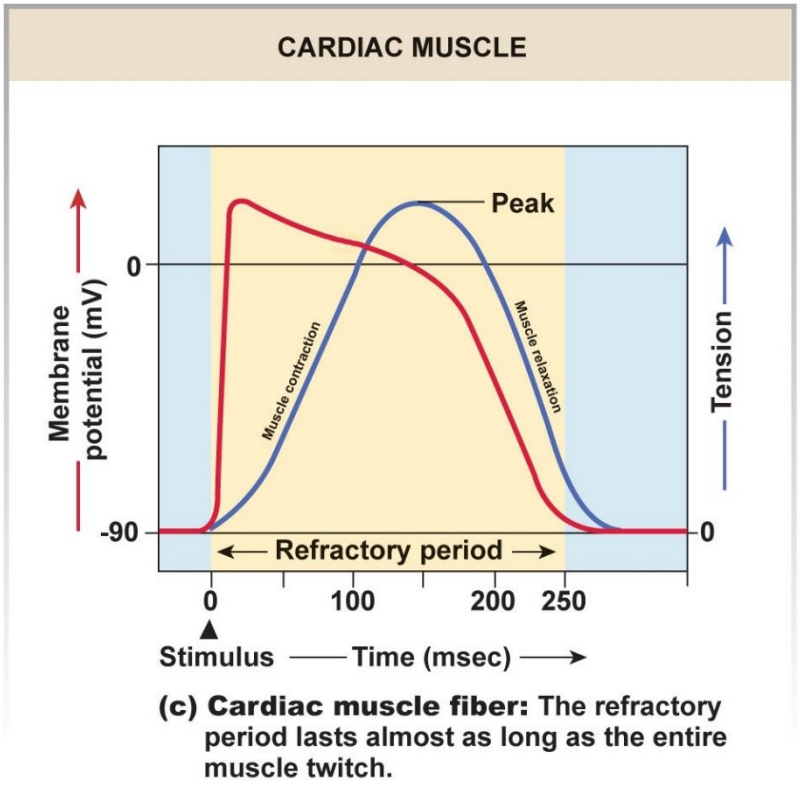
Myocardial Physiology

Contractile Cells

- Skeletal Action Potential vs Contractile Myocardial Action



(a) Skeletal muscle fast-twitch fiber: The refractory period (yellow) is very short compared with the amount of time required for the development of tension.

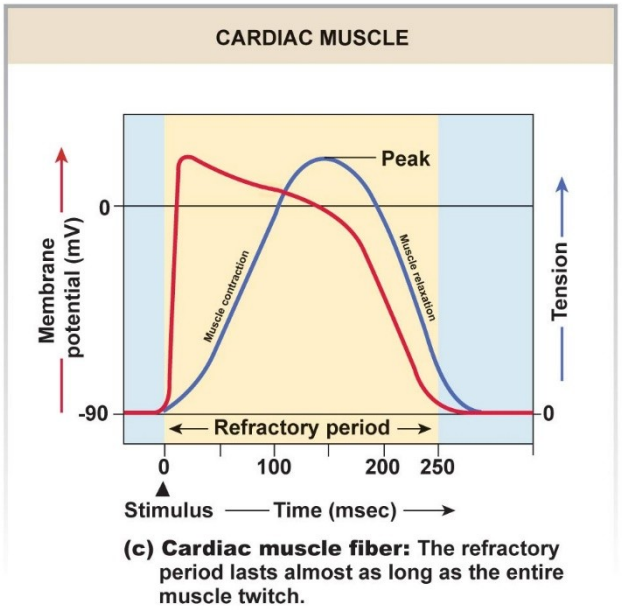


(c) Cardiac muscle fiber: The refractory period lasts almost as long as the entire muscle twitch.

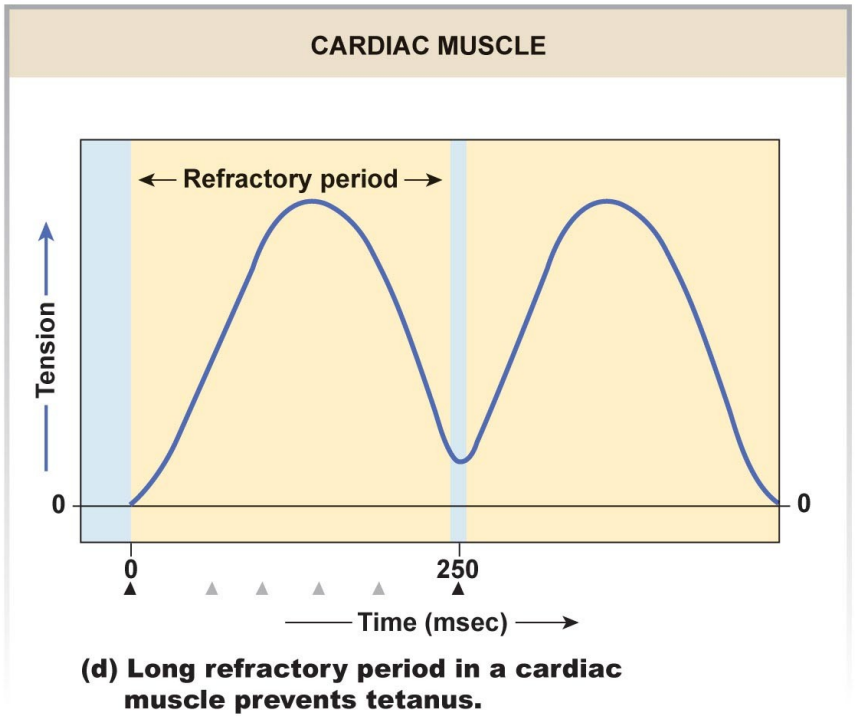
Myocardial Physiology

Contractile Cells

- Plateau phase prevents summation due to the elongated refractory period
- No summation capa
  - fata



(c) **Cardiac muscle fiber:** The refractory period lasts almost as long as the entire muscle twitch.



(d) **Long refractory period in a cardiac muscle prevents tetanus.**

Summary of Action Potentials

TABLE 14-3 Comparison of Action Potentials in Cardiac and Skeletal Muscle

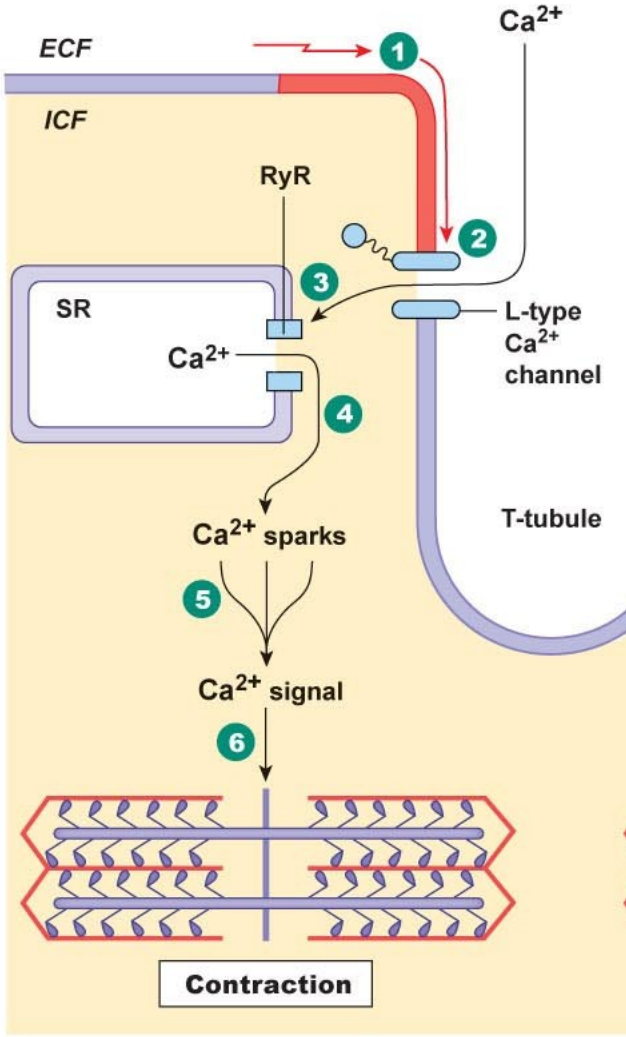
	SKELETAL MUSCLE	CONTRACTILE MYOCARDIUM	AUTORHYTHMIC MYOCARDIUM
Membrane potential	Stable at −70 mV	Stable at −90 mV	Unstable pacemaker potential; usually starts at −60 mV
Events leading to threshold potential	Net Na^+ entry through ACh-operated channels	Depolarization enters via gap junctions	Net Na^+ entry through I_f channels; reinforced by Ca^{2+} entry
Rising phase of action potential	Na^+ entry	Na^+ entry	Ca^{2+} entry
Repolarization phase	Rapid; caused by K^+ efflux	Extended plateau caused by Ca^{2+} entry; rapid phase caused by K^+ efflux	Rapid; caused by K^+ efflux
Hyperpolarization	Due to excessive K^+ efflux at high K^+ permeability when K^+ channels close; leak of K^+ and Na^+ restores potential to resting state	None; resting potential is −90 mV, the equilibrium potential for K^+	Normally none; when repolarization hits −60 mV, the I_f channels open again. ACh can hyperpolarize the cell.
Duration of action potential	Short: 1–2 msec	Extended: 200+ msec	Variable; generally 150+ msec
Refractory period	Generally brief	Long because resetting of Na^+ channel gates delayed until end of action potential	None

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Myocardial Physiology

Contractile Cells

- Initiation
  - Action potential via pacemaker cells to conduction fibers
- Excitation-Contraction Coupling
  1. Starts with CICR (Ca^{2+} induced Ca^{2+} release)
     - AP spreads along sarcolemma
     - T-tubules contain voltage gated L-type Ca^{2+} channels which open upon depolarization
     - Ca^{2+} entrance into myocardial cell anc opens RyR (ryanodine receptors) Ca^{2+} release channels
     - Release of Ca^{2+} from SR causes a Ca^{2+} "spark"
     - Multiple sparks form a Ca^{2+} signal

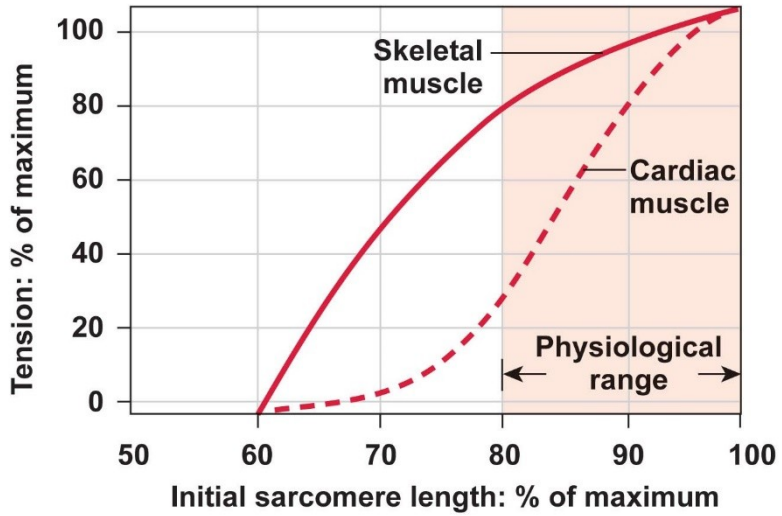


Spark Gif

Myocardial Physiology

Contractile Cells

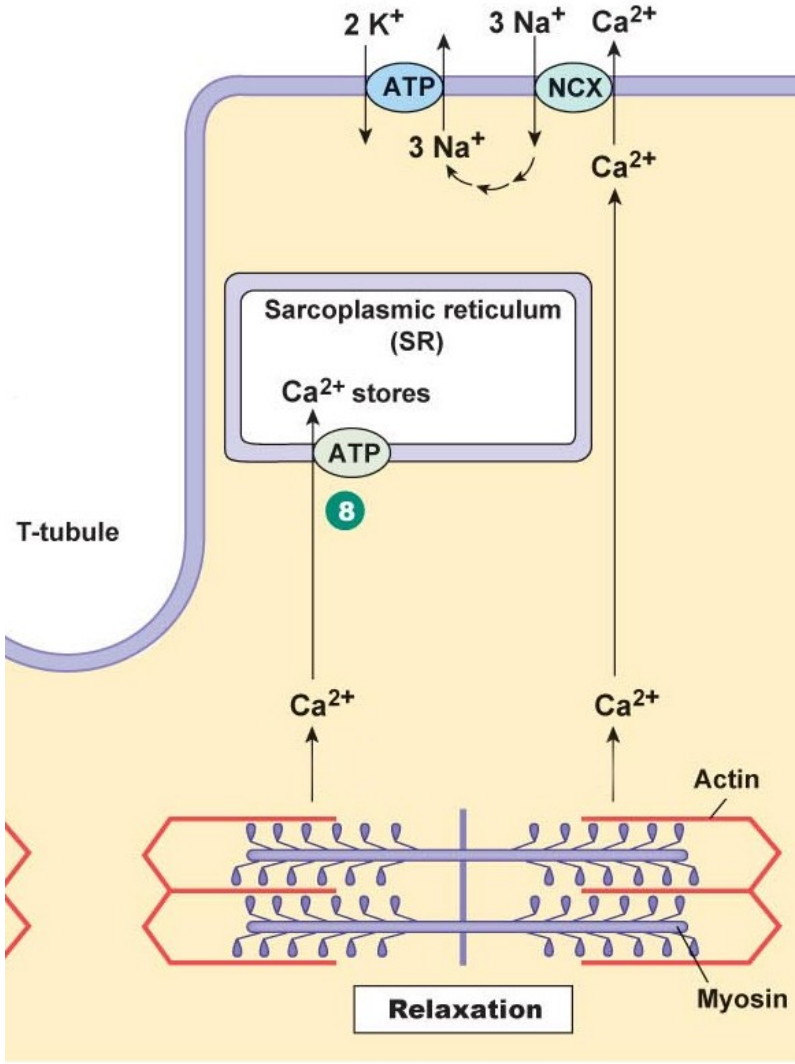
- Excitation-Contraction Coupling cont…
  2. Ca^{2+} signal (Ca^{2+} from SR and ECF) binds to troponin to initiate myosin head attachment to actin
- Contraction
  - Same as skeletal muscle, but…
  - Strength of contraction varies
    - Sarcomeres are not “all or none” as it is in skeletal muscle
      - The response is graded!
        - » Low levels of cytosolic Ca^{2+} will not activate as many myosin/actin interactions and the opposite is true
    - Length tension relationships ex
      - Strongest contraction generate when stretched between 80 & 100% of maximum (physiologi range)
      - What causes stretching?
        - » The filling of chambers with blood



Myocardial Physiology

Contractile Cells

- Relaxation
  - Ca^{2+} is transported back into the SR and
  - Ca^{2+} is transported out of the cell by a facilitated Na^{+}/Ca^{2+} exchanger (NCX)
  - As ICF Ca^{2+} levels drop, interactions between myosin/actin are stopped
  - Sarcomere lengthens



Lecture Outline

- Cardiovascular System Function
- Functional Anatomy of the Heart
- Myocardial Physiology
  - Autorhythmic Cells (Pacemaker cells)
  - Contractile cells
- **Cardiac Cycle**
- Cardiac Output Controls & Blood Pressure

Cardiac Cycle

Coordinating the activity

- Cardiac cycle is the sequence of events as blood enters the atria, leaves the ventricles and then starts over
- Synchronizing this is the Intrinsic Electrical Conduction System
- Influencing the rate (chronotropy & dromotropy) is done by the sympathetic and parasympathetic divisions of the ANS

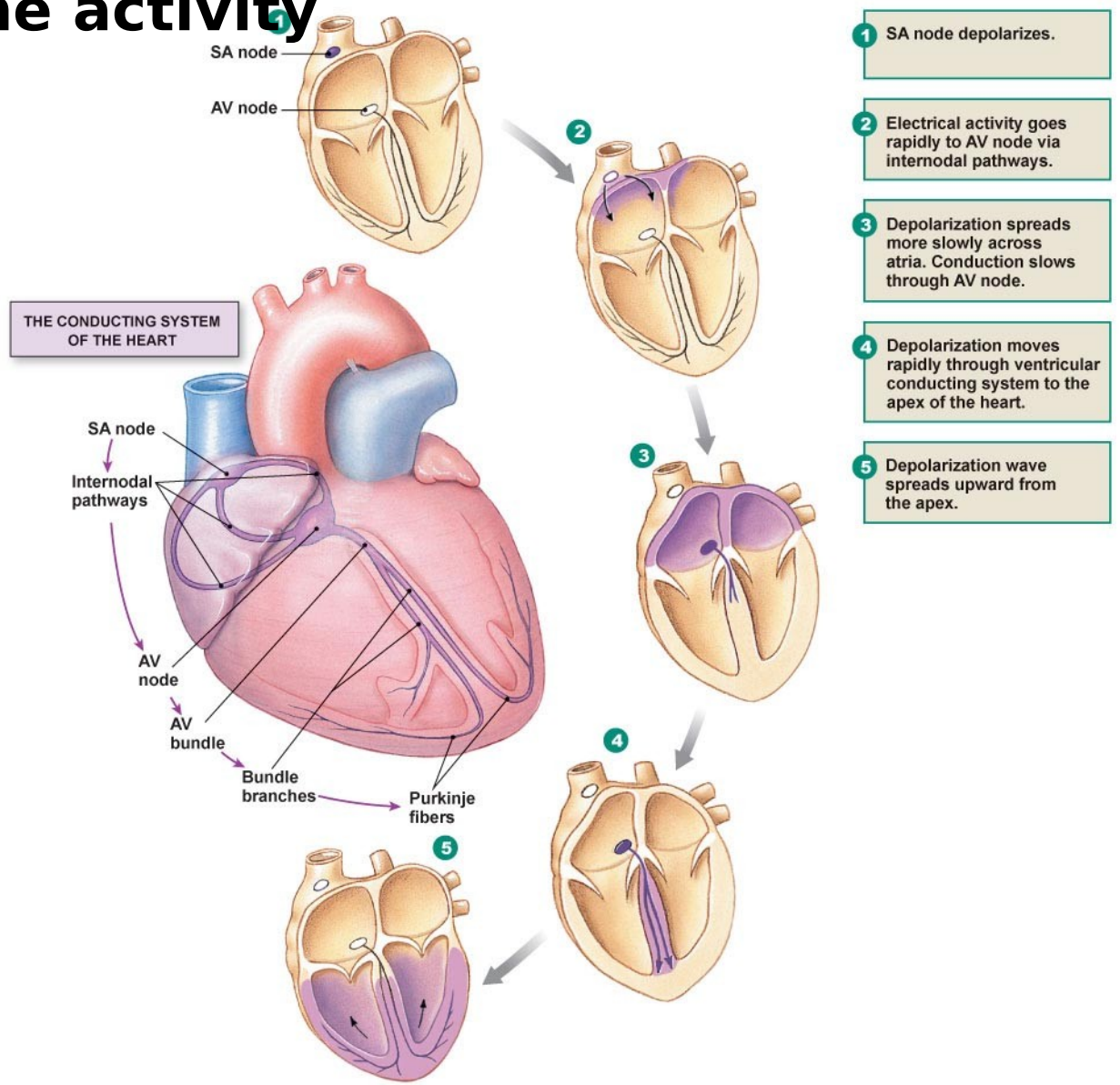
Cardiac Cycle
Coordinating the activity

- Electrical Conduction Pathway
  - Initiated by the Sino-Atrial node (SA node) which is myogenic at 70-80 action potentials/minute
  - Depolarization is spread through the atria via gap junctions and internodal pathways to the Atrio-Ventricular node (AV node)
    - The fibrous connective tissue matrix of the heart prevents further spread of APs to the ventricles
    - A slight delay at the AV node occurs
      - Due to slower formation of action potentials
      - Allows further emptying of the atria
  - Action potentials travel down the Atrioventricular bundle (Bundle of His) which splits into left and right atrioventricular bundles (bundle branches) and then into the conduction myofibers (Purkinje cells)
    - Purkinje cells are larger in diameter & conduct impulse very rapidly
      - Causes the cells at the apex to contract nearly simultaneously
        - » Good for ventricular ejection

Cardiac Cycle

Coordinating the activity

- Electrical Conductio n Pathway

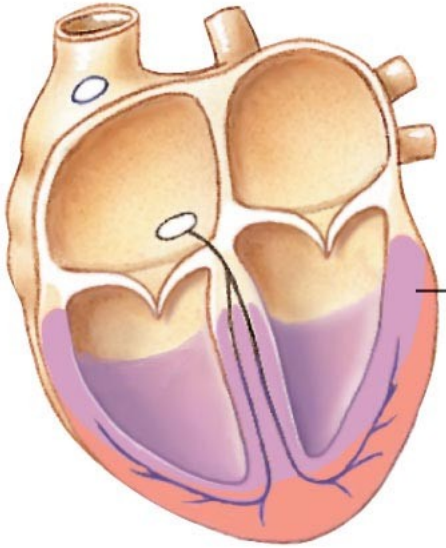


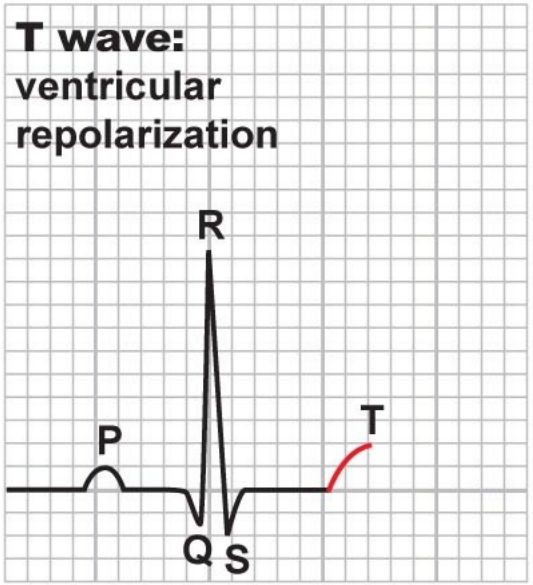
Cardiac Cycle

Coordinating the activity

- The electrical system gives rise to electrical changes (depolarization/repolarization) that is transmitted through isotonic body fluids and is recordable
  - The ECG!
    - A recording of electrical activity
    - Can be mapped to the cardiac cycle

ELECTRICAL EVENTS OF THE CARDIAC CYCLE





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Cardiac Cycle

Phases

- Systole = period of contraction
- Diastole = period of relaxation
- Cardiac Cycle is alternating periods of systole and diastole
- Phases of the cardiac cycle
  1. Rest
     - Both atria and ventricles in diastole
     - Blood is filling both atria and ventricles due to low pressure conditions
  2. Atrial Systole
     - Completes ventricular filling
  3. Isovolumetric Ventricular Contraction
     - Increased pressure in the ventricles causes the AV valves to close… why?
       - Creates the first heart sound (lub)
     - Atria go back to diastole
     - No blood flow as semilunar valves are closed as well

Cardiac Cycle

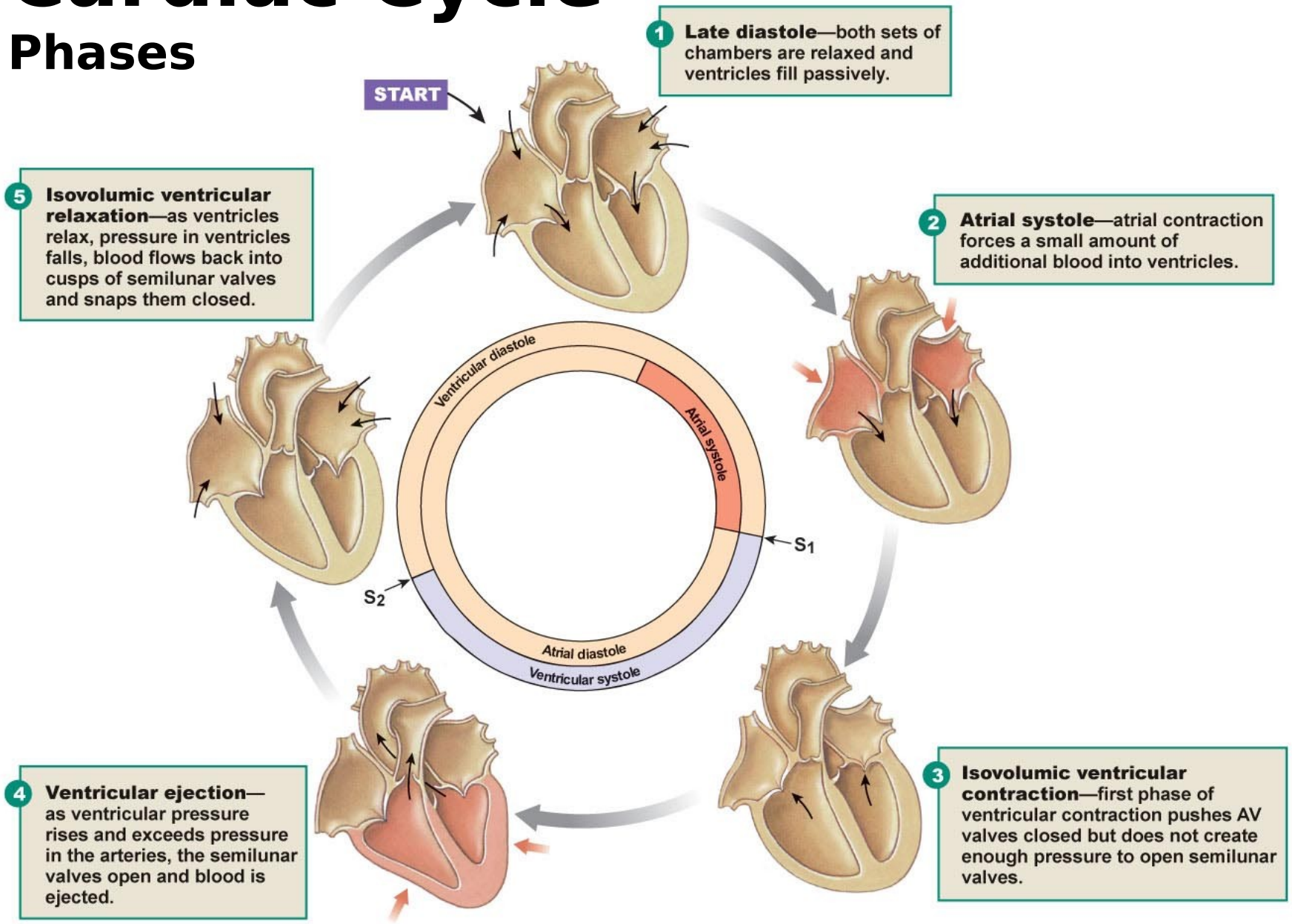
Phases

- Phases of the cardiac cycle
  4. Ventricular Ejection
     - Intraventricular pressure overcomes aortic pressure
       - Semilunar valves open
       - Blood is ejected
  5. Isovolumetric Ventricular Relaxation
     - Intraventricular pressure drops below aortic pressure
       - Semilunar valves close = second heart sound (dup)
     - Pressure still hasn’t dropped enough to open AV valves so volume remains same (isovolumetric)

  Back to Atrial & Ventricular Diastole

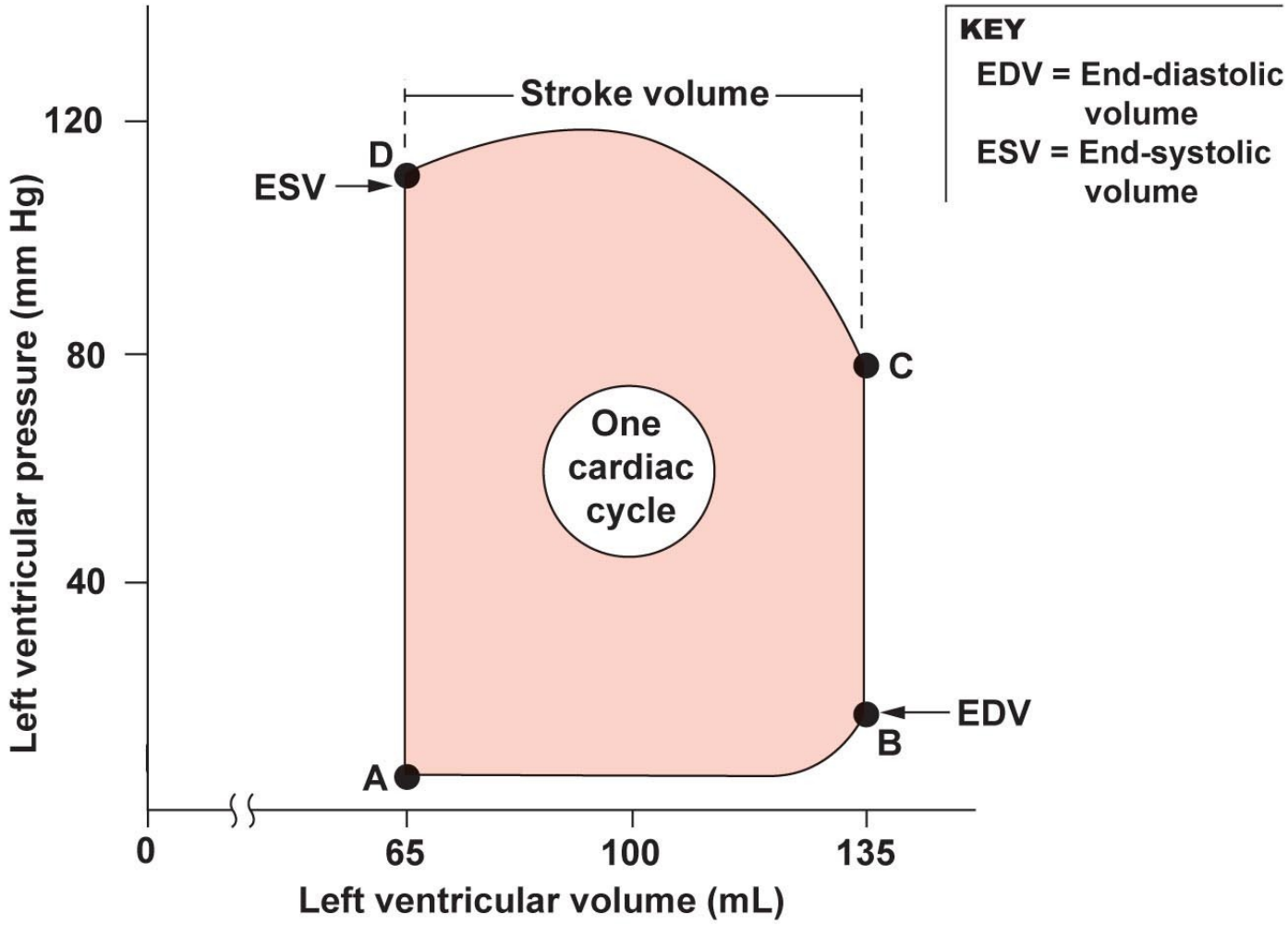
Cardiac Cycle

Phases



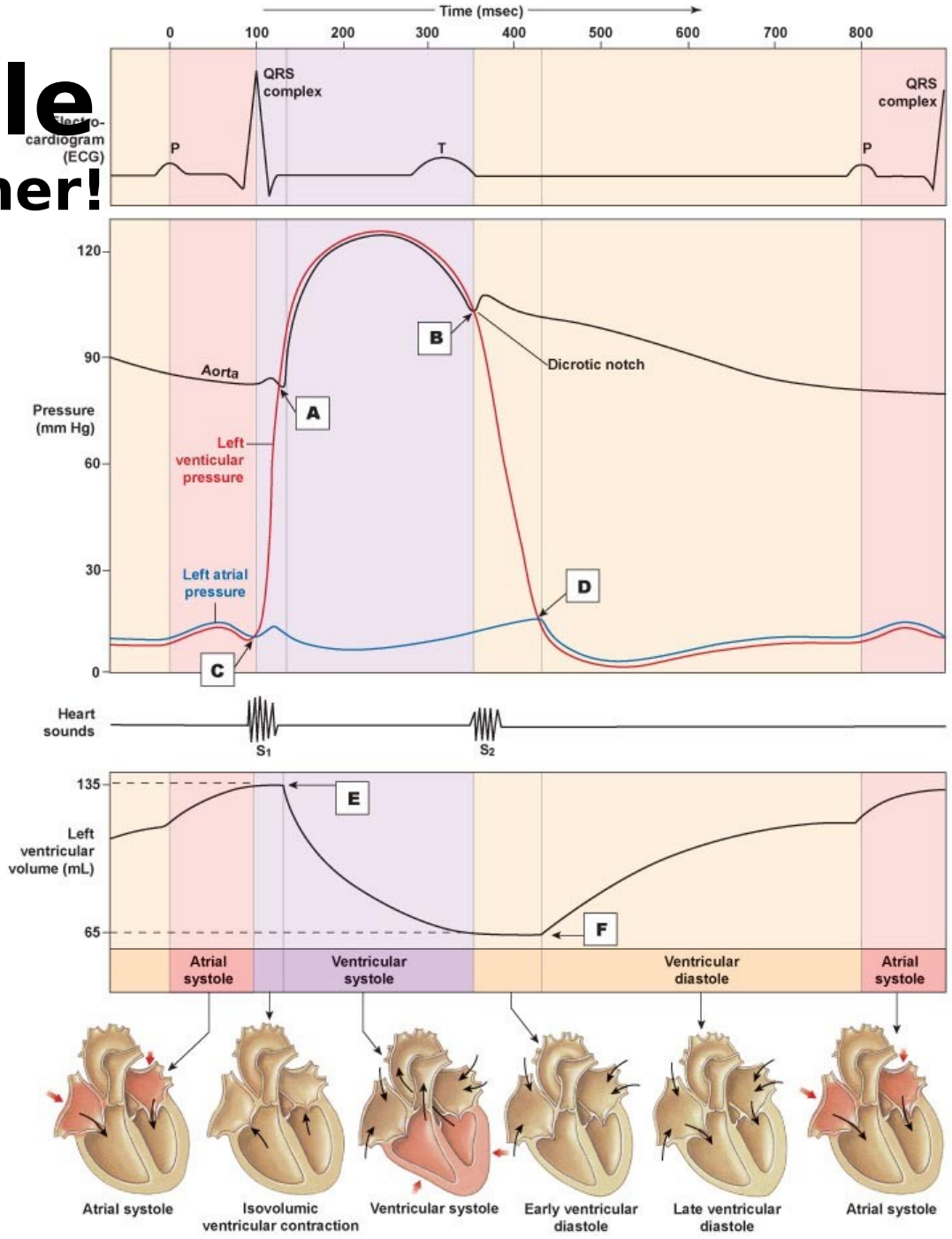
Cardiac Cycle

Blood Volumes & Pressure



Cardiac Cycle

Putting it all together!



Lecture Outline

- Cardiovascular System Function
- Functional Anatomy of the Heart
- Myocardial Physiology
- Cardiac Cycle
- **Cardiac Output Controls & Blood Pressure… next time!**

Cardiovascular Physiology

Part 2

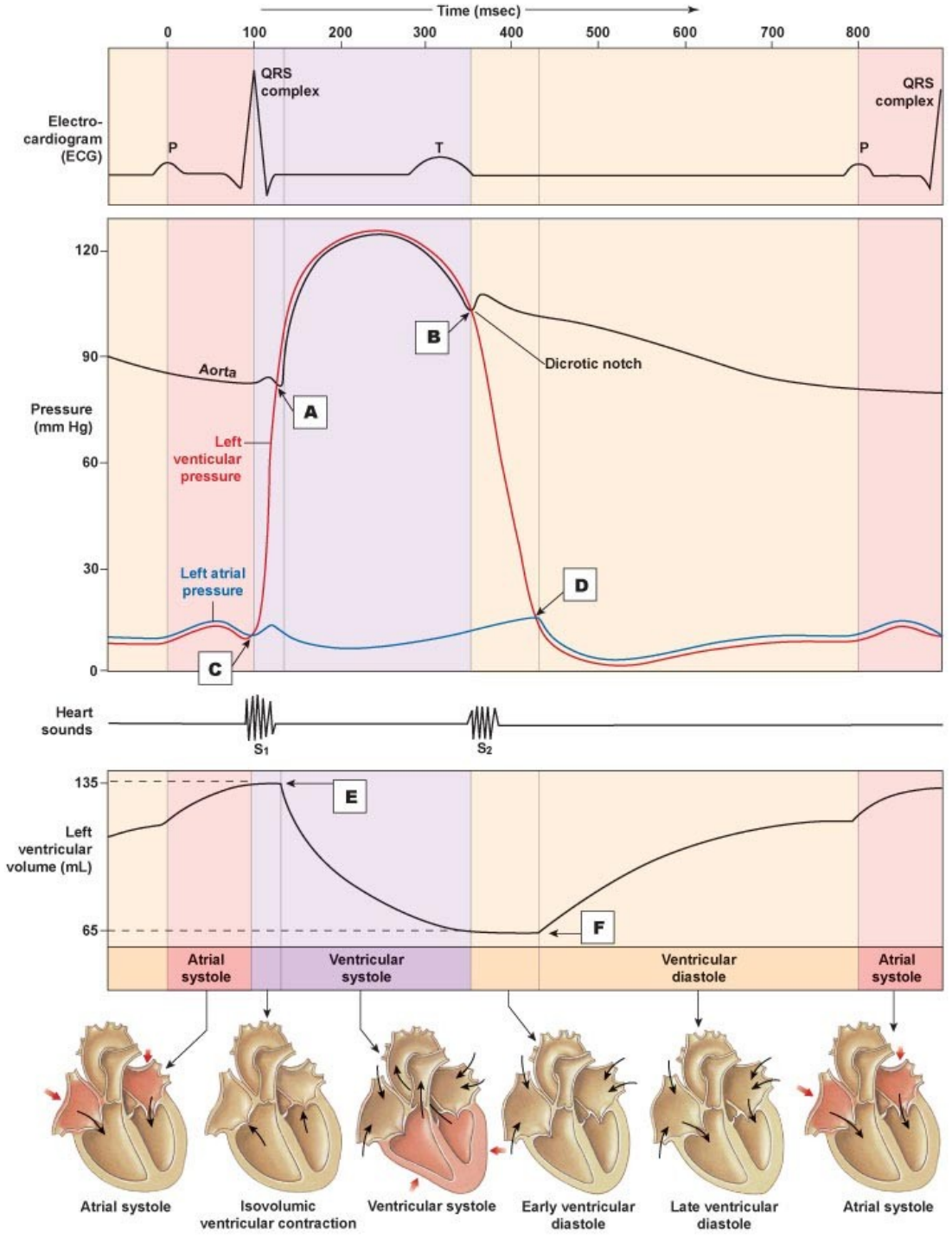
Cardiac Output & Control Systems

Lecture Outline

- **Review Integrated Cardiac Page**
- Cardiac Output & Controls
- Blood Flow & Blood Pressure Controls
- Medullary Center for Cardiovascular Control & the Baroreceptor Reflex

Cardiovascular Physiology Integrated Review

[Heart Animation]



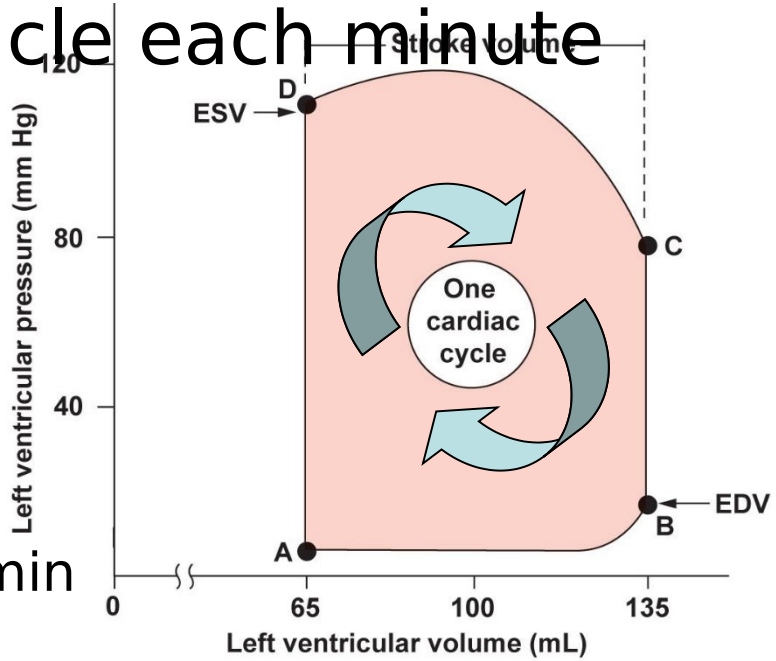
Lecture Outline

- Review Integrated Cardiac Page
- **Cardiac Output & Controls**
- Blood Flow & Blood Pressure Controls
- Medullary Center for Cardiovascular Control & the Baroreceptor Reflex

Cardiovascular Physiology

Cardiac Output

- Cardiac Output (CO) is the volume pumped by the left ventricle each minute
  - influenced by
    - Stroke Volume (SV)
      EDV – ESV = SV
      135ml – 65ml = 70ml
    - Heart Rate (HR) bpm
      80 bmp
  - CO = SV x HR
    70ml/b x 72bpm = 5040 ml/min
    =5.04L/min
  - How is this controlled to account for changing conditions? (exercise, disease, stress…)
    - What influences SV?
    - What influences HR?

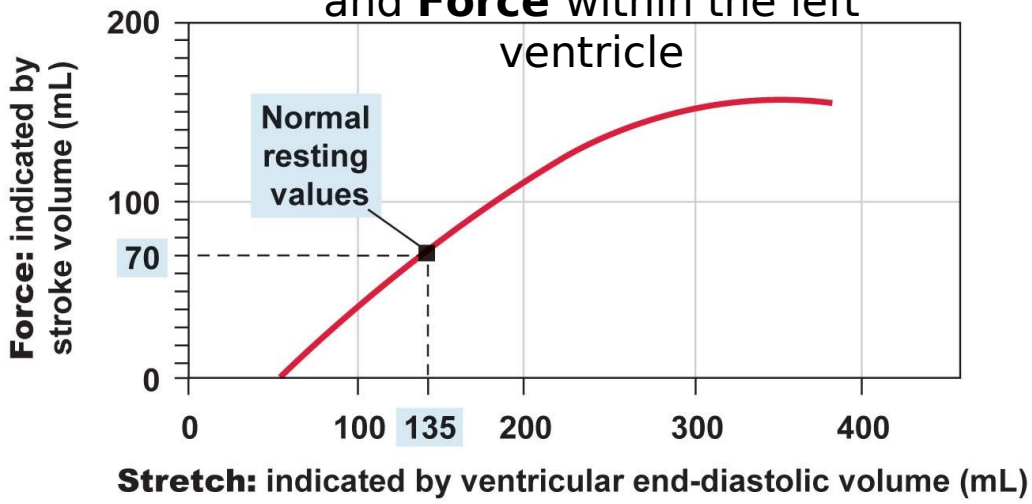


Cardiovascular Physiology

Cardiac Output

- Influencing stroke volume
  - Pre Load
    - The amount of stret within the contracti myocardial fibers
    - Represents the “loa placed on the musc fibers before they contract
    - They respond according to length tension patterns observed in muscle tissue by Frank, then by Starling
      - Became known as the Frank-Starling Law of the Heart
      - “The heart will pump all the blood that is returned to it”

Relationship between **Stretch** and **Force** within the left ventricle



Cardiovascular Physiology
Cardiac Output

- Influencing stroke volume
  - Pre Load
    - operates under Frank-Starling Law of the Heart
    - What then influences the stretch applied to cardiac muscle tissue prior to contraction?
      - Venous return, driven by
        - » Skeletal muscle pump
        - » Respiratory pump
        - » Atrial Suction

Cardiovascular Physiology

Cardiac Output

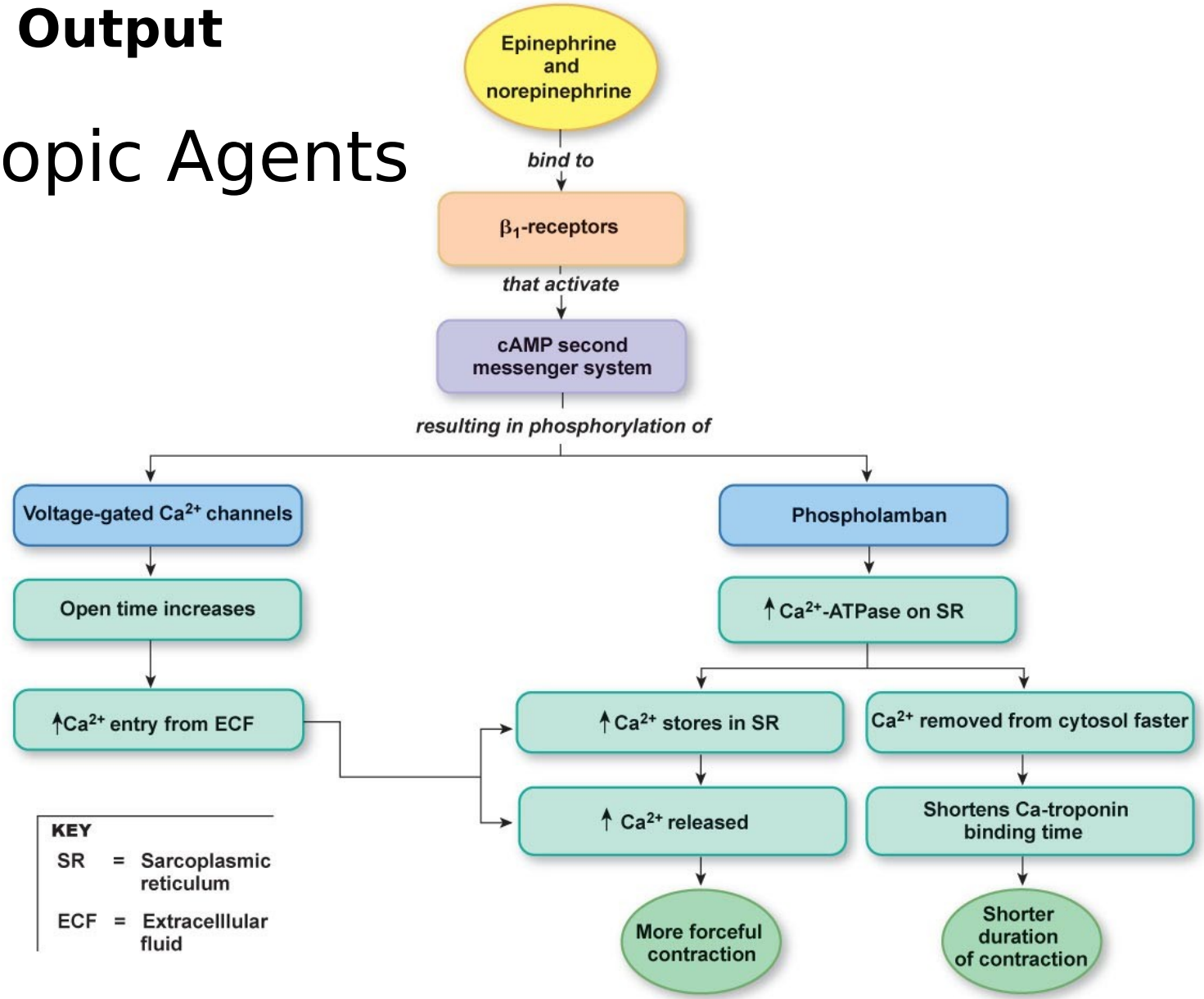
- Influencing stroke volume
  - Contractility
    - Stronger contraction = larger stroke volume
    - Due to inotropic agents
      - Epinephrine, Norepinephrine, Digitalis* are (+) inotropic agents
      - ACh is a (-) inotropic agent
      - How do they work?

*digitalis – a cardiac glycoside drug that lowers Na^+/K^+ ATPase activity and therefore the NCX transporter activity, resulting in elevated ICF Ca^{2+} which creates a stronger graded contraction.

Cardiovascular Physiology

Cardiac Output

- Inotropic Agents



Cardiovascular Physiology
Cardiac Output

- Influencing stroke volume
  - Afterload
    - This is the amount of pressure that is sitting on the semilunar valves that must be overcome before ventricular ejection can occur
    - The more pressure that must be built up during Isovolumetric ventricular contraction reduces the time that ejection can occur
      - Reduces the ejection fraction (SV/EDV)
        - » Normal 70ml/135ml = 52%
        - » Elevated aortic pressure causes the reduction from normal
        - » 60ml/135ml = 44%
    - indirect relationship
      - Higher aortic pressure = lower stroke volume
    - Causes?
      - Elevated blood pressure
      - Loss of compliance in aorta (loss of elasticity)

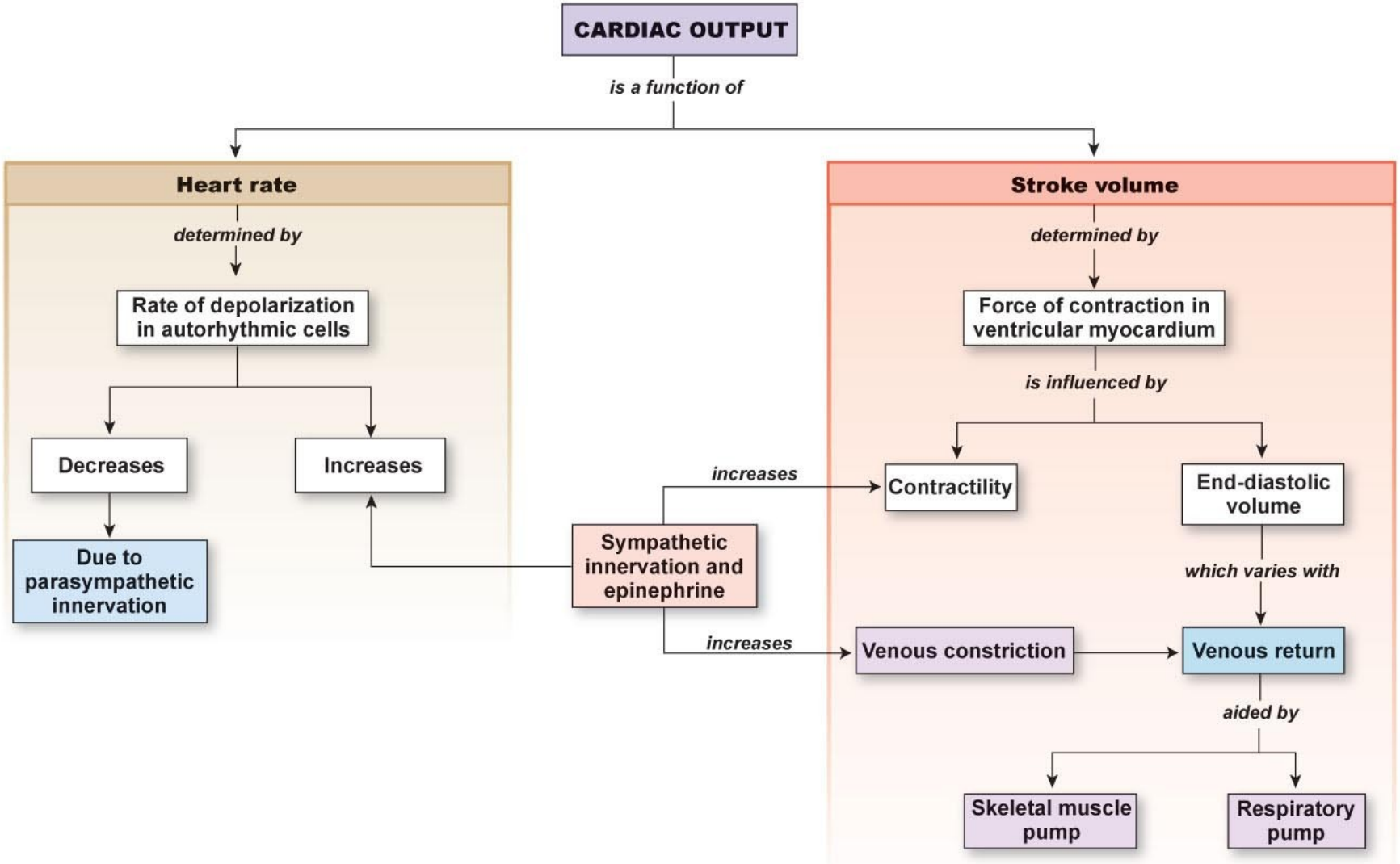
Cardiovascular Physiology

Cardiac Output

- Influencing Heart Rate
  - Rate is set by pacemaker cells rate of depolarization
    - Chronotropic effects may be excitatory
      - Sympathetic activity
    - Or inhibitory
      - Parasympathetic activity

Cardiovascular Physiology

Cardiac Output Overview of Influences



Lecture Outline

- Review Integrated Cardiac Page
- Cardiac Output & Controls
- **Blood Flow & Blood Pressure Controls**
- Medullary Center for Cardiovascular Control & the Baroreceptor Reflex

Cardiac Physiology

Blood Flow & Blood Pressure Controls

- CO tells us how much blood is ejected per minute and is influence by both intrinsic & extrinsic factors
- Extrinsic factors (besides ANS) include
  - blood vessels & blood pressure
  - blood volume & viscosity
  - capillary exchange & the lymphatic return
  - cardiovascular disease

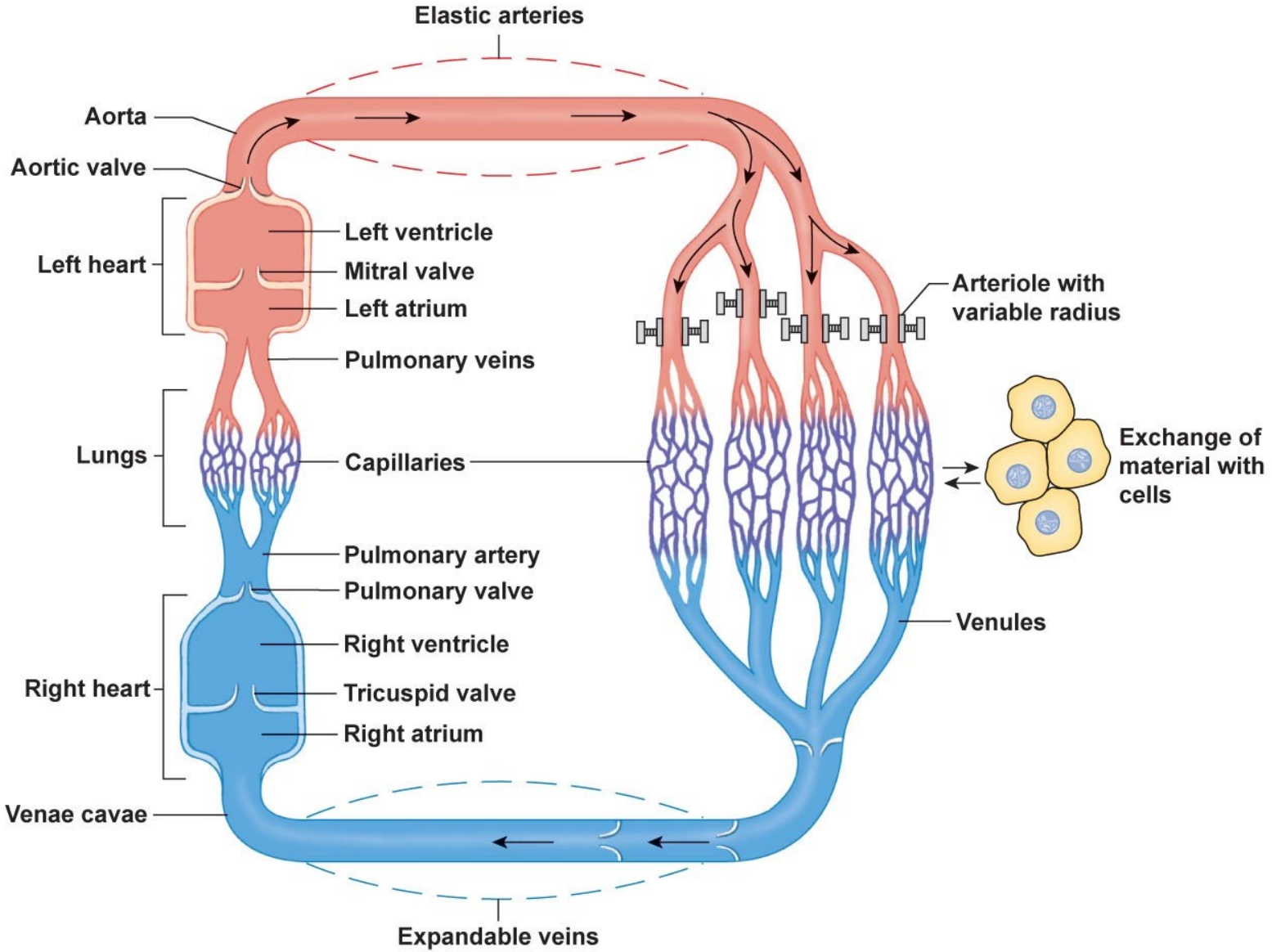
Cardiac Physiology

Blood Flow & Blood Pressure Controls

- Blood Vessels Function to
  - Provide route (arteries – away, veins – visit)
  - Allow for exchange (capillaries)
  - Control & regulate blood pressure

Cardiac Physiology

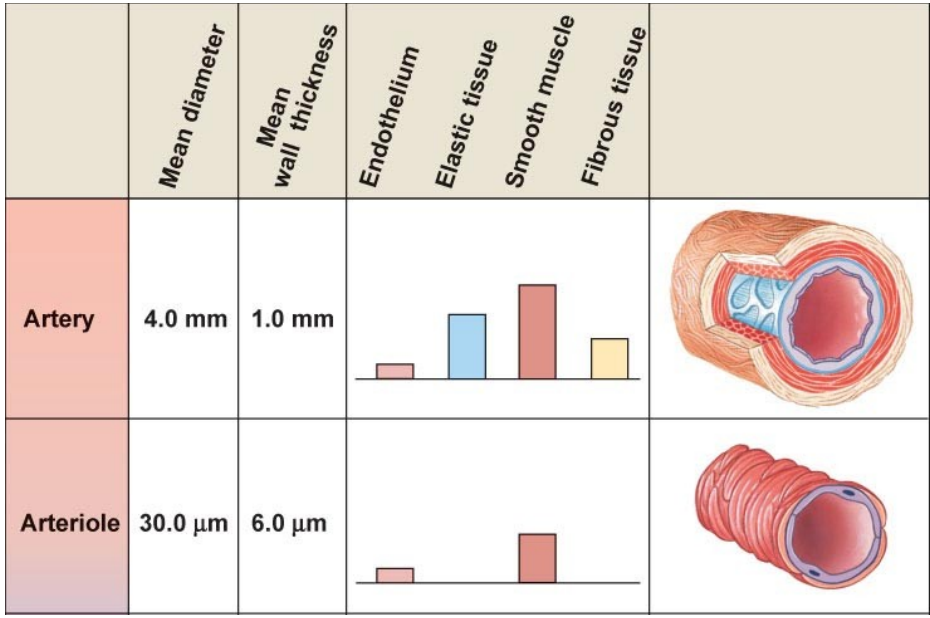
Blood Flow & Blood Pressure Controls



Cardiac Physiology

Blood Flow & Blood Pressure Controls

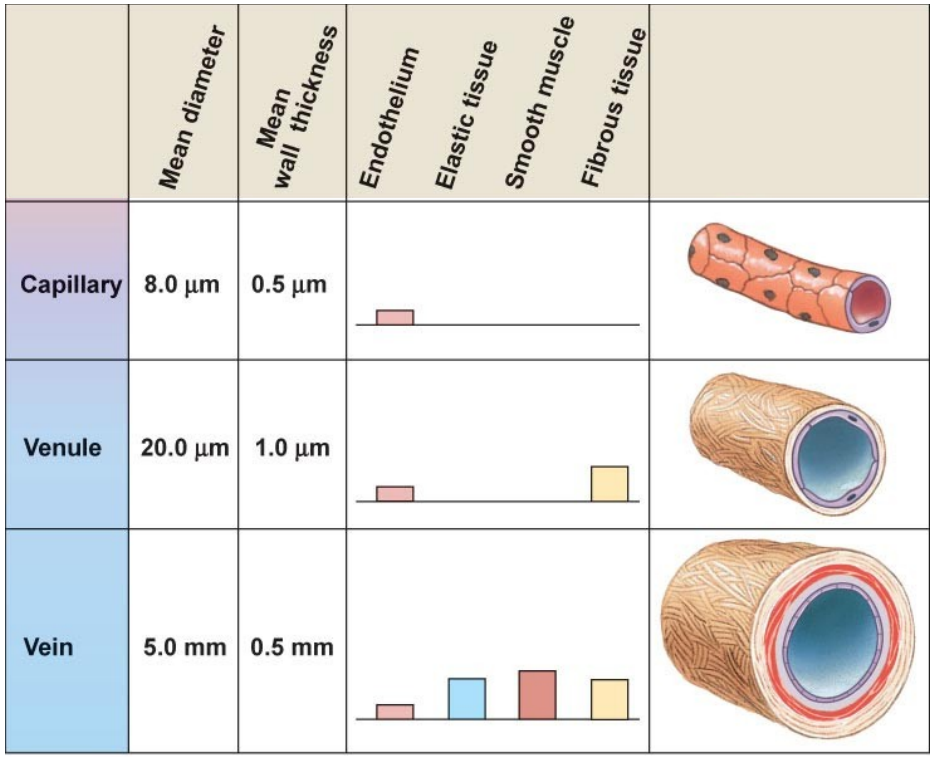
- Blood Vessel Structure enables specific functions
  - Aorta
    - absorb pulse pressure (systolic pressure – diastolic pressure) and release energy creating diastolic pulse
  - Large arteries
    - conduct and distribute blood to regional areas
  - Arterioles
    - Regulate flow to tissues and regulate MAP (mean arterial pressure)



Cardiac Physiology

Blood Flow & Blood Pressure Controls

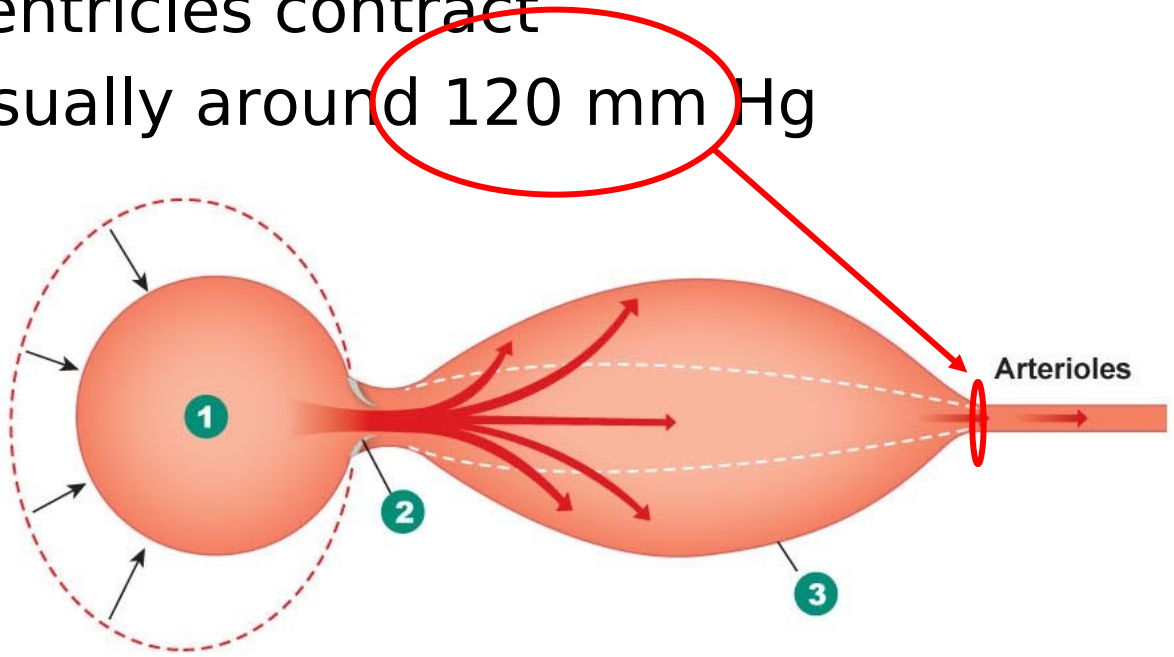
- Capillaries
  - Allow for exchange
- Venules
  - Collect and direct blood to the veins
- Veins
  - Return blood to heart and act as a blood reservoir



Cardiac Physiology

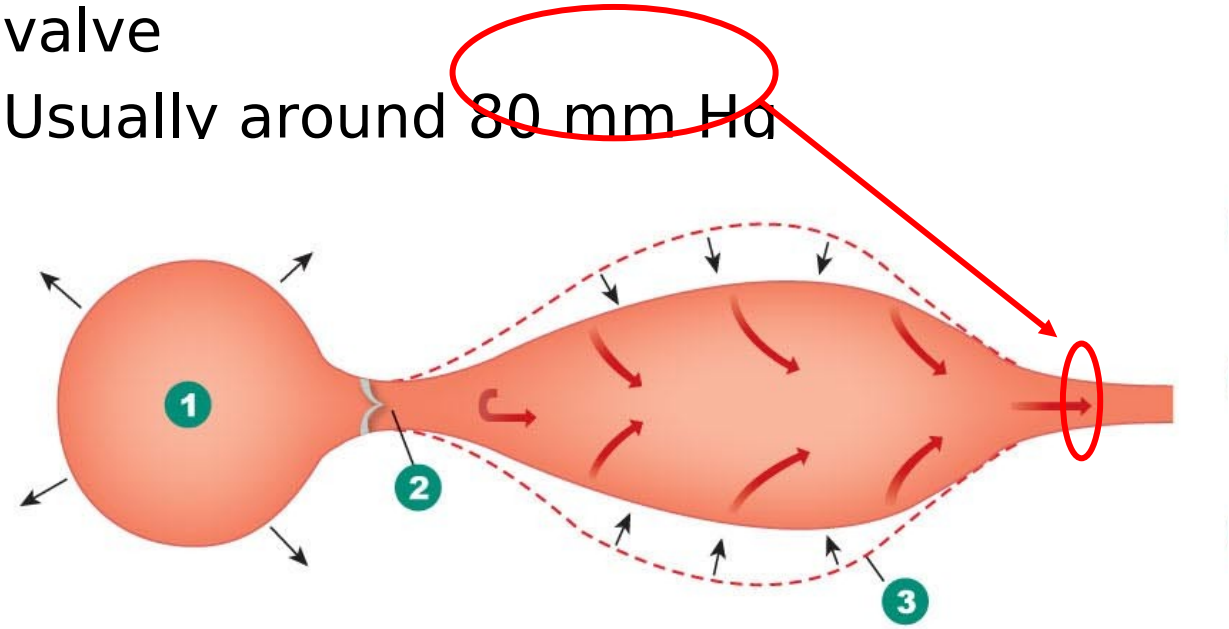
Blood Flow & Blood Pressure Controls

- Blood Vessels & Blood Pressure
  - Systolic Pressure
    - The pressure that is created when the ventricles contract
    - Usually around 120 mm Hg



Cardiac Physiology
Blood Flow & Blood Pressure Controls

- Blood Vessels & Blood Pressure
  - Diastolic Pressure
    - The pressure that is created by the recoil of the aorta AND the closure of the aortic semilunar valve
    - Usually around 80 mm Hg



Cardiac Physiology

Blood Flow & Blood Pressure Controls

- Blood Vessels & Blood Pressure
  - Pulse Pressure
    - The difference between the systolic and diastolic pressures
      - Usually 40 mm Hg (120 mm Hg – 80 mm Hg)
    - Only applies to arteries
  - Why do we care about systolic, diastolic and pulse pressures?
    - We can determine the average pressure within the arterial system = Mean Arterial Pressure (MAP)

      MAP = diastolic Pressure + 1/3 Pulse Pressure

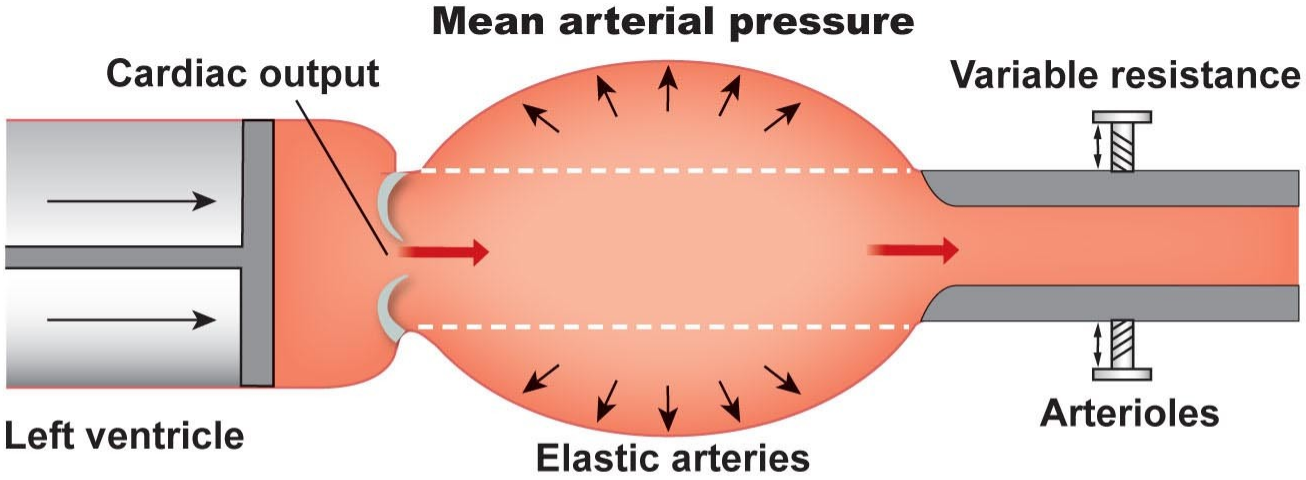
      MAP = 80 mm Hg + 1/3(120 mm Hg – 80 mm Hg)

      MAP = 93 mm Hg
    - Then we can determine general health of the cardiovascular system

Cardiac Physiology

Blood Flow & Blood Pressure Controls

- MAP is proportionate to the cardiac output and the amount of peripheral resistance
  - If CO increases but resistance to the outflow does not change
    - Then more blood is flowing into the system than out and arterial pressure must go up to allow inflows to equal outflows



Mean arterial pressure $\propto$ cardiac output $\times$ resistance

Cardiac Physiology

Blood Flow & Blood Pressure Controls

- MAP is proportionate to the cardiac output and the amount of peripheral resistance
  - The opposition to blood flow in the arterioles
    - Resistance is directly proportional to the length (L) of the vessel, and the viscosity(η) (thickness) of the blood and inversely proportional (to the 4^{th} power) of the vessel radius, so….

$$R \propto L\,\eta/r^4$$

However as the L and η should remain relatively constant, we can determine that peripheral resistance is mainly a factor of the vessel diameter

$$R \propto 1/r^4$$

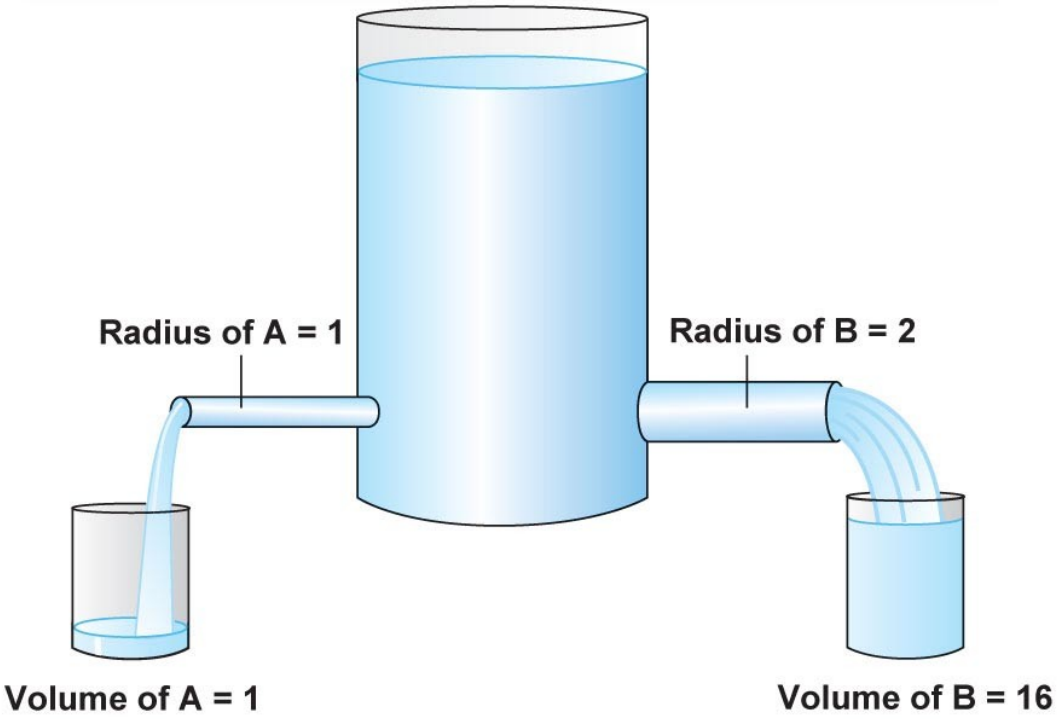
Cardiac Physiology

Blood Flow & Blood Pressure Controls

- So… if resistance is affected by the radius, and flow is inversely proportionate to the resistance
  - What effect will vasoconstriction / vasodilation have on blood pressure and blood flow? And what controls it?
  - What will obesity do to blood pressure and blood flow & why?

$\text{Resistance} \propto \frac{1}{\text{radius}^4}$	
Tube A	Tube B
$R \propto \frac{1}{1^4}$ $R \propto 1$	$R \propto \frac{1}{2^4}$ $R \propto \frac{1}{16}$

$\text{Flow} \propto \frac{1}{\text{resistance}}$	
Tube A	Tube B
$\text{Flow} \propto \frac{1}{1}$ $\text{Flow} \propto 1$	$\text{Flow} \propto \frac{1}{\frac{1}{16}}$ $\text{Flow} \propto 16$



Cardiac Physiology
Blood Flow & Blood Pressure Controls

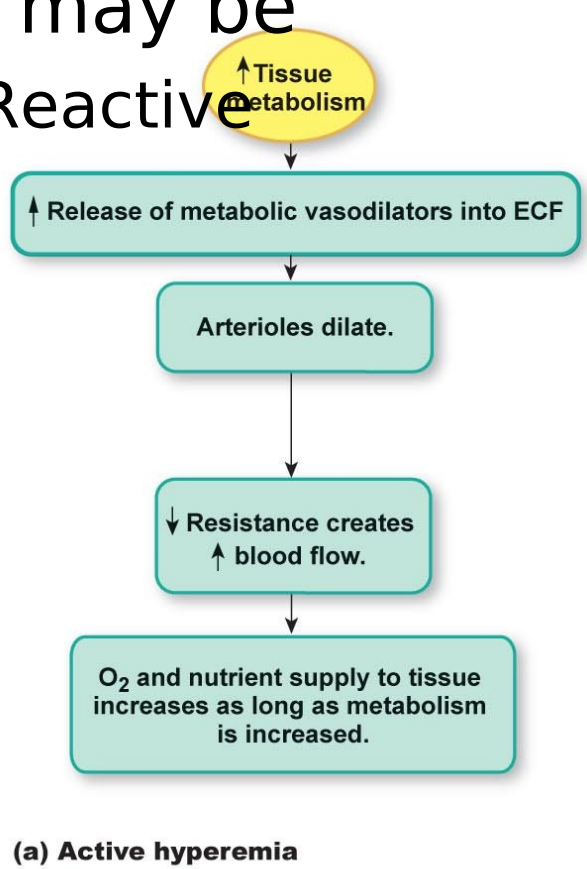
- The controls of vessel diameter are both local and systemic
  - Enables tissues to control their own blood flow
  - Local controlling mechanisms include
    - Myogenic response by smooth muscle of arterioles
      - Increased stretch due to increasing blood pressure causes vessel constriction due to mechanically gated Ca^{2+} channel activation
    - Paracrines – local substances which alter smooth muscle activity

vasoconstrictors
- Serotonin
  - » Secreted by activated platelets
- Endothelin
  - » secreted by vascular endothelium

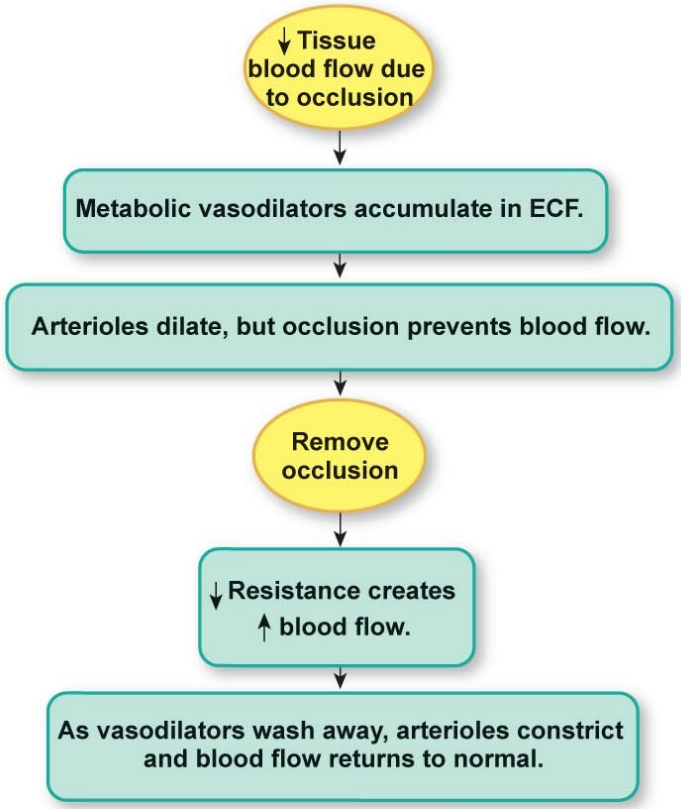
vasodilators
- NO secreted by vascular endothelium
- Bradykinin – from various sources
- Histamine – from mast cells in connective tissues
- Adenosine secreted by cells in low O_2 (hypoxic) conditions
- $\downarrow O_2$, $\uparrow CO_2$, $\uparrow K^+$, $\uparrow H^+$, $\uparrow$temp

Cardiac Physiology
Blood Flow & Blood Pressure Controls

- Hyperemia is locally mediated increases in blood flow, may be
  - Active or Reactive



(a) Active hyperemia



(b) Reactive hyperemia

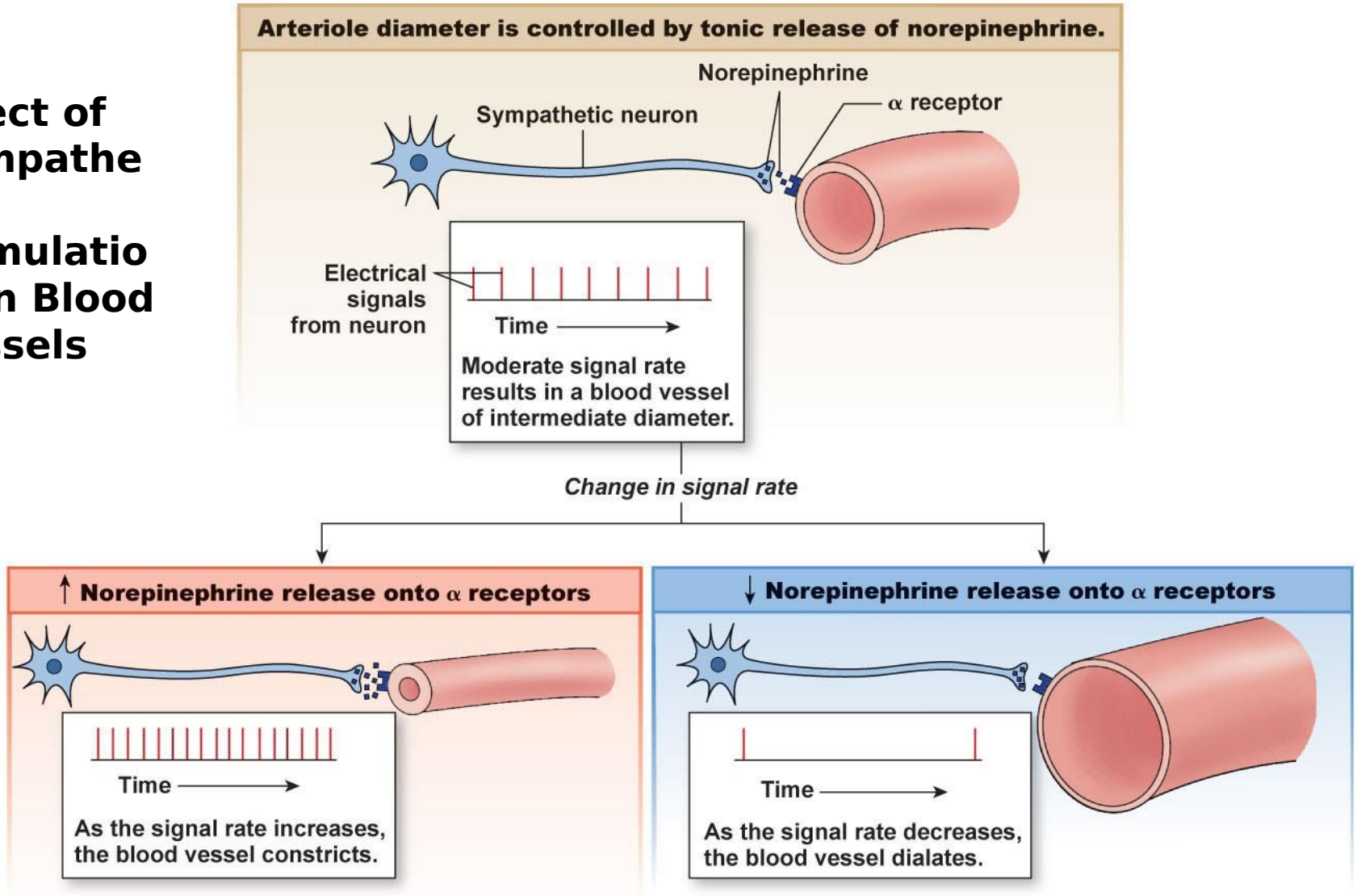
Cardiac Physiology
Blood Flow & Blood Pressure Controls

- The controls of vessel diameter are both local (intrinsic) and systemic (extrinsic)
  - Systemic controlling mechanisms for vasoconstriction include
    - NE – sympathetic postganglionic neurons
    - Serotonin – neurons
    - Vasopressin (ADH) – posterior pituitary
    - Angiotensin II – part of renin-antiogensin pathway
  - Systemic controls for vasodilation include
    - Beta-2 epinephrine – from adrenal medulla
    - ACH – parasympathetic postganglionic neurons
    - ANP (atrial natriuretic peptide) – from atrial myocaridum and brain
    - VIPs (vasoactive intestinal peptides) – from neurons

Cardiac Physiology

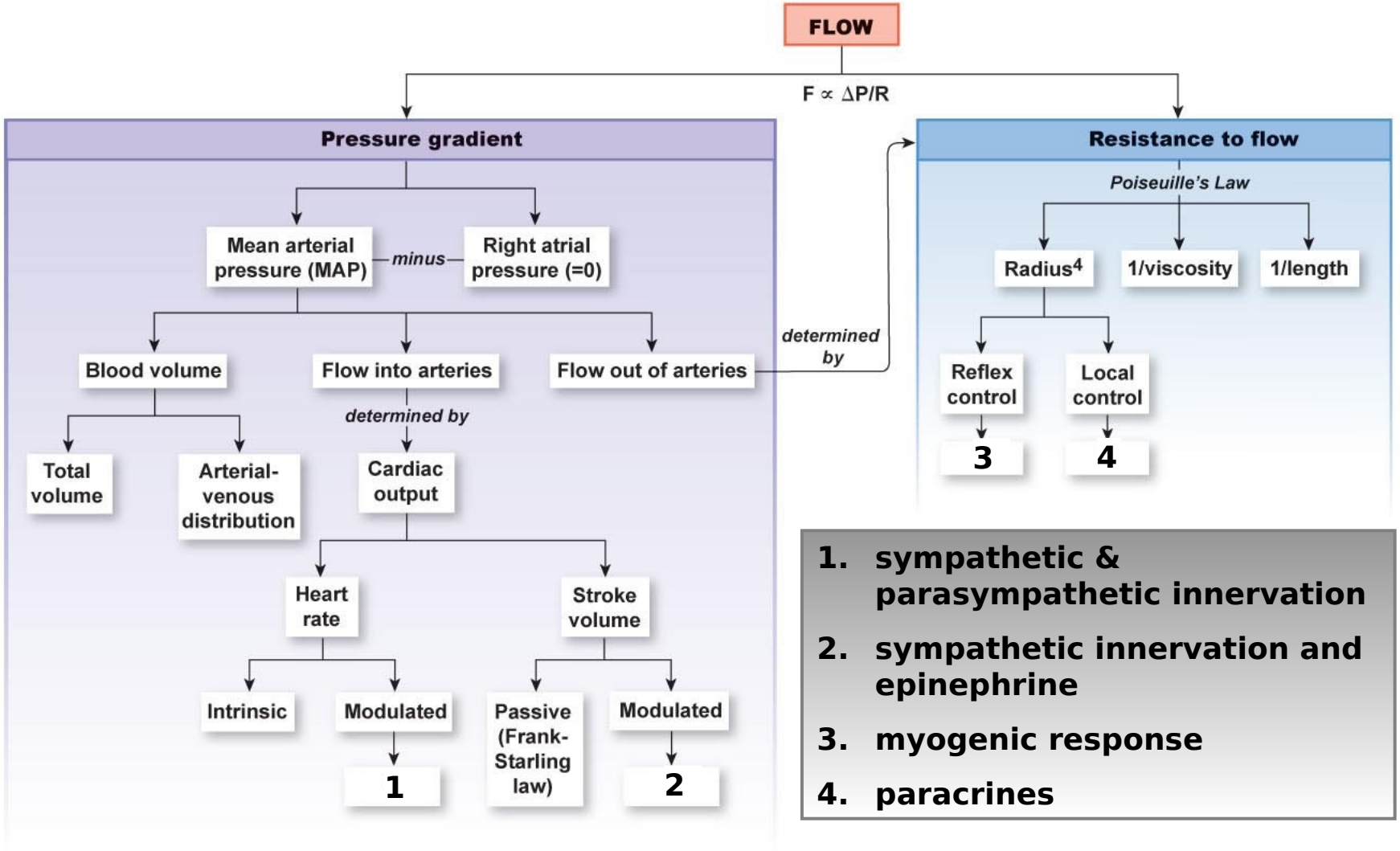
Blood Flow & Blood Pressure Controls

Effect of Sympathetic Stimulation on Blood Vessels



Cardiovascular Physiology

Review of Factors Influencing Blood Flow



1. sympathetic & parasympathetic innervation
2. sympathetic innervation and epinephrine
3. myogenic response
4. paracrines

Lecture Outline

- Review Integrated Cardiac Page
- Cardiac Output & Controls
- Blood Flow & Blood Pressure Controls
- **Medullary Center for Cardiovascular Control & the Baroreceptor Reflex**

Cardiac Physiology

Neural Regulation of Blood Pressure

- CNS contains the Medullary Cardiovascular Control Center
  - Receives inputs from carotid and aortic baroreceptors
  - Creates outflow to sympathetic and parasympathetic pathways
    - Sympathetic to SA & AV nodes and myocardium as well as to arterioles and veins
    - Parasympathetic to the SA Node
  - Baroreceptors initiate the **baroreceptor reflex**

The Baroreceptor Reflex Pathways

