Heart valves prevent backflow to ensure one-way blood flow.  
- Atrioventricular (AV) valves (i.e., right AV valve and left AV valve) are between atrium and ventricle
- Semilunar valves (i.e., pulmonary semilunar valve and aortic semilunar valve) are between ventricle and arterial trunk

**Two pumps**

Each pump has a receiving chamber (atrium) and a pumping chamber (ventricle).
- Right side: pumps deoxygenated blood to the lungs
- Left side: pumps oxygenated blood to the body

**Great vessels**

Arteries (arterial trunks) transport blood away from the heart.
- Pulmonary trunk transports from right side
- Aorta transports from left side

Veins transport blood toward the heart.
- Vena cavae (SVC and IVC) drain into right side
- Pulmonary veins drain into left side

**Valves**

- Aortic semilunar valve
- Pulmonary trunk
- Right AV valve
- Left AV valve
- Inferior vena cava (IVC)
- Superior vena cava (SVC)
- Pulmonary veins
- Arteries
- Veins
- Right atrium
- Left atrium
- Right ventricle
- Left ventricle
- Aorta
- Pulmonary trunk
- Pulmonary semilunar valve
- Aortic semilunar valve
- Right side
- Left side
- to body
- to lungs
- to body
- to lungs
- to body
- to lungs
Coronary Blood Flow

coronary blood flow: 250 ml/min
5% of resting cardiac output
60-80 ml blood/100g tissue/min
entirely during diastole
  ◦ ~ aortic diastolic pressure minus LVDP
  ◦ ~ duration of diastole
pressure < 150 mmHg
oxygenated by superb membrane oxygenator-”the lungs”

Cerebral Blood Flow

• Cerebral blood flow: 750 ml/min
• 15% of resting cardiac output
• 50-55 ml blood/100g tissue/min
**Natriuretic Peptides**

In response to a rise in blood pressure, the heart releases two peptides:

- **A-type Natriuretic Peptide (ANP)**
  - This hormone of 28 amino acids is released from stretched atria (hence the "A").

- **B-type Natriuretic Peptide (BNP)**
  - This hormone is released from the ventricles. (It was first discovered in brain tissue; hence the "B").

Both hormones lower blood pressure by:

- relaxing arterioles
- inhibiting the secretion of renin and aldosterone
- inhibiting the reabsorption of sodium ions by the kidneys.

The latter two effects reduce the reabsorption of water by the kidneys.

- So the volume of urine increases as does the amount of sodium excreted in it.
- The net effect of these actions is to reduce blood pressure by reducing the volume of blood in the circulatory system.

These effects give ANP and BNP their name (natrium = sodium; uresis = urinate).
• Pulmonary capillary wedge pressure (PCWP; in mm Hg) is a good approximation of left atrial pressure.
• In mitral stenosis, PCWP > LV end diastolic pressure.
• PCWP is measured with pulmonary artery catheter (Swan-Ganz catheter).

Cardiac myocyte physiology

Cardiac muscle contraction is dependent on extracellular calcium, which enters the cells during plateau of action potential and stimulates calcium release from the cardiac muscle sarcoplasmic reticulum (calcium-induced calcium release).

In contrast to skeletal muscle:
1. Cardiac muscle action potential has a plateau, which is due to Ca^{2+} influx
2. Cardiac nodal cells spontaneously depolarize, resulting in automaticity
3. Cardiac myocytes are electrically coupled to each other by gap junctions
Cardiac and vascular function curves

Cardiac output (CO) or venous return

Right atrial pressure or EDV

↑ blood volume

(-) inotropy

(+/-) inotropy

Venous return

↓ blood volume
Differences Between Skeletal and Cardiac Muscle Physiology

**Action Potential**
- **Cardiac**: Action potentials conducted from cell to cell.
- **Skeletal**: action potential conducted along length of single fiber

**Rate of Action Potential Propagation**
- Slow in cardiac muscle because of gap junctions and small diameter of fibers.
- Faster in skeletal muscle due to larger diameter fibers.

**Calcium release**
- Calcium-induced calcium release (CICR) in cardiac
  - Movement of extracellular Ca$^{2+}$ through plasma membrane and T tubules into sarcoplasm stimulates release of Ca$^{2+}$ from sarcoplasmic reticulum
  - Action potential in T-tubule stimulates Ca$^{++}$ release from sarcoplasmic reticulum
Cardiac Muscle Contraction

Heart muscle:
- Is stimulated by nerves and is self-excitile (automaticity)
- Contracts as a unit
- Has a long (250 ms) absolute refractory period
- Pacemaker can function for many years without interruption

Cardiac muscle contraction is similar to skeletal muscle contraction

- **Ach** (from ParaSym terminals of vagus nerve Xth cranial nerve) $\Rightarrow$ slows HR by increasing $K^+$ conductance & reducing $Ca^{2+}$ conductance of pacemaker cells
- **Norepinephrine** (Sym NS) accelerates pacemaker potential $\Rightarrow$ increasing HR

![Cardiac Muscle Contraction Diagram](image-url)
Heart Physiology: Intrinsic Conduction System

**Autorhythmic cells:**
- Initiate action potentials
- Have unstable resting potentials called pacemaker potentials
- Use calcium influx (rather than sodium) for rising phase of the action potential
Cardiac muscle cells

1. The action potential initiated in the conduction system is propagated across the sarcolemma of cardiac muscle cells.

Muscle contraction
Thin filaments slide past thick filaments and sarcomeres shorten within cardiac muscle cells.

(a) Conduction system

1. Initiation
SA node initiates action potential.

Spread of action potential
An action potential is propagated throughout the atria, the conduction system.

(b) Cardiac muscle cells

Sarcomeres shorten.
PACEMAKERS (in order of their inherent rhythm)

- **Sino-atrial (SA) node**: The autorhythmic cells are concentrated in the following areas.
  - **The sinoatrial (SA) node**, located in the upper wall of the right atrium, initiates the cardiac cycle by generating an action potential that spreads through both atria through the gap junctions of the cardiac muscle fibers.
  - **The atrioventricular (AV) node**, located near the lower region of the interatrial septum, receives the action potential generated by the SA node. A slight delay of the electrical transmission occurs here, allowing the atria to fully contract before the action potential is passed on to the ventricles.
  - **The atrioventricular (AV) bundle (bundle of His)** receives the action potential from the AV node and transmits the impulse to the ventricles by way of the right and left bundle branches. Except for the AV bundle, which provides the only electrical connection, the atria are electrically insulated from the ventricles.
  - **The Purkinje fibers** are large-diameter fibers that conduct the action potential from the interventricular septum, down to the apex, and then upward through the ventricles.

- **Atrio-ventricular (AV) node**
- **Bundle of His**
- **Bundle branches**
- **Purkinje fibers**
Sequence of excitation

1. sinoatrial (SA) node - spreads to both atria
   - 90 - 100 action potentials per minute

2. atrioventricular (AV) node
   - 40 - 50 action potentials per minute

3. atrioventricular (AV) bundle (bundle of His)
   - 20 - 40 action potentials per minute

4. right & left bundle branches
   - in the interventricular septum

5. Purkinje fibers
   - conduction myofibers
The firing of the SA node sets off a chain reaction in cardiac conduction.

- Bachmann's bundle
- SA node
- Internodal tract
  - Posterior (Thorel's)
  - Middle (Wenckebach's)
  - Anterior
- AV node
- Bundle of His
- Right bundle branch
- Left bundle branch
- Purkinje fibers
**Impulse Conduction through the Heart**

**STEP 1:**
SA node activity and atrial activation begin.
Time = 0

**STEP 2:**
Stimulus spreads across the atrial surfaces and reaches the AV node.
Elapsed time = 50 msec

**STEP 3:**
There is a 100-msec delay at the AV node. Atrial contraction begins.
Elapsed time = 150 msec

**STEP 4:**
The impulse travels along the interventricular septum within the AV bundle and the bundle branches to the Purkinje fibers and, via the moderator band, to the papillary muscles of the right ventricle.
Elapsed time = 175 msec

**STEP 5:**
The impulse is distributed by Purkinje fibers and relayed throughout the ventricular myocardium. Atrial contraction is completed, and ventricular contraction begins.
Elapsed time = 225 msec
Heart Excitation Related to ECG

SA node generates impulse; atrial excitation begins

Impulse delayed at AV node

Impulse passes to heart apex; ventricular excitation begins

Ventricular excitation complete
Depolarization of SA Node

- **SA node** - no stable resting membrane potential

- **Pacemaker potential**
  - gradual depolarization from -60 mV, slow influx of Na⁺

- **Action potential**
  - occurs at threshold of -40 mV
  - depolarizing phase to 0 mV
    - fast Ca²⁺ channels open, (Ca²⁺ in)
  - repolarizing phase
    - K⁺ channels open, (K⁺ out)
    - at -60 mV K⁺ channels close, pacemaker potential starts over

- Each depolarization creates one heartbeat
  - SA node at rest fires at 0.8 sec, about 75 bpm
Pacemaker and Action Potentials of the Heart

**Figure 18.13**

- **Ca^{2+} channels close; K^+ channels open**
  - Action potential

- **Ca^{2+} permeability**

- **K^+ permeability**

- **K^+ channels close; slow Na^+ channels opening (Na^+ enters)**

- **Pacemaker potential**

### Occurs in the SA and AV nodes. Key differences from the ventricular action potential include:

- **Phase 0** = upstroke—opening of voltage-gated Ca^{2+} channels. Fast voltage-gated Na^+ channels are permanently inactivated because of the less negative resting potential of these cells. Results in a slow conduction velocity that is used by the AV node to prolong transmission from the atria to ventricles.

- Phases 1 and 2 are absent.

- **Phase 3** = repolarization—inactivation of the Ca^{2+} channels and ↑ activation of K^+ channels → ↑ K^+ efflux.

- **Phase 4** = slow spontaneous diastolic depolarization due to I_f (“funny current”). I_f channels responsible for a slow, mixed Na^+/$K^+$ inward current; different from $I_{Na}$ in phase 0 of ventricular action potential. Accounts for automaticity of SA and AV nodes. The slope of phase 4 in the SA node determines HR. ACH/adenosine ↓ the rate of diastolic depolarization and ↓ HR, while catecholamines ↑ depolarization and ↑ HR. Sympathetic stimulation ↑ the chance that I_f channels are open and thus ↑ HR.
Pacemaker Function

(a) Normal (resting) - Heart rate: 75 bpm
- Prepotential (spontaneous depolarization)
- Threshold

(b) Parasympathetic stimulation - Heart rate: 40 bpm
- Hyperpolarization
- Slower depolarization

(c) Sympathetic stimulation - Heart rate: 120 bpm
- Reduced repolarization
- More rapid depolarization
Reaching threshold
Slow voltage-gated Na⁺ channels open. Inflow of Na⁺ changes membrane potential from -60 mV to -40 mV.

Depolarization
Fast voltage-gated Ca²⁺ channels open. Inflow of Ca²⁺ changes membrane potential from -40 mV to just above 0 mV.

Repolarization
Fast voltage-gated Ca²⁺ channels close. Voltage-gated K⁺ channels open allowing K⁺ outflow. Membrane potential returns to RMP - 60 mV, and K⁺ channels close.
PHASE
0 = Rapid Depolarization (inward Na\(^+\) current)
1 = Overshoot
2 = Plateau (inward Ca\(^{++}\) current)
3 = Repolarization (outward K\(^+\) current)
4 = Resting Potential

Mechanical Response
Myocardial action potential

Also occurs in bundle of His and Purkinje fibers.

Phase 0 = rapid upstroke and depolarization—voltage-gated Na⁺ channels open.
Phase 1 = initial repolarization—inactivation of voltage-gated Na⁺ channels. Voltage-gated K⁺ channels begin to open.
Phase 2 = plateau—Ca²⁺ influx through voltage-gated Ca²⁺ channels balances K⁺ efflux. Ca²⁺ influx triggers Ca²⁺ release from sarcoplasmic reticulum and myocyte contraction.
Phase 3 = rapid repolarization—massive K⁺ efflux due to opening of voltage-gated slow K⁺ channels and closure of voltage-gated Ca²⁺ channels.
Phase 4 = resting potential—high K⁺ permeability through K⁺ channels.

In contrast to skeletal muscle:
- Cardiac muscle action potential has a plateau, which is due to Ca²⁺ influx and K⁺ efflux.
- Cardiac muscle contraction requires Ca²⁺ influx from ECF to induce Ca²⁺ release from sarcoplasmic reticulum (Ca²⁺-induced Ca²⁺ release).
- Cardiac myocytes are electrically coupled to each other by gap junctions.
Cardiac Membrane Potential

(a) Graph showing the relation between membrane potential and time.
- Action potential
- Plateau
- Tension development (contraction)
- Absolute refractory period

(b) Graph showing the relative membrane permeability over time.
- Na⁺ permeability (inward flux)
- Ca²⁺ permeability (inward flux)
- K⁺ permeability (outward flux)
Fig. 19.19

(a) Skeletal muscle

(b) Cardiac muscle
SINGLE VENTRICULAR ACTION POTENTIAL

ECG

P

Q S

R

T

Depolarization of atria

Depolarization of ventricles

Repolarization of ventricles

ATRIAL FIBER

ENDOCARDIAL FIBER

EPICARDIAL FIBER

1 mV
The Action Potential in Skeletal and Cardiac Muscle

**STEP 1: Rapid Depolarization**
- Cause: Na⁺ entry
- Duration: 3–5 msec
- Ends with: Closure of voltage-regulated (fast) sodium channels

**STEP 2: The Plateau**
- Cause: Ca²⁺ entry
- Duration: ~175 msec
- Ends with: Closure of slow calcium channels

**STEP 3: Repolarization**
- Cause: K⁺ loss
- Duration: 75 msec
- Ends with: Closure of slow potassium channels
Base the heart physiology

- Automaticity
- Excitability
- Conductivity
- Contractility
Cardiac Cycle: the electrical, pressure and volume changes that occur in a functional heart between successive heart beats.

- Phase of the cardiac cycle when myocardium is relaxed is termed **diastole**.

- Phase of the cardiac cycle when the myocardium contracts is termed **systole**.
  - **Atrial systole**: when atria contract.
  - **Ventricular systole**: when ventricles contract.
Mechanical Events of the Cardiac Cycle

1. **Ventricular Filling Period** [ventricular diastole, atrial systole]
2. **Isovolumetric Contraction Period** [ventricular systole]
3. **Ventricular Ejection Period** [ventricular systole]
4. **Isovolumetric Relaxation Period** [ventricular diastole]
Phases of the Cardiac Cycle

**Ventricular filling – mid-to-late diastole**
- Heart blood pressure is low as blood enters atria and flows into ventricles
- AV valves are open, then atrial systole occurs

**Ventricular systole**
- Atria relax
- Rising ventricular pressure results in closing of AV valves
- Isovolumetric contraction phase
- Ventricular ejection phase opens semilunar valves

**Isovolumetric relaxation – early diastole**
- Ventricles relax
- Backflow of blood in aorta and pulmonary trunk closes semilunar valves

**Dicrotic notch** – brief rise in aortic pressure caused by backflow of blood rebounding off semilunar valves
Heart sounds:

**S1**—mitral and tricuspid valve closure. Loudest at mitral area.

**S2**—aortic and pulmonary valve closure. Loudest at left upper sternal border.

**S3**—in early diastole during rapid ventricular filling phase. Associated with filling pressures (eg, mitral regurgitation, HF) and more common in dilated ventricles (but can be normal in children, young adults, and pregnant women).

**S4**—in late diastole (“atrial kick”). Best heard at apex with patient in left lateral decubitus position. High atrial pressure. Associated with ventricular noncompliance (eg, hypertrophy).

Left atrium must push against stiff LV wall. Consider abnormal, regardless of patient age.

### Jugular venous pulse (JVP):

- **a** wave—atrial contraction. Absent in atrial fibrillation (AF).
- **c** wave—RV contraction (closed tricuspid valve bulging into atrium).
- **x** descent—downward displacement of closed tricuspid valve during rapid ventricular ejection phase. Reduced or absent in tricuspid regurgitation and right HF because pressure gradients are reduced.
- **v** wave—right atrial pressure due to filling (“villing”) against closed tricuspid valve.
- **y** descent—RA emptying into RV. Prominent in constrictive pericarditis, absent in cardiac tamponade.
The black loop represents normal cardiac physiology.

Phases—left ventricle:
1. Isovolumetric contraction—period between mitral valve closing and aortic valve opening; period of highest O₂ consumption
2. Systolic ejection—period between aortic valve opening and closing
3. Isovolumetric relaxation—period between aortic valve closing and mitral valve opening
4. Rapid filling—period just after mitral valve opening
5. Reduced filling—period just before mitral valve closing
Control of mean arterial pressure

↑ sympathetic activity (heart and vasculature)

Medullary vasomotor center senses ↓ baroreceptor firing

↓ MAP

JGA senses ↓ MAP (effective circulating volume)

↑ renin-angiotensin system (kidneys)

β₁ (↑ heart rate, ↑ contractility)—↑ CO
α₁ (venoconstriction: ↑ venous return)—↑ CO
α₁ (arteriolar vasoconstriction)—↑ TPR

Angiotensin II (vasoconstriction)—↑ TPR
Aldosterone (↑ blood volume)—↑ CO

↑ MAP
**What is Cardiac Index?**
It is cardiac output per minute per square meter of body surface area.
Normal Cardiac Index = 3.2 Liter/min/sq meter body surface area.

**What is Cardiac Reserve?**
It is the difference between cardiac output at rest and maximum volume of blood that heart can pump per minute.
Preload and Afterload

(a) Preload

(b) Afterload
**Ejection fraction (EF)** is the percentage of ventricular end diastolic volume (EDV) which is ejected with each stroke.

\[
\text{EF} = \frac{\text{SV (EDV – ESV)}}{\text{EDV}} \times 100
\]

\[
\frac{75}{120} \times 100 = 62.5\%
\]

- Normal ejection fraction is about 60 – 65 %.
- Ejection fraction is good index of ventricular function.
Cardiac output (CO) = 5 L

Cardiac output (CO) = (stroke volume) \times (heart rate).

Fick principle:

\[
CO = \frac{\text{rate of } O_2 \text{ consumption}}{\text{arterial } O_2 \text{ content} - \text{venous } O_2 \text{ content}}
\]

Mean arterial pressure = \left( \frac{\text{cardiac output}}{\text{total peripheral resistance}} \right)

MAP = \frac{1}{3} \text{ diastolic pressure} + \frac{2}{3} \text{ systolic pressure.}

Pulse pressure = \text{systolic pressure} - \text{diastolic pressure.}

Pulse pressure is proportion to stroke volume.

\[
SV = \frac{CO}{HR} = EDV - ESV
\]

During exercise, CO ↑ initially as a result of an ↑ in SV. After prolonged exercise, CO ↑ as a result of an ↑ in HR.

If HR is too high, diastolic filling is incomplete and CO ↓ (e.g., ventricular tachycardia).
Cardiac Output (CO) and Reserve

- **CO** is the amount of blood pumped by each ventricle in one minute.

*CO is the product of heart rate (HR) and stroke volume (SV)*

- Stroke volume is determined by three factors:
  - **Preload**
  - **Afterload**
  - **Contractility**

- **HR** is the number of heart beats per minute.
- **SV** is the amount of blood pumped out by a ventricle with each beat.
- Cardiac reserve is the difference between resting and maximal CO.

**SV is the amount of blood pumped out by a ventricle with each beat**

- **SV = EDV - ESV**
  - **EDV** = amount of blood collected in a ventricle during diastole. It is about 120 – 130 ml.
  - **ESV** = amount of blood remaining in a ventricle after contraction. It is about 50 to 60 ml.

**Ejection Fraction (EF) = Stroke Volume / End Diastolic Volume**

**Example of Cardiac Output**

- **CO (ml/min) = HR (75 beats/min) x SV (70 ml/beat)**
- **CO = ________________**

**CO increases during exercise**, and depending on exercise, it can increase to **20–25 liters/min [up to 35 liters/min is recorded in trained athlete during heavy exercise]**.

- **How?**
  - By increasing stroke volume and heart rate.
Factors Affecting Cardiac Output

Stroke volume can be increased by TWO mechanism:

1. **INTRINSIC CONTROL** – by increasing venous return to the heart
2. **EXTRINSIC CONTROL** – due to the sympathetic stimulation of the heart
### Effect of Autonomic Nervous System on Heart

<table>
<thead>
<tr>
<th>Area Affected</th>
<th>Effect of Parasympathetic Stimulation</th>
<th>Effect of Sympathetic Stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA Node</td>
<td>Decreases the rate of depolarization to threshold; decreases the heart rate</td>
<td>Increases the rate of depolarization to threshold; increases the heart rate</td>
</tr>
<tr>
<td>AV Node</td>
<td>Decreases excitability; increases the AV nodal delay</td>
<td>Increases excitability; decreases the AV nodal delay</td>
</tr>
<tr>
<td>Ventricular Conduction Pathway</td>
<td>No effect</td>
<td>Increases excitability; hastens conduction through the bundle of His and Purkinje cells</td>
</tr>
<tr>
<td>Atrial Muscle</td>
<td>Decreases contractility; weakens contraction</td>
<td>Increases contractility; strengthens contraction</td>
</tr>
<tr>
<td>Ventricular Muscle</td>
<td>No effect</td>
<td>Increases contractility; strengthens contraction</td>
</tr>
</tbody>
</table>

**SYMPATHETIC**: It regulates the action potential frequency of the SA node.

- Regulates vasoconstriction.
- Regulates venomotor tone.
- Stimulate the secretion of epinephrine and renin.
Factors Affecting Stroke Output

**Preload** - amount ventricles are stretched by contained blood

**Contractility** - cardiac cell contractile force due to factors other than EDV

- Increase in contractility comes from:
  - Increased sympathetic stimuli
  - Certain hormones
  - Ca2+ and some drugs

- **Agents/factors that decrease contractility:**
  - Acidosis
  - Increased extracellular K+
  - Calcium channel blockers

**Afterload** - back pressure exerted by blood in the large arteries leaving the heart

**Frank-Starling Law of the Heart**

- Preload, or degree of stretch, of cardiac muscle cells before they contract is the critical factor controlling stroke volume
- Slow heartbeat and exercise increase venous return to the heart, increasing SV

\[ SV = \text{end diastolic volume (EDV)} - \text{end systolic volume (ESV)} \]

\[ \text{EDV} = \text{amount of blood collected in a ventricle during diastole} \]

\[ \text{ESV} = \text{amount of blood remaining in a ventricle after contraction} \]
Frank-Starling Law of the Heart

Preload, or degree of stretch, of cardiac muscle cells before they contract is the critical **factor controlling stroke volume**;

$\uparrow$EDV leads to $\uparrow$stretch of myocardial tissue.

- $\uparrow$preload $\rightarrow$ $\uparrow$stretch of muscle $\rightarrow$ $\uparrow$force of contraction $\rightarrow$$\uparrow$SV
- Unlike skeletal fibers, cardiac fibers contract MORE FORCEFULLY when stretched thus ejecting MORE BLOOD ($\uparrow$SV)
- **If SV is increased, then ESV is decreased!!**

**Slow heartbeat and exercise increase venous return (VR) to the heart, increasing SV**

- VR changes in response to blood volume, skeletal muscle activity, alterations in cardiac output
- $\uparrow$VR $\rightarrow$ $\uparrow$EDV and $\downarrow$in VR $\rightarrow$ $\downarrow$in EDV
- Any $\downarrow$ in EDV $\rightarrow$ $\downarrow$ in SV

**Mechanism of Cardiac Length – Tension Relationship**

- When there is increase in the length of cardiac muscle fiber to the optimal length, there is **maximum sliding of actin and myosin and we get maximum contraction**.

- Preload, or degree of stretch, of cardiac muscle cells before they contract is the critical factor controlling stroke volume
- **Slow heartbeat and exercise increase venous return to the heart, increasing SV**
- Blood loss and extremely rapid heartbeat decrease SV
Blood pressure is the force exerted on a blood vessel wall by the blood.

Blood must circulate through the body and organs to maintain life.

The Heart is the pump that circulates the blood.

Pressure difference in the vascular system ensures that blood flows around the body.
# Location and Effects of Stimulation of Adrenergic Receptors

## Alpha-1 Receptors
- Arterioles and Veins:
  - Constriction (epinephrine and norepinephrine)
- Glands:
  - ↓ secretions
- Eye:
  - Constriction of radial muscle
- Intestine:
  - ↓ motility

## Alpha-2 Receptors
- CNS Postsynaptic Terminals:
  - ↓ sympathetic outflow from brain
- CNS Presynaptic Terminals:
  - Norepinephrine release
- Beta Islet Cells of Pancreas:
  - ↓ secretion

## Beta-1 Receptors
- Heart:
  - ↑ heart rate (SA node)
  - ↑ contractility
  - ↑ conduction velocity
  - ↑ automaticity
- Kidney:
  - ↑ renin secretion

## Beta-2 Receptors
- Trachea and Bronchioles:
  - Dilation
- Pregnant/nonpregnant Uterus:
  - Relaxation
- Arterioles (no beta-2 receptors in skin or brain):
  - Dilation (epinephrine)
Factors Affecting Stroke Volume

**Preload** – amount ventricles are stretched by contained blood

**Contractility** – cardiac cell contractile force due to factors other than EDV

**Afterload** – back pressure exerted by blood in the large arteries leaving the heart
A Simple Model of Stroke Volume

(a) Ventricular diastole
(b) Stroke volume
(c) Ventricular systole
(d) End-systolic volume (ESV)

End-diastolic volume (EDV)
<table>
<thead>
<tr>
<th>Cardiac output variables</th>
<th>Stroke Volume affected by Contractility, Afterload, and Preload. ↑ SV when ↑ preload, ↓ afterload, or ↑ contractility.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SV CAP.</td>
</tr>
<tr>
<td></td>
<td>SV ↑ in anxiety, exercise, and pregnancy.</td>
</tr>
<tr>
<td></td>
<td>A failing heart has ↓ SV.</td>
</tr>
<tr>
<td></td>
<td>Myocardial O₂ demand is ↑ by:</td>
</tr>
<tr>
<td></td>
<td>1. ↑ afterload (∝ arterial pressure)</td>
</tr>
<tr>
<td></td>
<td>2. ↑ contractility</td>
</tr>
<tr>
<td></td>
<td>3. ↑ heart rate</td>
</tr>
<tr>
<td></td>
<td>4. ↑ heart size (↑ wall tension)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Contractility (and SV) ↑ with:</td>
<td>1. Catecholamines (↑ activity of Ca²⁺ pump in sarcoplasmic reticulum)</td>
</tr>
<tr>
<td></td>
<td>2. ↑ intracellular calcium</td>
</tr>
<tr>
<td></td>
<td>3. ↓ extracellular sodium</td>
</tr>
<tr>
<td></td>
<td>4. Digitalis (↑ intracellular Na⁺, resulting in ↑ Ca²⁺)</td>
</tr>
<tr>
<td>Contractility (and SV) ↓ with:</td>
<td>1. β₁ blockade</td>
</tr>
<tr>
<td></td>
<td>2. Heart failure</td>
</tr>
<tr>
<td></td>
<td>3. Acidosis</td>
</tr>
<tr>
<td></td>
<td>4. Hypoxia/hypercapnea</td>
</tr>
<tr>
<td></td>
<td>5. Non-dihydropyridine Ca²⁺ channel blockers</td>
</tr>
<tr>
<td>Preload and afterload</td>
<td>Preload = ventricular EDV.</td>
</tr>
<tr>
<td></td>
<td>Afterload = mean arterial pressure (proportional to peripheral resistance).</td>
</tr>
<tr>
<td></td>
<td>Venodilators (e.g., nitroglycerin) ↓ preload.</td>
</tr>
<tr>
<td></td>
<td>Vasodilators (e.g., hydralazine) ↓ afterload.</td>
</tr>
<tr>
<td></td>
<td>Preload ↑ with exercise (slightly), ↑ blood volume (overtransfusion), and excitement (sympathetics). Preload pumps up the heart.</td>
</tr>
</tbody>
</table>
Baroreceptors and chemoreceptors

**Receptors:**
- Aortic arch transmits via vagus nerve to solitary nucleus of medulla (responds to ↓ and ↑ in BP).
- Carotid sinus (dilated region at carotid bifurcation) transmits via glossopharyngeal nerve to solitary nucleus of medulla (responds to ↓ and ↑ in BP).

**Baroreceptors:**
- Hypotension—↓ arterial pressure → ↓ stretch → ↓ afferent baroreceptor firing → ↑ efferent sympathetic firing and ↓ efferent parasympathetic stimulation → vasoconstriction, ↑ HR, ↑ contractility, ↑ BP. Important in the response to severe hemorrhage.
- Carotid massage—↑ pressure on carotid sinus → ↑ stretch → ↑ afferent baroreceptor firing → ↑ AV node refractory period → ↓ HR.
- Component of Cushing reflex (triad of hypertension, bradycardia, and respiratory depression)—↑ intracranial pressure constricts arterioles → cerebral ischemia → ↑ pCO₂ and ↓ pH → central reflex sympathetic ↑ in perfusion pressure (hypertension) → ↑ stretch → peripheral reflex baroreceptor-induced bradycardia.

**Chemoreceptors:**
- Peripheral—carotid and aortic bodies are stimulated by ↓ Po₂ (< 60 mm Hg), ↑ Pco₂, and ↓ pH of blood.
- Central—are stimulated by changes in pH and Pco₂ of brain interstitial fluid, which in turn are influenced by arterial CO₂. Do not directly respond to Po₂.
Regulation of Heart Rate

Positive chronotropic factors increase heart rate

Negative chronotropic factors decrease heart rate

- **Sympathetic nervous system** (SNS) stimulation is activated by stress, anxiety, excitement, or exercise
- **Parasympathetic nervous system** (PNS) stimulation is mediated by acetylcholine and opposes the SNS
- **PNS** dominates the autonomic stimulation, slowing heart rate and causing vagal tone
**Atrial (Bainbridge) Reflex**

**Atrial (Bainbridge) reflex** – a sympathetic reflex initiated by increased blood in the atria

- Causes *stimulation* of the *SA node*
- Stimulates *baroreceptors* in the atria, causing *increased SNS stimulation*
The hormones **epinephrine and thyroxine** increase heart rate.

Intra- and extracellular ion concentrations must be maintained for normal heart function.
Factors Involved in Regulation of Cardiac Output

Crisis stressors (exercise, physical or emotional trauma, increased body temperature)

Low blood pressure, low blood volume (hemorrhage, excessive sweating)

Increased activity of muscular pump and respiratory pump

Increased renal activity (conservation of Na⁺ and water)

Increased blood volume

Venous return

EDV EDV ESV

Increased contractility of cardiac muscle

Sympathetic nervous system activity

Chemicals: Bloodborne thyroxine, epinephrine, excess Ca²⁺ (short-term effects only)

Parasympathetic nervous system controls via cardioinhibitory center and vagus nerves

Crisis has passed

Stroke volume (SV) (ml/beat)

Heart rate (HR) (beats/min)

Cardiac output (CO) (ml/min)

Increases, stimulates

Reduces, inhibits

Initial stimulus

Physiological response

Result

Figure 18.23
Circulation through organs

Liver  Largest share of systemic cardiac output.
Kidney Highest blood flow per gram of tissue.
Heart  Large arteriovenous $O_2$ difference. ↑ $O_2$ demand is met by ↑ coronary blood flow, not by ↑ extraction of $O_2$.

Autoregulation

<table>
<thead>
<tr>
<th>Organ</th>
<th>Factors determining autoregulation</th>
<th>Note: the pulmonary vasculature is unique in that hypoxia causes vasoconstriction. In other organs, hypoxia causes vasodilation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>Local metabolites—$O_2$, adenosine, NO</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>Local metabolites—$CO_2$ (pH)</td>
<td></td>
</tr>
<tr>
<td>Kidneys</td>
<td>Myogenic and tubuloglomerular feedback</td>
<td></td>
</tr>
<tr>
<td>Lungs</td>
<td>Hypoxia causes vasoconstriction</td>
<td></td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>Local metabolites—lactate, adenosine, $K^+$</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Sympathetic stimulation most important mechanism—temperature control</td>
<td></td>
</tr>
</tbody>
</table>
Regulation of blood circulation

Mechanisms of regulation:

Local
- Humoral (chemical) – O₂, CO₂, H⁺
- Nervous
- Enzymatic and hormonal

General
- **Fast** = short-term (regulate blood pressure)
- **Slow** = long-term (regulate blood volume) – several days
Local chemical regulatory mechanisms

The most obvious in the heart and the brain

**Goal:** autonomic regulation of resistance by organ based on its metabolic needs

**Principal:** accumulation of products of metabolism (CO$_2$, H$^+$, lactacid) or consumption of substances necessary for proper function (O$_2$) directly affects smooth muscles of vessels and induce vasodilatation

Local nervous regulatory mechanisms

The most obvious in the skin and mucous

**Goal:** central regulation of blood distribution

**Principal:** Autonomic nervous system

- **Sympaticus**
  - **Vasoconstriction** – activation of α receptors in vessels- noradrenalin (glands, GIT, skin, mucous, kidneys, other inner organs)
  - **Vasodilatation** – activation of β receptors in vessels – adrenalin (heart, brain, skeletal muscles)

- **Parasympaticus - Acetylcholin**
  - **Vasoconstriction** – heart
  - **Vasodilatation** – salivatory glands, GIT, external genitals
Noradrenaline (NA) from sympathetic nerves and circulating adrenaline, increase the heart rate and enhances conduction of the AP.

Acetylcholine (ACh) released from parasympathetic nerves reduces the heart rate and conduction across the AV node.
Local enzymatic and hormonal regulatory mechanisms

**Kinin ↑ = vasodilatation**
- Cells of GIT glands contain kallikrein – changes kininogen to kinin → kallidin → bradykinin (vasodilatation)
- Kinins are any of various structurally related polypeptides, such as bradykinin and kallikrein, that act locally to induce vasodilation and contraction of smooth muscle.
- A role in inflammation, blood pressure control, coagulation and pain.

**Hormones of adrenal medula:** adrenalin (vasodilatation), noradrenalin (vasoconstriction)
General fast (short-term) regulatory mechanisms (1)

Nervous autonomic reflexes

- **Baroreflex**
  - glomus caroticum, glomus aorticum
  - Afferentation: IX and X spinal nerve
  - Centre: medulla oblongata, nucleus tractus solitarii
  - Efferentation: X spinal nerve, sympathetic fibres
  - Effector: heart (atriums), vessels
  - Effect: After acute increase of blood pressure – activation of receptors – **decrease of blood pressure (vasodilatation, decrease of effect of sympathetic)**
General fast (short-term) regulatory mechanisms (2)

**Receptors in the heart**
- Reflex of atrial receptors – mechano- and volumoreceptors – activated by increased blood flow through the heart
- A receptors – sensitive to ↑ of wall tension after systole of atriums
- B receptors – sensitive to ↑ of wall tension after systole of ventricles
- Ventricular receptors – mechano- and chemical receptors - activated in pathological cases
- Hypoxia of myocardium → decrease of heart rate (Bezold-Jarisch reflex) → protection of myocardium of larger damage

**Humoral mechanisms**
- Adrenalin – β receptors → vasodilatation → ↓ peripheral resistance → blood from skin and GIT to skeletal muscles, heart and brain → ↑ minute heart volume
- Noradrenalin – α receptors → vasoconstriction → ↑ blood pressure
- Renin-angiotensin – activated by ↓ pressure in vas afferens
General slow (long-term) regulatory mechanisms

Regulatory mechanisms of water and electrolytes exchanges

**Regulation of total blood volume by kidneys**
- When ↑ blood pressure → ↑ of filtration pressure in glomeruli → ↑ production of urine → ↓ volume of circulating blood → ↓ blood pressure

**Increase of ADH (vasopressin)**
- ↑ ADH → ↑ of the permeability of collecting ductus for the water → water is reabsorbed → ↑ volume of circulating blood → ↑ blood pressure

**Increase of Aldosterone**
- ↑ aldosterone → ↑ reabsorption Na⁺ and water → ↓ volume of urine → ↑ volume of circulating blood → ↑ blood pressure
**Intracardial regulatory mechanisms**

**Ionotropic effect of heart rhythm**
- ↑ heart frequency → ↑ amount of Ca$^{2+}$ that goes into heart cells → ↑ Ca$^{2+}$ available for tubules of sarkoplasmatic reticulum → ↑ Ca$^{2+}$ that is freed by each contraction → ↑ strength of contraction

**Extracardial regulatory mechanisms**

**Cardiomotoric centers**
- **Inhibition** – ncl. Ambiguus (beginning of n. vagus in medulla oblongata)
- **Excitation** - Th1-3 beginning of sympathetic fibres

**Vasomotoric centers**
- In brain stem (medulla oblongata, Pons Varoli)
- In the hypothalamus (controls activity of vasomotoric centers in brain stem)
- Brain cortex – control both the hypothalamus and the brain stem
Blood volume
leads to
Blood pressure

Fast response
Compensation by cardiovascular system
Compensation by kidneys

Slow response

Vasodilation
Cardiac output
Excretion of fluid in urine
Blood volume

Blood pressure to normal

Negative feedback
Stretch of atria of heart due to BP
Releases
Atrial natriuretic peptide (ANP)

Targets

Effects
JG apparatus of the kidney
Hypothalamus and posterior pituitary
Adrenal cortex

Renin release

Effects
Angiotensin II

Inhibits
Collecting ducts of kidneys

Effects
Vasodilation

Results in
Na+ and H2O reabsorption

Blood volume

Results in
Blood pressure
Resistance, pressure, flow

$\Delta P = Q \times R$

Similar to Ohm's law: $\Delta V = IR$.

Resistance = \frac{\text{driving pressure ($\Delta P$)}}{\text{flow ($Q$)}} = \frac{8\eta (\text{viscosity}) \times \text{length}}{\pi r^4}$

Viscosity depends mostly on hematocrit.

Viscosity ↑ in:
1. Polycythemia
2. Hyperproteineic states (e.g., multiple myeloma)
3. Hereditary spherocytosis

Resistance is directly proportional to viscosity and inversely proportional to the radius to the 4th power.

Arterioles account for most of total peripheral resistance → regulate capillary flow.

Ejection fraction (EF)

$\text{EF} = \frac{SV}{EDV} = \frac{EDV - ESV}{EDV}$

EF is an index of ventricular contractility.

EF is normally ≥ 55%.
Stroke volume decreases

Increases resistance to pump blood into the arteries

Arteries become more narrow in diameter

Atherosclerosis, which is deposition of plaque on the inner lining of arteries, is typically only a factor as we age

Resistance in arteries to ejection of blood

(c) Afterload

Increased venous return (occurs with greater venous pressure or slower heart rate)

InCREASES stretch of the heart wall (preload), which results in greater overlap of thick and thin filaments within the sarcomeres of the myocardium

Additional crossbridges form, and ventricles contract with greater force

Stroke volume increases

(a) Venous return

Volume of blood returned to the heart per unit

The opposite is seen with smaller venous return (e.g., occurs with hemorrhage or extremely rapid heart rate)

(b) Inotropic agents

Substances that act on the myocardium to alter contractility

Positive inotropic agents (e.g., stimulation by sympathetic nervous system)

Increased Ca^{2+} levels in the sarcoplasm results in greater binding of Ca^{2+} to troponin of thin filaments within sarcomeres of the myocardium

Additional crossbridges form, and ventricles contract with greater force

Stroke volume increases

The opposite is seen with negative inotropic agents (e.g., calcium channel blockers)

Increased venous return (occurs with greater venous pressure or slower heart rate)

InCREASES stretch of the heart wall (preload), which results in greater overlap of thick and thin filaments within the sarcomeres of the myocardium

Additional crossbridges form, and ventricles contract with greater force

Stroke volume increases

The opposite is seen with smaller venous return (e.g., occurs with hemorrhage or extremely rapid heart rate)

(c) Afterload

Resistance in arteries to ejection of blood

Atherosclerosis, which is deposition of plaque on the inner lining of arteries, is typically only a factor as we age

Arteries become more narrow in diameter

Increases the resistance to pump blood into the arteries

Stroke volume decreases

The opposite is seen with negative inotropic agents (e.g., calcium channel blockers)
Summary of mechanisms that affect cardiac output.

- **Cardiac output**
  - **Heart rate**
  - **Stroke volume**
  - **Contractility**
    - ↑ Sympathetic nerve activity or ↓ parasympathetic nerve activity
    - ↑ Circulating epinephrine
  - ↑ Ventricular end-diastolic volume (Frank–Starling law)
Cardiac output (blood pumped per minute)

Heart rate (beats per minute)

Venous return (volume of blood returning to heart)

Is directly correlated with

Stroke volume (blood pumped per beat)

Is inversely correlated with

Afterload (increased resistance in arteries)

Inotropic agents (alter Ca\(^{2+}\) levels in sarcoplasm)

Is directly correlated with

Chronotropic agents (alter SA node and AV node)

Is inversely correlated with

Positive agents  Negative agents

Positive agents  Negative agents

Positive agents  Negative agents

Positive agents  Negative agents
Starling curve

Force of contraction is proportional to initial length of cardiac muscle fiber (preload).

CONTRACTILE STATE OF MYOCARDIUM

Exercise

Sympathetic nerve impulses

Normal

CHF + digitalis

CHF

Circulating catecholamines
Digitalis
Sympathetic stimulation

Pharmacologic depressants
Loss of myocardium (MI)
## Factors Controlling Blood Pressure

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart</strong></td>
<td></td>
</tr>
<tr>
<td>Peripheral resistance</td>
<td>↑ mean arterial pressure</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>↑ mean arterial pressure</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>↑ pulse pressure</td>
</tr>
<tr>
<td>Arterial compliance</td>
<td>↑ pulse pressure</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>↓ pulse pressure</td>
</tr>
<tr>
<td>Blood Volume</td>
<td>↑ arterial &amp; venous</td>
</tr>
</tbody>
</table>

- **Heart**: The heart is responsible for contracting and expelling blood into the arteries, which can affect blood pressure by changing cardiac output.
- **Peripheral resistance**: This is the resistance to blood flow in the peripheral arteries. An increase in peripheral resistance raises arterial blood pressure.
- **Arterial compliance**: The ability of arterial walls to stretch and return to their original shape. A decrease in arterial compliance can increase pulse pressure.
- **Blood Volume**: The amount of blood present in the circulation, which can affect mean arterial pressure and pulse pressure.

These factors interact to influence blood pressure, which is a critical parameter in cardiovascular health.
### Vascular Baroreceptor Reflex

- Reduced arterial blood pressure decreased baroreceptor activity.
- Increased sympathetic tone to blood vessels.
- Elevated total peripheral resistance and blood pressure.
- (Coronary and cerebral circulation are largely unaffected.)
- Elevated venous tone.
- Reduced venous capacitance, reduced venous volume.
- Increased circulating volume, increased venous return.
- Increased stroke volume, cardiac output and blood pressure.

### Acute Autoregulation

Three mechanisms have been suggested to explain acute autoregulation.

1. **Myogenic mechanisms**
   - Increased pressure increases arteriolar wall tension.
   - Vascular smooth muscle contracts when stretched and relaxed when passively shortened.
   - Action is purely myogenic, no mediators required.
   - Involves stretch sensitive ion channels on the cell membrane.

2. **Tissue pressure**

3. **local metabolites**

### Summary of Metabolic Mediators

- **O₂**: Vasoconstrictor (not pulmonary)(import. brain)
- **Glucose**: vasoconstrictor (at least coronary vessels)
- **K⁺**: Vasodilator (skeletal muscle)
- **CO₂**: vasodilator (not pulmonary)(import. brain)
- **Adenosine**: vasodilator (coronary)
- **H⁺**: vasodilator (import. brain)
- **PO₄³⁻**: vasodilator
- **Osmolarity**: vasodilator
Inputs to blood pressure control includes

- Sympathetic activity
- Parasympathetic activity
- Chemical secretion
- Kidney
Kidney activity regulation

Kidney regulates the secretion of:

- **Renin**
- **Angiotensin II**
- **Aldosterone**

Renin and Angiotensin II controls Total Peripheral Resistance.

Aldosterone controls the urine output.
Pressure Diuresis

- Increased arterial pressure increases filtration and urine production.
- Increased urine production reduces extracellular fluid (ECF) and blood volume.

Urine production is dependent on arterial blood pressure.

A renal output curve (ROC) shows the relationship between pressure and urine volume.

ECF volume is continually lost as urine.

- ECF volume is maintained only if intake is sufficient to balance loss.
- Loss of ECF volume is dependent on blood pressure.
- Increased blood pressure increases ECF volume loss and blood pressure falls.
- Net loss of ECF stops when blood pressure is sufficient for ECF loss from urine to just balances fluid intake.
- Imbalance in osmolarity is controlled by the osmoreceptor system.
- Salt load is generally more important than water as the osmoreceptors regulate water to the salt load.

Figure 19-1. A typical renal output curve measured in a perfused isolated kidney, showing pressure diuresis when the arterial pressure rises above normal.
Auscultation of the heart

Aortic area:
- Systolic murmur
- Aortic stenosis
- Flow murmur
- Aortic valve sclerosis

Pulmonic area:
- Systolic ejection murmur
- Pulmonic stenosis
- Flow murmur (e.g., atrial septal defect)*

Left sternal border:
- Diastolic murmur
- Aortic regurgitation
- Pulmonic regurgitation

Tricuspid area:
- Pansystolic murmur
- Tricuspid regurgitation
- Ventricular septal defect
- Diastolic murmur
- Tricuspid stenosis
- Atrial septal defect*

Mitral area:
- Systolic murmur
- Mitral regurgitation
- Diastolic murmur
- Mitral stenosis

Where to listen:
APT M

*ASD commonly presents with a pulmonary flow murmur (↑ flow through pulmonary valve) and a diastolic rumble (↑ flow across tricuspid). The murmur later progresses to a louder diastolic murmur of pulmonic regurgitation from dilatation of the pulmonary artery.
Heart Sounds

S4
S1 = Mitral, Tricuspid then pulmonary artery valve, aortic valve
S2 = Aortic, Pulmonary valve then tricuspid mitral valve
S3

- Right side lower pressure open first, closed second
- Left side higher pressure open second, closed first.
Heart sounds are not caused by opening of the valves.

Heart sounds (lub-dup) are associated with closing of heart valves:

- First sound occurs as AV valves close and signifies beginning of systole.
- Second sound occurs when SL valves close at the beginning of ventricular diastole.

*S1* forms the "lub" of "lub-dub".

*S2* forms the "dub" of "lub-dub".

S1, S2, S3 sound like "Ken-tuck-y" (lub-dub-dub).
Effects of inhalation/expiration

• **Inhalation** pressure causes an **increase in the venous blood return to the right side of the heart**.
  • Therefore, **right-sided murmurs generally increase in intensity with inspiration**.
  • The increased volume of blood entering the right sided chambers of the heart restricts the amount of blood entering the left sided chambers of the heart.
  • This causes **left-sided murmurs to generally decrease in intensity during inspiration**.

**Expiration**, the opposite hemodynamic changes occur.

• **This means that left-sided murmurs generally increase in intensity with expiration**.
• **Having the patient lie supine and raising their legs up to a 45 degree angle facilitates an increase in venous return to the right side of the heart producing effects similar to inhalation-increased blood flow.**
S1:
✧ The S1 sound is normally the first heart sound heard.
✧ The S1 is best heard in the *mitral area*, and corresponds to closure of the mitral and tricuspid (AV) valves.
✧ A normal S1 is low-pitched and of longer duration than S2.

S2:
✧ The S2 sound is normally the second sound heard.
✧ The S2 is best heard over the *aortic area*, and corresponds to closure of the pulmonic and aortic valves.
✧ A normal S2 is higher-pitched and of shorter duration than S1.

- The flow from the ventricles is more forceful than the flow from the atria.
  - Therefore, S2 will normally be the louder sound.
Gradations of Murmurs (Defined based on use of an acoustic, not a high-fidelity amplified electronic stethoscope)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Very faint, heard only after listener has &quot;tuned in&quot;; may not be heard in all positions. Only heard if the patient &quot;bears down&quot; or performs the Valsalva maneuver.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Quiet, but heard immediately after placing the stethoscope on the chest.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Moderately loud.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Loud, with palpable thrill (i.e., a tremor or vibration felt on palpation)</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Very loud, with thrill. May be heard when stethoscope is partly off the chest.</td>
</tr>
<tr>
<td>Grade 6</td>
<td>Very loud, with thrill. May be heard with stethoscope entirely off the chest.</td>
</tr>
</tbody>
</table>