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ПАТОФИЗИОЛОГИЯ ОРГАНОВ И СИСТЕМ. ИЗБРАННЫЕ ТЕМЫ

Учебное пособие для студентов

PATHOPHYSIOLOGY OF ORGANS AND SYSTEMS. SELECTED THEMES

Manual for students

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Переиздание дополненного учебного пособия, предназначенного для подготовки студентов, обучающихся на языке-посреднике в рамках учебного курса патофизиологии. Пособие содержит материал для семинарских и практических занятий по частной патофизиологии.

CONTENTS

BLOOD CELLS. THE COMPLETE BLOOD COUNT TEST

The blood cells include the erythrocytes or red blood cells, the leukocytes or white blood cells, and platelets. The blood cells, or formed elements, are not all true cells, and most are present only a few days in the circulation or tissues as a result of their function. They do not divide and thus must be continually renewed by the process of hematopoiesis in the bone marrow.

Erythrocytes

The erythrocytes, or red blood cells, are the most numerous of the formed elements, are derived from the myeloid stem cells and live approximately 120 days in the circulation.

Reticulocytes, immature forms of erythrocytes, circulating in the bloodstream 1-2 days, they constitute 0.5-2% of the total number of erythrocytes. Because the reticulocyte stage of erythroid differentiation only lasts a few days, the number of reticulocytes in the blood is a useful clinical indicator of the rate of erythropoiesis. With increasing erythropoietic stimulation, such as following bleeding or hemolysis, the number of reticulocytes increases in the marrow and blood.

Leukocytes

The leukocytes, or white blood cells, constitute only 1% of the total blood volume. They originate from the bone marrow stem cells and migrate throughout the tissues of the body. They include the granulocytes, the lymphocytes, and the monocytes.

Granulocytes.

The granulocytes are mostly phagocytic and secretory cells and are identifiable because of their cytoplasmic granules; they are divided into three types (neutrophils, eosinophils, and basophils) according to the staining properties of the granules.

Neutrophils, which constitute 45% to 65% of the total number of white blood cells, have granules that are neutral and hence do not stain with an acidic or a basic dye. Because these white cells have nuclei that are divided into three to five lobes, they are often called polymorphonuclear leukocytes.

The neutrophils are primarily responsible for maintaining normal host defenses against invading bacteria and fungi, cells remains, and a variety of foreign substances. The cytoplasm of mature neutrophils contains fine granules. These granules contain degrading enzymes that are used in destroying foreign substances and correspond to lysosomes found in other cells. Enzymes and oxidizing agents (free radicals) associated with these granules are capable of degrading natural and synthetic substances, including complex polysaccharides, proteins, and lipids.

The neutrophils have their origin in the myeloblasts that are found in the bone marrow. The myeloblasts are the committed precursors of the granulocyte pathway and do not normally appear in the peripheral circulation. When they are present, it suggests a disorder of blood cell proliferation and differentiation (leukemia). The myeloblasts differentiate into promyelocytes and then myelocytes. The myelocytes mature to become metamyelocytes (from Greek meta-, «beyond»), at which point they lose their
capacity for mitosis. Subsequent development of the neutrophil involves reduction in size, with transformation from an indented to an oval then to a horseshoe-shaped nucleus (band neutrophils) and then to a mature cell with a segmented nucleus. These mature neutrophils are often referred to as segs because of their segmented nucleus. Development from stem cell to mature neutrophil takes approximately 2 weeks. It is at point that the neutrophil enters the bloodstream.

After release from the marrow, the neutrophils spend only approximately 4 to 8 hours in the circulation before moving into tissues. Their survival in the tissues lasts approximately 4 to 5 days. They die in the tissues in discharging their phagocytic function or they die of senescence.

The pool of circulation neutrophils (i.e., those that appear in the blood count) is in closely maintained equilibrium with a similar-sized pool of cells marginating along the walls of small blood vessel. These are the neutrophils that respond to chemotactic factors and migrate into the tissues toward the offending agent.

Eosinophils. The cytoplasmic granules of the eosinophils stain red with the acidic dye eosin. These leukocytes constitute 1% to 5% of the

total number of white blood cells and increase in number during allergic reaction and parasitic infections. In allergic diseases they release enzymes and chemical mediators that are associated with allergic reactions. In parasitic infections, the eosinophils use surface markers to attach themselves to the parasite and then release hydrolytic enzymes that kill it.

Basophils. The granules of the basophils stain blue with a basic dye. These cells constitute only approximately 0.0% to 1% of the white blood cells. The granules in the basophils contain heparin and histamine. The basophils share properties of mast cells and are involved in the inflammatory, allergic and stress responses.

Lymphocytes.

The lymphocytes constitute 20% to 40% of the white blood cells count. They originate in the bone marrow from lymphoid stem cells. They have no identifiable granules in the cytoplasm and are also called agranulocytes.

The lymphocytes play an important role in the immune response. They move between blood and lymph tissue, where they may be stored for hours or years. Their function in the lymph nodes or spleen is to defend against microorganisms in the immune response. The B lymphocytes differentiate to form antibody-producing plasma cells and are involved in humoral – mediated immunity. The T lymphocytes are involved in cell – mediated immunity.

Monocytes- Macrophages.

Monocytes are the largest of the white blood cells and constitute approximately 3% to 8% of the total leukocyte count. They are derived from the myeloid stem cell. The life span of the circulating monocyte in the blood stream is approximately 1 to 3 days, three to four times longer than that of the granulocytes. These cells survive for months to years in the tissues. The monocytes, which are phagocytic cells, are referred to as macrophages when they enter the tissues. The monocytes engulf larger and greater quantities of foreign material than the neutrophils. These cells engulf apoptotic and injured cells, play an important role in acute and especially in chronic inflammation and are also involved in the immune response by activating lymphocytes through cytokines and by presenting antigen to T cells.

Thrombocytes.

Thrombocytes, or platelets, are circulating cell fragments of the large megakaryocytes that are derived from the myeloid stem cell. They function to form a platelet plug after injury to a vessel wall. Their cytoplasmic granules release mediators required for hemostasis and inflammation. Throbocytes have no nucleus, cannot replicate, and, if not used, last approximately 8 to 9 days in the circulation before they are removed by the phagocytic cells of the spleen.

THE COMPLETE BLOOD COUNT TEST

Interpretation of a complete blood count

TYPE OF CELL	INCREASE	DECREASE
white blood cells	leukocytosis	leukopenia
neutrophils	neutrophilia	neutropenia
lymphocytes	lymphocytosis	lymphocytopenia
monocytes	monocytosis	monocytopenia
eosinophils	eosinophilia	eosinopenia
basophils	basophilia	-
red blood cells	erythrocytosis	anemia
platelets	thrombocytosis	thrombocytopenia
all three cell lines	polycytemia	pancytopenia

The complete blood count is the calculation of the cellular (formed elements) of blood. Specially designed machines that analyze the different components of blood in less than a minute generally determine these calculations. The complete blood count (CBC) or full blood count (FBC) also known as a "hemogram" is generated by testing a simple blood sample. Abnormally high or low counts may indicate the presence of many forms of disease, and hence blood counts are amongst the most commonly performed blood tests in medicine.

The main values for a complete blood count

The values generally included are the following:

- RED BLOOD CELLS (RBC). The number of red blood cells in a volume of blood. Normal range varies slightly between laboratories but is generally between 3.7 - 5.0 million cells/cmm. This can also be referred to as the erythrocyte count and can be expressed in international units as 3.7 - 5.0 x 10^{12} cells per liter.
- Normal range for RBC is different between the sexes and is 4.0 - 5.0 x 10^{12} cells per liter for men and 3.7 – 4.7 x 10^{12} cells per liter for women
- HEMOGLOBIN (Hb). The amount of hemoglobin in a volume of blood.
- Normal range for hemoglobin is different between the sexes and is approximately 130 - 180 grams per liter for men and 120 - 160 for women.

International units 8.1 - 11.2 millimoles/liter for men, 7.4 - 9.9 for women).

- RETICULOCYTE (Rt) count measures the numbers of reticulocytes, immature forms of erythrocytes, circulating in the bloodstream.
- Normal ranges for reticulocytes are 0.5% to 1.5% of the total numbers of red blood cells in men and 0.5% to 2.5% in women.

A low reticulocyte count is seen with iron, B_{12} and folic acid deficiency, bone marrow failure. A high reticulocyte count indicates that the bone marrow is responding to the need for increased red blood cell production as with hemolytic and acute blood loss anemias. A person who is responding to treatment for anemia would be also expected to have a high reticulocyte count.

- Mean cell volume (MCV) is a measure of the average red blood cell size (80–100 femtolitres). Anemia is classified as macrocytic or microcytic based on whether this value is above or below the expected normal range.
- Mean cell hemoglobin (MCH) hemoglobin amount per red blood cell (28 – 35 picograms/cell).
- Color index (CI) – hemoglobin amount in the average red cell. CI=MCH x 0.03

It can be calculated manually as following:

CI= Hb (grams per liter) x 0,3/ first 2 figures of RBC number
e. g. Hb-130 g/ l; RBC-4,1 x 10^{12}/ l;
CI=130x0.3/41=39/41=0.95

Anemia is classified as hypochromic or hyperchromic based on whether this value is below or above the expected normal range (0.85-1.05). The most common hypochromic anemia is due to iron deficiency, hyperchromic – to vitamin B12 and folic acid deficiencies.

RBC disorders

RBC	↓ Anemia		↑ Eritrocytosis
Rt	→regeneration	↓hyporegeneration	↑hyperregeneration
		aplasia	hemolysis acute blood loss
MCV	→normocyte	↓microcyte	↑macrocyte
	hemolysis acute blood loss	iron deficiency chronic disease	B12 and folic acid deficiencies
MCH	→normochromia	↓hypochromia	↑hyperchromia
(CI)	hemolysis aplasia	iron deficiency chronic disease	B12 and folic acid deficiencies

Iron metabolism which is important in differentiation of hypochromic anemias is characterized by additional biochemical findings – SI – serum iron, TIBC – total iron binding capacity, Fer – ferritin.

Disease	Iron	TIBC	Ferritin
Iron deficiency anemia	Decrease	Increase	Decrease
Anemia of chronic disease	Decrease	Decrease	Increase

- WHITE BLOOD CELLS (WBC). The number of white blood cells in a volume of blood.

- Normal range varies slightly between laboratories but is generally between 4,000 and 10,000 cells per cubic millimeter. This can also be referred to as the leukocyte count and can be expressed in international units as 4.0 - 10.0 x 10^9 cells per liter.
- "Differential counts" subclassifies each component of the white cell population. The normal ranges of these counts are:

o Neutrophil 2.0 - 7.5 x 10^9/L	
Bands	(1-5%)
Segmented	(55-65%)
o Lymphocyte 1.0 - 4.0 x 10^9/L	(20-40%)
o Monocyte 0.1 - 1.2 x 10^9/L	(4-8%)
o Eosinophil 0.0 - 0.4 x 10^9/L	(1-5%)
o Basophil.0-0.1x10^9/L	(0-1%)

Certain **disease** states are defined by an absolute increase or decrease in the number of a particular type of cell in the bloodstream.

Neutrophils and neutrophil count.

- High levels may indicate an active infection and inflammation, trauma, infarctions and necrosis.

Epinephrine, exercise, stress, and corticosteroid drug therapy can cause rapid increases in the marginating to the circulation pool of neutrophils.

- A left shift indicates the presence in blood of neutrophils less mature than segmented neutrophils, e.g. band neutrophils and earlier stages, such as metamyelocytes. A left shift usually indicates a response to inflammatory cytokines, which are stimulating accelerated production and/or release of neutrophils. A left shift also indicates chronic myelocytic leukemia characterized by neoplastic accumulation of all forms of mature and immature granulocytes.
- In some severe infections, inflammations and traumas the neutrophil count is very high with immature myelocytes, metamyelocytes present, it is known as leukemoid reaction.
- If more band neutrophils are counted than segmented neutrophils, the term degenerative left shift applies. This indicates

severe inflammation. In this setting, neutrophils demonstrate features of toxic change or immaturity.

- A low count may indicate a depressed bone marrow (low neutrophil production),

  compromised immune system as with toxic reactions and drug effects.

  Endotoxins produce a transient decrease in neutrophils by attracting neutrophils into the tissues.

  A decrease in the absolute neutrophil count is associated with a significant incidence of infection.

Lymphocytes and lymphocyte count.

- High levels – lymphocytosis may indicate an active viral infection (such as influenza, measles, rubella, chickenpox, or infectious mononucleosis …), chronic infection. Also raised in chronic lymphocytic leukaemia.
- Low level – lymphocytopenia - a decrease in the absolute lymphocyte count can be seen in steroid treated patients, treatment with radiation therapy, patients with uremia, marrow aplasia.

Monocytes and monocyte count.

- High levels are seen in bacterial infection - tuberculosis, listeriosis, fungal infections or chronic inflammatory diseases, monocytic leukemia or lymphomas.
- Low levels are indicative of a state of health.

Eosinophils and eosinophil count.

- High levels may indicate parasitic infections, especially with worms. Seen also in allergic reactions.
- Elevated level of eosinophils and basophils can be seen in chronic myelocytic leukemia.
- Low count is normal.

Basophils and basophils count.

High levels can be found in allergic reactions, low levels are normal.

PLATELET COUNT. The number of platelets in a volume of blood. Platelets are not complete cells, but actually fragment of cytoplasm from megakaryocyte. Normal range varies slightly between laboratories but is in the range of 150,000 - 400,000/ cmm (150 - 400 x 10^9/liter). Platelets numbers are given, as well as information about their size (mean platelet

volume MPV) and the range of sizes in the blood (platelet distribution width PDW).

DYSRHYTHMIAS AND CONDUCTION DISORDERS
Lesson № 1

Cardiac Conduction System

Heart muscle is unique among other muscles in that it is capable of generating and rapidly conducting its own action potentials (*i.e.,* electrical impulses). These action potentials result in excitation of muscle fibers throughout the myocardium. Impulse formation and conduction result in weak electrical currents that spread through the entire body. When electrodes are applied to various positions on the body and connected to an electrocardiograph machine, an electrocardiogram (ECG) can be recorded.

Specialized pacemaker cells generate impulses at a faster rate than do other types of heart tissue, and the conduction tissue transmits impulses at a faster rate than do other types of heart tissue. Because of these properties, the conduction system usually controls the rhythm of the heart.

The conduction system consists of:

- the sinoatrial node (SA node), where the rhythmic impulse is generated;
- the internodal pathways, which conduct the impulse from the SA node to the atrioventricular (AV) node;
- the AV node, in which the impulse from the atria is delayed before passing to the ventricles;
- the AV bundle, which conducts the impulse from the atria to the ventricles;
- the left and right bundles of the Purkinje system, which conduct the cardiac impulses to all parts of the ventricles.

The sinoatrial (SA) node has the fastest intrinsic rate of firing (60 to 100 beats per minute) and is normally the pacemaker of the heart.

The heart essentially has two conduction systems: one that controls atrial activity and one that controls ventricular activity. The AV node connects the two conduction systems and provides one-way conduction between the atria and ventricles.

Within the AV node, atrial fibers connect with very small junctional fibers of the node itself. The velocity of conduction through these fibers is very slow (approximately one half that of normal cardiac muscle), which greatly delays transmission of the impulse into the AV node. A further delay occurs as the impulse travels through the AV node into the transitional fibers and into the AV bundle, also called the bundle of His. This delay provides a mechanical advantage whereby the atria complete their ejection of blood before ventricular contraction begins. Under normal circumstances, the AV node provides the only connection between the two conduction systems. The atria and ventricles would beat independently of each other if the transmission of impulses through the AV node were blocked.

The Purkinje fibers lead from the AV node through the AV bundle into the ventricles where they divide to form the right and left bundle branches that straddle the interventricular septum. The main trunk of the left bundle branch extends for approximately 1 to 2 cm before fanning out as it enters the septal area and divides further into two segments: the left posterior and anterior fascicles. The Purkinje system has very large fibers that allow for rapid conduction and almost simultaneous excitation of the entire right and left ventricles.

Electrocardiography (ECG)

The ECG is a recording of the electrical activity of the heart. The electrical currents generated by the heart spread through the body to the skin, where they can be sensed by appropriately placed electrodes, amplified, and viewed on an oscilloscope or chart recorder.

The deflection points of an ECG are designated by the letters P, Q, R, S, and T (Figure 1). The P wave represents the SA node and atrial depolarization; the QRS complex (*i.e.,* beginning of the Q wave to the end of the S wave) depicts ventricular depolarization; in practice, the Q, R and S waves are not always present. The Q wave is defined as any

initial downward deflection. The R wave is defined as any deflection upwards. The S wave is defined as any down deflection that is not Q (it arises after the R wave). And the T wave portrays ventricular repolarization.

The isoelectric line between the P wave and the Q wave represents depolarization of the AV node, the PQ interval is caused by the slow propagation of the depolarisation through the AV node; this allows time for the ventricles to fill. PQ is measured from the start of P to the start of Q (or R).

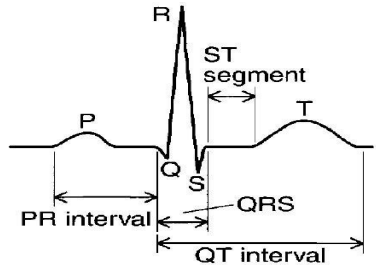


Figure 1. Normal ECG record

Atrial repolarization occurs during ventricular depolarization and is hidden in the QRS complex.

The horizontal axis of the ECG measures time in seconds, and the vertical axis measures the amplitude of the impulse in millivolts (mV). Each heavy vertical line represents 0,1 or 0.2 second, and each thin line represents 0.02 or 0.04 second (depends on ECG recorder).

The widths of ECG complexes are commonly referred to in terms of duration of time. The connections of the ECG are arranged such that an upright deflection indicates a positive potential and a downward deflection indicates a negative potential.

The shape of the recorder tracing is determined by the direction in which the impulse spreads through the heart muscle in relation to electrode placement. A depolarization wave that moves toward the recording electrode registers as a positive, or upward, deflection. Conversely, if the impulse moves away from the recording electrode, the deflection is downward, or negative. When there is no flow of charge between electrodes, the potential is zero, and a straight line is recorded at the baseline of the chart.

Conventionally, 12 leads are recorded for a diagnostic ECG, each providing a unique view of the electrical forces of the heart from a different position on the body's surface.

Six limb leads view the electrical forces as they pass through the heart on the frontal or vertical plane. The electrodes for the limb leads are attached to the four extremities or representative areas on the body near the shoulders and lower chest or abdomen.

Six chest electrodes provide a view of the electrical forces as they pass through the heart on the horizontal plane. They are moved to different positions on the chest, including the right and left sternal borders and the left anterior surface. The right lower extremity lead is used as a ground electrode.

Rate and rhythm

The determination of rhythm is complex. Careful examination of the intervals, durations, and segments in the ECG tracing can reveal a great deal about the conducted action potential One must answer the following questions:

- Where is the heart's pacemaker?
- What is the conduction path from the pacemaker to the last cell in the ventricles?
- Is the pacemaker functioning regularly and at the correct speed?

The normal pacemaker is the SA node; the signal then propagates through the AV node, and activates the ventricles. When the heart follows this pathway at a normal rate and in this sequence, the rhythm is called a normal sinus rhythm (Figure 2).

Normal sinus rhythm is defined by:

- QRS largely regular
- each and every QRS is preceded by a P, P must be positive in II but negative in Avr .

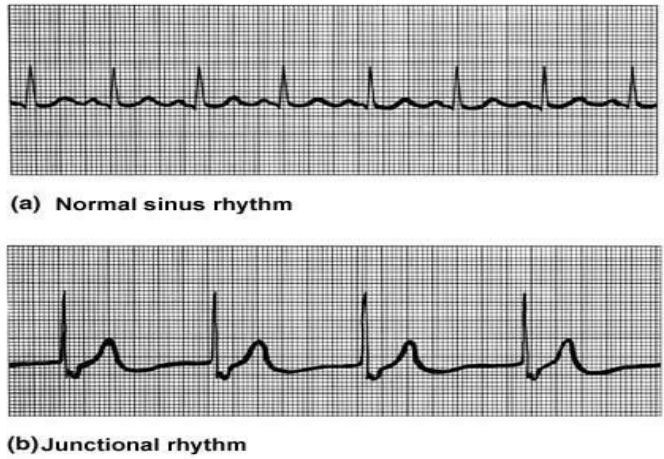


Figure 2. Positive P in sinus rhythm, negative P in AV rhythm

Heart rate can be calculated by dividing 60 by the number of seconds between consecutive R waves. For an irregular ECG report the shortest and longest periods are
calculated and an average rate is given.

A regular sinus rhythm is normal in adults. In children and teenagers sinus arrhythmia is a variant of normal.

The PQ (PR) interval indicates how long it takes the action potential to conduct through the AV node before activating the ventricles.

The QRS duration reveals how long it takes for the wave of depolarization to spread throughout the ventricles.

The QT interval indicates how long the ventricles remain depolarized, and is thus a rough measure of the duration of the overall "ventricular" action potential. The QT segment gets shorter as the heart rate increases, reflecting the shorter action potentials that are observed at high rates.

Vector (or axis) of a wave in the frontal plane. Determining the vector of current flow through the heart is not just an intellectual exercise, but can be of great clinical importance. The normal axis of ventricular depolarization in the frontal plane lies between +30 and +70 degrees. However, this axis can change in a number of pathologic situations, including hypertrophy of one or both ventricular walls (a

common sequela of severe or prolonged hypertension) and conduction blocks in one or several of the ventricular conducting pathways.

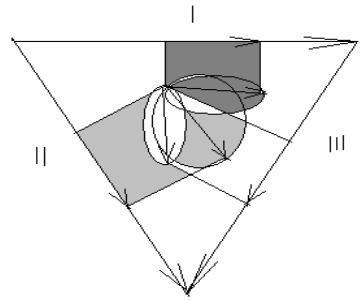


Figure 3. Cardiac axis: normal axis is light grey, right axis deviation – white, left axis deviation – dark grey.

The normal cardiac axis is seen in leads I, II and III of the ECG (Figure 3). The cardiac axis is the predominant direction of ventricular depolarization in the frontal plain. Thus the axis is parallel to that frontal lead with the largest QRS complex

1. In the normal cardiac axis there is predominantly an upward deflection in all of these leads. The deflection will be greater in II than I or III.

In right axis deviation III becomes greater and I becomes predominantly negative. In left axis deviation I becomes greater, III becomes negative, II also becomes more negative.

2. The axis is also deduced using different vector diagrams of the amount of deflection (for example, hight of R above the line minus the depth of Q and S below the line) in two leads (I, III).

We can use these two approaches for measuring the axis of a wave within the frontal plane (i.e., using limb leads). The first is quicker and easier, but the second is more accurate.

Dysrhythmias

Dysrhythmias represent disorders of cardiac rhythm.

1. Cardiac dysrhythmias are commonly divided into two categories: supraventricular and ventricular dysrhythmias.

- The supraventricular dysrhythmias include those that are generated in the SA node, atria, AV node, and junctional tissues.
- The ventricular dysrhythmias include those that are generated in the ventricular conduction system and the ventricular muscle. Because the ventricles are the pumping chambers of the heart, ventricular dysrhythmias (*e.g.,* ventricular tachycardia and fibrillation) are the most serious in terms of immediate life-threatening events (even heart failure).

2. Disorders of cardiac rhythm can range from excessively rapid heart rate (tachyarrhythmias) to an extremely slow heart rate (bradyarrhythmias).

- Tachyarrhythmias may be triggered by exercise, emotional stress, excessive alcohol consumption, smoking, or use of drugs that contain stimulants.
- Bradyarrhythmias may be triggered by pain, hunger, fatigue, digestive disorders (such as diarrhea and vomiting), or swallowing, which can stimulate the vagus nerve excessively.

There are following pathological irregular rhythms:

- heart block,
- ectopic beats - these may be atrial, junctional or ventricular,
- fibrillation.

Conduction disorders disrupt the flow of impulses through the conduction system of the heart. Heart block occurs when the conduction of impulses is blocked, often in the AV node. Under normal conditions, the AV junction provides the only connection for transmission of impulses between the atrial and ventricular conduction systems; in complete heart block, the atria and ventricles beat independently of each other. The most serious effect of some forms of AV block is a slowing of heart rate to the extent that circulation to the brain is compromised.

Sinoatrial block is a failure in the conduction of electrical impulses to both atria and ventricles from SA node:

- partial (second-degree) block- a periodically non-conducted depolarisation,

- complete block, in which there is a failure of conduction from the SA node, continuing ventricular activity depends upon the emergence of an escape rhythm.

Atrioventricular heart block is caused by disorders of the atrioventricular node, it is a failure in the conduction of electrical impulses from the atria to the ventricles:

- atrioventricular block may be intermittent or permanent:
  - can progress from minimal asymptomatic conduction delay to the ventricles (first-degree), to partial second-degree atrioventricular block, or complete (third-degree) atrioventricular block, in which there is no conduction between the atria and ventricles,
  - partial atrioventricular block is usually asymptomatic, but it carries a high risk of progression to complete block.

In first-degree heart (AV) block there is a delay in the conduction pathway from the sino-atrial node to the ventricles. This is illustrated on an ECG as a PR interval of greater than 0.2 seconds (Figure 4). A finding of first-degree heart block may have no pathological significance. However it may be a sign of underlying disease.

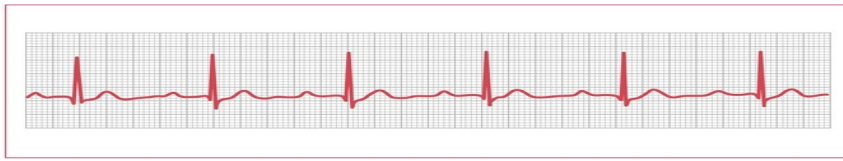


Figure 4. First-degree AV block

The second-degree block (the Wenkebach phenomenon).

Type I second degree AV block) is characterized by the progressive lengthening of the PR interval with successive heartbeats, culminating in a non-conducted atrial depolarization. The next beat has a short PR interval and so the cycle continues. The level of the block is generally at the level of the atrioventricular node, the QRS complexes are of normal duration and junctional automaticity, in general, is unimpaired (Figure 5). In the healthy individual the Wenkebach phenomenon is often due to increased vagal tone and is abolished by exercise and atropine.

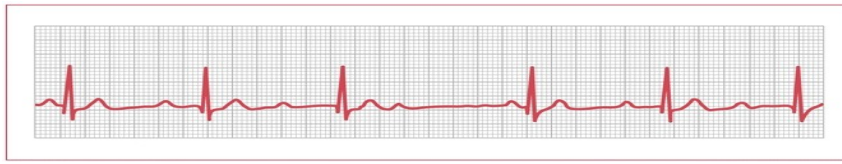


Figure 5. The Wenkebach phenomenon

Type II second-degree AV block (Mobitz type II) In this type of second degree heart block there is intermittent failure of the AVN to conduct the atrial depolarization to the ventricles. Generally the level of block is below the AVN and almost always occurs in patients with bundle branch disease (Figure 6).

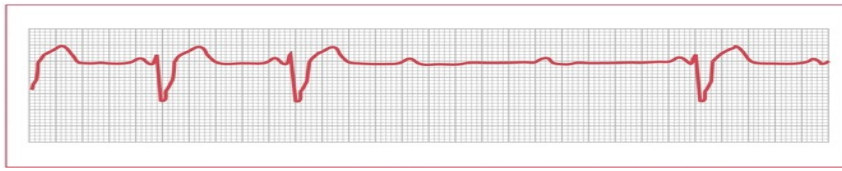


Figure 6. Mobitz type II

In third degree heart block there is complete failure of conduction through the AVN (Figure 7):

- there is no relation between P and QRS,
- the P wave rate is about 90 per minute and the QRS is about 36 per minute,
- the QRS complex may be wide because of the abnormal spread of depolarisation from a ventricular focus.

Continuing ventricular activity depends upon the emergence of an escape rhythm.

If the block is in the AVN then the escape rhythm usually originates in the bundle of His and is fast enough to prevent symptoms. If however there is bundle damage the escape rhythm is generated lower down the conducting system resulting in a slow and unreliable heart beat and life-threatening asystoles. A normal QRS and a rate of >40 per minute, which responds to exercise, suggests a pacemaker focus near the AVN.

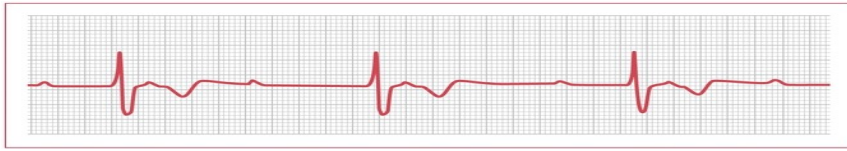


Figure 7. Complete heart block

Bundle branch block- In this condition there is abnormal conduction through the right or left bundle branches and a consequent delay in the depolarisation of part of the ventricular muscle. When the heart is in sinus rhythm, ventricular conduction along a
slower, abnormal pathway results in a QRS complex of greater than 0.12 sec but with a constant PR interval (Figure 8).

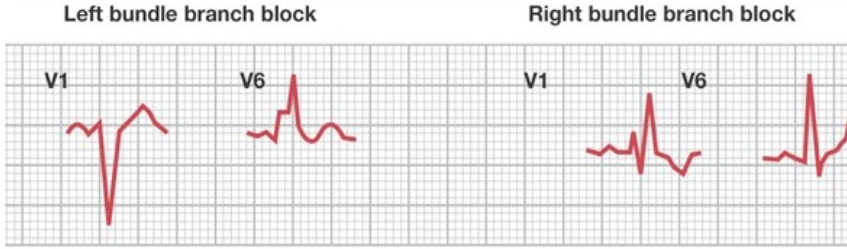


Figure 8. Bundle branch blocks

Thus three types of bundle branch block may occur:

- bundle branch block involving both branches
- a right bundle branch block
- a left bundle branch block

Right bundle branch block:

- abnormally wide QRS complexes, principle indicator is "M" in V1 and V2.

Left bundle branch block:

- abnormally wide QRS complexes, principle indicator is "M" in V5 and V6.

A block of both bundles is equivalent to third degree, or complete, heart block.

Lesson № 2

Ectopic beats – extrasystoles.

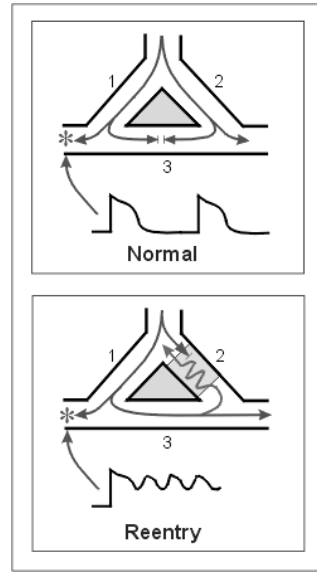
An ectopic pacemaker is an excitable focus outside the normally functioning SA node. A premature ventricular contraction (PVC)-extrasystola occurs when an ectopic pacemaker initiates a beat.

It can arise from three basic mechanisms:

(1) Increased automaticity can cause a more rapid heart rate.

(2) Spontaneous depolarizations can cause tachycardia which is called “triggered activity”, since it is dependent on the existence of a preceding action potential.

(3) Most commonly, extrasystolas arise from a reentrant circuit (mechanism of reentry) in abnormal cardiac tissue (Figure 9).



Any condition that gives rise to adjacent regions with different conduction velocities (such as the border zone of a myocardial infarction) can serve as the substrate for a reentrant circuit. Reentry is the electrophysiologic mechanism responsible for most of the clinically important arrhythmias, including atrial fibrillation, atrial flutter, ventricular tachycardia after myocardial infarction, and ventricular fibrillation.

In normal tissue (top panel), a single Purkinje fiber forms two branches (1 & 2), the action potential will travel down each branch. An electrode (*) would record single, normal action potentials.

Reentry (bottom panel) can occur if branch 2 has a unidirectional block. In such a block, impulses can travel retrograde (from branch 3 into branch 2) but not orthograde. When this condition exists, an action potential will travel down the branch 1, into the common distal path (branch 3), and then travel retrograde through the unidirectional block in branch 2. Within the block (gray area), the conduction velocity is reduced because of depolarization. When the action potential exits the

block, if it finds the tissue excitable, then the action potential will continue by traveling down (i.e., reenter) the branch 1.

Atrial ectopics have the following characteristics on the ECG:

- premature P waves,
- most atrial ectopic beats will be conducted through the AVN, hence the QRS complex is normal (narrow) (Figure 10),
- incomplete compensatory pause before next sinus beat.

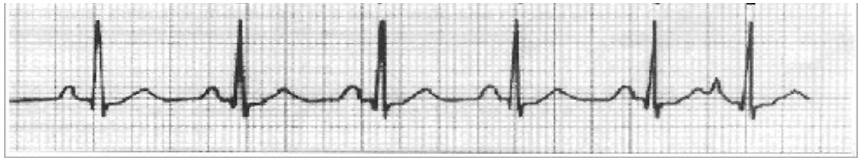


Figure 10. Atrial ectopic

Junctional AV ectopics have the following characteristics on the ECG:

- a premature QRS complex with normal morphology (narrow),
- the negative P wave precedes, follows or coincides with the QRS,
- incomplete compensatory pause before the next sinus beat (Figure 11).

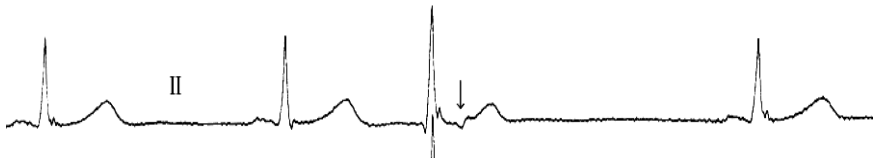


Figure 11. AV ectopic

Ventricular ectopics (Figure 12).

- These are caused by the premature discharge of a ventricular ectopic focus, which produces an early and broad QRS complex. Ventricular extrasystoles have abnormally wide QRS complexes (>120 ms).
- ST segment and T wave are usually opposite in polarity to the QRS,

- complete compensatory pause - the underlying sinus rhythm continues undisturbed,
- the P wave has a normal morphology but is usually not conducted through the AVN.

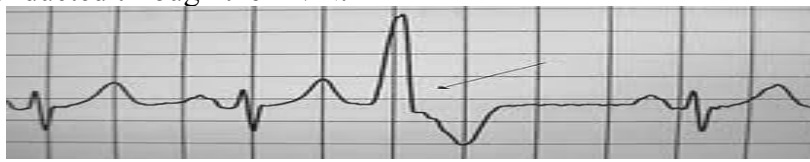


Figure 12. Ventricular ectopic

Single extrasystoles are usually normal, being common in middle age. The patient may feel an occasional missed beat. Episodically occurring ectopics are common and usually of no clinical significance. Rarely they have the potential to induce ventricular fibrillation particularly if they coincide with the T wave of a preceding beat.

Supraventricular reentrant tachycardias. These types of tachyarrhythmias are often paroxysmal in nature (sudden onset and disappearance). The heart rate is usually between 160 and 200 beats per minute.

Atrial tachycardia (Figure 13) is characterized by a narrow QRS complexes and a regular, rapid rhythm. The atrial rate, stimulated by reentrant impulses, drives the ventricular rate so there is still a one-to-one correspondence between the atrial and ventricular rates.

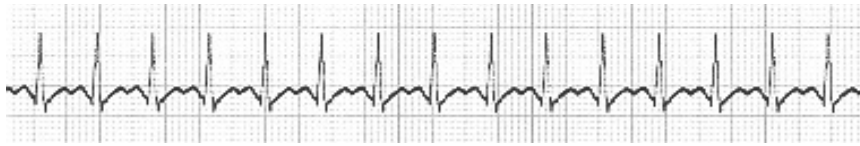


Figure 13. Atrial tachycardia

AV nodal reentrant tachycardia: a reentry circuit is formed within or just next to the atrioventricular node. Is characterized by a narrow QRS complexes, P wave is negative or absent (Figure 14).

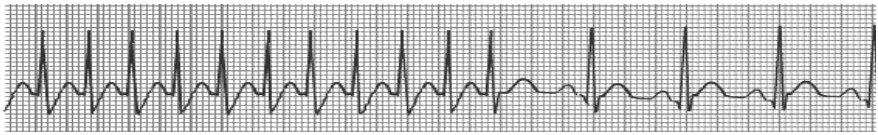


Figure 14. AV tachycardia

Ventricular tachycardia: fast heart rhythm that originates in one of the ventricles. It is generated from increased automaticity of a single point in the ventricle, or due to a reentry circuit within the ventricle. Is characterized by a wide QRS complexes (Figure 15).

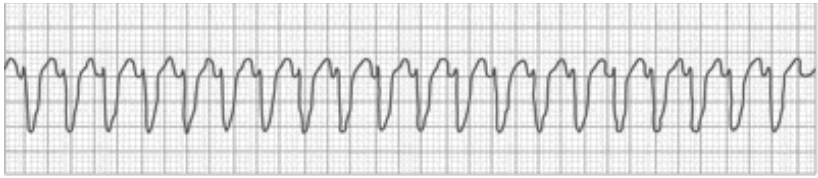


Figure 15. Ventricular tachycardia

Fibrillation is the result of disorganized current flow within the atria (atrial fibrillation) or ventricle (ventricular fibrillation). Fibrillation interrupts the normal contraction of the atria or ventricles. In ventricular fibrillation, the ventricle quivers but does not contract. When the ventricle does not contract, there is no cardiac output, and there are no palpable or audible pulses. Ventricular fibrillation is a fatal event unless treated with immediate defibrillation.

Atrial fibrillation is a condition where there is disorganized electrical and mechanical activity of the atria with a mechanism of multiple re-entrant wavelets. Recent electrophysiological evidence has indicated that the triggering ectopic foci act on predisposing substrates to initiate single- or multiple-circuit reentry, leading to AF. The most important histopathological change in AF is atrial fibrosis (Figure 16).

The characteristic ECG changes seen in atrial fibrillation are:

- no P waves - a irregular baseline is seen
- irregular QRS complexes
- narrow QRS complexes

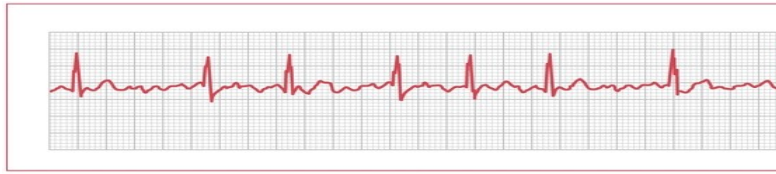


Figure 16. Atrial fibrillation.

This condition is sometimes confused with atrial flutter; where the atrial rate is greater than 250 and there is a consequent atrio-ventricular block because the ventricles cannot match the atrial rate. The QRS complexes are normal and regular in atrial flutter (Figure 17).

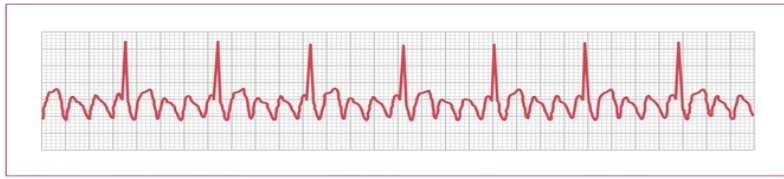


Figure 17. Atrial flutter

The characteristic ECG changes seen in ventricular fibrillation are: no P waves, no QRS complexes - irregular baseline is seen (Figure 18).

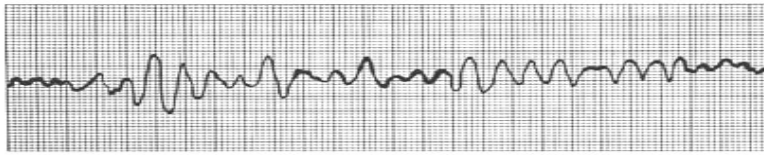


Figure 18. Ventricular fibrillation

HEART FAILURE

The efficiency and work of the heart as a pump often is measured in terms of *cardiac output* or the amount of blood the heart pumps each minute. The cardiac output (CO) is the product of the *stroke volume* (SV) and the *heart rate* (HR) and can be expressed by the equation: CO=SV x HR.

The cardiac output varies with body size and the metabolic needs of the tissues. It increases with physical activity and decreases during rest and sleep. The average cardiac output in normal adults ranges from 3.5 to 8.0 L/minute. In the highly trained athlete, this value can increase to levels as high as 32 L/minute during maximum exercise.

The cardiac reserve refers to the maximum percentage of increase in cardiac output that can be achieved above the normal resting level. The normal young adult has a cardiac reserve of approximately 300% to 400%.

Cardiac performance is influenced by the work demands of the heart and the ability of the coronary circulation to meet its metabolic needs. The heart's ability to increase its output according to body needs mainly depends on four factors:

- the *preload,* or ventricular filling;
- the *afterload,* or resistance to ejection of blood from the heart;
- *cardiac contractility;* and
- the *heart rate.*

Preload

The preload represents the volume work of the heart. It is called the *preload* because it is the work imposed on the heart before the contraction begins. Preload represents the amount of blood that the heart must pump with each beat and is largely determined by the venous return to the heart and the accompanying stretch of the muscle fibers.

The increased force of contraction that accompanies an increase in ventricular end-diastolic volume is referred to as the *Frank-Starling mechanism* or Starling's law of the heart. The anatomic arrangement of the actin and myosin filaments in the myocardial muscle fibers is such that the tension or force of contraction is greatest when the muscle fibers are stretched just before the heart begins to contract. The maximum force of contraction and cardiac output is achieved when venous return produces an increase in left ventricular end-diastolic filling (*i.e.,* preload) such that the muscle fibers are stretched about two and one-half times their normal resting length.

When the muscle fibers are stretched to this degree, there is optimal overlap of the actin and myosin filaments needed for maximal contraction. The Frank-Starling mechanism allows the heart to adjust its pumping ability to accommodate various levels of venous return. Cardiac output is less when decreased filling causes excessive overlap of the actin and myosin filaments or when excessive filling causes the filaments to be pulled too far apart.

Afterload

The afterload is the pressure or tension work of the heart. It is the pressure that the heart must generate to move blood into the aorta and lung arthery. It is called the *afterload* because it is the work presented to the heart after the contraction has commenced.

The systemic arterial blood pressure is the main source of afterload work on the left heart and the pulmonary arterial pressure is the main source of afterload work for the right heart. The afterload work of the left ventricle is also increased with narrowing (*i.e.*, stenosis) of the aortic valve. For example, in the late stages of aortic stenosis, the left ventricle may need to generate systolic pressures as great as 300 mm Hg to move blood through the diseased valve.

Cardiac Contractility

Cardiac contractility refers to the ability of the heart to change its force of contraction without changing its resting (*i.e.,* diastolic) length. The contractile state of the myocardial muscle is determined by biochemical and biophysical properties that govern the actin and myosin interactions in the myocardial cells. It is strongly influenced by the number of calcium ions that are available to participate in the contractile process.

An *inotropic* influence is one that modifies the contractile state of the myocardium independent of the Frank-Starling mechanism. For instance, sympathetic stimulation produces a positive inotropic effect by increasing the calcium that is available for interaction between the actin and myosin filaments. Hypoxia exerts a negative inotropic effect by interfering with the generation of adenosine triphosphate (ATP), which is needed for muscle contraction.

Heart Rate

The heart rate influences cardiac output and the work of the heart by determining the frequency with which the ventricle contracts and blood is ejected from the heart.

Heart rate also determines the time spent in diastolic filling. While systole and the ejection period remain fairly constant across heart rates, the time spent in diastola and filling of the ventricles becomes shorter as the heart rate increases. This leads to a decrease in stroke volume, and at high heart rates, may produce a decrease in cardiac output. One of the dangers of ventricular tachycardia is a reduction in cardiac output because the heart does not have time to fill adequately.

Bradyarrhythmias also reduces cardiac output as the heart rate is lower. Bradyarrhythmias arise from loss of normal pacemaker activity in the SA and AV nodes or block of the impulse at some point in the conduction system, usually at the AV node.

CONGESTIVE HEART FAILURE

Inadequate pump function of the heart, which leads to congestion resulting from fluid (edema) in the lungs and peripheral tissues, is a common end result of many disease processes. The clinical presentation is highly variable; for an individual patient, symptoms and signs depend on how quickly heart failure develops and whether it involves the left, right, or both ventricles.

LEFT VENTRICULAR FAILURE

Clinical Presentation

Patients with left ventricular failure most commonly present with a sensation of breathlessness and difficulty breathing (dyspnea), particularly increased heart rate. Finally, cardiac muscle can hypertrophy and ventricular volume can increase. While each of these compensatory mechanisms can temporarily maintain cardiac output, each is of limited potential, and if the underlying reason for systolic dysfunction remains untreated, the heart ultimately fails.

Etiology

Heart failure is a pathophysiologic complex or syndrome associated with dysfunction of the heart and is a common end point for many

diseases of the cardiovascular system. As such, there are many possible causes of heart failure, and the specific reason for heart failure in a given patient must always be sought. In general, heart failure can be caused by:
(1) inappropriate workloads placed on the heart, such as volume overload-preload or pressure overload- afterload,
(2) restricted filling of the heart,
(3) myocyte loss or decreased cardiac contractility,
(4) the impared heart rate.

Pathophysiology

Pathophysiologically, heart failure can arise from worsening systolic or diastolic function or, more frequently, a combination of both.

In systolic dysfunction reduced stroke volume of the heart with a concomitant decrease in cardiac output is seen. In order to maintain cardiac output, the heart can respond with three compensatory mechanisms:

1. First, increased return of blood to the heart (preload) can lead to increased contraction of sarcomeres (Frank-Starling relationship). Stroke volume increases—but at the cost of increased end-diastolic pressure.
2. Second, increased release of catecholamines can increase cardiac output both by increase in the heart rate and the velocity and force of cardiac contraction.
3. Finally, cardiac muscle can hypertrophy and ventricular volume can increase. While each of these compensatory mechanisms can temporarily maintain cardiac output, each is of limited potential, and if the underlying reason for systolic dysfunction remains untreated, the heart ultimately fails.

In diastolic dysfunction, an increase in left ventricular end-diastolic pressure is seen and symptoms of congestive heart failure occur. Diastolic dysfunction can be present in any disease that causes decreased relaxation, decreased elastic recoil, or increased stiffness of the ventricle. Hypertension, which often leads to increases in left ventricular wall thickness, can cause diastolic dysfunction by changing

all three parameters. Lack of sufficient blood to myocytes (ischemia) can also cause diastolic dysfunction by decreasing relaxation. If ischemia is severe, as in myocardial infarction, irreversible damage to the myocytes can occur, with replacement of contractile cells by fibrosis, which will lead to systolic dysfunction.

In most patients, a combination of systolic and diastolic dysfunction is responsible for the symptoms of heart failure.

Clinical Manifestations

1. Shortness of breath, orthopnea, paroxysmal nocturnal dyspnea.

Although many details of the physiologic mechanisms for the sensation of breathlessness are unclear, the inciting event probably is a rise in pulmonary capillary hydrostatic pressures as a consequence of elevated left ventricular and atrial pressures. The rise in pulmonary capillary pressure relative to plasma oncotic pressure causes fluid to move into the interstitial spaces of the lung (pulmonary edema), which can be seen on chest x-ray.

Interstitial edema probably stimulates juxtacapillary J receptors, which in turn causes reflex shallow and rapid breathing. Replacement of air in the lungs by blood or interstitial fluid can cause a reduction of vital capacity, restrictive physiology, and air trapping due to closure of small airways. The work of breathing increases as the patient tries to distend stiff lungs, which can lead to respiratory muscle fatigue and the sensation of dyspnea.

Alterations in the distribution of ventilation and perfusion result in relative ventilation/perfusion(V/Q) mismatch, with the consequent widening of the alveolar-arterial 0_2 gradient, hypoxemia, and increased dead space. Edema of the bronchial walls can lead to small airway obstruction and produce wheezing ("cardiac asthma").

Shortness of breath occurs when lying down (orthopnea) because of reduced blood pooling in the extremities and abdomen and, any increase in blood return leads to marked elevations in ventricular pressures. Patients usually trying to minimize orthopnea by sleeping with the upper body propped up by two or more pillows. Sudden onset of severe respiratory distress at night−"paroxysmal nocturnal dyspnea"− probably occurs because of the reduced adrenergic support of ventricular function

that occurs with sleep, the increase in blood return as described above, and normal nocturnal depression of the respiratory center.

2. Fatigue, confusion. Fatigue probably arises because of inability of the heart to supply appropriate amounts of blood to skeletal muscles. Confusion may arise in advanced heart failure because of under perfusion of the cerebrum.

3. Nocturia.Heart failure can lead to reduced renal perfusion during the day while the patient is upright, which normalizes only at night while the patient is supine, with consequent diuresis.

4. Chest Pain. If the cause of failure is coronary artery disease, patients may have chest pain secondary to ischemia (angina pectoris). In addition, even without ischemia, acute heart failure can cause chest pain from unknown mechanisms.

RIGHT VENTRICULAR FAILURE

Table 1

Causes of right ventricular failure.

Left-sided failure	Most common cause
Precapillary obstruction – congenital shunts	Vasoconstriction of the pulmonary arteries occurs in response to increased flow
Idiopathic pulmonary hypertension	Also known as primary pulmonary hypertension
Primary right ventricular failure- right ventricular infarction	Can occur with obstruction of the right coronary artery. Often associated with inferior wall myocardial infarction.
Sequela to pulmonary disease – Cor pulmonale	Result of destruction of the pulmonary capillary bed
Hypoxia-induced vasoconstriction, Pulmonary embolism, Chronic obstructive lung disease.	

Clinical Presentation

Symptoms of right ventricular failure include shortness of breath, pedal edema, and abdominal pain. Inspection of the neck reveals elevated jugular venous pressures. Since the most common cause of

right ventricular failure is left ventricular failure, signs of left ventricular failure are often also present.

Etiology

Right ventricular failure can be due to several causes. As just mentioned, left ventricular failure can cause right ventricular failure because of the increased afterload placed on the right ventricle. Increased afterload can also be present from abnormalities of the pulmonary arteries or capillaries-pulmonary hypertension. For example, increased flow from a congenital shunt can cause reactive pulmonary artery constriction, increased right ventricular afterload, and, ultimately, right ventricular failure. Right ventricular failure can occur as a sequela to pulmonary disease (cor pulmonale) or hypoxia-induced vasoconstriction of the pulmonary arterioles. Right ventricular failure can also be caused by right ventricular ischemia, usually in the setting of an inferior wall myocardial infarction (Table 1).

Pathophysiology

The pathophysiology of right ventricular failure is similar to that described for the left ventricle. Both systolic and diastolic abnormalities of the right ventricle can be present and usually occur because of inappropriate loads placed on the ventricle, or primaly loss of myocyte contractility.

Patients with isolated right ventricular failure (pulmonary hypertension, cor pulmonale) can have a mechanical reason for left ventricular failure. The inter-ventricular septum is usually bowed toward the thinner-walled and lower-pressure right ventricle. When right ventricular pressure increases relative to the left, the interventricular septum can bow to the left and prevent efficient filling of the left ventricle, which may lead to pulmonary congestion.

Clinical Manifestations

1. Shortness of Breath: In patients with right-sided failure due to pulmonary disease, shortness of breath may be a manifestation of the underlying disease (eg, pulmonary embolus, chronic obstructive pulmonary disease). In some patients with right ventricular failure, congestion of the hepatic veins with formation of ascites can impinge on normal diaphragmatic function and contribute to the sensation of dyspnea. In addition, reduced right-sided cardiac output alone can cause

acidosis, hypoxia, and air hunger. If the cause of right-sided failure is a left-sided defect such as mitral stenosis, the onset of right heart failure can sometimes lessen the symptoms of pulmonary edema because of the decreased load placed on the left ventricle.

2. Elevated Jugular Venous Pressure: The position of venous pulsations of the internal jugular vein can be observed during examination of the neck.

Elevated atrial pressures indicate that the preload of the ventricle is adequate but ventricular function is decreased and fluid is accumulating in the venous system. Other causes of elevated jugular pressures besides heart failure include pericardial tamponade, constrictive pericarditis, and massive pulmonary embolus.

3. Anasarca, Ascites, Pedal Edema, Hepato-jugular Reflux, Abdominal Pain: Elevated right-, sided pressures leads to accumulation of fluid in the; systemic venous circulation. Venous congestion can be manifested by generalized edema (anasarca), ascites (collection of fluid in the peritoneal space), and dependent edema (swelling of the feet and legs). Pressing on the liver for approximately 5 seconds can lead to displacement of blood into the vena cava when the right ventricle cannot accommodate this additional volume, an increase in jugular venous pressure ("hepato jugular reflux") can be observed. Expansion of the liver from fluid accumulation can cause distention of the liver capsule with accompanying right upper quadrant abdominal pain.

PULMONARY DISEASES

Lesson № 1

Respiration in a human body is composed of four steps: 1) ventilation (or breathing), 2) gas exchange in the lungs, 3) circulation of blood between the lungs and tissues and, 4) gas exchange between the blood and tissues.

- The respiratory system of the body (lungs, airways and muscles) is involved in the exchange of O_2 and CO_2 between the blood in the lungs and the inspired air (external respiration).

- Cellular or internal respiration refers to the cellular metabolic processes that break down nutrient molecules, using O_2 and producing CO_2.

During inspiration, air is forced into the lungs due to expansion of the thoracic cavity. Expansion of the thoracic cavity is caused by the contraction (flattening out) of the diaphragm at the bottom of the rib cage and the contraction of the external intercostal (between rib) muscles, causing the ribs to move upwards and outwards. The expansion of the thoracic cavity increases thoracic volume and decreases thoracic pressure so that the net flow of air is down its pressure gradient and into the lungs. Thus, ventilatory pump operates by a negative pressure suction mechanism. Contraction of the diaphragm lowers pleural pressure, which results in lung expansion, together with a tendency for the rib cage to collapse (caused by the negative pressure difference between inside and outside of the rib cage).

LUNG VOLUMES, CAPACITIES, AND THE SPIROGRAM

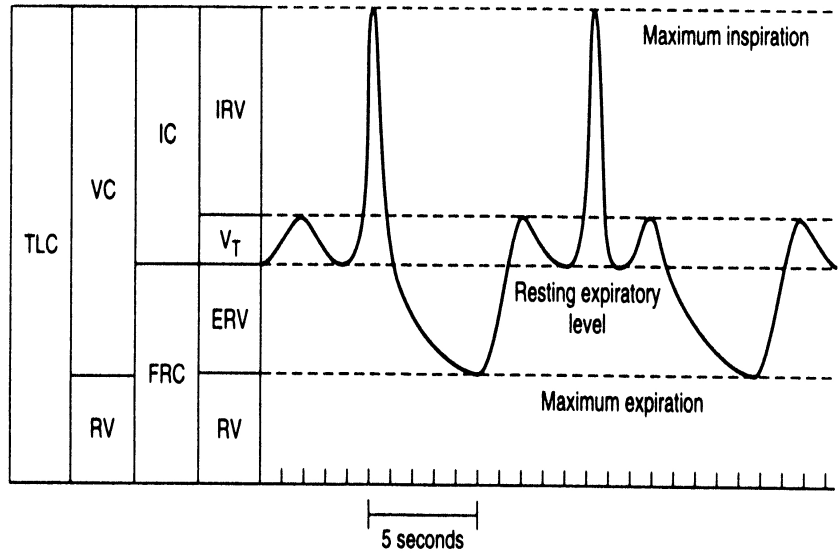


Figure 19. Lung volumes, capacities, and the normal spirogram

Spirometry is a method for measuring lung volumes during ventilation. It is used to assess lung function and is particularly helpful for diagnosing obstructive and restrictive lung diseases. Spirometers display the following graphs, called spirograms:

1. a volume-time curve, showing volume (liters) along the Y-axis and time (seconds) along the X-axis,
2. a flow-volume loop, which graphically depicts the rate of airflow on the Y-axis and the total volume inspired or expired on the X-axis.

The volume of gas in the lungs is divided into volumes and capacities as shown in the bars to the left of the Figure 19.

A. LUNG VOLUMES are primary and do not overlap each other.

1) Tidal volume (V_T) is the amount of gas inhaled and exhaled with each resting breath. A normal tidal volume in a 70-kg person is approximately 350-400 mL.

2) Inspiratory reserve volume (IRV) is amount of air that can be forcibly inspired at the end of normal inspiration; it is the amount of air, which can be inspired on top of the tidal volume.

3) Expiratory reserve volume (ERV) is amount of air that can be forcibly expired at the end of normal expiration. It is the amount of air, which can be exhaled on bottom of the tidal volume

4) Residual volume (RV) is the amount of gas remaining in the lungs at the end of a maximal exhalation. Therefore, RV is that part of the air in the lung which cannot be exhaled. It is calculated by subtracting expiratory reserve volume from functional residual capacity (FRC- see below). The residual volume is usually 20-25% of total lung capacity. The residual volume increases in diffuse airway obstruction. In this situation there is also an increase in the of RV/TLC (total lung capacity) ratio.

B. LUNG CAPACITIES are composed of two or more lung volumes.

1) The vital capacity (VC) is the total amount of gas that can be exhaled following a maximal inhalation. The VC is the total lung capacity minus the residual volume. The VC is reduced in both obstructive and restrictive respiratory disease. The VC is usually 3-6 liters, varying with age, gender and height and reduced in obstructive

and restrictive defects

2) The VC and the RV together constitute the total lung capacity (TLC), or the total amount of gas in the lungs at the end of a maximal inhalation.

3) The functional residual capacity (FRC) is the amount of gas in the lungs at the end of a resting tidal breath. In other words, FRC represent the amount of air left in the lungs at the end of a normal - not forced - expiration. It is the sum of the residual volume and the expiratory reserve volume.

4) The inspiratory capacity (IC) is defined as the tidal volume (V_T) plus the inspiratory residual volume (IRV). It is therefore the amount that can be inspired from normal expiration.

Basic pulmonary function test (spirometry)

Measurement of lung volumes and forced expiratory flow rates are useful in the clinical setting. Two types of lung disorders can be identified by spirometry measurements:

1. Obstructive lung disorders such as bronchitis and asthma. In these conditions, there is an obstructive process in the airways (the bronchi) of the lung and this is detected by a decreased ability to empty the lungs quickly during a forced expiration.

2. Restrictive lung disorders are characterized by a decrease in lung compliance, in diseases such as interstitial fibrosis, scoliosis, and loss of surfactant (acute respiratory distress syndrome-ARDS), which results in reduced alveolar volume (VC).

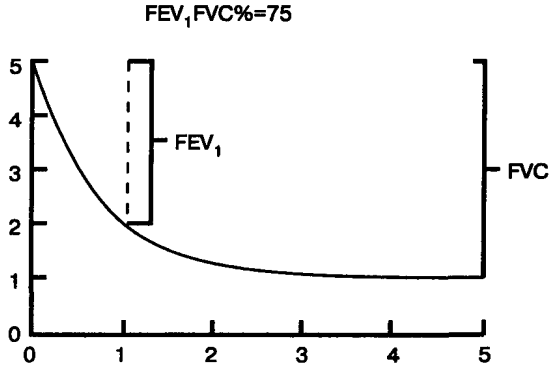


Figure 20. The spirometry of healthy subject

If the physician could only run a single pulmonary function test on a patient, the choice would probably be to determine the patient's forced vital capacity (FVC). In this test, the patient inspires maximally, and then exhales forcibly and rapidly. The volume of air the patient exhales is measured as a function of time.

The forced vital capacity (FVC) maneuver begins with an inhalation from FRC to TLC (lasting about 1 second) followed by a forceful exhalation from TLC to RV (lasting about 5 seconds). The amount of gas exhaled during the first second of this maneuver is the forced expiratory volume in 1 second (FEV_1).

Normal subjects expel approximately 75% of the FVC in the first second (Figure 20). FEV_1/FVC ratio is the ratio of the forced expiratory volume in the first one second to the forced vital capacity of the lungs.

Patients with obstructive lung disease get the air into their lungs satisfactorily, but cannot get it out. Patients with restrictive lung disease can't get the air into their lungs, thus they can't get out what they didn't get in. Even in subjects with normal lungs, the airways are subjected to negative transmural pressures during a forced expiration (dynamic compression), and therefore airways tend to collapse. In obstructive lung disease the airways are more likely to collapse during a forced expiration, thus greatly increasing resistance to airflow. As a result, FEV-1 is below normal. In restrictive lung disease, the airways do not have an increased tendency to collapse during expiration, but the expansion of the lungs during inspiration is restricted. As a result, FVC and FEV-1 both are below normal, but decrease proportionately. As a result, the ratio, FEV1/FVC, is below normal in patients with obstructive lung disease, but is normal or above normal in patients with restrictive lung disease.

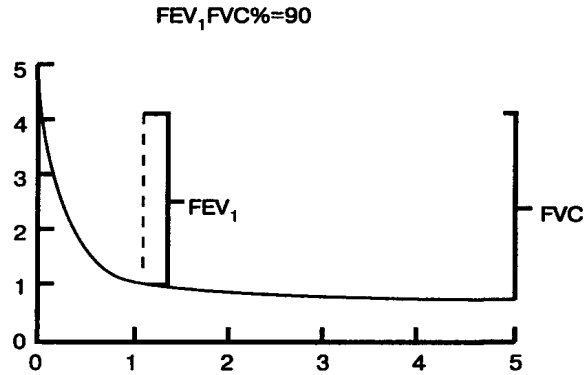


Figure 21. The spirometry of patient with restrictive lung disease, the FEV_1 and FVC fall proportionately, resulting in normal or increased values for FEV_1/FVC

Restrictive pulmonary diseases are characterized by restriction of filling of a thorax by air: pulmonary parenchima is changed in such a manner that lungs become rigid. The function of conductive airways remains normal and, hence, speed of an air stream does not undergo changes. Though FVC and FEV_1 are decreased, FEV_1/FVC ratio remains normal or even increased (Figure 21).

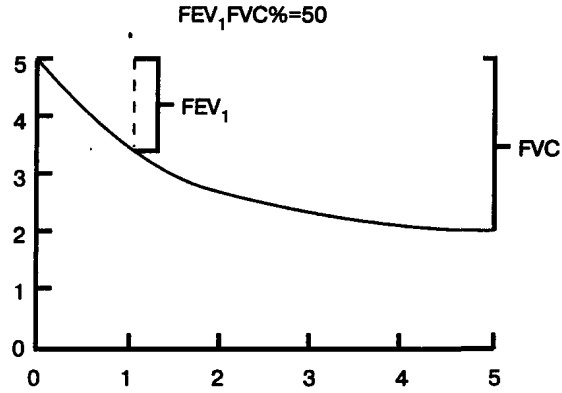


Figure 22. The spirometry of patient with obstructive lung disease, the FEV_1 is disproportionately reduced as compared to the FVC, resulting in a low FEV_1/FVC ratio

Obstructive pulmonary diseases are characterized by the narrowing of conductive airways. Therefore FEV_1 will be decreased. The function of pulmonary parenchima remains normal. Hence, FVC may be even normal (decreased with the disease progression, but to a lesser degree than FEV_1). Simultaneous decrease of FEV_1 and FVC value contribute in decreased FEV_1/FVC ratio (Figure 22).

The FEV1 is a very important landmark in assessing the overall status of the patient and quality of the test. This test result is also important in pre- and post-bronchodilator tests in determining the effects of bronchodilators on the airways.

Measurements on the Flow Volume Loop

The forced volume excursion when plotted against flow rate reveals the most recognizable shape in pulmonary function testing. There are many measurements that can be taken from this single dynamic effort (Figures 23, 24).

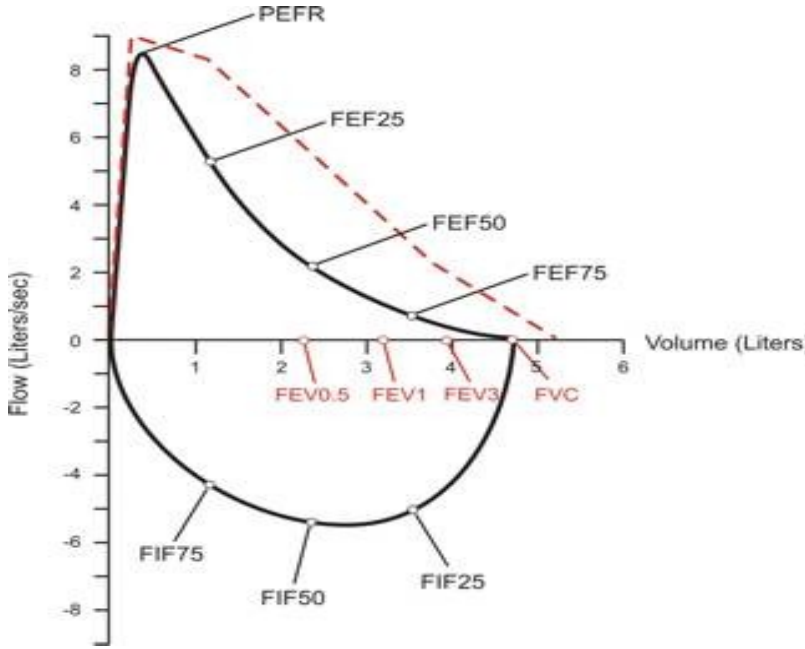


Figure 23. Flow Volume Loop

Peak Expiratory Flow Rate (PEFR). The first landmark reached is the PEFR. The first blast of air exhaled from the patient reaches this flow rate almost immediately. The flow rate then progressively slows, due to dynamic compression of airways. This landmark is very important in judging if the patient is giving maximal effort, strength of expiratory muscles, and the condition of the large airways, such as the trachea and main bronchi.

Forced Expiratory Flow at 25% of FVC (FEF25%). The FEF25% is the flow rate at the 25% point of the total volume (FVC) exhaled. Assuming maximal effort this flow rate is indicative of the condition of fairly large to medium size bronchi. (This landmark is used in calculations with the FEF75% to give FEF25-75%, the middle half of the FVC, which many physicians look at as not being dependent on patient effort and an indicator for obstruction in the small airways).

Forced Expiratory Flow at 50% of FVC (FEF50%). The FEF50% is the flow rate at the 50% point of the total volume (FVC) exhaled. This landmark is at the midpoint of the FVC and indicates the status of medium to small airways.

Forced Expiratory Flow at 75% of FVC (FEF75%). The FEF75% is the flow rate at the 75% point of the total volume (FVC) exhaled. This landmark indicates the status of small airways and is used in the FEF25-75% calculation. The damage done by most chronic pulmonary diseases show up in the smallest airways first and early indications of this damage begin to appear toward the end of the expiratory part of the Flow Volume Loop.

The inspiratory flow rates are relatively unimportant in assessing the COPD. Abnormalities here are indicators of upper airway obstructions. Areas of the mouth, upper and lower pharynx, larynx, and vocal-cords impact the inspiratory flow rates.

Forced Inspiratory Flow at 25% of FVC (FIF25%). The FIF25% is the flow rate at the 25% point on the total volume inhaled. Peak Inspiratory Flow Rate (PIFR). The fastest flow rate achieved during inspiration. Forced Inspiratory Flow at 50% of FVC (FIF50%). The FIF50% is the flow rate at the 50% point on the total volume inhaled. Forced Inspiratory Flow at 75% of FVC (FIF75%). The FIF75% is the flow rate at the 75% point on the total volume inhaled.

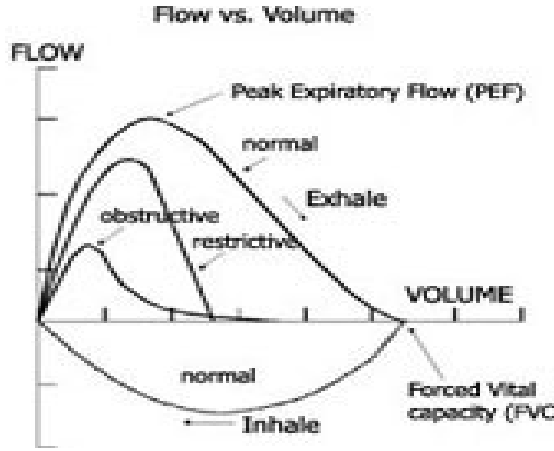


Figure 24. Flow Volume Loop in obstructive and restrictive diseases

Lesson № 2

The principal physiologic role of the lungs is to make oxygen available to tissues for metabolism and to remove the by-product of that metabolism, carbon dioxide. The lungs perform this function by placing inspired air in close proximity to the pulmonary capillary bed to permit gas exchange by simple diffusion. This is accomplished at a minimal workload and takes place with close matching of ventilation to lung perfusion.

VENTILATION TO PERFUSION MISMATCH

The functional role of the lungs is to place air in close proximity to circulating blood to permit gas exchange by simple diffusion. To accomplish this, air and blood flow must be directed to the same place at the same time. In other words, ventilation and perfusion must be matched. A failure to match ventilation to perfusion, or V/Q mismatch, lies behind most abnormalities in O_2 and CO_2 exchange.

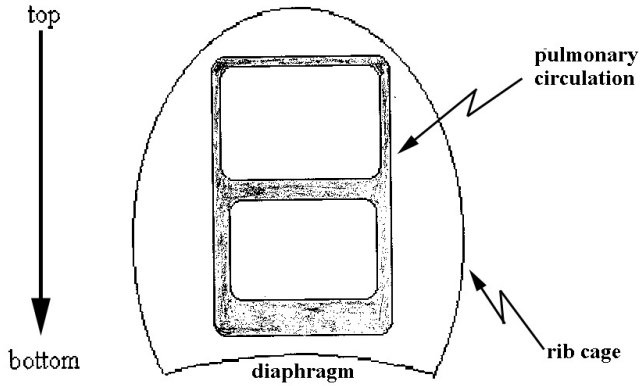


Figure 25. Gravity-dependent pulmonary flow

In the normal subject, typical resting minute ventilation is 6 L/min. approximately one-third of this amount fills the conducting airways and constitutes dead space or wasted ventilation. Resting alveolar ventilation is therefore approximately 4 L/min, while pulmonary artery blood flow is 5 L/min. This yields an overall ratio of ventilation to perfusion of 0.8. Neither ventilation nor perfusion is homogeneously distributed. Both are preferentially distributed to dependent regions at rest, though the increase in gravity-dependent flow is more marked with perfusion than with ventilation. Hence, the ratio of ventilation to perfusion is highest at the apex and lowest at the base (Figure 25).

Alterations in the normal ratio of ventilation to perfusion of 0.8 are extremely important and underlie the functional impairment in many disease states. It may increase to high V/Q ratios, with the limiting case being alveolar dead space (ventilation without perfusion, or $V/Q = \infty$, or toward low V/Q ratios, with the limiting case being a shunt (perfusion without ventilation, or $V/Q = 0$). These two shifts affect respiratory function differently (Figure 26). As noted above, approximately one-third of resting minute ventilation in normalsubjects goes to fill the main conducting airways. This is the *anatomic* dead space; it represents ventilation to areas that do not participate in gas exchange.

If gas-exchanging regions of the lung are ventilated but not perfused, as may occur in pulmonary embolism, various forms of pulmonary vascular

disease or cardiac arrest, these regions fail to function in gas exchange. They are referred to as alveolar dead space, or wasted ventilation (Figure 26).

In the absence of respiratory compensation, an increase in alveolar dead space will tend to cause disturbances in both arterial PO_2 and arterial PCO_2: PaO_2 will fall and $PaCO_2$ will rise. However, since the respiratory control center is exquisitely sensitive to small changes in $PaCO_2$, the most common response to an increase in wasted ventilation is an increase in total minute ventilation that maintains $PaCO_2$ nearly constant. PaO_2 is normal or may be reduced if the fraction of wasted ventilation is large. The A-a ΔPo_2 is increased (see below).

Abnormalities in the distribution of ventilation can result from bronchial narrowing that causes one lung unit to receive only a fraction of the ventilation of the other unit. When pulmonary blood flow is evenly distributed, the ventilation/perfusion ratio of the poorly ventilated but well perfused lung unit is low as compared to the normal lung unit. The poorly ventilated compartment will have a lower alveolar and capillary PO_2 and a higher PCO_2 than the unit with a normal V_A/Q_C (in the poorly ventilated unit only a little amount of oxygen flows in with each inspiration, and only a little amount of CO_2 can be exhaled).

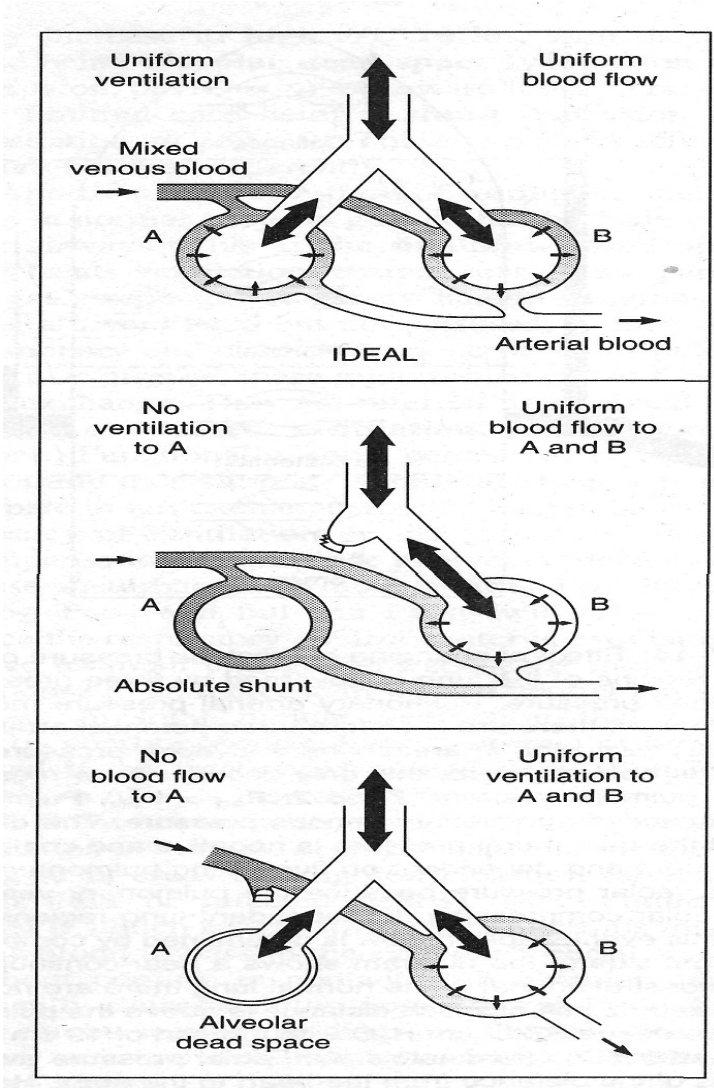


Figure 26. Three models of the relationship of ventilation to perfusion. The shaded channels represent the pulmonary blood flow, which enters the capillary bed as mixed venous blood (dark) and leaves it as arterialized blood (light). Large arrows show distribution of inspired gas; small arrows show diffusion of O_2 and CO_2. In the idealized case, the PO_2 and PCO_2 leaving both units are identical.

If the level of ventilation to the abnormal lung unit were to fall to zero, the capillary PO_2 and PCO_2 would approximate those in mixed venous blood (there is no oxygen delivered during inspiration, and no CO_2 can be removed from the alveoli). Therefore, the blood would pass unchanged from the right heart throughout the lungs to the left heart: right to left shunt.

From the gas exchange point of view, this blood flow is "wasted". Under this condition arterial PO_2 decreases if the patient is breathing air. (A simultaneous increase in PCO_2 can be compensated by the reflex increase in alveolar ventilation). A physiological mechanism exists which reduces the hypoxaemia resulting from areas of low V/Q ratio, by producing local vasoconstriction in these areas and diverting blood to other, better-ventilated parts of the lung. This effect, known as hypoxic pulmonary vasoconstriction (HPV), is mediated by local factors. A shunt might happen with atelectatic lung or in areas of lung consolidation (alveoli filled with fluid or infected debris) (Figure 27).

Such a right-to-left shunt permits mixed venous blood to pass to the systemic arterial circulation without coming in contact with alveolar gas. This typically causes a fall in *both* pO_2 and pCO_2. The reason can be seen in the diagram: The remaining respiratory unit is overventilated relative to its blood flow (large arrow).

The hyperventilation of some lung regions can compensate for a shunt through other regions but only for a possible rise in pCO_2 and not for the fall in PO_2. The reason is straightforward: The CO_2 content of blood is linearly related and inversely proportionate to alveolar ventilation. Increased ventilation to one respiratory unit can reduce the CO_2 content of blood leaving that unit. The CO_2 content of the mixture is the mean of the two units. Since the pCO_2 is directly proportionate to the CO_2 content, the reduced CO_2 content of the hyperventilated units compensates for lack of ventilation to the dead space The O_2 content of blood is not linearly related to alveolar ventilation.

The sigmoid shape of the hemoglobin-oxygen dissociation curve leaves blood nearly maximally saturated with oxygen at basal ventilation. Increased ventilation to one respiratory unit cannot significantly increase the O_2 content of blood leaving that unit. The O_2 content of the mixture is essentially the mean of normal blood oxygen content and desaturated,

shunted blood. The result is that modest falls in oxygen content lead to large discrepancies in the pO_2.

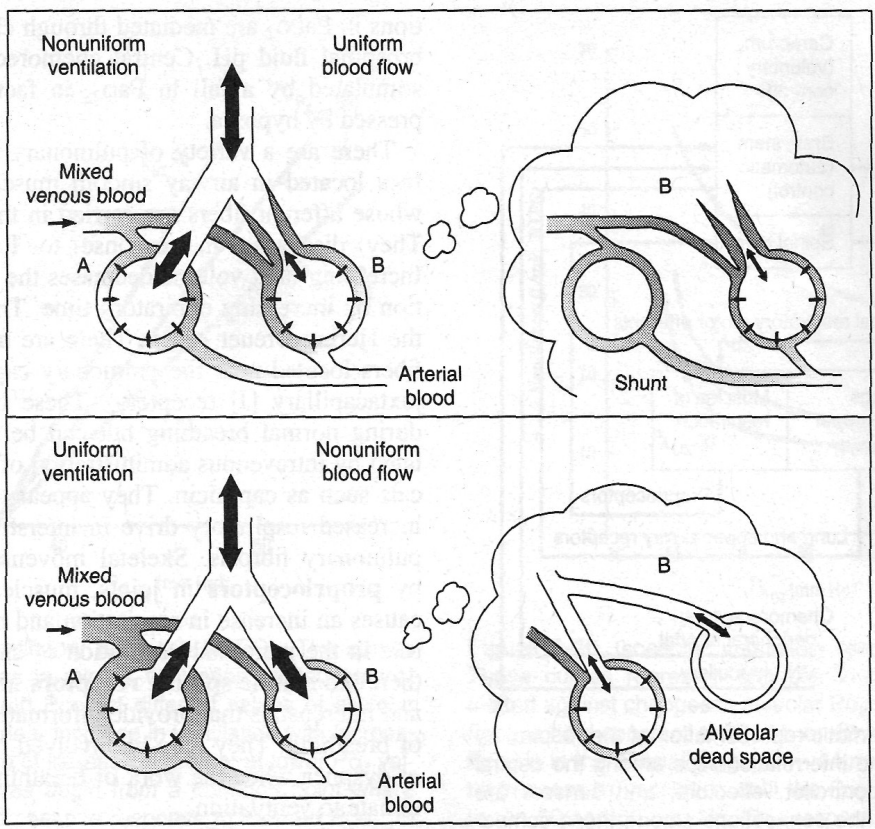


Figure 27. Ventilation-perfusion mismatching.

Ventilation/perfusion mismatching commonly falls between the extremes of shunts and wasted ventilation. In areas where the V/Q ratio lies between 0 and 0.8 or between 0.8 and °°, the effect on arterial blood gases can be predicted from the discussion of the limiting cases (Figure 27). At the top of Figure 27 is a respiratory unit where on one side ventilation has been reduced but perfusion maintained. This defines an area of low V/Q ratio. The effect on lung function can be understood by dividing it into an area with a normal V/Q ratio and an area of shunted blood.

The physiologic effect of low V/Q areas is similar to the effect of shunts: hypoxemia without hypercapnia. The difference between them can also be seen in this schematic. A true shunt is the limiting case of a low V/Q area where the ratio is zero. Shunted blood comes into no contact with inspired air; therefore, no amount of additional oxygen supplied to the inspired air will reverse the fall in systemic arterial Po_2. A low V/Q area does come in contact with inspired air and can be reversed with increased inspired oxygen.

At the bottom of Figure 27 is a respiratory unit where on one side blood flow has been decreased but ventilation maintained. This defines an area of high V/Q ratio. The effect on lung function can be understood by dividing it into an area with a normal V/Q ratio and (this time) an area of wasted ventilation. As expected, the effect of high V/Q ratios is to increase the amount of ventilation necessary to maintain a normal arterial Pco_2. Since the respiratory control system is very sensitive to small changes in $Paco_2$ and since the lungs have enormous excess capacity, the physiologic effect of high V/Q areas is to increase respiration to maintain $Paco_2$. This may be done unconsciously. It becomes a clinical problem when the subject can no longer maintain increased minute ventilation.

V/Q ratio can be assessed by ventilation-perfusion scanning.

This is a radiological procedure, which is often used to confirm or exclude the diagnosis of pulmonary embolism. It may also be used to monitor treatment.

The ventilation part of the scan is the inhalation of Krypton 81m, which has a short half-life and is a pure gamma emitter. Ventilation is assessed under a gamma camera.

The perfusion part of the scan is achieved by injecting the patient with Technetium 99m, which is coupled with macroaggregated albumin (MAA). This molecule has a diameter of 30 to 50 micrometres, and thus sticks in the pulmonary capillaries.

An unmatched perfusion defect in a ventilation perfusion scan, i.e. a perfusion defect in the absence of any ventilation defect, is pathognomic of an early pulmonary embolism - within the first three days. If a chest radiograph has been performed, there may be radiological signs of embolism. It is at this stage that there will be some reversiblity with

anticoagulant therapy.

A matched perfusion defect in ventilation perfusion scans occurs where there is both altered ventilation and perfusion over the same area of lung. In this situation the diagnosis should be apparent from the chest radiograph; there may a region of water density - which includes the possible diagnosis of an established infarction - or there may be overinflation.

CAUSES OF HYPOXEMIA
ABNORMAL V/Q RATIOS AS THE MAJOR CAUSEOF HYPOXEMIA

Respiratiry failure - Type I-hypoxemic (PaO2<60),
Type II-hypercapnic - hypoxemia, hypercapnia (PaCO2>45).

Abnormally low oxygen in the blood is caused by one or more of the following:

1. decreased FiO2/increased altitude (discussed in hypoxia),
2. hypoventilation;
3. diffusion impairment;
4. right to left shunt (usually in the lungs, but can be in the heart);
5. abnormal ventilation/perfusion ratios.

Hypoventilation: Hypoxemia develops when the pulmonary alveoli are inadequately ventilated. Clinically, the hallmark of inadequate ventilation is hypercapnia, an elevated systemic arterial pCO_2 (pCO_2 > 45 mm Hg) (Figure 28). One of the most common causes of hypoventilation is depression of the medullary respiratory center. pAO_2 is depressed approximately to the same extent that $pACO_2$ is elevated. Note, that even a 50% decrease in alveolar ventilation leaves pAO_2 at 50 mmHg, a value high enough to produce 80% saturation of Hb with O_2. The hypoxemia that is caused by hypoventilation can be remedied by administering air that is only slightly enriched with O_2.

Impairment of diffusion: this means that equilibration does not occur between the pO_2 in the pulmonary capillary blood and alveolar gas.

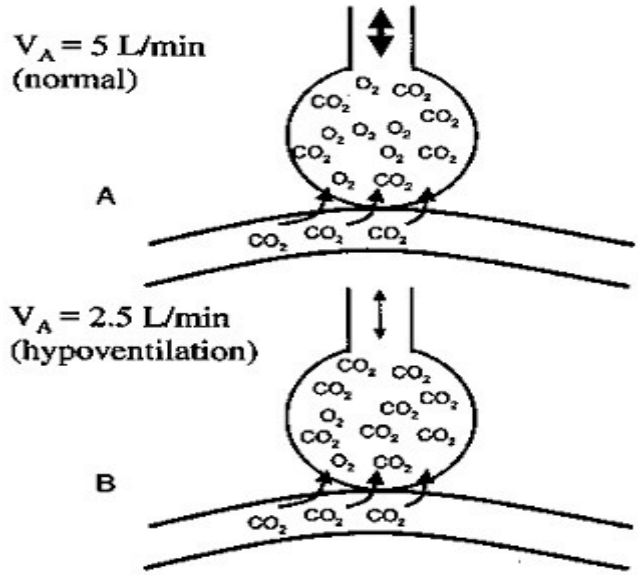


Fig. 28. Gas renewal in the air sack in hypoventilation

Under typical resting conditions, the capillary pO_2 reaches that of alveolar gas when the red cell is about one-third of the way along the capillary. Even when the capillary transit time is shortened (by exercise), the capillary blood equilibrates completely with alveolar air. However, in some abnormal circumstances when the diffusion properties of the lung are impaired, the blood does not reach the alveolar value by the end of the capillary.

Diffusion limitation seldom causes systemic hypoxemia at rest, but may cause hypoxemia during exercise when there is less time for equilibration with alveolar gas. Diseases in which diffusion impairment may contribute to hypoxemia include diffuse interstitial fibrosis, asbestosis and sarcoidosis. Impaired diffusion is also likely to develop when pAO_2 is abnormally low, such as at high altitudes. Here, the impairment occurs because the ΔP for O_2-diffusion is low. Important points - Carbon dioxide elimination is generally unaffected by diffusion abnormalities. This is because the diffusion of CO_2 is $\geq$20 times faster than O_2. Clinically, significant hypercapnia (elevations in arterial pCO2) is never caused by a diffusion defect. Hypoxemia can be easily corrected

by breathing an enriched oxygen mixture.

Shunt: Blood returning to the right heart and entering the lungs through the pulmonary artery is called mixed venous blood. If some the cardiac output bypasses functioning lung through a shunt, then arterial blood will be a mixture of normally oxygenated blood and poorly oxygenated mixed venous blood. A shunt can occur in one of two situations:

- An anatomic shunt occurs when blood bypasses the lung through an anatomic channel, such as from the right to left ventricle through a ventricular septal defect.
- A physiological shunt occurs when a portion of the cardiac output goes through the regular pulmonary vasculature without coming into any contact with alveolar air. Physiological shunting is often seen in conditions such as pulmonary edema, pneumonia, collapse of a portion of the lung (pneumothorax), and occlusion of the main bronchus.

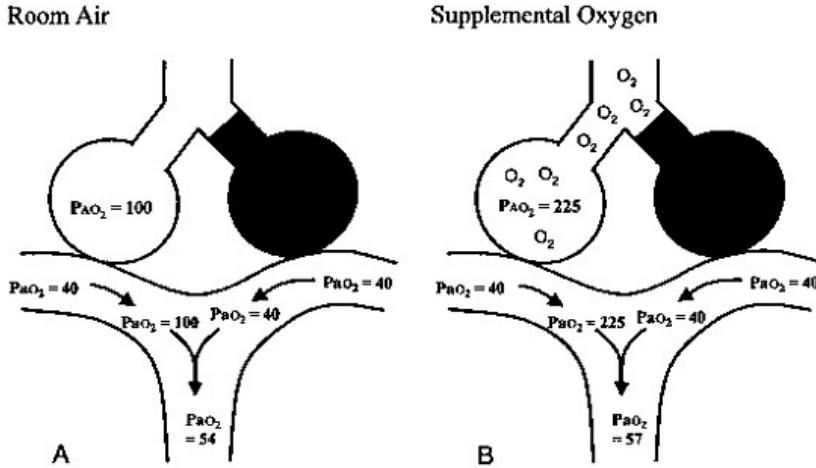


Figure 29. Supplemental oxygen cannot improve oxygenation in shunt

Since shunted blood contacts no air, increasing the fraction of inspired oxygen will not improve oxygenation (except by adding more dissolved oxygen to the normally oxygenated blood) (Figure

29.). $paCO_2$ will usually be normal or low because increased alveolar ventilation (stimulated by hypoxemia) lowers $paCO_2$.

Ventilation-perfusion abnormalities V/Q ratio determines the pO_2 and $paCO_2$ for an individual alveolar-capillary unit. V/Q imbalance is the most common cause of hypoxemia, a result of lung units with low V/Q ratios. An extreme case is easy to grasp: figure illustrates the relationship between PAO2 and PACO2 as the V/Q ratio is changed (Figure 30) The lung on the right gets all the ventilation and no blood flow; the lung on the left gets no ventilation and all the blood flow. In this case, you have a big dead space and a big shunt. This will clearly result in severe hypoxemia. In less extreme cases, a portion of the lung may be relatively underventilated and another portion of the lung may be relatively overventilated. As was already mentioned V/Q imbalance will also cause an increase in pCO_2 in the poorly ventilated alveoli. Nevertheless, systemic arterial pCO_2 will remain normal because the hypoxemia stimulates increased ventilation in rest of the lung.

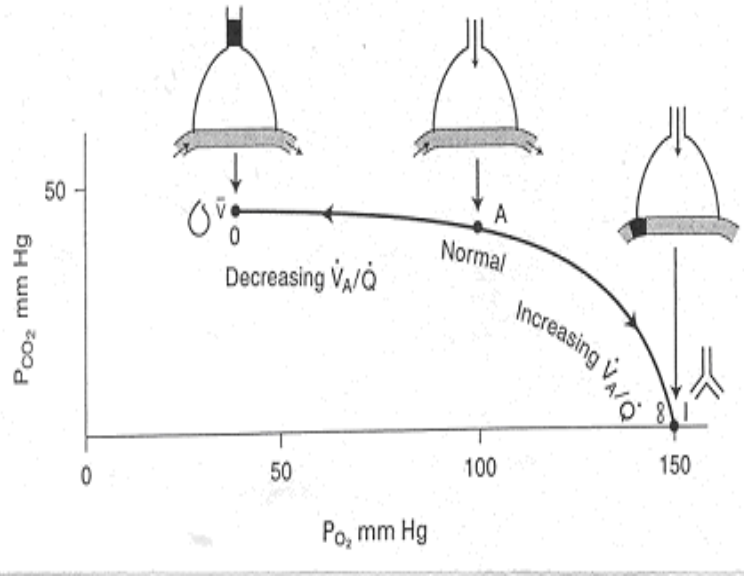


Figure 30. The relationship between PAO2 and PACO2 as the V/Q ratio is changed

The reason why increasing ventilation can lower $CaCO_2$ but cannot raise CaO_2 has to do with the shape of the oxygen and the carbon dioxide dissociation curves.

Note that the oxygen dissociation curve is nearly flat in the range of physiologic paO_2 values (above 70 mm Hg) and falls steeply below 60 mm Hg. Hyperventilation of some units does not add enough oxygen to balance out the low oxygen content from the hypoventilated units. The result is a final oxygen content determined mainly by the low V/Q areas. The carbon dioxide curve is nearly linear over the physiological range of $paCO_2$'s and its slope is much steeper than the slope of the oxygen dissociation curve. Thus a reduction in alveolar pCO_2 and corresponding increase in alveolar pO_2 due to hyperventilation cause a large decrease in the carbon dioxide content but only a small increase in oxygen content. The hyperventilation in the remainder of the lung increases the physiological dead space (V_{DAS}) of the lung. The increase V_{DAS} represents "wasted ventilation" because it is not able to raise the pO_2 of the pulmonary venous blood to normal. In most lung diseases in which ventilation is sufficiently impaired to produce hypoxemia, V_{DAS} is increased.

A-a gradient (Alveolar to arterial gradient)

Arterial blood gases detect major disturbances in respiratory function. One attempt to assess more subtle abnormalities of gas exchange is to calculate the difference between the alveolar and arterial PO_2. This is referred as the A-a ΔPo_2. The alveolar-capillary membrane permits full equilibration of alveolar and arterial oxygen tension under normal V/Q matching.

Alveolar-arterial gradient (A-a gradient) tells us about the difference in oxygen partial pressure between the alveolar and arterial blood, efficiency of gas exchange between alveolus and artery. It is a widely used variable for assessing intrapulmonary oxygen exchange and can be calculated by subtracting PaO2 from alveolar oxygen tension (PAO2).

$$\text{A-a gradient} = PAO_2 - PaO_2.$$

PaO_2 (partial pressure of O2 in the artery) - obtained from the arterial blood gases.
PAO_2 (partial pressure of O_2 in the alveoli) - obtained from the Alveolar gas equation.

Alveolar gas equation:

$$PAO_2 = FiO_2 * (P_B - P_{H2O}) - (PaCO_2 / R).$$

F_iO_2 (fraction of inspired oxygen), on room air = 0.21(21%)
$PaCO_2$ (value from your ABG)
P_B = barometric pressure (760 mmHg at sea level)
P_{H2O} Water vapor pressure (47 mm Hg at 37 °C)
R = Respiratory quotient = ratio of carbon dioxide production to oxygen consumption , V_{CO2} / V_{O2} = 0.8 (usual)

$$PAO_2 = (0{,}21\ (760 - 47)) - (PaCO_2 / 0.8) = 150 - PaCO_2 / 0.8$$

Thus, at sea level, in room air, the humidified air is usually about 150 mmHg,
PaCO2 from ABG, for normal subject, 40 mmHg,
PAO2 = 150 - 40/0.8 = 100 mmHg.

Normally, the A-a gradient increases with age,
A-a gradient = (Age+10) / 4 = 5 - 20 is normal up to middle age

Alveolar-arterial gradient can be used in diagnosing the source of hypoxemia. In conditions of high altitude or hypoventilation in which the lung parenchyma is normal, the A-a gradient should be within normal limits. In contrast, in persons with diffusion defects, ventilation-perfusion mismatch, or right-to-left shunting, oxygen is not effectively transferred from the alveoli to the blood and this results in an elevated A-a gradient.

Diagnosing respiratory failure:

Hypoxemia present (partial pressure of O2 in arterial blood (PaO2) is below normal)

|

Calculate A-a gradient

Normal	Increased
Low PaO2 is caused by 1/Hypoventilation - decreased respiratory drive or neuromuscular disease 2/Or low FiO2 (FiO2 <21%)	1/V/Q imbalance - most common cause of arterial hypoxemia or 2/Shunting (perfusion without ventilation)

||

Give 100% O2

PaO2 increases	No Change
V/Q imbalance	Shunt

JAUNDICE

Jaundice (also known as icterus), is yellowing of the skin, sclera and mucous membranes caused by increased levels of bilirubin in the human body. Jaundice comes from the French word jaune, meaning yellow

The yellow pigment is from bilirubin, a byproduct of old red blood cells. Normally, about 1% of our red blood cells retire every day, to be replaced by fresh red blood cells. When red blood cells die, the heme in their hemoglobin is converted to bilirubin in the spleen and in the Kupffer cells in the liver. The bilirubin is processed by the liver, enters bile and is eventually excreted through feaces.

1. Bilirubin originates from hemoglobin turnover (~80%) during the degradation of erythrocytes by reticuloendothelial macrophages. The remainder of bilirubin formation results from hemoprotein turnover in systemic tissues.

2. Bilirubin (BR) passes to the serum where it circulates in a complex with serum albumin. This is a fraction of serum unconjugated or bilirubin A.
3. Unconjugated BR is taken up by the liver by facilitated diffusion, involving organic ion transporters. BR is conjugated in hepatocytes by uridine diphosphate (UDP) glucuronyltransferase.
4. Conjugated BR (mono- and di-glucuronides) is pumped from hepatocytes across the canalicular membrane and excreted through the bile to the intestine.
5. Conjugated BR can be reabsorbed in the intestine and re-enter the portal circulation.
6. The metabolism of BR in the intestine by bacterial action generates urobilinogen (UB) and its oxidation product urobilin, the latter which is eliminated in the feces.
7. Intestinal urobilinogen can be reabsorbed by the intestine and eliminated in the urine as urobilin (Fig. 31).

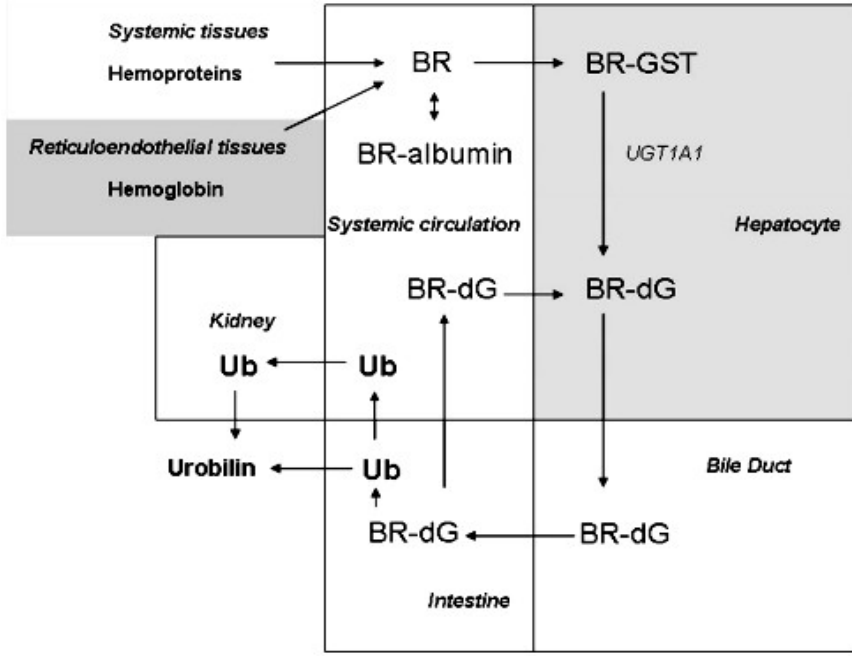


Figure 31 Biodistribution of bilirubin.

Physiologic jaundice is the name for normal jaundice commonly seen in healthy babies. Most babies have some jaundice during the first week of life. The ordeal of birth can send many red blood cells to an early retirement (especially if a vacuum is used!), and babies' livers are often unprepared for the load. Before mothers's milk comes in and stooling begins in earnest, bilirubin accumulates more easily. Jaundice is even more common in premature babies.

Pathologic jaundice is the name given when jaundice presents a health risk, either because of its degree or its cause. It arises for many reasons, including blood incompatibilities, hemolytic anemias, genetic syndromes, hepatitis, cirrhosis, bile duct blockage, infections, or medications.

Consequently, there are three different classes of jaundice. 1. Pre-hepatic, where too many red blood cells are broken down, 2.Hepatic, where the processing of bilirubin in the liver does not function correctly, and 3. Post-hepatic, where the removal of bile is disturbed.

Causes in adults include:

1. hemolytic anemias,
2. -viral hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, and hepatitis E),
   -chronic active hepatitis,
   -drug-induced hepatitis (hepatitis triggered by erythromycin sulfa drugs, antidepressants, anti-cancer drugs, oral contraceptives, testosterone, propylthiouracil…),
   -alcoholic liver disease (alcoholic cirrhosis),
   -ischemic hepatocellular jaundice (jaundice caused by inadequate oxygen or inadequate blood flow to the liver)
   -disorders present since birth that cause problems processing bilirubin (Gilbert's syndrome, Dubin-Johnson syndrome, Rotor's syndrome, or Crigler-Najjar syndromes),
3. -blocked bile ducts (by infection, tumor or gallstones) biliary stricture,
   -drug-induced cholestasis (bile pools in the gallbladder because of the effects of drugs),

-cancer of the pancreas.

Hyperbilirubinemia. Hyperbilirubinemia refers to an increased serum bilirubin concentration (i.e.,>17 micromol/l). At serum bilirubin concentrations above 20 to 25 micromol/l, the skin and sclerae turn yellow.

Classification.

Unconjugated hyperbilirubinemia. This is characterized by elevated serum levels of unconjugated bilirubin; levels of conjugated bilirubin are within normal limits. This finding typifies conditions associated with increased red blood cell destruction (e.g., hemolytic anemia, uneffective erythropoiesis), reduced hepatic bilirubin uptake (e.g., as from such drugs as rifampin), and impaired bilirubin conjugation (e.g., Crigler-Najjar and Gilbert's syndromes). These disorders usually are not associated with cholestasis.

Conjugated hyperbilirubinemia. Levels of both conjugated and unconjugeted bilirubin rise in this disorder. Intrinsic liver disease and extrahepatic biliary obstruction are the underlying causes of conjugated hyperbilirubinemia. Although most of these diseases are associated with cholestasis, some are not.

Cholestasis refers to decreased hepatocytic secretion of bilirubin, bile acids, and water, accompanied by decreased bile flow through the bile canaliculi. Cholestasis may be defined in several ways. Clinically, cholestasis refers to the presence of jaundice and pruritus in addition to elevated serum levels of conjugated bilirubin, cholesterol, and bile acids (cholemia), which normally accumulate only in the bile. Other findings include an elevated serum alkaline phosphatase level.

Congenital disorders associated with decreased bilirubin conjugation and uconjugated hyperbilirubinemia.

Crigler-Najjar syndrome (congenital hyperbilirubinemia). This relatively rare inherited disorder results from deficiency of uridine diphosphate (UDP)-glucuronyl transferase, the hepatic enzyme

responsible for bilirubin conjugation. Crigler-Najjar syndrome occurs in two forms.

Type I disease, the more severe form, is characterized by complete absence of UDP-glucuronyltransferase. It is inherited as an autosomal recessive trait. The serum bilirubin level may rise as high as 500 mg/l, reflecting severe unconjugated hyperbilirubinemia. The bile is colorless.

Type I disease often causes severe neurologic disturbances (bilirubin encephalopathy) reflecting toxic bilirubin accumulation in the brain. Type I disease is invariably fatal; however, liver transplantation and enzyme replacement may prove to be useful treatment modalities.

Type II disease, the milder form, is characterized by only partial enzyme deficiency. It is inherited as an autosomal dominant trait with incomplete penetrance. Typically, the serum bilirubin level is 60 to 200 mg/l.

Type II disease often causes jaundice during adolescence but only rarely causes bilirubin encephalopathy. Patients with type II disease may receive phenobarbital, which induced hepatic UDP-glucuronyltransferase activity.

Gilbert's syndrome. This chronic abnormality is characterized by mild, persistent unconjugated hyperbilirubinemia (the serum bilirubin level rarely exceeds 60 mg/l). It affects roughly 3% to 7% of the population, is due to underactivity of the conjugating enzyme system bilirubin–uridine diphosphate glucuronyl transferase.

Gilbert's syndrome usually is inherited as an autosomal dominant trait. Most patients are asymptomatic or have nonspecific complaints; about half have mild hemolysis of uncertain etiology. Jaundice is common and may be exacerbated by fever, infection, prolonged fasting, or excessive exercise. Phenobarbital may reduce the serum bilirubin level. Patients have an excellent prognosis, with no long-term sequelae.

Disorders associated with selective defects in intracellular transport of conjugated bilirubin and conjugated hyperbilirubinemia

Dubin-Johnson syndrome. Chronic or intermittent jaundice occurs in this syndrome in association with conjugated hyperbilirubinemia. This autosomal recessive disease involves defective hepatocyte

excretion of conjugated bilirubin and other organic anions intro the bile canaliculus. Patients commonly are asymptomatic or have vague symptoms. The conjugated hyperbilirubinemia may be exacerbated during pregnancy or with the use of oral contraceptives.

Rotor`s syndrome. This form of chronic conjugated hyperbilirubinemia also is characerized by impaired hepatic excretion of conjugated bilirubin and other organic anions. Like Dubin-Johnson syndrome, it is inherited as an autosomal recessive trait.

Toxicity of bilirubin.

Bilirubin accumulation can be harmful, especially in infants with neonatal hyperbilirubinemia. The selective toxicity of BR to the neonate is due to incomplete establishment of the blood–brain barrier. Neonatal unconjugated hyperbilirubinemia is associated with severe neurological side effects, including neurological encephalopathy. To avoid risk of neurotoxicity, phototherapy is applied or exchange transfusion is used to reduce the levels of unconjugated BR in jaundiced newborns.

Laboratory findings in jaundice

Pre-hepatic

- Serum / blood:
- bilirubin (micromoles/l) 50-150; normal range 3-17
- AST I.U. < 40U/l; normal range <40
- ALTI.U. <45 U/I; normal range <45
- albumin g/l 40-50; normal range 40-50
- reticulocytes(%) 10-30; normal range 0.5-2
- prothrombin time (seconds) 13-15; normal range 13-15
- Urinary changes:
  - bilirubin: absent
  - urobilinogen: increased or normal
- Faecal changes: stercobilinogen: increased or normal

Hepatic

- Serum / blood:

- bilirubin (micromoles/l) 50-250; normal range 3-17
- AST I.U. 300-3000; normal range <40
- ALT I.U. 250-700; normal range <45
- albumin g/l 20-50; normal range 40-50
- reticulocytes(%) 0.5-2; normal range 0.5-2
- prothrombin time (secs) 15-45; normal range 13-15
- Urinary changes:
  - bilirubin: normal or increased
  - urobilinogen: increased, normal or reduced

Faecal changes: stercobilinogen: normal or reduced

Post-hepatic

- Serum / blood:
- bilirubin (micromoles/l) 100-500; normal range 3-17
- AST I.U. 40-400; normal range <40
- ALT I.U.45-500; normal range <45
- albumin g/l 30-50; normal range 40-50
- reticulocytes(%) 0.5-2; normal range 0.5-2
- prothrombin time (secs) 15-45; normal range 13-15
- (" + parenteral vitamin K) falls
- Urinary changes:
  - bilirubin: increased
  - urobilinogen: reduced or absent

Faecal changes: stercobilinogen: reduced or absent

OVERVIEW OF LIVER DISEASES

Most of clinical consequences of liver disease can be understood either as a failure of one of the liver's four functions or as a consequence of portal hypertension.

Energy metabolism and substrate interconversion:

glucose production, glucose consumption;
cholesterol synthesis, cholesterol and triglyceride uptake;
deamination of aminoacids and convertion of ammonia to urea,
transamination and de novo synthesis of aminoacids;

Diminished energy generation and substrate interconversion.

A first category of altered liver function involves the intermediary metabolism of carbohydrates, fats, and proteins.

Carbohydrate Metabolism: Severe liver disease can result in either hypo- or hyperglycemia. Hypoglycemia results largely from decrease in functional hepatocyte mass, while hyperglycemia is a result of portal-to-systemic shunting, which decreases the efficiency of extraction of glucose from portal blood by hepatocytes, thus elevating systemic blood glucose concentration.

Lipid Metabolism: Disturbance of lipid metabolism in the liver can result in syndromes of fat accumulation early in the course of liver injury. This is because the complex steps in assembly of lipoprotein particles for export of cholesterol and triglycerides from the liver are more sensitive to disruption than the pathways of lipid synthesis, resulting in a buildup of fat within the liver.

In certain chronic liver diseases such as primary biliary cirrhosis, bile flow decreases as a result of destruction of bile ducts. The decrease in bile flow results in decreased lipid clearance via bile with consequent hyperlipidemia. These patients often develop subcutaneous accumulations of cholesterol termed xanthomas.

Protein Metabolism: Finally, any disturbance of protein metabolism in the liver can result in a syndrome of altered mental status and confusion known as hepatic encephalopathv. As with carbohydrate metabolism, altered protein metabolism can result from either hepatocyte failure or portal-to-systemic shunting, with the net effect of elevation of blood concentrations of centrally acting toxins.

Protein synthetic function

Diminished Synthesis and Secretion of Plasma Proteins. The clinical significance of liver protein synthesis and secretion derives from the wide range of functions carried out by these proteins. For example, since albumin is the major contributor to plasma oncotic pressure, hypoalbuminemia as a consequence of liver disease or nutritional deficiency presents with marked edema formation. Other important proteins synthesized and secreted by the liver include clotting factors and hormone binding proteins.

Solubilization, transport and storage function:

drug and poison detoxification through biotransformation,

solubilization of fats and fat-soluble vitamins in bile for enterocyte uptake,

synthesis and secretion of VLDL and pre-HDL particles and clearance of HDL, LDL and chylomicron remnants,

synthesis and secretion of binding proteins- transferrin, steroid hormone-binding globulin, thyroid hormone-binding globulin…,

uptake and storage of vitamins A,D,B_{12} and folate.

Loss of Solubilization and Storage Functions.

Impaired Drug Detoxification:

Two features of the mechanisms of drug detoxification are of particular clinical importance. One is the phenomenon of enzyme induction. The presence in the bloodstream of any of the large class of drugs inactivated by phase I enzymes (oxidation, reduction…) increases the amount and activity of these enzymes in the liver. This property of enzyme induction makes physiologic sense (as a response to the body's need for increased bio-transformation) but can have undesired effects as well. A patient who chronically consumes large amounts of a substance that is metabolized by phase I enzymes (eg, ethanol) will induce high levels of these enzymes and thus speed up the metabolism of other substances metabolized by the same detoxifying enzymes (eg, anticoagulant medications, resulting in subtherapeutic blood levels of the drugs).

A second clinically important phenomenon in drug metabolism is that phase I reactions often convert relatively benign compounds into more reactive and hence
more toxic ones. Normally, this heightened reactivity of phase I reaction products serves to facilitate phase II reactions (conjugation), making detoxification more efficient. However, under certain conditions when phase II reactions are impaired (eg, glutathione deficiency from inadequate nutrition), enhanced phase I enzyme activity can cause increased liver injury. This is because the products of phase I reactions, in the absence of glutathione, may react with and damage cellular components. Such damage can rapidly kill a hepatocyte.

Thus, the combined effects of certain common conditions can make the individual abnormally sensitive to the toxic effects of drugs. For

example, the combination of induced phase I activity (eg, due to alcoholism) with low phase II activity (eg, due to low glutathione levels from nutritional deprivation) can result in heightened generation of reactive intermediates •(ROS) with an inadequate capacity to conjugate and detoxify them.

Disordered Bile Secretion:

The clinical significance of bile synthesis can be seen in the prominence of cholestasis—failure to secrete bile—in many forms of liver disease. Cholestasis can occur as a result of extrahepatic obstruction (eg, from a gallstone in the common bile duct) or of selective dysfunction of the bile synthetic and transplant machinery within the hepatocytes themselves—intrahepatic obstruction. The clinical consequences of severe cholestasis may be profound: a failure to secrete bile results in a failure to solubilize substances such as dietary lipids and fat-soluble vitamins, resulting in malabsorption and deficiency states.

The solubilization function of bile works both to excrete and to absorb substances. Thus, in cholestasis, endogenous substances that are normally excreted via the biliary tract can accumulate to high levels. One such substance is bilirubin, a product of heme degradation. The buildup of bilirubin results in jaundice or icterus. In the adult, the most significant feature of jaundice is that it serves as a readily monitored index of cholestasis, which may occur alone or with other abnormalities in hepatocyte function (ie, as part of the presentation of acute hepatitis).

Similarly, cholesterol is normally excreted either by conversion into bile salts or by forming complexes, termed micelles, with preexisting (recycled) bile salts. In cholestasis, the resultant buildup of bile salts can lead to their deposition in the skin, manifested as intense itching, or pruritus. Disorders of bile production are a basis for the formation of cholesterol gallstones. Nevertheless, other hepatocyte functions are often relatively well preserved in the face of significant cholestasis.

Lipoprotein Dynamics and Dyslipidemias:

Deficient functional LDL receptor renders the liver unable to clear LDL cholesterol from the bloodstream, resulting in markedly elevated serum cholesterol and accelerated atherosclerosis and coronary artery disease.

In liver diseases, the serum cholesterol is also elevated in biliary tract obstruction, which blocks cholesterol excretion in bile; and diminished in severe alcoholic cirrhosis, in which fat malabsorption prevents cholesterol intake.

Altered Hepatic Binding and Storage Functions:

Liver disease influences the liver's ability to store various substances. As a result, patients with liver disease have a high risk of developing certain deficiency states such as folic acid and vitamin B_{12} deficiency. Since these vitamins are needed for DNA synthesis, their deficiency results in macrocytic, hyperchromic anemia, a common finding in patients with liver disease.

4. Protective and clearance function:

clearance of bacteria and antigens from the portal circulation,
detoxification of ammonia,
clearance of damaged cells and proteins, hormones and activated clotting factors from the portal circulation.

Loss of Protective and Clearance Functions.

A crucial protective function of the liver is its role as a filter of blood from the gastrointestinal tract, by which various substances are removed from portal blood before it reenters the systemic circulation.

Clearance of Bacteria and Endotoxin:

Clearance of bacteria by Kupffer cells of the liver is the final line of defense in keeping gut-derived bacteria out of the systemic circulation. Loss of this capacity in liver disease due to portal-to-systemic shunting may help to explain why, in patients with severe liver disease, infections can rapidly decompensate into sepsis.

Altered Ammonia Metabolism:

Impairment of the liver's ability to detoxify ammonia to urea leads to hepatic encephalopathy, manifested as an altered mental status. This may be an early manifestation of acute fulminant hepatitis with massive hepatocellular dysfunction even before the development of maximal hepatocellular necrosis. It can be a final step in progressive chronic liver disease with diminished hepatocyte functional capacity. Most often it is a consequence of an increased ammonia load in a patient with marginal liver function or significant portal-to-systemic shunting.

Hepatic encephalopathy may occur as a first sign of renewed gastrointestinal bleeding (as a result of increased production of ammonia and other products due to breakdown of blood protein and urea by gastrointestinal tract microbes) or may simply be due to increased protein intake (eg, a cheeseburger eaten by a patient with cirrhosis).

Finally, the development of sepsis in these predisposed patients results in increased endogenous protein catabolism and therefore elevated ammonia production. Thus, the development of encephalopathy in a patient with chronic liver disease calls for investigation of possible acute gastrointestinal bleeding as well as potentially catastrophic infection. Pending the outcome of diagnostic studies (eg, serial hematocrit measurements and cultures of blood, urine, and ascitic fluid), therapy is designed to improve mental status by diminishing the absorption of ammonia and other noxious substances from the gastrointestinal tract. When the patient is given the nonabsorbable carbohydrate lactulose, whose metabolism by microbes creates an acidic environment, ammonia is trapped as the charged NH_4^+ species in the gut lumen and excreted by the resulting osmotic diarrhea. Thus, this toxin is prevented from ever entering the portal circulation, and the patient's mental status gradually improves.

Altered Hormone Clearance in Liver Disease:

Normally, the liver removes from the bloodstream the fraction of steroid hormones not bound to steroid hormone-binding globulin. Upon uptake by hepatocytes, the hormones are oxidized, conjugated, and excreted into bile, where a fraction undergoes enterohepatic circulation. In liver disease accompanied by significant portal-to-systemic shunting, steroid hormone clearance is diminished; extraction of the enterohepatic circulated fraction is impaired; and peripheral aromatization of androgens to estrogens is increased. The net effect is an elevation of blood estrogens. Thus, male patients with liver disease display both gonadal and pituitary suppression as well as feminization.

Sodium and Water Balance

Patients with liver disease often display renal abnormalities and complications, most commonly sodium retention and difficulty in excreting water. An intrinsic renal lesion is apparently not involved, since the kidneys of patients with liver disease typically function

normally when transplanted into patients with normal livers. Instead, renal abnormalities associated with liver disease are functional, occurring because liver disease induces altered intravascular pressures. As a result, homeostatic mechanisms perceive intravascular volume as being inadequate when it is really only maldistributed. Renal mechanisms of salt and water retention are then stimulated to correct what has been sensed as volume depletion. Moreover aldosterone clearance is diminished, causing hyperaldosteronism with sodium and water retention. In addition, patients with severe liver disease are at risk of developing renal failure.

Common Laboratory Tests in Liver Diseases

The diagnosis of liver diseases depends upon a combination of history, physical examination, laboratory testing, serologic and sometimes radiological studies and biopsy. One must keep in mind that abnormalities of these laboratory tests are not diagnostic of specific diseases. The hepatobiliary tree represents hepatic cells and biliary tract cells. Inflammation of the hepatic cells results in elevation in the alanine aminotransferase (ALT), aspartate aminotransferase (AST) and the bilirubin. Inflammation of the biliary tract cells results predominantly in an elevation of the alkaline phosphatase. In liver disease there are crossovers between purely biliary disease and hepatocellular disease.

Alanine aminotransferase (ALT)

ALT is an enzyme produced in hepatocytes. ALT is often inaccurately referred to as a liver function test, however, its level in the blood tells little about the function of the liver. The level of ALT in the blood is increased in conditions in which hepatocytes are damaged or die. As cells are damaged, ALT leaks out into the bloodstream. All types of hepatitis (viral, alcoholic, drug-induced, etc.) cause hepatocyte damage that can lead to elevations in the serum ALT activity. The ALT level is also increased in cases of liver cell death resulting from other causes, such as shock or drug toxicity. The level of ALT may correlate roughly with the degree of cell death or inflammation, however, this is not always the case. An accurate estimate of inflammatory activity or the amount cell death can only be made by liver biopsy.

Aspartate aminotransferase (AST)

AST is an enzyme similar to ALT but less specific for liver disease as it is also produced in muscle and can be elevated in other conditions (for example, early in the course of a heart attack). AST is also inaccurately referred to as a liver function test by many physicians. In many cases of liver inflammation, the ALT and AST activities are elevated roughly in a 1:1 ratio. For unclear reasons, perhaps somehow related to liver cell polarity, certain forms of liver disease typically result in disproportionate elevations in some parameters. Thus, in alcoholic and other toxic hepatitis but not in viral hepatitis, AST is often disproportionately elevated relative to ALT (AST:ALT ratio > 2.0). Likewise, in cholestasis, alkaline phosphatase is disproportionately elevated relative to AST or ALT.

Alkaline phosphatase

Alkaline phosphatase is an enzyme, or more precisely a family of related enzymes, produced in the bile ducts, intestine, kidney, placenta and bone. An elevation in the level of serum alkaline phosphatase, especially in the setting of normal or only modestly elevated ALT and AST activities, suggests disease of the bile ducts. Serum alkaline phosphatase activity can be markedly elevated in bile duct obstruction or in bile duct diseases such as primary biliary cirrhosis or primary sclerosing cholangitis, gallstones in choledocholithiasis. However, considering the above other etiologies must also be entertained. One way to assess the etiology of the alkaline phosphatase is to perform a serologic evaluation called isoenzymes. Another more common method to asses the etiology of the elevated alkaline phosphatase is to determine whether the GGT is elevated or whether other function tests are abnormal (such as bilirubin).

Bilirubin

Bilirubin is a major breakdown product of hemoglobin. Bilirubin concentrations are elevated in the blood either by increased production, decreased uptake by the liver, decreased conjugation, decreased secretion from the liver or blockage of the bile ducts.

In cases of increased production, decreased liver uptake or decreased conjugation, the unconjugated or so-called indirect bilirubin will be primarily elevated.

In cases of decreased secretion from the liver or bile duct obstruction, the conjugated or so-called direct bilirubin will be primarily elevated. Many different liver diseases, as well as conditions other than liver diseases (e. g. increased production by enhanced red blood cell destruction), can cause the serum bilirubin concentration to be elevated.

Most adult acquired liver diseases cause impairment in bilirubin secretion from liver cells that cause the direct bilirubin to be elevated in the blood. In chronic, acquired liver diseases, the serum bilirubin concentration is usually normal until a significant amount of liver damage has occurred and cirrhosis is present. In acute liver disease, the bilirubin is usually increased relative to the severity of the acute process. In bile duct obstruction, or diseases of the bile ducts such as primary biliary cirrhosis or sclerosing cholangitis, the alkaline phosphatase and GGT activities are often elevated along with the direct bilirubin concentration.

Gamma-glutamyltranspeptidase (GGT)

An enzyme produced in the bile ducts that, like alkaline phosphatase, may be elevated in the serum of patients with bile duct diseases. Elevations in serum GGT, especially along with elevations in alkaline phosphatase, suggest bile duct disease. Measurement of GGT is an extremely sensitive test, however, and it may be elevated in virtually any liver disease and even sometimes in normal individuals. GGT is also induced by many drugs, including alcohol, and its serum activity may be increased in heavy drinkers even in the absence of liver damage or inflammation.

Albumin

Albumin is the major protein that circulates in the bloodstream. Albumin is synthesized by the liver and secreted into the blood. It is only one of many proteins that are synthesized by the liver. However, since it is easy to measure, it represents a reliable and inexpensive laboratory test for physicians to assess the degree of liver damage present in any particular patient. Low serum albumin concentrations indicate poor liver function. The serum albumin concentration is usually normal in chronic liver diseases until cirrhosis and significant liver damage is present. When the liver has been chronically damaged, the albumin may be low.

Albumin levels can be low in conditions other than liver diseases including malnutrition, some kidney diseases.

Serum protein electrophoresis

In this test, the major proteins in the serum are separated in an electric field and their concentrations determined. The four major types of serum proteins whose concentrations are measured in this test are albumin, alpha-globulins, beta-globulins and gamma-globulins. Serum protein electrophoresis is a useful test in patients with liver diseases as it can provide clues to several diagnostic possibilities. In cirrhosis, the albumin may be decreased (see above) and the gamma-globulin elevated (disproteinemia). Gamma-globulin can be significantly elevated in some types of hepatitis as they are immunoglobulins. The alpha-globulins can be high in inflammation as they are acute phase reactants (acute phase proteins).

Prothrombin time (PT)

Many factors necessary for blood clotting are synthesized in the liver. When liver function is severely abnormal, their synthesis and secretion into the blood is decreased. The prothrombin time is a type of blood clotting test performed in the laboratory and it is prolonged when the blood concentrations of some of the clotting factors made by the liver are low.

In chronic liver diseases, the prothrombin time is usually not elevated until cirrhosis is present and the liver damage is fairly significant. In acute liver diseases, the prothrombin time can be prolonged with severe liver damage and return to normal as the patient recovers. Prothrombin time can also be prolonged in cases of vitamin K deficiency, by drugs (warfarin, used therapeutically as an anti-coagulant, prolongs the prothrombin time) and in non-liver disorders. Since a prolonged PT is not a specific test for liver disease, confirmation of other abnormal liver tests is essential. This may include reviewing other liver function tests or radiology studies of the liver. Diseases such as malnutrition, in which decreased vitamin K ingestion is present, may result in a prolonged PT time. An indirect test of hepatic synthetic function includes administration of vitamin K subcutaneously over three days. Several days later, the prothrombin time may be measured. If the

prothrombin time becomes normal, then hepatic synthetic function is intact.

GLOMERULAR FILTRATION RATE (GFR)

The glomerulus, the filtering unit of the kidney, is a capillary network interconnected between the afferent and efferent arteriole. The four determinants of glomerular filtration are:
the blood flow and filtration pressure
the physico-chemical properties of the filtrate
the structure of the capillary wall
surface area of the capillary wall

The glomerular capillary pressure is much higher than in most other capillaries. This pressure, which is directly derived from the hydrostatic blood pressure, is the driving force behind the filtration of water and solute over the capillary wall into the urinary space. The net effective filtration pressure starts at about 15 mm Hg as a result of the intracapillary hydrostatic pressure of 45 mm Hg minus the sum of the pressure in Bowman's capsule (10 mm Hg) and the plasma colloidal osmotic pressure of 20 mm Hg at the entrance of the glomerulus.

Other factors, which determine the filtration capacity, are the blood flow, the structure of the capillary wall (which factor is also called the ultrafiltration coefficient) and the filtration surface. Elevation of blood pressure and intracapillary flow will both lead to an increase in filtration. Such a higher pressure has a dangerous side: the endothelium can easily be injured as is seen in hypertension in general, a process which may lead to sclerosis.

Autoregulation of filtration.

Autoregulation is of great importance in the maintenance of filtration during changes in blood pressure. Autoregulation is achieved by the interplay of afferent and efferent arteriolar constriction and dilatation in concert with the macula densa and the mesangium. An important role is played by angiotensin II, the vasoconstrictive effector hormone of the renin angiotensin system (RAS), and in addition by prostaglandins, endothelins and nitric oxide.

Endothelins. The endothelins are peptides with a strong vasoconstrictor action, but a very short half-life. The hemodynamic actions of endothelins are limited to local effects, because little of this hormone escapes into the general circulation.

In the kidney, several agents — ANG II, epinephrine, thrombin and shear stress — trigger release of endothelins from the endothelium of renal cortical vessels and mesangial cells. The endothelins act locally to constrict smooth muscles of renal vessels and thus most likely are a link in the complex network of local messengers between endothelium and smooth muscle. When administered systemically, endothelins constrict the afferent and efferent arterioles and reduce the ultrafiltration coefficient (K_f). The result is a sharp reduction in GFR.

Leukotriens. Probably in response to inflammation, the renal vascular smooth-muscle cells and glomeruli as well as leukocytes and blood platelets produce leukotrienes from arachidonic acid, via the lipoxygenase pathway. These locally acting vasoactive agents are strong vasoconstrictors; their infusion reduces GFR.

Prostaglandins. In the kidney, vascular smooth-muscle cells, endothelial cells, mesangial cells, and tubule and interstitial cells of the renal medulla are particularly important for synthesizing the locally acting prostaglandins from arachidonic acid, via the cyclooxygenase pathway. The effects of prostaglandins are complex and depend on the baseline vasoconstriction exerted by ANG II.

Prostaglandins appear mainly to be protective and are important under conditions when the integrity of the renal circulation is threatened. In particular, local intrarenal effects of prostaglandins provide a buffer against excessive vasoconstriction, especially during increased sympathetic outflow to the kidney or activation of the renin-angiotensin system. Accelerated prostaglandin synthesis and release are responsible for maintaining fairly constant blood flow and GFR in conditions of high ANG II levels — for example, during surgery, following blood loss, or in the course of salt depletion.

Nitric oxyde. The endothelial cells of the kidney use nitrous oxide synthase (NOS) to generate NO from L-arginine. NO has a strong smooth-muscle-relaxing effect and — under physiological, unstressed conditions — produces significant renal vasodilation. NO probably

defends against excess vasoconstrictor effects of agents such as ANG II and epinephrine. Injecting NOS inhibitors into the systemic circulation constricts afferent and efferent arterioles, increasing renal vascular resistance and producing a sustained fall of renal blood flow and GFR.

Autoregulation

1. When the systemic blood pressure rises, the glomerular blood pressure is maintained at a constant level by constriction of the afferent arteriole. In this way filtration pressure is maintained constant and glomerular capillaries are protected against the injurious effects of hypertension. A drop in glomerular pressure with maintenance of a normal flow at decreased intracapillary pressures can be achieved by dilatation of the efferent arteriole, which may be enhanced by inhibition of angiotensin converting enzyme.

2. When the systemic blood pressure drops, the afferent arteriole is dilated, allowing sufficient pressure to be transduced to the glomerular capillary network. Efferent constriction may help to potentiate this effect. As a result the pressure in the glomerular capillaries will be maintained.

In this way changes in systemic blood pressure can easily be compensated for and filtration during systemic hypo- or hypertension can be maintained constant, at least within certain limits. Furthermore, the glomerulus uses this balance to achieve adaptation in glomerular filtration pressure in circumstances where more water or salt have to be filtered or in order to supersede increased capillary wall resistance, for example during glomerular inflammation.

The filtration equilibrium

The filtration equilibrium illustrates the relative contributions of the three forms of pressure which result in the net filtration pressure:

the intracapillary (hydrostatic) pressure

the colloidal osmotic pressure

the Bowman's capsule pressure

At the beginning of the glomerular capillary tuft at the afferent arteriolar side of the glomerulus, the intracapillary pressure is maximal and the colloidal osmotic pressure is minimal. During the glomerular

passage of circulating blood, the colloidal osmotic pressure will rise, because an increasing amount of water and salt migrates from the capillary lumen to the urinary space resulting in an increase of plasma protein concentration. At a given moment, the colloidal osmotic pressure has reached a level at which the Bowman's capsule pressure equals that of the capillary filtration pressure. As a consequence net filtration pressure is zero. The higher the intracapillary flow, the farther along the glomerular capillary tuft this point of equilibrium will be reached.

Pathological changes which are due to alterations in glomerular hemodynamics can be subdivided into injury caused by hypertension and injury caused by hypotension.

Hypertension usually leads to atherosclerosis in arteries and arterioles leading towards the glomerulus. This will result in narrowing of arteriolar lumina with an ultimate ischemic collapse of the glomerular capillary tuft and a loss of the nephron with tubular atrophy. In some patients with hypertension however systemic hypertension permeates into the glomerular tuft, probably due to a failure of afferent vasoconstriction. As a result higher filtration pressure will lead to filtration of proteins (glomerular proteinuria) and to endothelial injury causing sclerotic changes with endothelial activation, coagulation, hyalinosis, mesangial cell proliferation and increase of matrix deposition. The morphological changes are usually defined as secondary focal and segmental glomerulosclerosis.

Hypotension usually is without consequences for the glomeruli, but can have severe effects of tubules because of their high need for oxygen consumption. Tubular cell dysfunction and morphological degeneration with tubular cell necrosis can be the consequences of hypotension. Hypotension of short duration usually shows these changes to be reversible.

The glomerular capillary wall structure and physico- chemical properties of the filtrate

The glomerular capillary wall (GCW) is composed of fenestrated endothelium, a glomerular basement membrane (GBM) and a layer of

highly differentiated arborised interdigitating visceral epithelial cells also called podocytes.

The podocytes are interlinked by cytoplasmic foot processes, interconnected through slit pores, which resemble hemidesmosomes. These slit pores function as filtration slits. In concert with the GBM, the podocytes constitute the capillary wall that has to sustain the intracapillary filtration pressure. At the basis of all glomerular capillaries a third cell type is situated: the mesangial cell. The cell is continuous with the smooth muscle cells of the afferent and efferent arterioles. Mesangial cells have contractile filaments and angiotensin receptors; they can contract upon exposure to angiotensin II and thus determine the width of the capillary lumina and the filtration surface area.

The fenestrated endothelial cell is the only barrier between the capillary lumen and the mesangial area without interposition of the GBM. As a result water and solute can easily penetrate the mesangial area, but also larger circulating proteins and cells can reach this compartment. The mesangium is able to clear these filtration residues by a process of phagocytosis in which mesangial smooth muscle cells as well as mesangial macrophages are involved.

The peripheral glomerular capillary wall functions as a size and charge selective filter. The pores in the wall are composed of the fenestrae of the endothelium, the matrix proteins of the GBM containing collagen IV, laminin, nidogen and heparan sulphate proteoglycans, and the filtration slits between the podocytes. The negative charge of the GCW is attributed to acid mucopolysaccharides on the cell surface of endothelial and epithelial cells and to the heparan sulphate moieties decorating the proteoclycans along the inner and outer side of the GBM. The sieve structure and the overall negative charge render the GCW its size and charge selective function, which retards circulating molecules in their filtration, proportionally to their molecular radius and their negative molecular charge.

The pathophysiological relevance of charge selectivity is illustrated by the filtration of albumin. Albumin is a protein with a molecular radius compatible with relatively unhindered passage through the filter. In reality albumin is greatly restricted from filtration, solely due to its

negative charge. The negative charge of the GCW also has a negative side: positively charged circulating molecules such as histone- covered nucleosomes and bacterial cell wall components can easily attach to the negatively charged capillary wall. By consecutive binding of specific circulating antibodies (anti-DNA in patients with systemic lupus erythematosus and antistreptolysin in streptococcal infections) can result in immune complex formation leading to an inflammatory response.

In addition to size and charge the molecular configuration of a molecule is also important for its passage through the filter: a sugar molecule with the same molecular weight as a protein can pass the GCW at a higher rate than the protein because it can unfold while the protein has a fixed, globular configuration. This illustrates to which extent filtration is determined by physico-chemical properties of the GCW and the filtrate.

Pathological changes in the process of filtration can occur by injury of the GCW or by a change in the size, charge or configuration of the filtrate. Injury of the GCW can follow two major pathways:

- the filter can be clogged, for example by endothelial swelling during acute inflammation, or by connective tissue deposition in chronic inflammation which results in decreased filtration of water and solute,
- in the alternative case, the filter can show increased permeability, for example by injury of the podocytes, allowing the development of large pores and loss of size and charge selectivity resulting in increased filtration of plasma proteins together with an unhindered filtration of water and solute

In cases of severe inflammation endothelial swelling may lead to a severe loss of glomerular filtration rate, and disruption of parts of glomerular capillary walls may occur, resulting in leakage of plasma proteins and circulating leukocytes into the urine.

MEASURING RENAL CLEARANCE

Clearance is the volume of blood plasma, which is totally cleared each minute of a given indicator by a specific organ (eg, renal clearance).

The renal clearance approach compares the rate at which the glomeruli filter a substance (water or a solute) with the rate at which the kidneys excrete it into the urine.

$$C_X = \frac{U_X \cdot \dot{V}}{P_X}$$

This is the classic clearance equation that describes the virtual volume of plasma that would be totally cleared of a solute in a given time. We need to know only three parameters to compute the clearance of a solute X:
the concentration of X in the urine (U_X),
the volume of urine formed in a given time (V),
the concentration of X in systemic blood plasma (P_X).

We can use a clearance approach to estimate glomerular filtration rate (GFR), which is the volume of fluid filtered into the Bowman capsule per unit time.

Imagine a solute X that fulfills two criteria:
first, X is freely filtered (i.e., concentration of X in Bowman's space is the same as that in blood plasma),
second, the tubules do not absorb, secrete, or metabolize X.

Thus, the amount of X that appears in the urine per unit time ($U_X \cdot V$) is the same as the amount of X that the glomerulus filters per unit time ($P_X \cdot GFR$).

$$\overbrace{P_X \cdot GFR}^{\text{Input to Bowman space}} = \overbrace{U_X \cdot \dot{V}}^{\text{Output into urine}}$$

Rearranging previous equation:

$$GFR = \frac{U_X \cdot \dot{V}}{P_X}$$

This equation is in exactly the same form as the classic clearance equation. In other words, GFR is C_X if X has the required properties. Any substance X that has the same concentration in the glomerular filtrate as in plasma, and is neither reabsorbed nor secreted along the nephron, could serve as a glomerular marker for measuring GFR. Thus, the plasma clearance of a glomerular marker is the glomerular filtration rate. Inulin is an exogenous starch-like fructose polymer that is freely filtered at the glomerulus, but neither reabsorbed nor secreted by the

renal tubules. Additional requirements for a glomerular marker, which inulin also fulfills, are that the substance is not metabolized or synthesized by the kidney, is nontoxic, and has no effects on GFR. Although the inulin clearance is the most reliable method for measuring GFR, it is not practical for clinical use. One must administer inulin intravenously to achieve reasonably constant plasma inulin levels.

The Clearance of Creatinine is a Clinical Index of GFR

The problems of intravenous infusion of a GFR marker can be completely avoided by using an endogenous substance with inulin-like properties. Creatinine is such a substance, and its clearance is a reasonable estimate of GFR in humans. The source of plasma creatinine is the normal metabolism of creatine phosphate in muscle. In the steady state, the rate of urinary creatinine excretion equals this rate of metabolic production. Therefore, to avoid errors in estimating the GFR from the creatinine clearance, one must take care to exclude non-steady state pathologic conditions of creatinine release, such as hyperthermia or other conditions of muscle wasting or damage. Ingestion of meat, which has high creatinine content, also produces non-steady state conditions. To minimize the effects of such ingestion, the patient collects urine over an entire 24-hour period, and the plasma sample is obtained by venipuncture in the morning prior to breakfast.

In numbers filtration can be summarised as follows: every minute, 120 mL plasma with all its small molecules is filtered from the capillary lumen into the urinary space by approximately 1.5 to 2.0 million glomeruli

Example of GFR calculation.

P_{cr}=1.2 mg/dl

U_{cr}=100 mg/dl

V=1080 ml/day :1440 min/day = 0.75 ml/min

$$C_{Cr} = \frac{U_{Cr} \cdot \dot{V}}{P_{Cr}}$$

C_{cr}= 100·0.75/1.2 = 63 ml/min (50% of normal GFR).

Another useful parameter for gauging how the kidney handles a freely filtered solute is the fractional excretion (FE). The fractional

excretion is the ratio of the amount excreted in the urine (U_X) to the filtered load (P_X):

$$FE_X = \frac{U_X \cdot \dot{V}}{P_X \cdot GFR}$$

Fractional excretion of sodium

$FE_{Na} = U_{Na} \bullet V/GFR \bullet P_{Na}$

As the GFR is $U_{cr} \bullet V / P_{cr}$ the final equation is

$FE_{Na} = U_{Na} \bullet P_{cr} / U_{cr} \bullet P_{Na}$

P_{Na} = 140 mmol/l

U_{Na} = 20 mmol/l

P_{cr} = 10 mg/l

U_{cr} = 150 mg/l

FE_{Na}=20 mmol/l •10 mg/l /150 mg/l•140 mmol/l =0.0095 or 0.95%

This value allows accurate identification of sodium retention states. In the given example FE_{Na} is less than 1%. It is more than 1% when the Na reabsorbtion is impared.

Table 2

Relationship between estimated GFR and stages of chronic kidney disease.

Stage 1 chronic kidney disease (CKD)	Normal GFR plus evidence of kidney change such as proteinuria: GFR > 90%
Stage 2 CKD	mild CKD: GFR 90-60%
Stage 2 CKD	moderate CKD: GFR 60-30%
Stage 3 CKD	severe CKD: GFR 30-15%
Stage 4 CKD	end-stage renal failure: GFR < 15%

GLOMERULONEPHRITIS AND NEPHROTIC SYNDROME

A number of disorders result in structural alterations of the glomerulus and present with some combination of the following findings:

hematuria,
proteinuria,
reduced GFR,
hypertension.

Disorders resulting in glomerular disease, following categories:

1) Acute glomerulonephritis, in which there is an abrupt onset of hematuria and proteinuria with reduced GFR and renal salt and water retention, followed by full recovery of renal function. Patients with acute glomerulonephritis are a subset of those with an intrarenal cause of acute renal failure.

2) Rapidly progressive glomerulonephritis, in which recovery from the acute disorder does not occur. Worsening renal function results in irreversible and complete renal failure over weeks to months. Early in the course of rapidly progressive glomerulonephritis, these patients can be categorized as having a form of acute renal failure. Later, with progression of their renal failure over time, they display all of the features described for chronic renal failure.

3) Chronic glomerulonephritis, in which renal impairment following acute glomerulonephritis progresses slowly over a period of years but which eventually results in chronic renal failure (Table 2).

4) Nephrotic syndrome, manifested as marked proteinuria, particularly albuminuria (defined as 24-hour urine protein excretion greater than 3.5 g), hypoalbuminemia, edema, hyperlipidemia, and fat bodies in the urine. Nephrotic syndrome may be either isolated (e.g., minimal change disease) or part of some other glomerular syndrome (e.g., with hematuria and casts).

5) Asymptomatic urinary abnormalities, including hematuria and proteinuria (usually in amounts below what is seen in nephrotic syndrome) but no functional abnormalities associated with reduced GFR, edema, or hypertension. Many patients with these findings will develop chronic renal failure slowly over decades.

Etiology

Acute postinfectious glomerulonephritis is a complication of throat and skin infections with β-hemolytic streptococcus, but can also develop after infections with other bacteria (pneumococcus, staphylococcus,

meningococcus), viruses (cytomegalovirus, hepatitis-B virus, Coxsackie virus) or parasites (malaria, toxoplasma). This form of glomerulonephritis develops seven to ten days after infection.

Rapidly progressive glomerulonephritis appears to be a heterogeneous group of disorders, all of which display pathologic features common to various categories of necrotizing vasculitis.

Chronic glomerulonephritis and nephrotic syndrome are also of unclear origin. For some reason, progressive renal deterioration in patients with chronic glomerulonephritis proceeds slowly but inexorably, resulting in chronic renal failure as many as 20 years after initial discovery of an abnormal urinary sediment.

Some cases of nephrotic syndrome are variants of acute glomerulonephritis, rapidly progressive glomerulonephritis in which massive proteinuria is a presenting feature. Other cases of nephrotic syndrome fall into the category of minimal change disease, in which massive proteinuria is the sole laboratory abnormality and progression to end-stage renal disease does not occur.

The most common cause of asymptomatic urinary abnormalities is IgA nephropathy, immune complex disease characterized by diffuse mesangial IgA deposition.

Pathogenesis

Different forms of glomerulonephritis and nephrotic syndrome probably represent differences in the nature, extent, and specific cause of immune-mediated renal damage.

Antibodies. Glomerular deposition of antibodies can lead to cell and tissue injury along three different pathways.

1. Antibodies can bind to the cellular surface and change the biological behaviour of glomerular cells leading to dedifferentiation, metabolic disturbances or detachment of the underlying basement membrane.

2. They can induce inflammation by binding and activation of complement.

3. Antibody-mediated injury can develop through leukocyte adhesion after binding of antibodies to Fc-receptors. These receptors can be found on phagocytes, natural killer cells and platelets.

Complement. Antibodies upon binding and aggregation in the glomerulus activate the serine proteases of the complement cascade through the classical route, involving C1q. Subsequently granulocytes and platelets are bound and activated through Fc- and complement receptors.

The complement components C3a and C5a, which are activated by enzymatic digestion, will recruit leukocytes through chemotactic properties. In addition to chemotaxis, the complement cascade can also exert a direct cytotoxic effect. Through complement components C5b-9 the so-called membrane attack complex (MAC) is formed on the surface of the target cell leading to irreversible injury. Complement as an opsonizing factor plays an important role in phagocytosis and removal of immunoglobulin deposition.

Platelets and leukocytes. Chemotaxis of leukocytes and platelets may occur upon complement activation. Activation of endothelial cells is important in the induction of the inflammatory reaction. Cytokines and endotoxins induce endothelial cells to an increased production and expression of leukocyte adhesion molecules by which granulocytes, lymphocytes and monocytes can adhere and infiltrate.

Degranulation of platelets and granulocytes leads to the release of proteases and oxygen radicals, which are lytic to cell membranes and matrix components. Pro-inflammatory substances derived from granulocytes and macrophages (proteases and oxygen radicals) induce the proliferation and protein production of resident glomerular cells.

Proteases. Granulocytes contain three populations of azurofilic granules, which contain protein cleaving enzymes: serine proteases, collagenases and acid hydrolases. The proteases play an important role in cellular injury and in the induction of proteinuria. Macrophages also contain a number of roteolytic enzymes (MMPs).

Reactive oxygen metabolites. In addition to proteases, reactive oxygen metabolites play an important role in tissue injury induced by granulocytes and macrophages. Activation of leukocytes is characterized by increased oxygen consumption and the formation of oxygen radicals, which are highly toxic: the superoxide-ion, hydrogen peroxide, hypochloride acid and hydroxyl radicals.

The morphological and clinical expression of antibody-mediated glomerular injury is largely dependent upon the localisation of immune complex accumulation in the glomerulus. In this respect, three compartments can be recognized:

1. the subendothelial space including the GBM;
2. the subepithelial compartment;
3. the mesangial area.

The endothelial pattern of injury. Antibodies accumulating in the subendothelial space or along the GBM, for example in postinfectious glomerulonephritis (GN), in anti-GBM nephritis or in lupus nephritis type III and IV, may lead through a mechanism involving complement activation and Fc-receptor binding to chemotaxis and influx of phagocytes. The leukocytes can cause endothelial injury characterized by cellular edema, proliferation and necrosis.

The clinical expression of this pattern of endothelial injury is that of a rapid decrease in GFR associated with oliguria, hematuria (due to disruption of the glomerular cell wall), usually slight proteinuria, systemic hypertension and a drop in serum complement levels. This clinical pattern of endothelial injury is clinically known as the “nephritic syndrome” which can also been seen in patients with malignant hypertension, hemolytic uremic syndrome and systemic vasculitis.

The epithelial pattern of injury. Binding of antibodies in the subepithelial compartment leads to complement binding and activation and the formation of the membrane attack complex (MAC – C5b-9) on the epithelial cell surface. This leads to podocyte injury with cellular degeneration, dedifferentiation and detachment from the underlying GBM. Complement activation in this compartment of the glomerulus does not lead to chemotaxis of circulating leukocytes, because the filtration gradient will carry the complement components towards the urinary space. As a result no inflammatory response is seen in the renal biopsy. A thickened capillary wall is observed due to the accumulation of immune aggregates along the outer side of the GCW.

Clinically, subepithelial deposition of immune aggregates is characterised by nephrotic type proteinuria, i.e. over 3.5 grams of urinary protein loss per day usually without a decrease of GFR, at least in the early phases of the disease, but can decrease during the course of

the disease. A similar pattern of epithelial injury can occur due to metabolic, hypertensive, toxic and a number of unknown factors in diseases which are associated with a nephrotic syndrome, such as: diabetic nephropathy, amyloidosis, metabolic storage diseases, minimal change disease, focal glomerular sclerosis, and podocyte injury due to toxic drugs.

The mesangial pattern of injury. The third pattern of glomerular injury is that of mesangial pathology due to the deposition of complement activating antibodies in this glomerular compartment. This pattern of injury is clinically associated with microscopic and macroscopic hematuria and asymptomatic proteinuria. The GFR is usually normal in the early phase, but can show progressive deterioration during the course of the disease.

Chronic glomerular injury. A number of glomerulopathies is transient and injury can disappear with complete morphological and clinical recovery. This can be seen for example in minimal change disease and postinfectious GN patients in whom the underlying disease has been successfully treated.

In many patients however the glomerulopathy turns out to be chronic and progressive and the glomerular tuft will show capillary collapse, fibrous adhesions to Bowman's capsule, an increase in mesangial matrix and cellularity and accumulation of macrophages and other white blood cells. This picture is often complicated by glomerular and vascular hyalinosis, clinically in association with proteinuria and a progressive loss of GFR. This pattern of chronic, sclerosing GN is the final common pathway of chronic, persistent injury in which genetic, hemodynamic, metabolic and inflammatory factors contribute to matrix accumulation and cell proliferation.

Common Clinical Manifestations.

1. Damage to the glomerular capillary wall results in leakage of red blood cells and proteins, which are normally too large to cross the glomerular capillary, into the renal tubular lumen, giving rise to hematuria and proteinuria.
2. A fall in GFR results either because glomerular capillaries are infiltrated with inflammatory cells or because contractile cells (e.g.,

mesangial cells) respond to vasoactive substances by restricting blood flow to many glomerular capillaries.

3. Edema and hypertension are a direct consequence of fluid and salt overload secondary to the fall of GFR in the face of excess consumption of salt and water.
4. A transient fall in serum complement is observed as a result of complex and complement deposition in the glomerulus.
5. An elevation of titer of antibody to streptococcal antigens is observed in cases associated with group A beta-hemolytic streptococcal infections. Another characteristic of the clinical course in poststreptococcal acute glomerulonephritis is a lag between clinical signs of infection and the development of clinical signs of nephritis.
6. Patients with the nephrotic syndrome have profoundly decreased plasma oncotic pressures, peripheral edema. Due to decreased effective circulating volume - activated renin-angiotensin-aldosterone system, the sympathetic nervous system, and the secretion of vasopressin. Nevertheless, they may develop signs of intravascular volume depletion, including syncope, shock, and acute renal failure.
7. Hyperlipidemia associated with nephrotic syndrome appears to be a result of decreased plasma oncotic pressure, which stimulates hepatic VLDL synthesis and secretion.
8. Loss of other plasma proteins besides albumin in nephrotic syndrome may present as any of the following:
   - A defect in bacterial opsonization and thus increased susceptibility to infections (e.g., due to loss of IgG).
   - Hypercoagulability (e.g., due to antithrombin III deficiency, reduced levels of protein C and protein S, hyperfibrinogenemia, and hyperlipidemia).
   - Vitamin D deficiency state and secondary hyperparathyroidism (e.g., due to loss of vitamin D-binding proteins).
   - Altered thyroid function tests without any true thyroid abnormality (due to reduced levels of thyroxine-binding globulin).

GASTROINTESTINAL DISEASES

Lesson 1

In the stomach, ingested food is subjected to thorough mixing and attack by hydrochloric acid and the proteolytic enzyme pepsin. The mucosal surface of the stomach is a simple columnar epithelium of mucus-secreting cells interrupted occasionally by various types of glands in the form of surface invaginations. Within these glands, the surface epithelial cells are replaced by specialized exocrine or endocrine secretory cells. The exocrine cells secrete various substances from their apical surface (eg, acid from parietal cells and pepsin from chief cells of the oxyntic glands in the fundus and body of the stomach) into the gastrointestinal tract lumen. The endocrine cells secrete hormones from their basolateral surface (eg, gastrin from so-called G cells of the antral glands in the antral mucosa) into the adjacent capillary bloodstream.

Despite the constant attack on the gastroduodenal mucosa by noxious agents (acid, pepsin, bile acids, pancreatic enzymes, drugs, and bacteria), integrity is maintained by a system that provides mucosal defense and repair (Figure 32).

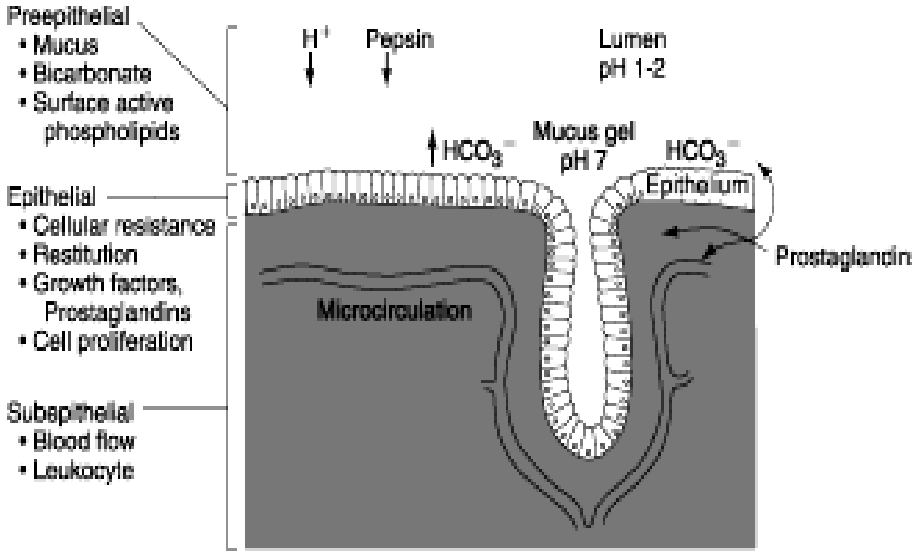


Figure 32 Factors of mucosal defense

ACID-PEPTIC DISEASE

Clinical Presentation

Patients with acid-peptic disease typically present with chronic, mild, or severe burning abdominal or chest pain due to superficial or deep erosion of the gastrointestinal mucosa; with sudden complications such as gastrointestinal bleeding, resulting in hematemesis or melena; or with perforation and infection, resulting in severe abdominal pain and signs of an acute abdomen (absence of bowel sounds, guarding, rebound tenderness). The latter presentation reflects the fact that in some cases, acid-peptic disease can be painless in the early stages, to be detected only when acid-peptic disease leads to an intra-abdominal catastrophe.

Classically, duodenal ulcer presents as gnawing or burning epigastric pain occurring 1-3 hours after meals, often waking the patient at night, with antacids or food producing relief. However, many patients later documented to have duodenal ulcer do not fit this symptom profile. Elderly patients in particular often present Pathogenesis with a complication of duodenal ulcer but no history of pain.

Corrosive agents (acid and pepsin) secreted by the stomach play a key role in gastric ulcer, duodenal ulcer, and acute erosive gastritis. Each of

these diseases has a distinctive but overlapping pathogenesis with the common themes of either excessive acid secretion or diminished mucosal defense. Exactly why one but not another form of acid-peptic disease should develop in a given individual remains unclear. A specific infectious agent, the bacterium Helicobacter pylori, has been implicated in predisposition to a number of forms of acid-peptic disease, presumably by diminishing mucosal defenses through inflammation. The role of H. pylori is particularly important to remember since conventional therapies for acid-peptic disease without eradication of H. pylori infection are associated with much higher rates of recurrence of acid-peptic disease.

Gastric ulcer is distinguished from gastritis by the depth of the lesion, with gastric ulcers penetrating through the mucosa. The actual ulcer crater is often surrounded by an area of intact but inflamed mucosa, suggesting that gastritis is a predisposing lesion to development of gastric ulcer. Most gastric ulcers occur on the lesser curvature of the stomach. It is likely that gastric ulcer represents the outcome of a number of different abnormalities summarized below.

Table 3.

Factors and mechanisms involved in defense of mucosal surface of gastointestinal tracts

Forms of Defense	Structural Adaptations	Mechanism of Defense
Defense from acid		
Mucus production	Large numbers of mucus-secreting goblet cells	Prevents direct contact of acid with epithelium
Bicarbonate production (alkaline tide)	Capillary blood flow to surface	Neutralizes any acid that breaches epithelium
Prostaglandin production		Attenuates acid production
Tight junctions	Tight junction formation	Prevents breach of epithelium
Bicarbonate from	Pancreatic duct	Neutralizes acid leaving

pancreas	opening into duodenum	stomach
Defense from infection		
Secretory immune system		Extends to gastrointestinal tract lumen the protective umbrella of blood-borne immunity
Rapid turnover of enterocytes	Villi with cell proliferation in crypts and cell release at tips	Limits the consequences of enterocyte infection
Normal colonic microflora		Impedes invasion or colonization by pathogenic organisms
Stomach acid	Gastric glands containing parietal cells	Kills pathogenic organisms upon ingestion

Some gastric ulcers are believed to be related to impaired mucosal defenses (Table 3), since the acid and pepsin secretory capacity of some affected patients is normal or even below normal.

Motility defects have been proposed to contribute to development of gastric ulcer in at least three ways:

- By a tendency of duodenal contents to reflux back through an incompetent pyloric sphincter. Bile acids in the duodenal reflux material act as an irritant and may be an important contributor to a diminished mucosal barrier against acid and pepsin.
- By delayed emptying of gastric contents, including reflux material, into the duodenum.
- By delayed gastric emptying and hence food retention, resulting in increased gastrin secretion and gastric acid production.

Mucosal ischemia may play a role in the development of a gastric ulcer. Prostaglandins are known to increase mucosal blood flow as well as bicarbonate and mucus secretion and to stimulate mucosal cell repair and renewal. Thus, their deficiency resulting from NSAID ingestion or other insults may predispose to gastritis and gastric ulcer, as might diminished bicarbonate or mucus secretion due to other causes.

Subsets of gastric ulcer patients with each of these defects have been identified. Thus, the risk factors (NSAID ingestion, smoking, psychologic stress, H pylori infection) that have been associated with gastric ulcer probably act by diminishing one or more mucosal defense mechanisms.

Inflammation of the gastric mucosa as a result of H pylori infection, aspirin and other NSAIDs, bile salts, alcohol, or other insults, may predispose to ulcer formation: (1) by attenuating the barrier created by the epithelial cells or the mucus and bicarbonate they secrete or (2) by reducing the quantity of prostaglandins the epithelial cells produce that might otherwise diminish acid secretion.

The clinical features of a gastric ulcer include:

- epigastric discomfort or pain:
  - may vary from a mild discomfort, which is ignored, to a very severe pain that makes the patient lie down
  - the pain occurs 15 to 30 minutes after eating
  - the pain is relieved by vomiting and made worse by eating - thus these patients often complain of weight loss rather than the weight gain associated with duodenal ulcers - the patient may complain of being 'afraid to eat'
  - pain often worst during the day; (pain is often worst during the night in duodenal ulceration)
  - pain lasts for a period of about 2 weeks and occurs in cycles of every 1-2 months
- haematemesis and melaena may complicate all forms of peptic ulceration
- examination is likely to be normal, there is usually no more than mild to moderate epigastric tenderness.

Acute erosive gastritis includes inflammation due to superficial mucosal injury, mucosal erosion, or shallow ulcers due to a wide variety of insults, most notably alcohol, drugs, stress. Ethanol ingestion predisposes to gastritis but not to development of gastric ulcer. Unlike gastric or duodenal ulcers, in erosive gastritis the submucosa and muscularis mucosae are not penetrated.

Acid hypersecretion, gastric anoxia, altered natural defenses (especially diminished mucus secretion), epithelial renewal, tissue

mediators (eg, prostaglandins), reduced intramucosal pH, and intramucosal energy deficits have been suggested as factors in the development of superficial gastric mucosal injury.

Chronic atrophic gastritis is a heterogeneous group of syndromes, characterized by inflammatory cell infiltration with gastric mucosal atrophy and loss of glands. In chronic disease unlike acute erosive gastritis endoscopic abnormalities may not be grossly apparent. The capacity to secrete gastric acid is progressively reduced, and the serum levels of gastrin are elevated.

Autoantibodies to parietal cells, intrinsic factor, and gastrin are common findings. Chronic atrophic gastritis is associated with H pylori infection, development of pernicious anemia, gastric adenocarcinoma, and gastrointestinal endocrine hyperplasia with carcinoids (neuroendocrine tumors of the gastrointestinal tract producing serotonin metabolites and associated with dramatic symptoms of flushing and diarrhea).

Duodenal ulcer.

Like gastric ulcer, duodenal ulcer is believed to be a consequence of excessive acid and pepsin secretion plus diminished mucosal defenses.

Excessive secretion is believed to play the more important role, however, since duodenal ulcer rarely occurs in individuals who secrete less than 10 meq of acid per hour.

Since duodenal ulcer is an intermittent and recurrent disease, all of the predisposing factors may not be present in every patient at any given time. Patients found to have a duodenal ulcer are more likely to have:

- increased acid and peptic secretory capacity;
- increased basal acid secretion;
- increased postprandial acid secretory response;
- increased sensitivity of gastrin secretory cells to secretagogues and impaired acid inhibition of gastrin release;
- impairment of other feedback mechanisms of gastric acid secretion;
- rapid gastric emptying.

However, considerable overlap exists between patients who develop duodenal ulcer and those who do not, which may mean that important variables in pathogenesis are still unrecognized.

Various risk factors, including diet, smoking, H pylori infection, and excessive alcohol consumption may influence the development of duodenal ulcers, though specific associations (eg, between coffee or spicy foods and the development of ulcers, or between bland diets and the healing of ulcers) have not been demonstrated. Genetic factors also play a role, with studies supporting the existence of a heritable component in duodenal ulcers distinct from that involved in gastric ulcer. Likewise, psychologic stress has been implicated in duodenal ulcer disease, perhaps by the autonomic-mediated influence of acid secretion.

Clinical Manifestations

Those forms of acid-peptic disease characterized by exclusively superficial mucosal lesions (eg, acute erosive gastritis) can result in either acute or chronic gastrointestinal bleeding, accompanied by a significant drop in hematocrit and related complications (eg, precipitating angina in a patient with coronary artery disease). Patients with acute massive bleeding will present with hematemesis (vomiting blood), rectal bleeding, or melena (tarry stools from the effect of acid on blood) depending on the site of origin, the rate of transit of blood through the gastrointestinal tract, and the extent of hemorrhage. Acute massive hemorrhage (> 10% of blood volume over minutes to hours) is manifested by hypotension, tachycardia, and orthostatic blood pressure and heart rate changes on standing, often with dizziness.

In addition to hemorrhage, complications of duodenal ulcer and gastric ulcer include life-threatening perforation and obstruction.

Ulcer treatment

The most effective ulcer therapy is known as 2 weeks of triple therapy. Treatment of H. pylori peptic ulcers usially involves a combination of drugs that are able to:

1. kill the bacteria (antibiotics),
2. reduce stomach acid (H_2 blockers and proton pump inhibitors),
3. protect the stomach lining (bismuth subsalicylate).

Drugs Used to Treat H. pylori Peptic Ulcers:

Antibiotics: metronidazole, tetracycline, clarithromycin, amoxicillin

H_2 blockers: cimetidine, ranitidine, famotidine, nizatidine

Proton pump inhibitors: omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprozole

Two types of acid-suppressing drugs might be used: H_2 blockers and proton pump inhibitors. H_2 blockers work by blocking histamine, which stimulates acid secretion. They help reduce ulcer pain after a few weeks. Proton pump inhibitors (PPIs) suppress acid production by halting the mechanism that pumps the acid into the stomach. H_2 blockers and proton pump inhibitors have been prescribed alone for years as treatments for ulcers. But used alone, these drugs do not eradicate H. pylori and therefore do not cure H. pylori- related ulcers.

Bismuth subsalicylate, a component of Pepto-Bismol, is used to protect the stomach lining from acid. It also kills H. pylori.

Stop NSAIDs if used, use Cox-2-selective NSAID.

If NSAID continuation is necessary, after ulcer healing offer long-term gastric protection or consider substitution to a newer Cox-2-selective NSAID. In the 1980's Needleman showed that COX (cyclooxygenase) enzyme was increased in inflamed tissue and that COX was stimulated by interleukin-1 (IL-1) on cultured human cells. In 1990 he demonstrated the induction of COX by endotoxin. An increase in COX was prevented by glucocorticoids. However it was noted that dexamethasone did not affect baseline prostaglandin formation. They therefore postulated a second COX enzyme. In 1991 the second COX isoform was cloned. This represented what is now known as COX-2.

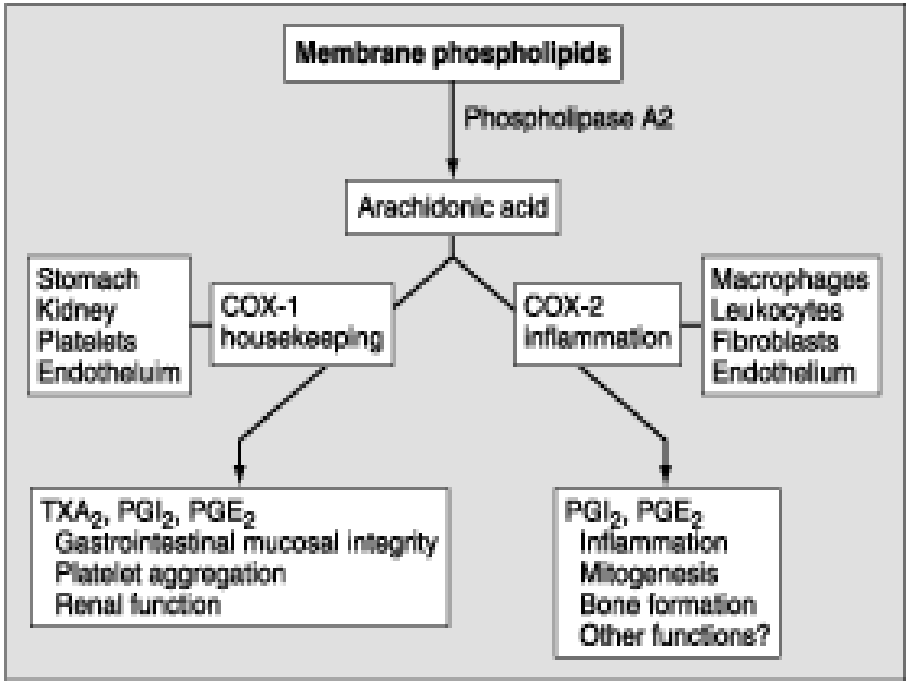


Figure 33. Convertion of arachidonic acid

COX-1 is now known to be present in most tissues as the housekeeper enzyme. COX-2 is inducible by inflammation. It is not present at baseline, but increases in response to inflammation. COX-1 maintains normal gastric mucosa and influences kidney function. The inhibition of COX-1 is therefore undesirable. The inhibition of COX-2 on the other-hand is a desirable effect. Both have the same affinity to convert arachidonic acid to prostaglandin (Fig. 33). Truly specific COX-2 inhibitors, Celecoxib (Celebrex), and Bextra are now commercially available, and others are currently being researched.

Lesson 2

PATHOPHYSIOLOGY OF THE EXOCRINE PANCREAS

The pancreas is a gland with both exocrine and endocrine function. The exocrine pancreas contains acini that secrete pancreatic juice into

the duodenum through the pancreatic ducts. Pancreatic juice contains a number of enzymes, some of which are initially made in an inactive form. Once activated, these enzymes help to digest food and prepare it for absorption in the intestine. Disorders interfering with normal pancreatic enzyme activity (pancreatic insufficiency) cause maldigestion of fat and steatorrhea (fatty stools). Dysfunction of the exocrine pancreas results from inflammation (acute pancreatitis, chronic pancreatitis), neoplasm (pancreatic carcinoma), or duct obstruction by stones or abnormally viscid mucus (cystic fibrosis).

The endocrine pancreas is composed of the islets of Langerhans. The islets are distributed throughout the pancreas and contain several different hormone-producing cells. The islet cells manufacture hormones such as insulin that are important in nutrient absorption, storage, and metabolism. Dysfunction of the endocrine pancreas causes diabetes mellitus. Both exocrine and endocrine pancreatic dysfunction occur together in some patients.

The exocrine pancreas is drained by a major central duct called the duct of Wirsung, which runs the length of the gland. This duct is normally about 3- 4 mm in diameter. In most individuals, the pancreatic duct enters the duodenum at the duodenal papilla alongside the common bile duct. The sphincter of Oddi surrounds both ducts. In about one-third of individuals, the duct of Wirsung and the common bile duct join to form a common channel before terminating at the ampulla of Vater.

Many individuals also have a separate accessory pancreatic duct called the duct of Santorini that runs from the head and body of the gland to enter the duodenum about 2 cm proximal to the duodenal papilla. Occasionally, the accessory duct joins with the major pancreatic duct.

The exocrine pancreas consists of clusters of acini, or lobules, which are drained by ductules. Each pancreatic acinus is composed of several acinar cells surrounding a lumen (Figure. 34). The acinar cells synthesize and secrete enzymes. On histologic examination, acinar cells are typical protein-secreting cells. They are pyramidal epithelial cells arranged in rows. Their apexes join to form the lumen of the acinus.

Granules in acinar cells containing digestive enzymes are called zymogen granules. These granules are discharged by exocytosis from the apexes of cells into the lumen. The number of zymogen granules in the cells varies, with more being found during fasting and fewer after a meal.

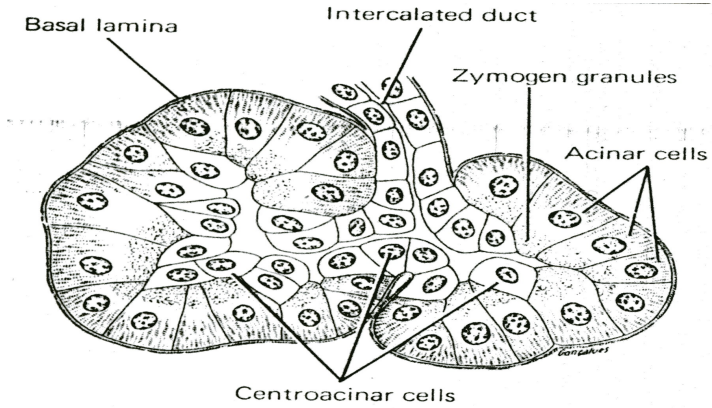


Figure 34. Schematic drawing of the pancreatic acini. Acinar cells are pyramidal in shape, with zymogen granules at their apexes.

Composition of Pancreatic Juice.

About 1500 mL of pancreatic juice is secreted each day. Pancreatic juice contains water, ions, and a variety of proteins. The principal ions in pancreatic juice are HCO_3^-, CL^-, Na^+ and K^+. Of these, HCO_3 is particularly important. At maximum flow rates, the concentration of HCO_3 in pancreatic juice may reach 150 meq/L (versus 24 meq/L in plasma), and the pH of the juice may reach 8.3. The alkaline nature of pancreatic juice plays a major role in neutralizing the gastric acid entering the duodenum with ingested food from the stomach. The pH of the duodenal contents rises to 6.0-7.0, and by the time the chyme reaches the jejunum, its pH is nearly neutral.

Most of the proteins in pancreatic juice are enzymes and proenzymes (enzyme precursors that require some structural change to render them active). These enzymes aid in the intraluminal phase of

digestion and absorption of fats, carbohydrates, and proteins. The rest of the proteins in pancreatic juice are plasma proteins, mucoproteins, and trypsin inhibitors.

Some of the pancreatic enzymes (lipase, amylase, desoxyribonuclease and ribonuclease) are secreted by the acinar cells in their active forms. The remaining enzymes are secreted as inactive proenzymes or zymogens (trypsinogen, chymotrypsinogen, proelastase, procarboxypeptidase, and phospholipase A2) that are activated in the lumen of the proximal intestine. Activation of zymogens within the acinar cells might otherwise lead to acute pancreatitis and pancreatic autodigestion.

When the pancreatic juice enters the duodenum, trypsinogen is converted to the active form trypsin by an enzyme found in the intestinal brush border called enteropeptidase (or enterokinase). Trypsin then converts the remaining proenzymes into active enzymes, eg, chymotrypsinogen into chymotrypsin. Trypsin can also activate its own precursor, trypsinogen, producing the potential for an autocatalytic chain reaction. It is thus not surprising that pancreatic juice normally contains a trypsin inhibitor so that this autocatalytic reaction does not occur under normal circumstances.

Regulation of Secretion of Pancreatic Juice.

Between and after meals, pancreatic secretion is regulated by hormonal and neural actions and by neurohumoral interactions. Secretion of pancreatic juice is controlled primarily by two different hormones: secretin and cholecystokinin (CCK), they are produced by specialized enteroendocrine cells of the duodenal mucosa.

Secretion of secretin is triggered by gastric acid and by the products of protein digestion when they enter the duodenum. Secretin acts chiefly on the pancreatic duct cells to cause an outpouring of very alkaline pancreatic juice. In response to secretin, the pancreas produces a large volume of watery fluid rich in bicarbonate content, but with little enzyme activity.

Secretion of CCK is triggered by the products of protein and fat digestion (peptides, amino acids and fatty acids) when they enter the duodenum. CCK acts chiefly on the acinar cells to cause release of

enzymes from zymogen granules. Thus, in response to CCK, the pancreas secretes a small volume of juice low in bicarbonate but very high in enzyme content. In addition, CCK increases the secretion of enteropeptidase (enterokinase) from other endocrine cells of the duodenal mucosa. The integrated action of both secretin and CCK produces abundant secretion of enzyme-rich, alkaline pancreatic juice.

The secretion of pancreatic juice is also controlled in part by a reflex mechanism. Acetylcholine released by the vagus nerve acts like CCK on acinar cells to cause discharge of zymogen granules. Thus, stimulation of the vagus nerve causes production of a small volume of pancreatic juice rich in enzymes.

Digestive Functions of Pancreatic Juice.

The secretion of pancreatic juice aids digestion in several ways. The large amount of bicarbonate in the juice helps to neutralize the acidic chyme from the stomach so that the pancreatic enzymes can function optimally in a neutral pH range. In addition, each of the enzymes has an important digestive function.

- In digesting carbohydrates, pancreatic amylase splits straight-chain glucose polysaccharides (so-called amyloses in starch) into smaller sugars, maltose and maltotriose.
- In digesting fat, pancreatic lipase splits triglycerides into fatty acids and monoglyceride.
- Phospholipase A_2 splits a fatty acid off lecithin, forming lysolecithin.
- Ribonuclease and decoxyribonuclease attack the nucleic acids.

The remaining enzymes help to digest proteins. Trypsin, chymotrypsin, and elastasc are endopeptidases; that is, they cleave peptide bonds in the middle of polypeptide chains. Carboxypeptidase is an exopeptidase; that is, it splits peptide bonds adjacent to the carboxyl end of peptide chains. Together, these proteases break down proteins into oligopeptides and free amino acids.

ACUTE PANCREATITIS

Clinical Presentations.

Acute pancreatitis is a clinical syndrome resulting from acute inflammation and destructive autodigestion of the pancreas and peripancreatic tissues. Clinically, acute pancreatitis is a common and important cause of acute upper abdominal pain, nausea, vomiting, and fever. Laboratory findings of marked elevations of serum amylase and lipase help to differentiate it from other entities causing these symptoms. The severity of inflammation varies, and the prognosis ranges from mild, self-limited illness lasting 1-2 days to death from pancreatic necrosis, hemorrhage, or sepsis. Acute pancreatitis often recurs (relapsing acute pancreatitis). With repeated attacks, the gland may eventually be permanently damaged, resulting in chronic pancreatitis. The two most common conditions associated with acute pancreatitis are alcohol abuse and biliary tract disease.

Pathogenesis

The symptoms, signs, laboratory findings and complications of acute pancreatitis can all be explained on the basis of the pathologic damage to the ductules, acini, and islets of the pancreas. However, both the degree of damage and the clinical consequences are quite variable.

When the damage is limited in extent, the pathologic features consist of mild to marked swelling of the gland, especially the acini, and mild to marked infiltration with polymorphonuclear neutrophils. However, damage to tissue is usually only minimal to moderate, and there is no hemorrhage. In some cases, suppuration may be found along with edema, and this may result in tissue necrosis and abscess formation. In severe cases, massive necrosis and liquefaction of the pancreas occurs, predisposing to pancreatic abscess formation. Vascular necrosis and disruption may occur, resulting in hemorrhage. Hemorrhagic pancreatitis, which usually involves the entire gland, is the most serious form of pancreatitis.

In addition, a brownish serous fluid is often found in the peritoneal cavity ("pancreatic ascites"). This fluid contains blood, fat globules ("chicken broth"), and high levels of amylase and other pancreatic enzymes.

The mechanism by which enzymes and bioactive substances become activated within the pancreas is a major unanswered question in

acute pancreatitis. The early initiating events probably occur at a membrane or intracellular level.

1) A recently proposed theory of the pathogenesis of alcoholic pancreatitis emphasizes disordered agonist-receptor interaction on the membrane of pancreatic acinar cells. According to this theory, alcohol induces alterations in the control of exocrine pancreatic secretion, which in turn result in hyperstimulation of pancreatic acinar cells and their muscarinic receptors. This hyperstimulation mimics the mechanism of acute pancreatitis caused by scorpion sting, anti-acetylcholinesterase-containing insecticide poisoning, or administration of supramaximal doses of secretagogues such as acetylcholine and CCK.

2) Other recent studies suggest that lysosomal enzymes within the pancreatic acinar cell may play an important role. Morphologic studies during the first 24 hours after ligation of the pancreatic duct in animals indicate that the earliest lesions occur in acinar cells. Digestive enzyme zymogens and lysosomal hydrolases such as cathepsin B become localized together, suggesting that intraacinar cell activation of the zymogens by lysosomal hydrolases may be an important initiating event.

The pathologic changes all result from the action of activated pancreatic enzymes on the pancreas and surrounding tissues. In a manner still not understood, small amounts of trypsin escape from the duct system into the pancreatic parenchyma to initiate pancreatitis, perhaps through inhibition of the trypsin inhibitor. Once there, trypsin activates the proenzymes of chymotrypsin, elastase, and phospholipase A_2, and the activated enzymes cause damage in several ways (Figure. 35).

- Chymotrypsin activation leads to edema and vascular damage.
- Similarly, elastase, once activated from proelastase, digests the elastin in blood vessel walls and causes vascular injury and hemorrhage; damage to peripancreatic blood vessels can lead to hemorrhagic pancreatitis.
- Phospholipase A_2 splits a fatty acid off lecithin, forming lysolecithin, which is cytotoxic to erythrocytes and damages cell membranes. Formation of lysolecithin from the lecithin in bile may

contribute to disruption of the pancreas and necrosis of surrounding fat.

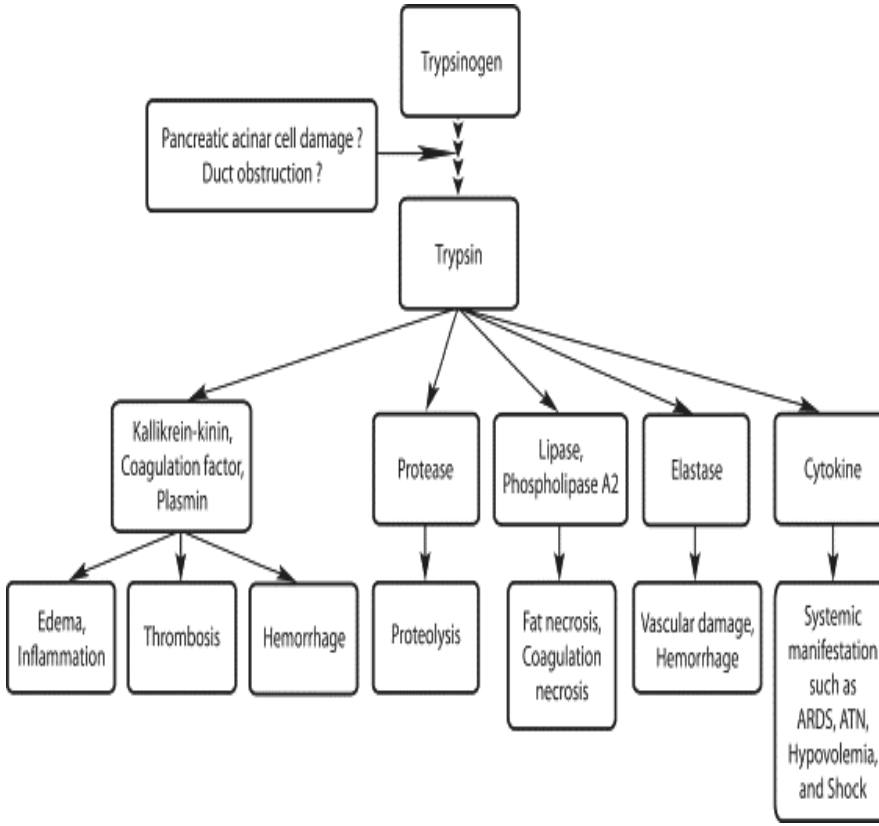


Figure 35. Pathogenesis of acute pancreatitis

- Phospholipase A_2 also liberates arachidonic acid, which is then converted to prostaglandins, leukotrienes, and other mediators of inflammation, contributing to coagulation necrosis.
- Pancreatic lipase, released directly as a result of pancreatic acinar cell damage, acts enzymatically on surrounding adipose tissue, causing fat necrosis.
- Furthermore, trypsin and chymotrypsin activate kinins, complement, coagulation factors, and plasmin, leading to edema, inflammation, thrombosis, and hemorrhage within the gland. For

example, trypsin activation of the kallikrein-kinin system leads to the release of bradykinin and kallidin, causing vasodilation, increased vascular permeability, edema, and inflammation.

Finally, the activated pancreatic enzymes enter the bloodstream and may produce effects elsewhere in the body. Circulating phospholipases interfere with the normal function of pulmonary surfactant, contributing to the development of an acute respiratory distress syndrome (ARDS) in some patients with acute pancreatitis. Elevated serum lipase levels are sometimes associated with fat necrosis outside of the abdomen.

CHRONIC PANCREATITIS

Clinical Presentations

Chronic pancreatitis is a recurrent, sometimes relapsing disorder, causing severe abdominal pain, exocrine and endocrine pancreatic insufficiency, severe duct abnormalities, and pancreatic calcifications. In chronic pancreatitis, there is chronic inflammation of the parenchyma, leading to progressive destruction of the acini, stenosis and dilation of the ductules, and fibrosis of the gland. Eventually, there is impairment of the gland's exocrine functions. However, findings on conventional diagnostic studies may be normal in the early stages of chronic pancreatitis, as the inflammatory changes can be seen only by histologic examination.

By definition, chronic pancreatitis is a completely different process from acute pancreatitis. In acute pancreatitis, the patient presents with acute and severe abdominal pain, nausea, and vomiting. The pancreas is acutely inflamed (neutrophils and edema), and the serum levels of pancreatic enzymes (amylase and lipase) are elevated. Full recovery is observed in patients with acute pancreatitis, whereas in chronic pancreatitis, the primary process is a chronic irreversible inflammation (involving monocytes, lymphocytes and pancreatic stellate cells) that leads to fibrosis with calcification. The patient with chronic pancreatitis clinically presents with chronic abdominal pain and normal or mildly elevated pancreatic enzyme levels; when the pancreas lose its endocrine

and exocrine function, the patient presents with diabetes mellitus and steatorrhea.

Pathophysiology:

The proposed pathologic mechanisms of chronic pancreatitis are as follows:

- Intraductal plugging and obstruction (stones, tumors).
- Direct toxins and toxic metabolites: These act on the pancreatic acinar cell to stimulate the release of cytokines, which stimulate the stellate cell to produce collagen and to establish fibrosis. Cytokines also act to stimulate inflammation by neutrophils, macrophages, and lymphocytes.
- Oxidative stress (eg, idiopathic pancreatitis)
- Necrosis-fibrosis (recurrent acute pancreatitis that heals with fibrosis)
- Ischemia (from obstruction and fibrosis), which is important in exacerbating or perpetuating disease rather than in initiating disease
- Autoimmune disorders: Chronic pancreatitis has been found in association with other autoimmune diseases, such as Sjögren syndrome, primary biliary cirrhosis, and renal tubular acidosis. Autoimmune pancreatitis is a recently described new entity. Clinical characteristics include symptomatic or asymptomatic diffuse enlargement of the pancreas, diffuse and irregular narrowing of the main
pancreatic duct, increased circulating levels of gamma globulin, the presence of autoantibodies, and a possible association with other autoimmune diseases. Fibrosis with lymphocytic infiltration is seen on pathology. The disorder is associated with elevated immunoglobulin G4 (IgG4) concentrations.

While alcohol greatly influences the understanding of chronic pancreatitis pathophysiology because it is the most common etiology (60-70%), approximately 20-30% of cases are idiopathic and 10% of cases are due to rare diseases. Although a linear relationship exists between the amount of alcohol ingested and the risk of developing chronic pancreatitis, the fact that fewer than 10% of people with alcoholism actually develop the disease is not understood.

In the affected gland, alcohol appears to increase protein secretion from acinar cells while decreasing fluid and bicarbonate production from ductal epithelial cells. The resulting viscous fluid results in proteinaceous debris becoming inspissated within the lumen, causing ductular obstruction, upstream acinar atrophy, and fibrosis. GP2, which is secreted from the acinar cell and homologous to a protein involved in renal tubular casts, is an integral component of these ductal plugs. Lithostathine (formerly pancreatic stone protein), which also is produced by acinar cells, accounts for about 5% of secretory protein and inhibits the growth of calcium carbonate crystals. Abnormal lithostathine S1, whether inherited or acquired through trypsin digestion, appears to play a role in stone formation; it is insoluble at the neutral pH of pancreatic juice and is the major constituent of pancreatic stones.

A competing theory suggests that the persistent demands of metabolizing alcohol (and probably other xenobiotics, such as drugs, tobacco smoke, environmental toxins, and pollution) causes oxidative stress within the pancreas and may lead to cellular injury and organ damage, especially in the setting of malnutrition. Both oxidative and nonoxidative pathways metabolize ethanol. Alcohol dehydrogenase oxidatively metabolizes ethanol first to acetaldehyde and then to acetate. When the alcohol concentration increases, cytochrome P-450 2E1 is induced to meet the metabolic demands. Although these reactions occur principally in the liver, further increases in ethanol concentration induce pancreatic cytochrome P-450 2E1, and the level of acetate within the pancreas begins to approach that observed in the liver. Reactive oxygen species produced by this reaction may overwhelm cellular defenses and damage important cellular processes.

In an effort to explain why so few people with alcoholism actually develop chronic pancreatitis, researchers have studied genetic polymorphisms of ethanol-oxidizing enzymes; to date, none have correlated with a susceptibility to alcohol-induced pancreatitis. Although nonoxidative metabolism of ethanol is a minor pathway, the fatty acid ethyl esters produced by this reaction may cause cellular injury and are synthesized in the pancreas to a greater extent than in other organ systems.

Whatever the etiology of chronic pancreatitis, pancreatic fibrogenesis appears to be a typical response to injury. This involves a complex interplay of growth factors, cytokines, and chemokines, leading to deposition of extracellular matrix and fibroblast proliferation. In pancreatic injury, local expression and release of transforming growth factor–beta (TGF-beta) stimulates the growth of cells of mesenchymal origin and enhances synthesis of extracellular matrix proteins, such as collagens, fibronectin, and proteoglycans. Recent evidence indicates involvement of distinct chemokines in the initiation and perpetuation of chronic pancreatitis.

Lesson 3

PATHOPHYSIOLOGY OF DIARRHEA

Flow in the gastrointestinal tract is a steady state involving massive fluid secretion into and absorption from the gastrointestinal lumen. Each process is controlled by both extrinsic and intrinsic factors. Subtle aberrations in input or output at any of several levels can result in diarrhea with or without nutrient malabsorption.

Thus, an excessive osmotic load, increased secretion, or diminished fluid resorption may result in diarrhea.

Therefore, diarrhea may be characterized as secretory, osmotic, or malabsorptive, depending on the pathophysiologic basis for altered gut fluid homeostasis (Figure 36).

- Osmotic (or malabsorbed) diarrhea occurs when the ability to digest or absorb a particular nutrient is defective (e.g. enzyme deficiency). Thus, malabsorbed nutrients or poorly absorbed electrolytes retain water in the lumen.
- Secretory diarrhea is due to an elevated rate of fluid transport out of epithelial cells.

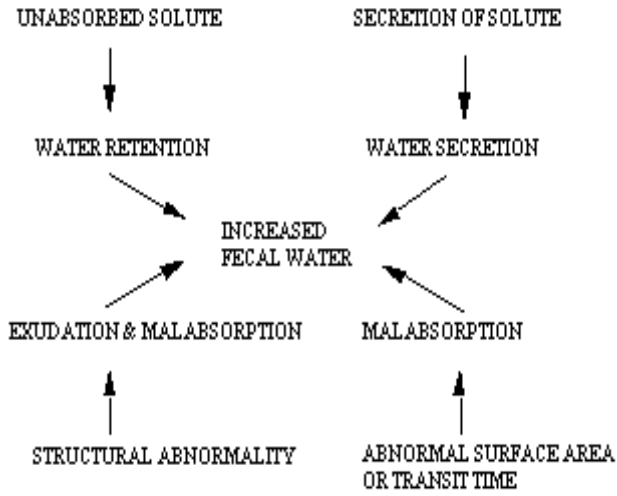


Figure 36. Types of diarrhea

These pathophysiologic distinctions are useful in both diagnosis and therapy of diarrheal disorders. In transport capacity, the small intestine far exceeds the colon (owing to the enormous surface area of the brush border). Thus, infectious, toxic, or other causes of heightened secretion in the small intestine can overwhelm absorptive mechanisms in the colon, resulting in diarrhea.

Osmotic diarrhea. An excessive osmotic load in the gastrointestinal tract may come about in three different ways:

1) by direct oral ingestion of excessive osmoles;

2) by ingestion of a substrate that may be converted into excessive osmoles (eg, when bacterial action on the non-digestible carbohydrate lactulose generates a diarrhea-causing osmotic load in the colon);

3) as a manifestation of a genetic disease such as an enzyme deficiency in the setting of a particular diet (eg, milk consumption by a lactase-deficient individual).

In malabsorbed diarrhea the absorption of fluid, electrolytes, and nutrients can be diminished by many factors, including the toxic effects of alcohol; mucosal damage from infectious agents; prokinetic agents that speed up gastrointestinal motility, thereby diminishing the time available for absorption of any given nutrient, fluid, or electrolyte load. Finally,

inflammatory and other disorders resulting in loss of mucus, blood, or protein from the gastrointestinal tract may be manifested as diarrhea.

Secretory diarrhea Secretion is increased by either blood-borne or intraluminal secretagogues. These include endogenous endocrine products (eg, overproduced by a tumor), exotoxins due to direct ingestion (eg, acute food poisoning) or infection (eg, cholera), or gastrointestinal luminal substances (eg, bile acids) that stimulate secretion.

Etiology.

Diarrheas can be classified into 5 groups.

1. Toxin-Mediated, Cytotoxic Bacterial Gastroenteritis.

Infectious diarrhea can be due to toxin elaborated by pathogenic bacteria within the gut lumen or adherent to the mucosa. The classic example is *Vibrio cholerae* infection. *Vibrio cholerae* is the prototypic cause of toxigenic diarrhea. The *Vibrio cholerae* organisms elaborate a toxin that attaches to the inner cell membrane and activates adenylate cyclase. The presence of adenylate cyclase then elevates cyclic AMP (cAMP) levels. Cyclic AMP then stimulates the enterocyte to secrete fluid and electrolytes while at the same time impairing their absorption. Stool output can exceed 1 L/hour. Treatment is based on restoring fluid and electrolyte balance and maintaining intravascular volume. Even though fluid and electrolyte transport is impaired, glucose transport is intact. Since glucose absorption carries Na^+ (and thus water with it), an oral rehydration solution containing glucose, sodium and water will enhance water absorption during the profound dehydration stage of cholera.

Cholera is characterized by an abrupt onset of massive watery diarrhea that is isotonic with plasma. Volumes of diarrhea as high as 1 L/h or up to 15 L/d can result. If fluid replacement is inadequate, profound dehydration leading to renal failure can rapidly occur. Without treatment, the mortality rate can approach 50%. The cholera toxin acts by covalently modifying a heterotrimeric G protein in the cytosol of the enterocyte, as a result of which adenylyl cyclase is activated, thereby driving chloride secretion and with it sodium and water loss.

The disease is largely due to dysfunction of the small intestine, with the resulting large volumes of fluid overwhelming the colon's capacity

for absorption. Since the organisms do not penetrate the mucosa, supportive therapy alone, with or without antibiotics, is lifesaving. The organism is cleared spontaneously if the patient does not succumb to dehydration.

Oral rehydration with glucose-containing salt solutions has been developed for use in developing nations where cholera remains endemic. This therapy takes advantage of the fact that sodium uptake is coupled to that of glucose in enterocytes of the villus. Ingestion of large volumes of glucose-containing electrolyte solutions provides glucose that is absorbed along with sodium. Water moves with the sodium osmotically and counters the toxin-mediated chloride secretion occurring in the crypts.

2. Enteroinvasive Bacterial Gastroenteritis. Bacterial pathogens may directly invade the mucosa and proliferate within the enterocytes. These organisms may elaborate a variety of toxins, some of which are cytotoxic and may kill enterocytes, whereas others serve as secretagogues directing fluid secretion. A characteristic of these gastroenteritides is an intense submucosal inflammatory reaction with necrosis of areas of overlying mucosa. Together, the necrosis and inflammation result in the typical findings of blood, pus, and mucus in the stool. *Salmonella, Shigella, Campylobacter*, and certain strains of *E. coli* are classic examples of enteroinvasive pathogens. Antibiotic therapy may limit the course of these illnesses, though typically they resolve spontaneously in an immunocompetent host. Therapy to slow or stop the diarrhea can actually prolong the course of the illness by preventing elimination of toxins and organisms in diarrheal stools.

3. Toxin Ingestion. Common "food poisoning" is a constellation of self-limited syndromes resulting from ingestion of preformed bacterial toxins in contaminated food with or without live bacteria. The toxin produces nausea, vomiting, and diarrhea within hours after ingestion. These illnesses can be mild to severe but are typically self-limited and require only supportive therapy to prevent dehydration. *Clostridium perfringens*, *Staphylococcus aureus*, and *Bacillus cereus* elaborate these heat-stable toxins

4. Viral Gastroenteritis. A number of viruses, including rotaviruses and Norwalk virus, when ingested, can bind to receptors on enterocytes, causing invasion and infection. In some cases, the enterocytes are killed in the process of viral replication; in others, the enterocytes are not killed but their normal protein synthetic functions are disrupted. In either case, the net effect is loss of absorptive capacity by the small intestine, resulting in diarrhea. Since the host's immune mechanisms normally respond rapidly to such viral infections with the development of humoral immunity and since the lifetime of mature enterocytes is short, these disorders are generally self-limited, as the infected cells are sloughed and replaced by new cells that are protected by specific antibodies.

5. Parasitic Diseases A number of parasites, including protozoa, roundworms, and tapeworms, can colonize the small intestine and colon, producing either acuteself-limited or chronic intermittent diarrheal syndromes. The most important diarrhea-producing parasites are Giardia lamblia, a small intestinal pathogen, and Entamoeba histolytica, a colon pathogen.

Diarrheal episodes may be acute or chronic (or persistent) based on their duration. An acute diarrhea is defined as an episode that has an acute onset and lasts no longer than 14 days; chronic or persistent diarrhea is defined as an episode that observed longer than 14 days

Pathogenesis.

Recognition of pathophysiologic subtypes of secretory, malabsorptive or osmotic diarrheas provides a means of approaching diagnosis and therapy of diarrheal disorders. For example, nonbloody diarrhea that continues in the absence of oral intake must be due to a secretory mechanism, whereas diarrhea that diminishes as oral intake is curtailed (eg, in a patient receiving intravenous hydration) suggests an osmotic or malabsorptive cause. Likewise, the presence of white blood cells in the stool suggests an infectious or inflammatory origin of diarrhea, though their absence does not rule out such causes.

Of the many causes of diarrhea, infectious agents are among the most important because they cause acute, sometimes life-threatening diseases whose pathogenesis is relatively well understood and because they are usually treatable. The symptoms of diarrhea due to infectious agents are due either to toxins that alter small bowel secretion and absorption or to direct mucosal invasion.

Acute bacterial diarrheas can be classified into toxigenic types, in which an enterotoxin is the major pathogenic mechanism, and invasive types, in which the organism penetrates the enterocyte as a primary event, although an enterotoxin may be produced as well. The noninvasive toxin-producing bacteria are generally small bowel pathogens, while the invasive organisms are localized typically to the colon. Enterotoxins are either cytotonic (producing intestinal fluid secretion by activation of intracellular enzymes, without damage to the epithelial surface) or cytotoxic (causing injury to the enterocyte as well as inducing fluid secretion).

To distinguish between the secretory and osmotic diarrhea stool osmotic gap is usually calculated.

Stool osmotic gap = stool osmolality – 2 x (stool Na + stool K)

The stool osmolality is usually not directly measured, and is often given a constant in the range of 290 to 300.

Na+: ~30mmol/L

K+: ~75 mmol/L

A normal gap is less than 50 mOsm/kg.

1) Diarrhea associated with a low stool osmolal gap (less than 100 mOsm/kg) is considered as a secretory.

Potential causes include:

-Bile salt enteropathy;

-Laxative abuse;

-Congenital diarrhea;

-Drugs: (e.g. colchicine, SSRIs, prostaglandins, quinine, cholinesterase inhibitors);

-Enterotoxin-producing bacterial pathogens (e.g. clostridium, cholera and shigella.);

-Hyperthyroidism;
-Lymphocytic or collagenous colitis;
-Neuroendocrine tumors (VIPomas, gastrinomas, carcinoid tumors).

2) Diarrhea associated with a high stool osmolal gap (more than 100 mOsm/kg) is considered as a osmotic
Potential causes:
-Hexitols (poorly absorbed): sorbitol, mannitol, xylitol;
-Lactulose;
-Sugar intolerance (e.g. lactose intolerance);
-Unabsorbable water-soluble solutes used as laxatives: (PEG, Mg salts, Na Phosphate);
-Chorinc pancreatitis;
-Celiac sprue;
-Whipple's disease.

An exact molecular mechanism of diarrhea in each of particular case might differ from each other. For instance, chronic pancreatitis causes slow destruction of the pancreatic cells (see above) that produce digestive enzymes. Consequently, the foods arriving in your intestine are not efficiently digested and absorbed. Thus, in many people who suffer from chronic pancreatitis, this chain of events results in severe osmotic diarrhea. In opposite, VIPomas (in majority the tumors of cases arise from the pancreas) are known as a neuroendocrine tumors accomplished with hyperproduction and secretion of vasoactive intestinal polypeptide (VIP). VIP is a 28 amino acid polypeptide that binds to high affinity receptors on intestinal epithelial cells, leading to activation of cellular adenylate cyclase and cAMP production. This results in net fluid and electrolyte secretion into the lumen and secretory diarrhea. An exact mechanism specific for each particular cases of the diarrheas shown above will be discussed on the seminar.

References:

1. Essentials of Pathopsyiology: Concepts of Altered Health State. Kathleen Schmidt Prezbindowski // Lippincott Williams&Wilkins.─2004.─363p.
2. Pathophysiology of Disease. An introduction to Clinical Medicine. S. J..McPhee, V. R. Lindappa, W. F. Ganong, J. D. Lange // Appleton & Lange.─ 1995.─521p.
3. Pathology. V.A. LiVolsi, M.J.Merino, J.S.J.Brooks, S.H. Saul, J.E. Tomaszewski // Williams&Wilkins.─1989.─534 p.
4. K. Kaushansky. Lineage-Specific Hematopoietic Growth Factors // N Engl J Med.─ 2006.─Vol. 354.─P.2034-2045.
5. B. J. Bain. Diagnosis from the Blood Smear // N Engl J Med.─ 2005.─ Vol. 353.─ P.498-507.
6. J. A. Epstein. Cardiac Development and Implications for Heart Disease // N Engl J Med.─ 2010.─ Vol.363.─P.1638-1647.
7. J. J. V. McMurray. Systolic Heart Failure // N Engl J Med.─ 2010.─Vol. 362.─P.228-238.
8. M. T. Gladwin, E. Vichinsky. Pulmonary Complications of Sickle Cell Disease // N Engl J Med.─ 2008.─ Vol.359.─P.2254-2265.
9. N. R. Henig, D. J. Pierson. Respiratory Care // Clinics of North America. –2000. –V. 6:№ 4. – P.46-58.
10. John G. Laffey, Brian P. Kavanagh.Hypocapnia // N Engl J Med.─2002.─Vol. 347.─P.43-53.
11. West JB. Respiratory Physiology: the Essentials (8th ed.).// Baltimore, Lippincott, Williams & Wilkins.─ 2008.─210p.
12. R. Botev, J-P Mallié, C. Couchoud, O. Schück, J-P Fauvel, J. F.M. Wetzels, N. Lee, N. G. De Santo, M. Cirillo. Estimating Glomerular Filtration Rate: Cockcroft–Gault and Modification of Diet in Renal

Disease Formulas Compared to Renal Inulin Clearance // Clin J Am Soc Nephrol.– 2009.– Vol.4:№5 .– P.899–906.
13. T. W. Meyer, T. H. Hostetter. Uremia // N Engl J Med.– 2007.– Vol.357.–P.1316-1325.
14. L. A. Stevens, J. Coresh, T. Greene, A. S. Levey. Assessing Kidney Function. Measured and Estimated Glomerular Filtration Rate // N Engl J Med.–2006.–Vol. 354.–P.2473-2483.
15. G. Remuzzi, T. Bertani. Pathophysiology of Progressive Nephropathies // 1998.–Vol. 339:1448-1456.
16. M. Bishr Omary, Aurelia Lugea, Anson W. Lowe, Stephen J. Pandol. The pancreatic stellate cell: a star on the rise in pancreatic diseases // J Clin Invest.– 2007.–Vol.117:№1.–P.50–59.
17. Marshall M. Kaplan, M. Eric Gershwin. Primary Biliary Cirrhosis // N Engl J Med.– 2005.–Vol. 353.–P.1261-1273.
18. Kenneth E.L. McColl. *Helicobacter pylori* Infection // N Engl J Med.– 2010.–Vol. 362:№1.–P.597-1604.
19. Joseph H Sellin The pathophysiology of diarrhea Article published online: 7 JAN 2005 DOI: 10.1111/j.1399-0012.2001.00002.x.
20. Michael Field. Intestinal ion transport and the pathophysiology of diarrhea // J Clin Invest. .–2003.–Vol. 111:№7 .– P.931-940.
21. V. Savkovic, S. Gaiser, J. L. Iovanna, H. Bödeker. The Stress Response of the Exocrine Pancreas // Digestive diseases.– 2004.– Vol.22:№3.–P.229-231.
22. Graham DY. Therapy of *Helicobacter pylori*: Current status and issues. // Gastroenterology.– 2000.–Vol. 118.–P.2-8.