Sodium balance disorders: hypervolemia and edema
Zsolt Bagosi, MD, PhD
Basic principles

- Disorders of sodium (Na) balance are manifested as hypovolemia or hypervolemia.

- Disorders of water ($H_2O$) balance are manifested as hyponatremia or hypernatremia.
Hypervolemia

- Definition of hypervolemia: the volume of the extracellular fluid (ECF) compartment is expanded in relation to its capacitance

- Forms of hypervolemia
  - Without clinical symptoms: ↑Na intake is matched by ↑Na excretion
    - Salt sensitivity (present in 20% of population): high salt intake → hypertension, without hypervolemia
  - With clinical symptoms of volume overload: Na retention is ongoing and inappropriate for the ECF volume (true hypervolemia)

- Causes of hypervolemia
  - 1. Effective circulatory volume is increased
  - 2. Effective arterial blood volume (EABV, an unmeasured, functional parameter of tissue perfusion) is decreased
Effective circulatory volume is increased

<table>
<thead>
<tr>
<th>Hormonal</th>
<th>Primary H₂O retention</th>
</tr>
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<tbody>
<tr>
<td>Primary Na retention</td>
<td>Primary aldosteronism: Conn syndrome</td>
</tr>
<tr>
<td></td>
<td>Hypercortisolemia: Cushing’s syndrome</td>
</tr>
<tr>
<td></td>
<td>Na level is normal (due to aldosterone escape), hypertension is present, no edema</td>
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<tr>
<td></td>
<td>Primary polydipsia</td>
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<tr>
<td></td>
<td>Hyponatremia with no hypertension and no edema</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Renal</th>
<th>Secondary Na retention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Na retention</td>
<td>Heart failure (systolic and diastolic dysfunction)</td>
</tr>
<tr>
<td></td>
<td>Cirrhosis (portal hypertension)</td>
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<td></td>
<td>Pregnancy and premenstrual edema</td>
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<td></td>
<td>Idiopathic edema</td>
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<tr>
<td>Intrinsic kidney disease</td>
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<td>Acute kidney injury</td>
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<tr>
<td>Chronic kidney disease</td>
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<td>Acute and chronic glomerular disease</td>
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Effective arterial blood volume (EABV) is reduced

- Relative hypovolemia: no Na loss, but ↑ capacitance of ECF compartment: due to ineffective arterial blood volume the symptoms resemble hypovolemia
- Due to decrease in effective arterial blood volume → compensatory increase of EC volume → edema development
  - 85% of the blood volume is on the venous side: an increase can occur relatively undetected
  - 15% of the blood volume is on the arterial side: a decrease is sensed relatively early by systems regulating the Na and H₂O balance

<table>
<thead>
<tr>
<th>Extrarenal</th>
<th>Renal</th>
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<tbody>
<tr>
<td>Generalized edema (heart failure, cirrhosis, malnutrition)</td>
<td>Generalized edema (nephrotic syndrome)</td>
</tr>
<tr>
<td>Generalized vasodilation (sepsis, pregnancy, cirrhosis)</td>
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<tr>
<td>Third-space loss (pancreatitis, peritonitis, ileus, rhabdomyolysis)</td>
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</tbody>
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Compensatory mechanisms

Activation of the sympathetic nervous system (SNS)

Activation of the renin-angiotensin-aldosterone system (RAAS)
### Definition and major causes of edema

- **Definition:** A clinically apparent accumulation in the interstitial fluid volume

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<thead>
<tr>
<th>Major causes of edematous states</th>
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<tbody>
<tr>
<td><strong>Increased capillary hydraulic pressure</strong></td>
<td><strong>Decreased plasma oncotic pressure</strong></td>
</tr>
<tr>
<td>Increased plasma volume due to renal Na retention</td>
<td>Protein loss: nephrotic syndrome, protein-losing enteropathy</td>
</tr>
<tr>
<td>Venous obstruction</td>
<td>Reduced albumin synthesis: liver disease, malnutrition</td>
</tr>
<tr>
<td>Hepatic cirrhosis</td>
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<tr>
<td>Acute pulmonary edema</td>
<td></td>
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<tr>
<td>Local venous obstruction</td>
<td></td>
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<tr>
<td>Decreased arteriolar resistance</td>
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<tr>
<td>Ca channel blockers (?)</td>
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<td>Idiopathic edema (?)</td>
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<tr>
<td><strong>Increased capillary permeability</strong></td>
<td><strong>Lymphatic obstruction</strong></td>
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<tr>
<td>Burns, trauma, inflammation or sepsis</td>
<td>Lymph node enlargement</td>
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<td>Allergic reactions, including certain forms of angioneurotic edema</td>
<td>Increased lymph production</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
<td>Hypothyroidism</td>
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<td>Malignant ascites</td>
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# Major forms and pathomechanism of edema

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<th>Systemic</th>
<th>Local</th>
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<tr>
<td>Cardiac (anasarca, due to right heart failure)</td>
<td>Pulmonary (due to left heart failure)</td>
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<tr>
<td>Hepatic (ascites, due to cirrhosis)</td>
<td>Inflammatory edema</td>
<td></td>
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<td>Renal (due to nephrotic syndrome or chronic kidney disease)</td>
<td>Limb edema (e.g. due to thrombophlebitis)</td>
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<tr>
<td>Protein-energy malnutrition (kwashiorkor)</td>
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- Generalized edema is caused by low cardiac output or increased arterial vasodilation
- Pathomechanism: due to decrease in EABV → compensatory increase of EC volume → fluid accumulation (2.5 - 3 liter) in the interstitial space → anasarca (severe, pitting edema), pleural effusion

  - Compensatory mechanisms: neurohumoral/baroreceptor reflexes
    - Activation of sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS) and non-osmotic ADH release
    - Effective compensation after hypovolemia due to bleeding, vomiting, diarrhea
    - Ineffective compensation in hypervolemia - the role of kidney is maladaptive and therefore adverse effects develop: edema, cardiac remodeling, increased preload / afterload, pulmonary edema, hyponatremia
Compensation of the low cardiac output

- Reduced extracellular fluid volume
- Low output heart failure, pericardial tamponade, constructive pericarditis
- Low cardiac output, effective arterial volume
- Activation of ventricular and arterial receptors
  - SNS stimulation
  - Increased systemic and renal arterial vascular resistance
- Restoration of effective arterial volume
- Reduced oncotic pressure and/or increased capillary permeability
- Renal Na+ retention

Harrison's Principles of Internal Medicine, 19th Edition
by Dennis Kasper, Anthony Fauci, Stephen Hauser, Dan Longo, J. Larry Jameson, Joseph Loscalzo, 2015
Compensation of the increased arterial vasodilation
Cardiac edema (due to congestive heart failure)

- **Pathomechanism:**
  - Decrease in cardiac output and mean arterial pressure → activation of SNS, RAAS and non-osmotic release of ADH
  - Hyponatremia is developed due to non-osmotic ADH release and aggravated by concomitant stimulation of the catecholamine and aldosterone production, which decrease distal fluid delivery by decreasing glomerular filtration rate (GFR) and enhancing tubular Na reabsorption
  - Endothelin-1 (ET-1) a potent vasoconstrictor released by endothelial cells also contributes to the renal vasoconstriction, Na retention and edema
  - Natriuretic peptides, such as ANP and BNP, released from the atrial and ventricular myocytes, respectively, induce compensatory natriuresis, diuresis and vasodilation

- **History:** dyspnea with exertion prominent, often followed by dyspnea at rest, orthopnea and paroxysmal nocturnal dyspnea

- **Physical examination:** elevated jugular venous pressure, ventricular (S3) gallop, displaced apical pulse, peripheral cyanosis, cool extremities, small pulse pressure

- **Laboratory findings:** elevated urea nitrogen-to-creatinine ratio, reduced serum Na level, elevated natriuretic peptide levels (BNP used as marker!)
Pathomechanism of congestive heart failure

Right heart failure
- Backward congestion
  - Peripheral edema (weight gain)
  - Increased pressure in the jugular veins
  - Pulmonary crepitations, pleural effusions
  - Tachycardia, tachypnoe
  - Cardiomegaly
  - Hepatomegaly, ascites
  - Cachexia (weight loss)

Forward insufficiency
- Hypoxia
- Cyanosis
- Fatigue

Objective signs
- Venous overfilling

Cardiomyopathies
- Congenital heart diseases
- Acquired valvular diseases

Left heart failure
- Backward congestion
- Dyspnea on exertion
- Dyspnea at rest
- Orthopnoea
- Paroxysmal nocturnal dyspnea
- Asthma cardiale
- Cheyne-Stokes breathing
- Pulmonary edema

Forward insufficiency
- Fatigue
- Weakness
- Syncope

Subjective symptoms
- Arterial underfilling

Systemic hypertension
- Myocardial infarction

Pulmonary hypertension
- Pulmonary diseases

Peripheral edema (weight gain)
- Increased pressure in the jugular veins
- Pulmonary crepitations, pleural effusions
- Tachycardia, tachypnoe
- Cardiomegaly
- Hepatomegaly, ascites
- Cachexia (weight loss)

Hypoxia
- Cyanosis
- Fatigue

Dyspnea on exertion
- Dyspnea at rest
- Orthopnoea
- Paroxysmal nocturnal dyspnea
- Asthma cardiale
- Cheyne-Stokes breathing
- Pulmonary edema

Fatigue
- Weakness
- Syncope

SNS and RAAS activation
- Non-osmotic ADH release

Netter's Internal Medicine, 2nd Edition
by Marschall S. Runge and M. Andrew Greganti, 2008
Hepatic edema (ascites, due to liver cirrhosis)

- Pathomechanism:
  - Characterized by formation of ascites, an accumulation of excess fluid (>500 ml) in the peritoneal cavity due to increased hydrostatic pressure (intrahepatic, rare in prehepatic hypertension), decreased oncotic pressure (due to decreased albumin production) and increased lymphatic drain (as a compensation of sinusoidal hypertension)
  - Retention of Na and H$_2$O despite an actual increase in total body Na, due to the effects of increased aldosterone and ADH levels
  - Retention of Na and H$_2$O is compensated by increased prostaglandin (PG) production

- History: dyspnea uncommon, except if associated with significant degree of ascites, ethanol abuse

- Physical examination: presence of ascites, jugular venous pressure normal or low, blood pressure lower than in cardiac or kidney disease, additional signs of chronic liver disease (jaundice, palmar erythema, Dupuytren’s contracture, spider angiomata, gynecomastia, asterixis, hepatic encephalopathy)

- Laboratory findings: reductions in serum albumin, cholesterol, transferrin, fibrinogen, elevation in liver enzymes, hypokalemia, respiratory alkalosis, macrocytic anemia
Stages of ascites formation

- Stages of ascites formation
  - I. Pre-ascitic phase: splanchnic vasodilation
    - The kidneys retain Na and H₂O before the onset of ascites
    - Vasodilators, such as NO, glucagon, vasoactive intestinal peptide (VIP), substance P, platelet-activating factor (PAF) and PG produce splanchnic and systemic vasodilation (opening of a-v shunts) → arterial underfilling
    - Decrease in EABV leads to hypotension → renal Na and H₂O retention to maintain volume
    - Increase in cardiac output and volume → compensated hyperkinetic circulation
  - II. Ascitic phase: arterial underfill
    - Hepatic sinusoidal block due to cirrhosis → portal hypertension ↑ → congestion in the GI tract
    - Cardiac output and intravascular volume depletion, development of underfill (ascitic) phase
    - Catecholamine, aldosterone and ADH level increase progressively → Na and H₂O retention → fluid transudation into the abdominal cavity
  - III. Last phase: venous overfill
    - Catecholamine, aldosterone and ADH levels are normalized
    - Mean arterial pressure, water excretion and serum sodium levels are reduced
    - The latter is a bad prognostic sign → hepatorenal syndrome: extreme a. afferent vasoconstriction due to generalized SNS activation
Pathomechanism of ascites formation

Alcohol
Toxins
Viruses
Immune diseases
Genetic diseases

Cirrhosis

Increased resistance to portal flow

Portal hypertension

Splanchnic vasodilatation

Increase in splanchnic capillary pressure

Lymph formation that exceeds lymph return

Ascites

Arterial underfilling

Activation of vasoconstrictor and antinatriuretic factors

Sodium and water retention

Expansion of plasma volume

Dilutional hyponatremia

Impaired free-water excretion

Arterial and cardio-pulmonary receptors

Renal vasoconstriction

Hepatorenal syndrome

Pathophysiology of Disease: An Introduction to Clinical Medicine, 7th Edition
by Gary D. Hammer and Stephen J. McPhee, 2014
Renal edema (due to nephrotic syndrome)

● Pathomechanism:
  ○ Underfill theory: albuminuria leading to intravascular volume contraction during acute phase
    ■ Mechanism: activation of SNS, RAAS and non-osmotic ADH release
    ■ Kidney function: good, GFR > 75% and serum albumin < 20 g/l, no hypertension
  ○ Overfill theory: primary defect in Na excretion in the chronic stage or during relapses
    ■ Mechanism: yet to be explained, but plasmin is present in the tubular fluid and activates epithelial Na channels in principal cells of the cortical collecting ducts → Na retention + resistance to natriuretic peptides
    ■ Kidney function: deteriorating, GFR < 50%, serum albumin > 20 g/l, hypertension

● History: minimal change disease or diabetes mellitus in childhood

● Physical examination: periorbital and generalized edema, rarely hypertension

● Laboratory findings: proteinuria (≥ 3.5 g/day), hypoalbuminemia, hypercholesterolemia, microscopic hematuria
Pathomechanism of nephrotic syndrome

Minimal change glomerulopathy (MCD)
Membranous nephropathy (MNP)
Focal segmental glomerulosclerosis (FSGS)

Underfill theory
GFR > 75 %

Proteinuria
Increased glomerular permeability

Hypertension
Loss of endogenous anticoagulants and HDL-cholesterol

Na retention
H2O retention

Edema

Hypoproteinemia

Hyperlipidemia

Hypercoagulability
Renal vein thrombosis

Iron, vitamin B12 and folate deficiency
Anemia and other deficiency states

SNS activation
RAAS activation
Non-osmotic ADH release
Decreased EABV

Iron, vitamin B12 and folate deficiency
Decreased EABV

Netter's Internal Medicine, 2nd Edition
by Marschall S. Runge and M. Andrew Greganti, 2008
Renal edema (due to chronic kidney disease)

● Pathomechanism:
  ○ Progressive loss of nephron mass is compensated initially by polyuria (adaptation by glomerular hyperfiltration and decreased tubular reabsorption of Na); single nephron GFR (snGFR) is increased
  ○ Later it results in oliguria and uremia (characterized by retention of toxic wastes in the blood and maladaptation leading to renal osteodystrophy and anemia); global GFR decreases progressively
  ○ Edema develops due to hypoproteinemia and RAAS activation and is manifested in stage IV and V (end-stage renal disease, ESRD)

● History: edema associated with uremic signs and symptoms, including decreased appetite, disturbances of taste and smell, disturbances of sleep, difficulty concentrating, restless legs syndrome, muscle cramps and convulsions, seizures, dyspnea can be present, but less prominent than in congestive heart failure

● Physical examination: elevated blood pressure, hypertensive retinopathy, uremic fetor, pericardial friction rub in advanced cases

● Laboratory findings: elevation of serum creatinine and cystatin C levels, albuminuria, hyperkalemia, metabolic acidosis, hyperphosphatemia, hypocalcemia, normocytic anemia
Pathomechanism of chronic kidney disease

Diabetes mellitus  
Systemic hypertension  
Chronic glomerulonephritis

Progressive loss of nephron mass

Adaptation

Glomerular hyperfiltration  
Polyuria  
Decreased tubular Na reabsorption

I. stage: GFR > 90 ml/min

Increased glomerular permeability

II. stage: GFR < 90 ml/min

Proteinuria  
Hyperfiltration damage  
Hypertension

Increased snGFR

III. stage: GFR < 60 ml/min

Secondary FSGS and tubulointerstitial fibrosis  
Edema

IV. stage: GFR < 30 ml/min

Decreased GFR  
Uremia

Oliguria

V. stage: GFR < 15 ml/min

Renal osteodystrophy  
Anemia

Netter's Internal Medicine, 2nd Edition  
by Marschall S. Runge and M. Andrew Greganti, 2008
Other causes of edema

<table>
<thead>
<tr>
<th>Endocrine</th>
<th>Drugs</th>
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<tbody>
<tr>
<td>Hypothyroidism (myxedema)</td>
<td>Nonsteroidal anti-inflammatory drugs</td>
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<tr>
<td>Hyperthyroidism (pretibial myxedema secondary to Basedow-Graves’ disease)</td>
<td>Antihypertensive agents</td>
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<tr>
<td>Pregnancy</td>
<td>Calcium channel antagonists</td>
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<tr>
<td>In the 1st trimester systemic arterial</td>
<td>α-adrenergic antagonists</td>
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<tr>
<td>vasodilation may occur due NO, PG, relaxin, placental a-v fistulas, mean arterial pressure ↓, cardiac output and renal blood flow ↑; compensatory mechanisms are activated due to arterial underfilling (enhanced chance to develop edema)</td>
<td>Thiazolidinediones</td>
</tr>
<tr>
<td>Osmotic threshold for ADH release and thirst is decreased causing polydipsia; vasopressinase produced by placenta inactivates oxytocin and ADH causing polyuria</td>
<td>Steroid hormones</td>
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<td></td>
<td>Glucocorticoids</td>
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<td></td>
<td>Anabolic steroids</td>
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<td>Estrogens</td>
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<td>Progestins</td>
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<td>Cyclosporine</td>
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<td>Growth hormone</td>
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<td>Immunotherapies</td>
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</tbody>
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References
Sodium balance disorders: hypovolemia, circulatory shock and syncope
Hypovolemia (a sodium balance disorder)

- Hypovolemia: the volume of the extracellular fluid compartment (ECF) is reduced in relation to its capacitance
  - Absolute hypovolemia: combined Na\(^+\) and water loss exceeding fluid intake leading to reduced ECF
  - Relative hypovolemia: no Na\(^+\) deficit, capacitance of ECF ↑ (see before)
    - Effective arterial blood volume (EABV) reduced
  - Dehydration: water loss only or water loss > water intake that results in elevation of plasma Na\(^+\) and subsequent intracellular volume contraction
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<td><strong>Renal</strong></td>
</tr>
<tr>
<td>Urinary Na is low &lt; 10 mmol/l, with oliguria and hyperosmolar urine</td>
<td>Urinary Na is normal or high &gt; 20 mmol/l, no oliguria; osmolality varies</td>
</tr>
<tr>
<td><strong>Decrease in fluid intake</strong></td>
<td><strong>Defective salt-water absorption</strong></td>
</tr>
<tr>
<td><em>Per os</em>: infant, geriatric and psychiatric patients</td>
<td>Tubular nephropathies: renal tubular acidosis, Bartter’s syndrome, nephrogenic diabetes insipidus, interstitial nephritis</td>
</tr>
<tr>
<td>Parenterally: long-lasting unconsciousness, lack of sufficient water supplementation (infusion)</td>
<td>Acute renal failure (polyuric phase), chronic diuretic abuse, postobstructive diuresis, chronic kidney failure (polyuric phase)</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td><strong>Osmotic diuresis</strong></td>
</tr>
<tr>
<td>1. External loss: hemorrhage, trauma, surgery, hemophilia, anticoagulants, thrombolytics</td>
<td>HCO₃⁻, glucose (diabetic ketoacidosis, hyperosmolar coma), mannitol, glycerol, urea</td>
</tr>
<tr>
<td>2. Internal loss: aneurism rupture, hemothorax, hematoma</td>
<td><strong>Hormone deficiency</strong></td>
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<tr>
<td><strong>GI tract</strong></td>
<td>Vasopressin deficit (central or peripheral diabetes insipidus)</td>
</tr>
<tr>
<td>1. External loss: vomiting, diarrhea – especially infants, children and elderly patients. GI fistulas, GI fluid drain</td>
<td>Mineralocorticoid deficiency – aldosterone insufficiency (primary hyperaldosteronism, Addison’s disease, hyporeninemic hypoaldosteronism: salt wasting + hyperchloremic acidosis)</td>
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<td>2. Internal loss: peritonitis, pancreatitis, ileus</td>
<td><strong>Skin</strong></td>
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<tr>
<td><strong>Lung</strong> (hyperventilation, wind-instrument player)</td>
<td><strong>1. External loss: sweating, cystic fibrosis, lacrimation, skin inflammation (generalized exfoliative dermatitis)</strong></td>
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<td><strong>2. Internal loss: excessive burn, inflammation</strong></td>
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● Laboratory changes in hypovolemia
  ○ Increased blood urea nitrogen (BUN) – prerenal azotemia
  ○ Plasma protein and hematocrit ↑, plasma Na⁺ ↓↔↑ depends on the cause
  ○ Alkalosis: vomiting, diuretics
  ○ Acidosis
    ■ Hypovolemia – reduced oxidative processes – increased formation of acidic metabolites
    ■ Poor circulation – retention of acids by kidney
  ○ Urine: Na⁺ (useful in differentiation – see above), osmolality and specific gravity↑
• Adaptation to volume depletion depends on the rate, magnitude, composition of fluid loss and the renal and vascular responses

• Clinical manifestation
  ○ Thirst, reduced skin turgor, sunken eyes
  ○ Elevation of body temperature (especially in children)
  ○ Orthostatic hypotension & tachycardia, reduced cardiac output, circulatory collapse

• Inadequate/insufficient adaptation → hypovolemic shock
  ○ Volume depletion or hypovolemia ≠ hypovolemic (traumatic) shock
Clinical features: pallor, tachycardia, hypotension, dyspnea, diaphoresis
10% acute volume loss – compensated by tachycardia, increased systemic vascular resistance
20% acute volume loss – mild hypotension, decreased cardiac output, marked systemic vascular resistance, mild lactic acid accumulation
40% acute volume loss – severe hypotension, with signs of shock, if persists for more than 2 hours the shock is irreversible

<table>
<thead>
<tr>
<th>Loss of 1 liter fluid</th>
<th>%</th>
<th>Signs</th>
</tr>
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<tr>
<td>Whole body water – water loss</td>
<td>2.5</td>
<td>Minimal effect on the circulation</td>
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<tr>
<td>Extracellular water – salt and water loss</td>
<td>6.6</td>
<td>Oliguria, tachycardia</td>
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<td>Intravascular loss – bleeding</td>
<td>20</td>
<td>Severe oliguria, circulatory shock</td>
</tr>
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</table>
Definition & classification of circulatory shock

- Shock is an acute circulatory failure with profound and widespread reduction of effective tissue perfusion leads first to reversible, and then if prolonged, to irreversible cellular injury
  - Arterial hypotension (< 90 mmHg), tachycardia
  - Signs of hypoperfusion
    - Cold, clammy, cyanotic skin
    - Oliguria
    - Altered mental states (dazed, confused)
  - Elevated lactate levels > 1.5 mmol/l
Blood pressure = cardiac output \times \text{systemic vascular resistance}

Cardiac output ↓

Heart rate

Bradycardia or tachycardia

Stroke volume ↓

Systemic vascular resistance ↓

Low systemic vascular resistance – vasodilation

Classification of circulatory shock

1. Distributive shock
2. Hypovolemic shock
3. Cardiogenic shock
4. Obstructive shock

• Inflow problems (preload ↓) obstruction or hypovolemia
• Intrinsic pump problems
• Outflow obstruction: (afterload ↑)
4. Obstructive shock

Mechanical obstruction of blood flow through great veins, heart or lungs

Inflow obstruction (impaired diastolic filling i.e. preload ↓)
- Intrathoracic tumor, tension pneumothorax, constrictive pericarditis, restrictive CMP, cardiac tamponade

Outflow obstruction (impaired systolic contraction i.e. afterload ↑)
- Pulmonary embolism (massive, saddle), severe pulmonary hypertension, severe / acute tricuspid obstruction

Cardiogenic shock

1. Myocardial insufficiency
   - MI, myocardial depression
2. Tachy / brady arrhythmias
3. Acute mechanical disturbances
   - Valvular rupture, retrograde ao dissection

Distributive shock

Hypovolemic (traumatic) shock
Hemorrhagic (traumatic, non traumatic) and non hemorrhagic fluid loss
Stages of shock

- Stages of shock can be explained the best by using hypovolemic / traumatic shock as a model
  - 1. Compensated shock
    - Reflex compensatory mechanisms, perfusion to vital organs is maintained
  - 2. Decompensated / progressive shock
    - Generalized tissue hypoperfusion, metabolic acidosis
  - 3. Irreversible shock
    - Multiple organ dysfunction syndrome (MODS), death
Compensated shock

1. Neural or immediate response (within minutes)
   - Mild volume loss: activation of low pressure receptors (atria, pulmonary vessels, great veins and ventricles)
   - Further volume loss: activation of high pressure stretch receptors (aortic arch, carotid sinus)
   - MAP ≤ 50 mmHg: activation of chemoreceptors (carotid and aortic bodies)
   - MAP ≤ 40 mmHg: CNS ischemic response; activation of sympathetic and parasympathetic nervous system to increase heart rate, myocardial contractility, peripheral arterial and venous tone leading to shunting of blood to vital organs

   ■ Due to rapid adaptation, baroreceptor mechanisms act only for a few hours
2. Intrinsic or intermediate response (over a period of hours)
   ○ Mobilization of endogenous blood storage: abdominal veins, spleen, liver (~ 300 ml)
   ○ Auto-transfusion:
     ■ reduced capillary pressure (Starling’s effect) provides fluid movement from the interstitium to the vascular compartment (~1 l in the 1st h)
     ■ protein (albumin) moves from the interstitium to plasma (~ 2 l in 24-48 h)
     ■ osmotic effect of glucose (due to sympathetic activation): for each mmol/l increase in sugar app. 17 ml fluid from IC

3. Humoral or delayed response (within days) to provide renal retention of fluid and increase intravascular volume
   ○ Release of vasopressin (5-10% decrease of blood volume)
   ○ Stimulation of thirst
   ○ Activation of RAAS
Sepsis

Activation of Ventricular and Arterial Receptors

Nonosmotic Vasopressin Stimulation

RENAL WATER RETENTION

V₂ receptor

Stimulation of Sympathetic Nervous System

PERIPHERAL AND RENAL ARTERIAL VASCULAR RESISTANCE

MAINTENANCE OF ARTERIAL CIRCULATORY INTEGRITY

Systemic vascular resistance↓

Cardiac output ↓

Fluid intake

Fluid replacement

Activation of the Renin-Angiotensin-Aldosterone System

RENAL SODIUM RETENTION

Adrenal gland activation

+ Adrenaline

Noradrenaline

↓ Extracellular Fluid Volume
Summary of compensatory mechanisms

● Maximize cardiac performance (↑contractility)
● Redistribute perfusion to vital organs (brain, heart, kidney) at the expense of GI, skin, muscle
● Maintain normal venous pressure by
  ○ ↑ Volume
    ■ Fluid redistribution to vascular space – auto-transfusion
    ■ Decrease renal loss (↑ aldosterone, vasopressin)
  ○ ↑ Pressure
    ■ Decrease in venous capacitance / pooling (↑ angiotensin, vasopressin, sympathetic activity and circulating epinephrine)
● Maintain cellular function: optimize oxygen unloading to the periphery (pH↓, pCO₂↑, 2.3 DPG↑, temperature↑, Sulf Hb↑)
Decompensated (progressive) shock

- Compensatory mechanisms are not intended for long-term use to maintain blood pressure
- Detrimental effects of compensatory mechanisms:
  - Cardiac dysfunction: decreased force of contraction, decreased coronary blood flow, myocardial ischemia
  - Peripheral effects: relaxation of precapillary sphincters due to acidosis (arterial vasodilatation), continued contraction of postcapillary sphincters, peripheral pooling of blood → decreased venous return → decreased cardiac output
  - Lactic acidosis, low intracellular ATP → cell dysfunction
    - Arrhythmias and conduction disturbances
Cardiogenic dysfunction
– Impaired coronary perfusion causing myocardial hypoxia, systolic and diastolic dysfunction, arrhythmias

Sympathetic escape
– Loss of vascular tone (↓ SVR) causing progressive hypotension and organ hypoperfusion
– Increased capillary pressure causing increased fluid filtration and hypovolemia
○ Endothelial damage
  ■ Vasodilator substances, activated leukocytes ↑
  ■ Permeability is increased → fluid extravasation → tissue edema
○ Altered gene expression
  ■ Heat shock proteins – apoptosis ↑
  ■ Cytokines, adhesion molecules, inducible NO synthesis ↑
○ Release of inflammatory mediators and free radicals
  ■ Systemic release of endotoxin, TNF-α, IL-1→ sepsis / septic shock
  ■ Free radicals are released during ischemia/reperfusion
    □ DNA damage, protein inactivation, lipid peroxidation, cell lysis & tissue injury
Irreversible shock

- Postcapillary sphincter relaxation, loss of peripheral vascular resistance, decrease of cardiac output
- Accumulation of washout products
  - *Rouleaux* formation (lung microembolisation)
  - Systemic metabolic acidosis
- Irreversible shock leads to shock lung, acute renal failure, gastrointestinal ulcerations, disseminated intravascular coagulation (DIC), MODS
  - See Complications of shock
Oxigen delivery/demand

+ 

Compensated shock
Decompensated shock
Acute irreversible shock
Subacute irreversible shock
Subacute reversible shock

Exsanguination
Ongoing hemorrhage
Acidosis
Coagulopathy

Septic shock
MODS, DIC
Vasodilatory shock

Time

†

Ongoing hemorrhage
Acidosis
Coagulopathy
Distributive shock

- Due to loss of blood vessel tone (neurogenic, anaphylactic and vasodilatory shock) or enlargement of vascular compartment (septic shock)

1. Neurogenic shock
   - Loss of sympathetic tone of arterial smooth muscle due to acute brainstem injury, epidural anesthesia or spinal cord injury (above the midthoracic level)
   - Hypotension in spinal cord injury is usually a transient phenomenon (3-7 day)
2. Anaphylactic shock: presence of vasodilators in the blood
   ○ Side effects, pharmacologic effects or overdose of vasodilator
drugs: opiates, sedato-hypnotics, ß-blockers, anticholinergics,
antidepressants, nitrates, and antihypertensives
   ○ The most severe form of systemic immediate hypersensitivity
reaction: response to allergen that directly enters the blood (e.g.,
hypersensitivity to bee/wasp/hornet stings, penicillin, foods,
latex)
   ■ Basophils and mast cells are enlisted throughout the body
   ■ Systemic histamine, PAF, PG, LT and TNF-\(\alpha\) release
   □ Sudden vasodilation (arterioles and venules) and fluid loss from
the bloodstream → hypotensive shock complicated by broncho-
constriction, wheezing, laryngeal swelling and obstruction
(death)
3. Hypoadrenal shock: acute adrenocortical failure or Addisonian crisis
   - Abrupt discontinuation of steroid therapy
   - Waterhouse-Friderichsen syndrome (acute meningococcal sepsis)
     - DIC, extensive purpuras, rapidly progressive hypotension → shock, massive bilateral adrenal hemorrhage → acute adrenocortical insufficiency & death

4. Septic shock: the most common type of distributive shock
Septic shock

- Sepsis is defined as life-threatening organ dysfunction (determined by sepsis-related organ failure assessment [SOFA] scoring system) caused by a dysregulated host response to infection.
- Septic shock is defined as the subset of sepsis in which underlying circulatory and cellular or metabolic abnormalities are profound enough to increase mortality substantially.
  - Genetic variations in the innate immune system (receptors, adhesion molecules etc) & risk factors (alcohol) can contribute to the development of septic shock. *H. influenzae* vaccination is protective.
○ Septic shock can develop in immunosuppressed (HIV, cirrhosis, asplenia, autoimmune) & cancer patients, elderly, after surgery, infections (urinary / respiratory / GI tract) & extended burns

● Stages of septic shock
○ Initially normal / elevated cardiac output, normal stroke volume, tachycardia and decreased systemic vascular resistance (normovolemic shock)
○ Venodilatory fluid leakage – preload ↓(volume replacement can correct)
Infection controlled

Host defenses

Infection

Toxins

Dysregulated

Inadequate

Overwhelming infection

Death

Multiple organ failure

Sepsis

Survival

Adequate

Survival
Molecular & cellular changes in septic shock

- A self-reinforcing hyperinflammatory response: TNF-α, IL-1 ↑
  - Detection of PAMPs and DAMPs by innate immune cells & increased survival of these cells (↓ apoptosis)
  - Increased adhesion and chemokine molecule expression by endothelial cell
- Neutrophil hyperfunction
  - NET formation, release of pro-coagulants to make place for platelet activation
  - ↑ chemotactic response to CXC → ARDS, MSOD
- Acute phase protein secretion: complement, fibrinogen
- Microparticle release from leukocytes, endothelial cells, platelets: tissue (TF) & von Willebrand factor
- Upregulation of TF expression by monocytes + NET + microparticles → activation of clotting (microthrombosis, DIC)
Systemic changes in septic shock

- Systemic injury mediated by inflammatory cytokines
  - ROS & NOS↑: protein, lipid, DNA damage & mitochondrial dysfunction
  - Complement activation (C3a, C5a): enhancement of the inflammatory response (ROS, granulocyte enzyme release, TF expression, ↑vasodilation & vascular permeability), adrenal medullary cell death
  - Development of DIC (occurs in 30-50% of patients)
    - Protease-activated receptors provide molecular link between inflammation and clotting
    - Blood coagulation is dysregulated in septic shock: initial activation of clotting, followed by suppression of fibrinolysis
DIC in shock

1. Entry of procoagulants* into circulation; systemic activation of clotting & platelets → fibrin/platelet thrombus → RBC (microangiopathic hemolytic anaemia) & WBC fragmentation and/or MODS caused by microthrombi
   - Anticoagulant mechanisms (protein-C, antithrombin III, tissue-factor inhibitor) are impaired
   - Consumption of clotting factors / platelets exceeds liver protein synthesis / bone marrow megakaryocyte formation → bleeding
     - Prothrombin & activated partial thromboplastin time ↑
     - SOFA: thrombocytopenia (consumption, auto transfusion, volume replacement and immune-mediated platelet destruction)

2. Suppression of fibrinolysis
   - Increased level of PAI-1 and thrombin activated fibrinolysis inhibitor (TAFI)

*TF in sepsis and massive trauma or trypsin in pancreatitis
Petechia

Ecchymoses
Infection

Proinflammatory cytokines (TNF-α, IL-1,6)

Inflammation

Protease activated receptor-1

Thrombin↑

Coagulation

TAI↑

Fibrinolysis

t-PA↓

Endothelial injury

TF↑

PAI-1↑

Thrombin activated platelets

TF – tissue factor
PAI-1 – plasminogen activator inhibitor
TAFI – thrombin-activated fibrinolysis inhibitor
t-PA – tissue plasminogen activator
Sepsis

Impaired fibrinolysis

Systemic inflammation

Coagulation

MODS

Death

*tissue factor pathway inhibitor↓, protein-C (Va, VIIIa)↓, antithrombin-III (thrombin, Xa)↓

Endothelial cells

Cytokines

IL-6

IL-1

TNF-α

IL-1

TNF-α

Impairment of physiologic anticoagulant mechanisms*

Inhibition of fibrinolysis because of high levels of PAI-1

Microvascular thrombosis & modulation of inflammation

Inflammatory cells
a-PC, activated protein C; APL, acute promyelocytic leukemia; AT-III, antithrombin III; CP, cysteine protease; HCII, heparin cofactor II; prothrombinase complex, membrane complex of factors Xa and Va and prothrombin; PS, protein S; tenase complex, membrane complex of factors IXa, VIIIa, and X; TF, tissue factor; TF · FVIIa, tissue factor–factor VIIa complex; TFPI, TF pathway inhibitor; TM, thrombomodulin; tPA, tissue plasminogen activator
Anti-inflammatory pathways in shock

- Anti-inflammatory pathways are activated parallel with sepsis
  - IL-10↑: suppresses IL-6 & IFN-γ; stimulates TNF-R & IL-1R antagonist
  - Autophagy ↑: eliminates PAMPs, DAMPs
  - Efferocytosis: IL-10, TFG-β, lipoxins, maresins, resolvins & protectins↑

- Survivor of sepsis may result in a prolonged immunosuppression & secondary infections
  - Malfunction / apoptosis of monocytes/macrophages, neutrophils, endothelial, dendritic, T and B cells
    - Neutrophil dysfunction → sepsis
    - Endothelial cell apoptosis: tissue factor ↑
    - Lymphocyte apoptosis ↑ → blunted inflammatory response: TNF-α, IL-1 ↓, but not IL-10
  - Viral (CMV, EBV, HHV), fungal and secondary bacterial infections
Metabolic dysfunctions in shock

1. Increased catabolism
   ○ Carbohydrate utilization & protein breakdown
     ■ Acute/early effects
       □ Stress hormones (cortisol, catecholamines, glucagon etc) stimulate the liver to increase glucose output from glycogen breakdown and from lactate, pyruvate & alanine (gluconeogenesis), which are released from skeletal muscle catabolism
       □ Pain, immobility & inflammatory cytokines aggravate muscle breakdown to fuel energy needs of innate immune cells
       □ Skeletal muscle becomes more resistant to substrate uptake (FFA glucose) and continues to release lactate, which becomes the main fuel source for the heart in shock
     ■ Chronic/late effects: hypoglycemia (glycogen depletion, depressed glucose synthesis) & hyperlactatemia
Glycogenolysis↑

Lipolysis
Lipid metabolism
- Acute effects: increased catabolism (FFA & TG↑)
- Late effects: lipid peroxidation due to ROS↑

2. Mitochondrial dysfunction
- ROS↑ → generalized ↓ ATP production (“mitochondrial hibernation”) → multiorgan failure / MODS
  - MODS: kidney, lung, liver, brain and heart dysfunction – life threatening condition especially in septic shock with high mortality rate
Complications of shock

- Acute kidney injury (AKI)
  - The early stage: afferent vasodilation; then later contraction → ↓ GRF
  - In septic shock, AKI is due to cytokine and immune-mediated microvascular and tubular dysfunction and not to ↓ perfusion
    - SOFA: measurement of creatinine and urinary output
- GI complications
  - The earliest organ affected by hypoperfusion, widespread blood redistribution & vessel constriction → poor perfusion of the GI tract (breakdown of barriers)
  - Hypercytokemia → bacterial translocation & gut injury by luminal (ileus, pancreatitis) content (vicious cycle) → septic shock
  - Liver: failure bilirubin transport (cholestasis), synthetic function
    - SOFA: measurement of bilirubin
• Acute respiratory distress syndrome (ARDS)
  ○ Cytokine-mediated inflammatory damage to the alveoli; fibrin, leukocyte aggregates in micro vessels → interstitial and alveolar edema
  ○ Impaired gas exchange, decreased compliance (surfactant ↓), ventilation-perfusion mismatch → respiratory failure (mortality ~ 50%)

■ SOFA: partial pressure of O\(_2\) (P\(_{a}\)O\(_2\)) / fraction of inspired O\(_2\) (F\(_{i}\)O\(_2\))

* Carrico index, P\(_{a}\)O\(_2\)/F\(_{i}\)O\(_2\) ratio: measures the lung capacity to transfer O\(_2\) to the blood
Cardiovascular failure

○ Heart failure
  ■ Tachycardia, arrhythmias, myocardial ischemia and cardiogenic shock (sympathetic over activation)
  ■ Myocardial depression by TNF-α, IL-1 (stroke volume and ejection fraction ↓, ventricular dilatation); iNOS, NO, peroxinitrate ↑ - myocardial contractility ↓ or toxic injury

○ Vascular dysfunction due to smooth muscle and endothelial cell injury. Vasodilatory shock leading to progression of septic shock or of long-lasting shock of any cause
  ■ NO – hyperpolarization of smooth muscle cells (unresponsive to catecholamines)
  ■ Vasopressin and cortisol deficiency upon profound, sustained baroreceptor reflex stimulation (normally vasopressin potentiates the effect of norepinephrine)
  ■ Endothelial dysfunction leads to loss of vascular tone and capillary leak
• CNS dysfunction
  ○ In early phase: anti-inflammatory role, vagal cholinergic efferents inhibit inflammatory cytokines (spleen, gut)
  ○ Late stage: acidosis & blood-brain barrier damage due to ischemia and inflammatory mediators.
    ■ This leads to neural damage (impaired concentration, confusion, coma) as a result of perivascular edema, and influx of toxins due to kidney and liver failure
    ■ DIC and exhaustion of autoregulation (<50-60 mmHg) may lead to development of further ischemia and bleeding
  ○ SOFA: Glasgow coma scale
Hypotension – low blood pressure

- Hypotension: Systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg
- Acute hypotension
  - Syncope (faintness, postural collapse)
  - Circulatory shock
- Chronic hypotension – well-tolerated drop in blood pressure
  - Thin (lanky or gangly) stature
  - Cachexia, anorexia nervosa, marasmus
  - Endocrine diseases: hypothyroidism, Addison’s, Simmonds’-syndrome
  - Hematological: chronic anemia
  - Cardiac: brady/tachycardia, aortic stenosis, pump failure
  - Neuropathy: DM, amyloidosis
Syncope (faintness, postural collapse)

- Syncope is a transient loss of consciousness (TLOC)* due to global cerebral hypoperfusion and characterized by
  - Rapid onset (prodromal symptoms [nausea, sweating, weakness, visual disturbances])
  - Short duration (less than 20 sec; rarely several minutes)
  - Spontaneous complete recovery (post-recovery fatigue, retrograde amnesia in older individuals)

*TLOC is defined as a state of real or apparent LOC with loss of awareness, characterized by amnesia for the period of unconsciousness, abnormal motor control, loss of responsiveness, and a short duration.

The two main groups of TLOC are TLOC due to head trauma and non-traumatic TLOC. Non-traumatic TLOC is classified into in their rate of occurrence: syncope, epileptic seizures, psychogenic TLOC, and rare causes.
Causes/types of syncope

1. Reflex-mediated syncope
   - Vasovagal (neurocardiogenic, vasodepressor) syncope
   - Situational (pressor-postpressor) syncope
   - Carotid sinus hypersensitivity

2. Cardiovascular syncope

3. Orthostatic syncope
Reflex-mediated syncope

- Vasovagal (neurocardiogenic*, vasodepressor) syncope or „fainting” – the most frequent form of syncope in young
  ○ Simple faint – postural collapse
    ■ Increased venous pooling due to diminished vascular tone (motionless standing) + increased vagal tone (↓heart rate) → cerebral hypoperfusion
      □ Eyes open, upward gaze, dilated pupils. Consciousness is rapidly regained – if recumbent. No post-ictal syndromes
    ■ Increased sympathetic tone (fear, pain, sight of medical instruments) potentiates vagal tone + preceding vasodilatation (warm shower, alcohol) or hypovolemia

* Left ventricular receptors are involved along with the autonomic nervous system
• Situational syncope (pressor-postpressor syncope)
  ○ Coughing, laughing, micturation, defecation, weight lifting (Valsalva maneuver)
    ■ Decreasing venous return due to Valsalva maneuver
    ■ Increased cranial pressure → secondary decrease in cerebral perfusion
    ■ Increased vagal tone and reflex vasodilatation
  ○ Carbonated, cold drinks
    ■ Activation of esophageal receptors → reflex bradycardia, AV block or angina
• **Syncope due to carotid sinus hypersensitivity**
  ■ Physiology of carotid sinus reflex (unilateral stimulus)
    ♦ Afferent limb: Carotid sinus baroreceptors → nerve of Hering (n. glossopharyngeus) → medulla oblongata
    ♦ Efferent limb: Sympathetic nerve fibers, cardiac vagal efferents
  □ Result: ↓blood pressure and heart rate
  ○ Males, over 50, with atherosclerosis the reflex is exaggerated → syncope, dizziness, confusion, even unconsciousness
  ○ **Forms of carotid sinus hypersensitivity**
    ■ Cardioinhibitory response: bradycardia, sinus arrest or AV block with fall of (50 mmHg) the systolic blood pressure
    ■ Vasodepressor response: due to vasodilatation (50 mmHg fall in the systolic blood pressure) and the absence of bradycardia
    ■ Mixed response
Cardiovascular syncope

- Sudden reduction in cardiac output
- Cardiac arrhythmias are the most frequent causes (No reduction in cerebral blood flow between 30-180 bpm)
  - Bradyarrhythmias
    - Sinus node disease, Stokes-Adams-Morgagni syndrome (sudden onset of 3rd degree AV-block), drugs
  - Tachyarrhythmias
    - Wolff-Parkinson-White syndrome, *torsade de pointes*
- Disorders of the left ventricular emptying
  - Aortic stenosis, severe systolic heart failure
- Disorders of the left ventricular filling
  - Pulmonary embolism, mitral stenosis, pericardial effusion
Orthostatic syncope

- Orthostatic hypotension: sudden change in postural position (from recumbent to standing) ≥20 mmHg decrease in systolic or ≥10 mmHg decrease in diastolic blood pressure within 3 mins of standing (Schellong test)

- Forms
  - Sympathicotonic forms – heart rate ↑ in the Schellong test
    - Drugs (antihypertensive, antidepressive and drugs to cause volume depletion or result in vasodilation)
    - Autonomic failure after prolonged illness
    - In elderly up to 30 % of all syncope
  - Non-sympathicotonic forms – no increase in heart rate
    - Neurogenic syncope: degenerative, systemic, peripheral neurological diseases (Parkinson’s, amyloidosis, diabetic, alcoholic neuropathy)